OPEN TEXTBOOK OF EXERCISE PHYSIOLOGY (MACINTOSH)



Brian R. MacIntosh

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Glossary

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1: INTRODUCING THIS OPEN TEXTBOOK

1.1: Chapter 1 - To Help You Learn Exercise Physiology

1.2: Chapter 2 - Historical Perspective on Canadian Exercise Physiology*

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1.1: Chapter 1 - To Help You Learn Exercise Physiology



Photo 3-1
Mountain Bike Launch. Like launching a study of the physiological response to exercise, mountain biking can be an exploration into unknown territory.
"Mountain biker jumping over rocks" by ID 12019 is licensed under Pixabay License.

Learning Objectives

After reading this Chapter, you will be able to:

- Describe the scope of topics covered in this textbook.
- Understand how to interpret some general graphic representations of data.
- Understand some fundamental concepts important for learning exercise physiology.
- Describe how statistical evaluation allows interpretation of data.
- Understand the concepts of validity and reliability.
- Find additional information on exercise physiology, from reliable sources.

Key Terms

research, Canadian Society for Exercise Physiology, exercise intensity, exercise physiology, graphs, half-time, exercise intensity, inferential statistics, kinetics, moderate to vigorous exercise, rate of oxygen uptake ($\dot{V}O_2$), partial pressure, proportionality constant, skinned fibre, time-constant, variance

Introduction

In this chapter, the range of topics to be covered in this textbook is introduced, some fundamental concepts of exercise physiology are presented as we go through these topics, and some general hints and tips that will serve to enhance your learning of exercise physiology are provided. You will be introduced to some normal values for physiological measurements that are commonly made during exercise. This chapter also provides some background on the science behind the study of exercise physiology and some basic information about National and International organizations that promote the work of professional and academic exercise physiologists. For example, the Canadian Society for Exercise Physiology (CSEP), which is an academic organization composed of exercise professionals who guide exercise programs and academics who conduct fundamental and

applied research in exercise physiology. CSEP certifies health and fitness professionals in Canada.

Using the Glossary

There is a good reason that there is an extensive glossary to be used with this textbook (see Glossary). There are two forms of the Glossary available; one is at the end of this textbook and one is online. The hyperlinks associated with words and expressions in this book connect to the online glossary. There is also an ebook (pdf) available that links to the online glossary. As you begin to read this textbook, you will notice that exercise physiology seems to have a language all to itself. To master an understanding of exercise physiology it is very important that you understand the meaning of the terms that are unique to this field of study. Language is the way we communicate concepts and ideas, so it is incredibly important that you learn the language (jargon) of exercise physiology. The Glossary can help you learn this language.

Rather than spend a few hours now, learning what is in the Glossary, it would be advisable to learn the new terms and expressions as you make your way through the textbook. To help you with this learning, important terms that are in the Glossary are presented in blue when used in a given chapter. When you come across a term that is blue, make sure you understand the meaning of the term before you progress further through the textbook. Hover your cursor over the term to see a brief definition. This is a digital textbook so it provides a direct link between the term in the text and the Glossary. Make use of the Glossary whenever you are in doubt of the meaning of one of these bolded terms. If you come across other terms you are not familiar with, be sure to look up the meaning before you continue reading. If you believe others would benefit from having a definition for a term that is not currently defined, feel free to contact the Editor.

Learning the Meaning of a Word from the Context

It is an important and valuable skill to be able to learn the meaning of a word from the context of its use. This is not always possible, but when it is, you might be able to detect subtle differences in the way some authors use a given term. It is useful to be able to do this, and something that you should watch out for, as you read. A good example of a term that can have different meaning with different authors is “anaerobic threshold”. This is a key term for exercise physiologists, and it is important that you have a good understanding of its meaning. When you get to this topic in the textbook (the term appears in several chapters), you might want to have a look at a review (Svedahl & MacIntosh, 2003) to gain more insight into this complex concept, and the common misrepresentations associated with it. Poole and colleagues have recently published a comprehensive review of the topic (Poole, Rossiter, Brooks, & Gladden, 2020) with a slightly different definition.

In research articles dealing with exercise physiology, the terms that are used are often defined by the author or implied by the way in which something is measured. For example, it has become customary to define muscle fatigue as a decrease in maximal isometric force. This is a very restricted definition of fatigue. It means that fatigue can only be detected when effort or nerve stimulation allow maximal activation of a muscle or muscle group. It also means that length change cannot occur, so the contraction to evaluate fatigue must be isometric. With this definition of muscle fatigue, decreased performance while cycling on an ergometer cannot necessarily be attributed to fatigue. In cases like this, the definition is not very useful, beyond the scope of the research article. It is important to realize that the concept of fatigue probably does exist beyond the scope of some limiting definitions (MacIntosh & Rassier, 2002).

A Comment about www and Wikipedia

The world-wide web (www, also known as the internet) is a potentially valuable source of information, but in many cases, there is no guideline to tell you what you should accept and what you should take with a grain (or more) of salt. Believe it or not, not everything you find on the web is true! Anybody can say anything on the web. A valuable skill to develop is to critically evaluate the information you are presented with and discard what is not useful.

Wikipedia is an open online dictionary. Anyone can contribute a definition, and the rules of contribution encourage methods of verification; (About Wikipedia). However, mistakes do occur, and when you consult Wikipedia for the definition of a term, you should be cautious. Nevertheless, Wikipedia is improving with time, so our Glossary provides links to additional information, often from Wikipedia. However, in some cases we decided that the definition provided in Wikipedia was not specific enough to exercise physiology and the use of that definition is not encouraged. In these cases, no link to Wikipedia is given.

A Few Key Concepts in Exercise Physiology

Exercise is a systematic use of skeletal muscles to move the body. These skeletal muscles need energy to contract and generate heat in addition to force development and movement. Muscle contraction results in changes in ion distribution across the membranes of our muscle cells and increased use of fuel and O_2 and production of CO_2. These changes result in a disturbance to homeostasis; a disruption to the environment inside and outside the cells of the body. For example, the activation of nerve and muscle cells during exercise will result in a decrease in intracellular potassium concentration [K^+] and an increase in extracellular potassium concentration. These changes in [K^+] represent disturbance to the neutral environment that we maintain for the benefit of our cells. Control mechanisms are in place to recognize this disturbance, and make adjustments to the movement of K^+ across membranes throughout the body including in the kidneys to help return the plasma and extracellular fluid concentration of K^+ to the normal level. Similarly, we all maintain our arterial blood pressure within narrow limits. Our body has regulatory mechanisms that allow this control of arterial blood pressure in the face of changes in our external environment: posture, physical activity, or changes within our body such as blood volume, vascular resistance. There are many other physiological parameters that require similar control as part of homeostasis, from such things as ion concentrations both within cells and in the space between cells, or body temperature.

Exercise represents a considerable challenge to homeostasis. For skeletal muscle to maintain contractile activity, it requires the maintenance of an appropriate environment surrounding the muscle fibres. This environment is the interstitial space. It also requires the maintenance of an appropriate environment within each skeletal muscle fibre (the intracellular space) and the replenishment of adenosine triphosphate (ATP), which is the “energy currency” of the body, at a rate that matches its consumption. As you will learn in subsequent chapters, the many processes involved in muscle contraction use a number of substances and produce a number of other substances, and heat. If homeostasis is the maintenance of relatively stable conditions, then you can appreciate that muscle contractions add some and remove other substances both within and between muscle cells and are therefore disrupting homeostasis. Minimizing such disruption requires mechanisms that balance the removal or addition of these substances. Exercise physiology is therefore essentially about the mechanisms in skeletal muscle that create muscle contraction force (Chapter 5), and the myriad of mechanisms in other physiological systems that act to offset the disturbance to homeostasis that results from skeletal muscle contractions (Chapters 7, 8, 9, 10 and 11).

The fluid between the muscle fibres becomes changed with respect to a number of ions, substrates (glucose and fatty acids) and gas composition. These changes extend into the blood flowing through the muscles and the blood flow transmits these changes through-out the body. In order to minimize the disturbance to homeostasis and to return to that state following exercise, sensors must detect the disturbance to homeostasis and changes must be made to restore the composition of extracellular and cellular spaces. This restoration is accomplished by control and regulation. The concept of control and regulation is described below, but first, an example of some of the physiological changes associated with exercise will be presented.

Jill is a middle-aged working mom of three. When lunch break comes she tells her colleagues that she is “going out to get some exercise!” It is a beautiful summer day and she starts off on a brisk walk. It is quite hot at this time of the day. As Jill begins her walk, we would notice that her breathing increased, and if Jill felt her pulse she would be able to confirm that her heart rate has increased to a level well above the rate when she was sitting at her desk. After a while, Jill also begins to sweat. If we could take a blood sample, we could measure changes in concentration of several things in her blood. Venous oxygen content decreases and carbon dioxide increases. Plasma [K^+] increases but just a little bit because her exercise is of a moderate intensity. Concentration of glucose will not likely change in the arterial blood, but might be decreased in venous blood. When she finishes her walk and returns to her work space her breathing and heart rate would eventually decrease to where they were prior to the walk and she would eventually stop sweating. Other changes would also change towards the preexercise values.

So, why and how do these (and a myriad of other) familiar physiological responses to exercise occur? Will Jill eventually be able to walk/jog faster and for longer if she regularly exercises? What physiological changes occur and why? How do these changes allow her to exercise with less disturbance to homeostasis? The chapters in this textbook address these questions. But first, in this introductory section we will establish an understanding of key concepts and principles that govern all physiological function. While there are many physiological systems with countless “parts” and complexity that are involved in meeting the challenge of exercise. These key concepts and principles are universal in dictating how these the body systems interact to achieve the required integrated physiological response necessary to support exercise. Understanding these principles and learning to recognize their components in physiological systems will allow you to not just know facts about exercise physiology, but to be an exercise physiology problem solver. In other words, strive to understand how and why the body responds the way it does during exercise.

Control and Regulation

In order to survive, the volume, temperature and composition of the extracellular fluid must be controlled very carefully. A parameter that is controlled is something that is kept as constant as possible. For example, the following parameters are controlled: blood pressure, plasma [K^+], [Na^+], [H^+] and body temperature. Control means there is a set point, or target value for the parameter being controlled, a means to detect the current value and effectors to regulate or bring the current value back close to the set point. Sensor(s) detect the current value, and inform the controller (usually the brain) so it can compare the detected value with the set-point. If a difference is detected, the controller will regulate effectors that allow changes to keep the parameter within a narrow range of values. If blood pressure falls, baroreceptors detect the change and inform the brain of the current value. The brain regulates effectors like the heart and blood vessel smooth muscles to modulate the pressure back to the desired level. If blood pressure falls below the set-point, like it might do when you stand up too quickly, the brain will send a message to the arterioles to constrict, increasing blood pressure. The brain would also send a message to the heart to increase cardiac output, contributing to the increase of blood pressure. This kind of control system is referred to as feed-back control (see below for another example).

Our body is organized in such a way that the concentration of various substances, processes and physical parameters are controlled as carefully as possible, so disturbance to homeostasis can be minimized. Our body accomplishes this objective by regulating the movement of ions through ion channels and pumps, mobilizing or sequestering substrates and activating or inhibiting smooth muscle. Even total body water is controlled. Fluid loss by sweating is a mechanism to lose heat from the body, but fluid content of the body is controlled, so loss of fluid from the body results in a regulated decrease in loss of fluid by the kidneys, and initiating a thirst mechanism to increase fluid intake.

There are two key principles of physiological function that allow us to understand the processes that disturb homeostasis and the mechanisms that act to minimize such disturbance. These principles are universal to all the physiological processes involved in all of the physiological systems addressed in this textbook on exercise physiology. The first is the principle of mass balance, and the second is the principle governing the movement of a substance, or its conversion from one form to another as occurs in metabolism. We will call all such movement and conversion “flow”, so this is the principle of flow.

Mass Balance Principle

If homeostasis is the tendency to maintain a specific environment within acceptable limits, mass balance represents the fundamental components of such a process. First, there is the “mass”. In this context, mass refers to any substance or quantity of energy in the form of heat, in a given compartment. Your body is a compartment and body temperature would be the mass of heat in that compartment. Your circulation is a compartment and blood volume would be a mass in that compartment. Your muscle cell is a compartment and ATP would be a mass in that compartment.

Next is the movement of a given mass into a compartment (we will call this “inflow”) and out of a compartment (we will call this outflow). There may be a number of inflows and outflows. For the mass of heat in the body, metabolic processes that produce heat would represent an inflow. Evaporation of sweat which releases heat into the environment would represent an outflow. Absorption of water into the blood at the small intestine would be an inflow for the mass of fluid in the circulation. Removal of water from the blood by the kidneys would be an outflow for the mass of blood in the circulation. Splitting of ATP into adenosinediphosphate (ADP) and inorganic phosphate (Pi), a metabolic process, would be the outflow for ATP. Production of ATP through the metabolic pathway of glycolysis would be an inflow for ATP.

The above examples are analogous to a lake with one or more rivers flowing into it and one or more rivers flowing out. If the inflow rivers have the same total flow as the outflow rivers, then the volume of the lake remains constant. If it rains upstream and more water enters the inflow rivers, the inflow to the lake will increase relative to the outflow and the water level of the lake will rise until it increases the flow in the outflow rivers enough to match that of the inflow rivers. With no further rain, the inflow will gradually return to that before the rain, the lake level will decrease and ultimately so will the outflow until we are once again at the original lake level with the original inflow and outflow balance.

Based on the above, it now makes sense to ask what determines a flow, given that changing inflow relative to outflow is the fundamental process of mass balance. This brings us to the key principle of Flow.

Flow Principle:

So, what creates flow? And what determines the magnitude of flow? The flow of any mass requires an energy gradient. If we

consider in Figure 1-1a the inflow of oxygen into the cell, that gradient would be represented by the amount of oxygen outside the cell relative to the amount inside. The more oxygen there is outside relative to inside the cell, the larger the gradient from outside to inside the cell. In this case the energy gradient is a concentration gradient. The type of "flow" here is diffusion, whereby random movement of molecules means that if there are more molecules of oxygen outside the cell, the number of molecules moving into the cell will be greater than the number of molecules moving out, such that there is a "net" flow of oxygen into the cell. There are other types of energy gradients and you will come across them as you read the chapters of this textbook. What is important to recognize is that the flow created by an energy gradient will increase as the gradient increases, and decrease as the gradient decreases.

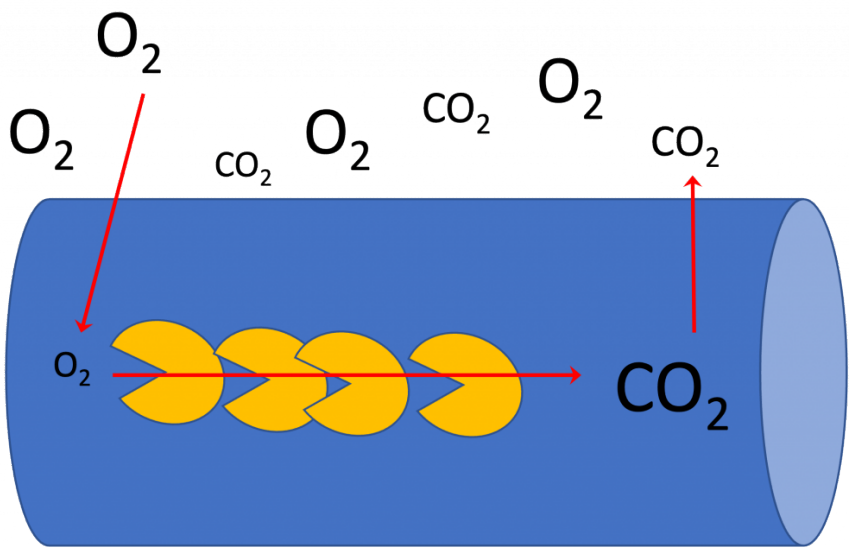


Figure 1-1a illustrates mass balance where the compartment is a cell. Each of the substances illustrated has inflow and outflow, and the concentration of a substance (think of this as a mass of the substance) in the cell is determined by the balance between the inflow and outflow for that mass. A disturbance to the stability of the masses in the cell would have to disrupt the balance between the inflow and outflow for that mass, and physiological mechanisms would have to counteract this disruption by having an opposing effect on the balance of inflow and outflow. This dynamic is illustrated in Figure 1-2. As you read the chapters in this textbook, try to define every substance as a mass and identify the compartment within which that mass exists. Then identify what the inflows and outflows for that compartment mass are. Not all of those masses are "homeostatic". In other words, not all need to be kept in narrow limits, but rather some may be changed in order to achieve an important physiological function.



Figure 1-2. Energy gradient causes flow Here, "flow" is represented by the movement of a table. Flow is dependent on an imbalance of force applied by the people at each end of the table. Rate of flow is dependent on the energy gradient and the conductance (ease with which flow can occur).

There is another factor that determines flow which we will call “conductance”. Conductance refers to the “ease” with which flow can occur for a given energy gradient. The greater the conductance, the greater the flow. In physiological systems there are structures and characteristics of structures that determine conductance for the flow of a substance. If we take the example in Figure 1-2, you can well imagine that if the table is on a smooth floor it is easily moving from left to right in proportion to the difference in force (i.e. the gradient) applied by the two individuals. However, if the table were to move onto a carpet, it would slow down with the same force gradient. We can think of the “conductance” for movement of the table on wheels to be lower on carpet than on a smooth floor. The inverse of conductance is resistance. It refers to the same thing but rather than describing the ease with which flow can occur it describes the opposition to flow. So the carpet would have less conductance for, but more resistance to, the movement of the table on carpet than the smooth floor. In this textbook you may find places where resistance is the term used and others where conductance is the term used. Just remember they refer to the same characteristic as just described.

So FLOW = Energy Gradient × Conductance

or, FLOW = (High Energy – Low Energy) × Conductance

Now let us return to the mass balance model in Figure 1-1 where disturbances change inflow relative to outflow of a mass in a compartment, and physiological mechanisms can counteract that via opposite effects on inflow/outflow balance. Based on the flow principle, you should now recognize that there are only two factors that can be manipulated in order to affect inflow/outflow balance and thereby virtually all the physiological processes you will learn about in this textbook on exercise physiology! Either disturbances and physiological mechanisms can affect either a gradient or a conductance. That’s it!

So, as you read the chapters in this textbook, try to identify flows and the gradient which creates flow and the conductance which allows flow. Recognize that when flows change in the body, it is because either a gradient or a conductance for that flow has been changed.

Given the above, the next question you might ask is, “how are flows controlled in order to determine mass balance?” This is where the concepts of feed-forward and feed-back control are helpful to understand.

Feed-forward control:

When a parameter is regulated in anticipation of a change in mass, and the regulation reduces or prevents disturbance to homeostasis, this is called feed-forward control. For example, ventilation increases at the instant that exercise begins, before any change in oxygen content of the blood can be detected. This increase in ventilation prevents or minimizes the decrease in oxygen content of the arterial blood.

Feed-back control:

When something is controlled within narrow limits by detection of that something to inform a control mechanism of the current value and that control system can effect change to bring that something back towards the controlled value, then the system is referred to as feed-back control.

The nature of the human body is that from minute to minute the size and general composition of intracellular and extracellular fluid is preserved. Consider the possibility that exercise results in increased use of glucose as a metabolic substrate. Increased uptake of glucose by muscle cells will result in a decrease in blood glucose concentration. Blood glucose concentration is regulated by a feedback control mechanism. Blood glucose concentration is continuously monitored by cells in the pancreas. When the blood coming to the pancreas has lower concentration of glucose, the cells of the pancreas will secrete glucagon. Glucagon is a hormone that mobilizes glucose from the liver by accelerating glycogenolysis. This is an example of a feed-back control system that does not require the brain to compare sensor input and respond by changing or regulating some effector in the body. The brain is bypassed by the cells in the pancreas that respond directly to the change in blood glucose concentration.

Elastic Recoil

Elastic recoil is another universal concept in physiology. Many tissues in the body have a tendency to return to their original size by elastic recoil. This is true for individual cells, organs and tissues. A good example of this elastic recoil is seen on observation of the lungs. When we breathe in, the lungs are expanded but when we relax the inspiratory muscles (primarily the diaphragm), the lungs have a natural tendency to return to their natural relaxed size. Exhaling is a passive process during resting ventilation. Blood vessels and airways have a natural elasticity as well. Even individual cells have an elastic recoil when they are temporarily

expanded by fluid moving into them.

Sources of Additional Information

Access and Type of Information

It is almost certain that you will find several topics presented in this textbook, for which you will want additional information. This is a general textbook on exercise physiology, in which it is impossible to cover all topics that are relevant to this broad and expanding field of study, and for which most topics can only be covered at a superficial level. Advanced study on any topic, or clarification of the information presented here can be obtained from a number of sources, including: advanced and specialized textbooks, the internet, journal articles, the Gatorade Sport Science Institute, and conferences and seminars. Each of these sources will be described briefly here.

Internet

The internet brings a wealth of information, and misinformation, to your fingertips with the simple typing of a few search terms. The ease with which this information is made available brings with it a serious concern. Do you know who put that information there? In most cases, the answer is no, and in all cases, it is important to consider this information with some degree of skepticism. The “value” of information you find on the internet depends on how it got there and when it got there. Keep in mind that much of what is presented on the internet is the opinion of the writer. Another writer might very well have a different opinion.

Listed in Table 1-1 are several internet sources, and an associated crude index of certainty for the value of the information there. This index represents the personal opinion of the author and is an arbitrary scale where 0 means ‘no certainty’ and 9 represents ‘maximum certainty’ for the value of the information presented.

Table 1-1 ***Internet Sources of Information***

Peer-Refereed Journals	Society or Publisher	5-9
Gatorade Sport Science Institute	GSSI	7-9
Textbooks	Publishers	6-9
Wikipedia	Wikimedia Foundation	4-9
Newspapers	News Publishers	2-9
Specialty Magazines	Publishers/Experts	1-9
Blogs	Individuals	0-9
Health	Medical Organizations	5-9

Facebook/Twitter	Individuals	0-9

[a] Certainty, here, is a purely subjective assessment of the apparent quality of the information available from the designated source. When the number is low, the information may be biased, misleading or absolutely incorrect. When the number is high, the information is informative and correct. Note that for most sources, the quality range is high.

Two very valuable sources of information on the internet are peer-refereed journals and the Gatorade Sport Science Institute**.** These are further described below.

Peer-Refereed Journal Articles

Research is the source of all knowledge in the field of exercise physiology, and that research is typically published in peer-refereed journals. Some of the more relevant journals for exercise physiology are listed in Table 1-2. Your library probably has a subscription to these journals, so the content will be free to you. Much of it is accessible on the internet.

Table 1-2 ***Peer-Refereed Journals in Exercise Physiology***

Journal Name*	Publisher
Applied Physiology, Nutrition and Metabolism**	Canadian Science Publishing
Journal of Applied Physiology	American Physiological Society
Medicine and Science in Sports and Exercise	American College of Sports Medicine
European Journal of Applied Physiology	Springer
European Journal of Sport Science	Taylor & Francis
Sports Medicine	Adis International Ltd
International Journal of Sports Medicine	Thieme
Scandinavian Journal of Medicine and Science in Sports	Wiley-Blackwell
Exercise and Sport Science Reviews	American College of Sports Medicine

Journal Name*	Publisher
Frontiers in Physiology	Frontiers.org

*Note: this is not an exclusive list. Other journals do publish excellent articles in exercise physiology. This list encompasses the most common journals for good articles in the field of exercise physiology.

**Applied Physiology, Nutrition and Metabolism is the official journal of the Canadian Society for Exercise Physiology.

The Peer-Referee Process

The journals listed in Table 1-2 all have a peer referee process. This means that when a scientist submits an article for publication, the Editor of the journal will either reject the paper without review, or assign the article to an Associate Editor, who sends that manuscript to (usually) two individuals with expertise on the topic to review the paper for quality of the research and accuracy of the information presented. Typically, the referees will submit a report, offering an opinion on whether or not the manuscript should be accepted for publication, and often this recommendation will include specific requests for revision. The Editor chooses whether or not to accept the article, or alternatively will reserve judgement and will delay that decision until suitable revisions have been made to address the concerns raised by the referee.

Many journals have rejection rates as high as 60%. This means that they accept for publication only 40% of the manuscripts submitted for publication, and this is only after 2-3 rounds of revision and assessment. The peer-referee process serves to enhance the quality of what is published, and hopefully prevent the publication of research that should not be published: poorly designed and unconvincing research. However, it accomplishes this with some delay in the publication. The peer referee process typically takes several months. Often there is further delay from the time an article is accepted until it is published. Many journals offset this extra delay by publishing articles on-line as soon as they are accepted for publication.

In spite of the peer referee process, errors and omissions or misrepresentations do persist in some of the articles that reach publication. Ultimately this is the fault of the authors, but referees must accept some of this blame. It is truly unfortunate, but the old adage: “don’t believe everything you read” still holds true in peer-refereed published work. In general, journals publishing within a field of study can be ranked from best to lowest quality. Scientists will attempt to publish their work in the best journal that will accept it. Although errors still exist in the research literature, it is still the most valuable source of information and knowledge. A concept or idea can only be fully understood when several papers demonstrate consistent data related to the concept. Ultimately, journal articles have provided the information for this textbook.

Conferences and Seminars

If you want to hear the latest research on a given topic, consider attending a conference or seminar. You might be surprised to hear how affordable this can be! The Canadian Society for Exercise Physiology (CSEP) hosts a conference each year, in some part of Canada. Check their web-site (CSEP.ca) for the location of the next meeting (see below). CSEP also hosts more casual regional meetings each year.

Your University or College might also have a series of seminars, usually on a weekly basis, presenting the most recent research that is happening on campus. These seminars are often presented by graduate students, and sometimes by local faculty members. Occasionally, the speakers may be national or international experts, and these experts may be local or invited from out of town. If regular events such as this are not occurring at your Institution, you can be a catalyst to try to make it happen, by talking with graduate students and faculty members about instituting a “journal club” or regular seminar series.

Gatorade Sport Science Institute

I am sure you know what Gatorade® is. Yes, Gatorade® is a sports drink; the first of its kind. Gatorade® was scientifically formulated as a fluid replacement beverage to help the University of Florida Gators football team! A renal physiologist, Dr. Robert Cade, led a team of physicians in developing this beverage. The success of the football team became a resounding endorsement

of the beverage. The rest, as they say, is history.

Gatorade® began with science, and in addition to its commercial success, the company that makes, markets, and sells Gatorade® maintains a strong connection to science; not only through their labs and sponsored research, but through the Gatorade Sport Science Institute (www.GSSIweb.com). It would be worthwhile for you to go to this web-site to see what they present there. They have an extensive library of sports and exercise physiology articles, written by experts in their field. Of course, there is a focus on hydration and exercise in the heat, but articles on athlete training and performance are also available, as are articles on injuries, health, and nutrition. Although Gatorade® is now owned by PepsiCo, the University of Florida receives millions of dollars each year from the profits of Gatorade® sales.

Importance of Critical Appraisal

Wherever you find your information, you need to evaluate it critically. The ability to evaluate critically involves familiarity with the topic, identifying differences of opinion, and trying to resolve why there is a difference. Sometimes the difference exists because the information was obtained in different studies with different methodology, and sometimes the difference represents a difference of opinion. Heaven forbid that one source might actually be wrong. This is a possibility, even for peer refereed journal articles. The peer referee process is the strongest way we have of assuring quality of published work, but mistakes are still made.

As you learn, you will formulate a paradigm of how you believe things (like exercise physiology) work. When you read something that does not fit your paradigm, you need to consider whether or not it is appropriate to shift your paradigm or refuse to believe the new information. Alternatively, you might want to consider the possibility that the new information is correct but may only apply in certain circumstances. This possibility addresses the issue of external validity that is further discussed below. Before we get to that topic, we will comment on a problem that needs to be avoided in your written work.

Plagiarism

When you present information, you have gathered from a source other than your own mind, without acknowledging where the information came from, it is called plagiarism. When you gather information from various sources to write an essay for a course, you are gathering information from others and it is appropriate to give credit to the source of information. This is true whether the information was published in print form or on the internet or broadcast by radio/TV or podcast. Even public broadcast, notes of fellow students and lecture material should be acknowledged as sources (though in the case of lectures, you need to be careful because the information could be considered here-say). Giving credit to the source means presenting a reference stating where the information came from; usually the instructor for the course will provide you with guidelines for the format of such referencing. If you use the direct words of the source, this is a quote and it is necessary to use quotation marks. If you translate the message into your own words, you still need to acknowledge where the information came from. You should make it clear what information was obtained from the cited source and what are your own thoughts on the topic. There are often strict penalties for plagiarism, so be careful when borrowing information from others.

Note on Units for Oxygen Uptake

When the units for any measure are given relative to another measure, like per min or per kg, there are two ways these can be presented: 1) $ml \cdot kg^{-1} \cdot min^{-1}$ like above, or 2) ml/kg/min. This book will use the former convention. The dot between units signifies multiplication and the superscript -1 indicates the equivalent of the inverse (1 over x). If the superscript was -2, it would be the equivalent of 1 over x squared. You will notice that the units for oxygen uptake presented above are given per kg of body mass. This is conventional for exercise that is body mass dependent, like running or walking. When the exercise is not body mass dependent, like swimming or cycling on a level road, it is conventional to express oxygen uptake as $litres \cdot min^{-1}$.

It is important to recognize, in a quantitative way, how physiological capacities contribute to limitations in physical performance. It is also important to recognize that these capacities can be represented by a broad range of values, and that factors like: genetics, training, inactivity, and disease can influence many of these values. Body size, sex, and body composition can also influence some of these values. It is simply misleading to expect every normal person to have a maximal cardiac output of 25 $litres \cdot min^{-1}$, a value that is often given for a “normal” cardiac output during intense exercise. It is also more reasonable to express the maximum cardiac output relative to body size, similar to the idea that we have a blood volume that is the equivalent of about 8% of body mass. To extrapolate this to maximal cardiac output, it is reasonable to expect a healthy person to have a maximal cardiac output of about 4-6 blood volumes per min. This would equate to a blood flow from the heart of about 350 $ml \cdot kg^{-1} \cdot min^{-1}$. As you read through the chapters in this book, pay close attention to the units associated with values presented. It is not enough

to know the number, you must also know the units associated with that number. A table of normal values is presented in Appendix A.

You will have noticed that "%" has been used in the above paragraph. Expression of many parameters of exercise physiology in % can be useful. However, it is important to keep in mind what the values representing 100% is. It is also relevant to identify whether the value presented is % change or % of a standard value. This seemingly small difference can be a huge difference in reality. Consider the example of a measure of change in $\dot{V}O_2$max over a period of inactivity. The change might have been a decrease in 10%. This would be a large change if the initial value was high, like 75 ml·kg^{-1}·min^{-1}, but small change if initial value was 20 ml·kg^{-1}·min^{-1}. It is also quite different to say the change was 10% or the change was to 10%.

Conventions in Exercise Physiology

As mentioned above, the language of exercise physiologists includes a lot of jargon and several conventions. One of the important conventions is the use of the dot over a letter to indicate rate. For example,Q is a blood volume (ml), and $\dot{Q}$ is a rate of flow (ml · min^{-1}). Similarly, VO_2 is a volume of oxygen uptake (litres) and $\dot{V}O_2$ is a rate of oxygen uptake (litres·min^{-1}). Another convention is that when the energy cost is proportional to body mass, as it is for weight-bearing exercise, the $\dot{V}O_2$ is expressed relative to body mass (ml·kg^{-1}·min^{-1}), but when the energy cost is independent of body mass, the $\dot{V}O_2$ is expressed as ml·min^{-1}.

Now, I would like to identify the topics that will be covered in the remaining chapters of this textbook. Following this brief introduction to the chapter contents, I will present some information on interpreting graphs and statistics; information that will help you understand the knowledge presented in the following chapters.

The Contents of this Textbook

This textbook is unique among exercise physiology textbooks. First of all, it is unique that it is Canadian. The Canadian content is present in several ways: the authors of the individual chapters are Canadian, Chapter 2 provides a summary of the history of exercise physiology in Canada. Canadians have contributed substantially to the global growth of knowledge in the field of exercise physiology, and will most certainly contribute further over the next decades. Other countries have also contributed substantially to the high rate of growth of knowledge in exercise physiology.

Another unique feature of this textbook is the use of a cast of fictional characters throughout the textbook to present the measurements relevant to exercise physiology. You will meet some of these characters in this chapter, but others will appear as you make your way through the textbook. There is a brief description of these characters in Appendix C where you can find out a little about them, including values for some of the basic measurements that exercise physiologists are concerned with. You will have to read the individual chapters to find out more details about these interesting fictional characters. Please note that any similarity between these characters and anyone you may know is simply coincidence.

One of the advantages of presenting fictional characters to describe the fundamentals of exercise physiology is that you will learn that there is considerable variation from the "normal". Some of that variability relates to differences in size and body composition, but some relates to sedentary living or training effects related to the amount and intensity of physical activity regularly obtained. A third but substantial factor contributing to this variability is genetics. Just to give an example of variability in exercise physiology, consider the measurement of maximal oxygen uptake ($\dot{V}O_2$max)**.** $\dot{V}O_2$max is the highest rate at which the body can use oxygen for aerobic metabolism. $\dot{V}O_2$max is typically measured by quantifying the amount of oxygen breathed in over a period of time and the amount of oxygen breathed out in the same time. The difference is the oxygen uptake used for mitochondrial metabolism. If these measures are done while exercise intensity continuously increases to exhaustion, a peak value can be obtained. The term $\dot{V}O_2$peak is often used to describe the highest value for oxygen uptake reached in an incremental test. If exercise intensity increases but oxygen uptake does not, then you have achieved a plateau in oxygen uptake. This plateau indicates you have reached maximal oxygen uptake for that exercise. Values for maximal oxygen uptake can be as low as 10 ml · kg^{-1} · min^{-1} or as high as 95 ml · kg^{-1} · min^{-1}. Note that the units here follow SI convention (Systeme Internationale). This format will be followed through-out the Online Textbook of Exercise Physiology. The dot at mid-height (·) indicates multiplication and the superscript ($^{-1}$) indicates "*raised to the power of*". When the power is negative, the units indicate divided by, so ml · kg^{-1}·min^{-1} is similar to ml/kg/min.

For a given individual, maximal oxygen uptake will depend on the exercise used in the graded exercise test. Cycling will typically

result in a lower maximal oxygen uptake than will running on a treadmill. This is thought to occur because of the difference in muscle mass used in the task. However, it is interesting that cyclists will achieve a higher maximal oxygen uptake while cycling than while running.

An Overview of the Chapters of this Textbook

Chapter 2: History of Exercise Physiology in Canada

As indicated above, Canadians have contributed substantially to the growth of knowledge in exercise physiology. This contribution probably resulted primarily from the early establishment of doctoral programs in physical education at the University of Toronto and the University of Alberta. This pioneering spirit was also responsible for the establishment of the first two (in the world) programs in Kinesiology at Simon Fraser University and University of Waterloo. In Chapter 2 you will learn of some of the early scientists who helped establish exercise physiology as a strong Canadian discipline. Many of those identified in this chapter are still active in teaching and doing research today.

Chapter 3: Neural Control of Muscle Activation

Motor nerves control activation of our muscles. This can happen willingly, by motor pathways beginning in the brain and passing down the spinal column to the ventral horn where the cell bodies of the motoneurons live, or involuntarily by spinal reflex. motor neurons connect via the spinal nerve to individual muscles. Each muscle will have a collection of cell bodies in the ventral horn of the spinal cord and each of these cell bodies will have a single axon that branches multiple times to innervate a number of muscle cells. A single motor neuron and all the muscle fibres it innervates is called a motor unit. Any given motor unit can be activated by action potential generation and propagation, but in most cases, there is an orderly sequence of activation that relates closely to the fibre-type of the muscle fibres activated by a given motor neuron.

Chapter 4: Muscle Structure and Organization

I am sure you are aware of the amazing physical capabilities of your own skeletal muscle . What you might not realize is the intricate structural features of muscle tissue that allows this impressive functional capability. Chapter 4 will present the structure of skeletal muscle, from the macro-organization to the submicroscopic level. Our muscles have an extensive repeating structure from whole muscle to sarcomeres. Connective tissue separates muscles from each other, surrounds bundles of muscle fibres, and envelopes each individual muscle cell (also called a fibre). Within each cell, long tubes called myofibrils contain the contractile proteins in repeating units called sarcomeres. All contractile properties can be explained at the sarcomere level, and sarcomeres along the length of the fibre will respond to activation in a similar manner. Recent advances have made substantial contributions to our understanding of how muscles are put together.

Chapter 5: Skeletal muscle Contraction

The “Strong-Man” competitions that are often shown on television, illustrate a wide variety of ways that muscle can contract in extremely forceful ways. In contrast, muscle can also have tremendous endurance; repetitively contracting for hours through an ironman competition or ultra-marathon or simply during a shift at work in a physically demanding job. Remarkably, these same muscles can execute skilled micro-surgery, repairing structures in the body that we cannot even see without visual aids. The primary properties of muscle can be categorized as the following: force-length relationship, force-velocity relationship, force-frequency relationship, and force-calcium relationship. The broad range of functional capability of our muscles is presented in Chapter 5, where we will learn how muscles can be called upon through the day to perform routine tasks like climbing the stairs or carrying a laptop, in addition to the remarkable feats described above.

Chapter 6: Energy Supply for Muscle Contraction

In one of the “Back to the Future” movies, the time machine (modified DeLorean) is fueled by garbage. Our muscles can be fueled by junk food. However, I am sure you are aware that this should not be the case. In Chapter 6, you will learn how muscles transfer the chemical energy in the food we eat to a form that is readily available for the contractile functions described in the previous chapter. These processes have historically been divided into two systems: aerobic

and non-aerobic. The aerobic system involves – oxidation of fats, glycolysis of carbohydrates, as well as two paths common to

both fat and carbohydrate metabolism called the citric acid cycle and oxidative phosphorylation. The non-aerobic system, also referred to as the anaerobic system, involves two sources of energy: 1) the high-energy phosphate compounds adenosine and creatine phosphate and 2) glycolysis, leading to lactate formation.

Chapter 7: Pulmonary Function During Exercise: Gas Exchange Between Environment and Blood

One of the key functions of the circulatory system is to get oxygen to all of the cells of the body, and to remove carbon dioxide. We must breathe to remove the carbon dioxide from our blood, and to provide it with oxygen. The ventilatory system involves the lungs, ventilatory muscles, and airways. In Chapter 10, you will learn how this system is structured to optimize the transfer of gases from the atmosphere to the blood, and how in most cases this system is overbuilt; we have a capacity to breathe that most of us will never use.

Chapter 8: Circulatory Response: Delivering Substrates and Removing Metabolic Products

Single cell organisms do not need a circulatory system, but complex multicellular organisms, like mammals do. Our circulatory system serves to maintain the extracellular space around each cell in the body in a state that supports life for the cells in that vicinity. The circulatory system involves the heart, blood vessels, blood, and the lymphatic system. It is important to realize that the circulation is important not only for delivery of gases (oxygen and carbon dioxide) but also transportation of metabolic substrates, waste products, ions, amino acids, as well as hormones and cytokines. In order to keep the extracellular space around our muscle cells in a state that supports life, it is necessary to increase blood flow during exercise. This is achieved with a marvelous regulatory system that not only increases cardiac output by a factor of 2-8 fold, but also distributes most of this increase in cardiac output to the exercising muscles, while maintaining or even increasing the blood pressure. In Chapter 9 you will learn how this remarkable adjustment is achieved.

Chapter 9: Homeostasis and Disturbance of Homeostasis During Exercise

Exercise has the capacity to disturb the homeostatic condition that otherwise exists in the extracellular space, particularly that in the skeletal muscle. Each activation of a motor unit results in exchange of Na and K across muscle and nerve membranes, changing concentrations both inside and outside these cells. Blood composition changes during exercise: PO_2 decreases in the venous blood while PCO_2 increases and acidosis results from increase PCO_2 and metabolic acid production. Note that the capital P here denotes partial pressure of the gas. Muscles begin using carbohydrates and fats at an increased rate, potentially decreasing their concentrations in plasma. Homeostatic regulation keeps the changes to the internal milieu to a minimum. These mechanisms of homeostatic regulation are presented in Chapter 9.

Chapter 10: Measuring Metabolic Responses and Capacities

The energy cost of performing a task can be quantified in a number of ways. Considering that aerobic metabolism can account for most tasks that we perform, the measurement of oxygen uptake is a reasonably easy, yet accurate way to quantify the energy cost of tasks that can be sustained at a reasonably low metabolic rate. In contrast with this, higher intensity tasks rely at least partly on non-aerobic metabolism, and this energy contribution is not as easily quantified. Muscle biopsy has been used to quantify the disappearance of high energy phosphate compounds: adenosine triphosphate and creatine phosphate. A more expensive, but less invasive technique is to use magnetic resonance spectroscopy to monitor change in these non-aerobic sources of energy. Chapter 10 presents these measurement techniques, the value and limits to their use and some values that illustrate how much or how fast this energy can be made available.

Chapter 11: Nutrition and Energy Balance in Active People

In spite of the reference to junk food above, a proper balance of nutritional foods is required for a healthy life. Chapter 11 provides the background to understand what is needed, what should be avoided and how these nutrients contribute to muscle metabolism, disease prevention, and athletic capabilities. The nutrients we require can be broadly classified as: fats, carbohydrates, proteins, water, minerals and vitamins. The frequency, type, and duration of exercise you engage in will affect how much of some of these you need on a daily basis.

Chapter 12: Body composition: the Stuff We Are Made Of

The truth is that our bodies are composed of water, protein, fat, and minerals, but it is convenient to divide this collection of ions and molecules into two or three measurable components: fat mass and fat-free mass, with or without bone separated into its own category. Chapter 12 provides the information you need to understand the expected distribution between these compartments and how they relate to health and exercise. Measurement techniques including: hydrostatic weighing, bioelectric impedance, skinfolds, and dual energy X-ray absorptiometry (DEXA) are also addressed.

Chapter 13: Consequences of Repetitive Muscle Activation: Potentiation and Fatigue

When a muscle is repetitively activated, each activation can have an effect on subsequent contractile response. Initially, there is an effect that increases the Ca^2 sensitivity, resulting in stronger contractions per activating pulse when activation is submaximal. However, continued use of a muscle will result in fatigue; a decline in contractile response. Chapter 12 presents the circumstances surrounding these changes and the cellular mechanisms associated with these changes to the contractile response.

Chapter 14: Molecular Basis of Exercise Training: Adaptations in Skeletal Muscle

Gene expression dictates the actual sequence of amino acids that constitute a given protein. Over the past decade, tremendous advances have been made in understanding the complex signaling process that regulates which genes get expressed. In Chapter 14, these signaling pathways will be presented. Here, you will learn how packages of genes get turned on or off as a result of chronic training or inactivity. These signaling pathways typically involve extracellular cytokines, receptors, and intracellular response that include phosphorylation of enzymes and possibly altered ion movement.

Chapter 15: The Immune System Response to Acute and Chronic Exercise

Your immune system is incredibly important! Your body has several lines of defense against invading organisms, and exercise can increase your exposure to such invaders, but regular exercise promotes the defense mechanisms. In Chapter 15, you will learn about cell signaling mechanisms that trigger immune responses, the process of inflammation, and how exercise enhances your defenses against bacteria and viruses. You will also learn about polymorphonuclear lymphocytes and an array of cytokines.

Chapter 16: Determinants of Success in Athletic Performance

Chapter 16 guides you through a 10 km time-trial for a highly gifted athlete, Jake. To achieve international performance in the 10 km run, Jake must: have a high maximal oxygen uptake, be able to maintain a steady-state at a high fraction of his maximal oxygen uptake, and he must have a relatively low energy cost of running. An estimation of his physiological responses will be provided while he performs this feat, at a pace that approaches world record time. The pace that he holds for much of the time-trial is sufficient to just exceed his anaerobic threshold, so his blood lactate continues to climb slowly throughout the effort. His oxygen uptake also increases throughout the trial. This increase relates to what is called the slow component of oxygen uptake. Chapter 16 gives you a glimpse of phenomenal physiology at work.

Chapter 17: The Child: Responses and Adaptations to Physical Activity and Training

Although the physiology of a child works much like that of an adult, there are some special considerations that are deserved here, and are presented in Chapter 17. For example, children use the same heat dissipating mechanisms as adults, but the different surface area to body mass ratio affects the relative contribution of the different factors. It is also important to realize that physical activity patterns adopted during childhood are likely to persist through adulthood. Childhood is an important time to establish the habit of obtaining regular exercise.

Chapter 18: Aging and Exercise: Capabilities and Consequences

As we age, our physical capabilities deteriorate. Chapter 18 looks at the specific changes that occur during the aging process

and identifies which are preventable with appropriate training practices. Many of the changes we associate with aging can be attributed to declining participation in high intensity exercise. More research is needed to further investigate these phenomena.

Chapter 19: What Are the Physiological and Health Benefits of Regular Physical Activity?

It has been known for decades, if not centuries, that regular exercise is an important lifestyle feature that is essential for optimal health. Several chronic diseases have “inactivity” or sedentary living as a major risk factor. This includes cardiovascular disease, diabetes, osteoporosis, and several kinds of cancer. The next big challenge of the health care systems will be to promote an active lifestyle and ensure that the majority of individuals are adopting an appropriate pattern of physical activity to minimize their risk for such conditions. Chapter 19 provides the evidence for regular physical activity as a strong measure for disease prevention.

Chapter 20: High Altitude Physiology: Climbing Earth’s Highest Peak

Our atmosphere contains nearly 21% oxygen. This is true whether you are in Vancouver at sea level, or on top of Canada’s highest mountain (Mount Logan at 5959 m). However, the barometric pressure changes, so the PO_2 is greatly reduced at higher altitudes. Partial pressure difference is the primary factor that determines the rate of transfer of a gas by diffusion. This low partial pressure at high altitude can limit the arterial oxygen content and reduce your exercise capability. Chapter 20 reviews the impact of altitude on exercise capability and presents some ways that you can minimize this impact.

Additional Chapters Planned

Anaerobic Threshold and the Various Measures Estimating This Intensity of Exercise

Mild exercise is easy to persist at for hours. However, as the intensity of exercise increases, the duration that you can persist decreases. There are a variety of reasons for this relationship between intensity and duration of exercise. The anaerobic threshold is an important intensity that marks the boundary between exercise that can be sustained with entirely aerobic metabolism and exercise that requires persistent anaerobic metabolism. Above the anaerobic threshold, lactate will accumulate in the muscles and/or blood.

The Exercise Challenge for Astronauts

The human body has evolved in an environment that includes substantial gravity. Travel to space places this body, which has the capacity to adapt quickly to new physical demands (or lack thereof), in a situation where effort is minimized. The consequences of zero or no gravity and this minimized daily effort while in space has an impact on: muscles, bones, the cardiovascular system, and the nervous system. In this Chapter, the physiological consequences of space travel are presented, and various countermeasures and their effectiveness are reviewed.

Sex and Gender Issues in Exercise Physiology

Much of what we know about exercise physiology applies only to males. Females have not been studied nearly as extensively as males and may differ from males in their response to exercise. These differences may relate to hormonal differences or differences in body composition. Some of the key differences and similarities of response to exercise for males and females are presented in this chapter. There is an urgent need for the study of the physiological response of females to exercise. Some of the reasons for difference in response between males and females include the following: body composition, hormonal responses, and cultural differences

Ergogenic Aids: Perceived and Real, Legal and Illegal

An ergogenic aid is an item, a substance, or a procedure that enhances physical performance. There are many examples to illustrate this concept: training, water, power gels, erythropoietin, blood doping, caffeine, and anabolic steroids, to name but a few. This chapter will identify several ergogenic aids and elaborate on a few of them, providing research evidence for or against their

effectiveness and describing the understood mechanism of action.

Tools of the Exercise Physiologist

Researchers in exercise physiology have played an important role in identifying the relationship between sedentary living and chronic disease, and they will now play an important role in guiding the adoption of the appropriate intensity and frequency of exercise. A list of tools and the units of measurements obtained is presented in Table 1-3.

Table 1-3 Examples of Tools and Measurements in Exercise Physiology

Instrument	Variable measured	Common Units
Metabolic Cart	Oxygen uptake	litres·min^{-1} or ml·min^{-1}·kg^{-1}
Dynamometer	Moment about a joint	newton-meters
Respirometer	Ventilation	litres, ratios, litres·min^{-1}
Electrocardiogram	Electrical currents of the heart	millivolts, time parameters in milliseconds, heart rate in beats·min^{-1}
Heart rate monitor	Heart rate	beats·min^{-1}
Dual X-ray Absorptiometer	Body density	algorhythm calculates %fat and expression of bone density
Hydrostatic balance	Body density: %fat and fat-free mass	% and kg
Skinfold calipers	Skinfold thickness	mm
Bioelectric impedance	Relative water content	% fat
Pulse Oximeter	Oxygen saturation	% saturation
Magnetic resonance spectrometer	Chemical concentrations; typically phosphocreatine, ATP and inorganic phosphate	% change and ratios
Near-infrared spectroscopy	Oxyhaemoglobin and deoxyhaemoglobin	% saturation
Microchip	Presence of messenger RNA	yes/no
Muscle biopsy	Muscle structure, biochemical content	Variety

Instrument	Variable measured	Common Units
Ultrasound imaging	Muscle or cardiac structure	mm and ratios
Magnetic resonance imaging	Tissue density	internal image
Microchip	Presence of messenger RNA	yes/no
Muscle biopsy	Muscle structure, biochemical content	Variety

At this time, it is desirable to discuss some of the general ways that information is presented in a textbook of Exercise Physiology.

Key Skills for Learning Exercise Physiology

The topics covered in the study of exercise physiology are fascinating and intriguing. However, they can also be complex and confusing. There are some simple skills that you can master that will facilitate the learning of the content of this textbook, and these skills are described here. In addition to learning the new vocabulary referred to earlier in this chapter, there are two very important skills you can learn that will facilitate the comprehension of the topics presented in this textbook: understanding statistics and interpretation of graphs. Some valuable background on these topics is presented here.

Statistical Considerations

One of the important features of biology is the variability in the value for various measures that can be made. For example, we could weigh all members of a class and come up with a mean value. As exercise physiologists, we often use mean values to represent typical values that would be expected for a given measurement. It is important to realize that this value would not necessarily be expected for a given measurement of a single subject, but represents a value that is not too different from any one value.

However, when making any measurement, it is important to recognize how variable the measurements should be, so you can detect an error when it is made. It is just as important to recognize the units that are used for a given measurement. If you are recording measurements made by a classmate and he tells you that somebody's height is 175 inches, would you faithfully write it down, or would you ask if that was supposed to be the height measured in cm?

Although it is beyond the scope of this textbook to provide lessons in statistics, it seems appropriate to review some fundamental concepts that will help the understanding of information presented throughout the textbook. Statistics can be described as a process to find the following:

- An equation to describe the relationship between two variables
- A measure of the strength of a relationship between two (or more) variables
- A description of the middle value and distribution of a measure of interest
- A measure of the confidence that two mean values are truly different

Descriptive statistics

Descriptive statistics are used to describe the quantity, distribution, and variability in a measure of interest. Probably the most common descriptive statistic used is the mean. The mean is a measure of central tendency, or an expression of the average value for a repeated measurement. Other measures of central tendency include the median and the mode. The median is the middle value if you rank all measurements from the lowest to the highest. There are just as many values above the median as there are below. However, the mean and the median can be different in value. The mode is, by definition, the most often represented value. For example, if the measurements of weight of your classmates resulted in 5 people with a weight of 65 kg, and no other weight had more people measured at that weight, then the mode would be 65 kg. Each of these measures of central tendency has advantages and disadvantages.

In all cases of measures of central tendency, it is informative to have a measure of dispersion. A measure of dispersion will inform the reader how close to the measure of central tendency most of the measurements were. variance, standard deviation, and standard error of the mean are examples of measures of dispersion. It is useful to recognize that when a given measurement is distributed normally (see Figure 1-3a) then 96% of the measurements will fall within 2 standard deviations of the mean value. Fortunately, (for statistical evaluation) many biological measures are distributed normally. However, there are some measures that have values that are skewed, so that more measurements occur near one of the extremes, rather than near the middle value. A skewed distribution is shown in Figure 1-3b. In this case, the mean and the median will be quite different, whereas with a normal distribution the mean and the median are the same.

Normal distribution

Many biological measures yield a normal distribution or bell-shaped frequency distribution curve. A frequency distribution curve is a plot of how many measurements at each value (or range of values). In Figure 1.1, the black line represents the mean and the green lines are 1 standard deviation from the mean. The red lines are 2 standard deviations from the mean. There are more values close to the mean and fewer in a given range as you move away from the mean.

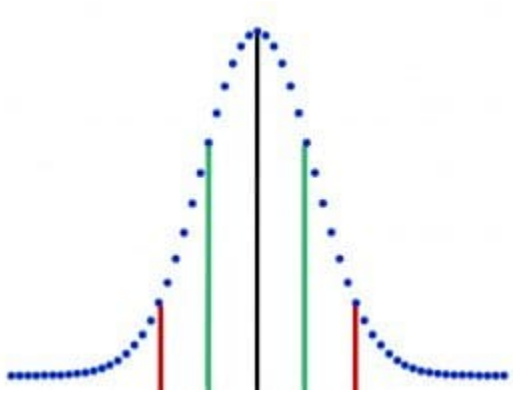


Figure 1-3a Normal distribution: Many biological measures yield a normal distribution or bell-shaped curve. This distribution occurs when the frequency or incidence of values fall mostly near the middle of the range of values. The black line represents the mean and the green lines are 1 standard deviation from the mean. The red lines are 2 standard deviations from the mean.

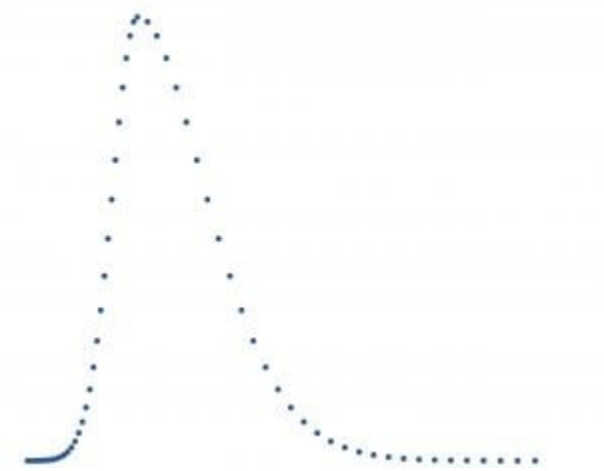


Figure 1-3b Skewed distribution: A skewed distribution can have many shapes, but the general idea is that the most frequent values do not fall near the middle of the range of values. A skewed distribution is not symmetrical *Inferential statistics*

quite often, the purpose of a given research study is to determine if there is a difference between conditions or treatments. For example, it may be of interest to know if one type of warm-up is better than another. In this case, a researcher might have a group of athletes perform a competitive event like a 60 m sprint, with each of two warm-ups. Ideally, the two warm-ups are performed in random order, and data for each test are obtained on separate days. The dependent variable of interest is the performance (measured in seconds) after each warm-up.

Consider that this research has been done, and the results presented in Table 1-4 were found. The question now is: was

performance different between these two trials? The inferential statistical test that is appropriate for this determination is the paired t-test. This test will tell us if the difference from one to the other of these trials is significant. Sometimes a difference between the means of two measures occurs simply due to chance. When we say the difference is significant, we are saying that we have confidence that the difference is not simply due to chance. More specifically we are saying that 95 times out of 100 trials we would likely see this difference. Factors that would make it difficult to detect a significant difference include the following:

- There is too much variability in the measure of interest
- The real difference is too small to detect, or does not exist
- The number of subjects was too few to allow detection of a significant difference

Table 1-4 ***Time for 60 m Run After Warm-up A (WU A) and Warm-up B (WU B)***

Subject	Time for 60 m (s)-WU A	Time for 60 m (s)-WU B	Fat free mass (kg)	Age of the participant
1	9.81	9.75	44	8
2	8.47	8.49	53	12
3	9.05	9.00	51	10
4	9.75	9.78	48	9
5	8.43	8.55	58	11
6	9.25	9.10	60	14
7	8.75	8.62	56	13
8	8.68	8.69	57	12
9	8.42	8.40	62	14
10	7.85	7.85	58	15
Mean	8.85	8.82	54.7	11.8
SD	0.62	0.60	5.64	2.3

The results of a paired t-test on the data presented in Table 1-5 are shown in the following table:

Table 1-5 Statistical Results for Comparison Between Warm-ups

Parameter	Trial Warm-up A	Trial Warm-up B
Mean	8.85 s	8.82 s
Variance	0.39	0.36
N	10	10
Correlation	0.992	
T-statistic	0.919	
Critical T (0.05)	2.26	
Probability significant (p)	0.3822	

The interpretation of these results would be that warm-up B is no better than warm-up A in preparing these athletes for a 60 m run. This interpretation is based on the observation that the T-statistic is not greater than the critical T. The value p represents the probability that you would make a type I error or be incorrect in declaring these means different. In general, we hope to keep type I error less than 5% (<0.05), so when p>0.05, the conclusion is that the means are not different. A type II error occurs when you conclude that the conditions are not different when in fact they are. We are more willing to make a type II error than a type I error in most statistical comparisons. Keeping type I error (α) small means that type II error has a higher probability. The correlation indicates that these two measures shown in Figure 1-4 are highly related. When one is high, the other is also high; when one is low the other is also low. We use the letter "r" to represent correlation. The correlation can range from values = –1 to 1. Values close to zero indicate no relationship between the measures. When the correlation is negative, the slope of the relationship is also negative. This means that when one variable increases, the other one decreases.

External validity would restrict interpretation to this event, and for subjects of this description. This conclusion would not necessarily apply to warm-up for high jumping or shot put, and it may not apply to elite athletes or to adults. One important factor that limits the ability to find a significant difference in trials of this nature is variability. If the variability in the result of the time-trial is large even when circumstances prior to the event are similar, then warm-up procedures that might have a small effect may not be detectable by statistical analysis.

Recently, many sport scientists have developed and subsequently used a different statistical approach to make inferences about potential differences between trials in the case where traditional inferential statistics deemed these differences not significant. This approach is called magnitude-based inferences (MBI). Consider the case above: while not statistically significant, is it possible that the mean difference in 60 m time as a result of warm-up A and warm-up B is clinically significant or meaningful? Is the observed difference between warm-up A and warm-up B of 0.03 s meaningful? We could calculate the size of the effect, using a magnitude-based inference approach. The benefit of using this approach in exercise physiology is that, in many cases, we simply do not have a large enough sample size and/or the real effect is very small. Consider an athlete who wins an Olympic 100 m race by <0.03 s as a result of using warm-up B compared to warm-up A. While not statistically significant, statistical approaches like MBI or effect sizes allows the coach/athlete/sport scientist to make their own judgment along a continuum of a trial's effectiveness based on the observed effect shown, rather than perhaps rejecting the use of warm-up B because it is not statistically significant.

Shapes of Relationships: Linear, Exponential, Quadratic, Sigmoid

Exercise Physiologists often use graphs to convey important information. Graphs are simply a pictorial way of conveying data that illustrate some concept. It is important to carefully look at the graphs in this textbook, to obtain as much information as possible from them. Most of the graphs in this textbook will be two-dimensional, but graphs can be three-dimensional. A two-dimensional graph plots the independent variable on the abscissa (also known as the x axis) and the dependent variable on the ordinate (also known as the y axis).

Graphs can convey information as simple as a frequency distribution or as complex as the relationship between load and mechanical work. Here, we will present a few graphs to illustrate some of the different concepts that are conveniently presented as graphs and show how these graphs should be interpreted. This information will help you interpret the graphs presented throughout the textbook.

Before we describe the typical relationships that are frequently depicted in graphs, it is worth considering a simple convention that makes interpretation of graphs more apparent. It is important to understand that variables can usually be considered either independent or dependent. The easiest way to think of these is that the independent variable is controlled by the experimenter and the dependent variable is measured at different levels of the independent variable. It is convention to plot the independent variable on the abscissa (x axis) and the dependent variable on the ordinate (y axis).

Linear Relationships

The linear relationship is the simplest and probably the most common relationship that can be demonstrated in a graph. Figure 1-4 illustrates a simple experiment, where heart rate (dependent variable) was measured while power output (independent variable) increased during an incremental test on the cycle ergometer. An equation can be used to describe the observed relationship between power and heart rate. This equation is shown in the graph**,** and has four important components, similar to the standard equation for a line (equation 1-1).

$$y = m\,x + b \quad \textbf{Equation 1-1}$$

where y is the value on the ordinate, that corresponds to a value x on the abscissa, m is the slope or proportionality constant, and b is the intercept or offset.

The value of the information made available by the calculation of r is more obvious in Figure 1-5a. Here, the data do not fit as well to the line, and correlation (r) = 0.5. In this case, there is still a significant correlation between the two variables, but the strength of the relationship is less than in Figure 1-5b. If the r was between -0.1 and 0.1, the presence of a line representing the data would be difficult to visualize. Another way of using the correlation coefficient is to take the square of the value (r^2), which provides an estimate of the variability in the dependent variable that appears to be accounted for by variability in the independent variable. Thus, in our example (Fig 1-5a) for r = 0.75, calculating r^2 (0.75 · 0.75) would equal 0.55, or only 55% of the variability in Y is explained by variability in X. This means that 45% of the variability of Y is unrelated to variability in X. This means that X is only a moderate predictor of Y.

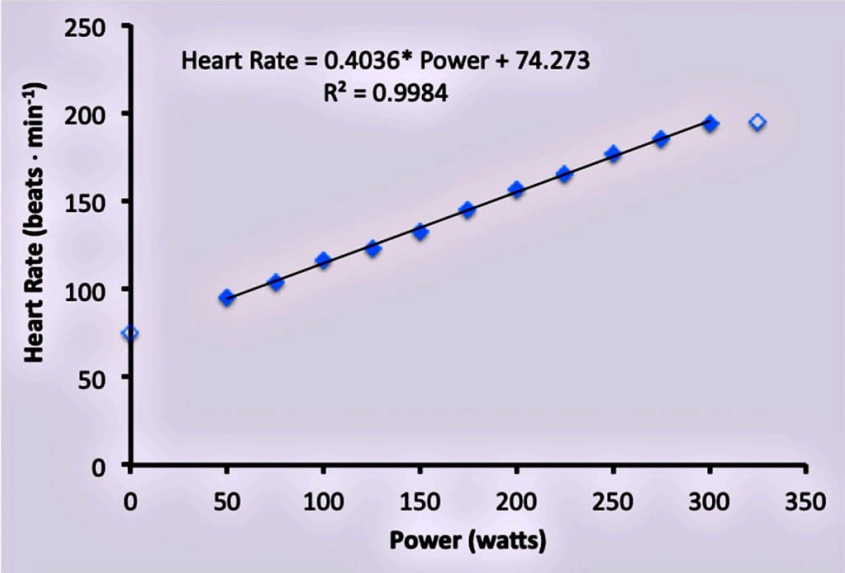


Figure 1-4 Relationship between heart rate and power output.

Linear regression and Curve-fitting

Curve-fitting is a statistical procedure that is useful in finding an equation that describes the relationship between two variables. Consider the data presented in Figure 1-4. The first decision to make is to determine the shape of the relationship: is it linear, exponential or sigmoidal? These terms represent different shapes of relationships, and graphs presenting these shapes are shown later in this chapter. Clearly in this case, the data are linear. It might be argued that the exception to this linearity occurs at the resting heart rate and at the highest power output.

Linear regression uses a common equation for a straight line (y = mx b; where y is the value on the ordinate and x is the value on the abscissa; m is the slope; rise over run of the relationship and b is the intercept or value of y when x = 0). This equation will find the values for the constants (m and b) representing a straight line that passes through the data with the least deviation between the line and the data. This approach is referred to as the least squares method. This approach finds the values for the constants that yield the lowest value for the sum of squares of the differences between predicted and actual values for the dependent variable. The iterative process finds the line that passes through the data with the smallest sum of squares of the differences between the data and the line. This is called the line of best fit.

The result of the linear regression of heart rate vs power output is presented in 1-4. Here, linear regression was done without including the lowest (resting) and the highest (peak power) heart rates. The line fits the data quite well. Clearly the lowest and the highest heart rate have more deviation from the line than the values that were included in the regression. The closeness of fit of the line to the data can be quantified by calculating the correlation coefficient (r). The value of r can vary from -1 to plus 1.

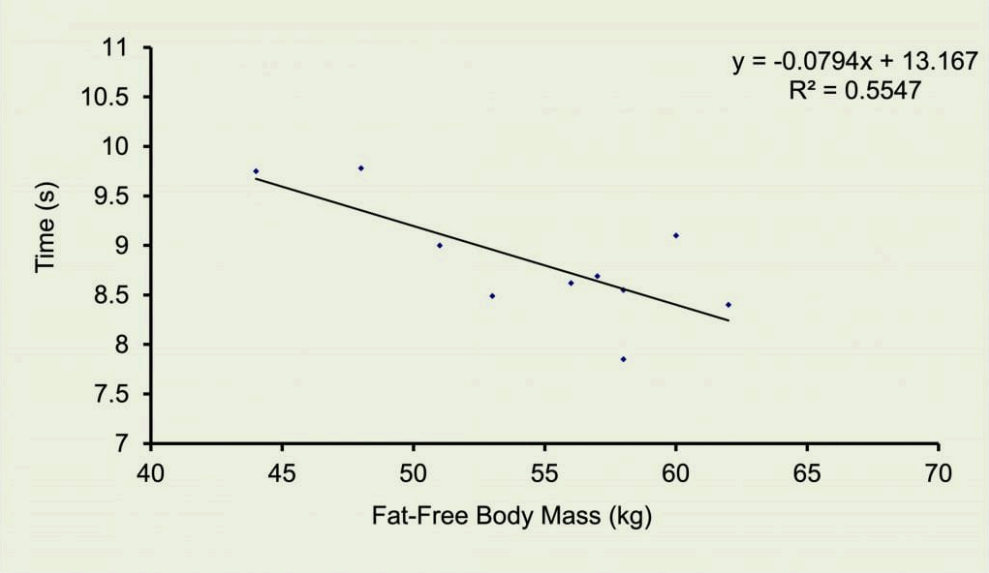


Figure 1-5a Linear relationship between fat-free body mass and time to complete a 60 m dash. As fat-free body mass increases, time to complete the 60 m decreases. This result would seem counterintuitive, but the reason becomes clear once you consider the way the results are presented in this Figure. Participants of this study ranged in age from 8 to 15 years.

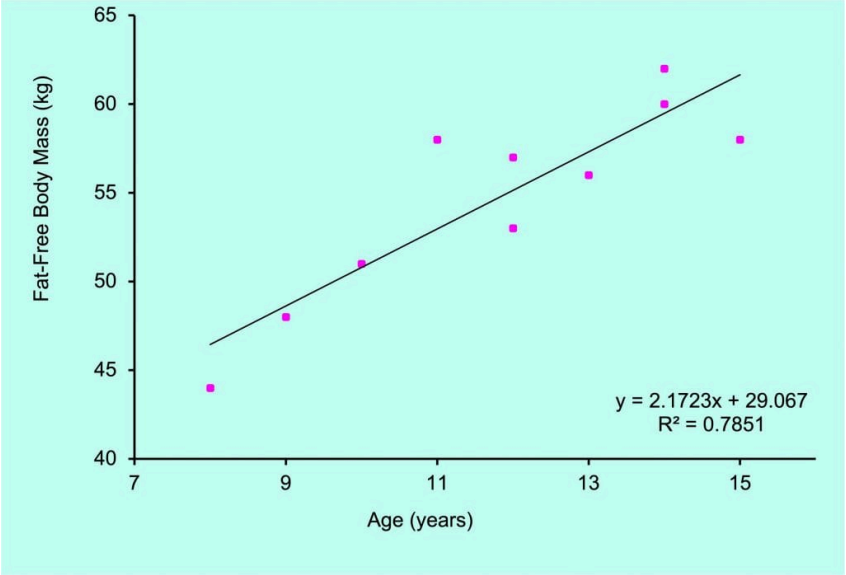


Figure 1-5b Linear relationship between age and fat-free mass. Not surprisingly, as children develop, they increase their fat-free mass. This results in a positive relationship between age and fat-free body mass.

When r is near zero, then there is little or no relationship between the variables. In these circumstances, it would be difficult to choose an appropriate line through the data. As the value for r approaches 1 or -1, the strength of the relationship improves, meaning the data appear to be arranged in a more linear fashion. The relevance of the negative sign is that when the values of the two variables change in the opposite direction (one increasing as the other decreases), the correlation will be negative. Note also that in this case, the slope of the relationship will be negative. When the two variables change in the same direction, one increases when the other increases, then the correlation is positive and so is the slope of the relationship. Further examples of curve-fitting are given later in this chapter, in the section dealing with graphical presentation of data.

Several software programs allow you to find appropriate constants for an equation you have entered. Even Microsoft Excel will permit curve-fitting to pre-selected equations including: linear, exponential, and polynomial

Note, resting heart rate and heart rate at highest power achieved were not included in the regression. The line represents the best fit across values for heart rate from the first exercise intensity (50 watts) to the penultimate exercise intensity (300 watts). This graph shows that the increase in heart rate is constant for any increase in power output. It is important to realize that each individual could be a little different, but in general a fairly good linear relationship is obtained when these two variables are

plotted. However, the power output at which maximal heart rate is reached will vary considerably. Can you plot a similar graph for someone with pulmonary disease?

Curve-fitting is a valuable method to find the nature and the strength of the relationship between two variables. You will notice in Figures 1-5a and 1-5b that although the data follow the general trend of the lines, there is a random disparity between individual values for the dependent variable and the estimate of the value given by the equation for the line. It is important to realize that the equation representing the best fit through the data is typically obtained by finding values for the constants that minimize the disparity between the actual values and the values predicted by the equation. The process of finding appropriate values for the constants is called the least squares method.

Interpretation of Linear Relationships

A graph such as that shown in Figure 1-4 illustrates a relationship. It shows that the value of heart rate is proportional to the power output, and the proportionality constant or slope of the relationship is 0.4036. This tells you that for each unitary increase in value on the abscissa, the value on the ordinate increases by 0.4036. There appears to be an offset in the relationship such that at zero power output, the heart rate would be 74.3. This is the intercept of the relationship, obtained by least squares fitting an equation for a straight line to the data.

The fact that two variables change in a proportional way and are described by a linear relationship should be interpreted to indicate that the two values are related; this may be, but is not necessarily a cause and effect relationship. In the case of the power–heart rate relationship, it is clear that cycling at a given power output necessitates a given heart rate, so there is a cause and effect relationship. However, this could just as easily be interpreted as an indirect relationship. Cycling at a given power output requires a certain oxygen uptake by the active muscles. This oxygen is delivered by the cardiac output. The increased cardiac output requires an increased heart rate. In other words, the relationship between heart rate and power exists because these variables are related through a third variable, oxygen uptake.

Although linear relationships are quite common in exercise physiology, a straight line does not always fit well in describing the relationship between two variables. Two additional graphic presentations that are relevant in exercise physiology are described below: exponential relationships and sigmoidal relationship.

Exponential Relationships

When the value of a variable changes in proportion to its current value, an exponential relationship exists. In this case, the slope is continuously changing. The standard exponential relationship is the decay curve for radioactivity. In this case, the rate of emitting radioactivity is dependent only on the amount of radioactive material left. When the amount of radioactive material has decreased, the slope or rate of emission of radioactivity will decline more slowly. A key feature of an exponential relationship is that a single determinant is the underlying cause of the changing slope of the relationship.

Relaxation from a muscle contraction is considered to be exponential. An example of a muscle contraction is shown in Figure 1-6a. It can be seen that once relaxation is well underway, the high initial value for force is associated with a steep rate of decline and as the force decreases, the slope or rate of force decline, decreases as well. This graph shows the whole contraction, but only the relaxation is considered exponential. In reality, only late relaxation (shown in Figure 1-6b) should be considered exponential.

One of the unique features of an exponential decline or exponential rise to a plateau is the notion of a half-time. The time for the value on the ordinate to change to half of any value is constant, if the property is truly exponential. In Figure 1-6b, the half-time is 18.5 ms. Pick any point on the decline of force, and note that exactly 18.5 ms later, the value is half of that initial value.

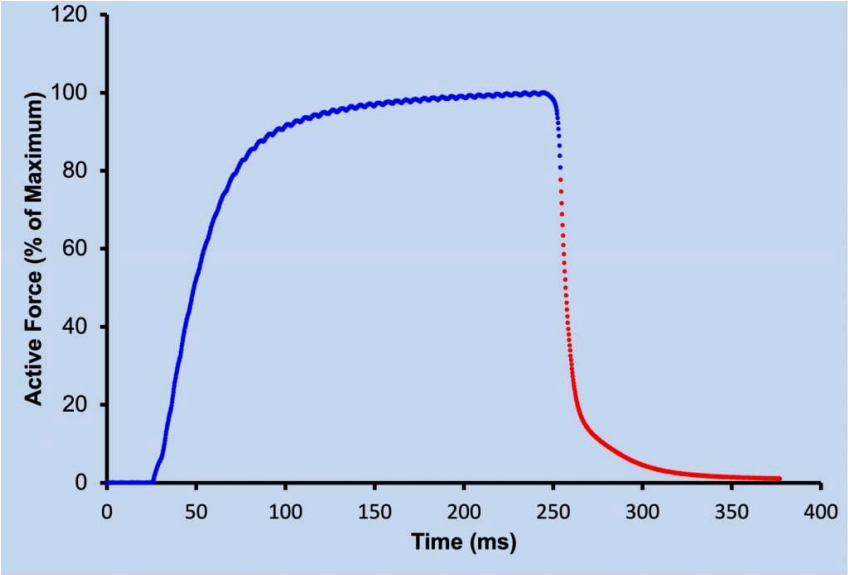


Figure 1-6a Force of contraction from high frequency stimulation. This is a tetanic contraction of the rat gastrocnemius muscle, in situ. Of particular interest is the rate of relaxation, which slows as force decreases. This decreasing slope as force decreases is similar to a classical exponential decline like radioactive decay. However, it is evident that an exponential equation can only accurately describe this decay curve after substantial relaxation has occurred (see Figure 1.5b).

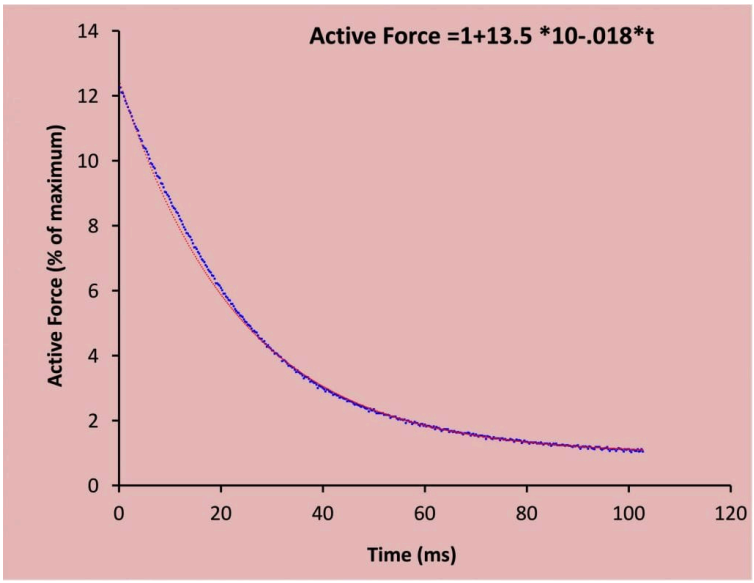


Figure 1-6b Exponential decline of active force. Here, the measured (blue) decline in active force from 12.7% of maximum is shown. The equation (red) superimposes on the measured data with a very good agreement. Note that to obtain this very good fit, the equation was modified with a constant (1), indicating that within the time shown, the active force appears to be leveling off at 1% of maximum force. This is probably due to very slow relaxation of some motor units within the gastrocnemius muscle. If the data were illustrated for the next 2-3 s, it is certain that the equation would not continue to fit the data because force would actually decrease below 1%. This divergence between measurement and mathematical equation fitting the data demonstrates the danger of using equations to extrapolate to values outside the measured range of values.

Exponential decline of active force**.** Here, the measured (blue) decline in active force from 12.7% of maximum is shown. The equation (red) superimposes on the measured data with a very good agreement. Note that to obtain this very good fit, the equation was modified with a constant (1), indicating that within the time shown, the active force appears to be leveling off at 1% of maximum force. This is probably due to very slow relaxation of some motor units within the gastrocnemius muscle. If the data were illustrated for the next 2-3 s, it is certain that the equation would not continue to fit the data because force would actually decrease below 1%. This divergence between measurement and mathematical equation fitting the data demonstrates the danger of using equations to extrapolate to values outside the measured range of values.

A time-constant can also be associated with exponential change. The Greek symbol τ is usually used to denote time-constant.

To illustrate τ, we have plotted an increasing exponential relationship in Figure 1-7. Here, oxygen uptake rises quickly at first, then more slowly. This curve represents the change in oxygen uptake from the beginning of exercise at a moderate intensity for a relatively trained individual. The slope of the relationship decreases as the value approaches a steady-state (SS). A SS is a constant level of any variable measured in the body (oxygen uptake, temperature, concentration of an ion, etc.). By definition, the time-constant is the time for the value of a variable to change to $(1\text{-}1\cdot e^{-1})$ where e is the natural log. This approximates 63.2%, so the time-constant is the time needed for a change of 63.2%. The following equation can be used to represent the relationship between oxygen uptake and time, as oxygen uptake increases from the resting level to the SS.

$\dot{V}O_2t = \dot{V}O_2r + \dot{V}O_2SS\ (1- e^{-t/\tau})$. **Equation 1-2**

Where $\dot{V}O_2t$ is rate of oxygen uptake at time t; $\dot{V}O_2SS$ is the increase from resting to SS rate of oxygen uptake, and τ is the time-constant. Note that as t increases, the ratio of $t\cdot\tau^{-1}$ increases. This ratio is a negative exponent, so as it increases in value, the expression $(1- e^{-t/\tau})$ approaches one. Therefore, oxygen uptake approaches the sum of resting and SS difference. In this example, $\dot{V}O_2$ reaches a SS by about 2 min. You will learn in Chapter 13 that τ changes (becomes shorter) with training. A well-trained individual will reach SS in 1 min or less. It is important to realize that it takes approximately 4 τ to approach the SS You will also learn that the exponential rise in oxygen uptake measured across the lungs does not begin at the instant that exercise begins. There is a delay due to the time required for venous blood exiting the muscles to get to the lungs.

Sigmoidal Relationship

There are several important relationships in exercise physiology that are sigmoidal in shape. That is, at low values of the independent variable, the dependent variable changes very little. However, as the value of the independent variable increases, the rate of change of the dependent variable increases dramatically. Eventually at higher values for the independent variable, the dependent variable reaches a plateau where further increases in magnitude of the independent variable result in no change to the dependent variable.

An example of a sigmoidal relationship is the binding of oxygen to haemoglobin (Hb), shown in Figure 1-8. Here, it can be seen that at low partial PO_2, there is virtually no O_2 bound to Hb. As partial pressure increases, there is little change, until partial pressure exceeds x, then the curve becomes increasingly more steep with increasing saturation of Hb with oxygen. However, there is a maximum amount of O_2 that can bind to Hb, so the rate of increase slows and a plateau occurs, where further increases in PO_2 result in no further increase in oxygen saturation. You will learn more about this relationship in Chapter 9.

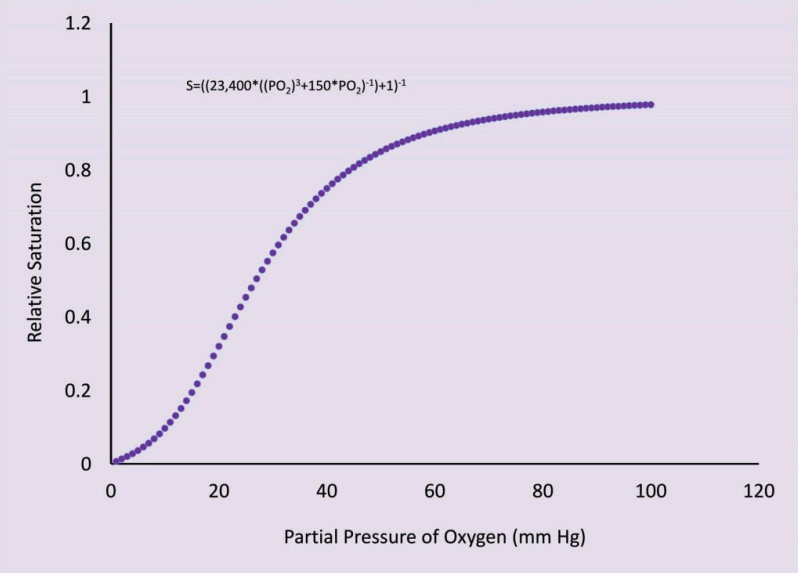


Figure 1-8 The relationship between partial pressure of oxygen in the blood and % saturation. Arterial PO_2 is typically 95-100 mm Hg, resulting in nearly full saturation of the Hb. The line displayed here would typically represent a line of best fit for several measurements of O_2 saturation over a range of partial pressures. This equation (inset) was determined by Severinghaus, a famous physiologist.

Normal Values for Physiological Measurements

Throughout this textbook, you will be presented with values for a variety of measurements that can be made on human subjects during exercise. Often these will be compared with resting values, or values at different intensities of exercise. It is useful to pay attention to these values, so you can recognize whether or not any measurements you might be making are yielding normal or abnormal results. For example, if you are measuring someone's heart rate at rest, and you find that the rate is 95 beats·min^{-1}, you might wonder why their heart rate is so high. Furthermore, it is useful when considering some of the factors that limit human physical performance capabilities to use a quantitative approach. Often, the difference between elite athletes and the rest of us can be expressed by the values of their physiological measurements. Pay close attention to the units of the measurements!

When considering normal values for physiological measurements, it is convenient to qualify the physical exercise in a relative sense (see Appendix A for a table of normal values). To do this, we use the terms: mild, moderate, vigorous and supramaximal intensities. These terms are defined with respect to the intensity at maximal oxygen uptake, the highest rate at which oxygen can be taken into the body and used for aerobic metabolism. Although we use the descriptor "maximal" to refer to exercise at maximal oxygen uptake, it is possible to exercise at intensities above this. When intensity of exercise exceeds maximal oxygen uptake, it is referred to as supramaximal exercise.

The choice of normalizing values ($\dot{V}O_2$max in this case) is somewhat arbitrary. It has recently been suggested that a more appropriate normalizing factor is the intensity associated with anaerobic threshold (Fletcher & MacIntosh, 2018, Svedahl & MacIntosh, 2003) . This approach takes into consideration that anaerobic threshold, which is a valuable indicator of the relative difficulty of exercise, occurs at a different % of $\dot{V}O_2$max in trained and untrained individuals.

Why Study Exercise Physiology?

The study of exercise physiology provides an understanding of the changes that occur in the body during exercise. This includes movement associated with simple tasks like opening a jar, walking, or climbing stairs to complex elite physical performance like participating in a hockey game or running a marathon. These changes in the body can be divided into acute (occurring at the time of the exercise and in the immediate recovery period), or chronic (occurring as a consequence of repeated engagement in the physical activity over a period of days, weeks or years).

Understanding Athletic Performance

Much of what we know about the factors that limit ultimate physical performance has to do with exercise physiology. This is true whether you consider the limits of performance in sprinting events like the match sprint in track cycling or endurance events, like the marathon. "Determinants of Success" is a chapter that provides a description of the physiological capabilities of Jake, a successful 10 km runner (Chapter 16). Much of his success in athletics can be attributed to remarkable physiological capacities. In contrast, Len, who is a successful sprinter, has much less impressive aerobic and cardiovascular capacities, but has remarkable muscle properties that contribute to his success.

Although genetics is known to contribute considerably to the tremendous physiological capabilities of athletes, training is also important. The adaptations to regular exercise that we call training represent important aspects of exercise physiology.

Understanding the Human Body During Exercise

It obviously is not enough to understand the need for exercise and the physiological properties of elite athletes. It is just as important to understand the adjustments needed in the average individual as they undertake a moderate or vigorous intensity bout of exercise. These adjustments to exercise become important cell signaling processes (see Chapter 14) that stimulate the adaptive adjustments to exercise that contribute to performance enhancements due to training and to health benefits of regular physical activity.

Understanding Limitations Due to Disease

Various diseases will impose limitations on the exercise capabilities. These limitations are rarely restricted only to the realm of the disease but have wide-ranging implications for the physiological measurements we can make. For example, those suffering primary pulmonary disease have serious muscle atrophy that results in decreased strength and impaired endurance. These

changes are thought to relate to a detraining effect of the lack of regular exercise, and much research is now being conducted to see if the inability of the pulmonary patients is more dependent on their muscle atrophy or is a direct consequence of the pulmonary disease. Any disease or condition that restricts mobility will ultimately lead to an impaired cardiovascular system. The old adage; “use it or lose it” comes to mind. Challenging the cardiovascular system with regular exercise leads to adaptations that improve cardiopulmonary performance. Inactivity or lack of exercise, whether volitional or imposed by disease, leads to the reverse; impaired cardiopulmonary performance.

Understanding Adaptations to Regular Exercise/Training

You might have come to realize that the second time you perform a strenuous exercise, it is easier than it was the first time. This is not just your imagination! Our body undergoes adaptations that are intended to resist disturbance to homeostasis when exposed to a stress. Exercise is a stress, and the body responds to exercise by adapting; changing protein content and structure to prepare the body for subsequent challenges.

The repeated performance of a given type of activity will result in adaptations that we call training. Some of the general adaptations that occur with regular exercise include the following: heart rate is lower for a given metabolic rate, stroke volume is greater for a given metabolic rate, temperature increase during exercise is less and sweating is more, fats are mobilized for metabolic substrates more easily, and the adrenergic response to exercise is blunted. Muscle fatigue is delayed as a result of the increased metabolic capacities that result from some kinds of training.

Measurement Considerations

In research and in clinical assessment, it is necessary to make measurements. This could be as simple as measuring heart rate, skinfold thickness, blood pressure, or muscle force generation. The tools and instruments available for measurement in exercise physiology are quite varied and yield a wide variety of precision and reproducibility.

Whenever measurements are made, there are sources of error and, in some cases, uncertainty with respect to meaning of the value obtained. Error can occur in some measurements, even as simple as measuring height, if inconsistencies occur in the way the measurement is made. For example, consider the possibility that you have measured the height of our character, Arthur (see Appendix C) on three consecutive days. You obtain measures of 181.2, 180.7, and 181.9 cm. How can measures of height vary so much? If you go back to the video recording of your measurements, you might discover that Arthur wore his shoes during the measurements, and he had a different pair of shoes on each day. That could have contributed to the variability! If you want accurate, consistent measurements, you must be consistent in the way you make the measurements.

When we use electronic devices to obtain measurements, how do we know that the number provided by the machine is correct? quite often, now, electronics provide the measurements that in the past were obtained mechanically. For example, if you are using an electronic cycle ergometer in the local fitness centre, how do you know that the power output it gives is correct? It is important to calibrate this equipment, to be sure that the correct value is obtained.

Concepts of Validity and Reliability

The concepts of validity and reliability are tremendously important. Reliability has to do with the reproducibility of a measure and validity has to do with the meaning and correctness of a measure; does the equipment measure what it is thought to measure? Validity also has a second, closely related meaning; does the result of your experiment apply beyond the group that served as your subjects? This is called external validity. External validity is often compromised by the nature in which the participants for a study are selected. Most studies of exercise physiology do not randomly select participants from the pool of potential participants described by the exclusion criteria for the study.

Reliability is assessed by demonstrating that repeated measurements of the same thing will yield the same result. For example, if you measure the height of Julia (another one of our characters often mentioned in this textbook) on consecutive days and get: 187.9, 188.0, and 187.9 cm. These measurements are very close, so you would have some confidence that you knew her height. However, in spite of the reproducibility of these measures, you do not know yet if they are valid. Reproducibility alone does not make a measurement correct! How could you be sure your measurements were accurate?

Limitations of the Research to Date

The development of knowledge in exercise physiology has come a long way in the past 50 years. Research continues, and it will still be a long time before a full understanding of the acute and chronic physiological responses to exercise are fully understood. For this reason, the information presented in this textbook is incomplete. You may have questions after you read a given section of this book. Your questions are important, and you should consider following up on them by looking up additional information. However, don't be too disappointed if you can't find the answer. It could be that we just don't know yet!

There may also be disagreements between what you read in this textbook and what you read elsewhere. This is because exercise physiologists do not all agree on a given idea, theory, or concept. Hopefully in the more controversial areas, this textbook will also provide you with the alternative view, but that may not always be the case. It is also possible that some long-held interpretation of information has recently changed, and a new paradigm has evolved. As you read this textbook, keep in mind that new research could change the way exercise physiologists view how the body functions during exercise. At this time, consider an example of how ideas can change. In this example, the history of the development of theories of muscle fatigue will be considered.

Acidosis and Muscle Fatigue

Everybody understands that when they exercise, or repetitively contract their muscles, there will eventually be a decrease in the ability to perform that task. The capability of their muscles to contract decreases. I am sure you have all experienced this. We call this decrease in contractile performance, muscle fatigue. For about 100 years, it was strongly believed that intracellularacidosis was a primary cause of muscle fatigue. Recent research has suggested that this may not be true.

Consider the evidence for the persistence of the strong belief that acidosis was the cause of muscle fatigue. It probably began with an early (1807) report of the presence of lactic acid in the muscles of a stag that had been chased to the point of exhaustion before it was shot (Needham, 1971). It is not clear why a sample of muscle was evaluated for lactic acid, but the presence of a high concentration of lactic acid was associated with the coincidental existence of exhaustion. Is this cause and effect, or simply a case of two events happening at the same time?

Much later, an experimental approach was followed, and the casual observation of a correlation between fatigue and lactic acid was confirmed. AV Hill, a well-known muscle physiologist, supported the notion that fatigue in frog muscle was associated with acidosis (Hill, Long, & Lupton). However, it was not until years later that a mechanism for this assumed relationship was found. It was discovered that in muscle fibres with the membrane removed (skinned fibres), acidosis decreased Ca^2 sensitivity (Fabiato & Fabiato, 1978). This means that less force was observed at a given [Ca^2]. You will learn in Chapter 5 that intracellular release of Ca^2 triggers muscle contraction, and that the force of contraction is dependent on [Ca^2]. This observation that Ca^2 sensitivity was decreased provided a mechanism for the assumed effect of acidosis in causing muscle fatigue. However, it is important to consider the circumstances and the concept of external validity. Does the fact that acidosis impairs Ca^2 sensitivity in skinned frog muscle fibres at 8C (the temperature used by Fabiato and Fabiato) mean it will also decrease Ca^2 sensitivity at body temperature of mammalian muscle?

In spite of occasional experiments that indicated a lack of effect of acidosis on contractile response at normal mammalian temperatures (MacIntosh, 1979; Pannier, Weyne, & Leusen, 1970), the notion that acidosis caused muscle fatigue was generally accepted (Fitts, 1994). Then in 1995, a paper was published that shed light on the external validity of the 1978 paper. Pate and colleagues (Pate, Bhimani, Franks-Skiba, & Cooke, 1995) demonstrated that Ca^2 sensitivity was not decreased by acidosis in skinned fibres when the muscle temperature approached physiological temperature. Later, Westerblad showed that acidosis does not affect contraction of intact mammalian muscle fibres when tested at physiological temperature (1997).

It seems that researchers have made an about-face on this topic, and it is now proposed that acidosis actually helps to preserve muscle function during exhausting exercise. It has been demonstrated that acidosis delays the attenuation of contractile response that would otherwise occur when plasma [K] increases during exercise (Pedersen, Nielsen, Lamb, & Stephenson, 2004). It is important to keep in mind that under some circumstances, acidosis can have a negative impact on muscle, and some experts believepH interacts with inorganic phosphate to still impair muscle contraction at physiological temperature (Nelson & Fitts, 2014). It is with interest that we should watch theresearch on this topic over the next several years.



Drawing by Danton Thomas, with permission

Value and Limitations of Animal Research

It might be noticed by the astute student that much of the research described above was done with animals. I am not sure where we would be with respect to knowledge in exercise and muscle physiology without the huge contribution from animal research. It is tremendously important, but as indicated above, care must be taken in interpreting that work. In particular, it should be noted that investigation of isolated tissue (like the skinned fibre experiments described above), might not have relevance to function in the body at 37°C. It is not that the observations were wrong, they just did not have external validity! This external validity (see earlier in chapter) had more to do with the temperature at which the measurements were made than with the fact that animals were used.

In the modern exercise physiology lab, animal experimentation is important. Regulations govern the way animals are used, and care is taken to minimize the stress and pain that these animals experience. The value in using animals is that invasive measurements that would not be ethically considered in human subjects can be done with animals, whose lives are essentially dedicated to science.

National and International Organizations for Exercise Physiology

The Canadian Society for Exercise Physiology

Most academics who teach and do research in exercise physiology in Canada are members of the Canadian Society for Exercise Physiology (CSEP). This is one of the largest and most influential academic organizations in Canada (CSEP.ca). CSEP, with funding from the Public Health Agency of Canada, is responsible for originating and maintaining Canada's Physical Activity Guidelines and the Sedentary Living Guidelines (CSEP guidelines.ca). CSEP also has fostered the use of the PAR-Q for those contemplating a change in their exercise routine, including regular updates. The physical activity readiness is now evaluated with the Get Active questionnaire (CSEP.ca) a document that is available from CSEP for those who need it. CSEP is also responsible for introducing the "Exercise is Medicine" campaign to Canada. This campaign was initiated by the American College of Sports Medicine with the goal to bring exercise prescription and physical activity monitoring into mainstream medical practice. With success in this program, more jobs will open up for those with special training in exercise physiology.

Certifications for Working as a Fitness Consultant or Exercise Physiologist

The Canadian Society for Exercise Physiology offers two levels of certification: Certified Personal Trainer and Clinical Exercise Physiologist. Information about these certifications can be found on the CSEP website: https://csep.ca/.

The European College of Sport Science

The European College of Sports Science (ECSS) is a large multinational organization with academic members not only from throughout Europe but also from other countries, including Canada and the United States. ECSS was founded in 1995 and organizes a conference each year at which researchers present their latest findings. The official journal of ECSS is the European

Journal of Sport Science. The vision of ECSS is “to lead the promotion and application of world-class, multidisciplinary science in sport and exercise.”

The American College of Sports Medicine (ACSM)

The American College of Sports Medicine, though based in the United States, is an international organization of academics and practitioners of disciplines related to sports medicine. Membership now exceeds 50,000. They host an annual conference that typically has over 5000 attendees. The official journal of ACSM is Medicine and Science in Sports and Exercise. The ACSM was founded in 1954 and the journal was initiated in 1969. The Mission of ACSM is “... advances and integrates scientific research to provide educational and practical applications of exercise science and sports medicine.”

Summary

This is an introductory chapter that is presented with the purpose of giving you a glimpse of what is to follow, and to provide you with some important skills and ideas that will facilitate your understanding of exercise physiology. Learning the language of exercise physiology is very important in facilitating the learning of the concepts in exercise physiology. In some cases, you may be able to learn the meaning of unique terms from the context of its use, but in many cases, you will want to consult the glossary. Although the internet is a fast and easy way to access information, caution must be exercised when you are obtaining information from this source. Some web sites provide information of high quality while other sources can be misleading.

Your learning of the concepts of exercise physiology will be facilitated by representation of the relationships and concepts in graphic form. Some of the common relationships in exercise physiology yield straight-line relationships while others are sigmoidal or exponential. A basic understanding of the concepts of probability and statistics is important to allow you to understand variability, probability, and the notion of significant difference. Statistical evaluation requires measurement, and it is important to understand the concepts of validity and reliability in the context of the measurements that are commonly done in exercise physiology.

As you read through this textbook you will be exposed to a variety of measurements and you will learn to recognize the range of normal values that can be expected for these measurements. You will also become familiar to a substantial range of units for these varied measurements. These units are part of the language of exercise physiology and it is very important to become familiar with these.

One of the most interesting aspects of exercise physiology is the application to elite athlete performance. Although there are many determinants of success in athletics, including: nutrition, psychology, motor coordination, anatomy, and biomechanics; exercise physiology plays a key role in many sports and challenges. For this reason, evaluation of athletic performance becomes a fascinating way to look at the extremes of physiological capability.

Of course, where athletic performance is the epitome of the capacities and capabilities of exercise physiology, disease is the opposite. There are many diseases that compromise the ability to exercise and maintain a reasonable homeostatic condition of the internal milieu. Evaluation of these limits permits an understanding of the importance of the various physiological systems in contributing to the capability to exercise.

Now, we will turn our attention to the history of exercise physiology in Canada. Canadians can be proud of the substantial contribution that has been made to the growth in knowledge and understanding that has arisen from the pioneering work of early Canadian Exercise Physiologists.

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Dr. Brian MacIntosh completed his doctoral training at the University of Florida in Medical Sciences (1979) followed by postdoctoral training at Queens University in Physiology. This training was followed by faculty appointments at Concordia University in Exercise Science (1980-1986), University of Saskatchewan in Physiology (1986-1989) and University of Calgary in

Kinesiology (1989-2019). At the University of Calgary, he has taught elementary and advanced undergraduate and graduate level courses in Exercise Physiology and Skeletal Muscle. Dr. MacIntosh has published research on muscle contractile properties and energetics from single cell to whole body exercise. He is a former President of the Canadian Society for Exercise Physiology and one of the first Fellows of the Society. Dr. MacIntosh introduced Exercise is Medicine to Canada, serving as Chair of the Task Force for EIMC from 2012 until 2016. He is a fellow of the American College of Sports Medicine and Professor Emeritus at the University of Calgary.

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Dr. Michael Tschakovsky completed doctoral training in Kinesiology at the University of Waterloo, Waterloo, Ontario (1998) followed by postdoctoral training at the Mayo Clinic in Rochester, Minnesota. He began a faculty appointment at Queen's University in 2000 and is currently a Full Professor in the School of Kinesiology and Health Studies at Queen's University. Dr. Tschakovsky teaches undergraduate and graduate level courses in Exercise Physiology and Cardiovascular Function in support of exercising skeletal muscle. Dr. Tschakovsky's research has focused on oxygen delivery:demand matching in exercising muscle and its implications for muscle contractile function and exercise tolerance.

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Dr . Jared Fletcher obtained his PhD in Applied Muscle Physiology from the University of Calgary. There, he studied the

relationship between tendon mechanics, muscle energetics and whole-body energy cost of running in distance runners. Following postdoctoral training in the Faculty of Kinesiology and the Cumming School of Medicine and O'Brien Institute of Public Health, he was appointed as an Assistant Professor in the Department of Health and Physical Education at Mount Royal University, where he currently teaches courses in exercise physiology, biomechanics and statistics. He is also an Adjunct Assistant Professor in the Faculty of Kinesiology at the University of Calgary, and was a sport physiologist with the Canadian National Para-Swimming team (2006-2015) and the lead sport physiologist from 2015-2018. His current research integrates physiology and biomechanics to better understand skeletal muscle and tendon function during exercise in individuals across the lifespan, to better understand the metabolic cost of exercise. These findings will help inform exercise prescription and improve exercise tolerance and performance, from clinical rehabilitation to elite athletes.

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1.2: Chapter 2 - Historical Perspective on Canadian Exercise Physiology*

Chapter 2: Historical Perspective on Canadian Exercise Physiology*

Roy J Shephard

*Much of the material in this chapter previously appeared on the web-site of the Canadian Society of Exercise Physiology under the title: “The first 50 years: A personal perspective on the history of Canadian Exercise Physiology.” Ottawa, ON: Canadian Society of Exercise Physiology. (https://web.archive.org/web/20180412174251/http://www.csep.ca/view.asp?ccid=545). The material is reproduced with the kind permission of the Society.



Photo 2-1 A **Canadian pastime, in spite of the weather conditions; modern exercise physiologists play a large role in understanding the health/fitness effects of all forms of exercise.** Image from: https://pixabay.com/en/snow-sunset-hiking-cold-1185469/, used under a Pixabay License

Learning Objectives

After reading this chapter, you will:

- Have an appreciation for the role played by key Canadian Exercise Physiologists in the early development of the discipline.
- Be able to identify several key events that shaped the role that Canada would play in the early development of exercise physiology.
- Name several pioneers of Canadian Exercise Physiology.

Key Terms

5-BX, 10-BX, Canadian Association of Sport Sciences (CASS), Canadian Association for Health Physical Education and Recreation (CAHPER), Canadian Fitness and Lifestyle Research Institute (CFLRI), Canadian Home Fitness Test (CHFT), Canadian Society for Exercise Physiology (CSEP), exercise physiology, exercise scientists, fitness, kinesiology, maximal oxygen intake, PAR-Q, PAR-

MED-X, particiACTION, PWC_{170}, physical education, World Health Organization (WHO).

Introduction

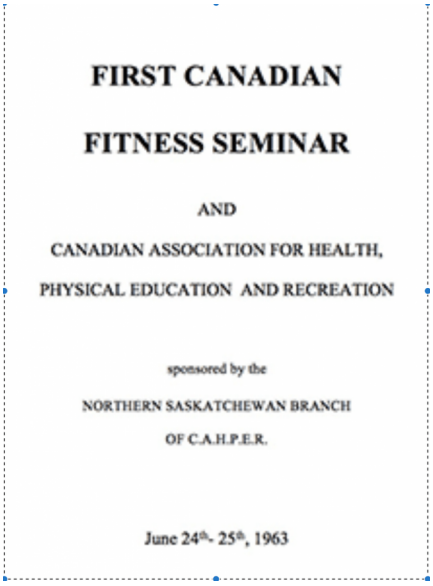
There are other sources that provide a general introduction on the history of exercise physiology, health and fitness; in particular texts authored by Dr. Charles Tipton of Arizona State University (Tipton, 2010) and myself (Shephard, 2015, 2018). The objectives of the present chapter are to suggest why Canada has played a major role in the development of this particular area of knowledge, to highlight certain Canadians who have gained outstanding national and international reputations as exercise scientists, and to provide a sampling of some of the major Canadian contributions to knowledge in this area.

Why Has Canada Played a Major Role in the Development of Exercise Physiology?

There are many reasons why Canada has made an important contribution to the development of exercise physiology. Among these influences, we may note some comments made by HRH the Duke of Edinburgh, the establishment of specific Fitness Research Units, the change in name of many former university physical education programs, the possibly related academic acceptance of exercise physiology in Canada, the hosting of seminal international conferences, the early establishment of opportunities for graduate education in the exercise sciences, and the willingness of Canadians to debate their current knowledge on the world stage.

The Role of the Duke of Edinburgh

In 1959, HRH the Duke of Edinburgh became the first lay president of the Canadian Medical Association, and in his inaugural address to this group he made some characteristically blunt comments on the perceived lack of fitness in Canadian youth. His warning words were noted and circulated in a Royal Bank newsletter, and the resulting furor quickly spread to the Federal parliament, where members urged the early establishment of a program to correct the perceived problem. Thus, in 1961, Bill C-131 (“An act to encourage fitness and amateur sport”) received the Royal Assent. The enactment of this legislation in turn led to the establishment of a Directorate of Fitness and Amateur Sport in Ottawa, with an annual operating budget of $5 million. One of their early initiatives was to propose the establishment of three university-based fitnessresearch units (see below). In 1963, the Canadian Association for Health, Physical Education, and Recreation **(**CAHPER**)** also hosted its first fitness seminar in Saskatoon (Photo 2-2).


FIRST CANADIAN

FITNESS SEMINAR

AND

CANADIAN ASSOCIATION FOR HEALTH,

PHYSICAL EDUCATION AND RECREATION

sponsored by the

NORTHERN SASKATCHEWAN BRANCH

OF C.A.H.P.E.R.

June 24th- 25th, 1963

Photo 2-2 One response to the Duke of Edinburgh’s 1961 criticism of the fitness of Canadians was the organization of a fitness seminar by the Canadian Association for Health, Physical Education and Recreation (CAHPER), held in Saskatoon (1963).

The Fitness Research Units

Given the realities of Canadian politics, the Federal Directorate of Fitness and Amateur Sport decided that it was desirable to establish three fitnessresearch units across the country, one located in central Canada, one on the Prairies, and one in French Canada. Dr. John Merriman (Photo 2-3), then a cardiologist at the University of Saskatoon, and President (1972-3) of the Canadian Association of Sport Sciences(CASS) assumed responsibility for peer review of the program, with an almost manic enthusiasm. The University of Toronto, the University of Alberta, and the University of Montreal were selected as appropriate locations for the three units, and Dr. Merriman paid searching and somewhat dreaded periodic site visits as investigators at each location initiated a five-year program of research in fitness and exercise physiology. The base budget of $50,000 per year per unit was, in the mid-1960s, sufficient to provide each unit with 2 academic staff, 2 technicians, a secretary and a modest quantity of supplies.

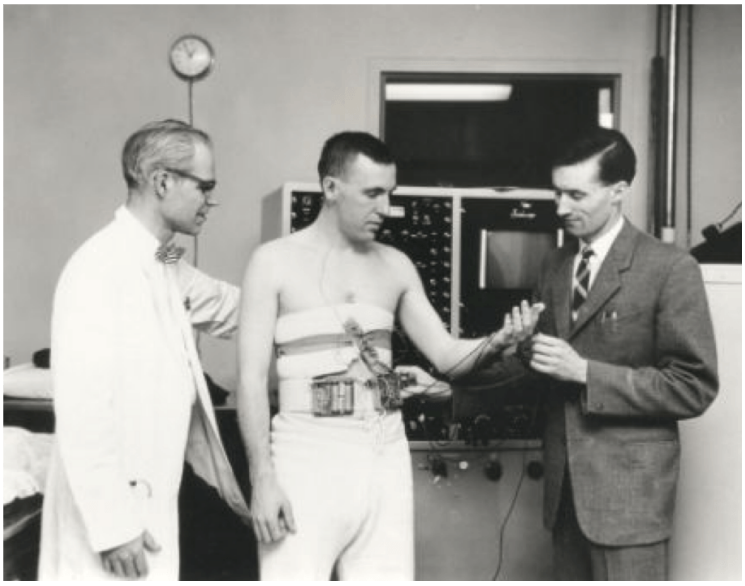


Photo 2-3 Dr. John Merriman (left) in his Saskatoon exercise science laboratory in 1961. He is testing Dr. Don Bailey, and to the right of Dr. Bailey stands Dick Cobbald, professor of bioengineering, who had designed a telemetry unit, which weighed about 5 kg and had a range of maybe 50 m.

I was persuaded to emigrate to Canada as Director of the Toronto Fitness Research Unit. This initiative led to the development of a doctoral program in Exercise Sciences at the University of Toronto, with an initial focus upon the limiting links in the oxygen transport chain. Other important events for the Toronto unit included: hosting a World Health Organization working group on the standardization of methodology for the measurement of maximal oxygen uptake, testing the current fitness level of various populations, and organizing an international conference on physical activity and cardiovascular disease (Photo 2-4). The University of Alberta unit focused largely on cellular aspects of exercise physiology, and Dr. Bert Taylor (CASS President 1974-75, Honour Award recipient in 1986, and recently retired from the University of Western Ontario), assumed a dominant role in these studies. The Montreal unit was dogged by problems of ill-health in its leadership, and its achievements were more limited, although it may have provided the initial stimulus towards development of the widely used shuttle-run test of Luc Léger.

Name Change of Former Physical Education Departments

Another possible influence has been a change in either the name of many programs, or (more probably) a change in the underlying curricular philosophy of university Schools and Faculties formerly identified as “Physical Education.” The emphasis of undergraduate teaching has shifted from the practical preparation of coaches, trainers and physical education teachers to the preparation of students with a broad understanding of the science underlying human performance and health. The trend began in two of Canada’s newer universities, Simon Fraser and Waterloo, as in 1967 they each established Kinesiology programs. The term Kinesiology remains popular, although there have been other choices (for example Kinanthropology, initially in Ottawa, then in Sherbrooke), and Human Kinetics (at the University of Guelph and the University of Windsor, and currently in Ottawa). Some schools, like Ottawa and Guelph have undergone multiple name changes.

Many schools in the United States have now adopted a similar change in name and emphasis, but the shift apparently occurred more readily in Canada than in the U.S., where many schools were under heavy pressure to keep the name Physical Education, to

sustain Alumni funding/support, primarily through the excellence of their sports teams.

Academic Acceptance of Exercise Physiology in Canada

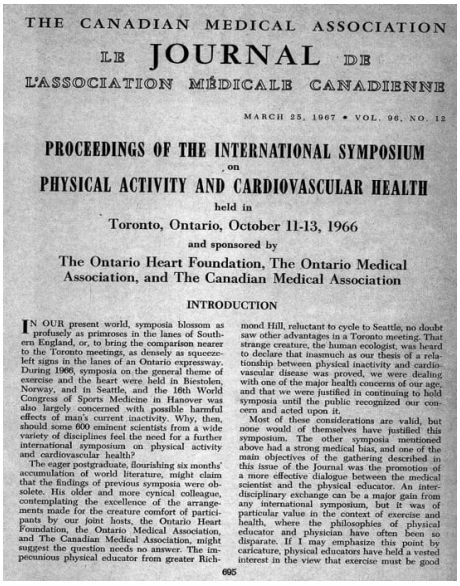
Exercise physiology is a well-respected academic discipline in Canada, and has been so for many years; acceptance of the discipline has probably been helped by the change in name and philosophy of many faculties, as discussed above.

However, in Britain and some other European countries applied research (including human exercise physiology) was welcomed with less open arms. My early training was as a classical physiologist, and I can recall attending meetings of the British Physiological Society when leading members of the Society would pointedly walk out of the lecture hall rather than audit a paper on any aspect of applied physiology. Persistence of this attitude throughout much of the last century caused many European scientists with interests in applied science to emigrate to Canada, severely hampering the research endeavors of those who remained in Europe. Acceptance of the need for studies of exercising humans, the provision of appropriate research funding, and the welcoming of those denied opportunity for such investigations in their countries of birth have all contributed to the strength of exercise physiology in Canada.

Hosting of Seminal International Conferences

The hosting of four major international conferences, in the latter half of the 20th century, contributed greatly to both the development of knowledge of exercise physiology within Canada, and to the global recognition of Canadian expertise in this area of research.

The first such conference was a three-day meeting at Toronto's Inn on the Park in October of 1966 (Photo 2.4). It was sponsored jointly by the Toronto Fitness Research Unit, the Canadian Heart Foundation, and the Ontario and Canadian Medical Associations. Financial support was provided by the Canadian Life Insurance Association, and the Province of Ontario. The planning committee for this conference met at the noon hour in the former offices of the Ontario Heart Foundation (OHF, Davenport Rd., Toronto), and a light "healthy heart" lunch was usually served. The fare may have been adequate for the petite representative of the OHF, but I often left these meetings ravenously hungry! The meeting itself tackled the (then) novel topic of physical activity in the prevention and treatment of cardiovascular disease, and it attracted some 600 participants from many nations. The format was unusual, with a rigid time limit of 15 minutes for principal speakers, and a mere three minutes for nominated commentators. After a few brushes with the chair of the session, this plan was well respected by participants. Evening visits were paid to local sites of interest, including the Toronto Rehabilitation Centre, and North York's luxurious "Fitness Institute" (recently opened by Lloyd Percival); I recall my teaching assistant for 1966 at York University (the very young but dapper Norm Gledhill) efficiently marshaling delegates into a fleet of TTC buses.



THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

MARCH 25, 1967 • VOL. 96, NO. 12

PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM
on
PHYSICAL ACTIVITY AND CARDIOVASCULAR HEALTH
held in
Toronto, Ontario, October 11-13, 1966
and sponsored by
The Ontario Heart Foundation, The Ontario Medical Association, and The Canadian Medical Association

INTRODUCTION

IN OUR present world, symposia blossom as profusely as primroses in the lanes of Southern England, or, to bring the comparison nearer to the Toronto meetings, as densely as squeezeleft signs in the lanes of an Ontario expressway. During 1966, symposia on the general theme of exercise and the heart were held in Biestolen, Norway, and in Seattle, and the 16th World Congress of Sports Medicine in Hanover was also largely concerned with possible harmful effects of man's current inactivity. Why, then, should some 600 eminent scientists from a wide variety of disciplines feel the need for a further international symposium on physical activity and cardiovascular health?

The eager postgraduate, flourishing six months' accumulation of world literature, might claim that the findings of previous symposia were obsolete. His older and more cynical colleague, contemplating the excellence of the arrangements made for the creature comfort of participants by our joint hosts, the Ontario Heart Foundation, the Ontario Medical Association, and The Canadian Medical Association, might suggest the question needs no answer. The impecunious physical educator from greater Richmond Hill, reluctant to cycle to Seattle, no doubt saw other advantages in a Toronto meeting. That strange creature, the human ecologist, was heard to declare that inasmuch as our thesis of a relationship between physical inactivity and cardiovascular disease was proved, we were dealing with one of the major health concerns of our age, and that we were justified in continuing to hold symposia until the public recognized our concern and acted upon it.

Most of these considerations are valid, but none would of themselves have justified this symposium. The other symposia mentioned above had a strong medical bias, and one of the main objectives of the gathering described in this issue of the Journal was the promotion of a more effective dialogue between the medical scientist and the physical educator. An interdisciplinary exchange can be a major gain from any international symposium, but it was of particular value in the context of exercise and health, where the philosophies of physical educator and physician have often been so disparate. If I may emphasize this point by caricature, physical educators have held a vested interest in the view that exercise must be good

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Photo 2-4. The Fitness Unit at the University of Toronto played a lead role in organizing the International Symposium on Physical Activity and Cardiovascular Health, held at the "Inn on the Park," Toronto, in October 1966, in cooperation with the Ontario Heart

Foundation, the Ontario Medical Association and the Canadian Medical Association. The proceedings were published five months later as two special issues of the Canadian Medical Association Journal.

The organizers of many such conferences have found themselves struggling to collect papers from speakers two years after such an event has been held, but the full proceedings of the Inn on the Park meeting were published and distributed to some 25,000 physicians and physiologists as two special issues of the Canadian Medical Association Journal within the span of four months (Shephard, 1967). One of the main reasons for the quick turn around was that speakers were not paid their traveling expenses until they had furnished a manuscript of appropriate quality! Typewriters were available to errant participants, and there were reports that at least one overseas delegate spent most of two nights typing in order to receive his reimbursement! One speaker also argued that theCMAJ was not prestigious enough for his paper. He was politely reminded that he had agreed to publication, and was given two options- immediate submission of his manuscript, or publication of a taped transcript of his somewhat garbled talk. One look at what he had said convinced him to forward the manuscript without delay.

In 1988, a team of exercise physiologists headed by Claude Bouchard hosted a second major international conference at L'Hotel, and the Toronto Convention Centre. This conference lasted for four and a half days, and it was designed to develop a consensus on the mechanisms linking exercise, fitness, and health, both in healthy individuals and those with a variety of chronic conditions. More than 60 topics were considered by a carefully selected panel of international experts, who had circulated written preprints of their presentations. At the conclusion of each public presentation a panel of some 70 speakers and consultants vigorously debated the conclusions that should be drawn, and a final consensus statement on each topic was approved by the entire conference of some 1000 participants. At the banquet, American delegates were somewhat bemused by a bilingual loyal toast, a multicultural grace that invoked the Mighty Manitou, and Selma, Great Mother of the sea-creatures, a selection of choice Ontario wines, and a spirited concert from the Canadian Brass. The findings from the meeting (Photo 2-5) were published as a major text in 1990 (Bouchard, et al., 1990).

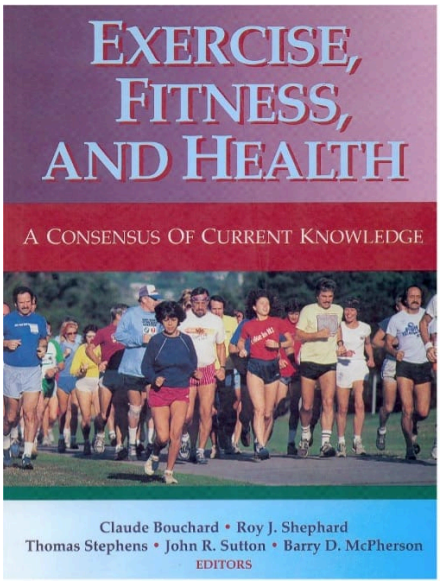


Photo 2-5 The 1988 International Consensus Conference on Exercise, Fitness and Health was held in the Toronto Convention Centre, and the proceedings were published by Human Kinetics in 1990.

Based on this experience, a somewhat similar event (again headed by Claude Bouchard) was held at Toronto's Skydome Hotel in 1992. On this occasion, a computer search of literature databases was used to identify the best-informed and most widely published investigators for each of some 70 topics. Each of the individuals who were thus identified prepared a draft consensus statement on their assigned topic three months prior to the conference, and they also submitted a detailed supporting document. This information was debated by the three editors of the final publication, with input where necessary from a panel of seven international advisors in exercise physiology. Thus, those attending the conference were able to review a carefully revised consensus statement that was near to its final format. In 1994, the conclusions were again published as a major scientific text (Bouchard, et al., 1994, Photo 2-6).

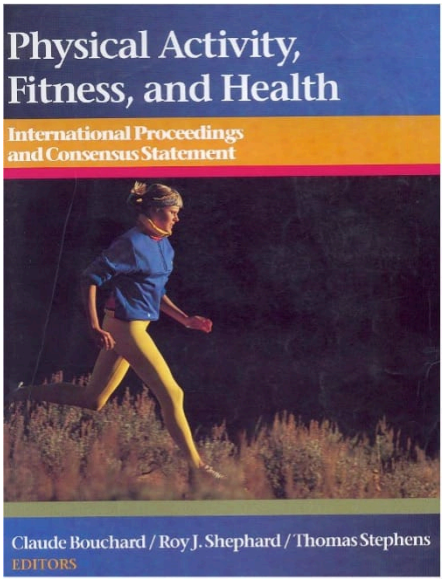


Photo 2-6 The second International Consensus Conference was held at the Skydome Hotel, Toronto, in 1992, and the proceedings were published by Human Kinetics in 1994.

At this stage, exercise physiologists had reached a fair degree of consensus on the merits of regular physical activity in the prevention and treatment of a multiplicity of chronic disorders, but little was known about the optimal dose of exercise to prescribe for various conditions. Dr. Bouchard and his colleagues thus embarked on a further consensus conference that focused on a careful rating of "levels of evidence" concerning dose-response relationships. The selected panel of experts met in October of 2000, the venue on this occasion being the Hockley Valley Resort, to the north of Toronto. A few of the less fit American delegates were disturbed to find that the proceedings included an opportunity to enjoy the fall colours through a substantial hike along the physically demanding Bruce Trail! The conference documented much new information, using processes developed from the previous conferences, although unfortunately there was still insufficient evidence to specify clear dose-response statements for many of the conditions that were considered. The findings from this meeting were published as a special supplement of the journal Medicine & Science in Sports & Exercise (Kesaniemi et al., 2001).

The organizing committee recognized that although the consensus conferences had been very helpful to the development of exercise physiology as a discipline, the bulk of the new information presented at these gatherings was not reaching those working on the front lines of exercise testing and programming. Art Salmon of Fitness Ontario thus collaborated with Health Canada and the U.S. Centers for Disease Control in offering a more practically-oriented "translation" of the findings through a conference entitled "Communicating physical activity and health messages: science into practice." This meeting was scheduled for the resort of Whistler, B.C. in September of 2001, but because the terrorist attacks in that month caused a temporary fear of air travel, the conference was postponed until December of 2001. A fleet of luxury coaches awaited delegates at Vancouver International Airport, but some delegates from sunnier climes elected to rent cars for the 130 km journey along the (subsequently much improved) mountain road to Whistler. Most of the rental vehicles were not equipped with snow tires, and by the time the delegates reached Squamish, a heavy snowfall persuaded many of the group to make an ignominious return to the airport in search of the official transport! Art Salmon, always the consummate booster of things Canadian, arranged for two RCMP officers in full dress uniform to greet participants. A summary of papers presented at this meeting appeared in the American Journal of Preventive Medicine (Shephard, 2002).

Opportunities for Graduate Education

As noted throughout this chapter, a number of the early Canadian leaders in the activity sciences found it necessary to travel to the United States (frequently to Tom Cureton, at the University of Illinois) in order to complete their doctoral training. Nevertheless, with the impetus provided by the Fitness Research Units and the change in focus at other universities, Canada began to develop its own Ph.D. programs in the exercise sciences during the 1960s. The first candidates graduated from both the University of Toronto and the University of Alberta in 1966. The emphasis of these programs was rigorously physiological, backed by laboratory facilities and curricula that were in some respects superior to what was available in many U.S. physical education centred programs. Some Scandinavian countries had at least equally good doctoral programs in clinical physiology during this era, but in other European countries, applied science was still held in low regard.

It is possible to trace a pedagogic genealogy for some of the more outstanding programs, with students spreading the ideas and the reputation of Canadian universities around the world. I have watched this process at work in Toronto, where notable post-doctoral fellows have included the late Oded Bar-Or (previously at the Wingate Institute in Israel), Henri Vandevalle (Hôpital Pitié Salpetrière, Université de Paris VI), Dr. Vetencourt of Caracas, Venezuela, Dr. Dahong Zhuo (Ghuanzuo, China), several distinguished Japanese colleagues (Keiji Yamaji, Shoji Shinkai, Yuki Aoyaji and Masa Suzui), and members of the IBP Working Party on Exercise Testing (Drs. Bar-Or, Israel; Benade, South Africa; C.T.M. Davies, U.K.; Degré, Belgium; di Prampero, Italy; Hedman, Sweden; Ishii and Kaneko, Japan; LaCour, France; Myhre, Norway; and Seliger, Czechoslovakia). Doctoral graduates from the University of Toronto have also fanned out to academic appointments across Canada and the U.S.; names that I recall include Terry Anderson to the University of British Columbia, Don Paterson to the University of Western Ontario, Ken Sidney to Laurentian University, Veli Niinimaa to the University of New Brunswick, Gaston Godin and Luc Noreau to Laval University, Marc Tremblay to the University of New Brunswick, then Saskatoon and then Ottawa, Bill Montelpare to Lakehead University, Greg Gannon to the University of Manitoba, Heather Evans to UBC and subsequently the University of Cincinnati, Jack Goodman continuing at the University of Toronto, Ingrid Brenner to Trent University, and Brent Faught to Brock University.

Presence of Canadian Investigators on the World Stage

A final factor contributing to the rapid development of exercise physiology in Canada has been the consistent attendance of exercise scientists at major international gatherings throughout the world. On a per capita basis, Canadian attendance at international (and often American) meetings has exceeded that of their more wealthy U.S. peers. For example, Don Bailey tells me that at the 10th Annual meeting of the American College of Sports Medicine (ACSM, held in Minneapolis in 1963) 40 papers were presented, of which 5 came from Canada. Possibly the scattered population of Canada has accustomed its scientists to the rigours of international travel. Moreover, many Canadians possess fluency in one or more foreign languages, giving them an important advantage over their American counterparts. Canada has contributed three presidents to the ACSM (Claude Bouchard, John Sutton and myself), and Claude and I have also received the Honour Award of ACSM, as have other Canadians (John Faulkner and Jerome Dempsey).

Key Researchers in Canadian Exercise Physiology

It is somewhat invidious to single out a few people from the long list of investigators who have contributed to the development of exercise physiology in Canada. Indeed, there is a real danger that in pin-pointing a few of those who have been key researchers, I shall omit one or more of the reader's favourite personae. My short list would certainly include Bill Orban, Gordon Cumming, Don Bailey, John Faulkner, Roy Shephard, Claude Bouchard, David Cunningham, Norman Jones, Oded Bar-Or, Howie Green, and John Sutton.

Bill Orban

William Robert Orban (Photo 2.7) was perhaps the best known of Canadian exercise scientists during the mid-1950s. Born in Regina in 1922, he gained a hockey scholarship to the University of California at Berkeley, and after a brief period in the Faculty of Engineering, he switched to Physical Education. There was no exercise science Ph.D. program in Canada at this period, so he completed a Ph.D. program with Dr. Tom Cureton at the University of Illinois. In 1956, he accepted an appointment with the Canadian Department of National Defence, where he developed the widely acknowledged 5-BX (5 basic exercises) exercise program (see below). In 1958, Dr. Orban became the first Dean of Physical Education in the University of Saskatchewan, and he initiated a landmark longitudinal study of physical development in boys aged 7 to 17 years of age. In 1966, he returned to Ottawa to become Dean of Physical Education (later renamed to Kinanthropology then Human Kinetics) at the University of Ottawa, and he continued studying optimal patterns of training until his death from cancer in 2003.



Photo 2-7 Dr. Bill Orban, world renowned for authorship of the 5-BX and 10-BX exercise programs.



Photo 2-8 The 5-BX and 10-BX exercise programs developed by Dr. Bill Orban.

Gordon Cumming

Dr. Gordon Cumming, a pediatric cardiologist practicing at the Children's Hospital in Winnipeg, developed a strong interest in exercise physiology from the early 1960s, in part because of the involvement of his daughters in high-level skating competitions. He was an important player in organizing the 1967 Winnipeg Sports Science Meeting that accompanied the Pan American Games (Photo 2-9). It was here that CASS was founded. Dr. Cumming frequently took time out of his hospital practice to attend meetings of both CASS and the European Pediatric Work Physiology group. He quickly criticized the field performance tests that were widely used in the 1960s, underlining that a child's score on such a test battery reflected body size and maturity as much as physical fitness. He argued for the replacement of such testing by objective measurements such as the Physical Work Capacity at a pulse rate of 170 beats/min (PWC_{170}). He was an early advocate of the careful calibration of cycle ergometers, and made frequent surveys of PWC_{170} in healthy subjects and in children with congenital heart disease. He also highlighted urban/rural and seasonal differences of PWC_{170}, and underlined the apparent failure of the physical education programs of the 1970s to enhance the physical fitness of Canadian school children. His critical gaze rested on the Canadian Home Fitness Test (CHFT, see below), as he noted that the rhythm of the long-playing record setting the stepping cadence apparently differed from the intended beat

frequency by a margin as large as 10 percent. I traced the problem to a tendency of cheap turntables to slow as the centre of a record was approached, and humorous suggestions were made that we should set up a fund to buy Dr. Cumming a quality home stereo system. Nevertheless, Dr. Cumming's criticism of popular use of the CHFT recording was valid, since in that era most households were not using high quality turntables. Fortunately, the problem was soon solved as the vinyl record was replaced, first by a tape and subsequently by a CD.



Photo 2-9 CASS was inaugurated at a meeting of Sports Scientists that accompanied the Pan American Games of 1967, held in Winnipeg.

A second important interest of Dr. Cumming was the use of the electrocardiogram in identifying exercise-induced myocardial ischaemia. This interest led him to accept a post as Medical Director of Great West Life in 1981. He became Vice-President of this company, and his further involvement in exercise physiologyresearch was necessarily curtailed, although he continued to serve as an expert witness in Human Rights enquiries involving the development of myocardial ischaemia during physically demanding employment.

Don Bailey

Dr. Don Bailey (Photo 2-10) was born in Saskatchewan, and obtained a B.A. in mathematics from the University of Saskatchewan in 1955. Like other Canadians of his generation, he faced the problem of the absence of graduate exercise science programs in Canada, and travelled to Ohio and Indiana where he obtained a doctorate in physical education. In 1959, he returned to the College of Kinesiology at the University of Saskatchewan, and with the departure of Bill Orban for Ottawa, he assumed responsibility for the Longitudinal Study of Child Growth and Physical Development. With Roy Shephard (below), he developed the Canadian Home Fitness Test (Photo 2-11). He also undertook a major community-wide fitness promotion initiative in the city of Saskatoon, in collaboration with the Crown Agency ParticipACTION (directed by Russ Kisby, and charged to increase popular interest in physical activity). Don's expertise led to several prestigious appointments as Visiting Fellow, notably at the Institute of Child Health in London, at San Diego State University, and at the Universities of Queensland and Western Australia. In 1991, his interests shifted somewhat to the interactions between physical activity and bone health, and he initiated an innovative and widely acclaimed longitudinal study of bone mineral accrual in children and young women.

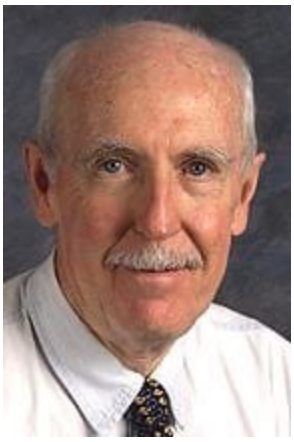


Photo 2-10 Dr. Don Bailey, for many years Director of the Longitudinal Study of Child Growth and Development in Saskatoon.



Photo 2-11 The Canadian Fit Kit, a package based on a long-playing record that allowed the population to test their cardiorespiratory fitness at home, and to choose an appropriate personal exercise program based on this information.

Don Bailey was one of an elite group of six individuals who saw the need to found CASS as a group that would marry the concerns of physicians and physical educators; representatives from the Canadian Medical Association were Sam Landa, John Merriman and Max Avren, and from CAHPER Don Bailey, Howard Nixon, and John Leicester. In 1991, Dr. Bailey received the Honor Award of CASS (now the Canadian Society for Exercise Physiology, CSEP); he also received an Honor Award from CAHPER. As a Professor Emeritus, his research studies are on-going both in Canada and in Australia.

John Faulkner

John Faulkner (Photo 2-12) is a Canadian-born investigator who has made major contributions to our understanding of exercise physiology. He served as a fighter pilot in the RCAF from 1942-1945, and on his discharge from the Air Force pursued studies at the University of New Brunswick, Queens University and the Ontario College of Education. He then taught high school for five years, pursuing graduate education during the summer months. After gaining his M.Sc. degree, he became an Assistant Professor and swim coach in the Department of Physical Education at the University of Western Ontario. In 1960, he moved to the University of Michigan (Ann Arbor), where he has continued for five decades.

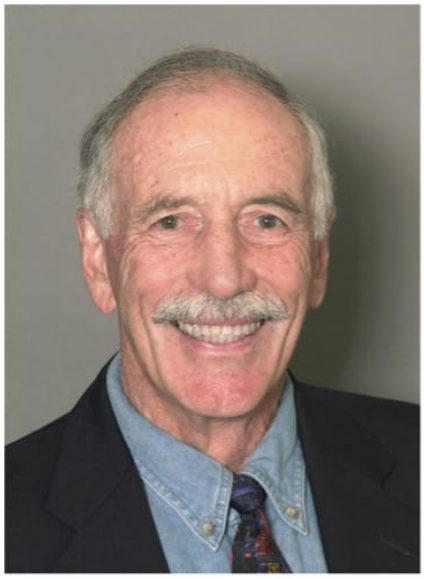


Photo 2-12 Dr. John Faulkner, a Canadian-born physiologist who has for many years studied muscle function in health, disease and aging at the University of Michigan, Ann Arbor, MI.

His more recent research has focused specifically on the contractile properties of whole skeletal muscles, motor units, and single skeletal muscle fibres from mice and rats, and single fibres from muscle biopsies of humans. In particular, he and his associates have focused on muscle fibre-typing, and the role of satellite cells. They have explored the changes that occur in the contractile properties of skeletal muscle during and following injuries caused by strong muscular contractions, denervation, reactive oxygen species, aging, and Duchenne and upper-limb girdle muscular dystrophy. Regardless of the cause of injury, skeletal muscle regeneration has been shown to involve the activation and division of satellite cells. Depending on the magnitude of injury to the muscle and its related vasculature, transient or permanent functional deficits develop in maximum force, rate and magnitude of length change, and consequently in power output. The long-term objective of the research team has been to elucidate underlying physiological mechanisms that lead to the substantial loss of peak force in aging muscle fibres, and thus to devise methods of reducing the functional losses associated with injury, aging and muscular dystrophies.

Most of Dr. Faulkner's professional career has been within the context of ACSM rather than CASS/CSEP, and in 1992 his contributions were recognized through the Honour Award of that College.

Roy Shephard

After completing doctoral studies in Physiology and in Cardiology at Guy's Hospital, a branch of the University of London (Photo 2.13), I worked as an applied physiologist at the Royal Air Force Institute of Aviation Medicine, the Department of Preventive Medicine in the University of Cincinnati, and the U.K. Chemical Defence Experimental Establishment at Porton Down. I was attracted to Canada in 1964 by the opportunity to serve as Director of the University of Toronto Fitness Research Unit, and establish a doctoral program in Exercise Sciences through the School of Hygiene, where I was initially quartered. Our first doctoral graduate, in 1966, was Dr. Terry Anderson; he examined various methods of measuring the pulmonary diffusing capacity during maximal exercise.



Photo 2-13 Dr. Roy Shephard, Director of the Toronto Fitness Research Unit, and for some 34 years Professor of Applied Physiology at the University of Toronto.

In addition to studying links in the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade from the atmosphere to the working muscle, assessing the fitness levels of various average and athletic Canadian populations, and writing a number of major textbooks addressing various aspects of exercise and fitness, early challenges included organization of the 1966 International Symposium on Physical Activity and Cardiovascular Health (above), hosting of the 1966 World Health Organization(WHO) working party on the measurement of 2 inhaled and O_2 exhaled" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">oxygen uptake (below), and synthesizing information on the physical working capacity of world populations for the International Biological Programme, with personal responsibility for physiological studies of Inuit living in the Canadian arctic (1969-1990).

Collaboration with Dr. Hugues Lavallée of the University of Québec at Trois Rivières allowed the initiation of a large-scale controlled and quasi-experimental study of physical education in Québec primary school students (1970-present). Collaboration with Dr. Terence Kavanagh and the Toronto Rehabilitation Centre began in the early 1970s; this initiative led to involvement in a multicentre trial of exercise for post-coronary patients (Photo 2-14), participation of cardiac patients in the Boston Marathon (below), and the use of exercise testing to determine long-term prognosis in various cardiac conditions. I also shared with Dr. Don Bailey in the development and testing of the Canada Home Fitness Test (1973-74) (Photo 2-10), and (in collaboration with Dr. Art Salmon) undertook a quasi-experimental study of work-site fitness programs (1978-1990).



Photo 2-14 The multi-centre Ontario Exercise-Heart Trial was a randomized controlled trial examining the value of exercise following myocardial infarction. Participants included: *(frontrow)* David Cunningham, Roy Shephard, Peter Rechnitzer, Norman Jones, Neil Lefcoe, John Sutton; *(back row)* Robin Campbell, Neil Oldridge, Mike Yuhasz, Terry Kavanagh, George Andrew, Sasha Sangal (statistician).

In 1979, I was appointed as Director of the School of Physical and Health Education at the University of Toronto, and moved my quarters to the newly constructed Warren Stevens complex. This move provided greatly expanded laboratory space, allowing the graduate program in Exercise Sciences to grow from a small handful of students to 40-50 candidates, often with several post-doctoral fellows also working in the laboratory. A close collaboration developed with the (then) Defence and Civil Institute of Environmental Medicine at Downsview, ON. This collaboration allowed an examination of exercise responses when combined with heat or cold stress, and permitted (in collaboration with Dr. Pang Shek) the development of the first major Canadian program in Exercise Immunology.

Throughout my career, I was closely associated with both CASS/CSEP (President 1970-71, first recipient of an Honour Award in 1985), and ACSM (President, 1974-75, Honour Award recipient 2001). I retired from the University of Toronto in 1994, but then served for a further four years as Canadian Tire Acceptance Distinguished Fellow in Exercise Physiology at Brock University. Since 1998, I have lived in the village of Brackendale (in rural British Columbia), but I continue writing and research through the magic of the internet and on-line journals. I was greatly honoured to receive the order of Canada in 2014, in recognition of my contributions to fitness and health in Canada.

Claude Bouchard

Dr. Claude Bouchard (Photo 2-15) is the most widely published of Canadian exercise physiologists, with data-bases such as HealthStar/Ovid listing more than 800 peer-reviewed publications. After completing a bachelor's degree at Laval University in 1962, he faced the problem common to his generation of the need to travel to the United States for graduate training. He completed his M.Sc. degree in exercise physiology at the University of Oregon, and a doctorate in population genetics at the University of Texas at Austin. He returned to Laval University, in Québec City, where he directed the Exercise Research Programme for many years. His interests spanned an impressively wide range of topics, but he attracted particular international attention for his "Québec Family Study" that explored relationships between the genetic and environmental components of an individual's inheritance, and many facets of human performance and the training response. The quality of his research attracted Honour Awards from both CASS (1988), and ACSM (2002), the Order of Canada (2001) and L'ordre National du Québec (2005), along with prestigious awards from a number of other professional societies in both Europe and North America. With the emergence of the human genome project, his laboratory played a leading role in identifying components contributing to physical performance and conditioning. He also became a leading international Photo in research on obesity, the metabolic syndrome, and diabetes; he carefully examined the contribution of genetic factors to development of these conditions, and served as president of both the North American Association for the Study of Obesity, and the International Association for the Study of Obesity. He was a prominent member of CASS, serving as its president (1985-86), and he played a leading role in organizing the international consensus conferences of 1988, 1992, and 2000 (see below). It was a great, if temporary, loss to Canadian exercise physiology

when he decided to accept the George A. Bray, Jr. Chair in Nutrition and serve as the Executive Director of the Pennington Biomedical Research Centre, a campus of the Louisiana State University System, in Baton Rouge. However, Claude has now returned to Laval University, where he continues his work as professor Emeritus.



Photo 2-15 Dr. Claude Bouchard was for many years Director of the Exercise Research Program and the Québec Family Study at Laval University, and a prominent player in the human genome project. For a period, he became Executive Director of the Pennington Biomedical Research Center of the Louisiana State University System, at Baton Rouge, LA, but has now returned as professor Emeritus to Laval University.

David Cunningham

Dr. David Cunningham (Photo 2.16) was born and raised in Toronto. He received a B.A. from the University of Western Ontario in 1960, and his M.Sc. from the University of Alberta in 1963, but like many of his contemporaries, he found it necessary to travel to the U.S. for his Ph.D, which he completed in 1966. He became involved in the landmark Tecumseh Community Health Study at Ann Arbor. In 1969, he returned to the University of Western Ontario (UWO), accepting joint appointments in Physiology and Physical Education; he continued in this role until 2001, and is now a Professor Emeritus of that institution.

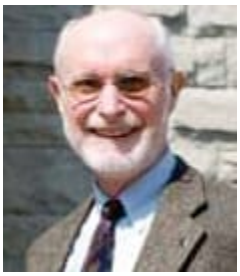


Photo 2-16 Dr. David Cunningham has pursued Exercise Physiology for many years at the University of Western Ontario. He is best known for his leadership in the Canadian Centre for Activity and Ageing.

Dr. Cunningham has made major contributions to many areas of research in exercise physiology, including the aerobic performance of young children, and the rehabilitation of cardiac patients (serving with Dr. Peter Rechnitzer, Norm Lefcoe, Mike Juhasz, and Sasha Sangal in the UWO component of the Ontario Multi-Centre Exercise Heart trial, Photo 2-14). However, perhaps his best-known contribution to the discipline has been in systematic studies of exercise and ageing. He was the driving force behind formation of the Centre for Activity and Ageing (now the Canadian Centre for Activity and Ageing) at UWO, and in collaboration with Don Paterson he has completed important longitudinal studies showing the importance of regular physical activity to the maintenance of health and independence in advanced old age. Dr. Cunningham has been a consistent supporter of CASS, serving two terms as editor-in-chief of the Canadian Journal of Sport Sciences, and receiving the Honour Award of the Association in 1995. He also founded the Ontario Exercise Physiology group, which has in essence served as a regional chapter of CSEP.

Norman Jones

Norman Jones (Photo 2-17) is another physician and exercise scientist who was attracted to Canada from Great Britain during the 1960s. He began his career at the Hammersmith (London) Post-graduate Medical School in the Department of Dr. Moran Campbell, in 1961. He emigrated to St. Joseph's Hospital in Hamilton along with Dr. Campbell, when the new Medical

School was established at McMaster University in 1968. Both scientists served in the Clinical Department of Respirology; Norman Jones continued and expanded his studies of the human exercise response when in Hamilton. He focused particularly on individuals with cardiorespiratory disease and disturbances of acid-base balance, linking acid/base changes to lactate levels, and exploring mechanisms of dyspnea. A second area where he made major contributions was in the estimation of cardiac output from the exchange of carbon dioxide, using the rebreathing method. In association with Lydia Makrides he worked towards the establishment of normal standards for maximal power output, heart rate, and ventilation. Collaboration with Tony Sergeant explored interactions between 2 inhaled and O_2 exhaled" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">oxygen uptake and strength. With John Sutton (below), he also directed the McMaster component of the Ontario Multi-Centre Exercise-Heart trial (Photo 2.14). He made a particularly important contribution to CASS by insisting on the standardization of laboratory methodology in Exercise Science, so that measurements of maximal oxygen intake and related variables could be compared reliably between laboratories. Previously, measurements on the same individual had sometimes shown inter-laboratory differences as large as 25 percent, a particularly important consideration in Canada, where problems of distance often led to athletes being tested in different laboratories at different times.



Photo 2-17 Dr. Norman Jones has made many notable contributions to cardiac and respiratory exercise physiology since accepting academic appointments at McMaster University Medical School and St. Joseph's Hospital in Hamilton, Ontario.

Image from http://fhs.mcmaster.ca/medicine/respirology/images/photo_faculty_jonesn.jpg

Dr. Jones' scientific contributions were recognized by the Award of a Citation by ACSM in 1986. He currently continues as Professor Emeritus within the Department of Respirology at McMaster Medical School in Hamilton.

Oded Bar-Or

Dr. Oded Bar-Or (Photo 2-18) graduated in Medicine from the Hadassah Medical School in Jerusalem. He then undertook post-graduate training in Exercise Physiology with Elsworth Buskirk at Penn State University, visiting the University of Toronto during the WHO Working Party on the Standardization of Fitness Testing (see below). He returned to Israel, and established an outstanding exercise physiology laboratory at the Wingate Institute in Netanya, which is perhaps best known for development of the "Wingate Test" of power and work capacity.



Photo 2-18 The late Dr. Oded Bar-Or, Director of the Chedoke-McMaster Children's Exercise and Nutrition Centre, and known world-wide for his expertise in the exercise responses of children.

From http://www.uwo.ca/actage/rechnitzer/lecture7.html

In 1981, Oded moved to McMaster University, becoming the founder and director of the Children's Exercise and Nutrition Centre, located at Chedoke Hospital in Hamilton. He became an acknowledged world expert in pediatric work physiology, serving as a prominent member of the European Work Physiology Group, and writing what has become a standard text of Pediatric Sports Medicine. His contribution to ACSM was recognized by the award of a Citation (1992). He was also strongly committed to CASS/CSEP, serving as its President (1987-88), and receiving the Honour Award in 2005.

Bar-Or focused his research and clinical attention particularly on overweight children, being one of the first to express concern about the growing epidemic of obesity. He developed a multi-disciplinary team of researchers who created and delivered effective individualized nutrition and physical activity programs for children, at the same time spearheading many research investigations of obesity in childhood. He is also well known for his studies of tolerance in children. He retired from McMaster University in 2003. Unfortunately his career as an Emeritus professor and world-wide lecturer was cut short by his death from cancer in 2005.

Howie Green

Dr. Howard Green (Photo 2-19) graduated from the physical education program at Queen's University, Kingston, ON in 1962, and completed an M.A. degree in Physical Education/Physiology at the University of Alberta before travelling to the University of Wisconsin, where he completed his Doctoral training in 1972. He played an important role in establishing the Kinesiology program at the University of Waterloo, beginning as a lecturer in 1965, and rising to the rank of Full Professor in 1983. His research has spanned a variety of aspects of exercise physiology, including the effects of 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia, ischemia, and hypervolaemia on oxygen transport, and various aspects of performance in ice-hockey. However, his main focus of interest has been the acute and chronic changes occurring in skeletal muscle in response to disturbances of energy homeostasis. With Bert Taylor, he played an important part in introducing the cellular physiology of exercise to Canadian investigators, and he has collaborated successfully with a number of renowned international laboratories in this area of research, most notably with Dr. Dirk Pette and his German colleagues at the University of Konstanz in Southern Germany. He has also made significant contributions to our understanding of skeletal muscle in such disease states as chronic heart failure and chronic obstructive pulmonary disease. His observations have challenged a number of long-held beliefs concerning metabolic regulation; in particular, he has demonstrated that adaptations designed to protect energy homeostasis occur soon after the onset of regular exercise, independently of any increases in mitochondrial potential, but closely integrated with sodium and potassium trans-membrane regulation, and sarcoplasmic reticulum calcium handling.



Photo 2-19 Dr. Howie Green, currently Distinguished Professor Emeritus at the University of Waterloo, has worked in many areas of exercise physiology, including studies of ice hockey and hypervolaemia, but is best known for his investigations of the cellular physiology of muscle in health and disease.

Dr. Green's scientific contributions were recognized by an Honour Award from CASS/CSEP (1987), and a Citation from ACSM (2002). His career has continued as a Distinguished Professor Emeritus at the University of Waterloo following his formal retirement in 2005.

John Sutton

The late Dr. John Sutton (Photo 2-20) was another distinguished migrant to Canada. After graduating in Medicine from the University of Sydney in 1965, he established the Sydney Human Performance Laboratory, and (as a marathon runner himself), he showed a keen interest in the physiology of distance running, underlining that participants in fun runs were vulnerable to heat stroke, and exploring the hormonal changes associated with endurance exercise. In 1972, he was awarded the Royal Australian College of Physicians Overseas Fellowship; this accolade brought him to McMaster University in Hamilton, Ontario. Here, he taught and conducted research on many aspects of exercise physiology, most notably studying 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia and altitude sickness both on Mount Logan and in high altitude chambers. Every summer between 1973 and 1980, John and his collaborators travelled to the Yukon, conducting rigorous experiments at altitudes of some 6,000 m. On at least one occasion, he had to run repeatedly over this rugged terrain to flatten a small snow-covered landing strip so that an aircraft could convey the research team back to Hamilton! His commitment to exercise physiology is marked in perpetuity by the prestigious biennial International Hypoxia Symposia that began in 1979, and the annual CSEP John Sutton Memorial Lecture.



Photo 2-20 The late Dr. John Sutton, faculty member of McMaster University best known for his contributions to Environmental Physiology, and the International Hypoxia Symposium.

Dr. Sutton played an important role in the McMaster component of the Ontario Multi-Centre Exercise-Heart study, and he served as a president of ACSM. It was a considerable loss to exercise physiology in Canada when Dr. Sutton (in 1989) decided to return to

Australia, accepting senior academic appointments at the then Cumberland College of Health Sciences, and the Medical Faculty of the University of Sydney. Exercise physiology suffered an even greater loss when he died in 1996, at the early age of 55 years.

Canadian Society for Exercise Physiology

This section considers the history of the Canadian Society for Exercise Physiology (CSEP) and two of its more important contributions – the publication of an internationally respected peer-reviewed journal (currently entitled Applied Physiology, Nutrition and Metabolism) and the certification of well-trained specialists in exercise physiology.

History of CSEP

The Canadian Society for Exercise Physiology (originally known as the Canadian Association of Sport Sciences) is a voluntary organization composed of both professionals involved in fitness and physical activity programs across the country and academics involved in the scientific study of exercise physiology, exercise biochemistry, physical fitness and health. Following preliminary discussions between representatives of the CMA (Sam Landa, John Merriman, and Max Avren), and CAHPER (Don Bailey, Howard Nixon, and John Leicester), it was formally established at a scientific meeting that accompanied the Winnipeg Pan American Games of 1967. The primary objective seen at that time was to achieve a rapprochement of the interests in physical activity and health represented by the CMA and CAHPER.

Two of the first three presidents of the newly formed association were physicians who cared for athletes (Drs. Sam Landa, and Max Avren). Although excellent clinicians, they had only a limited interest in the finer points of exercise physiology. The organization took a stronger physiological stance when I became its fourth president (1970-1971), and the only joint meeting ofCASS and the American College of Sports Medicine was hosted at Toronto's Inn on the Park in May of 1971 (Photo 2.21). I negotiated an agreement that the registration fees of participants would be distributed on the basis of nationality, and since many Canadians normally attended the ACSM annual meeting, but relatively few Americans participated in Canadian meetings, this agreement proved a very advantageous arrangement for our Canadian coffers. The meeting followed shortly after the FLQ (Front de Libération de Québec) crisis of October 1970, and the decision of the hotel chef to process a "bombe flambé" into the annual dinner produced a mixture of amusement and consternation!



Photo 2-21 Programme of the only joint meeting between CASS and ACSM, held at the Inn on the Park, Toronto, in 1971.

Because of travel costs, attendance at early meetings of CASS was relatively sparse. The economics of the annual meetings were further compromised by the decision to offer simultaneous translation of proceedings, even in strongly Anglophone cities such as Vancouver and Saskatoon. The Francophone attendance at meetings was quite limited, and almost all of those who attended the CASS sessions spoke excellent English. Speakers were occasionally disconcerted to see a group of Francophones at the rear of the room laughing helplessly at attempts of the translator to express scientific terms in acceptable French. I argued that we should expect Canadian academics to show reasonable fluency in both Canada's official languages, and myself presented some

papers in French at a meeting in Saskatoon; eventually it was decided that attempts to provide simultaneous translation of the proceedings were an unwarranted expense. However, the official documents of CSEP are still made available in both the official languages of Canada.

Although the initial intent of CASS was to bridge the gap between physical educators and physicians, as early as 1969 the physicians had established a steering committee to develop a Canadian Academy of Sport Medicine. From the viewpoint of the physicians, an organization specific to medical practitioners would give a stronger clinical focus to presentations; further, it would also permit the development of examinations that would allow certification of Sport Medicine as a distinct specialty recognized by the Canadian Medical Association. As knowledge of the exercise sciences increased, other members of CASS with interests in Biomechanics, Sociology, Psychology, and Psychomotor Learning also began organizing their own specialized conferences, further fragmenting Canadian sport science expertise. The issue of “separatism” was debated vigorously at a number of annual meetings of CASS, and the hope was frequently expressed that it might serve as an umbrella organization, bringing together all who were interested in the scholarly study of human movement.

Distinguished lecturers in disciplines other than exercise physiology were thus invited to give major presentations at our annual meetings, but sadly, they were sometimes greeted by an audience of only three or four people.

Finally, exercise physiologists recognized that they were the only people strongly committed to CASS, and in recognition of this situation the name was changed from CASS to the Canadian Society for Exercise Physiology in 1992. The new organizational format proved effective; meetings began to attract a growing attendance, including exercise scientists interested in biochemistry and nutrition, and there was a growing participation of investigators from northern U.S. States. The reformatted society also began a liaison with the Canadian Federation of Biological Societies, starting in 2000.

Important initiatives of CASS and CSEP have included the publication of an official journal (below), position stands on key issues in exercise physiology, and the certification of professional exercise physiologists. Currently, the annual meeting includes two or three days of scientific papers, and a final day when more general topics are communicated to certified exercise physiologists working in community rather than university settings.

Applied Physiology, Nutrition & Metabolism

When CASS was founded, my hope was that we might publish a scientific journal jointly with ACSM. I attended several committee meetings of ACMS, mostly in Chicago, but despite my strong pleas to the first editor-designate (Dr. Bruno Balke), the loudest of the U.S voices on the committee expressed confidence in their ability to publish a journal without any Canadian collaboration. As a small reward for my efforts, I was appointed a section editor of Medicine & Science in Sports (as it was then termed) for the first five years of its publication.

CASS continued to press for a journal that could be distributed to its members as a component of annual dues, and in 1976 it was decided to launch what was initially termed the Canadian Journal of Applied Sport Sciences. This journal was self-published, 1976-86, then published by the University of Toronto Press, 1987-1990, under the shortened title of Canadian Journal of Sport Sciences. The first editor was Bert Taylor (1975-79). He was succeeded by Eric Bannister (1980-84), David Cunningham (1985-1989), and myself (1989-1991). At this stage, CASS still hoped to attract disciplines other than exercise physiology, and the articles covered a correspondingly wide range of interests. In an attempt to introduce members to a broader spectrum of the exercise sciences, I took the initiative of commissioning short editorials to accompany submissions. Some members thought that Human Kinetics might offer a better deal than the University of Toronto Press in terms of printing costs, and production of the journal was transferred to Human Kinetics in 1990. In 1992, the name changed again (Canadian Journal of Applied Physiology) and the page size was reduced from quarto to octavo format (as used in most Human Kinetics journals); this change certainly did not increase the popularity of our journal with librarians! Editors during this period were David Cunningham (1992-94), and Phil Gardiner with François Perronet (1995-1999). Difficulty was experienced in negotiating increases of page length with Human Kinetics, and in 2006 the decision was made to transfer publication once again, this time to the Canadian National Research Council Press, under the new title of Applied Physiology, Nutrition & Metabolism (APNM). The new publisher proved a happy choice; the journal reverted to a quarto format, and it now appeared bimonthly, with a considerable increase in page allowance. Under the guidance of Dr. Terry Graham (editor 2000 – to 2019), the journal gained international contributors an improved their impact factor. Dr. Wendy Ward became co-Editor-in-Chief in April, 2019 and Phil Chillibeck joined Dr. Ward in Jan 2020). The journal is currently attracting considerable international attention, and high-quality articles are published from many corners of the globe.

CSEP currently has four position stands, published in APNM.

- resistance training in children and adolescents
- instability training of the core
- benefits and risks of physical activity in children
- getting the most out of your stretching routine

Certification of Physiologists

Professional certification of exercise physiologists was developed by the Health and Fitness Programme of CSEP in 1981, under the professional leadership of Dr. Norm Gledhill of York University (CASS President 1981-82, Honour Award Recipient 1999). The certification has twin objectives: to protect consumers by regulating standards for fitness professionals, and to give appropriate recognition to professionals with appropriate advanced qualifications.

There are two levels of certification, based on a candidate's academic background and work experience; Level 1 is introductory, and Level 2 (the advanced level) requires a university degree. Level 1 candidates earn the CSEP Certified Personal Trainer™ (CSEP CPT) qualification; they are required to complete successfully two modules covering Canadian Physical Activity, Fitness and Lifestyle Applications (CPAFLA) Fitness Assessment Protocols and Exercise Prescription. Level 2 candidates earn the CSEP Certified Exercise Physiologist™ (CSEP CEP) qualification. They must complete a 4-year university degree in Kinesiology/Human Kinetics/Exercise Sciences; such certification is intended for Kinesiologists who wish to specialize in the health, fitness, and rehabilitation industry.

A Sampling of Unique Canadian Contributions to Exercise Physiology

As with the listing of prominent exercise physiologists, it is controversial to pick out for more detailed discussion a few of the many unique Canadian contributions to the exercise sciences. I have chosen to consider the following:

- the 5-BX and 10-BX exercise program,
- hosting of the WHO Working Party on the Standardization of Maximal Oxygen Intake Measurements,
- International Biological Program (IBP) studies of the Inuit,
- the nation-wide testing of PWC_{170} in schoolchildren, by the Canadian Association of Health, Physical Education and Dance
- development of the Canadian Home Fitness Test
- related exercise clearance procedures (PAR-Q and PAR-MED-X),
- nation-wide surveys of physical fitness conducted by the Canadian Fitness and Lifestyle Research Institute (CFLRI),
- the Trois Rivières quasi-experimental study of physical activity in primary school students,
- the participation of post-coronary patients in the Boston Marathon, and
- the development of evidence-based guidelines for physical activity at various ages, and in various clinical conditions.

5-BX and 10-BX Exercise Program

The five and ten basic exercise plans 5-BX and 10-BX were created for Royal Canadian Air Force pilots by Dr. Bill Orban (Photo 2.7). These exercises offered an attractive approach to the enhancement of personal physical fitness in that no specialized equipment was required, and programs could be completed in as little as 11 minutes per day. The underlying concept was developed by Bill Orban while studying at the University of Illinois; he had noted that long periods of exercise did not necessarily enhance performance more than shorter training sessions, provided that subjects adopted an adequate intensity of exercise. His conclusions were not universally accepted, but nevertheless the 5BX pamphlet in particular proved very popular; 23 million copies were sold, and it has been translated into 13 different languages.

Standardization of Maximal Oxygen Intake Testing

The International Biological Program (IBP), initiated by Dr. J. S. Weiner of the London School of Hygiene during the late 1960s, included a concerted attempt to document the range of biological characteristics then existing in various small and geographically isolated tribes that had adapted culturally and genetically to challenging habitats, but had not yet been "contaminated" by modern civilization.

One issue of particular interest was to assess the range of maximal oxygen uptake values found in such disparate groups as very sedentary populations and elite endurance athletes. Data contributing to the IBP program were necessarily collected by

scientists drawn from a wide range of countries, and for meaningful comparisons between samples, it was vital to standardize methods of measuring maximal oxygen uptake and other indices of human physiological work capacity. In collaboration with the World Health Organization, the IBP thus convened a bench-level working group that met in our Toronto laboratories; participants included exercise physiologists drawn from the main centers involved in such measurements around the world. In order to test various potential protocols, a panel of 24 highly motivated subjects each completed measurements of maximal oxygen intake on each weekday for a total of five weeks. Direct measurements of maximal oxygen intake and a range of cognate variables were also made for the first time on a representative sample of Toronto schoolchildren. Canadian exercise science gained considerable recognition as a result of both this working party, and two resulting publications (Shephard, 1968; Shephard, 1978).

IBP Studies of Inuit

It was decided that one of the North American contributions to the IBP program should be a systematic study of adaptations to the arctic environment, as seen among three Inuit populations. The U.S. made some measurements of maximal oxygen uptake at Fort Wainwright, Alaska, and Scandinavian investigators also completed limited observations on a Greenlandic population, but the most comprehensive study was undertaken by our Toronto laboratory, operating a field station in the community of Igloolik, at the tip of the Melville Peninsula. Much modern laboratory equipment was flown to the arctic, allowing a full range of sophisticated tests of health and fitness to be completed on all willing villagers from primary school to old age. Investigators visited the village over the course of more than 20 years, thus allowing documentation of a progressive deterioration in fitness as the community became acculturated to a southern Canadian lifestyle (Shephard and Rode, 1996, Photo 2-22). Members of our research team also accompanied the Inuit on traditional hunting expeditions, obtaining unique data on the very high energy cost of such activities.

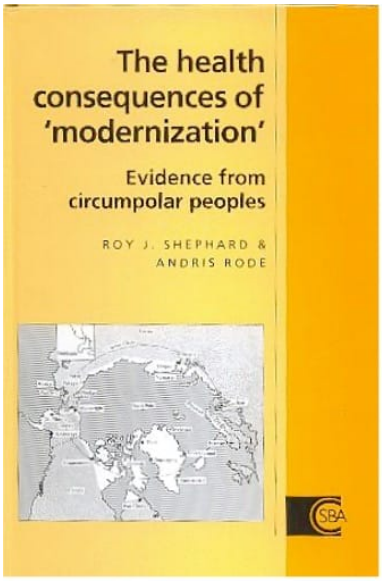


Photo 2-22 20-year IBP Study of the Canadian Inuit living at Igloolik, conducted largely by the University of Toronto CAHPER National Testing of PWC170 in Canadian Schoolchildren.

During the 1960s, most exercise physiologists paid little attention to issues of population sampling; observations were commonly made on the principal investigator, immediate colleagues and a few laboratory technicians. However, in 1966, the Canadian Association for Health, Physical Education, and Recreation **(**CAHPER**)** under the leadership of Max Howell (Photo 2-23) took the innovative step of measuring the PWC_{170} of schoolchildren aged 7-17 years, using a sample that was statistically representative of Canadian students in this age range (Howell & MacNab, 1968).



Photo 2-23 **Max Howell led the CAHPER study of PWC_{170} in a representative sample of Canadian schoolchildren in the summer of 1966.** He is here wearing the Order of Australia.

Development of the Canadian Home Fitness Test

One of the interesting findings from the Toronto IBP Working Party on the Standardization of Fitness Testing (above) was that subjects could be brought to within 3-4 percent of their treadmill maximal oxygen uptake using a simple double step (total height of 0.457 m, climbed and descended with three paces in each direction). Previous authors had tended to dismiss the effectiveness of step testing, perhaps because many of them had used taller steps that were difficult to climb. However, an effective step test offered a valuable alternative to the treadmill, particularly when testing people living in remote areas. In Igloolik, we lacked the 30 ampere power supply that a treadmill would have required, and it is doubtful if we would have been able to load most types of treadmill into a de Havilland Dash aircraft, so we substituted the 0.457 m double step for our exercise testing. In order to ensure that our subjects maintained an appropriate stepping cadence, we chanted the Inuit equivalent of 1-2-3 on rising and descending scales throughout a progressive, multi-stage test.

Don Bailey and I tested this approach further on a large sample of the Saskatoon population. Groups of sixteen subjects of similar age and sex climbed and descended long benches to an appropriate rhythm set by metronome (Bailey, Shephard & Mirwald, 1976; Photo 2-24). It occurred to us that large-scale home fitness testing would be possible, using a similar type of step, and a long-playing gramophone record to set age and sex appropriate rhythms. The idea seemed to have commercial potential, but neither Don Bailey nor I had much experience in the marketing of long-playing records, so we sold the idea to the crown corporation recently established to promote the fitness of the Canadian population (ParticipACTION, established in 1971). The contract specified that we would each be paid one third of a cent for exclusive rights to the concept, although we have yet to receive this unique coinage!

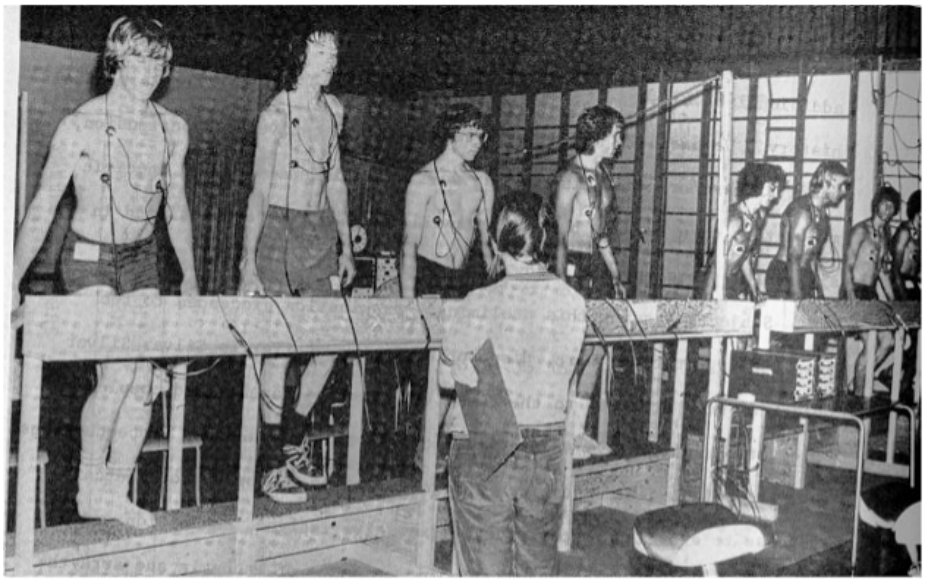


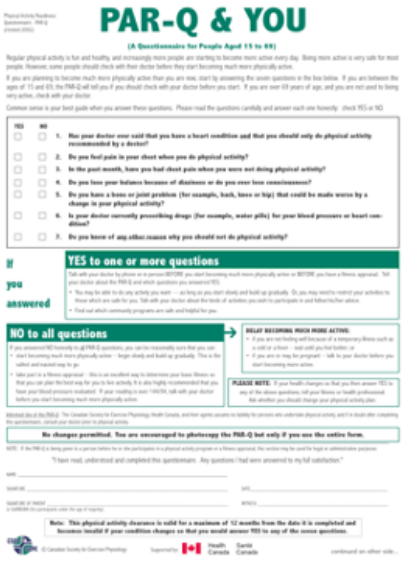
Photo 2-24 The idea for the Canadian Home Fitness Test was field-tested in Saskatoon in 1973, with groups of 16 age and sex-matched subjects performing the test simultaneously.

Under government sponsorship, the concept faced the usual bureaucratic hiccups. A high-priced band was hired to provide martial music, and only when it was delivered to the government did it occur to some civil servant that the music should be written in 3/4 rather than 4/4 time. However, a suitable package was eventually assembled that included the PAR-Q clearance sheet (below), the LP recording, instructions for submaximal exercise testing, and some simple exercises that subjects could perform based on their test results (Photo 2.10). As noted above, Dr. Cumming pointed out that if a cheap turn-table was used, a problem of cadence developed at the centre of the recording, but this difficulty was quickly resolved by the popularity of taped versions of the same music. The Canadian Home Fitness Test recording never achieved platinum sales, but a substantial number of copies were eventually sold through the unlikely outlet of official government book-stores; I suspect that with more aggressive commercial marketing, distribution could have been increased by at least one order of magnitude.

Development of Simple Exercise Clearance Procedures

When planning the Saskatoon evaluation of the Canadian Home Fitness Test, Don Bailey and I had an extensive discussion of test safety. We recognized that the test was essentially self-limited, and was carried to no more than 70-75 per cent of the individual's maximal oxygen uptake, so that risks were quite low for healthy subjects. However, we thought it important to develop a simple and brief questionnaire that would identify individuals who should consult a physician before engaging in the test.

The idea was developed further by Dr. David Chisholm and his associates; they applied what were essentially the questions that we had used in Saskatoon to people attending the Pacific National Exhibition in Vancouver (Chisholm, Collis, Kulak et al., 1975). Based on this assessment, the PAR-Q form was developed (Photo 2-25), and it has found widespread use both in Canada and around the world. Experience has suggested that it offers a safe clearance procedure for both exercise testing, and the prescription of moderate intensity exercise; the main complaint has been that a rather high proportion of the general population (about 20 per cent) are advised to seek further guidance. Minor modifications of the questionnaire were introduced in an attempt to correct unnecessary referrals, and a detailed restructuring by Dr. Darren Warburton led to the development of an evidence-based electronic version of the test, with probing questions exploring areas of uncertainty; this version of the test has been up-dated annually.



PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

If you answered

YES to one or more questions

NO to all questions

Photo 2-25 A version of the PAR-Q (Physical Activity Readiness) form used for exercise clearance.

Attempts to develop a similar screening form for use by physicians (the PAR-MED-X) have met less wide acceptance, but Dr. Warburton has now developed electronic versions of these forms.

Canadian Fitness Sur veys; CLFRI

Having devised a readily portable test of aerobicfitness (the double step test, above), and an appropriate screening procedure

(the PAR-Q test), Health Canada decided to undertake the ambitious project of measuring multiple components of health and physical fitness on a large and representative sample of the Canadian population at all ages between 7 and 65 years. The CFLRI was established in September of 1980 under the effective direction of Dr. Cora Craig (Photo 2-26), and the first such survey was completed in 1982 (Canada Fitness Survey, 1983). Partly because of the large costs involved in this endeavour, most subsequent surveys have used questionnaires rather than direct physiological measurements to track on-going levels of physical activity and fitness in the Canadian population. However, the use of direct measures was revived with the Canadian Health Measures Survey sponsored by Statistics Canada and the Public Health Agency of Canada.



Photo 2-26 Dr. Cora Craig, Director of the Canadian Fitness and Lifestyle Research Institute, has directed several samples testing the Fitness and Physical Activity of large and representative samples of the Canadian population of all ages from 7 to 65 years.

Trois Rivières Quasi-experimental Study of Primary School Students

The Trois Rivières study, led by Dr. Hugues Lavallée (Photo 2-27), was designed to examine the effects of incorporating five hours per week of professionally taught physical education into the primary school curriculum. The study was unique in many respects; similar experiments in the United States had a duration of only one or two years, but the Trois Rivières intervention continued throughout primary school, grades 1-6. Unlike other studies, a quasi-experimental design was adopted, with students in preceding and succeeding classes at the same school serving as controls. The intervention was carefully monitored to ensure that the five hours of supervised exercise per week were of adequate intensity, and it was demonstrated that there was no substantial compensatory reduction in leisure activity. The sample was large (546 students), and all attended an exercise physiology laboratory annually for a sophisticated range of investigations. Measures of academic attainments demonstrated that experimental students performed at least as well as the controls (although the latter spent 14 percent more time learning academic material). Finally, because of the low mobility of the population in this region, it was possible to make follow-up observations on the same subjects when they reached the age of 30-35 years and older; these follow-up studies showed a modest persistence of the intervention in terms of both physical activity habits and avoidance of cigarette smoking (Shephard & Trudeau, 2005).



Photo 2-27 Dr. Hugues Lavallée. Medical Director of the Trois Rivières study of physical education for primary school students.

Quasi-experimental Study of Worksite Fitness Programs

Another important first for Canada was a quasi-experimental trial of work-site fitness programs. This was initiated by the University of Toronto, with the enthusiastic support of Art Salmon and his colleagues at Fitness Ontario. Most previous work-site studies had simply reported short-term changes induced by al fitness program, and so were vulnerable to “Hawthorne” effects. However, the Toronto study compared responses between an experimental site (a large assurance company, Canada Life, Photo 2-28) and a control site (a nearby rival life assurance company, North American Life). A detailed analysis of potential economic benefits was undertaken in terms of productivity, absenteeism, and employee turnover, and a unique feature of the study was a direct comparison of OHIP Medicare billings between the two companies before and after institution of the program (Shephard, 1986).



Photo 2-28
Probably the first quasi-experimental study of the health and economic benefits of employee fitness programmes was conducted at the Canada Life Assurance Company in Toronto. The nearby North American Life Assurance Company served as the control site.

Participation of post-coronary Patients in the Boston Marathon

The Toronto Rehabilitation Centre, under its former Director, Terry Kavanagh, was one of the first institutions to offer vigorous rehabilitation programs for individuals who had sustained a myocardial infarction (and subsequently for those who had chronic cardiac failure or who had received a cardiac transplant). Through a close association with the University of Toronto graduate program in exercise sciences that began around 1970, detailed physiological data were obtained on all patients, including direct measurements of peak oxygen uptake. One noteworthy early episode was the participation (under close medical supervision) of eight post-coronary patients in the 1973 Boston Marathon. A carefully planned program of progressive aerobic training had increased the peak oxygen intake of these patients from an initial 24-27 $ml \cdot kg^{-1} \cdot min^{-1}$ to a peak of 53 $ml \cdot kg^{-1} \cdot min^{-1}$ in one subject; he was able to complete the marathon in the very respectable time of 3 hours 17 minutes (Kavanagh et al., 1974). Another early proponent of cardiac rehabilitation (Dr. Herman Hellerstein of Cleveland) was very upset to find himself upstaged in this way, declaring the run to be “criminal folly.” Nevertheless, he at the same time claimed that he had persuaded a patient to run the marathon distance prior to the Canadian exploit! The Toronto investigators made careful studies of fluid and mineral balance over several marathons, and (at a time when proprietary drinks were becoming popular among runners), it was established that in most situations, the best replacement fluid was simply water.

Development of Evidence-based Physical Activity Guidelines

The last, but by no means the least important Canadian contribution has been the development of evidence-based guidelines for activity in the general population, the elderly and youth (Health Canada/CSEP, 1998; 1999; 2002a, b, Photo 2-29). Canada has been in a unique position to develop such advice, given the series of major consensus conferences on physical fitness and health, noted above. It is interesting that at an early stage Canadian physiologists were urging that the volume of physical activity recommended in other countries such as the U.S. was insufficient to counter some of society’s current health problems,

particularly the obesity epidemic, a view that is now widely accepted.

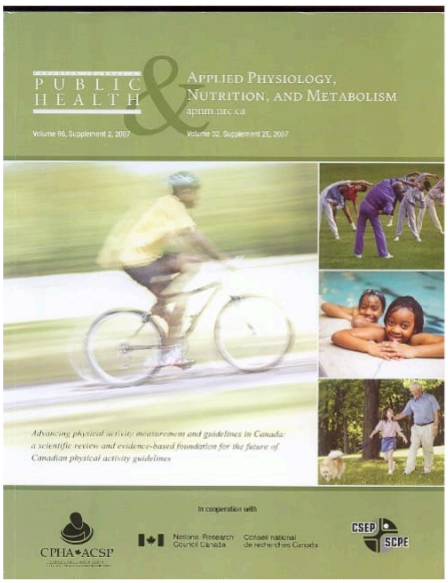


Photo 2-29 CSEP has been at the forefront internationally in developing physical activity recommendations for adults, children and the elderly.

What Does the Future Hold for Canadian Exercise Physiology?

Despite the major contributions that Canadian scientists have made to the development of exercise physiology over the past fifty, there remain many important challenges where further leadership can and will be contributed. Better information is needed on the safety of exercise testing and prescription both in health and disease, and the development of reliable statistics will require the establishment of a Canada-wide registry where all critical incidents occurring during exercise testing and programming can be recorded and evaluated.

Although many Canadian exercise programs have now been operating with apparent success for many years, there is still a need for more precise information on both safety and an appropriate dosage of exercise. The PAR-Q clearance process (and its medical counterpart) are undergoing extensive review and revision, it is hoped that in the future, a much larger fraction of those who wish to exercise will receive appropriate clearance using a suitably modified PAR-Q process. Modern computer technology is allowing a rapid and detailed interaction with the client, often without the need of intervention from a physiologist or a physician. Further, it is becoming possible to extend the clearance process originally designed for healthy individuals to include versions that are applicable to those affected by a variety of chronic medical conditions. This is requiring an extension of the responsibilities of certified exercise physiologists, with some extension of their training. Finally, definitive information is still required on that most elusive of goals, the optimal frequency, intensity, and duration of exercise to prescribe in both healthy individuals, and those with various clinical conditions.

To date, most assessments of the costs and benefits of regular physical activity have been made in terms of overall mortality, but from the viewpoint of the patient, the critical issue is any resulting change in the quality of life. Analyses of costs and benefits thus need repeating, with the quality-adjusted lifespan as the appropriate outcome measure.

Summary

A brief account is given of why Canada has played a major role in the development of exercise physiology. Description is given of key individuals leading this development, and noteworthy landmarks along this journey are highlighted. Canadian journals have a much smaller circulation than their U.S. counterparts, but many Canadian investigators have loyally communicated very important findings through the Canadian literature. Thus, major strides in knowledge made north of the U.S. border have not always received the recognition that they have merited. However, an objective review points to many Canadian firsts in exercise physiology. There remains much for the exercise scientist to discover, both in terms of fundamental research and its application to exercise prescription in health and disease, but Canadian laboratories seem well positioned to continue their leadership role

in this endeavour.

Review Questions

Exercises or Topics for Discussion

Pedagogic Genealogy: Identify an individual from the list of those presented in this chapter. Using the internet, identify the pedagogic genealogy of this person:

those who came before them, as supervisors and supervisors of the supervisors,

those who trained under that person (Masters and Doctoral students and postdoctoral trainees), and

those who collaborated with that individual in published scientific journals.

Using a map of the world, identify by colour (a red, b blue and c green) the location of these individuals, at the time of the collaboration or education.

Acknowledgment: I would like to thank many of my contemporaries who have contributed photographs and have helped me in recalling some of the exciting experiences that we have shared over the past 50 years; in particular, Don Bailey provided me with a wealth of historic photographs.

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Dr. Roy Shephard (1929-2023) was recruited to the University of Toronto in 1964. Prior to that time, he was working at Guys Hospital as an academic physician, among other things, performing catheterizations in children with congenital heart conditions, a procedure that lead to heart transplant surgeries. He also worked for the Royal Air Force, conducting research to facilitate operations of pilots under conditions of hypoxia. In Toronto, Dr. Shephard proceeded to publish an incredible number of peer refereed papers on a range of topics in exercise physiology, including fitness assessment and activity habits of a broad range of populations. He pioneered the use of the PAR-Q (physical activity readiness questionnaire) and was ahead of his peers in many aspects of exercise physiology. He authored or co-authored over 100 textbooks. Roy will be remembered as a humble mentor and leader who established Canada as one of the premier places in the world for research in exercise physiology.

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2: THE FUNDAMENTALS OF EXERCISE PHYSIOLOGY

2.1: Chapter 3 - Neural Control of Movement in Exercise

2.2: Chapter 4 - Skeletal Muscle Structure, Form for Function

2.3: Chapter 5 - Skeletal Muscle Contraction

2.4: Chapter 6 - Energy Supply at Rest and During Exercise

2.4.1: Chapter 6A - Energy Supply for Exercise

2.5: Chapter 7 - Pulmonary Function; Gas Exchange Between the Environment and Blood

2.6: Chapter 8 - The Circulatory System Response to Exercise and Training

2.7: Chapter 9 - Homeostasis And its Disturbance During Exercise

2.8: Chapter 10 - Measuring Metabolic Rates and Capacities

2.9: Chapter 11 - Nutrition and Energy Balance in Active People

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2.1: Chapter 3 - Neural Control of Movement in Exercise

This chapter is in preparation.

Authors: Jayne Kalmar, Greg Pearcey and Simon Sharples

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2.2: Chapter 4 - Skeletal Muscle Structure, Form for Function



Photo 4-1 Bodybuilder. This image by TotalShape is licensed under a Pixabay License.

Learning Objectives

After studying this chapter, you will be able to:

- Describe the general structure of skeletal muscle
- Describe the structure and function of connective tissue
- Describe the structure of motor units and relate to the central nervous system
- Describe the tendon and aponeurosis structure and function
- Identify structures associated with the neuromuscular junction
- Illustrate a single muscle fibre, myofibril and sarcomere at the microscopic level
- Describe the role played by membrane proteins
- Name and identify the function of a number of proteins that are important to muscle

Introduction

Skeletal muscle is an excitable contractile tissue that makes up 20-35% of total body mass in women and 30-45% in men (Janssen et al. 2000). As such it is an incredibly important tissue of the body. Many features of life can be directly attributed to skeletal muscle: body shape, speech, synchronized and coordinated movement, locomotion, posture, breathing, controlling the direction the eyes are looking and manual manipulation of objects. With such a broad range of functional roles, skeletal muscle must have an adaptable structure that in its elementary state can respond to neural activation with that may achieve a variety of outcomes. These outcomes include: maintain force or limb position, allow shortening or lengthening for joint motion, generate power and achieve or dissipate work. In this chapter we will look at muscle structure from a macroscopic perspective, considering how the cells are aligned and connected to bones through tendons. We will progressively zoom in on the tissues as we look at the subcellular structures and the specific proteins that make up muscle. Before we get to specific structural analysis, consider the Case Study presented next.

Case Study: Consider the Holiday Turkey

Ever since taking anatomy in a Kinesiology class, Rachel could not eat meat without relating it to muscles. She was enjoying turkey dinner with her family and picking delicately at the drumstick in front of her. There was a layer of oily under the skin. She noticed how the individual muscles pulled away from each other, maintaining a distinct shape. The Achilles tendon was connected to the large muscles on one side and ended bluntly where it had been cut away from the calcaneus. She knew that muscle fibres, too small to see separately were bundled by connective tissue into fascicles. She also recognized that dark meat, like that on the thigh and drumstick was composed of muscle fibres with high oxidative capacity, whereas white breast meat was composed of fast-twitch fibres with a high glycolytic capacity. With careful observation, she could see nerves and blood vessels disappearing into the meat near the end of the bone.



Photo 4-2 Turkey Dinner. Reading this Chapter may have just changed how you think about holiday dinners. Photo by Brian R MacIntosh (turkey by Sandra L Mann).

Gross Structure of Skeletal Muscle

All muscles are composed of individual muscle cells, also known as myocytes or muscle fibres, which are long, tubular cells, surrounded by a basement membrane and a thin layer of connective tissuecalled endomysium. At each end, the muscle cell is typically connected to tendon, which in turn connects to other tendons and bone. Contraction of the muscle fibre applies a force to the bone, which generates a moment about the joint. This moment (moment is a rotational force whose magnitude is the applied force times the perpendicular distance to the axis of rotation) can result in motion if the force is sufficient to overcome the load. Skeletal muscles are voluntary muscles in that we can decide when to cause contraction, controlling the timing and magnitude of in a coordinated fashion using the motor nerve pathways (see Chapter 3 on Neural Control). Skeletal muscle cells are striated; they have a banded appearance under the microscope, similar to cardiac muscle. This banded appearance arises from the regular pattern of sarcomeres along each cell. Sarcomeres are described later in this chapter.

In some cases, the whole muscle is much longer than any single fibre within the muscle; for example, sartorius and semitendinosus muscles, both of which extend from the pelvis to the upper parts of the shin. In these cases, individual fibres insert either into a connective tissue band called an inscription or the fibres are of varied length and occupy different portions of the full length of the muscle, interdigitating with each other. In the case of inscriptions, all fibres of a given segment are of a similar length and there may be two or more groups of fibres separated by inscriptions. It is generally thought that no muscle fibre is longer than about 12 cm in the average sized human body (MacIntosh et al. 2006). In contrast, some of the muscles of the body may be 30-40 cm in length. In many muscles of the body, individual fibres may only be a few cm in length.

Tendons connect our muscles to bone so that when a muscle contracts, the bone is pulled via the tendon. In some cases, the muscle fibres are oriented in line with the tendon, and in some cases, the angle of orientation of the muscle fibres is different from the line of direction for the tendon. In the latter case, the muscle is considered to be pinnate (see muscle shapes below).

Muscle Fascicles, Tendon and Aponeurosis

The gross structure of skeletal muscle is essentially what you see when the skin is removed, exposing muscle. The skeletal muscles obviously have a variety of shapes: long and thin (neck strap muscles) or long and wide (hamstrings); some muscles lie flat against the underlying body structures (abdominals) and some bulge, showing their large size (gluteals). Regardless of their shape, the muscles of the body serve specific functions related to generation of force, and movement. Function may be as diverse as to maintain posture, walk, run, throw, manipulate or support. Specialized functions exist for the muscles around the eyes and within the ears. Muscles give our faces expression, and in some cases, can cause wrinkling of the skin. This wrinkling can be overcome with injection of botulinum toxin (botox), an inhibitor of neuromuscular transmission. This practise is not recommended because there are long-term negative consequences of this treatment (Fortuna et al. 2011; Yaraskavitch et al. 2008).

A Simple Model of Muscle Contraction

Simple models of muscle have been presented in the research literature. Most of these originate in the models proposed by A.V. Hill (Hill 1953), before the sliding filament theory of muscle contraction was proposed (see Chapter 5). Figure 4-1 presents a common model of muscle contraction with a contractile element, in-series elastic component and a parallel elastic component. This simple model proposed by Hill has anatomical and physiological correlates that help us understand the relationship between muscle structure and function. Essentially, the contractile element represents the muscle fibres, or more specifically the myofibrils and the contractile proteins. The series elastic component represents the tendon, which lies in series between the muscle fibres and the bone. The parallel elastic component represents a series of tissues that support the muscle in the passive state: membrane, connective tissue and titin. These structures will be described below. An important feature of the parallel elastic component is that these structures provide a resistive force as the muscle is passively lengthened above a critical length. However, when a muscle contracts and generates force, the tendon (series elastic component) will stretch, allowing the muscle fibres and parallel elastic component to shorten. The parallel elastic component will hold less force as the muscle fibres shorten and the tendon elongates during an isometric (fixed end) contraction.

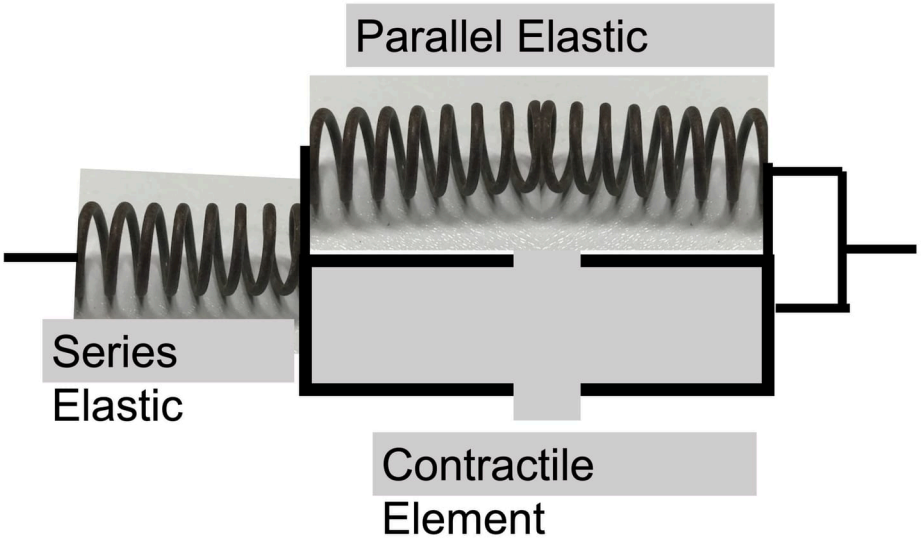


Figure 4-1 Hill Model of Muscle. The muscle is composed of structures that generate force (contractile component) and elastic tissues (tendon) in series with the contractile proteins (sarcomeres or myofibrils) as well as elastic tissues in parallel with the contractile proteins (membrane, connective tissue, titin).

Fascicles are Bundles of Muscle Fibres

Muscle fibres are bound together in bundles called fascicles. Fascicles are surrounded by connective tissue called perimysium. Motor units are a collection of myocytes innervated by a single motoneuron (see Figure 4-2). Each motor unit may contain hundreds of myocytes and these cells are distributed across several fascicles while each fascicle will contain myocytes from several motor units.

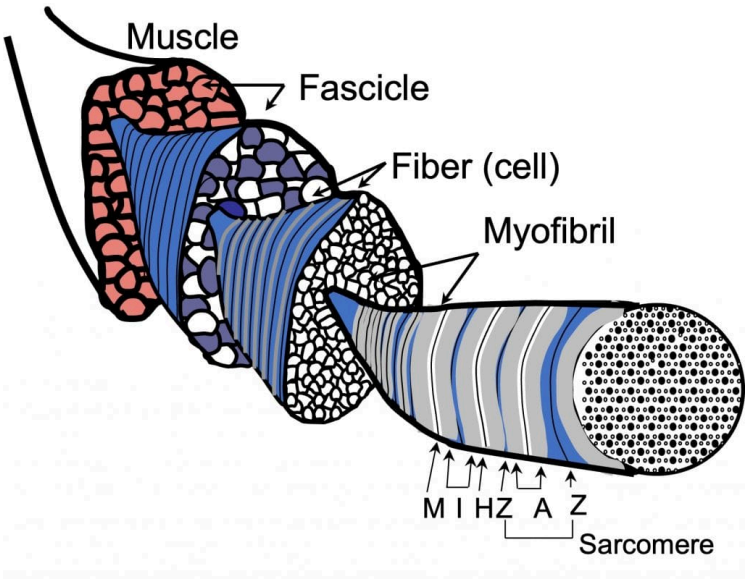


Figure 4-2: Muscle Structure. The whole muscle is surrounded by epimysium. Bundles of myocytes are called fascicles and these are surrounded by perimysium. Each fascicle contains several muscle fibres and each fibre is surrounded by endomysium. Within each fibre there are myofibrils, bundles of muscle proteins essential for contraction.

Shapes of Muscle Relate to Function

Skeletal muscles have a variety of shapes to accommodate a variety of functions. There are 3 primary categories of muscle shape:

- Parallel fibred
- Fusiform
- Pinnate
- Unipinnate
- Bipinnate
- Multipinnate

In general, muscle fibres are either oriented in line with the line of action of the muscle (parallel fibred and fusiform), or the fibres are aligned at some angle with respect to the direction of the line of action of the muscle (pinnate). Pinnate muscle can be unipinnate where all fibres are at a similar angle, bipinnate where the fibres are oriented in two primary directions or multipinnate where fibres are oriented in more than two directions. These muscle shapes are illustrated in Figure 4-3. Each shape of muscle has some advantages and some disadvantages, as will be described below.

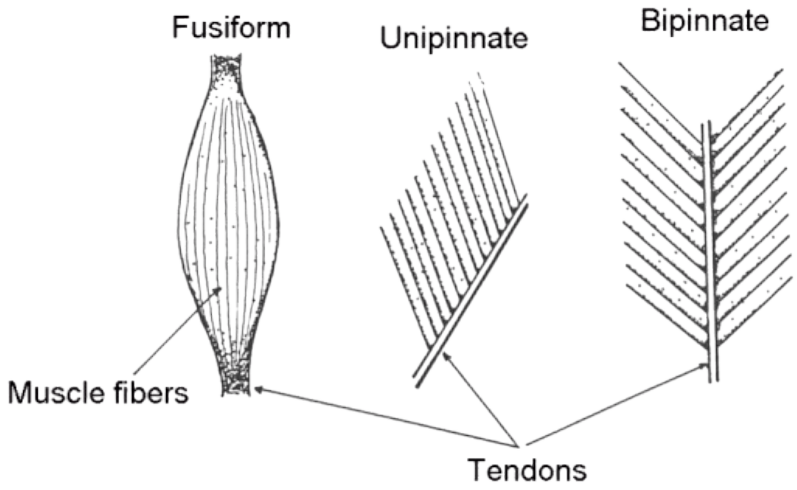


Figure 4-3 Muscle Shapes. Muscles of the body can be classified according to their shape: 1) parallel fibred (Sartorius), 2) fusiform (biceps brachii) and 3) pinnate (vastus medialis and rectus femoris). Source: Public Domain; modified from National Library of Medicine.

Parallel Fibred Muscle:

myofibrils and in many cases, more fibres arranged in series. Length of the muscle provides the advantage of a greater range of shortening and the potential for higher absolute velocities of shortening. The strap muscles of the neck are also parallel fibred muscles.

Fusiform Muscle:

fusiform muscle is one that is thick in the middle but narrows towards each end. The muscle fibres of a fusiform muscle tend to be aligned with the direction of pull of the whole muscle. This shape of muscle is of benefit for having a relatively large cross-sectional area but can originate and insert in relatively confined areas. An example of a fusiform muscle is the biceps brachii. Individual muscle fibres of a fusiform muscle are shaped the same as the whole muscle: wider in the middle range but narrow towards the ends. The muscle cells achieve this shape by terminating some myofibrils well before they reach the ends of the cell. The maximum isometric force that the muscle can generate is proportional to the cross-sectional area near the middle of the muscle and some fibres rely on lateral transfer of force. Lateral transfer of force is the transfer of force to adjacent structures (connective tissue) and also allows length change of all myocytes within a muscle even when only a few motor units are activated.

Pinnate Muscle:

A pinnate muscle (also called pennate) is a muscle that has the individual cells oriented in a direction that is at an angle to the direction of force application. The medial and lateral gastrocnemius muscles are examples of pinnate muscles. The deltoid is a multipinnate muscle, because the fibres are oriented in several directions. Pinnation, a term that derives from the Greek “pinne” or featherlike, allows packing a greater cross-sectional area into a given volume of muscle. A greater cross-sectional area allows greater force production by the muscle. However, individual fibres are shorter, so the property that allows greater force results in compromise of slower maximal absolute shortening velocity and possibly decreased range of motion.

Retinacula Decrease the Moment Arm of Skeletal Muscle

The tendons of some muscles are attached to bone at some distance from the joint, but the tendon is held close to the joint by a fibrous band called a retinaculum (the plural of retinaculum is retinacula). This is true in particular for muscles of the wrist and ankle. One feature of this arrangement is that it allows more individual muscles to operate across a joint, but the muscles can be attached at some distance from the joint. A retinaculum offers the advantage of decreasing the effective moment arm of a muscle (see Figure 4-4). This advantage allows a greater angular range of motion with less shortening of the muscle. Another advantage of the retinaculum is that a greater angular velocity of movement can be achieved for a given velocity of shortening.

The moment generated by a muscle is the product of the force times the motor arm distance. For this reason, a retinaculum effectively decreases the potential maximum moment that the muscle in question can generate.



Figure 4-4 Retinaculum. A retinaculum is a band of dense connective tissue, shown here at the ankle, that binds structures like tendons in close to the bones, thereby reducing the effective moment arm of the muscle. This short moment arm allows a faster angular rotation for a given velocity of muscle shortening. Source: Public Domain; modified from National Library of Medicine.

Connective Tissue in Skeletal Muscle

Connective tissue in skeletal muscle exists at five levels: around each cell, around bundles of cells called fascicles, around each whole muscle and connecting muscle to bone . These five levels of connective tissue are called:

- endomysium,
- perimysium,
- epimysium
- tendon
- aponeurosis

Connective tissue is a fibrous mesh of collagen, elastin and scattered cells called fibroblasts. Connective tissue serves several functions: it gives tissue form and guides initial formation as well as regeneration following injury. Connective tissue provides a space for blood vessels to penetrate the tissue and forms a protective sheath around muscle. The tendon is also composed of connective tissue and serves an important role in skeletal muscle function, as discussed below.

Endomysium

The endomysium is a thin layer of connective tissue around each myocyte. Individual fibrils of collagen, which run in all directions, are relatively thin (60 to 120 nm). The endomysium provides a protective layer around each cell, outside of the basement membrane. The endomysium and basement membrane provide a cylinder in which muscle regeneration can occur during recovery from muscle damage.

Perimysium

The perimysium is a thicker layer of connective tissue that divides the muscle into fascicles. Arterioles and nerve branches use the perimysium to distribute throughout the muscle.

Epimysium

The epimysium, also known as fascia, envelopes each muscle in a thick layer of connective tissue. Collagen and elastin provide protection for the muscle while still permitting the shape changes needed to accommodate muscle shortening and elongation.

Tendons

Tendons are also composed of connective tissue, primarily collagen with small amounts of elastin and proteoglycans. Tendons connect skeletal muscles to bone, and in most cases there is tendon at both ends of a skeletal muscle. In some cases, the tendon is relatively compliant and in other cases there is a stiff tendon. Tendons can occupy much of the muscle-tendon length or they can be relatively obscure. It is important to realize that a muscle can stretch the tendon in series with that muscle and the magnitude of stretch depends on the tendonstiffness and the force of muscle contraction. The important realization from this relationship is that when a muscle contracts without changing joint angle (at either end of the muscle if it is a two-joint muscle), the muscle fibres can still shorten to accommodate the stretch of the tendon. This means the contraction is not truly isometric, and should be referred to as a fixed-end contraction.

Aponeurosis

The aponeurosisis a connective tissuesurface to which myocytesof pinnatemuscles are attached. In this respect, aponeurosis is like tendon. However, the function of the aponeurosis is very different from the function of the tendon. The aponeurosis must be very compliant. It accommodates the shape change of the individual muscle fibres as they shorten and become wider or elongate and become narrow. The surface of the aponeurosis must allow individual fibres to remain tightly attached to neighboring myocytes while these shape changes occur. The aponeurosis also assists with transfer of force to the tendon. However, lateral transfer of forcealso helps in this matter (Monti et al. 1999). Lateral transfer of force relates to the ability of a myocyte to transfer force to adjacent cells along the length of the fibre.

Blood Supply of Skeletal Muscle

Like all tissues of the body, each muscle will receive blood flow through 1 or 2 arteries and this/these arteries will go through several branchings and become the following vessels:

- Small artieries
- Arterioles
- Capillaries
- Venules
- Small veins
- veins

Vascular arborization

skeletal muscle is important for several reasons: providing oxygen and substrates for metabolism, removing products of metabolism and excess heat, and communicating with and from muscle by hormonal and cytokine transportation. Most muscles in the human body have a primary artery providing all of the necessary blood flow. This primary artery will divide several times, with each division resulting in two vessels of smaller radius but increased total cross-sectional area. By this division, the speed of flow of blood and the resistance to flow will both decrease. Blood travels sequentially to arterioles, capillaries, venules and veins. This sequence is like the main water supply to your house or apartment, branching to provide water to the many sites inside that need it, (sinks, toilets, showers etc) and the drains combining to form a single waste water exit to the sewer system are like the veins of a muscle.

Arteries:

Arteries are thick-walled elastic vessels that conduct the blood from the heart to the target tissue (muscles in this case). A primary artery (sometimes two) will enter each muscle, and divide several times, each time decreasing the diameter of the branches relative to the vessel before the branch. Eventually, arteries give way to arterioles, the primary resistance vessels of the vascular system. Vasoconstriction of arteries and arterioles increases the resistance to blood flow and vasodilation of these

vessels decreases resistance allowing higher blood flow.

Arterioles:

Arterioles are smaller than arteries, but have relatively thicker walls, composed of smooth muscle layers and connective tissue. Arterioles will branch a few times before delivering blood to the capillaries. Arterioles are considered important for regulating the distribution of blood flow because they have the potential for very strong constriction.

Capillaries:

The purpose of the vascular system is to provide a means for delivering oxygen, substrates, hormones and cytokines to the various tissues and to remove substances that would otherwise accumulate in the extracellular space. It is in the that this function is achieved. Capillaries are thin-walled vessels that allow transport of these substances to and from the extracellular space within the tissues. The walls of capillaries are composed of a single layer of endothelial cells. Capillaries are barely large enough for red cells to squeeze in. The length of capillaries is about 1 mm on average. Exchange of substances between the vascular space and the extracellular space occurs by transport through or between the endothelial cells. In spite of being so short, the total number of capillaries in the body, when laid end-to-end would stretch all the way around the Earth (~40000km).

Venules:

Capillaries converge to form venules which are small enough and have thin enough walls that some exchange of gas, ions and small molecules can still occur here. However, the primary function of these vessels is directing blood flow from the tissues to the veins.

Veins:

Venules converge to form veins. Veins are the vessels that return blood flow to the heart from the periphery. Veins also serve as a large reservoir of blood, containing about 60% of the total blood volume. The walls of veins have smooth muscle in them, allowing to increase venous pressure. A higher venous pressure will allow a greater pressure difference between the veins and the heart, increasing blood return to the heart. Venous return is a primary determinant of cardiac output.

Lymph Vessels

In passing through tissue, blood will typically lose a small volume of fluid. To account for fluid distribution over time, this volume must be returned to the circulation. This return is accomplished by the lymphatic system, a series of thin-walled vessels that parallel the venous vascular system, emptying the contents into the subclavian veins.

The Motor Unit Organization of Skeletal Muscle

Structure and Distribution of Motor Units

A motor unit is a single motoneuron and all of the myocyte innervated by that motoneuron. Each muscle will have a number of neurons with soma in the ventral horn of the spinal cord. Each motoneuron soma in the ventral horn of the spinal cord gives rise to a single axon that exits the spinal cord to the ventral root and travels in the corresponding spinal nerve to the respective muscle. As the axon approaches the muscle, and within the muscle, it divides multiple times. Each myocyte is innervated by a single axon. The number of nerve branches, and therefore the number of myocytes innervated for each motor unit, depends on several factors: size and function of the muscle, as well as the fibre-type of the muscle fibres innervated. All myocytes of a given motor unit are the same fibre-type. Individual myocytes associated with a given motor unit are distributed through a region of a muscle. This means that when only a few motor units are active, it is highly unlikely that several adjacent myocytes are active.

Innervation and Neuromuscular Junctions

Each myocyte receives innervation from a single motoneuron. At the axon terminus, a specialized structure permits transmission

of the activation from the axon terminus to the myocyte membrane. This transfer of activation occurs via chemical communication resulting from an action potential arriving in the nerve terminal. The neuromuscular junction includes the nerve terminus, the muscle membrane immediately under the nerve terminus and the gap between these two. Figure 4-5 illustrates a neuromuscular junction.

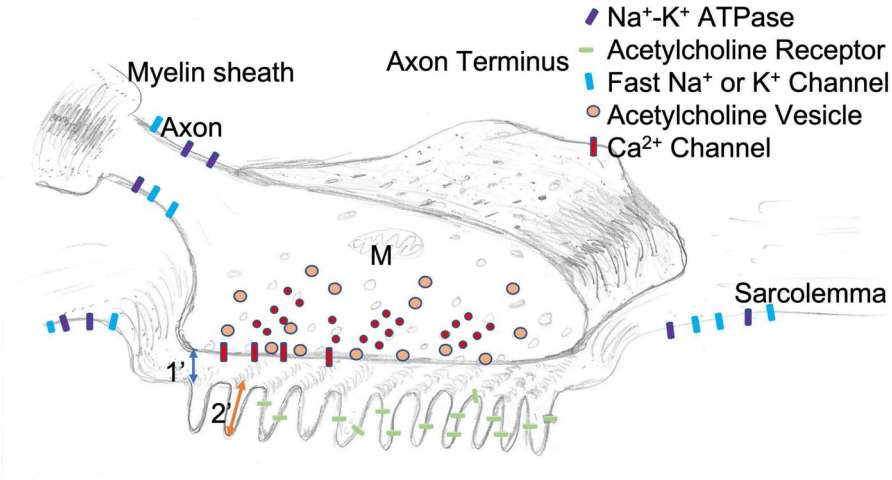


Figure 4-5 Neuromuscular Junction. The nerve terminal ends in a node that almost contacts the sarcolemma. Under the nerve terminal, is the primary synaptic cleft (1', ~70 nm) and the underlying sarcolemma is folded, forming troughs known as secondary synaptic clefts (2' ~500 nm). Under the nerve terminal the sarcolemma has a large number of acetylcholine receptors. Beyond the end-plate region, the sarcolemma does not have acetylcholine receptors. The membrane of the nerve terminal has rows of Ca^{2+} channels with nearby internal docked vesicles containing. Additional vesicles are tethered to the membrane and reserve vesicles are floating nearby.

The nerve terminal is a specialized neural structure with membrane vesicles containing acetylcholine and the neurolemma contains special membrane proteins that allow tethering, docking and fusion of membrane vesicles with the nerve terminus membrane. In addition to these proteins in the membrane of the vesicles there are special proteins in the nerve terminal membrane that complement the special membrane proteins of the vesicles and participate in the process of docking and fusion. The nerve terminal also contains mitochondria to provide energy for the active processes that go on here. The membrane of the nerve terminus contains several pumps, channels and binding proteins. In addition to the fast Na^+ channels and K^+ channels, a predominant protein in the nerve terminus membrane is a Ca^{2+} channel. This channel opens briefly when an action potential arrives at the nerve terminus. The resulting puff of Ca^{2+} that enters through the Ca^{2+} channels will cause the local $[Ca^{2+}]$ to increase. This increased concentration results in binding of Ca^{2+} to one of the specialized proteins associated with docked vesicles and results in fusion of some of the docked vesicles and the consequent release of acetyl choline into the synaptic cleft.

The End Plate

The muscle membrane under the nerve terminus and the cytoplasm immediately under that membrane have specialized structures that serve the purpose of receiving the signal from the motor nerve and transmitting that signal to a muscle membrane, resulting in an action potential. The end-plate is illustrated in Figure 4-5. A key feature that identifies the end-plate, besides the obvious nerve terminal over this region, is the deep infolding of the sarcolemma and the presence of acetylcholine receptors in this membrane. These secondary s increase the surface area of the end-plate, providing more area for the acetylcholine receptors and decreasing the chance that acetylcholine will diffuse away from the end-plate region. The primary feature of the end-plate is the high concentration of acetylcholine receptors. Other areas of the sarcolemma do not have acetylcholine receptors, unless innervation for that muscle fibre is lost (Axelsson and Thesleff 1959). Denervation results in loss of activation, and activation is necessary to inhibit synthesis of acetylcholine receptors. Normally, myotrophic factors released from the motoneuron will overcome this inhibition for nuclei close to the neuromuscular junction. This is why acetylcholine receptors are normally located only at the neuromuscular junction.

Motor Unit Size

We know that each muscle fibre is innervated by a single axon, and that each motoneuron innervates many muscle fibres. The actual number of myocytes innervated by a given motoneuron varies considerably in the muscles distributed throughout the body. Note that muscles with fine motor control have few myocytes per motoneuron whereas muscles with less demand for fine motor control have a large number of muscle fibres per motor neuron (see Table 4-1).

How do we Know How Many Motor *Units per Muscle*?

There are various methods for estimating the number of motor units in a given muscle. The most direct is to count the number of apparent motor nerves entering a muscle. This gives only an estimate since the count depends on identifying motoneurons and not counting the motoneurons. This approach requires counting the large axons to exclude sensory neurons. Estimates of the number of motor units per muscle are given in Table 4-1 for a few human muscles. In this Table, the fibres/unit represents an average but the actual number of fibres per unit in a given muscle will vary considerably because every muscle has small and large motor units.

Table 4-1 Numbers of Motor Units per Muscle

Muscle	No. of Motor Units	Muscle fibres/unit
First dorsal interosseous	119	340
Brachioradialis	333	>410
Tibialis anterior	445	562
Gastrocnemius (med)	579	1934
Masseter	1452	640
Temporalis	1331	936
Flexor digiti minimi	130	108

Source: MacIntosh, Gardiner and McComas, 2006

An alternative approach to estimate the number of motor units is to stimulate the motor nerve with a progressively larger pulse (beginning with a very low voltage and gradually increasing the intensity for sequential contractions) while measuring the (McNeil et al. 2005). If the voltage begins low enough to activate a single motor unit and each increment adds only one motor unit, then motor units can be counted. A small increase in voltage that does not result in an increase in EMG amplitude is a null result, no additional motor unit was activated.

Fibre-Types in Skeletal Muscle

Typically, individual motor units can be identified as specific fibre-types. In human muscles these fibre types can be separated

into fast and slow, but the fast fibre type has two subtypes. The classification of fibre type is either by contractile and metabolic factors or by myosinisoform identification. Although we classify motor units according to these fibre types, in reality, individual motor units can have properties that are intermediate between the classic fibre types. This occurs because some fibres can have two different isoforms of myosin heavy chain heavy chain, the major protein that distinguishes the fibre-types. Table 4-2 presents some typical contractile and metabolic properties that are associated with the classic fibre types.

Table 4-2 ***Contractile and Metabolic Properties of Muscle Fibre Types***

Property	Type I Slow-twitch	Type IIa Fast-twitch	Type IIx Fast-twitch
Twitch time	long	short	short
Twitch amplitude	small	large	largest
Maximal velocity of shortening	low	high	highest
Sag	no	yes	yes
Aerobic capacity	high	high	low
Glycolytic capacity	low	high	high
Relaxation rate	slow	fast	fast
Mitochondrial density	high	high	low
Myoglobin concentration	high	high	low
Fatigability	low	low	high

Contractile Properties and Classification of Fibre Types:

The initial classification of motor units into fibre-types was presented by Burke et al. (1973). These investigators identified three distinct categories of motor units in cat muscle according to contractile properties. They evaluated several possible contractile properties, but only a few of these had distinct characteristics that allowed separation of the motor units into three types: fast-twitch, fatigable, fast-twitch, fatigue resistant and slow-twitch. The key contractile properties included the following: force, twitch time, and fatigue index. The speed of the twitch contraction also contributes to fusion and the force-frequency relationship (described further in Chapter 5 on contractile properties). The separation of motor units into fibre-types is less distinct in human muscle than in cat, partly because of the presence of more hybrid fibres (see below).

A single stimulus to a motoneuron will result in propagation of a single action potential on the axon of the motoneuron. This single action potential will follow all branches of the motoneuron and transfer a single activation to each muscle fibre associated with that motor unit. The subsequent contraction of all these muscle fibres is called a twitch. A twitch contraction will have a rise and fall of force as illustrated in figure 4-6. The amplitude of the twitch is dependent on the average fibre size and how many fibres are innervated by that motoneuron. Typically, the force of a twitch is 15-20% of the force of a high frequency stimulation (tetanic contraction). Small motor units (type I) will result in small force and large motor units (type II) will result in large force. The duration of a twitch is also dependent on the fibre type. Two classifications of fibre type can be identified by twitch contraction time or time to peak force of a twitch: fast and slow (also known as type II and type I, respectively). It is important to realize that although within a species there is a difference in contraction time between fibre types, there is also a difference between species for any fibre type. The fast-twitch motor unit of a rat has a contraction time of 12-16 ms but the fast-fast-twitch motor unit of a human has a contraction time of 30-40 ms.

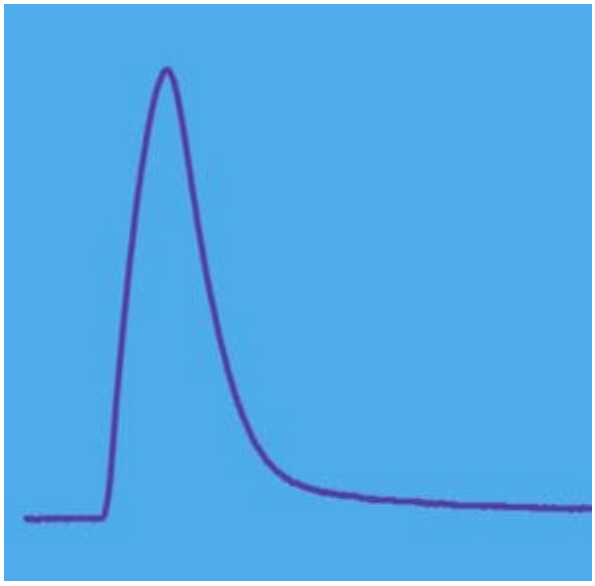


Figure 4-6 Twitch Contraction. A twitch is the contractile response to a single activation. This could be the response of a single fibre, a motor unit or a whole muscle. The twitch of a fast-fast-twitch motor unit is faster and stronger than that of a slow-slow-twitch motor unit of the same muscle. However, the force per cross-section is similar between human fast and slow-twitch fibres.

Myosin Isoforms and Classification of Fibre Types

There are minor differences in the amino acid sequence of the S1 segment that give the myosin head different kinetics. These differences in amino acid sequence are recognized as different isoforms of myosin. There are at least 9 different myosin isoforms recognized, but in adult human muscle there are only 3: type I, type IIa and type IIx. These myosin isoforms correspond to slow-twitch, fast oxidative (fast-twitchfatigue-resistant) and fast glycolytic (fast, fatiguable) respectively. Type I and IIa have high resistnce to fatigue and type IIx fatigues easily. A fatigue index can be calculated, based on the reduction in force observed over a fixed duration of time (usually, 0 to 2 or 60 min). This fatigue index is illustrated in Figure 4-7.

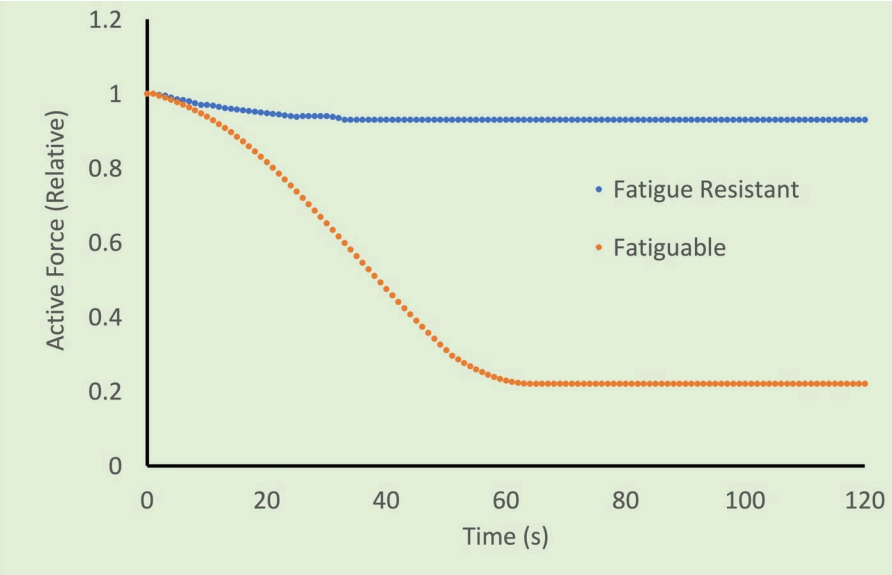


Figure 4-7 Fatigue Index. The fatigue index is calculated as the difference in force from initial to final force, divided by the initial force multiplied by 100 (% decline) when the muscle is stimulated at 50 Hz for 300 ms every second. In the figure, the fatigue resistant condition would have a fatigue index of 5% and the fatiguable condition would be 80%.

It should be pointed out that myosinisoform compliment is slightly different between species. Histochemical and contractile assessment identifies three fibre-types. However, there are 4 myosin isoforms, corresponding to type I fibre, type IIa, type IIb and type IIx. Type IIx was not identified until 1989 (Termin et al. 1989), so prior to that, it was thought that human muscle contained type IIb myosin, corresponding with the fast-twitch fatiguable contractile properties, similar to rat and cat muscle. However, identification of type IIx myosin in human muscle (initially referred to as IId), and the realization that type IIb does not exist in human muscle is an important fact.

Sag is a unique feature of fast-twitchmotor units. When motor unit stimulation results in incompletely fused tetanic contraction, the oscillations in force reach a peak early in the repetitions followed by a subsequent decrease in peak values (see Figure 4-8). This decrease in force, or sag, is recognized as a property of type II motor units. Similar stimulation in Type I motor units results in a that continues to rise to a plateau with no decrease in force during the incompletely fused contraction.

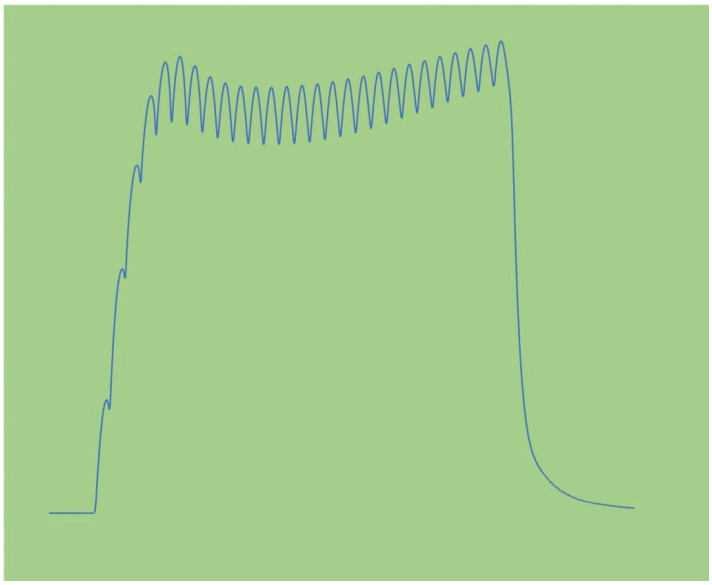


Figure 4-8. Incompletely fused tetanic contraction demonstrating sag. The reaches a peak after 6 stimulations, then the maximum force for each force transient decreases before increasing again later in the contraction. This decrease is called sag. This is a medial gastrocnemius muscle contraction with supramaximal motor nerve stimulation at 80 Hz.

Although not considered by Burke and colleagues when they were evaluating contractile properties of the motor units, the force-

frequency relationship can also be used to discriminate between motor unit fibre types. The force-frequency relationship has a sigmoidal shape (see Figure 4-9). The frequency of stimulation that gives the half-maximal force is dependent on the and relaxation times. A slow motor unit will achieve half-maximal force at a lower frequency. A fast-twitchmotor unit will achieve half-maximal force a higher frequency. This fibre-type difference is illustrated in Figure 4-9. Higher and lower here are relative and dependent on species. Generally speaking, small animals have muscles that contract on a shorter time-scale while large mammals have muscles that contract on a longer time-scale.

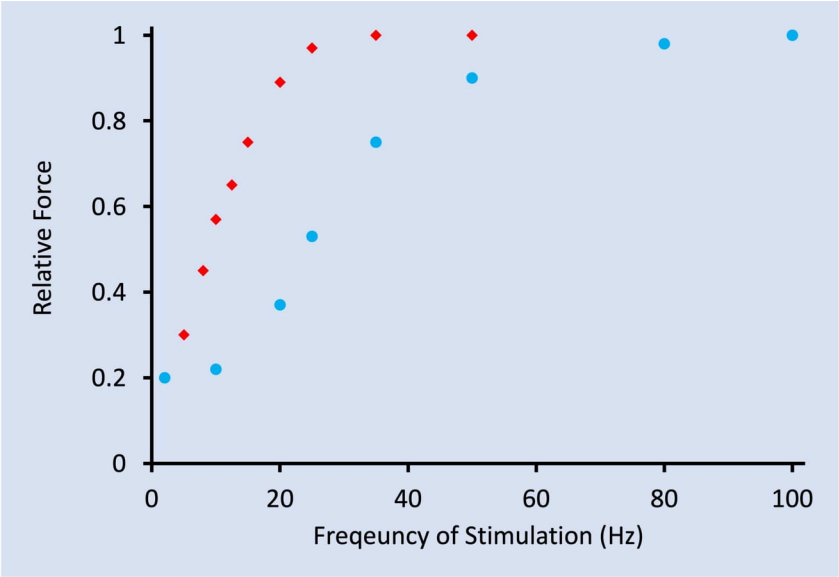


Figure 4-9 Force-Frequency Relationship. Human muscle reaches maximal force near 50 Hz stimulation. Single stimulation will yield twitch contractions, a brief rise and fall of tension reaching a force near 20% of maximum before falling again to resting force. The relationship between stimulation frequency and force is sigmoidal. Slow-twitch motor units will fuse at a lower frequency while fast-fast-twitch motor units require a faster stimulus frequency. Small animals, like rats have muscles that contract more quickly. For the gastrocnemius muscle of the rat, maximal force occurs at nearly 200 Hz.

Hybrid Fibres

Some muscle fibres contain more than one myosinisoform. These are called hybrid fibres. The presence of hybrid fibres is a factor that blurs the distinction of fibre types by contractile assessment. Considering the presence of hybrid fibres, it has been suggested that fibre types should be represented by a spectrum rather than distinct fibre types.

Spectrum of Skeletal Muscle Fibre-Types:

Type I ↔ Type I:IIa ↔ Type IIa ↔ Type IIa:IIx ↔ Type IIx

Myosin Light Chains

Contractile properties of motor units are also affected by isoforms of the light chains of myosin, which are attached to the myosin head (S1 segment). There are two classes of light chain: essential and regulatory. The regulatory light chain plays an important role in regulating the response to calcium sensitivity. Phosphorylation of the regulatory light chains improves calcium sensitivity (Persechini et al. 1985). These light chains are phosphorylated in response to high concentrations of Ca^{2+}. Calmodulin is a small protein in the muscle cell, which has the capacity to bind Ca^{2+}. When Ca^{2+} binds to calmodulin, this complex activates MLCK, an enzyme that phosphorylates the regulatory light chain of myosin. Phosphorylation of the regulatory light chains make the myosin head head more mobile (Levine et al. 1995). The myosin head tends to swing away from the backbone of the thick filament, bringing it closer to the actin. The proximity of the myosin head to the actin improves the probability for actin-myosin binding and crossbridge formation. The consequences of this increased mobility of the myosin heads are described in more detail in chapter 13 on history of muscle contraction.

Metabolic Relationships with Fibre-types

Red skeletal muscle fibres are associated with high capacity whereas white fibres have low aerobic capacity, but high capability. The red color is dependent on the presence of myoglobin**,** a protein similar to haemoglobin, but present in myocytes. You can probably guess that fatigueresistance relates to aerobic capacity, so slow-twitch and fast-twitchfatigue resistant motor units are red. White fibres are fatiguable. A high concentration of myoglobin is also associated with a high relative volume of mitochondria, which contributes to the high aerobic capacity of these red fibres. Mitochondria contain the enzymes responsible for aerobic replenishment of ATP. One of these enzymes, citrate synthase, has often been used to identify muscle with a high oxidative capacity.

Histochemical Identification of Fibre-types and Structural Differences

Historically, fibre-types were identified by histological treatments and staining. Histology is the study of microscopic tissue. Thin sequential slices of a muscle or biopsy of a muscle were preincubated in solutions of different then stained and inspected under a microscope. The pH of the solution affected the ability of specific isoforms of the myosin to lose or retain function. Subsequently, the slice of muscle was treated with a stain that developed only in fibres that preserved their ability to hydrolyze . As the ATP was split, the section of the slice of fibre got darker. By comparison of sequential slices of the muscle, individual fibres could be identified and classified as type I, type IIa or type IIb. In some cases, a fourth type was identified, and it was called type IIc. Only by analysis of myosin isoforms was it later demonstrated that fibres identified as Type IIc were actually hybrid fibres (type I-IIa). With the advent of fluorescence microscopy, and development of antibodies, it was further discovered that human muscle does not contain Type IIb myosin. Fibres thought to be Type IIb were actually Type IIx. There is some confusion in the research literature as this myosin isoform is sometime referred to as type IId. Histological determination of fibre type is based on myosin isoform. It is generally considered that the myosin isoforms also correspond with contractile properties. In human muscle the following myosin isoforms correspond to fibre types determined by contractile properties: type I is slow-twitch, type IIa is fast-twitchfatigue resistant and type IIx is fast-fast-twitch, fatiguable.

Sensory Receptors in Muscle

Before we consider the subcellular structures of muscle cells, the structures in muscle that detect various parameters will be presented. Sensory receptors in muscles are connected to the central nervous system byafferent neurons that travel in the peripheral nerve to close to the spinal cord where they depart from the motor nerves to enter the spinal cord via the dorsal roots. The cell bodies of these sensory neurons are located in the dorsal root bodies, just outside the spinal cord. Within the spinal cord, these sensory axons may synapse with other neurons at the same spinal level or travel up towards the brain. Motor control relies on input of some of these sensory receptors.

Muscle Spindle

Muscle spindles detect length in muscle. Muscle spindles are distributed through-out each muscle in varying density, depending on the need for length sensing. Muscles with fine motor control tend to have more spindles. The structure of a muscle spindle is illustrated in Figure 4-10.

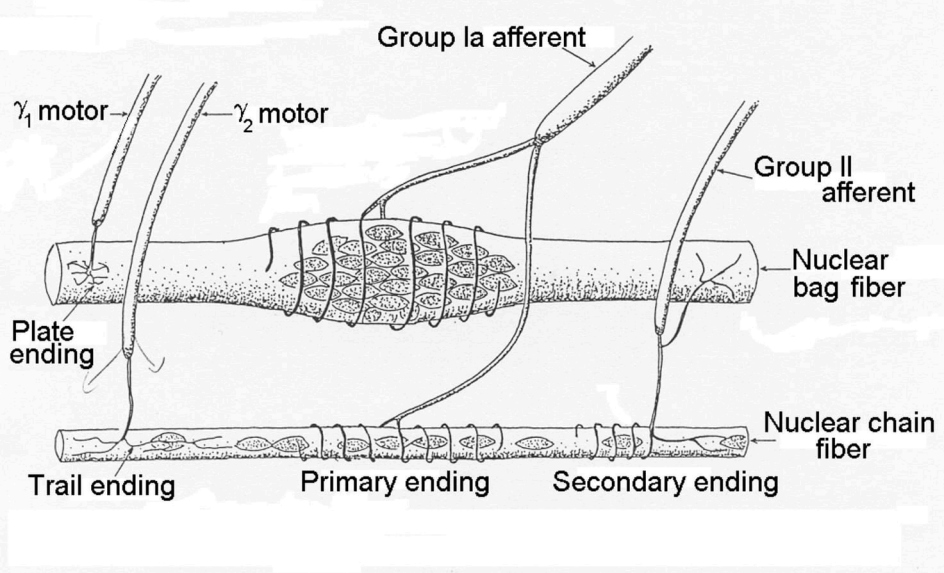


Figure 4-10 Illustrated spindle length sensor. Representative nuclear bag and nuclear chain fibres are shown, illustrating the typical innervation of these fibres. A muscle spindle will have only 1-2 nuclear bag fibres and several nuclear chain fibres. Figure from MacIntosh et al., 2006, with permission.

The cells within the spindle are called intrafusal fibres and they are either nuclear bag fibres or nuclear chain fibres. Typically, there are only one or two nuclear bag fibres and several nuclear chain fibres. It can be seen that the spindle is encapsulated and that several axons pierce the capsule. The efferent neurons are gamma motor neurons. The afferent neurons are Type Ia and Type IIa neurons that carry the signal from the intrafusal fibres to the central nervous system. The nuclear bag fibres are more important for sensing velocity of movement while the sensory chain fibres are activated in direct proportion to the length of the muscle. Afferent neurons from muscle spindles connect monosynaptically to alpha motor neurons of the same muscle, allowing a quick response to sudden stretch of the muscle. This is the response that is tested by the doctor's hammer tap on the patellar tendon.

Golgi Tendon Organ

Within the tendons, there are small free nerve endings that weave between tendon fibrils. These nerve endings are activated in a frequency dependent manner when the tenson is under strain. In this way, the brain receives information about the force of contraction. In addition to providing the brain with this information, these sensory neurons connect to the same muscle's alpha motor neurons , providing inhibitory input (Windhorst 2007).

Metaboreceptors

The term "metaboreceptors" refers to neural receptors that are sensitive to metabolic products in the interstitial space. Metabolic products include CO_2, potassium, and H+. Metaboreceptor is used for a collection of nerve endings that are sensitive to specific chemicals. It is generally thought that these receptors are sensitive to a variety of things including: oxygen, hydrogen, carbon dioxide, potassium. It is important to realize that these chemically sensitive nerve endings are located in the extracellular space. They do not detect intracellular chemical disturbance. These receptors are important for regulation of the blood flow in muscles. The ability to detect chemicals was confirmed by noting that these neurons continue to fire after muscle ends when blood flow is occluded (Piepoli et al. 1995).. Releasing the occlusion results in decrease in firing rate.

Mechanoreceptors

There are a number of receptors in each muscle that are sensitive to motion. These are mechanoreceptors or ergoreceptors (Francis et al. 1999). Not much is known about these receptors, but they probably provided the central nervous system with information about change of motion or muscle use. They adapt quickly, so firing is initiated on first use of a muscle, but declines in spite of continued These receptors are not active when the muscle ends activity.

The Skeletal Muscle Cells

Skeletal muscle cells are also called fibres or myocytes. Each fibre typically spans the distance between proximal and distal tendons. However, some long muscles have fibres arranged in series, either with a band of connective tissue, called an inscription separating bundles of fibres in series, or staggered in such a way that separations cannot easily be detected. In such long muscles, individual fibres do not extend from end to end. Skeletal muscle fibres are typically 20 to 90 µm in diameter and vary in length from a few mm to ~12 cm, depending on which muscle we are referring to. Muscles of the human body vary in size, so it is not fair to give an average number of fibres per muscle. Needless to say, the number can vary from a few thousand to several million. Although the number of fibres in a muscle can be different between individuals, the major difference between those with large muscles and those with small muscles is the diameter of individual fibres (MacDougall et al. 1984). Strength training leads to increased myocyte cross-sectional area, not an increase in number of myocytes (Alway et al. 1988).

Muscle Fibres (myocytes):

Skeletal muscle myocytes have most of the constituents that other cells of the body have: plasmalemma, nucleus (actually, several nuclei), mitochondria, endoplasmic reticulum, cytoskeleton. However, myocytes also have specialized structures associated with its special functions: contraction, force generation and mobility. Muscles have myofibrils containing contractile proteins actin and myosin as well as transverse tubules and sarcoplasmic reticulum.

Satellite Cells

Skeletal muscle also contains satellite cells, which are nonspecific cells, lying under the basement membrane of individual skeletal muscle cells. Considering that myocytes are multinucleated, it is difficult to distinguish myocyte nuclei and satellite cells, which are simple single cells containing very little cytoplasm, so they just look like myocyte nuclei. The only distinguishing feature is that satellite cells have a plasmalemma, in addition to a nuclear envelope whereas nuclei within the myocytes are surrounded only by a nuclear envelope. Satellite cells can undergo mitosis and some can become incorporated into the muscle cell during hypertrophy. This process keeps the number of nuclei per volume of muscle constant. When injury results in myocyte death, satellite cells can become myoblasts, and fuse to become new muscle cells. Since this process occurs within the basement membrane, this is a replacement process, not creation of new myocytes.

Subcellular Structure

Each myocytes is surrounded by a sarcolemma and contains a standard selection of intracellular components. In each myocyte, there will be several nuclei, a mitochondrial reticulum, sarcoplasmic reticulum, myofibrils and glycogen granules.

Sarcolemma

The sarcolemma is the membrane plus basement membrane of skeletal musclemyocytes. A unique feature of the sarcolemma is that there are periodic invaginations of the membrane called transverse tubules that allow conduction of the action potential into the cell. These structures are described below.

Plasmalemma

Like all cells of the body, the muscle fibre has a lipid bilayer cell membrane, referred to as plasmalemma. The combined plasmalemma and basement membrane of skeletal muscle is called the sarcolemma. Embedded in the sarcolemma are a variety of proteins: pumps, channels, receptors, enzymes and structural proteins that serve to strengthen the cell membrane and transfer force across the cell membrane. A unique feature of skeletal muscle is that adjacent cells are linked at recurring structures called costameres (see below).

Basement Membrane

The basement membrane, a fine mesh of glycoproteins, encircles each muscle fibre. It serves several functions. The basement membrane serves to attach the myocyte to the endomysium. At the neuromuscular junction the basement membrane tethers the enzymeacetylcholinesterase which is important for termination of activation of the myocyte. The basement membrane also

serves as a scaffolding for myocyteregeneration in the event of muscle damage. The basement membrane is also thought to be important for guiding regenerating motor axon to the end-plate region of the myocyte and regulating the formation of a nerve terminal.

Transverse Tubules

A unique feature of skeletal muscle is the regular invagination of the plasmalemma, forming tubes that go deep into the myocyte. These membrane tubes serve to transmit the surface action potential to the myofibrils that are distributed across the cell. Transverse tubules (T-tubules) occur at regular intervals along the length of the myocyte at what is referred to as the triad (two terminal cisternae and one T-tubule; see Figure 4-11). Although at the surface, the T-tubules appear as wells that go deep into the myocyte, they actually encircle each myofibril, providing a location for activation at each end of the sarcomere (frog muscle) or near each junction (mammalian muscle). The specific location of the T-tubule in mammalian muscle appears to be fixed at 500 nm from theZ-disk (Brown et al. 1998). This puts the release of calcium near the middle of the thin filaments in mammalian muscle.

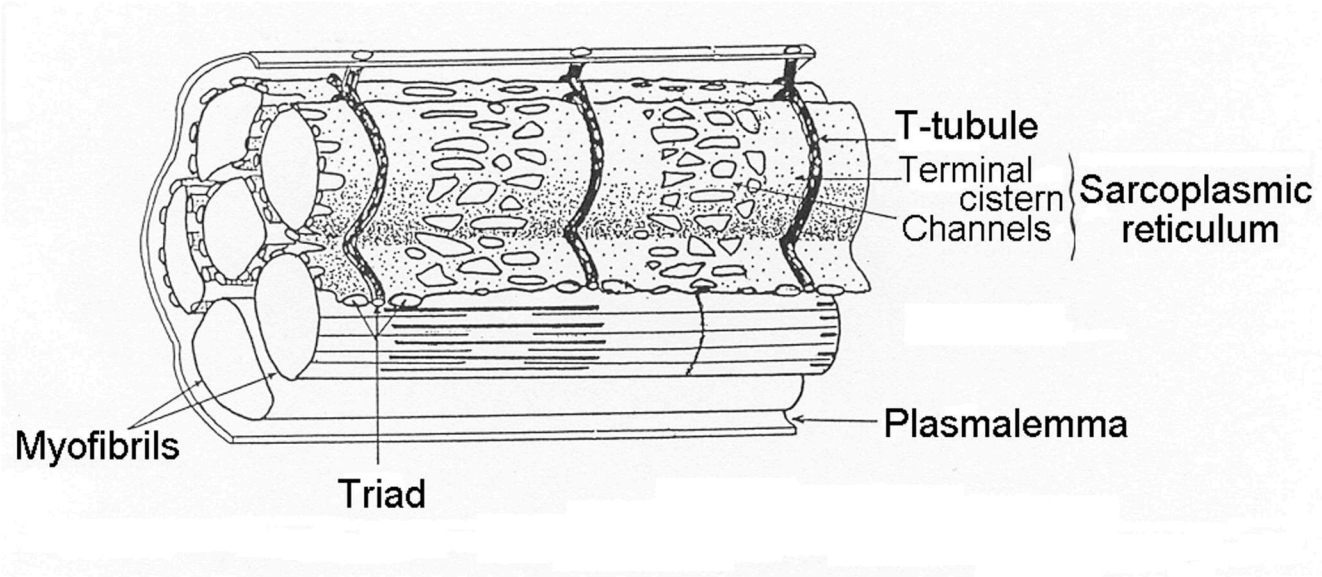


Figure 4-11 Myofibrils encircled by sarcoplasmic reticulum. The fenestrated (windows or channels) sarcoplasmic reticulum envelopes myofibrils. Transverse tubules are continuous with extracellular space and encircle the myofibrils at the ends of the thick filaments. In amphibian muscle, these T-tubules are situated at the Z-disk. The specialized sarcoplasmic reticulum adjacent to the transverse tubules is called the terminal cisternae. A triad is made up of a transverse tubule and terminal cisternae on each side. Fig from MacIntosh et al., 2006, with permission.

Cytoskeletal Proteins:

There are a number of proteins that serve the function of effectively transferring force across the membrane and of giving skeletal muscle shape and integrity. These proteins include a collection of proteins that connect the actins to the tendon through the folded plasmalemma at the ends of the myocyte, special proteins that connect to the dystroglycan complex and stiff proteins that keep things organized in the cell. These proteins are listed in Table 4-3

Table 4-3 Cytoskeletal Proteins in Skeletal Muscle

Connect Actin to Tendon	Connecting & Intermediate Proteins	Structural Proteins
actinin	Dystrophin	Actin

Connect Actin to Tendon	Connecting & Intermediate Proteins	Structural Proteins
Vinculin	Desmin	actinin
Talin	Laminin	Spectrin
Fibronectin	Vimentin	Myosin
Capping protein	Synemin	Troponin (T,I,C)
	Myomesin	Titin
	Creatine kinase	Nebulin

Myofibrils

Myofibrils are narrow tubes of contractile proteins, arranged in repeating units called sarcomeres. Each sarcomere**(**see Figure 4-12**)** spans the distance between Z-disks; a distance that can vary from about 1.6 µm to close to 4 µm as muscle changes length. Beyond 4.2 µm filament overlap no longer occurs and a sarcomere cannot generate active force through actin and myosin interaction. Each myofibril is about 1 µm in diameter and runs the full length of the muscle fibre, but can become narrow near the ends of a fusiform muscle. Titin and nebulin form a structural framework to align the filaments: actin and myosin in a highly structured myofilament lattice. Titin runs from the M-line to the Z-disk with 6 molecules of titin extending from the end of each thick filament. Nebulin runs along the thin filament, actin, and may serve as a template to limit the length of actin filaments.

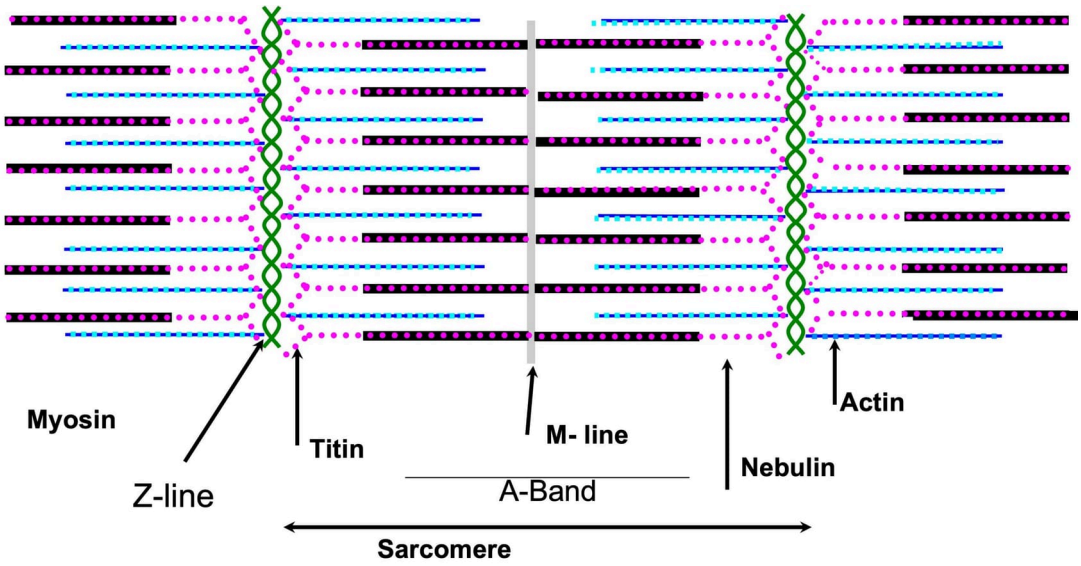


Figure 4-12 Sarcomere structure. The myofibril is composed primarily of the thick (myosin) and thin (actin) filaments with titin and nebulin associated with these, respectively. The Z-line marks the ends of each sarcomere. The M-line is in the middle of the sarcomere. The A-band is the dark band through the middle where the thick filaments are. The I-band (not labelled) is from the end of the A-band of one sarcomere to the end of the A-band of the adjacent sarcomere sarcomere; where no thick filaments are evident.

Sarcomeres: the Reason Skeletal Muscles are Striated

A sarcomere is defined by the myofibrillar unit from one Z-disk to the next (see Figure 4-12). The sarcomeres in adjacent myfibrils are connected by intermediate filaments collectively called the costamere. This connection allows the Z-disks in adjacent myofibrils to be aligned, The result is that skeletal muscle has a striped or striated pattern (see Figure 4-2 and 4-11) because the thick filament of adjacent myofibrils are lined up, giving a dark band across the myocyte. The sarcomere has been labeled for the pattern of dark and light regions of the myofibril. The m-line is the middle of the sarcomere, and the Z-line (or disk) is at each end of a sarcomere. The A-band is the dark region where the thick filaments are and the I band is where only thin filaments are present (on either side of the Z-disk). The H-zone is the middle section of the A-band where only thick filaments are present. As the sarcomere changes length, only the H and I bands change in magnitude.

Costameres Join the Myofibrils Together

There is a mesh of intermediate filaments that form the Z-disks of the myofibrils and extend between myofibrils, holding them together across the cell. This mesh is called the costamere. In fact, the intermediate filaments, including desmin, vimentin, synemin connect at the surface membrane to the dystroglycan complex, and extend into the endomysium. Adjacent cells are aligned such that sarcomeres line up not only across myofibrils within the myocyte, but between cells across the whole muscle. The result of this interconnection between myofibrils and cells with aligned sarcomeres is the striped or striated appearance characteristic of skeletal muscle.

M-Line Struts Join the Thick Filaments

The sarcomere is an amazing and complex structure that displays mirror symmetry across the middle of the sarcomere. The thick filaments which seem to be suspended in the middle of the sarcomere, share this mirror symmetry with a short bare middle region followed by rows of protruding myosin head heads on either side of the bare zone. The myosin heads can interact with actins when the muscle is activated. However, the thick filaments are not freely floating in the myofibril. They are attached through the middle by proteins at the M-line. The proteins that make up the M-line include myomesin, M-protein and ATP + Creatine" href="https://kinesiology.ucalgary.ca/maci...l-czz#creatine">creatine kinase. These proteins, along with titin which connects the thick filaments to the Z-disk, keep the thick filaments aligned in the middle of the sarcomere.

Mitochondrial Reticulum

Mitochondria serve an important function in the myocyte; they replenish by oxidative metabolism. Mitochondria are often depicted as jelly-bean shaped organelles in cells. This should not be construed as the only shape that mitochondria can have. In some cells, mitochondria are more stick-like and in skeletal muscle, particularly red skeletal muscle, the mitochondria form an elongated and apparently continuous reticulum. That is, a single cross-section of the cell does not reveal the extent of connection between mitochondria that otherwise appear to be in different regions of the cell. A careful analysis of three-dimensional structure of skeletal muscle reveals that a single mitochondrion can extend over a large volume of the muscle fibre. The proportion of muscle volume occupied by mitochondria is a function of the oxidative capacity of the muscle and can generally be related to muscle fibre-type (Alway 1991). Type I muscle fibres have about 6-9% of total volume occupied by mitochondria while Type IIa fibres have almost as much (4-7%). Type IIx fibres have the lowest volume of mitochondria with just 2-3% of their cell volume occupied by mitochondria. These values are in stark contrast with volumes of mitochondria in bumblebee flight muscle which has about 50% of total cell volume occupied by mitochondria.

Mitochondria can be described as existing in two designated regions of the myocyte: subsarcolemmal and intermyofibrillar. It is generally thought that subsarcolemmal mitochondria provideATP for transport across the sarcolemma and intermyofibrillar mitochondria provide ATP for crossbridge function and Ca^{2+} transport into the sarcoplasmic reticulum.

The mitochondrial reticulum has an inner and outer membrane, each of which is a lipid bilayer, similar to the plasmalemma. The inner membrane is folded back and forth across the reticulum, forming protrusions into the middle, called cristae (See Figure 4-13). The surface area of the inner membrane is much greater than the surface area of the outer mitochondrial membrane. This two-membrane structure divides the mitochondria into compartments; there is an intermembrane space and the mitochondrial matrix. Like the plasmalemma, there are proteins embedded in the mitochondrial membranes. These proteins areion channels and pumps as well as enzymes and transporters. Some of these proteins are presented in Table 4-4 with their location and function. The interior of the mitochondrial reticulum can be subdivided into the intermembrane space and the mitochondrial matrix. A recent review by Pfanner and colleagues presents a description of the location and function of a number of mitochondrial proteins (2019).

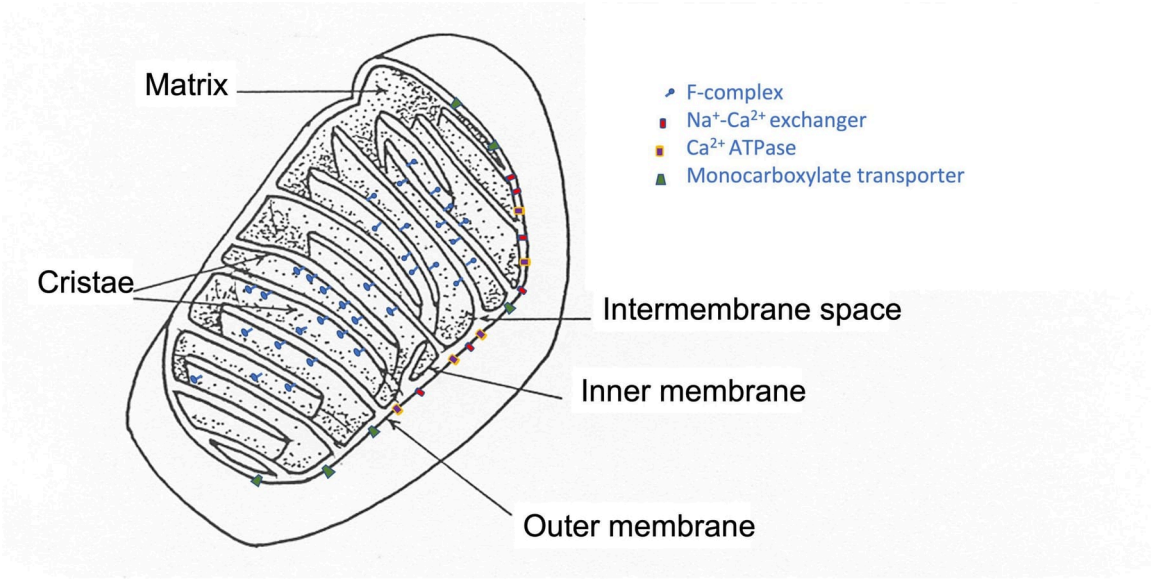


Figure 4-13 Inside a mitochondrion. The internal membrane folds back and forth, creating internal walls called cristae. Source: modified from MacIntosh et al., 2006, with permission.

Table 4-4 ***Proteins of the Mitochondria (a sampling)***

OuterMembrane	InnerMembrane	Matrix
ion transporters	Complex I-IV	TCA cycle enzymes
Protein transporters	F-Complex	
Monocarboxylate transporters	Oxidative phosphorylation	

Source: MacIntosh et al., 2006, with permission.

Mitochondria also have several unique enzymes associated with metabolism. These enzymes include the enzymes associated with the Kreb Cycle which begins with combining acetyl CoA with oxaloacetate to form citric acid, which is subsequently converted back to oxaloacetate by a sequence of reactions that result in formation of Guanosine triphosphate, CO_2 and NADH. See Chapter 6 for a list of these enzymes and the control of their function. In addition, the cytochromes associated with phosphorylation are present in the inner membrane, as is the very important F-complex, where the movement of H^+ across the inner membrane drives the production of ATP. More detail about the function of these mitochondrial proteins is presented in Chapter 6.

Although most of the proteins expressed in the mitochondria are produced from DNA in the nucleus, some mitochondrial proteins are encoded by DNA in the mitochondria.

Sarcoplasmic Reticulum

The sarcoplasmic reticulum (SR) is a membrane-bound space encircling myofibrils, and in muscle cells is a specialized version of the endoplasmic reticulum found in most cells (See Figure 4-11). The SR serves the purpose of storing Ca^{2+} ions that will be released in response to arrival of an action potential in the t-tubules. The SR makes up approximately 2% of myocyte volume; a little more in fast-fast-twitch fibres and less in slow-slow-twitch. There are three essential proteins contained in the SR that are required for the function of the SR in excitation-contraction coupling (Shishmarev 2020). The ryanodine ryanodine receptor (RYR) is a Ca^{2+} channel protein that opens on activation of the myocyte, allowing Ca^{2+} to move through the SR membrane and into the cytoplasm of the sarcomere. Calsequestrin (CASQ) is a Ca^{2+}-binding protein that buffers $[Ca^{2+}]$ in the SR and allows the SR to store large amounts of Ca^{2+} within a relatively small space. Finally, there is the Ca^{2+} pump, or Ca^{2+}ATPase which is important for transporting Ca^{2+} from the cytoplasm back to the lumen of the SR restoring the resting distribution of cytoplasmic $[Ca^{2+}]$, permitting relaxation to occur. This transport uses one molecule for each 2 Ca^{2+} ions transferred. The Ca^{2+}ATPase is also known as sarcoendoplasmic reticulum ATPase (SERCA) and there are more than ten different isoforms of this pump in the body, but two isoforms are found in the SR of skeletal muscle simply referred to as SERCA1 (in fast-twitch fibres) and SERCA2 (in slow-twitch fibres).

Longitudinal Sarcoplasmic Reticulum

As the SR wraps around each myofibril it displays, what at first glance looks like a random pattern of windows along the surface through which you can see the surrounded myofibril. Upon closer inspection these windows or fenestrations appear with a somewhat repeatable pattern, particularly over the middle part of the sarcomere.

The SR is continuous (lacks fenestrations) where it joins with the t-tubules (terminal cisterna) to form the triad and is mostly continuous where the SR stretches over the z-disk (as shown in Figure 4-11). However, between those positions on the SR large irregular oval fenestrations appear. The exact purpose of these fenestrations is not fully understood. However, they result in reduction of volume of the SR and decreases the surface available for removal of calcium via the membrane bound SERCA pumps. In mammals a pair of triads are positioned in each sarcomere about 500 nm from the T-tubule. As a result, mammalian

sarcomeres have twice as many t-tubules as amphibian muscle, and the RYR release Ca^{2+} directly over the actin and myosin myofilaments.

Terminal Cisternae

The longitudinal SR surrounding the myofibrils is bisected at regular intervals by the T-tubules. The SR in these sections exhibits several structural changes, and is referred to as the terminal cisternae although it remains continuous with the longitudinal SR. The luminal volume of the SR is greatly increased in the terminal cisternae and dotted with a series of membrane bound protein pores that give. In the terminal cisternae the SR is attached to the T-tubules through a series of membrane proteins imbedded in both the SR and T-tubules that are mechanically connected (See Figure 4-14). Dihydropyridine receptors (DHPR, also known as $Ca_V1.1$) are embedded in the t-tubule membrane and interact directly with a pair of RYRs embedded in the adjacent SR membrane through structures referred to as junctional feet, also referred to as the junctional membrane complex (JMC). There is a small gap between the DHPR's in the t-tubules and RYR that are embedded in the membrane of the SR and it is into this space that calcium ions are released from the lumen of the SR into the cytosol of the myofibril through the RYR upon activation by action potential.

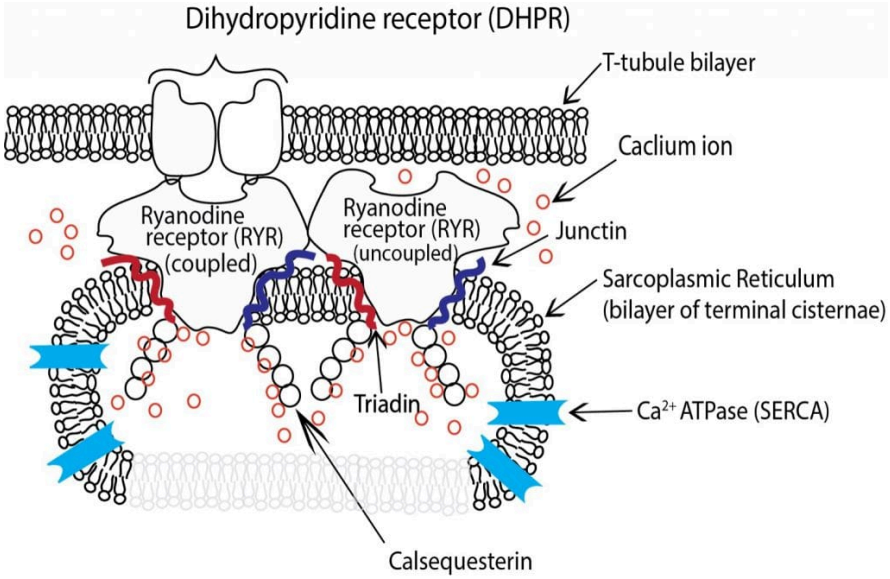


Figure 4-14 The Calcium release site of the transverse tubule. The dihydropyridine receptor embedded in the wall of the t-tubule connects to one of the ryanodine receptor pairs embedded in the wall of the sarcoplasmic reticulum. Figure by Barbara Holash

Junctional feet

The junctional feet in skeletal muscle are composed of several junctophilin proteins. Junctophilin 1 is the specific proteinisoform that tethers the t-tubule to the DHPR and along with the II-III loop on the DHPR forms the electromechanical link that couples the DHPR to one RYR of each pair to control calcium release from the SR (Landstrom et al. 2014). It has been demonstrated that in situations of prolonged and high calcium concentration that the calcium activated protease calpain can be activated by the prolonged high concentrations of calcium and sever the JMH1 connection between the SR and t-tubules disrupting the triad (Murphy et al. 2013) dramatically reducing the ability of the SR to release calcium in response to further activation.

Accessory Proteins in the Sarcoplasmic Reticulum

Calsequestrin

Calsequestrin (CASQ) is a protein found in the lumen of the SR (See Figure 4-14) primarily in the junctional SR, near the transverse tubule. CASQ binds calcium and facilitates calcium storage at high concentrations. In humans there are two isoforms of CASQ. CASQ I is the isoform found in skeletal muscle and CASQ II is the isoform found in the heart. In skeletal muscle each CASQ molecule can bind up to 80 calcium ions depending upon how it is configured (Sanchez et al. 2012). At free [Ca^{2+}] below 100μM CASQ is found as a monomer, whereas at higher [Ca^{2+}] CASQ polymerises, first into dimers, then into a chainlike structure,

binding more Ca^{2+} progressively. The binding of Ca^{2+} with CASQ allow the relatively small lumen of the SR to store calcium in concentrations up to 20 mM when the free concentration is about 1 mM.

Triadin & Junctin

In the lumen of the SR two additional proteins, triadin and junctin are associated with the RYR and play vital roles in Ca^{2+} handling and release (see Figure 4-14). Both junctin and triadin are concentrated on the luminal side of the SR membrane but have sections that extend to the cytosolic side. Triadin and junctin are located beside the RYR and both interact with CASQ to localize it near the luminal pore of the RYR.

Fine tuning of Calcium Release During Contraction

While the action potential is the primary signal that determines the open or closed state of the RYR. The open or closed state of the RYR is further modulated by the binding and interaction of ligands, both directly and through intermediary proteins such as ATP,ADP, CaM, CASQ, Triadin and Junctin. These ligands bind to either the cytosolic and luminal side of the RYR and alter its action. These interactions are complex, and our understanding of their influence on the behaviour of the RYR continues to evolve. The most common of these ligands, with the best-established influence on the opening probability of the RYR are listed in Table 4-5. While these ligands seldom override the direct control of the DHPR they do influence both the opening probability (OP) and duration which RYR are opened or closed during activation.

Table 4-5 Binding ligands that alter the Opening Probability (OP) of the RYR

Increased OP	Increase or decrease OP depending on concentration	Decreased OP
ATP	Ryanodine	FKBP12
Caffeine	Ca^{2+}	Dantrolene
S100A1	DHPR II-III loop-STAC3	Mg^{2+}
APOCaM	cAMP	Ruthenium red
CaMKII		CaM+Ca^{2+}
Triadin+CASQ		Junctin+CASQ

Acronyms: adenosine; S100A1 is a modulating protein with Ca^{2+} binding properties; APOCaM is a primary form of calmodulin another Ca^{2+} binding molecule; CaMKII is calmodulin activated kinase II, an enzyme that is activated by binding calmodulin; CASQ is calsequestrin; DHPR II-II loop-STAC3 is the luminal loop of the dihydropyridine receptor with STAC3, a modulating protein, bound to it; cAMP cyclic adenosine monophosphate; FKBP12 is a small protein that is essential for ryanodine receptor function; CaM is calmodulin a small molecule that binds Ca^{2+} and in the bound state is responsible for activation of a number of enzymes.

Glycogen Granules

Glucose is stored in muscle in the form of polymers where individual glucose molecules are joined together with phosphate. The binding point of glucose is either 1-5 or 1-6 binding. This combination of binding allows branching of the glucose chain, which allows more glucose units in a given volume of cytoplasm.

Insulin Transporter Rafts: Glut4

The transporter molecule for moving glucose across the sarcolemma is known as GLUT4. This transporter is normally found inside the cell, where it cannot transport glucose. GLUT4 is stored in a form referred to as a raft, where several transporter molecules are bound together. Activation of the transporter by insulin or by increased intracellular [Ca^{2+}] results in translocation of the raft to the sarcolemma where the GLUT4 molecules are inserted into the membrane. Here, they can transport glucose from the extracellular space into the myocyte.

Nuclei

The nucleus is an organelle that is the control centre of the cell; it controls protein expression and synthesis. Skeletal muscle myocytes, because they are so long, are multinucleated. The volume of the myocyte under the control of a single nucleus, which is called the myonuclear domain, is reasonably constant. As the cell grows by hypertrophy, nuclei are added and with atrophy, nuclei are removed (Ross et al. 2018). There is no evidence that skeletal muscle nuclei can divide to produce more nuclei. It is thought that satellite cells, located between the plasmalemma and the basement membrane divide and donate nuclei to the myocyte to keep the cell volume per nucleus relatively constant.

Membranes and Envelopes

Each nucleus is surrounded by a membrane called the nuclear envelope. The nucleus contains the chromosomes, which are made up of the genes for protein. A specialized structure within the nucleus is the nucleolus which regulates ribosome assembly.

DNA

DNA (deoxyribonucleic acid) is the molecule that contains the code for synthesis of proteins in the body. DNA is composed of nucleotides: cytosine, guanine, adenine and thymine.

Molecular Control and Protein Synthesis

Chapter 14 describes the control of protein from the perspective of cell signaling to turn on specific genes. This process serves to regulate which proteins are expressed in the cell as well as how much of the protein will be synthesized. The genes that encode the sequence of amino acids for a given protein are stored in the nucleus. Cell signaling activates the gene, causing transcription which forms a messenger RNA (mRNA). This mRNA is transported out of the nucleus to the ribosome where it serves as a template for protein. Newly synthesized proteins can be moved to where they are needed. Posttranslational regulation of proteins will alter their activity. This regulation can include adding phosphate group(s) to the protein, cleaving a portion or other modifications that allow change in the function of the protein.

Protein synthesis can occur to replace proteins that are already in the myocyte, to increase the amount of a protein or to change the isoform of the protein that is currently in the myocyte. Each protein in a cell has a typical time for which it “survives” in the cell. Protein turnover helps to keep the cell alive and functional by getting rid of old proteins, replacing them with newly synthesized molecules. The half-life of individual proteins (time over which half the molecules of that protein are replaced) varies considerably from days to years.

Proteins of Skeletal Muscle

There is a multitude of additional proteins found in skeletal muscle. The majority of these proteins can be categorized as follows: motor proteins, channels, pumps and transporters, enzymes, and structural proteins. Some of the key proteins in each of these categories will be described below.

Sarcomeric Proteins

The sarcomere is the fundamental contractile structure. Sarcomeres are placed end-to-end along the length of each myofibril. A sarcomere is the structure from one Z-disk to the next one, including thick and thin filaments, nebulin, titin, and M-band proteins.

Thick Filaments

The thick filaments are suspended in the middle of the sarcomere and normally situated equidistance from the Z-disks at ether end. The thick filament is mainly composed of myosin and long thin protein strands of titin that are continuous with the thick filament and extend from the ends of the thick filament to the Z-disks on either side.

Myosin the Molecular Motor

Myosin is a superfamily of motor proteins, serving several functions in living creatures. Myosin 2 is the class of myosin that serves the contractile function in skeletal muscle. Each myosin molecule is composed of heavy meromyosin and light meromyosin. The light meromyosin comprises much of the long strand of myosin that forms the thick filament. Heavy meromyosin constitutes the S1 and S2 segments of myosin. Each myosin molecule is formed by two identical halves with the light meromyosin wound together in a helix and the heavy meromyosin free from the thick filament. In mammalian and amphibian muscles, the thick filaments are 1.6 m long (see Figure 4-15). Half of the myosin molecules are oriented in one direction and half are in the other direction. The S2 segment is about 40 nm long and the S1 segment, which contains the actin-binding site and the nucleotide binding site is about 19 nm long.

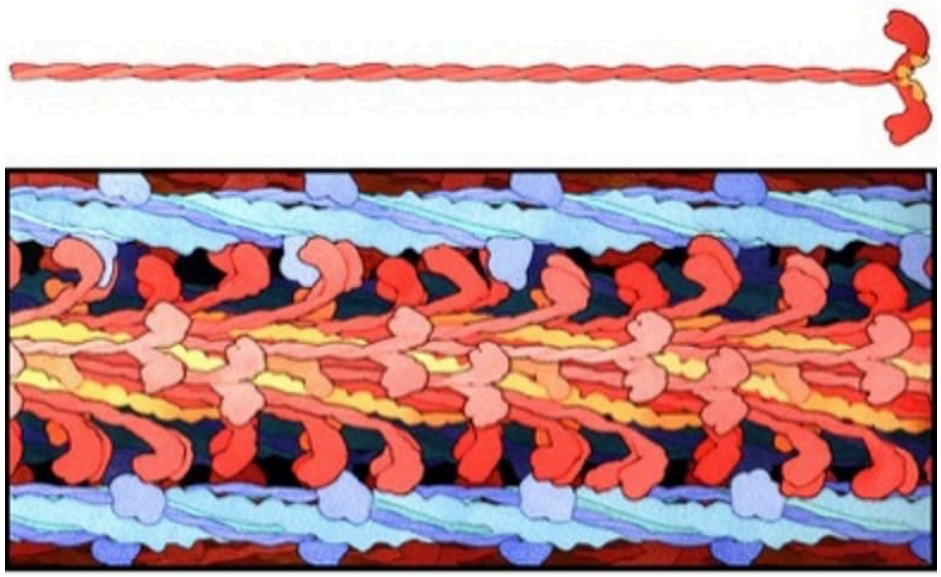


Figure 4-15 Myosin molecules and myofilaments combined to form thick filament. Above is a myosin molecule with long strand and globular heads (2 heads per molecule). In the compound image below, the myosin molecules are packed together to form the thick filament in yellow and orange (titin is not shown). The thin filaments are shown in blue. Each thick filament is surrounded by 6 thin filaments.(Image from the Protein Data Bank, Goodsell, 2001, doi: 10.2210/rcsb_pdb/mom_2001_6, licensed under CC BY 4.0 License)

Myosin S1 head

Each S1 head (see Figure 4-16) has an essential light chain and a regulatory light chain (also known as myosin light chain or MLC). The essential light chains interact with actin, facilitating ATPase activity (Sitbon et al. 2019). The regulatory light chains can be phosphorylated MLC-kinase and this phosphorylation results in increased Ca^{2+} sensitivity (Sweeney et al. 1993). Further discussion of this property is presented in Chapter 13.

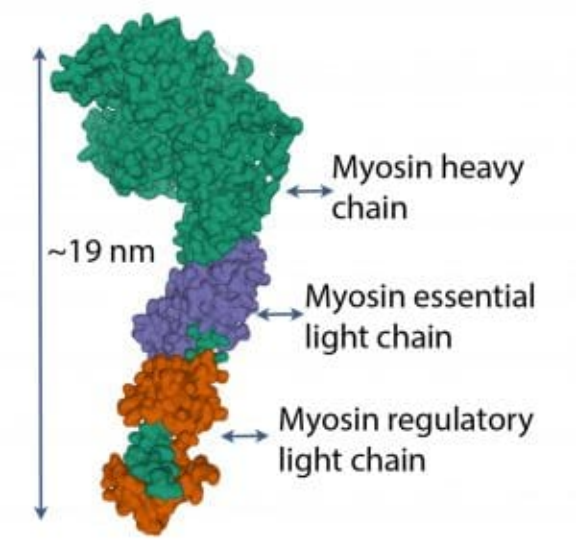


Figure 4-16 Myosin S1 protein head with protein chain locations indicated. Image of 1KK8 from Himmel, D. M. et al.,(2002), Created with Mol* Viewer {Sehnal, 2021 #19520)

Titin

Titin (previously called connectin) is very large protein, with lengths greater than 1 µm in human skeletal muscle, that is an integral part of the thick filament structure. Titin is the third most abundant protein in skeletal muscle; actin and myosin are more abundant (by mass). As titin connects the z-disk to the m-line in the sarcomere, forming the core of the thick filament (See Figure 4-17). Six strands of titin are associated with every thick myosin filament. The 6 titin strands that protrude from the myosin are each connected to one of the 6 surrounding thin filaments at the z-disk.

It has long been recognized that titin contributes to the passive force, that is the force maintained by the structure of the passive muscle, as opposed to the force created by a metabolic process such as actin-myosin–ATPase, during muscle (Joumaa et al. 2008; Maruyama et al. 1981). In this role it is considered to work like a passive spring. There is a growing amount of evidence that titin can and will change stiffness when the PVEK regions interact with calcium and increases the number of folds in the protein in those sections changing the passive force during subsequent stretch (DuVall et al. 2013). More recently, titin has been proposed as playing a role in residual force enhancement (Herzog 2018), although there is still much debate about the exact mechanism of the process.

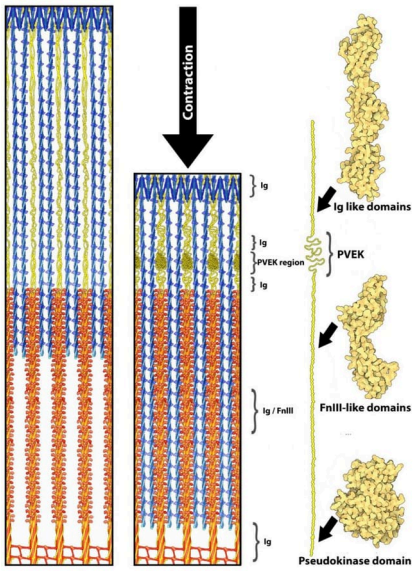


Figure 4-17 An illustration of the continuous nature of the titin, protein and thick filament. With further separation of the titin protein including the Ig like domain,PVEK region, FnIII like domain, and Pseudokinase domain. (Image from the Protein Data Bank, Goodsell, 2001, doi: 10.2210/rcsb_pdb/mom_2001_6, licensed under CC BY 4.0 License)

Thin Filaments

The thin filaments are composed of actin and nebulin and contain the regulatory proteins: troponin and tropomyosin. Thin filaments vary in length from 1 µm in amphibian skeletal muscle to 1.3 µm in human skeletal muscle. The length of the thin filament affects the relationship between sarcomere length and active force generated by the muscle (see Chapter 5). Thin filaments also have the regulatory proteins, troponin and tropomyosin associated with them. Each tropomyosin spans 7 actin monomers and has one troponin complex associated with it. The troponin complex is comprised of troponin I, troponin C and troponin T. Troponin C is the subunit that binds Ca^{2+} to initiate contraction.

Actin

Globular or G-actin is a small protein that polymerizes to form microfilaments. Each G-actin is about 6 nm in diameter (see Figure 4-18). The microfilaments of actin are important for two purposes: i) primary protein of the thin filaments in sarcomeres of muscle and ii) they form part of the cytoskeleton, contributing to the structure of the myocyte.

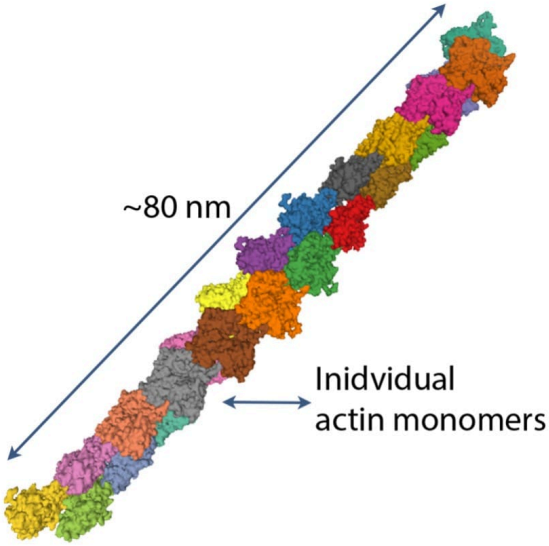


Figure 4-18 Actin filament segment. The actin is composed two strands of individual globular actin proteins wrapped in a helical spiral. The helical rotation twists each actin 180° per 7 globular actin Image of RMVY from (Paul et al. 2017), Created with Mol* Viewer (Sehnal et al. 2021).

Nebulin

Nebulin is a filamentous protein that binds to actin as it winds along the thin filament. It is not known for sure what the exact roles of nebulin are in the sarcomere, but nebulin has been proposed to play a role in guiding the synthesis of the thin filament.

Regulatory Proteins, Troponin and Tropomyosin

Without the regulatory proteins, troponin and tropomyosin, actin–myosin interaction would proceed randomly, without control. Muscles would always be contracting, and energy needs would be extremely high. This type of energy demand actually occurs during an episode of malignant hyperthermia, a situation where Ca^{2+} is spontaneously released from the sarcoplasmic reticulum in response to a volatile anesthetic, halothane. Halothane is no longer used in the operating room, because the heat generated from activated muscles of sensitive individuals was lethal.

Tropomyosin is a short filamentous protein that lies in the groove of the helix of f-actin, spanning a segment that is 7 actin monomers long (see Figure 4-19). When tropomyosin is lying in the groove in this way, it obstructs the interaction of the S1 head of myosin with actin. The troponin complex binds to tropomyosinand to actin.

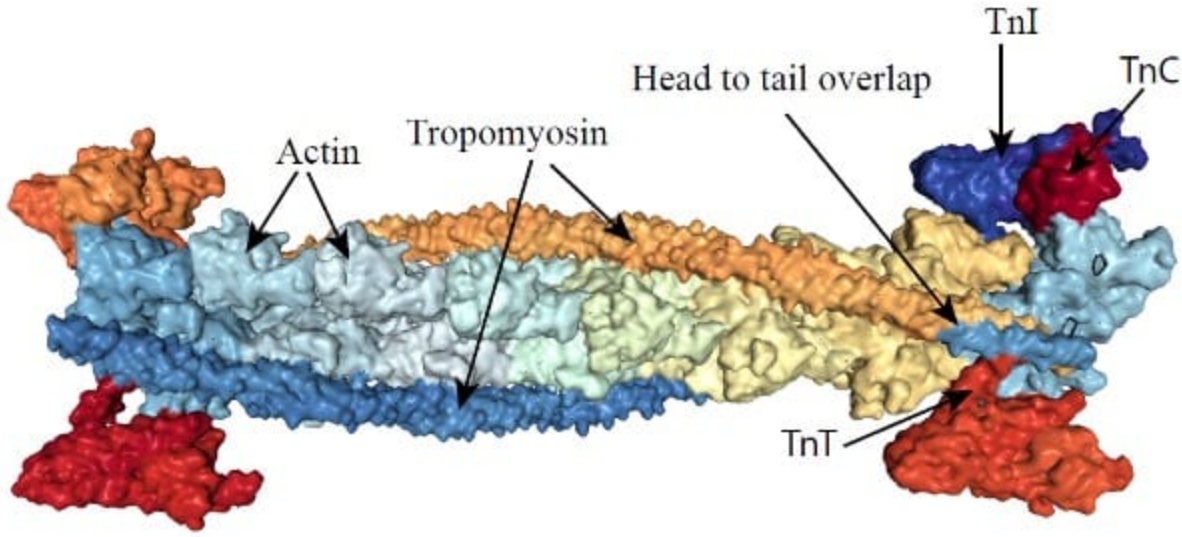


Figure 4-19 An actin encircled by two tropomyosin filaments, displaying 2 troponin-c and troponin-I complexes (one per tropomyosin strand). The actin is in the calcium bound state (calcium is bound to the troponin-C). Image of RMVY from (Paul et al. 2017), Created with Mol* Viewer (Sehnal et al. 2021).

Troponin is a complex of 3 smaller proteins. Troponin-T binds troponin to actin. Troponin-I combine tropomyosin filaments and hold them in the groove of the actin, inhibiting interaction of actin with myosin. Troponin-C is a calcium-binding protein, similar to calmodulin. When Ca^{2+} binds to troponin–C, the arrangement of the three troponins will change, resulting in the movement of tropomyosin out of the groove between the actin strands, revealing the myosin binding sites on the exposed actin molecules. This interaction and the consequences of it are further described in Chapter 5.

Enzymes

Enzymes. Catalyze reactions, allowing the reactions to proceed much faster than would otherwise be the case. There are several categories of enzymes that are prevalent in skeletal muscle including: kinases, synthases, dehydrogenases, and phosphatases. Some of these will be dealt with later in the appropriate chapters.

Receptors

Receptor proteins are embedded in lipid bilayer membranes. In skeletal muscle, membranes that contain receptor proteins include: plasmalemma, mitochondria, and sarcoplasmic reticulum. One of the major functions of receptor proteins is the transfer of information. For example, hormones will bind to their specific receptor proteins to effect a change in the target cell. Several hormones have specific binding proteins in the sarcolemma: insulin, epinephrine, thyroxin, testosterone, estrogen, growth hormone and others. In each case, a specific proteinreceptor is embedded in the membrane and this receptor may be linked to a series of additional proteins that function to translate the signal of a change in hormone concentration.

Channels and Pumps

Skeletal muscle membranes contain a number of channels and pumps (transporters). Channels allow the movement of ions down their concentration gradient and transporters move substances across the membrane with or against a concentration gradient. Channels have special structural features including gates, pores and binding sites. Gates allow opening and closing of the pore. The pore is an open space that allows movement of specific ions through the membrane. Restricting the passage of other ions is accomplished by a series of charged amino acids that are referred to as the selectivity filter. Some examples of channels and pumps are presented below. In addition to these channels and pumps, there are several additional transport proteins embedded in the membranes of the myocyte.

Voltage dependent Sodium Channel

The voltage dependent sodium channel in the sarcolemma allows Na^+ to move down it's concentration gradient into the myocyte during activation. This channel is activated by a depolarization of the sarcolemma to about -50 mV and closes when membrane potential depolarizes to +30 mV. This channel is somewhat unique in that it contains two gates (parts of the molecule that obstruct the pore). One of these gates is open in the resting state and the other one is closed. The closed one will open on depolarization to -50mV and the other will close to inactivate the channel at +30mV. Resetting to a state that can be activated requires closure of the open gate and opening of the closed one.

Voltage Dependent Potassium Channel

The voltage dependent potassium channel is just as important as the voltage dependent sodium channel. The voltage dependent potassium channel opens at a similar membrane voltage as the voltage dependent sodium channel, but movement of K^+ through the channel out of the myocyte is initially very slow because the electrochemical gradient does not favour movement of K^+. Once the action potential causes depolarization, and the Na^+ channel closes, the movement of K^+ out of the myocyte will repolarize the membrane. This channel closes when the membrane potential reaches -70 mV.

Potassium-ATP Channel

The potassium ATP channel (K_{ATP}) is a unique channel that may be involved in regulating activation of muscle when energy charge is challenged (MacIntosh et al. 2012). This K^+ channel is regulated by [ATP], making it a sensor of the energy charge in skeletal muscle. Binding of ATP to the channel will close the channel, so when [ATP] falls, resulting in less binding, the K_{ATP} channel will open. Opening the channel makes the membrane more permeable to K^+. This increased permeability will cause the action potential to be of smaller magnitude, resulting in a smaller magnitude of activation (less Ca^{2+} release).

Dihydropyridine Receptor (Cav1.1)

The skeletal muscle dihydropyridine dihydropyridine receptor (DHPR) is a specialized Ca^{2+} channel that exists at high density in the transverse-tubules where they are linked to ryanodine receptors (See Figure 4-14). The movement of Ca^{2+} through these channels is not necessary for activation of the myocyte. This is because the DHPR detects a voltage change in the plasmalemma and opens the ryanodine in response.

Ryanodine Receptor

The ryanodine ryanodine receptor (RYR) gets its name from the fact that ryanodine binds to this receptor at very low concentration, locking the receptor in the open configuration. The RYR are very large protein channels (> 2.2 MDa) that are found in the terminal cisternae of the SR (see Figure 4-14). The RYR are formed through the interlocking of four repeating protein structures (see Figure 4-20). The resulting physical channel formed by the four interlocking proteins opens and closes to allow or prevent the passage of Ca^{2+} based on the structural arrangement of the four proteins. The RYR is opened during the action potential by direct mechanical link to the DHPR. The RYR remains open very briefly as a high cytoplasmic [Ca^{2+}] causes the channel to close. There are three isoforms of the RYR found in the human body with RYR 1 being the isoform found in skeletal muscle. Every second RYR 1 is connected to a voltage sensitive DHPR embedded in the in the membrane of the adjacent transverse-tubule (See Figure 4-15) (Nelson et al. 2013).

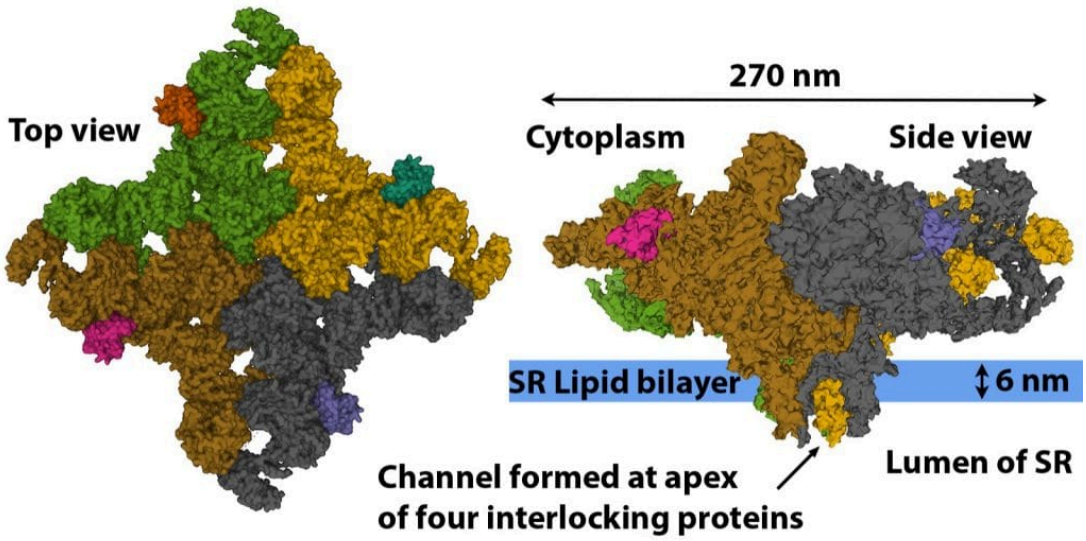


Figure 4-20 Ryanodine receptor channel protein complex. The channel is formed with four subunits, viewed from above on the left and in cross-section on the right. The pore of the channel is formed where the four units come together. Image 5T15 from des Georges, A. et al. (2016), Created with Mol* Viewer (Sehnal et al. 2021).

Sodium-Potassium ATPase

The sodium potassium ATPase (Na^+–K^+ATPase) is an important ion pump in the sarcolemma of both neurons and myocytes. These cells allow communication by propagation of action potential during which there is a loss of cellular K^+ and accumulation of intracellular Na^+. Recovery to the normal resting state is accomplished in part by the action of these ion pumps.

Sarcoendoplasmic reticulum calcium ATPase (SERCA)

Following activation of a myocyte, when Ca^{2+} has been released into the cytoplasm, it must be returned to the sarcoplasmic reticulum to allow relaxation. This transport of Ca^{2+} out of the cytoplasm is accomplished by a Ca^{2+}ATPase known as SERCA. This transporter moves 2 ions of Ca^{2+} for each ATP used. It has been estimated that the energy cost of transporting Ca^{2+} back into the SR can account for about 30% of the energy cost of an isometric muscle contraction.

Human skeletal muscles contain two isoforms of the SERCAprotein, which are uniquely associated with each muscle fibre type. Somewhat confusingly SERCA1 proteins are associated with type II muscle fibres whereas SERCA2 proteins are associated with Type I muscle fibres. While the different isoforms of SERCA function in nearly identical fashion, pumping 2 Ca^{2+} across the membrane for every molecule of ATP used, their calcium sensitivity, transport speed, and density in the SR are distinct between the two isoforms.

The density and sensitivity of the two isoforms of SERCA are aligned with the activity and morphology of the types of muscle fibres they are associated with. The SERCA2 in the slower type I fibres are more sensitive to calcium concentration and reach their peak activity at lower [Ca^{2+}] (~pCa 6.8) than SERCA1 in the faster type II fibres (pCa 6.6) (Lamboley et al. 2014). Also, within type II fibres, the density of SERCA1 is more than double that of the SERCA2 in the type I muscle fibres (Lombardi et al 2014).

SERCA pumps are effective in maintaining a very low resting [Ca^{2+}] of ~50nM and reducing [Ca^{2+}] after muscular activation. Lombardi et al. 2014 calculated that human SERCA from the vastus lateralis muscle have a maximum Ca^{2+} removal rates of roughly 0.9 mmol per litre per second, which would allow the muscle to completely relax in less than 0.25 of a second. It should be noted though that estimates of SERCA rates in exclusively IIx fibres are substantially higher.

SERCA contributes to the use of ATPduring muscle contraction—

The required abundance and density of SERCA proteins in the SR combined with their high activity rates make the SERCA pumps

a significant energy consumer during muscle contraction. This means SERCA pumps are a main contributor to heat production during muscle activity. Even at rest SERCA pumps within the muscle are actively pumping Ca^{2+} out of the cytosol and back into the SR to combat leak of Ca^{2+} from the SR. While this leak rate is low in humans it was measured as ~6 and ~4 µmol per litre per second in human type I and type II fibres (Lombardi et al 2014). The continual activity of the SERCA pumps is thought to help contribute to the maintenance of body temperature.

Summary

Our muscles give our body shape and the structures of muscle allow the many functions to be achieved. Muscles can be long or short, wide or narrow. Muscles are composed of connective tissue and myocytes. The myocyte generate force and shorten and the connective tissue allows transfer of force laterally and to the bones of our skeleton. Muscle cells are organized either in line with the action of the muscle (parallel fibred, or fusiform) or at some angle relative to the line of action (pinnate). Muscle cells (also called fibres or myocytes) are organized into units referred to as motor units where each motor unit is a single motoneuron and all of the myocytes that cell innervates. Motor units can be small with just a few myocytes, or very large with thousands of myocytes. Individual myocytes have the common parts that all cells of the body have: nucleus (several per cell), mitochondria, cytoskeleton, ribosomes and endoplasmic reticulum. Unique to muscle cells, they have myofibrils, or tubes composed of sarcomeres, repeating structures containing the contractile proteins, actin and myosin. The neuromuscular junction serves the important purpose of translating an activation signal from the motoneuron to activation of the myocyte. The neuromuscular junction includes the nerve terminal, and the end-plate of the myocyte as well as the gap between these two. The endplate is folded allowing increased membrane surface area, where large numbers of acetylcholine receptors are embedded. Muscles also have specialized sensors that serve to inform the central nervous system of the length, force and metabolic circumstances at any given time. The most elaborate of these sensors is the spindle which is composed of several intrafusal muscle fibres and has bothafferent and efferent innervation. Muscles also have several proteins, many of which are unique to contractile tissue. Generally, proteins can be categorized as: channels, pumps, receptors, enzymes, binding proteins and structural proteins. Additionally, muscles have motor proteins to allow them to generate force and movement.

Highlight Features- Research

For this research highlight, we turn to a classic paper, published in the early 70's. Burke and colleagues (Burke, 1973) experimented on anesthetized cats to investigate the contractile properties of motor units and established the nomenclature for assessment of fibre-types. They isolated the nerve of the gastrocnemius muscle and stimulated individual axons with an intracellular electrode. They discovered that the contractile properties of the motor units could be classified as three fibre-types: slow-twitch (S), fast-twitch fatigue resistant (FFR) and fast-twitch fatiguable (FF). Two properties in particular were consistent and valuable in identifying these fibre-types. The first of these properties was sag. When FF and FFR units were stimulated for 1 s with trains of pulses at subfusion frequencies, eliciting an incompletely fused tetanic contraction, they observed sag. Force would reach a peak early in the stimulation, then decrease, or sag, before the stimulation stopped. This sag or decrease in force was not evident when S motor units were stimulated in this way. The authors then stimulated the axon with a 330 ms train of pulses at 40 Hz, repeated every second. Some units (FF) decreased in force very quickly while other units (FFR and S) were slow to decline in force. A fatigue index was calculated. Fatigue index was calculated as the end active force divided by the initial active force. It was found that when the fatigue index was less than 0.25, motor units were FF. The fatigue index of FFR units was above 0.75. S units had a fatigue index of 0.9 or greater. When the axon of a motor unit was stimulated with a single pulse, eliciting a twitch, slow-twitch motor units had a long time to peak, and fast-twitch motor units had a short time to peak. However, this feature was not as useful as the properties described above for separating the 3 classifications of fibre-type. Note that a small percentage of units could not be classified with the fatigue index and presence of sag. It could be that these difficult units were hybrid motor units.

For some units, histochemical evaluation was completed. First, these units were stimulated for a long time to deplete the glycogen. Then the muscle was quick frozen to preserve it. Then, sequential slices were obtained, so individual fibres could be identified in sequential slices. Slices of the muscle were chemically treated to "stain" under certain circumstances. First, these slices were used to identify the individual fibres of the stimulated motor unit. This was done by staining for glycogen. The fibres belonging to the stimulated motor unit had very little glycogen, so they stained very pale in comparison to unstimulated fibres. The authors also performed histological assessment for the presence of enzymes in the aerobic pathways (succinyl dehydrogenase) and anaerobic pathway (lactate dehydrogenase). When staining for succinyl dehydrogenase the darkest fibres were in the S units and FFR units were almost as dark, while this stain was pale in the

FF units. When staining for lactate dehydrogenase, the darkest fibres were FF units and FFR units were almost as dark. S units stained less. This research article includes additional contractile and histochemical properties of motor units of the cat gastrocnemius muscle. Read the article to find out more about these fibre-type properties.

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Dr. Brian MacIntosh obtained his undergraduate degree in Human Kinetics at the University of Guelph in 1975. He completed his PhD in 1979 at the University of Florida in Medical Sciences under the supervision of Dr. Wendell Stainsby. After a brief postdoctoral fellowship at Queens University in the Dept of Physiology, he held faculty positions at Concordia University (1980-1986), University of Saskatchewan (1986-1989) and the University of Calgary (1989-2019). He is now retired, but still pursuing research as Professor Emeritus. During his career, Dr. MacIntosh published articles on a variety of topics: skeletal musclefatigue, activity dependent potentiation, atrophy, running economy, force-velocity properties and power output.

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Key Terms

tendon, aponeurosis, inscription, fascicle, myocyte, motor unit, connective tissue, sarcomere, cytoskeleton, myofilament, myofibril, sarcoplasmic reticulum, channels, ion pumps , transverse tubules, neuromuscular junction, end-plate, triad, terminal cisternae

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2.3: Chapter 5 - Skeletal Muscle Contraction

Chapter 5: Skeletal Muscle Contraction

Brian R MacIntosh



Photo 5-1 Young man body building. Photo by patrisyu from freedigitalphotos.net

Learning Objectives

After studying this Chapter, you should be able to:

- Explain the sliding filament theory of muscle contraction
- Explain how the cross-bridge theory works
- Describe the process of excitation-contraction coupling
- Compare action potentials of muscle and nerve
- Explain the aspects of muscle contraction that dictate energy cost
- Describe the location and function of various calcium handling proteins in muscle
- Draw a diagram illustrating the activation of muscle including calcium handling
- Describe the relationship between frequency of activation and summation of force
- Describe the relationship between frequency of activation and calcium concentration
- Draw graphs and explain the fundamental properties of skeletal muscle, including:
  - force-pCa^{2+}-relationship
  - moment-angle relationship
  - moment-angular velocity relationship
  - force-length relationship
  - force-frequency relationship
  - length dependence of force development
  - force-velocity relationship
  - force-power relationship and power-velocity relationship

Key Terms

filament, active force, Ca^{2+} sensitivity, calcium transient, cross-bridge theory, receptor, dynamometer, electromyography, endocytosis, exocytosis, fixed end contraction, force-frequency relationship, force-length relationship, force-pCa^{2+} relationship, force-velocity relationship, in vitro, in vivo, isometric contraction, length dependent activation, motor unit, muscle contraction, myosin filament, myosin head, optimal length, passive force, pCa^{2+}, stroke, power-velocity relationship, ryanodine receptor, sarcoplasmic reticulum, SERCA, sliding filament theory, summation, terminal cisternae, tetanic contraction, transverse tubule, tropomyosin, troponin, twitch contraction, ultrasound imaging, weak and strong-binding

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CaseStudy:Isokinetic Muscle Function Test

Julia has been recruited to be a subject in a research study at the University of Winnipeg. Part of the study requires that she be tested on a Biodex to determine her moment-angular velocity relationship. This is analogous to the force-velocity relationship but expresses the relationship between joint and angular velocity rather than the linear force-velocity relationship. Julia has been given strict instructions on her activity and diet leading into the test session. She is not to engage in anyvigorousphysical activity for 24 hours prior to the testing and she is to eat only a light breakfast at least 2 hours before her testing session at 11:00 AM.

Procedures During Julia's Biodex Test

On her arrival at the laboratory, Julia has electromyographic electrodes placed on the skin of her right leg. Application of these electrodes requires careful skin preparation (the area is shaved, then lightly abraded with sandpaper, cleaned with an alcohol swab, then the self-adhesive electrodes are applied once the skin has dried).EMG electrodes are typically applied in pairs with alignment in the direction of the underlying muscle fibres. The muscle fibre direction can be confirmed with ultrasound, though in most cases investigators will know the approximate alignment of fibres. Julia has electrodes placed on her biceps femoris, rectus femoris, vastus lateralis, and vastus medialis. A ground or common electrode is placed on her patella. She is allowed to warm-up for 15 min on a cycle ergometer, then she rests for 10 minutes. Julia is then strapped to the Biodex chair (hips, chest, and thigh straps) and range of motion is assessed by passive movement of the knee from full flexion to full extension. The chair limits knee flexion beyond 90 degrees and full extension means the knee comes to 180 degrees. Julia is given an emergency switch to use if the machine moves her leg to an uncomfortable position.

Julia is instructed to practice with submaximal effort at a variety of angular velocities. It feels strange to do these muscle contraction**s** because the speed of movement is restricted by the Biodex. When Julia pushes harder, she notices that the machine does not move faster. When the machine is set to higher speeds, Julia has difficulty maintaining effort because the lever arm moves so quickly. This is her second time using this machine and it still feels strange.

Data collection for this study requires Julia to perform maximal effort isometric (fixed-end) contractions at each of several joint angles, in random order. These contractions allow formulation of the relationship between and joint angle, analogous to the force-length relationship**.** Each contraction lasts 4-5 seconds with 4 min between sequential contractions to minimize fatigue. Following this, she is given 10 minute rest before maximal effort contractions are obtained at each of 8 angular velocities, again in random order. These contractions allow determination of the moment-angular velocity relationship. By the time Julia has finished the series of contractions**,** her leg muscles feel worn out.

In Figure 5-1, Julia's results for the second series of contractions are presented. Here, the torque generated at the knee during extension at a variety of angular velocities is presented. The relationship is nearly linear, but a slight curve can be detected. Note that the maximal velocity in this figure is 5 $rad{\cdot}s^{-1}$. Clearly, the knee joint can be extended at a faster angular velocity, but measurement of the moment during these movements is challenging. Tihanyi and colleagues (1982) overcame this obstacle by creating their own equipment to measure the relationship between moment and angular velocity at high relative angular velocities and found that the maximal rate of knee extension should be 14-18 $rad{\cdot}s^{-1}$. The subjects for this study were high and long jumpers.

Figure 5-2 presents the power-angular velocity relationship for Julia's tests. Here, it can be seen that power is low when angular velocity is low and rises to a peak around 4 $rad{\cdot}s^{-1}$. When the angular velocity is higher than this, power decreases. It is known that power is zero when angular velocity is zero and when torque is zero.



Photo 5-2 Using a Biodex to test muscle contractile properties. Courtesy of the University of Calgary.

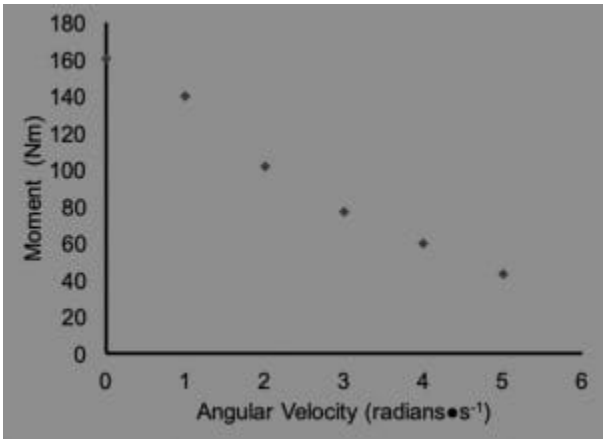


Figure 5-1 Moment-Angular Velocity Relationship. Peak at each angular velocity is plotted, showing the slightly curvilinear relationship typically obtained when maximal effort is applied to a variety of fixed angular velocities. Note that the isometric condition (0 angular velocity) does not quite fit the pattern of the other measures.

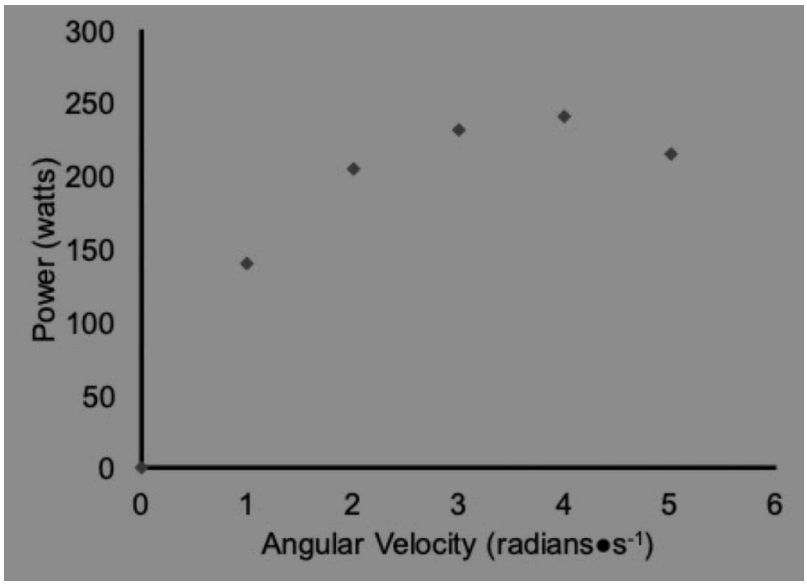


Figure 5-2 Power-angular velocity relationship. Power is the product of velocity and force. When velocity is angular velocity, measured in rad·s-1 and force is measured in Nm, the product is in watts.

Overview

Now, it is time to see how our muscles function. Muscle has a pretty simple function; it either contracts or it relaxes. Muscle contraction is the process of turning on and generating force which, if the load is not too great, allows motion. Alternatively, if the load can overcome the force generated by the muscle, lengthening will occur. Without muscle contraction, we are immobile lumps of tissue. Muscle can be stretched passively to permit range of motion, contract without length change to hold position or maintain posture and can shorten or elongate while contracting to achieve motion or slow the rate of movement.

Imagine that you do not know much about the structure of muscle. This is necessary to grasp that in the early 50's we did not have a good understanding of how muscle worked. In this chapter, before the mechanism of contraction in skeletal muscle is described, the early understanding of muscle is presented. Following this, a couple of long-standing yet perhaps incomplete theories are presented. Following this, the energy requiring processes are described. It is important to understand that although muscle contraction is a simple biochemical reaction between proteins **,** this reaction cannot occur without the use of chemical energy, in the form of adenosine triphosphate**(**ATP**)**. ATP is the universal form of chemical energy used through-out the body.

Regulating the contraction of muscle is important. We can voluntarily turn muscle on and choose to stop activation and allow muscle to relax. This process of turning muscle on and off requires the interaction of the nervous system and in particular the motor pathways of the central nervous system and the motor neurons of the peripheral nervous system. Action potentials on the motor axons travel to individual muscle fibres, activating them to contract. At the neuromuscular junction, nerve terminal activation is transferred to muscle activation and a sequence of events referred to as excitation-contraction coupling is initiated. This sequence results in turning on muscle contraction. There is no â€œoffâ€ switch for muscle. Relaxation is initiated by stopping activation.

Our muscles are called "skeletal muscle" for a very good reason. In most cases, the skeletal muscles are connected at both ends to tendon that connects the muscle to bone. Our muscles function by exerting force against the bones, allowing movement, grasping, or posture. Adjacent bones form joints where motion occurs, so muscles exert a about the joint axis. A moment is a force exerted at some distance from the axis of rotation, resulting in the tendency for rotational motion. The moment about a joint is the force of contraction multiplied by the motor arm, the perpendicular distance from the centre of rotation of the joint to the line of action of the muscle-tendon unit (see Figure 5-3).

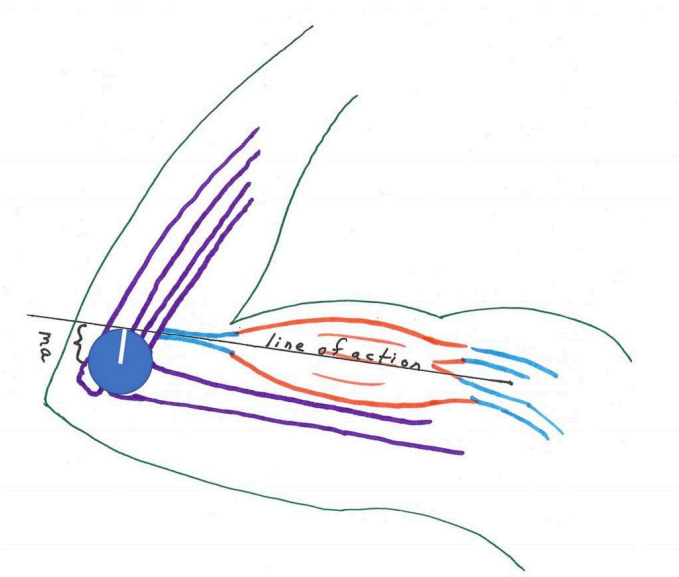


Figure 5-3 Moment arm for biceps muscle. The line of action is shown, following the direction of force application of the biceps muscle. The arm (ma) is the perpendicular distance between the joint centre of rotation and the line of action of the muscle.

When muscle contracts, it can either generate force without length change, or generate force while changing length. The maximal force generated while not changing length is greatest at a middle length and is less at longer or shorter lengths. This is called the force-length relationship. When muscle shortens, the force decreases as velocity increases. This is called the force-velocity relationship. These properties of muscle are typically studied with maximal activation, but a graded muscle response is possible. The force of contraction of individual motor units can be graded by activation of motor units at progressively faster frequency of activation. This relates to the force-frequency relationship, which is actually dependent on the force-calcium relationship. The frequency of activation dictates the concentration of Ca^{2+} in the myoplasm; a higher frequency results in higher concentration of Ca^{2+}. In addition to changing force by changing the frequency of activation (called rate coding), force can be graded by recruitment of more or fewer motor units.

Muscle is considered a “plastic” tissue; it has plasticity or adaptability. Muscle adapts to the demands we place on it. Muscles become stronger when we use them in more forceful movements and become less fatiguable when we use them often for endurance type exercise. Muscle also adapts in a negative manner, becoming smaller and weaker when we do not use them for forceful contractions and becoming less resistant to fatigue when we use them less often.

Astronauts can get by with minimal contraction of their muscles, so space travel results in atrophy unless countermeasures are taken.

The ories of Muscle Contraction

Early Theories of Muscle C ontraction

Before we knew about the microscopic structure of muscle, it was difficult to explain how muscle contracted. The microscopic structure was just beginning to be understood in the mid 1950’s. So, when AV Hill proposed a new theory of muscle contraction in 1925, he was literally treating the muscle like a “black box” and trying to understand how it worked, based on observations he and others had made. At the time a dominant theory of muscle contraction was the surface tension theory. Although not clearly worked out, the general idea was that muscle contraction had something to do with surface tension; the tension generated at the surface between two substances generated by molecular interactions of like molecules unable to interact with the neighboring substance. Hill, who had conducted several experiments with isolated muscle as well as intact human subjects performing exercise, pointed out that surface tension decreases with increased temperature, but muscle force increases with increased temperature. However, he also pointed out that lactic acid was produced in proportion to force, even as temperature changed, so if lactic acid was involved in the surface tension generation, then it might be feasible.

Hill calculated the amount of lactic acid formed during a twitch contraction and estimated the surface of a “tube” of lactic acid formed within the muscle. His estimate of the surface tension thus created was way too small to account for the tension generated

by the muscle. Therefore, he rejected the surface tension theory and proposed an alternative theory.

An Alternative Theory of Muscle C ontraction

Hill was not satisfied to simply reject the current theory and not provide an alternative, so he formulated a potential mechanism for muscle contraction that he thought could generate the necessary force. His proposal included protein tubes with negative charge and clouds of positively charged ions around them. This alternating negative and positive charge would behave like an electronic condenser. The liberation of lactic acid somehow resulted in formation of sodium lactate and corresponding discharge of the condenser (Hill, 1928), allowing collapse of the system (shortening). This theory was certainly interesting, and creative, but had very little in terms of experimental support. A more generally accepted theory of contraction was that protein folding along the length of the fibre resulted in contraction. This also proved to be wrong. It was careful evaluation of microscopic images of muscle at different lengths that lead to the current theory of muscle contraction**,** the sliding filament theory.

Sliding Filament Theory of Muscle Contraction

In the mid 50's of the 20th Century, two Huxleys simultaneously proposed a theory of muscle contraction that has persisted to the current time (H. E. Huxley & Hanson, 1954). This theory dictates that striated muscle is structured in such a way that thick and thin filaments interdigitate longitudinally in intricately organized structures called sarcomeres. The middle of the sarcomere has parallel thick filaments that do not change in length as muscle length changes. Both ends of the sarcomere have thin filament**s** attached and projecting towards the middle, with some overlap of the thick and thin filaments. Thin filaments also do not change length when muscle shortens or is stretched.

Muscle changes length by interdigitation of thick **(**myosin**)** and thin (actin) filaments. The thin filaments slide past the thick filament**s** towards the middle of the sarcomere (see Figure 5-4). This is kind of like pushing two hairbrushes together, but with a double-sided hair brush in the middle, representing the myosin matrix. However, the sarcomere is much more organized than the hair-brushes would be (see Chapter 4 on Muscle Structure). The sliding filament theory of muscle contraction did not explain how this sliding occurred but did explain how length change was accomplished. The cross-bridge theory was needed to provide an explanation for force generation. The sliding filament theory, and cross-bridge theory, though not without contradiction (Pollack, 1983), are still generally accepted.

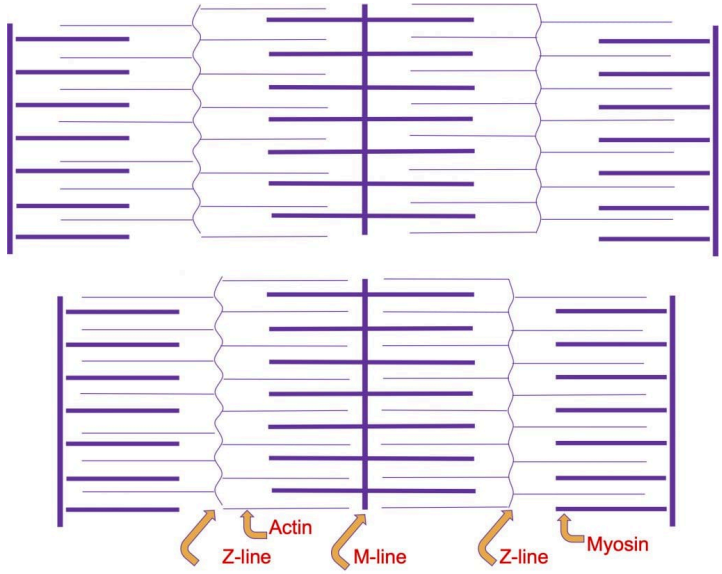


Figure 5-4 Interdigitating filaments allow muscle length change without proteins changing length. The top image shows a longer sarcomere length. On the lower image, the outer Z-lines have been moved inward toward the centre M-line allowing muscle shortening. Note that actin and myosin filaments have not changed length.

C ross-Bridge Theory of Muscle Contraction

In 1957, AF Huxley proposed his theory of muscle contraction that has come to be known as the cross-bridge theory of muscle contraction (A. F. Huxley, 1957). His elegant description of this theory provided an acceptable explanation for many of the known

contractile and energetics properties of muscle. He proposed that during contraction, force is generated by projections or side-pieces of the thick filament that form cross-bridges to the thin filaments. We now recognize that these side-pieces are myosin heads and although the cross-bridge cycle is much better understood now, Huxley's description and formulation of the cross-bridge theory is still accepted today. This theory and a description of the cross-bridge cycle follows.

The cross-bridge theory is based on the idea that myosin heads have some mobility about their attachment site on the thick filament. In the neutral position, the myosin head is not very likely to attach to actin, the adjacent thin filament. The probability of attaching to (this probability is denoted as f) and generating force is greater at some distance from the attachment site (towards theZ-disk). This function of the myosin head probably relates well with the notion that partial hydrolysis of results in a cocking of the myosin head, putting it in a position where it is more likely to attach to actin. It was proposed that each myosin head would function independently. Once the cross-bridge has been formed, there is a probability of detachment (denoted by g), and that probability rises to a high level if sliding of the thin filament relative to the thick filament is accomplished and the attachment site slides past the equilibrium point of the myosin head. Huxley also presented the idea that activation of contraction probably had something to do with making the binding sites on the thin filament available for binding with myosin. Without this availability, cross-bridge formation would not occur. This aspect of muscle control is further described below as part of excitation-contraction coupling. First, however, we will address the energy requiring processes associated with muscle contraction.

Energy Requiring Processes

The energy for muscle contraction comes from chemical energy in the terminal phosphate bond of ATP. The enzymes that are necessary for transducing the chemical energy to other forms of energy in muscle are classified as ATPase. Any form of ATPase will hydrolyze ATP, releasing the energy otherwise stored in the terminal phosphate bond, yieldingADP and inorganic phosphate (Pi). In particular, 3 such enzymes can account for most of the energy required during muscle contraction:actin-myosin-ATPase, sarcoendoplasmic reticulum ATPase (SERCA), and sodium-potassium ATPase (Na^+K^+ATPase). Each of these enzymes will now be discussed.



Photo 5.2. Leonardo da Vinci was known for finding clever ways to convert energy Photo by Brian MacIntosh.

Actin-M yosin ATPase

The cross-bridge cycle (described below) is a series of reactions between the myosin head and the filament. This series of reactions involves, first of all, the free head of the myosin molecule partially hydrolyzing and using the energy to reconfigure to a structure referred to as the "cocked" or primed position. This configuration is considered a high-energy structure. When Ca^{2+} binds to troponin–C, the binding site on actin becomes exposed and the myosin head can bind to the actin filament. This binding is initially a weak binding, but the binding triggers the release of Pi, and the system transitions to a strong-binding configuration. The strong-binding state is also the stroke phase of the cross-bridge cycle. This transition generates force or movement and releases the energy that was originally in the ATP molecule. The cross-bridge cycle can generate work and also releases energy as heat. Each cycle of a cross-bridge uses one ATP molecule. Actin-myosin ATPase uses the majority of energy associated with

muscle contraction.

SERCA

The pump that is responsible for maintaining intracellular [Ca^{2+}] at a very low level (<90 nM) is also known as the sarcoendoplasmic reticulumCa^{2+}ATPase (SERCA). This pump is known as a uniporter because it transfers just one kind of ion (Ca^{2+}) across a membrane in one direction. The density of SERCA on the surface of the sarcoplasmic reticulum is so high that there is little room for other proteins in this fenestrated organelle. Like most ion pumps, the energy needed to pump Ca^{2+} across the sarcoplasmic reticulum membrane is provided by ATP. For each hydrolyzed by this pump, two Ca^{2+} ions are transferred into the sarcoplasmic reticulum. The energy cost of transporting Ca^{2+} can account for up to 30% of the energy cost of muscle contraction. See the research highlight near the end of this chapter to see how this is experimentally determined. Any time ATP is split, there is some energy released as heat. This fact can explain the condition known as malignant hyperthermia (Gronert, 1980). Certain agents like halothane, a volatile anesthetic, can trigger widespread leak of Ca^{2+} from the sarcoplasmic reticulum, activating the SERCA and triggering actin-myosin ATPase activity. Due to the large rate of ion pumping throughout the body and cross-bridge cycling, and corresponding heat release, body temperature can rise to lethal levels. In spite of the fact that an antidote is available, halothane is no longer used for general anesthesia.

Sodium – Potassium ATPase

With each activation of a skeletal muscle fibre, some Na^+ is transferred into the myocyte and some K^+ is lost to the extracellular fluid. This ion transfer occurs through voltage-gated channels that briefly open, allowing Na^+ and K^+ to move down their electrochemical gradients. An increase in extracellular [K^+] activates the Na+K+ATPase, and is hydrolyzed to provide the energy for ion pumping. This pump can transfer 3 Na^+ ions and 2 K^+ ions with each molecule of ATP hydrolyzed. The amount of ATP used by the Na^+-K^+ pump can account for up to 10% of the total energy cost of a muscle contraction.

Now that you understand the processes that require energy, it is time to learn how muscle is turned on. As we talk about the process of excitation-contraction coupling (E-CC), it is important to realize that these processes are initiated at all neuromuscular junctions where action potentials have been propagated. This could be very few in a small muscle that is not activated very vigorously, or literally millions of muscle fibres in a large leg muscle that is activated very vigorously.

Excitation-Contraction Coupling

Our muscles are organized in motor units; each fibre is activated by a single motoneuron. Muscles are activated by descending motor pathways that excite the motor nerves of a given muscle in the ventral horn of the spinal cord. Each cell body and the corresponding dendrites will have literally thousands of excitatory and inhibitory nerve endings contributing to or inhibition of the axon hillock, the location of the nerve cell body where the action potential originates. If the axon hillock reachesthreshold, sodium and potassium channels will open and an action potential will be generated and propagated along the axon. Motor neurons are myelinated and conduction velocity is very fast (90-110 ms^{-1}). When an action potential gets to the nerve terminals, the activation is transmitted to the muscle fibre by neuromuscular transmission, a process that results in generation of an action potential on the surface membrane of the muscle fibre, for each action potential arriving at the nerve terminal. The process of activating a skeletal muscle fibre, which includes several steps from generation and propagation of the action potential to mechanical engagement of myosin cross-bridges is a complex process, which will be described after the description of the process involved in neuromuscular transmission.

Neuromuscular Transmission

The process of neuromuscular transmission involves several steps from arrival of the action potential at the nerve terminal to generation of an action potential on the muscle membrane. It is important to realize that these steps will occur at all terminals of the same motoneuron, thereby simultaneously activating all muscle fibres of the motor unit. The number of fibres associated with each motor unit can vary from 10 or so to thousands. Each step in the process of neuromuscular transmission is described below.

Voltage- G ated Calcium Channels

Depolarization of the nerve terminal membrane with arrival of the action potential results in activation (opening) of a few voltage-gated Ca^{2+} channels. These channels open and allow Ca^{2+} to diffuse down its concentration gradient into the nerve terminal from the extracellular space. The result of just a few of these channels opening is that just a “puff” of Ca^{2+} comes into the nerve terminal, near each activated Ca^{2+} channel. This “puff” of Ca^{2+} is sufficient to trigger a sequence of events that result in emptying of a few vesicles into thesynaptic cleft at each neuromuscular junction.

Fusion of Docked Vesicles

Vesicles within the nerve terminal contain acetylcholine. These vesicles are distributed such that some are freely floating throughout the nerve terminal, some are tethered close to the membrane across from the muscle and some are docked in this region. Vesicles have specialized proteins in their membrane that react with other specialized proteins in the nerve terminal membrane. Docking of the vesicle in this region is achieved by interaction of these special proteins. The local increase in $[Ca^{2+}]$ results in Ca^{2+} binding to one of these proteins that is part of the complex of proteins docking a synaptic vesicle to the nerve terminal membrane. This binding of Ca^{2+} triggers the fusion process; the vesicle membrane becomes nerve terminal membrane (exocytosis), essentially turning inside out and releasing acetylcholine into the synaptic cleft (see Figure 5-5). In a remarkable process of recycling, the membrane that was vesicle but is now part of the nerve terminal membrane can be reused to create a new vesicle. This preserves the specialized proteins needed in the vesicle membrane. The process of reforming the vesicle is called endocytosis.

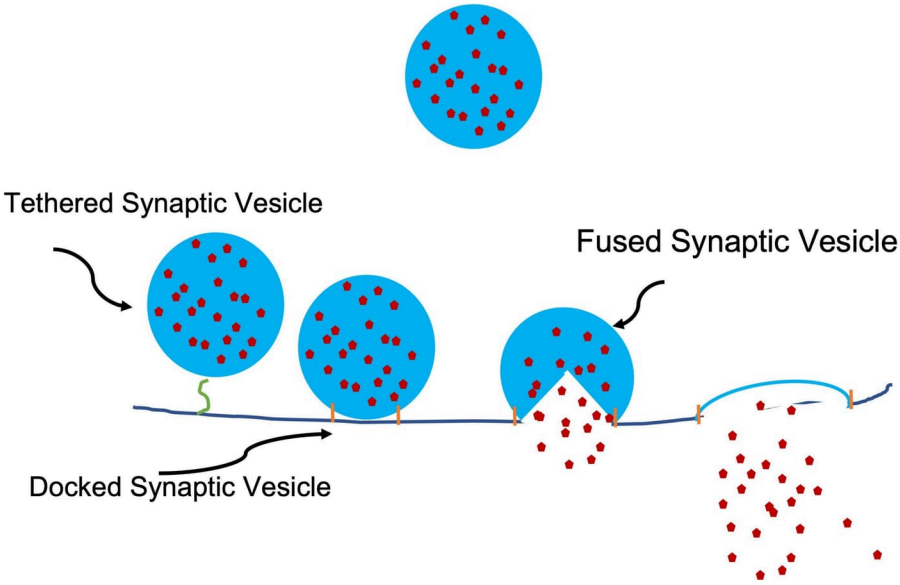


Figure 5.5 Exocytotic extrusion of acetylcholine into primary and secondary synaptic clefts at the neuromuscular junction. Vesicles are shown in sequential states: free vesicle (above), tethered vesicle, held near the nerve terminal membrane; docked vesicle, held to the membrane with specialized proteins; fused vesicle, emptying contents into the synaptic cleft and integration of the vesicle membrane with the nerve terminal membrane.

Binding of Acetylcholine to its Receptors

Acetylcholine is the neurotransmitter of the neuromuscular junction. Once acetylcholine is released, it diffuses across the primarysynaptic cleft and into the secondary synaptic clefts. On the postsynaptic membrane, there are specialized receptors for binding acetylcholine. In spite of the fact that only a few Ca^{2+} channels respond to depolarization of the nerve terminal, more than enough acetylcholine is released into the synaptic cleft to cause depolarization of the muscle end-plate region tothreshold, resulting in generation of a muscle fibre action potential. This depolarization results from opening of a in the acetylcholinereceptor that allows both Na^+ and K^+ to move across. Due to the fact that the electrochemical gradient for Na^+ is stronger than for K^+, more Na^+ moves across the membrane than K^+ and this causes depolarization**.** Once the depolarization reaches about -50 mV, voltage-gated Na^+ and K^+ channels open. These are the channels that are responsible for propagation of

the action potential across the muscle membrane, spreading in all directions from the neuromuscular junction.

Destruction of Acetylcholine Terminates Neuromuscular Transmission

The neuromuscular junction gap is very confined. Acetylcholine diffuses in this confined area, and is captured by an enzyme "acetylcholinesterase" that splits acetate from the choline. Acetylcholinesterase is tethered to the basement membrane in the end-plate region. As the acetylcholine is split, its concentration will decrease and acetylcholine will be released from its receptor on the muscle surface. This terminates activation of the muscle. Nearly all of the acetylcholine that is released is deactivated by acetylcholinesterase; very little escapes to the surrounding area. Again, the neuromuscular junction has a fabulous recycling program. The choline is transported back into the nerve terminal where it is used to resynthesize new acetylcholine. The recycled vesicles are resupplied with new acetylcholine.

Muscle Membrane Response

An action potential is generated on the muscle plasmalemma, similar to the action potential on an axon. Membrane voltage quickly changes from -85 mV to +20 mV then repolarizes to the normal resting membrane potential. For each axon action potential, there is a muscle fibre action potential that is propagated over the surface membrane of the myocyte at a rate of 2-5 $m \cdot s^{-1}$. This is quite slow in comparison with a motor axon conduction velocity (~100 $m \cdot s^{-1}$). The action potential is also conducted into the muscle fibre via the transverse-tubules. The transverse tubules are continuations of extracellular environment into the muscle fibres and encircle the myofibrils. The transverse-tubules are located at regular intervals along the muscle fibre, allowing activation of each sarcomere near the A-I junction. It appears that the transverse-tubules stay approximately 500 nm from theZ-disk as sarcomere length changes (Brown & Loeb, 1999).

There is no energy cost linked directly to the generation and propagation of the action potential**.** The ions Na^+ and K^+ move down their electrochemical gradient when the voltage-gated channels open. However, to preserve the ion concentration gradients, it is necessary to pump these ions back to where they originated; Na^+ is pumped out of the myocyte and K^+ is returned from the extracellular space to the cytoplasm. This active transport is achieved by Na^+K^+ATPase, a transporter that uses energy from to transfer 3 Na^+ and 2 K^+ with hydrolysis of each ATP molecule.

Internal Membrane Potentials

The transverse-tubules are continuations of the sarcolemma that go deep into the myocyte**,** encircling the myofibrils about 500 nm from the Z-disk. The surface action potential is propagated into the transverse-tubules. In addition to the Na^+ and K^+ channels in the sarcolemma of the transverse-tubules, this membrane also has receptors **(**DHPR**)** which function as voltage detectors. DHPR are actually modified Ca^{2+} channels, that do not require Ca^{2+} to go through them to serve the function of activating skeletal muscle. Half of the DHPR are linked directly to ryanodine receptors **(**RYR**)** which are actually embedded in the membrane of the terminal cisternae, the enlarged portion of the sarcoplasmic reticulum that lies adjacent to the transverse-tubule. The proximity of the terminal cisternae on either side of the transverse-tubule in cell cross-sections as a repeating structure of three membrane bound structures has been given the name of "triad". This structure is evident in Figure 5-6 where the grey ryanodine receptors are adjacent to the transverse tubule.

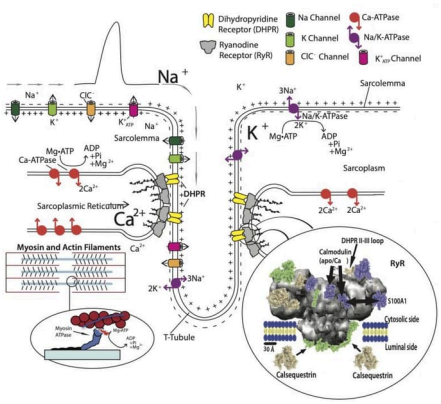


Figure 5-6 Excitation-Contraction Coupling. This diagram illustrates the essential steps in activating a muscle cell: 1. Action potential generation and propagation down the transverse tubules; 2. Detection of T-tubule depolarization by the receptor; 3. Opening of the ryanodine receptor; 4. Diffusion of Ca2+ out of the terminal cisternae into the myoplasm; 5. Binding of Ca2+ to troponin C; 6. Translocation of tropomyosin, revealing the myosin binding sites on actin, allowing cross-bridge cycling; and 7. Ca2+ pumping by SERCA back into the sarcoplasmic reticulum. Source: Diagram created by Barbara Holash, for "Skeletal muscle – regulation of excitation-contraction coupling to avoid metabolic catastrophe" in J Cell Science 125: 2105-2114, 2012. Used with permission of the authors.

Calcium Handling in the Muscle Cell

When the DHPR detects the membrane potential change associated with the action potential, they trigger the opening of the RYR to allow Ca^{2+} to move down its concentration gradient from the terminal cisternae into the sarcoplasm. Although this event (Ca^{2+} release) is happening at the sarcomere level of a myofibril, this occurs throughout the myocyte as the action potential is moving across the surface membrane and into all of the transverse tubules**.** The amount of Ca^{2+} released from the sarcoplasmic reticulum with each activation (action potential) is sufficient to raise the myoplasmic [Ca^{2+}] from the resting value of 70 nM to 200 µM. However, the actual increase in free [Ca^{2+}] with a single release event like this is less than 1 µM. The reason for this huge discrepancy is that much of the released Ca^{2+} binds immediately to a number of Ca^{2+} buffers in the myoplasm. These buffers include: ATP, calmodulin, SERCA, parvalbumin, and troponin**–**C.

The rise and fall of [Ca^{2+}] in the myoplasm is called the calcium transient. In response to a single activation, this calcium transient is very brief; it is over in a few milliseconds. However, when several activations occur in quick succession, the cumulation of calcium transients can result in a sustained elevation of [Ca^{2+}].

The buffering of Ca^{2+} by these molecules often has subsequent consequences. For example, binding of Ca^{2+} to calmodulin activates a number of enzymes, like myosin light chain kinase. This topic is further discussed in the chapter on Repetitive Contractions (see Chapter 12). Binding of Ca^{2+} to SERCA,results in transfer of Ca^{2+} into the sarcoplasmic reticulum, allowing further binding of Ca^{2+} and decreasing myoplasmic [Ca^{2+}]. Binding of Ca^{2+} to troponin-C is the event that activates muscle contraction**.**

Troponin and T ropomyosin

Troponin-C is a Ca^{2+}-binding protein**,** part of the troponin complex (Troponin-C, -I, and -T) associated with tropomyosin and the thin filament of the sarcomere (see Figure 5-7). The thin filament is composed mostly of actin. Each tropomyosin molecule spans 7 filaments, lying over the myosin-binding site. This position blocks binding of myosin to actin. Binding of Ca^{2+} to troponin-C causes a realignment of this protein complex such that tropomyosin is pulled out of the groove between the two strands, exposing the binding site for myosin on actin**.** This allows the crossbridge cycle to be initiated. The crossbridge cycle will continue as long

as Ca^{2+} is bound to troponin-C.

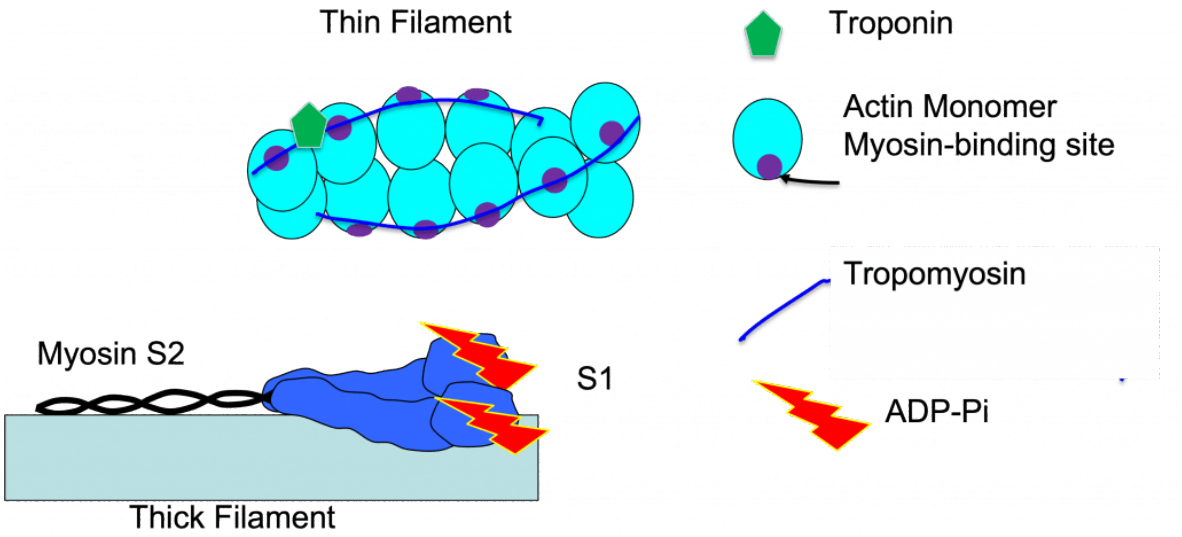


Figure 5-7 Structure of the thick and thin filaments; composed of and myosin. The thin filament is composed of two strands of sequential actin monomers with tropomyosin spanning 7 actin monomers, blocking the myosin-binding sites. Each myosin molecule is composed of a double-strand S2 segment and two S1 heads, each with ATPase function.

Crossbridge Cycle

The exposure of the binding site for myosin on the filament permits binding of the myosin head to actin, creating a crossbridge. The initial binding of the myosin head to actin is considered a weak-binding state. Once the crossbridge is formed, Pi is ejected from the myosin head and this reaction allows change to the strong-binding state. This transition is also called the power-stroke. The crossbridge maintains this force generating position until it disengages. Disengagement of the crossbridge results from the probability of dissociation (g), which increases to a high level if length change is associated with this crossbridge activity. This letting go requires release ofADP and binding of a molecule of . The binding of ATP to the myosin head allows disengagement of the crossbridge. The free myosin head now partially splits ATP to ADPPi. This partial splitting causes a structural rearrangement of the myosin head to the cocked position, a structure that can undergo the stroke, once it is again bound to actin. If the binding site on the actin filament is still available, this now cocked myosin head can bind and undergo another cycle. Cycling of the crossbridge will continue as long as Ca^{2+} is bound to troponin-C. See Figure 5-8.

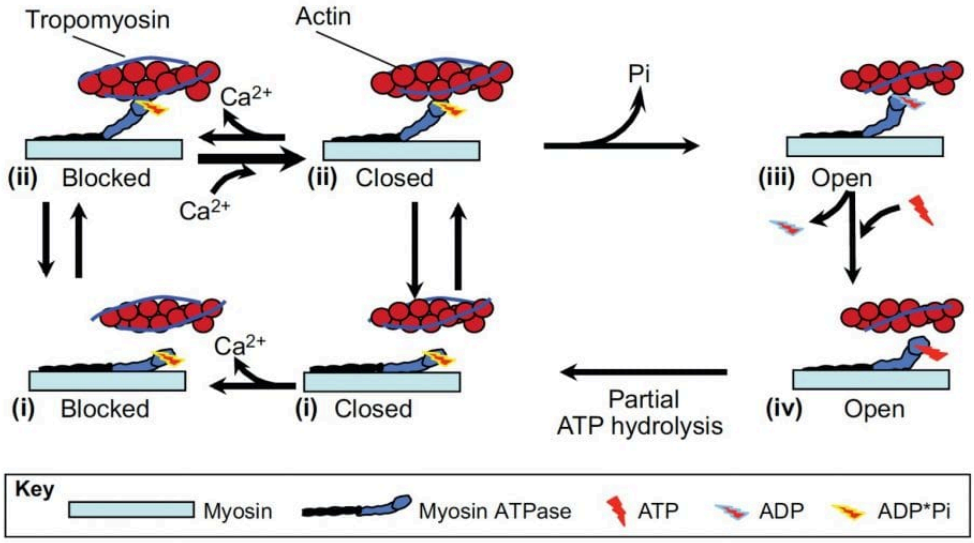


Figure 5-8 The sequence of events associated with activation of the crossbridge cycle are illustrated. Beginning in the lower left, the myosin heads are lying close to the myosin filament backbone. The tropomyosin is blocking the binding sites for myosin on the filament (1 blocked). Phosphorylation of the light chains of myosin will increase the mobility of the myosin heads (2 blocked), increasing the probability of actin-myosin interaction. Addition of Ca2+ to the cytoplasm results in binding of Ca2+ to troponin, which moves tropomyosin to the "closed" position (2 closed). The myosin head can now bind to actin. Binding of myosin to actin results in activation of myosin ATPase, and Pi is released, allowing a stroke. Engagement of a myosin head with actin results in further movement of tropomyosin away from the binding sites. This is called the open state (3 open). Subsequent release of ADP and binding of to the myosin head results in dissociation of the myosin head from actin (4 open). The myosin head then partially hydrolyzes the ATP to ADP*Pi resulting in reconfiguration of the myosin head into the cocked position that can attach to actin.

The collective effect of crossbridge cycling is that force is generated, and movement is possible. Force will be generated by each crossbridge that binds to actin. Total active force will be proportional to the number of crossbridges bound in parallel (across all parallel sarcomeres). The same force must be generated in all sarcomeres in series. If the resistance to shortening is sufficient, no length change will occur. Once the force generated by the crossbridges exceeds the resistance, shortening will occur. If the load on the muscle exceeds the force generated by the crossbridges, lengthening occurs.

Asynchronous Motor Unit Activation

The frequency of action potentials on the motor nerve dictates the frequency of action potentials on the muscle membrane because there is a one-to-one relationship between nerve and muscle action potentials. However, in a voluntary contraction, motor unit activation is asynchronous so the oscillations seen at subfusion frequencies are lost in a smoothing effect of activation of multiple motor units.

Types of Contraction

When a muscle is activated, crossbridge cycles are initiated, and force develops. The type of contraction is called fixed-end if the muscle-tendon length does not change. A truly isometric contraction occurs without muscle fibre length change. However, these two terms (fixed end contraction and isometric contraction) are sometimes used interchangeably. Often, the term isometric will be used to describe a contraction that does not have length change of the muscle-tendon unit. The muscle-tendon unit will shorten if the load on the muscle is not sufficient to prevent shortening or it will lengthen if the load exceeds the force generated by the muscle. When length change occurs, the contraction is called dynamic. The term "auxotonic" has also been used to describe muscle contraction where the force changes through-out the duration of the contraction and some fibre shortening occurs. A special form of dynamic contraction is one where the velocity of shortening is controlled. This is an isokinetic contraction.

Active and Passive Force and Types of Contraction

When you stretch an inactive muscle, it resists the stretch with a small force that is independent of activation, but this passive force increases with length. This is called passive force and is the property of passive structures like connective tissue, membrane,

and titin. When a muscle is activated, crossbridge cycles are initiated, and the force increases above the passive force. In general, muscle physiologists calculate the active force by subtracting the passive from the peak force. This calculation assumes that passive force remains constant during the contraction, and that active force simply adds to the passive force. However, it has been shown that passive force most likely decreases while active force is increasing (MacIntosh & MacNaughton, 2005). This happens because the tendon is stretched slightly as active force develops and the muscle fascicles decrease in length, decreasing the passive force across these passive structures.

Active force is calculated by subtracting the appropriate passive force from the peak force reached during a contraction (MacIntosh & MacNaughton, 2005). This should represent the actual force generated by energy-requiring processes (crossbridge cycling). The way of calculating active force is illustrated in Figure 5-9. The active force achieved by a given stimulation is dependent on several factors including frequency of activation, [Ca^{2+}], sarcomere length, and velocity of length change.

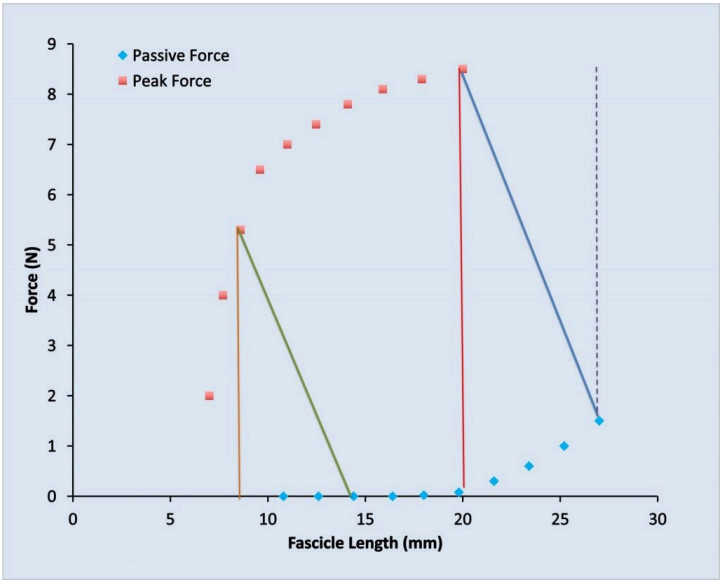


Figure 5-9 Force-length relationship showing calculation of active force. Active force is the difference between peak and passive force measured at a common fascicle length. The vertical dashed line indicates the assumption that fascicle length does not change during the contraction while the solid blue line indicates the actual path followed by the fascicle, shortening while force increases. Active force is indicated by the red vertical line. This is much greater than the active force that would be calculated with the assumption of the dashed line on the right. A contraction at shorter length is also shown.

This graph shows passive (blue diamonds) and peak (brown squares) force for a series of tetanic contractions of the rat medial gastrocnemius muscle obtained at different lengths. The blue diamonds show initial force for each contraction and the brown squares show peak force. Active force is calculated by subtracting the passive force from the peak force. Often, this is done by subtracting the passive force measured prior to the contraction, as indicated by the vertical dashed line. The correct way to calculate active force is to subtract the passive force that would be expected at the fascicle length reached at the peak of contraction as shown with the vertical red line. When the initial passive force is zero, the passive force before the contraction is the same as the passive force expected at the peak of the contraction. This is shown with the light brown line.

The Isometric Contractile Response

Activation of a muscle results in a contractile response that is dependent on the number and frequency of action potentials propagated across the surface membrane. With each activation, [Ca^{2+}] rises and falls, but with increasing frequency, the average [Ca^{2+}] achieved will be higher. The voluntary frequency of activation of human muscle is in the range of 8 Hz to 70 Hz, except for brief doublets or triplets (2-3 activations) at higher frequencies, often associated with initiation of ballistic contractions. The response to a single activation is called a twitch contraction while the response to repeated activations *without* complete relaxation between activations is known as a tetanic contraction.

Twitch Contraction

The rise and fall of active force during a twitch contraction is an elegant contractile response to a single activation (see Figure

5-10). The amplitude of force response depends on several factors, including: sarcomere length, temperature, prior activation (and activity dependent potentiation) as well as cross-sectional area of the cell, motor unit, or muscle stimulated. The term “twitch” is sometimes used to describe the contractile response to a doublet (two pulses) stimulation when the frequency is high. This alternative use of the term can only be understood by the context of the use, something the learner in exercise physiology needs to be aware of.

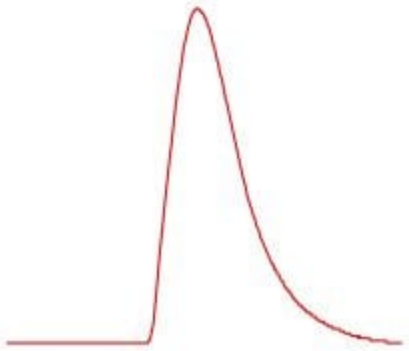


Figure 5-10 Twitch contraction. A single activation of a muscle will result in a transient increase then decrease in active force of contraction. This brief active force is called a twitch contraction.

Tetanic Contraction

When more than one activation is given and the interval between activations is within the time of the twitch contraction, summation occurs. That is, force will begin to rise again before relaxation is complete, like adding subsequent twitch contractions to what is already there. If oscillations of force are evident during repetitive activation, then this contraction is referred to as an incompletely fused tetanic contraction (Figure 5-11). If no oscillation of force is detected with each activation, then it is a completely fused tetanic contraction (Figure 5-12). The amount of relaxation between sequential activations depends on several factors: fibre-type, species, temperature, and sarcomere length.

Incompletely Fused Tetanic Contractions

The relationship between frequency of activation and active force is shown in Figure 5-13. When a muscle is activated at a very low frequency, independent twitch contractions will result. When sequential activations are delivered closer together, eventually an activation will arrive before complete relaxation has occurred. Now fusion occurs; first incomplete then complete as the frequency of activation increases. As frequency of activation increases, the average myoplasmic [Ca^{2+}] will increase. With higher myoplasmic [Ca^{2+}] active force will be higher, according to the force-Ca^{2+} relationship (see Figure 5-14).

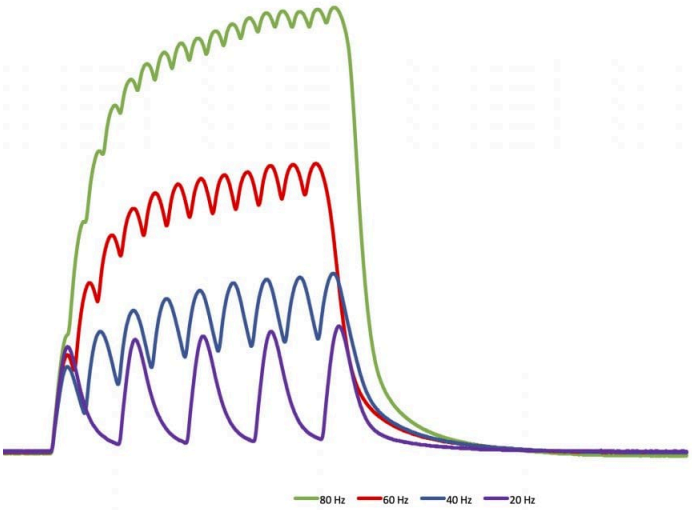


Figure 5-11 Incompletely fused tetanic contractions. These contractions were obtained by stimulation of the motor nerve at low (purple), moderate (blue, red) and high frequencies (green). As the frequency of stimulation increases, the amount of relaxation between stimulations decreases and the accumulated active force increases.

Completely Fused Tetanic Contractions

When sequential activations occur with a short interval, such that no relaxation is permitted between activations, the contraction is called a completely fused tetanic contraction. This complete fusion typically occurs near maximal active force.

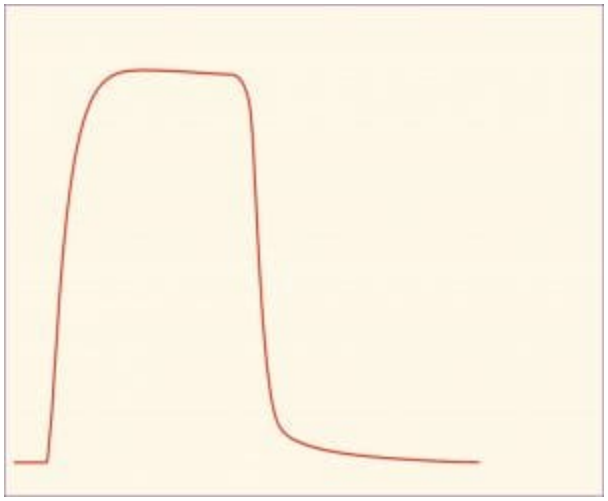


Figure 5-12 Completely fused tetanic contraction. When the frequency of stimulation is sufficiently high, no relaxation is seen between activations. In this case, active force is as high as it can be.

Dynamic Contractions

Muscle contraction is a process that is triggered by binding of Ca^{2+} to troponin. The amount of Ca^{2+} that binds to troponin depends on motor unitrecruitment (how many motor units are activated) and rate coding (frequency of activation of each motor unit). The consequence of muscle contraction is one of the following: shortening, lengthening, no change in length or stretch-shortening or shortening-stretch. One of the interesting and common types of contraction is the stretch-shortening contraction (Komi & Nicol, 2000). This is also known as a ballistic contraction where motion in one direction is slowed then reversed by contraction of the agonist for the shortening motion. For example, we often jump with a stretch-shortening contraction of our quadriceps muscles. The jump motion is preceded by a drop. We contract our quadriceps muscles to slow the drop, which is achieved with lengthening of these muscles and activate them more to accelerate upwards which requires shortening of the

quadriceps muscles.

Fundamental Contractile Properties of Skeletal Muscle

The force of skeletal muscle contraction can be considered to be modulated by several fundamental factors: calcium concentration or frequency of activation, sarcomere length, and velocity of shortening. Each of these fundamental properties of muscle will be described here. In addition, the force response is dependent on the history of activation. Potentiation and fatigue, resulting from prior activation, are presented in the Chapter on "Repetitive Muscle Activation" (see Chapter 12).

Force-Frequency Relationship

Individual twitch contractions have an active force that is typically 10-30% of the maximal active force obtained with a completely fused tetanic contraction. Keeping in mind that muscles are activated by action potentials on motor nerves, the frequency of activation of a motor unit depends on the frequency of activation on the corresponding motor neuron. Frequency is the inverse of interval between sequential activations. Typically, human motor units are activated initially at about 8 Hz, and a brief contraction may have a train of 6-20 action potentials. Frequency of activation is often presented as an average because the actual interval between activations varies somewhat from one interval to the next.

As intensity of contraction increases, the frequency of activation increases, up to 60 to 80 Hz for sustained frequency. However, there is sometimes a higher frequency for the initial two or three activations for ballistic contractions. Higher frequency means more fusion and higher active force. Figure 5-14 shows the relationship between frequency of activation and active force for a maximally activated whole muscle of mixed fibre-type composition. Typically, a slow-twitchmotor unit will have fusion at a lower frequency; a completely fused contraction will occur at a lower frequency. A fast-twitch motor unit will require a higher frequency of activation for complete fusion. The relationship between active force and frequency of activation is shifted to the left for slow-twitchmotor units and to the right for fast-twitch motor units. Since slow-twitch motor units are typically smaller than fast-twitch motor units, the peak active force for slow-twitch motor units will be less than peak active force for fast-twitch motor units.

The frequency of activation will determine the average [Ca^{2+}] in the myoplasm during the contraction. This concentration dictates the amount of binding to troponin-C. The binding of Ca^{2+} to troponin-C determines the number of crossbridges that are cycling. Therefore, the force-frequency relationship is closely linked to the force-calcium relationship. The relationship between frequency of activation and force is a sigmoidal relationship as seen in Figure 5-14.

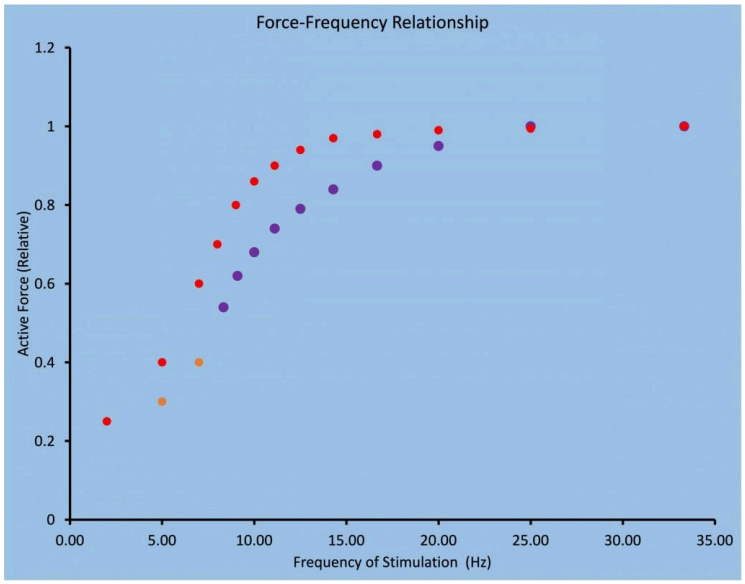


Figure 5-13 Force-frequency relationship. Active force, relative to maximum is presented for quadriceps muscles stimulated with brief trains of pulses at the corresponding frequency. Values in blue adapted from Binder-MacLeod et al., (1998). Values in orange estimated. Muscles with more slow-twitch fibre-type would be shifted to the left, like the red symbols.

Force-pCa^{2+} Relationship

As described above, muscle contraction is turned on by the release of Ca^{2+} into the myoplasm. The free [Ca^{2+}] determines what proportion of available troponin C has Ca^{2+} bound to it, and this binding allows crossbridge attachment and force generation along the adjacent thin filament. This same sequence of Ca^{2+} release, diffusion, and binding will occur simultaneously all along each activated muscle fibre. The force exerted by the muscle will depend on how many motor units are activated and the average [Ca^{2+}] in those activated muscle fibres. The [Ca^{2+}] depends on the frequency of activation within a contraction**.** This combination of recruitment and frequency of stimulation allow fine control over the force generated by a muscle.

The force-calcium relationship is typically quantified in a skinned fibre preparation (Stephenson, 1981; Wendt & Stephenson, 1983). With this approach, [Ca^{2+}] can be regulated carefully and force can be allowed to reach a plateau. Alternatively, the force-Ca^{2+} relationship can be determined in intact single muscle fibres with stimulation and measurement of both [Ca^{2+}] and force (Balnave & Allen, 1995; Glass, Cheng, & MacIntosh, 2018). The relationship between force generated by the muscle and [Ca^{2+}] obtained in this way is shown in Figure 5-15. It can be seen that the relationship is sigmoidal. At very low [Ca^{2+}], no active force is generated, though there may be passive force if the muscle is at a long length. At progressively increasing [Ca^{2+}] active force is progressively greater. The increase is small at low concentrations, but the increase in active force for a given increase in [Ca^{2+}] is greater through the middle range, then the slope decreases and active force reaches a plateau where further increases in [Ca^{2+}] result in no further increase in active force. Thegraph shows a discreet active force for any [Ca^{2+}]. However, the position of the line of the graph can be modulated. Several factors increase or decrease Ca^{2+} sensitivity**.** When Ca^{2+} sensitivity increases, the curve is to the left. There is more force at any given submaximal [Ca^{2+}]. When Ca^{2+} sensitivity decreases, the curve shifts to the right. There is less force at any given submaximal [Ca^{2+}]. Maximum force is not altered by Ca^{2+} sensitivity. The [Ca^{2+}] that results in half the maximal force is a measure of Ca^{2+} sensitivity. As sensitivity increases, the half-maximal [Ca^{2+}] decreases.

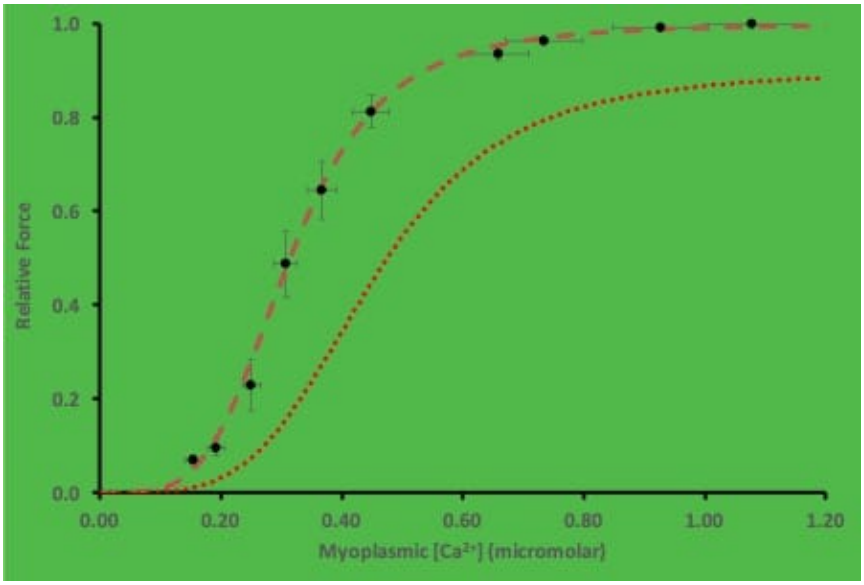


Figure 5-14 Force-Ca^{2+} Relationship. Relative force is plotted against [Ca^{2+}] for intact single fibre mouse muscle at 32°C. Black circles with error bars represent measurements in control muscle at different frequencies of stimulation. Dashed brown line is regression through these points. The dotted red line represents decreased Ca^{2+} sensitivity and decreased maximum force, similar to what would be expected for increased inorganic phosphate concentration.

The known factors that influence calcium sensitivity include the following:

- sarcomere length
- pH
- regulatory light chain phosphorylation
- temperature
- [Pi]

There are two potential mechanisms for altering the force at a given submaximal [Ca^{2+}] by which these cellular changes alter calcium sensitivity (MacIntosh, 2003). The predominant mechanism is related to affecting crossbridgekinetics, but it is also possible that binding of Ca^{2+} to troponin can be altered. This would certainly alter the magnitude of force of contraction at a given [Ca^{2+}].

Muscle Length and Ca^{2+} Sensitivity

When sarcomere length is changed, the diameter of the cell and of individual myofibrils changes. With increased sarcomere length, the myofilament lattice is compressed. With decreased sarcomere length, the myofilament lattice expands. This means at long lengths the myofilaments are close together and at short lengths there is more distance between the filaments. Increasing sarcomere length increases calcium sensitivity because the myosin heads are brought closer to the filaments, increasing the probability of crossbridge formation. When this approach is used with skinned fibres, the myofilament lattice can be 'shrunk' with addition of dextran (Wang & Fuchs, 2000) to the solution in which the muscle was immersed. Shrinking the myofilament lattice in this way increases Ca^{2+} sensitivity**,** confirming that it is the dimensions of the myofilament lattice that influence the length dependence of Ca^{2+} sensitivity.

pH and Ca^{2+} Sensitivity

Early reports of changes in Ca^{2+} sensitivity and were interpreted as evidence that acidosis contributes to decreased contractile response known as fatigue. Fabiato and Fabiato (1978) demonstrated that when pH was decreased from 7.4 to 6.2, both Ca^{2+} sensitivity and maximal force were decreased. These authors also demonstrated that the mechanisms for the inhibitory effect of acidosis was not related to competitive binding of Ca^{2+} with troponin. They suggest the mechanism had something to do with a step in the contractile process after binding of Ca^{2+} to troponin. These experiments were conducted on mechanically skinned frog muscle fibres at 22°C. The impact of this research was profound. Essentially a primary mechanism of had been found. The notion that acidosis was a primary factor in muscle fatigue persisted until 1995 when it was shown that the effectiveness of acidosis to decrease Ca^{2+} sensitivity was diminished when muscle was tested at 30°C (Pate, Bhimani, Franks-Skiba, & Cooke, 1995). This result suggests that at physiological temperatures, acidosis has very little impact on fatigue of skeletal muscle. It has been demonstrated that in alkalotic solutions, the myosin heads are more scattered, having greater mobility than in acidosis where the myosin heads are uniformly pressed against the thick filaments (Podlubnaya, Kakol, Moczarska, Stepkowski, & Udaltsov, 1999). This mobility of the myosin heads is thought to contribute to increased Ca^{2+} sensitivity by bringing the myosin heads in close proximity to the filaments, similar to the mechanism proposed for myosin light chain phosphorylation.

Regulatory Light Chain Phosphorylation and Ca^{2+} Sensitivity

Skeletal muscle myosin contains two light chains, one called essential, and one referred to as regulatory. The essential light chain is necessary for actin-myosin-ATPase activity (Harrington & Rodgers, 1984). The regulatory light chain can be phosphorylated and this phosphorylation results in increased Ca^{2+} sensitivity (Persechini, Stull, & Cooke, 1985). Repeated activation of skeletal muscle results in activation of myosin light chain kinase and this enzyme phosphorylates the regulatory light chain. Activity dependent potentiation is correlated with magnitude of light chain phosphorylation (Moore & Stull, 1984). The mechanism by which Ca^{2+} sensitivity is increased by regulatory light chain phosphorylation is similar to the mechanism associated with pH. Without light chain phosphorylation, the myosin heads lie close to the thick filament backbone. When the light chains are phosphorylated, the swing free with increased mobility (Levine, Kensler, Yang, Stull, & Sweeney, 1996). This increased mobility corresponds with increased probability of myosin head interaction with actin and crossbridge formation; more force is obtained at a given submaximal [Ca^{2+}]. The increased probability of crossbridge formation results in a faster rate of rise of force (Sale, 2002).

Temperature and Ca2+ Sensitivity

Mammalian muscle operates at temperatures ranging from 30°C to 40°C. In this temperature range, Ca^{2+} sensitivity is low. When muscle is cooled, as is often the case when it is studied in vitro, Ca^{2+} sensitivity increases. It is thought that the mechanism by which Ca^{2+} sensitivity is altered by temperature is similar to the mechanisms for regulatory light chainphosphorylation and

pH. Decreasing temperature causes the myosin heads to increase mobility, swinging away from the thick filament back-bone. Increasing temperature has the opposite effect. When the myosin heads have increased mobility, they have a greater probability of binding to actin, forming crossbridges and generating force. It should be noted that along with changing Ca^{2+} sensitivity, muscle temperature has other effects as well. For example, increasing temperature will increase the force per crossbridge, and maximal velocity. This effect of temperature is an important aspect of warm-up because output is improved across a range of velocities.

Inorganic Phosphate and Ca^{2+} Sensitivity

During repeated contractions, inorganic phosphate (Pi) accumulates due to the net breakdown of creatine phosphate. The concentration of Pi can increase from a few mM to 20-30 mM. An important step in the crossbridge cycle is the release of Pi. This step allows transition to the force-generating stage of the cycle. Increased [Pi] slows the release of Pi, slowing the transition to force generation. This means there will be less force at a given [Ca^{2+}] than would otherwise be expected; Ca^{2+} sensitivity is decreased. Maximal force is also decreased by Pi.

Interaction Among Factors Affecting Ca^{2+} Sensitivity

It is apparent when reading through the descriptions for mechanism of changes in Ca^{2+} sensitivity that there is a common theme. Proximity of the myosin heads to improves Ca^{2+} sensitivity. This is achieved with any of the following mechanisms:

- osmotic compression in skinned fibres
- increased sarcomere length
- increase
- decreased temperature
- increased regulatory light chainphosphorylation.

It should not come as any surprise that if you increase the mobility of the myosin heads by one mechanism, then other factors that operate by this mechanism become ineffective. For example, regulatory light chain phosphorylation is not very effective at increasing Ca^{2+} sensitivity at low temperature (room temperature or lower), or at long sarcomere length (Rassier & MacIntosh, 2002). Similarly, at warm temperature where myosin head mobility is already decreased, decreasing pH has little impact. These interactions are described further by MacIntosh (2003).

Force-Length Relationship and the Length Dependence of Force

The force-length relationship relates sarcomere length to maximal active isometric force and passive force of muscle. Passive force is typically zero until sarcomere length reaches the optimal length for peak active force. At this length or slightly longer, passive force will rise as length increases (see Figure 5-15). Maximal active force is very low at short sarcomere lengths and increases to a peak at a sarcomere length that allows the greatest overlap of thick and thin filaments (Gordon, Huxley, & Julian, 1966). This is the ascending limb of the force-length relationship. Myosin filaments are universally 1.6 µm in length, but (thin) filaments vary according to species. Human actin filaments are about 1.3 µm in length, so optimal sarcomere length (plateau) ranges from 2.6 µm to 2.8 µm. Beyond this sarcomere length, overlap decreases, so maximal force also decreases (Rassier, MacIntosh, & Herzog, 1999). This is the descending limb of the force-length relationship. If overlap decreased to zero, it would be expected that active force would be zero. In human muscle, this should happen at a sarcomere length of 4.2 µm. It seems unlikely that sarcomere length could reach this extreme, but it has been reported to occur (Lieber, Loren, & Friden, 1994).

Although it is easy to understand why active force is greatest on the plateau where overlap of the myofilaments is greatest, and active force decreases linearly at longer sarcomere lengths, the factors affecting active force on the ascending limb of the force-length relationship are more complicated. Several factors appear to contribute to this property of muscle. When sarcomere length decreases below the length associated with the length of two thin filaments, then the thin filaments must overlap with each other in the middle of the sarcomere. It is possible that this results in interference with the appropriate actin-myosin interaction. Thin filaments from the wrong end of the sarcomere may bind inappropriately with some myosin molecules. This overlap increases as sarcomere length decreases, increasing the likelihood of such interference. In addition, when the sarcomere length is no longer than the myosin filament (1.6 µm), the thick filaments will press against theZ-disks. This interaction of myofilaments with intermediate filaments may detract from generation of active force.

Submaximal Activation and the Length Dependence of Active Force

When activation of a muscle is submaximal (according to the force-frequency or force-pCa^{2+} relationship), the relationship between sarcomere length and submaximal active force is referred to as the length dependence of force. The active force still has an ascending limb, a plateau, and a descending limb. However, the plateau for submaximal contractions is shifted to the right. This indicates that some factor in addition to overlap of myofilaments has an influence on Muscle Blood Flow and Oxygenation. The Moxy monitor outputs two variables, the total hemoglobin (tHb) which reflects changes in microvascular blood volume 30, and the muscle oxygen saturation (SmO_2), which reflects the ratio of the oxygenated hemoglobin and myoglobin to the total hemoglobin and myoglobin and is suggested to indicate the balance between muscle oxygen delivery and utilization 30. During high-intensity isometric contractions, SmO_2 will tend to decline as the muscle rate of oxygen utilization exceeds its rate of delivery, while during the rest periods, the trend is reversed, creating a “sawtooth” pattern during an intermittent isometric test. As it has been shown to be more reliable than comparing more discrete time points 31, the change in SmO_2 during the contractions (ΔSmO_2-work) and during the rest periods (ΔSmO_2-rest) were averaged across all contractions and compared between conditions when activation is submaximal. This additional factor appears to be Ca^{2+} sensitivity (MacIntosh, 2017) and the property of muscle that causes this shift of optimal length is called length dependent activation. One of the key factors affecting the active force at a given submaximal [Ca^{2+}] is proximity of the myosin head to the binding site on filaments (MacIntosh, 2003). As muscle length increases, the distance between filaments decreases. This makes it easier for crossbridge formation, so myosin heads bind more quickly, increasing the rate of force development.

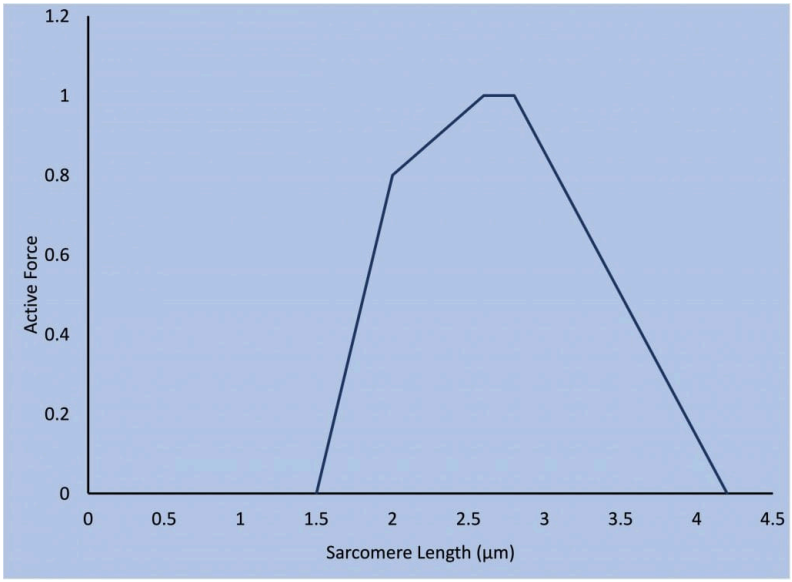


Figure 5-15 The theoretical force-length relationship for human muscle. The active force rises from a sarcomere length of 1.6 µm to 2.6 µm. This is the ascending limb of the force-length relationship. The plateau or maximal force is from 2.6 to 2.8 µm. On the descending limb, active force decreases linearly as length decreases from 2.8 µm to 4.2 µm.

Force-Velocity and Power – Velocity Relationship s

The relationship between active force and length described above relates entirely to isometric contractions**.** When the muscle length is allowed to change during the contraction**,** the force exerted by individual crossbridges will change, depending on whether length is increasing or decreasing. The force-velocity relationship describes the decrease in active force as the rate of shortening increases (see Figure 5-16). This relationship shows that as velocity of shortening increases, the force exerted decreases. The relationship is curved, and is described by the following hyperbolic equation:

$(P + a) (v + b) = b (Po + a) =$ constant **equation 5-1**

where P is force, v is velocity of shortening, Po is isometric force, a and b are constants. This equation can be rearranged to the following (MacIntosh, Herzog, Suter, Wiley, & Sokolosky, 1993):

$P = [b (Po + a) (v + b)^{-1}] - a$ **equation 5-2**

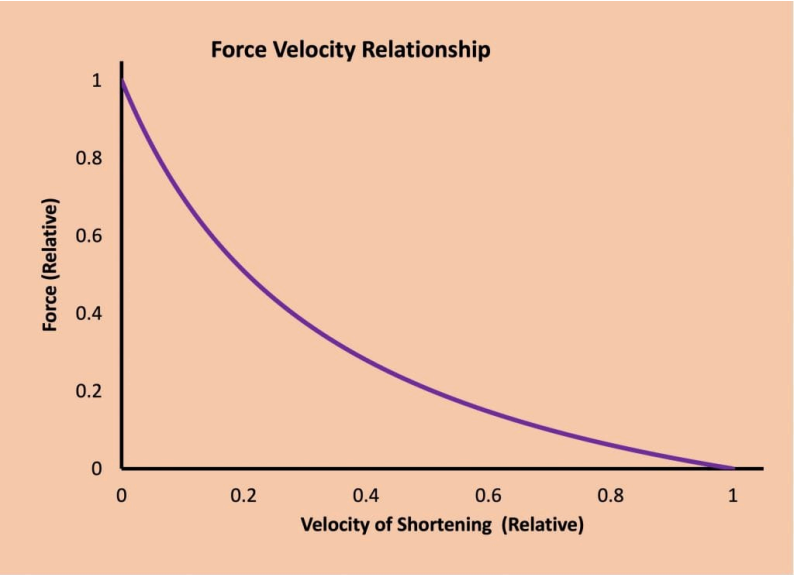


Figure 5-16 The Force-Velocity Relationship. The force of muscle contraction is lower when the velocity of contraction is higher. This graph shows a generalized relationship where force and velocity are normalized to maximal values.

The curvature of the force-velocity relationship is dependent on temperature, fatigue, and fibre-type composition. The ratio of a:Po from the above equation defines the curvature. The smaller the value of this ratio, the greater is the curvature. The curvature is increased as temperature decreases. This is particularly important to understand the extreme curvatures of some published work on skeletal muscle (Hill, 1938). These measures were obtained in amphibian muscle at a temperature ranging from 0 to 25C, and have an a:Po ratio near 0.22. More physiological assessments of human muscle, in vivo, have yielded less curvature (a:Po =0.22 to 0.48) (Wilkie, 1950) to little or no curvature (MacIntosh et al., 1993). Fatigue can apparently have varied effects on the force-velocity relationship**,** and it is not clear why these differences have been observed. Some reports of the impact of on the force-velocity relationship indicate greater curvature (De Ruiter, Jones, Sargeant, & De Haan, 1999) while other reports show decreased curvature (Andrea N. Devrome & MacIntosh, 2018). Additional work is clearly needed to understand these differences.

One thing is clear, the persistent changes observed in recovery are minimal with respect to the curvature. When mammalian muscle recovers from fatigue, low-frequency fatigue persists but the curvature of the force-frequency relationship returns to the control value (A. N. Devrome & MacIntosh, 2007).

Slow-twitch fibres have greater curvature in their force-velocity relationship than do fast-twitch fibres**.** This probably relates to the mechanism for the curvature described below. Combining fast and slow-twitch fibres in the same muscle accentuates the curvature. This is evident in figure 5-17 below, which shows 5 theoretical muscles with varying fibre-type composition (30-70% fast-twitch).

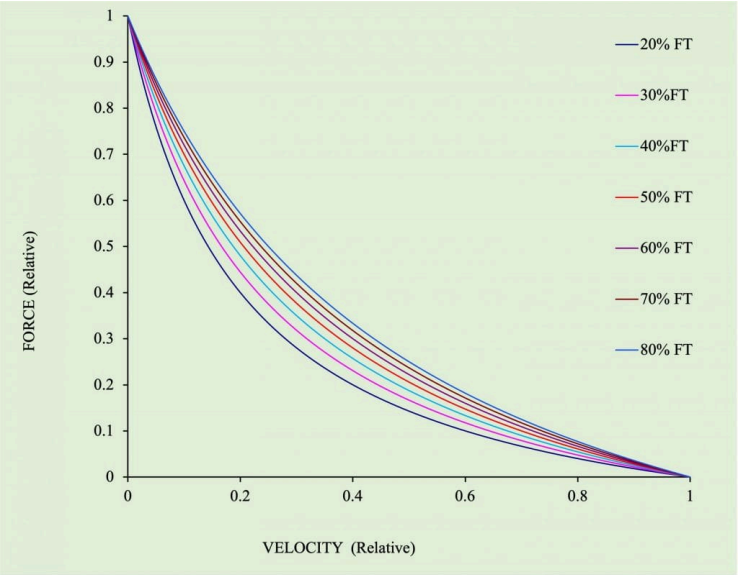


Figure 5-17 Force-velocity for varied fibre type composition. Each line represents the force-velocity relationship for a muscle. Fibre-type composition varies from relatively more slow-twitch fibres (lowest, most curved line) to more fast-twitch fibres (upper line, illustrating more force at any contractile velocity). Note that all lines converge at the same maximal velocity and force. This is because force and velocity are presented as relative, but the same would occur for absolute force and velocity if all muscles had the same cross-sectional area and the fastest motor unit had the same maximal velocity in all muscles compared.

Mechanism of Decreased Force with Increased Velocity of Shortening

Logistically, it can be predicted that there are two factors that contribute to the decrease in force as velocity of shortening increases. These two factors are less force per crossbridge and/or fewer crossbridges. It appears that both of these factors are important in determining the force-velocity relationship. It has been shown that in cardiac muscle, force per crossbridge decreases in a straight line as velocity increases (De Tombe & ter Keurs, 1992). A similar observation was made by Piazzesi and colleagues (2007) for skeletal muscle. However, in this case the linear decline was somewhat delayed (began decreasing after some increase in velocity). If decreased force per crossbridge can account for only a straight linear decrease, then decreased number of crossbridges must account for the remaining decrement in force as velocity increases. This possibility is illustrated in Figure 5-18. The blue line shows the magnitude of difference between the straight linear decrease in force and the curved decrease. This difference is expressed relative to the magnitude of the straight line at that velocity. The value of the blue line at any velocity represents the relative deficit of crossbridges in comparison with the number for an isometric contraction**.** For example, when velocity is 0.5 of maximal velocity, the deficit is 0.59. This means that only 41% of the number of crossbridges engaged during an isometric contraction will be engaged during this dynamic contraction**.**

Why are there fewer crossbridges attached as velocity increases? The number of crossbridges bound at one time are dependent on the rate constants for attachment and detachment such that $N = f\,(f + g)^{-1}$ (De Tombe & Stienen, 2007). It is generally thought that as shortening velocity increases, g, the rate constant for crossbridge disengagement increases. If this was the only change, then the ratio above would decrease, resulting in fewer crossbridges engaged. However, f, the rate constant for crossbridge engagement may decrease as velocity of shortening increases, contributing further to the crossbridge deficit.

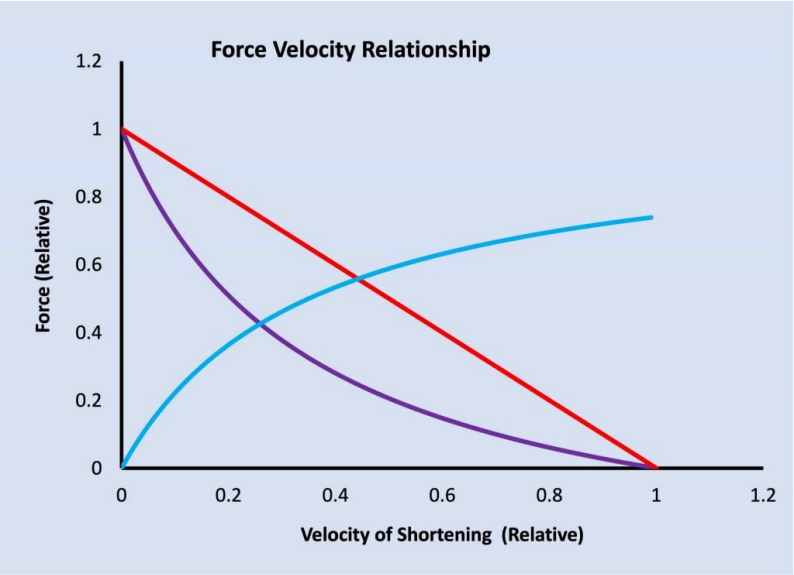


Figure 5-18 Force-velocity relationship and crossbridge deficit. The purple line shows the relationship between force and velocity. The red line represents the force per crossbridge and the blue line represents the force deficit (the difference between the red and the purple lines. The force deficit can only be caused by fewer crossbridges engaged at any instant during the contraction. Since the difference between the straight line and the curved (purple) force-velocity relationship is due to the curvature of the relationship, this curvature is due to decreased numbers of crossbridges.

Power – Velocity Relationship

The relationship between and velocity of shortening is dependent on the force-velocity relationship**.** Power is the product of force and velocity, so this relationship strictly determines the power-velocity relationship. Power of muscle contraction is zero when either force or velocity is zero. This happens at each end of the curve, so power is zero when velocity is zero and when velocity is maximal. The shape of the power-velocity relationship predicts the conditions where power is the highest. The velocity at which power is the highest is called the optimal velocity.

The curvature of the force-velocity relationship dictates the shape of the power-velocity relationship. As a/Po decreases (curvature increase), peak power decreases and optimal velocity decreases. These interactions can be seen in Figure 5-19.

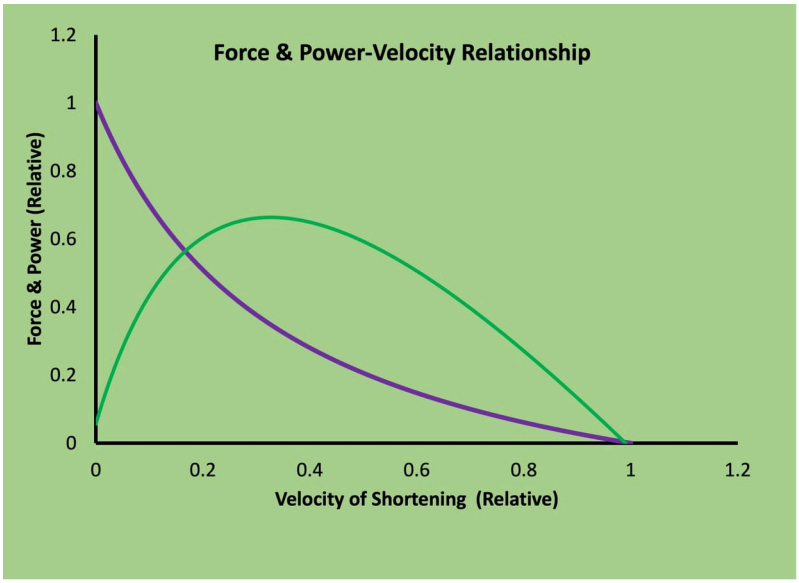


Figure 5-19 Power-velocity relationship and force-velocity relationship. The typical downwardly curved force-velocity relationship is shown in purple and the corresponding power output at each velocity is shown in green. Each scale is presented relative to the highest value. The values for power are calculated as the product of the corresponding force and velocity. Note that power is zero when either force or velocity are zero. There is a unique velocity at which power is maximal. This optimal velocity is dependent on temperature and fibre-type.

Figure 5.20 EMG-cadence relationship at 4 power outputs for an individual. This figure shows the relationship between magnitude of EMG (quantified as root mean square) for an average of 7 muscles involved in cycling at a variety of cadences at each of 4 power outputs from lowest line to upper line representing 100 W, 200 W, 300 W and 400 W. The data show that muscle activation is minimal at a unique cadence for each power output. The optimal cadence increases as power output increases. These data are from a single subject in the study described in the paper by MacIntosh and colleagues (2000).

Cycling: An Example of Dynamic Muscle Use

Cycling is a common exercise studied by exercise physiologists. Cycle ergometers have been available for research for as long as there have been exercise physiologists and these ergometers allow quantification of power output while keeping the subject stationary for monitoring heart rate, oxygen uptake, and of several muscles.

Muscle Activation InExercise

It is not easy to quantify motor unitrecruitment during cycling exercise. That would require intramuscular needle or fine wireEMG . However, a generalized notion of muscle activation can be obtained from measurement of the magnitude of surface EMG (integrated EMG or root mean square). Muscle activation is increased by increasing the frequency of activation on individual motor units (also known as rate coding), and by recruiting additional motor units. The pattern of muscle activation required depends not only on output but also on the cadence (crank revolutions per minute). At any cadence, muscle activation will increase with increased power output (MacIntosh, Neptune, & Horton, 2000). However, at a given power output, there is a cadence that will require the lowest amount of muscle activation and muscle activation must increase with lower or higher cadence at that power output. Figure 5-22 illustrates this interesting muscle activation requirement, which is dependent on the force-velocity properties of the key muscles involved in cycling.

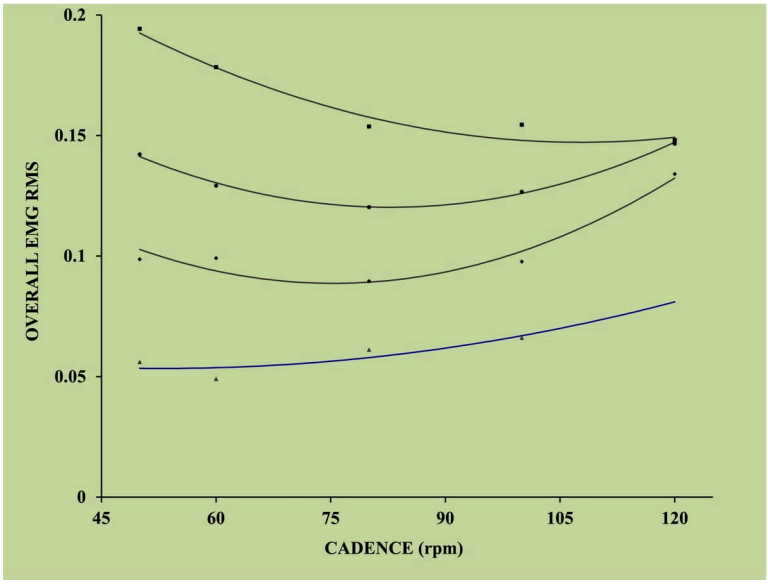


Figure 5-20 This figure shows the relationship between magnitude of (quantified as root mean square) for an average of 7 muscles involved in cycling at a variety of cadences at each of 4 power outputs from lowest line to upper line representing 100 W, 200 W, 300 W and 400 W. The data show that muscle activation is minimal at a unique cadence for each power output. The optimal cadence increases as power output increases. These data are from a single subject in the study described in the paper by MacIntosh and colleagues (2000).

Research Highlight: Presentation of article by C. Maganaris, 2003

Force-length characteristics of the in vivo human gastrocnemius muscle. Clinical Anatomy 16: 215-223. DOI: 10.1002/ca.10064

Ideally, you should read the paper by Maganaris (2003) before reading the following section of this chapter. The purpose of this paper was to evaluate the structure of the medial and lateral gastrocnemius muscles and Achilles tendon during maximal isometric (fixed-end) contractions initiated at a range of ankle joint angles. In this way, the force-length relationship could be evaluated in vivo. It is acknowledged in the Introduction of this paper that it is difficult to know the architecture of muscle as force develops; tendon stretches and fibres shorten. However, ultrasound imaging can be used to see what is happening during a muscle contraction.

The methods used for this study are fairly standard for current in vivo human muscle measurements. Note that the authors obtained approval from a local ethics committee before proceeding with the study and that their subjects gave informed written consent to participate in the study. The author used several techniques to assure that what was measured is accurate. The general approach is to ask their subjects to exert maximal effort against the dynamometer with the ankle at a variety of angles from -20 (20° of dorsiflexion relative to a foot in the neutral position (foot perpendicular to the shank)) to +30° (30° of plantarflexion relative to a foot in the neutral position). This is equivalent to a range from 70° to 120° for an angle measured between the foot and the shank.

Ankle plantar flexor was measured, correcting for the moment needed to overcome gravitational force (unmeasured force exerted by the ankle plantar flexors to support the weight of the foot and the equipment). Fascicle length and pinnation angle was measured with ultrasound imaging. To calculate muscle force from the measured moment, it is necessary to know the length of the arm. Moment arm length was estimated by the tendon travel (or excursion) method. This method uses ultrasound images of the muscle-tendon junction at two ankle positions, while the muscle is inactive, to allow determination of the change in position of the muscle-tendon junction. The moment arm is estimated as the change in position (measured in mm) relative to the change in angle (measured in radians). It is important that the moment about the ankle not change between these measurement positions, because this would potentially change the length of the tendon and violate the criteria for the tendon travel method. This technique assumes that a joint is like a pulley and that the tendon will move a distance equal to 1 radius as the joint moves through 57° (one radian).

The plantar flexor is generated by a number of muscles, including the medial and lateral gastrocnemius muscles. When the knee is straight (180°), the gastrocnemius generates considerable force. However, when the knee is at an angle less than 90°, the gastrocnemius muscle is thought to be at such a short length that it is incapable of generating force that would be measured as a moment at the ankle. The author took advantage of this property to subtract the moment generated with the knee at 120° of flexion with the ankle at each of the standard positions. This position of the knee would create a knee angle between the thigh and the shank of 60°. By performing this subtraction, the moment generated by all muscles crossing only the ankle joint would be subtracted from the moment generated by all muscles contributing to the ankle moment, including the gastrocnemius muscles. The difference would be the moment generated by the gastrocnemius muscles (medial and lateral head).

Dividing the net (peak moment of the gastrocnemius muscles minus passive moment) by the moment arm yielded the active force exerted on the tendon. Note that the author never presents the passive moment and does not present the initial fascicle length. For this reason, it is difficult to know how much the fascicles shortened during these contractions. Force generated by the fascicles was estimated by considering that force was exerted at some angle relative to the line of action of the muscle. Force exerted on the tendon was calculated by multiplying the measured moment by the cosine of pinnation angle. This is equivalent to dividing the force by the cosine of the pinnation angle (as stated in the paper) to yield moment.

To be certain that the effort of their subjects was maximal, the author used twitch interpolation. A superimposed twitch would reveal negligible force if the person was able to generate a true maximal effort. This technique is further described in Chapter 12.

Based on previous research, it was calculated that the medial head of the gastrocnemius (GM) provided 70% of the gastrocnemius force and the lateral head of the gastrocnemius (GL) provided 30%. This is based on the fact that the cross-sectional area of the medial gastrocnemius is greater than that of the lateral gastrocnemius. It was necessary to separate these synergistic muscles because agraph of fascicle length vs. active force is presented in the results and it is clear that the two muscles operate at a different fascicle length. This graph shows the primary observation of this study. Active force for each of these muscles increases linearly over the entire range of fascicle lengths. This linear change in force can be interpreted to mean the muscles are on the ascending limb of the force-length relationship (see Figure 5-21).

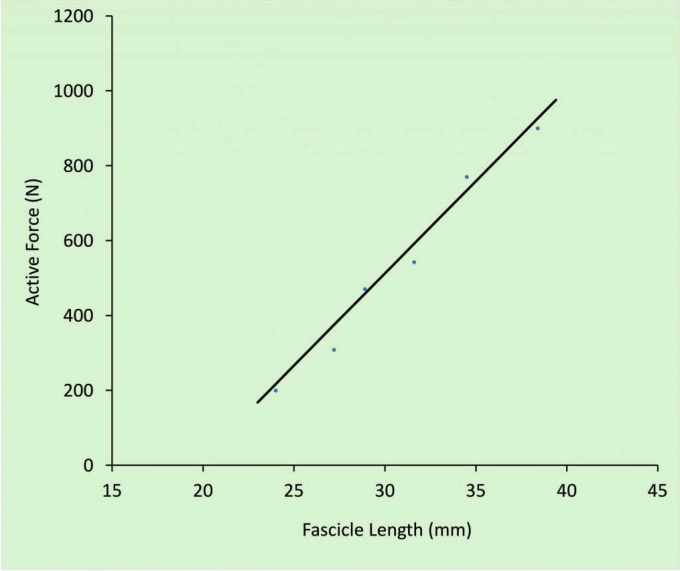


Figure 5-21 In vivo force-length relationship of the medial gastrocnemius muscle. Active force is shown vs fascicle length. Individual contractions are illustrated by the blue dots. The line represents a straight line fit to the data.

In the discussion of the paper, the author presents an estimate of the sarcomere length of the medial and lateral gastrocnemius muscles over the range of measured active force. It is assumed that the medial gastrocnemius muscle fibres have 17,600 sarcomeres in series and by dividing the measured fascicle length by the number of sarcomeres, the sarcomere length can be estimated. It is estimated that the sarcomeres range from 1.4 to 2.2 µm. This seems like a short sarcomere length for this muscle, considering the filament lengths of human muscle (see Figure 5-23 above). It seems unlikely that any active force could be generated at a sarcomere length below 1.6 µm. Most muscle physiologists would argue that the muscle should be at or near the plateau of the force-length relationship during maximal activation. The author argues that this range of sarcomere lengths is reasonable because the muscles would normally be used in submaximal contractions**,** and this would result in less stretch of the tendon and therefore a longer sarcomere length. The plateau of the force-length relationship should be 2.6-2.8 µm.

Fukunaga et al (2001) used a similar assumption to estimate that sarcomere length in the medial gastrocnemius muscle during walking was in the range of 2.75-2.92 µm. It would have been nice to know the resting length of the fascicle in this study.

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Summary

The structure of muscle, presented in Chapter 4 relates well to the function of muscle presented here in Chapter 5. Muscle is organized into motor units, groups of cells that are activated together with a series of action potentials on a given axon. When an action potential arrives at the nerve terminal, neuromuscular transmission allows activation of all of the muscle fibres associated with that motor unit. Excitation-contraction coupling is the process that turns the neural signal into a contraction. The action potential is transmitted along the sarcolemma and into the transverse tubules where the receptors detect the voltage change. The receptors signal the ryanodine receptors to open and allow Ca^{2+} to flow out of the terminal cisternae into the cytoplasm. Ca^{2+} initiates the contraction, which can be fixed-end or dynamic (shortening or lengthening The magnitude of response is dependent on many factors, including the concentration of Ca^{2+} achieved with the activation. Sensitivity to Ca^{2+} can also be altered. The energy for muscle contraction comes from adenosine triphosphate a universal biological energy source. Fundamental properties of muscle dictate the nature of the contractile response. These properties include the force-length relationship, the force-frequency relationship, the force-velocity relationship and the power-velocity relationship.

Exercises or Topics for Discussion:

- What are the factors that could allow two individuals with the same maximal isometric force when one of them was 2 m in

height and the other was 1.6 m in height?
- How would you determine the force-length relationship for the elbow flexor muscles?
- Describe the sequence of events in excitation-contraction coupling.
- What factors would be important in determining how fast a catapult could launch a pumpkin and how does this relate to muscle function?

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2.4: Chapter 6 - Energy Supply at Rest and During Exercise

This chapter is in preparation.

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2.4.1: Chapter 6A - Energy Supply for Exercise

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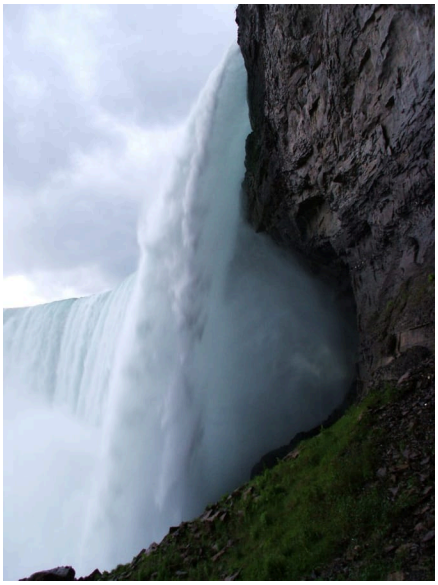


Photo 6.1 Renewable Energy *Water falling from a height represents natural renewable energy. Our body relies on nutrient intake to renew our supply of energy. Photo by Brian MacIntosh*

Learning Objectives

After reading this chapter, you should be able to:

- Explain the processes in muscle that use energy at rest and during contraction
- Describe in general, the processes and mechanisms by which ATP is made available in response to energy needs in muscle, including: creatine phosphate, glycogenolysis, glycolysis, KREBS cycle, phosphorylation and electron transfer chain
- Describe how and why the measurement of oxygen uptake can provide an estimate of the energy requirement of muscle contraction and/or exercise
- Describe how substrates for energy metabolism are mobilized and made available
- Explain the difference between economy and efficiency and justify the use of these terms
- Describe and explain the mechanism for the slow component of oxygen upta

Key Terms

energetics, indirect calorimetry, mitochondria, aerobic energy supply, oxygen uptake, anaerobic energy supply, glycolysis, Kreb's Cycle, Electron transfer chain, phosphorylation, biological work, adenosine diphosphate (ADP), adenosine triphosphate (ATP), creatine phosphate (CrP), inorganic phosphate (Pi), economy, efficiency, mechanical work, electrochemical gradient, enzymes, ion pump

Introduction

Physical activity requires energy. The processes that use energy and those that replenish the chemical energy supply needed by our muscles are critically important in the field of exercise physiology. Many of the systems we study in exercise physiology are designed to provide substrates for energy metabolism and to cope with the disturbance to homeostasis resulting from

increased energy metabolism during exercise (see Chapter 9). This includes the pulmonary system (Chapter 7) that provides oxygen for aerobic metabolism and removes carbon dioxide from the body, releasing it to the atmosphere. The cardiovascular system (Chapter 8) delivers oxygenated blood and substrates to the active muscles of the body and removes heat, carbon dioxide and metabolic by-products of energy metabolism. The neural and hormonal systems of the body help by controlling the pulmonary and cardiovascular systems, providing the communication needed to mobilize substrates for energy metabolism and initiating processes that dissipate heat from the body and informing the brain of the magnitude of effort and disturbance to homeostasis. These systems will be introduced here and further developed later in the textbook. A recent review (Hargreaves and Spriet 2020) presents a summary of the energetics of muscle metabolism and relates this to performance of events lasting seconds to hours. This is an excellent source of additional information.

All cells of the body require energy for maintenance of the living state. The cellular processes that require energy are referred to as biological work. For most cells, these processes include ion and molecule transport, synthesis reactions and simple heat generation. Of course, our muscles produce force and motion using energy metabolism. Our cells, including myocytes use chemical energy in the form of adenosine triphosphate (ATP). All forms of biological work including those mentioned above and force generation with and without movement require energy. The use of this energy results in release of heat within the body as well as accomplishment of biological work. Considering that energy cannot be created or destroyed (the first law of thermodynamics, also known as the law of conservation of energy), these processes merely transform energy from one form (usually chemical, to another chemical form (ATP), then to biological or mechanical work and/or heat). The metabolic pathways serve to prevent the depletion of ATP during active use of our muscles. It is the release of metabolic heat in the body that makes us feel warm when we exercise. However, it is important to be able to dissipate the heat generated by our active muscles to prevent unhealthy increase of body temperature (see chapter 9 for mechanisms of heat dissipation).

ATP is the primary currency of chemical energy in the body. All cells use ATP to power reactions and processes that require energy. In this chapter we will describe the need for ATP in our muscles and the ways that it is regenerated, to prevent a decrease in ATP concentration. A decrease in ATP concentration in muscle will lead to rigor mortis, an uncontrolled and sustained state of cross-bridge engagement that disables our muscles.

Although a small amount of energy is provided by anaerobic (nonaerobic) metabolism, the measurement of oxygen uptake can provide a reasonable estimate of muscle or whole-body energetics when the exercise persists for more than a few minutes, and reaches a steady-state for oxygen uptake. After a few minutes of exercise in the moderate and low end of vigorous intensity range, the rate of oxygen uptake can account for all of the continuing energy cost of exercise. For this reason, the measurement of oxygen uptake is often used as a substitute for energy cost. This is reasonable when an accurate estimate is not needed and when the intensity is not of sufficient magnitude to require sustained contribution from anaerobic metabolism (Fletcher et al. 2009). There are circumstances that can alter the amount of energy obtained by the use of an amount of oxygen. For example, 1 L of O2 will provide 5.047 kcal (21.117 kJ) of energy if carbohydrates are exclusively metabolized and 4.686 kcal (19.606 kJ) of energy if fats are exclusively metabolized. Generally, there is a mixture of these substrates used, yielding a value somewhere between these extremes. Another factor that can influence the amount of energy obtained per litre of O2 is the P:O ratio. That is, how muchATP is generated per atom of Oxygen? See Chapter 6B for further information on this topic.

When the energy cost exceeds the anaerobic threshold (Svedahl and MacIntosh 2003), there must be sustained provision of energy from anaerobic metabolism. Under these circumstances, measurement of oxygen uptake ($\dot{V}O_2$) does not allow calculation of the full energy cost. This exercise cannot be sustained for more than 30-40 min. In contrast, when the energy requirement is even a little bit below the anaerobic threshold, the exercise can be maintained for hours. It is generally assumed that the body has a limited amount of anaerobic energy available, perhaps in the range of 100-125 kJ. Current theory suggests that once this anaerobic energy is used, exercise requiring anaerobic contribution cannot continue (Moritani et al. 1981).

One of the consequences of the metabolic processes that provide energy for muscle contraction and the process of muscle contraction itself is conversion of chemical energy to heat. During exercise, heat production can be considerable and would result in increased temperature of the body. Fortunately, most of this heat generated in the body during exercise is lost to the environment through processes described in Chapter 9. In the following Case Presentation, the amount of heat generated during a time-trial is considered.

Case Presentation: Heat Generation During a Time-Trial

In Chapter 16, Jake runs a 10 km time-trial and his heat generation is calculated. Here, heat generation during a marathon is calculated for Jerry. Jerry has a running economy equal to 1.15 kcal × kg^{-1} × km^{-1}. This is equivalent to 4.812 kJ × kg^{-1} × km^{-1}. At the time he runs the event, he weighs 65 kg, just a little less than at the time he was measured for Appendix F

documentation. The distance of a marathon is 42.2 km. Remember that total energy is released in the body as work plus heat. Running a flat course will result in zero net mechanical work, which means that all of the work done during each step is absorbed and converted to heat during that or the subsequent step. The magnitude of biological work is negligible in comparison to the total energy transduction. Therefore, nearly all energy use is converted to heat. Some of this heat is lost to the ground on impact, but this small amount will be ignored. Total heat generation can be calculated by multiplying Jerry's economy by his body mass and the distance of this race:

1.15 kcal · kg^{-1} ·km^{-1} 65 kg 42.2 km = 3154.45 kcal Equation 1:

To convert this to kJ, multiply 3154.45 kcal by 4.184 kJ per kcal: giving 13198.2 kJ

This heat generation assumes that all energy cost of running is released in the body as heat. This calculation also tells us how much energy is burned in completing the marathon. Running is an oscillatory movement that results in zero net work, beyond that needed to accelerate the body to an average speed and to overcome air resistance. Assuming acceleration is complete within the first several seconds, then the work of overcoming air resistance is the only component of energy cost that would not result in heat release within the body (total energy cost results in heat plus work). For this example, we will ignore this minor component of work and assume that all measured energy contributes to heat build-up in the body. In reality, running a marathon at near record pace will result in measurable work against air resistance. This is why it is advantageous for a runner to run closely behind another runner. The air immediately behind any runner will be moving in the direction of the runner, providing less resistance to forward movement by the runner who is following (drafting).

Without heat dissipation, the release of this heat within the body would result in an increase in body temperature. The temperature increase would be approximately 1°C for each kcal per kg. Considering body mass is 65 kg (this ignores probable body mass change during the run, due to an imbalance of water consumption and sweat loss). The use of 3154 kcal of energy would result in a 48 degrees °C increase in body temperature. Of course, this would be lethal, so the body must have some way of dissipating the extra heat. In reality, body temperature will increase only a few °C over the course of a marathon. At the end of a marathon in warm weather, it is not unusual for body temperature to be above 39 °C (Cade et al. 1992) and this high temperature is thought to impair performance during the latter parts of a race.

Heat dissipating mechanisms are described in Chapter 9. The body has essentially 3 mechanisms of heat dissipation: evaporation, conduction/convection and radiation. Of these, evaporation is the most effective, particularly on a hot day when conduction/convection and radiation are ineffective. Evaporation of sweat from the body surface dissipates heat because energy is needed to convert sweat from the fluid state to the vapour state. This energy is equal to 40.65 kJ× $mole^{-1}$ of water evaporated. One mole of water weighs 18 grams, which is equivalent to 18 ml, so this energy lost with evaporation is equal to 2.26 kJ×ml^{-1}, or the volume of water evaporated is 0.44 ml × kJ^{-1} of heat lost. Of course, not all of the sweat produced by Jerry will be lost to evaporation. Some may drip off his body. Although this fluid will carry some of the extra heat produced during the marathon, much more heat is lost if that fluid is evaporated.

How much water would Jerry have to evaporate from his skin to dissipate the heat that would otherwise build up in his body during the marathon? If we consider not allowing an increase of body temperature, then the evaporation must be sufficient to prevent 48 °C change in body temperature.

13198.2 kJ · 0.44 ml·kJ^{-1} = 5844.2 ml or 5.84 litres Equation 2:

If Jerry was able to sweat enough to allow evaporation of 1 litre of water from his skin during each hour of running, and he completes the marathon in 3 hours, then he could dissipate 6780 of the 13198.2 kJ, or just over half of this heat load. If his temperature increased by 2 degrees C, he could accommodate another 1087 kJ. He still needs to dissipate 6266 kJ of heat by conduction and convection. Although he could sweat more than 1 litre per hour, it is not sweat rate we have calculated, it is the amount of evaporation. Losing sweat from the body and dripping to the ground does not cool the body. Maximal sweating rates can exceed 2 litres per hour (Baker 2017).

Now we return to our discussion of the energy cost in the body. First, we will deal with resting energy requirements, then for muscular exercise before we continue with a discussion of the metabolic sources of energy during exercise.

Resting Energy Requirements

Basal metabolic rate is the rate of metabolism in the body when no food has been consumed for 16 hours and the body has been recumbent and inactive for at least 30 min. In this state, only the essential metabolic processes of the body will be engaged. Very little energy will be used in the digestive system and muscle metabolism should be minimal, because lying down requires the least amount of muscle activation. The heart requires some energy because as long as you are alive, your heart will be beating intermittently. Similarly, the muscles that move air into your lungs will require some energy. Exhaling this air is a passive process and requires no additional energy. Other than these obvious needs for energy, most energy in this state is required to maintain ion gradients in the body. The slow leak of ions across membranes will require energy in the form of ATP to actively transport ions back across the membrane. Under these conditions, aerobic metabolism will be providing all of the energy required in the body and measurement of oxygen uptake will reveal that the body is using close to 3.5 ml · kg^{-1} · min^{-1}. This value decreases with age and during food deprivation (starving) and can be increased by hormonal influence (thyroid hormone or adrenaline). Basal metabolic rate is the energy cost required to maintain your body in a state of homeostasis, when factors that would disturb homeostasis are absent. Your resting metabolic rate is sufficient to maintain your body temperature in an appropriate environment, so metabolic heat production is balanced by heat loss from the body.

While you are sitting in class, or sitting somewhere comfortable while reading this textbook, your metabolic rate will likely be slightly higher than this; 3.7-3.9 ml · kg^{-1} · min^{-1}. This is because you will have some muscle activation, even if only to maintain posture or occasionally turn a page or hit a keyboard key. Your brain may be a little more active and you may still be digesting your last meal. Digestion requires energy for smooth muscle motility and transport of specific molecules across the digestive tract. If you were recently engaged in vigorous physical activity, you may also be in recovery from the exercise. The metabolic rate is increased by active use of your muscles and slowly returns to the resting state during a recovery period after the exercise. The oxygen uptake above the resting level during a recovery period is sometimes called the "excess postexercise oxygen consumption" (EPOC) (Gaesser and Brooks 1984). Others refer to this as simply the recovery oxygen uptake.

Processes that Require Energy in Muscle Contraction

As indicated above, energy is required in muscle for ion pumping and for molecular motors (actomyosin ATPase). The key ion pumps include Na^+-K^+ ATPase and Ca^{2+} ATPase which is also known as sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA). There are three isoforms of SERCA in the endoplasmic reticulum membranes of the human body. SERCA1 is found in the fast-twitch skeletal muscle. SERCA2 is found in cardiac and slow-twitch skeletal muscle and SERCA3 is found in smooth muscle and nonmuscle tissue. The implications of these energy-requiring processes are described below.

Ion Pumping

When an action potential is propagated in either an axon or a myocyte, Na+ and K+ move down their concentration gradients through voltage-gated ion channels, progressively along the full length of the cell (see Chapter 3). In the myocyte, this is the event that ultimately activates or "turns on" the muscle contractile process (see Chapter 5). In a resting muscle fibre, or an axon, there is a concentration gradient for Na^+, K^+ and Cl^-. These ions are distributed across the membrane as illustrated in Figure 6A-1. Na^+ and Cl^- are at a high concentration outside the cell and K^+ is at a high concentration inside the cell. When the channels open because the membrane depolarizes to threshold, these ions diffuse passively down their electrochemical gradient. The process of activating a muscle cell does not require energy. Recovery of ion concentration gradients does require energy. This energy, in the form of ATP is used to restore the concentration gradient for the ions that have crossed a membrane.

The voltage change associated with the action potential is detected by the dihydropyridine receptors in the transverse tubules and these modified Ca^{2+} channels cause opening of the ryanodine receptors; Ca^{2+} channels in the membrane of the terminal cisternae. The subsequent diffusion of Ca^{2+} into the sarcoplasm from the sarcoplasmic reticulum is a passive process, taking advantage of the open ryanodine receptors. However, to get the Ca^{2+} back into the sarcoplasmic reticulum requires energy.

The Na^+-K^+ATPase transports 3 Na^+ out of the cell and 2 K^+ ions into the cell for each ATP hydrolyzed. The Ca^{2+}ATPase of the sarcoplasmic reticulum (SERCA), transports 2 Ca^{2+} ions with each ATP that is split. The total amount of ATP used by ion transport processes can account for 20 to 40 % of total energy cost of a muscle contraction. Factors that affect this magnitude include not only the frequency and duration of activation but any factor that will influence the amount of energy used by cross-bridges. This includes: sarcomere length, velocity of contraction, and number of motor units activated. All of these factors affect

the energy cost of the acto-myosin ATPase, and frequency and duration of activation will also affect the need for ion transport. Any change in one or the other of these energy-requiring processes will alter the fraction of the total energy needed by the ion transporters.

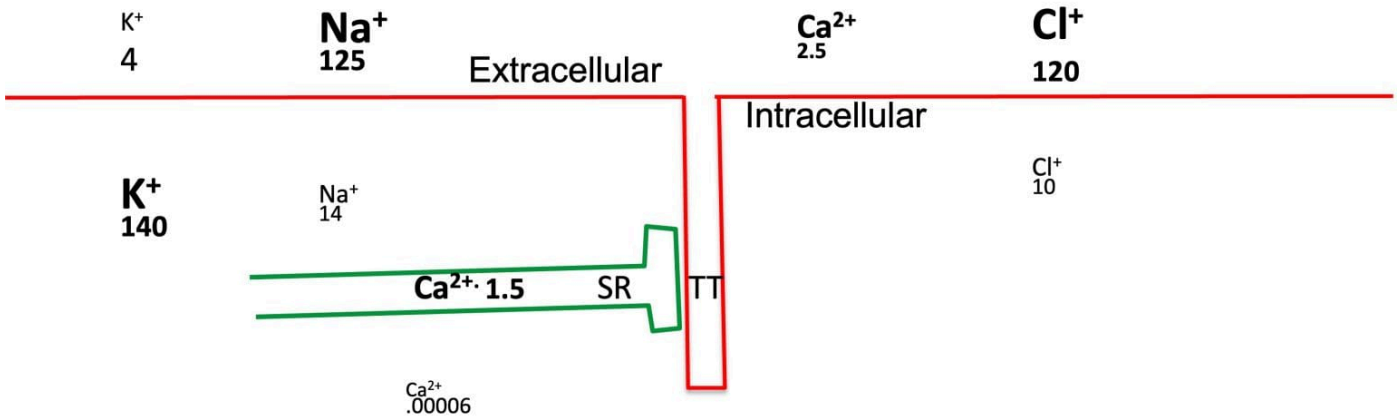


Figure 6A-1 Ion concentration gradients of the myocyte. *Here, the major ions contributing to the membrane potential and activation of the muscle are shown with their free concentrations (numbers adjacent to ion symbol; concentration is in mM). Note that Ca^{2+} concentration in the myoplasm will change from the nanomolar range to the micromolar range on activation of the muscle fibre. The free [Ca^{2+}] in the SR is about 1.5 mM, but considerably more Ca^{2+} here is bound to calsequestrin.*

Molecular Motors

Myosin is a molecular motor. The myosin molecule forms a cross-bridge with actin and undergoes a conformational transformation that results in exertion of force against the actin. The force can result in motion. Each myosin head can undergo repeated cycles of binding, generating force and/or motion and detaching. With each cycle of attachment and detachment, the energy associated with the terminal phosphate bond of ATP is released as Pi dissociates, resulting in the formation of ADP. This energy is converted to mechanical work and heat production. The cross-bridge cycle repeats for myosin heads with apposing actin filament binding sites along the full length of any activated muscle cell as long as [Ca^{2+}] is maintained high enough to keep Ca^{2+} bound to troponin (see Chapter 5). The total amount of energy used by these molecular motors can account for 60-80% of the total energy cost of muscle contraction. In a brief muscular effort, the rate of ATP use can increase 100 times greater than the resting rate. The magnitude of ATP use is dependent on: muscle size (volume), motor unit recruitment, rate coding, fibre-type, velocity of shortening, and sarcomere length.

Quantification of Energy Cost of Muscle Contraction

Muscle activation and contraction require energy and that energy is obtained from the chemical energy released on hydrolysis of ATP resulting in the formation of adenosine diphosphate (ADP) and release of inorganic phosphate (Pi). The energy is required by 3 primary ATPase processes: myosin ATPase, Na^+-K^+ATPase and Ca^{2+}ATPase. Myosin ATPase is activated by interaction of the myosin molecular motors with actin (the combination is referred to as actomyosin ATPase) for movement or force generation. Active transport of Na^+ and K^+ across the sarcolemma is accomplished by an ion pump, Na^+-K^+ ATPase that requires ATP. Active transport of Ca^{2+} into the sarcoplasmic reticulum is accomplished with the Ca^{2+} ATPase also known as SERCA. These energy-requiring processes are depicted in Figure 6A-2.

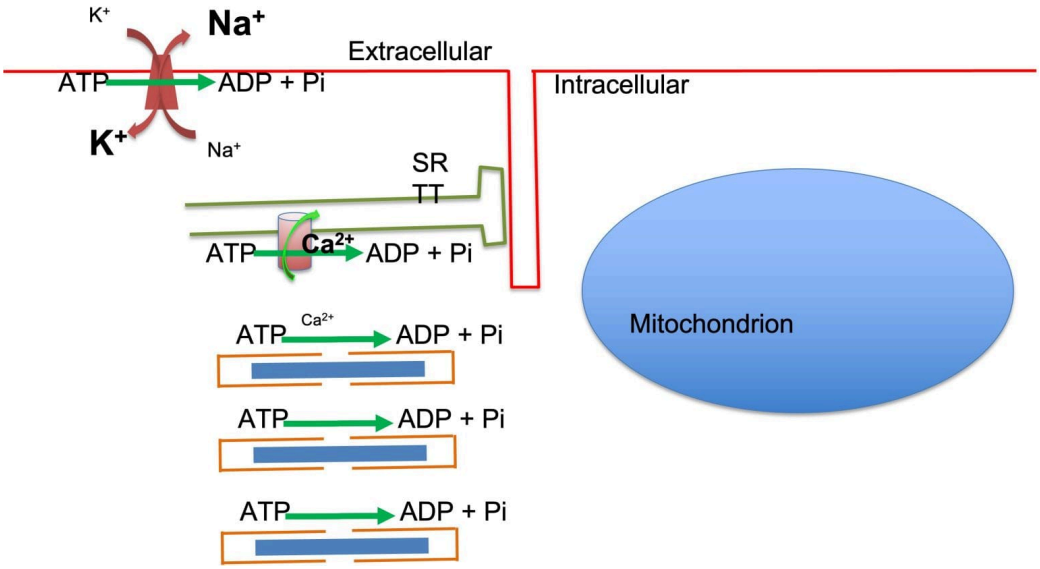


Figure 6A-2. Energy use in skeletal muscle. *Energy is used in skeletal muscle in the form of ATP, resulting in formation of ADP and Pi. Energy is used for ion transport (Ca^{2+}, Na^{+} and K^{+}) and for force generation and movement. SR is sarcoplasmic reticulum, TT is transverse tubule,*

When ATP is hydrolyzed to ADP and Pi, energy previously stored in the phosphate bond is released. This energy is converted to heat and work. Work can be subdivided into mechanical work and biological work (creating molecules or supplementing ion concentration gradients). The energy cost of muscle contraction has historically been studied by careful quantification of heat released during isometric contractions and heat plus work in dynamic contractions.

Measurement of Heat During Muscle Contraction

There is a long history of the use of heat measurement to quantify the energy cost of muscle contraction. The approach has involved removing a small muscle from an animal and mounting it in a chamber that is sealed and insulated (Hill 1938). The muscle is stimulated to contract and the heat generated during the contraction is measured. The heat is quantified in joules of energy, revealing how much energy was released by the muscle. When the muscle is allowed to do work, the sum of the work plus the heat released is the total energy transduced by the muscle (the Fenn effect). Much of what we know about muscle energetics can be attributed to this technique. However, most this this work on muscle energetics was done on frog muscles at room temperature. Room temperature in the labs at Kings College London was apparently much cooler than most of us keep our houses now, so reported temperatures were often ~15 °C. This means that much of what we know about muscle energetics does not necessarily apply to muscles functioning in the human body near 37°C.

Measurement of Oxygen Uptake During Muscle Contraction

The measurement of oxygen uptake provides the opportunity to calculate the energy obtained from substrates (fats and carbohydrates) by oxidative metabolism. Typically, this approach can be considered to provide all of the energy for replenishment of ATP during submaximal steady state conditions when there is no continuing net anaerobic metabolism. To satisfy this condition, there must be no net production of lactate within the muscle. Any lactate produced in a given cell must be oxidized in that cell or in a neighboring cell, without getting into the blood. Under these conditions, the measurement of $\dot{V}O_2$ can provide an estimate of how much energy was provided to a muscle by oxidative metabolism. It is important to realize that conversion of the chemical energy in substrates like fat and carbohydrate to ATP results in loss of about 40% of the energy that was available in these substrates. This energy is lost as heat. Considering that heat is also lost when the energy in ATP is transduced to mechanical work, muscles are not very efficient. Efficiency, when considering energy transduction, is essentially the proportion of energy conserved in a useful form. Heat is not generally considered a useful form of energy for biological purposes. The best a muscle can do is approximately 25% efficient.

Muscle Contraction

Two approaches have been used to quantify oxygen uptake during muscle contractions. One requires the surgical removal of

a muscle from an animal and sealing it in a chamber. The muscle can be stimulated to contract and the amount of oxygen disappearing from the solution around the muscle is the oxygen uptake. This decrease in oxygen content can be quantified with an oxygen sensor, detecting partial pressure of O_2 in the chamber, and the known relationship between O_2 content and partial pressure of O_2. The second technique for measuring muscle $\dot{V}O_2$, requires isolation of the vasculature for a muscle or muscle group and measuring muscle blood flow and arterial and venous oxygen content (Gladden et al. 1978). This approach has also been used to estimate oxygen uptake of a leg during one-legged cycling exercise (Jensen-Urstad et al. 1994). This latter technique relies on the Fick principle, which quantifies the amount of oxygen delivered to the muscle and the amount that is still in the venous blood leaving the muscle. The difference is the oxygen that was left in or used by the muscle. If the total content of oxygen in the muscle has not changed, this uptake was used for oxidative metabolism.

Fick Equation: $\dot{V}O_2 = \dot{Q}(CaO_2 - CvO_2)$ Equation 3

In this equation, C represents content, a and v represent arterial and venous blood. The dot over the V and Q represents per unit of time (usually per min).

Measurement of Oxygen Uptake During Exercise

During exercise, the most common way to quantify the energy cost is by measurement of oxygen uptake; that is, by gas exchange across the pulmonary system. This approach quantifies all aerobic energy transduction in the body, so it includes the ancillary energy costs like the cost of breathing, the cost of cardiac output and the cost associated with energy-requiring processes in all the living cells in the body, including postural and stabilizing muscles which may not be directly involved in the exercise. Some of those cells will have increased energy use during exercise and some will have decreased energy use. When the exercise in question involves a substantial muscle mass, then the measured oxygen uptake is a reasonable estimate of the energy cost of the exercise. Some scientists prefer to subtract the resting $\dot{V}O_2$ measured prior to the exercise from that measured during exercise, yielding net oxygen uptake. The danger in doing this is that there is no guarantee that the processes using O_2 prior to the exercise will continue using O_2 at the same rate during the exercise. Before we consider the metabolic processes that provide energy, the measurement of oxygen uptake will be described.

Measuring Oxygen Uptake at the Lungs

When we breathe, we inhale air from the atmosphere that contains 20.93% O_2, 78% N_2 and the balance other gases, including CO_2 which is only about .04% of the atmosphere. When we breathe out, the air that leaves our alveolar spaces will have less O_2 and more CO_2. The magnitude of change will depend on the blood flow and gas content of the blood flowing through the alveolar spaces and the rate of replacing the alveolar air (ventilation). Typical values for end-tidal gas (air flowing out of the lungs at the end of breathing out) concentrations, representing alveolar gas are 17% for O_2 and 5- 6% for CO_2. Calculating pulmonary oxygen uptake relies on the same Fick principle as described above, but substitute pulmonary values. Knowing the ventilation and the concentration (fraction) differences for O_2 and CO_2, the oxygen uptake and CO_2 output can be calculated. This calculation is described in the special feature box that follows.

Special Feature Box

Calculation of Oxygen Uptake

To measure oxygen uptake, it is necessary to know the concentration of O_2 in the inhaled air, the volume of inhaled air, the concentration of O_2 in the exhaled air and the volume of exhaled air. The volume of inhaled air is not necessarily the same as the volume of exhaled air because we usually remove more O_2 from the air we breathe than we add CO_2. If the time for which these data apply is known, then the VO_2 can be expressed as a rate (usually per min, designated by a dot over the V). $\dot{V}O_{2(STPD)} = (\dot{V}I_{(STPD)}\ FIO_2) - (\dot{V}E_{(STPD)}\ FEO_2)$

Where $\dot{V}E$ is expired minute ventilation, $\dot{V}I$ is inspired minute ventilation, STPD is standard temperature and pressure dry. The standard temperature is 273 (equal to 0 °C) and standard pressure is one atmosphere at sea level (760 mmHg). These are the conditions under which 1 mole of a gas occupies 22.4 Litres. Typically, only expiratory volume is measured, and the inspiratory volume is calculated, knowing that N_2 inhaled is equal to N_2 exhaled. Before this calculation can be made, the measured gas volumes must be converted to the standard condition (standard temperature and pressure dry). This is done to compensate for

the effects of these parameters on the volume of gas of concern (O_2 and CO_2). These calculations are shown with the following equations, which assume that expired volume is measured.

$$\dot{V}E_{(STPD)} = \dot{V}E_{(ATP)} \cdot \frac{273\ °K}{Tgas\ °K} \cdot \frac{PB - PH2O}{760\ mmHg}$$

ATP, in this context, is ambient temperature and pressure, or more specifically the conditions under which the measurement was made. is temperature at which the gas volume was measured (degrees Kelvin, obtained by 273 + temperature in C), PB is barometric pressure, PH_2O is partial pressure of water vapour (usually, this is saturated because exhaled air is fully saturated). Barometric pressure is typically measured in mm Hg but the units are not important if both ambient and standard pressure are expressed with the same units.

$$\dot{V}I_{(STPD)} = \dot{V}E_{(STPD)} \cdot \frac{F_E N_2}{F_I N_2}$$

Now, the entire string can be put together:

$$\dot{V}O_{2(STPD)} = (\dot{V}E_{(ATP)} \cdot \frac{273\ °K}{Tgas\ °K} \cdot \frac{PB - PH2O}{760\ mmHg} \cdot \frac{F_E N_2}{F_I N_2} \cdot FIO_2) - (\dot{V}E_{(ATP)} \cdot \frac{273\ °K}{Tgas\ °K} \cdot \frac{PB - PH2O}{760\ mmHg} \cdot FEO_2)$$

A similar calculation can be made for determination of carbon dioxide output.

$$\dot{V}CO_{2(STPD)} = (\dot{V}I_{(STPD)} \cdot FICO_2) - (\dot{V}E_{(STPD)} \cdot FECO_2)$$

This calculation will give a negative value, indicating output, but the this is ignored when expressing the value as carbon dioxide output ($\dot{V}CO_2$). Now that you know how to calculate oxygen uptake, it is time to consider all of the ways that ATP is replenished during exercise. Here, a brief description of these processes will be presented. A more detailed discussion will be given in the following chapter.

Processes that Replenish ATP

The metabolic processes that replenish ATP can be described as aerobic or anaerobic, depending on whether they use O_2 or not. It is important to recognize that the term “anaerobic” is used in this way when discussing metabolic processes in living tissue, in spite of the fact that oxygen is present. A true absence of O_2 would be incompatible with life. The anaerobic, or non-aerobic sources of energy include: ATP, creatine phosphate (CrP) and glucose or glycogen. Aerobic energy is derived from fatty acids, glucose, glycogen and, to a small extent, amino acids. The metabolic pathways that release the energy from these substrates are briefly described in the following sections and more completely in the following chapter. The metabolic pathways rely on enzymes, special proteins that facilitate chemical reactions, to achieve their goal.

Enzymes

Chemical reactions typically will proceed only very slowly if left on their own. This is because there is often a barrier or activation energy required for the reaction to occur. Enzymes facilitate the reaction by decreasing or overcoming this activation energy. Enzyme-facilitated reactions can proceed at a rate that is thousands of times faster than the spontaneous reaction without the enzyme. Enzymes have binding sites for the reactant(s) and release the product(s) of the reaction. The rate of the reaction is still dependent on the concentrations of reactants and products. Enzymes can also have binding sites for accessory molecules that modify the rate of the reaction. This form of regulation is called allosteric regulation. In many cases, enzymes remain in an inactive state until turned on or activated by allosteric regulation. Alternatively, the enzyme may be turned on by reacting with a regulatory enzyme and then modulated by allosteric regulation. In many cases, this regulatory enzyme (a kinase) will phosphorylate the enzyme to turn it on. Another enzyme (phosphatase) may be responsible for dephosphorylating this enzyme to return it to the inactive state.

Non-aerobic Energy Sources

Chemical energy is provided by 2 processes that do not require oxygen: immediate availability of high energy phosphates, and glycolysis leading to the formation of lactate. These processes are referred to as anaerobic. Note that the term “anaerobic”, is not used in the literal meaning: – in the absence of oxygen. In discussion of living biological systems, the term anaerobic is often used to describe processes that can proceed in the absence of oxygen, but these processes can also still proceed when oxygen is present. The fact that these chemical reactions occur in living cells should not be interpreted as indicating a lack of oxygen. Although it is true that a paucity of oxygen will result in greater reliance on these processes, the fact that some ATP is produced by anaerobic metabolism should not be interpreted as oxygen is limiting the aerobic processes.

These anaerobic metabolic processes include the following:

- Decreasing [ATP]: a net reduction in [ATP] is considered providing energy by anaerobic mechanisms
- The following processes replenish ATP by anaerobic metabolism
  - 2 ADP Þ ATP + AMP
  - Decreasing [CrP] CrP + ADP ÜÞ Cr + ATP
  - Glycolysis, using glucose and/or glycogen: glucose +2 ADP Þ 2 lactate + 4 ATP

High Energy Phosphates

ATP and CrP are considered high energy phosphates. These molecules can release substantial energy when the phosphate group (inorganic phosphate or Pi) is removed from the molecule. The energy stored in the chemical bond between a phosphate and the rest of the molecule can be used to accomplish biological work. ATP is the immediate source of chemical energy for all biological work performed in the body. The concentration of ATP in skeletal muscle at rest is in the range of 4-6 mM. During exercise, this can typically decrease by 10-30%, and during hypoxia, [ATP] can fall to 50% of the normal resting level. The fact that [ATP] does not normally decrease by very much is a testament to the ability of the metabolic pathways to replenish ATP nearly as fast as it is used in processes requiring energy. The other nonaerobic processes include the kinase reaction, the myokinase reaction and glycolysis. It is considered by some muscle physiologists that the muscle can regulate [ATP] by increasing the supply (aerobic and anaerobic metabolism) and/or reducing the rate of use of ATP (MacIntosh et al. 2012). Reducing the rate of use by impairing muscle activation is essentially a regulatory process that results in reduced force or power output that we call muscle fatigue.

The Creatine Shuttle

Consider that ATP is aerobically produced in the mitochondria and is needed for energy metabolism in the myofibrils. This separation of the location of energy use from the place where much of the energy is provided could create a problem. As you read through this section, keep in mind that to increase the rate of diffusion of molecules within the myocyte the concentration gradient must be increased. Creatine phosphate is typically available in the myocyte at rest at 3-5 fold higher concentration than ATP. This means that the potential for increasing the concentration gradient for CrP is greater than that for ATP. Also, the second factor important for the rate of diffusion of a molecule is its molecular weight. Creatine has a molecular weight of 131.13 $g \cdot mole^{-1}$ while that for adenosine diphosphate is 427.2 $g \cdot mole^{-1}$. Creatine will diffuse much faster than adenosine diphosphate. Similarly, creatine phosphate will diffuse much faster than adenosine triphosphate.

The enzyme that is responsible for the reaction depicted above in which CrP donates its Pi to ADP is kinase. Notice that the arrow indicates that the reaction can go in both directions. There are two isoforms of kinase in muscle. One of these is located at the M-line of the myofibril, right in the middle of the sarcomere. Here, this enzyme can quickly handle the ADP produced by myosin ATPase, keeping the [ADP] low by rephosphorylating it to ATP. The price of this action is that [CrP] can quickly decrease when muscle contractions begin. This reaction will result in an increasing concentration of creatine in the myofibrils. It is thought that kinase is unregulated and the rate of the reaction is dependent only on the concentrations of reactants and products.

The second isoform of creatine kinase is located in the membrane of the mitochondria. Here, kinase favours the reverse reaction, resulting in rephosphorylation of creatine. In this case, mitochondrial ATP reacts with cytoplasmic creatine to form CrP. ADP is the by-product of this reaction. This reaction has several important consequences. One consequence is that it will increase mitochondrial concentration of ADP, which in turn will stimulate oxidative metabolism in the mitochondria. The second is that it will decrease concentration of creatine around the mitochondria. Mitochondria are located in two regions within skeletal muscle; subsarcolemmal and intermyofibrillar. The use of CrP to replenish ATP in the myofibrils will result in a concentration gradient for creatine and diffusion of creatine from the myofibrils to the mitochondria. The primary advantage of CrP over simply higher [ATP] is that creatine is a smaller molecule than ADP, so creatine can diffuse faster to the mitochondria where it stimulates oxidative metabolism by undergoing the following reaction:

$$Cr + ATP \xrightarrow{CK} CrP + ADP$$

It is important to note that initial ATP demand is met by this important reaction and that oxygen uptake is slow to rise because ATP is provided independent of oxidative metabolism. Inhibition of creatine kinase (CK) will actually increase the rate of rise of oxygen uptake (Kindig et al. 2005), demonstrating that the slow rise in oxygen uptake at the beginning of exercise is a consequence of effective ATP regeneration by anaerobic metabolism. The additional advantage of this creatine shuttle (see Figure 6A-3) is that [ADP] in the cytoplasm can remain low. The energy charge associated with ATP hydrolysis is important for many reactions in the body, including the actomyosin ATPase. The energy charge is dependent on maintaining [ATP] and can be represented as the following:

Energy charge = ([ATP]+½[ADP])/([AMP]+[ADP]+[ATP])

Note that an increase in ADP concentration will decrease the energy charge. The resting concentration of ADP in skeletal muscle is in the micromolar range and although this increases during repeated muscle contractions, it remains in the micromolar range.

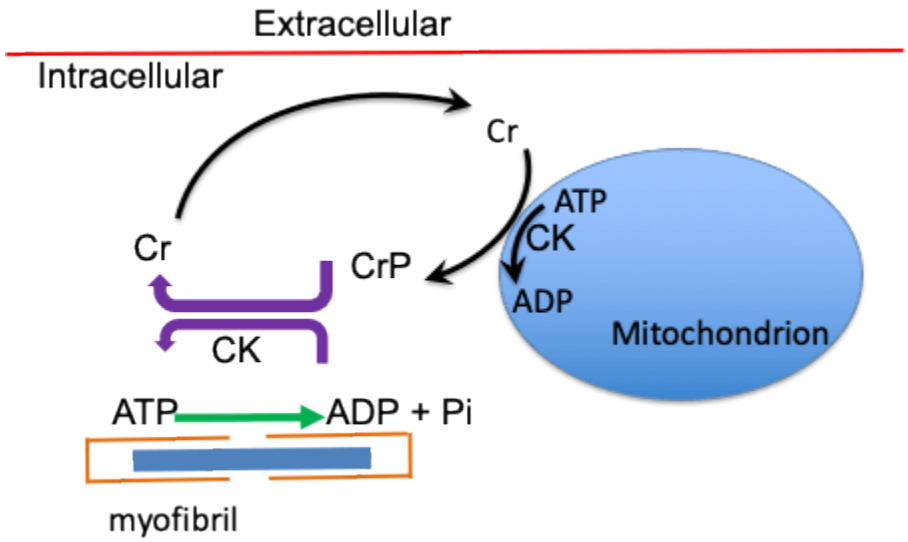


Figure 6A-3 Creatine Shuttle.

Here, the use of adenosine triphosphate (ATP) for energy in the myofibril is reflected as: ATP → ADP + Pi, where ADP is adenosine diphosphate and Pi is inorganic phosphate. The enzyme creatine kinase (CK) is located in the myofibril and catalyzes the reaction ADP+CrP → ATP + Cr where CrP is creatine phosphate, and Cr is creatine. Creatine

diffuses away from the myofibril and will reach the mitochondria where the reaction proceeds in the opposite direction, catalyzed by the mitochondrial creatine kinase which is embedded in the mitochondrial membrane. The mitochondrion is typically located between myofibrils, but some also is located next to the sarcolemma.

Glycolysis: From Glucose to Pyruvate

Glycolysis is a sequence of reactions that occur in the cytoplasm, where the 10 glycolytic enzymes are located. In fact, these enzymes are known to be associated with glycogen granules and with the thin filaments. The sequence of 10 steps of glycolysis is shown in Figure 6A-4. The starting point for glycolysis is either glucose, brought in across the sarcolemma by glucose transporters (GLUT 4 or GLUT 1), or glucose-1-Phosphate, derived from cleavage of a glucose unit from glycogen, a process called glycogenolysis. Glycogen granules are prevalent in skeletal muscle and liver. The enzymes of glycolysis are located within the glycogen granules and along the thin filaments. Glycogen is a macromolecule containing branched chains of glucose. At the onset of exercise, the enzyme glycogen phosphorylase is activated, resulting in a rapid increase in the availability of glucose-1 phosphate. For this reason, glycolysis is an important means for replenishing ATP for the first minute or two of exercise. Glycogenolysis is also accelerated by the catecholamines (see Figure 6A-5). As exercise becomes more stressful, the activation of the sympathetic nervous system will accelerate glycogenolysis and provide a stimulus for increased glycolysis.

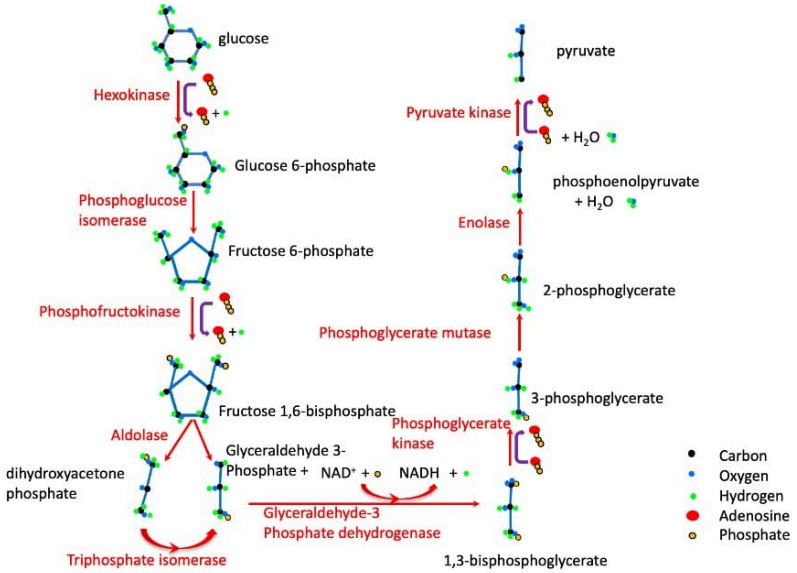
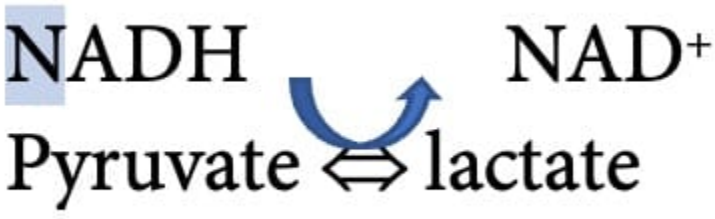


Figure 6A-4 Anaerobic ATP Regeneration by Glycolysis 10 Steps of Glycolysis are illustrated here with the enzymes for each step in red. Note that the step catalyzed by aldolase results in a change from one 6-carbon unit to two 3-carbon units (dihydroxy acetone phosphate and glyceraldehyde 3-phosphate). The dihydroxyacetone phosphate is subsequently converted to glyceraldehyde 3-phosphate, resulting in 2 of each subsequent molecule for each glucose that enters the pathway. The net reaction is given below: $C6H12O6 + 2NAD+ + 2ADP + 2Pi \rightarrow 2(CH3(C=O)COOH) + 2ATP + 2NADH + 2H+$

Glycolysis requires a glucose molecule as well as ADP, ATP and NAD+. The end products are pyruvate, ATP, H+ and NADH. The ATP produced in glycolysis can be used immediately for energy by the ion transporters and/or myosin ATPase. NADH can transfer electrons to the mitochondria for the electron transfer chain, or to lactate in the reaction:



which is catalyzed by lactate dehydrogenase. This is an important consideration in the discussion of aerobic vs anaerobic metabolism. In many ways, the formation of lactate is like a holding tank for reducing equivalents

and tricarboxylates. Lactate can accumulate in muscle and be transported out of a muscle to accumulate in blood and/or be taken up in another tissue (often a less active muscle). Lactate can be converted back to pyruvate for aerobic metabolism either in an adjacent myocyte or at some distance from where it was produced. Lactate can also be taken back up by the liver and used for gluconeogenesis. This conversion is referred to as the Cori cycle which is described later in this chapter.

The end-point of glycolysis is pyruvate, the precursor of the acetyl CoA, needed for mitochondrial oxidative metabolism. Pyruvate is also the precursor for lactate. Each molecule of pyruvate produced by glycolysis will either enter the mitochondria or be converted to lactate. The rate of conversion to lactate by the enzyme, lactate dehydrogenase is concentration dependent (proportional to the concentration of pyruvate). An absence or shortage of oxygen is not needed for this to occur. The entry of pyruvate to the mitochondria may be limited by a number of circumstances: transporter availability, which may also be dictated by concentration of pyruvate in the mitochondria, mitochondrial volume, and possibly oxygen availability. Oxygen is needed in phosphorylation as oxygen is the final electron acceptor in the electron transfer chain.

Accelerated glycogenolysis can provide the substrate for glycolysis, glucose (or more specifically, glucose 1-phosphate which needs to be transformed to Glucose 6-phosphate). Glycogenolysis is accelerated by an increase in [Ca^{2+}] but also by the catecholamines which are commonly secreted in conjunction with activation of the sympathetic nervous system which occurs during stressful exercise. Figure 6A-5 illustrates the pathway for activation of glycogenolysis in this way. Accelerating glycogenolysis will result in a high intracellular concentration of glucose and will drive glycolysis by mass action.

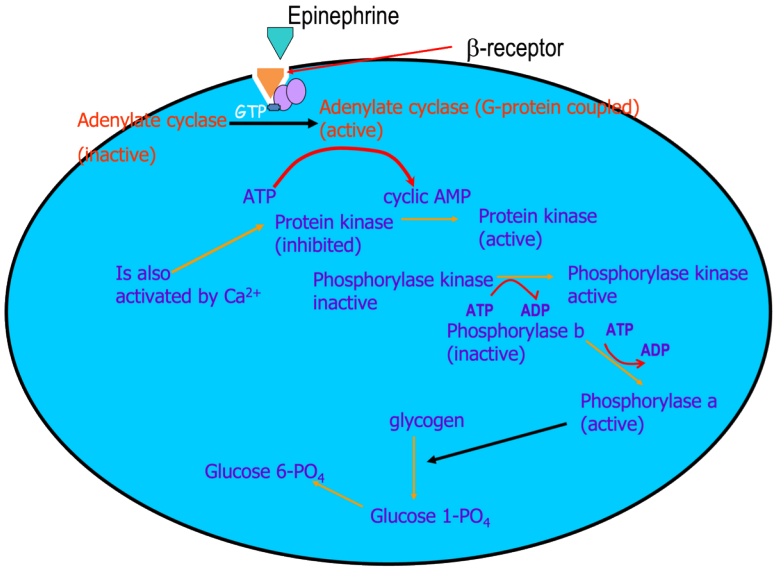


Figure 6A-5 Activation of Glycogenolysis by Epinephrine: An increase in [Ca^{2+}] and/or catecholamine binding to beta receptors on the muscle membrane will activate glycogenolysis, resulting in the cascade of events including phosphorylation of key enzymes and the release of glucose from glycogen.

Glycolysis and Lactate

The end-point of glycolysis is the formation of pyruvate. Pyruvate can be taken into the mitochondrion for oxidative metabolism, or converted to lactate in the cytoplasm. The formation of lactate results in the designation of the ATP produced by glycolysis to this point as anaerobic metabolism. The conversion to lactate can be considered the 11th step of glycolysis and this step is catalyzed by the enzyme lactate dehydrogenase, which is associated with the other enzymes of glycolysis. Although the formation of lactate is often interpreted to mean that oxygen delivery is limiting metabolism, this is not necessarily the case. In fact, lactate will be produced during glycolysis simply due to mass action. This means that even at rest a small amount of lactate will be produced and released into the blood from some muscle fibres. The higher the concentration of pyruvate, the faster the reaction proceeds (pyruvate to lactate). When glycolysis is accelerated at the beginning of exercise, pyruvate concentration will increase. This will increase the rate of lactate formation as well as the rate of pyruvate incorporation into the Kreb's Cycle (see below). When glycolysis yields pyruvate that is oxidized in the mitochondria, the entire process is considered to be aerobic. When there is a net production (more production than disposal) of lactate, the process is considered to be anaerobic (without the use of O_2).

Aerobic Energy Sources

The mitochondria, also commonly referred to as the power-house of the cell, is the site where aerobic metabolism replaces ATP that has been used to provide energy for biological work. Mitochondria are found in two locations: subsarcolemmal or intermyofibrillar. Mitochondrial structure is described in Chapter 4 and briefly recapped here, before the function of the mitochondria is described.

Mitochondria

The primary function of mitochondria is the regeneration of ATP, using the chemical energy from fats, carbohydrates and, to some extent, proteins. For example, glucose ($C_6H_{12}O_6$) is oxidized to 6 CO_2 and 6 H_2O, using 6 molecules of O_2. Long chain fatty acids undergo beta oxidation to form acetate which can be taken into the Kreb's Cycle for oxidative metabolism.

Subcellular Distribution: Mitochondria are subcellular organelles, located in two general regions in myocytes. Some mitochondria are located just under the membrane (subsarcolemmal) and others are located between the myofibrils. This places the mitochondria reasonably close to where ATP is used. The primary ATPase in the sarcolemma is the Na^+-K^+ATPase and the primary intracellular ATPase is myosin ATPase, located in the myofibrils.. Careful 3-dimensional evaluation of mitochondrial structure reveals what appears to be a continuous structure. This has led to the mitochondria being referred to as a reticulum, rather than a series of small organelles. The volume of mitochondria in human skeletal muscle myocytes varies from about 2 to 8 % of muscle volume, with lower values in fibres that are fast-twitch fatiguable and higher values in fast-twitch fatigue resistant and slow-twitch fibres (see Chapter 4). In some species, like the bumblebee, mitochondria of the flight muscles can make up 50% of the myocyte volume.

The Internal Structure of the Mitochondrial Reticulum

The mitochondrial reticulum (see Figure 6A-6) is a double-membrane structure with the internal membrane folding into the interior of the mitochondrion. These folds of the internal membrane are called cristae. The internal membrane has a series of lollipop shaped structures called F-complex (see Figure 6A-6). The F-complex is the site of active transport of H^+ into the intermembrane space associated with electron transport. As electrons are passed along the cytochromes of the electron transport chain, H^+ is transferred across the inner membrane. This action increases the concentration of H^+ in the intermembrane space and the return of H^+ to the matrix results in phosphorylation of ADP to ATP.

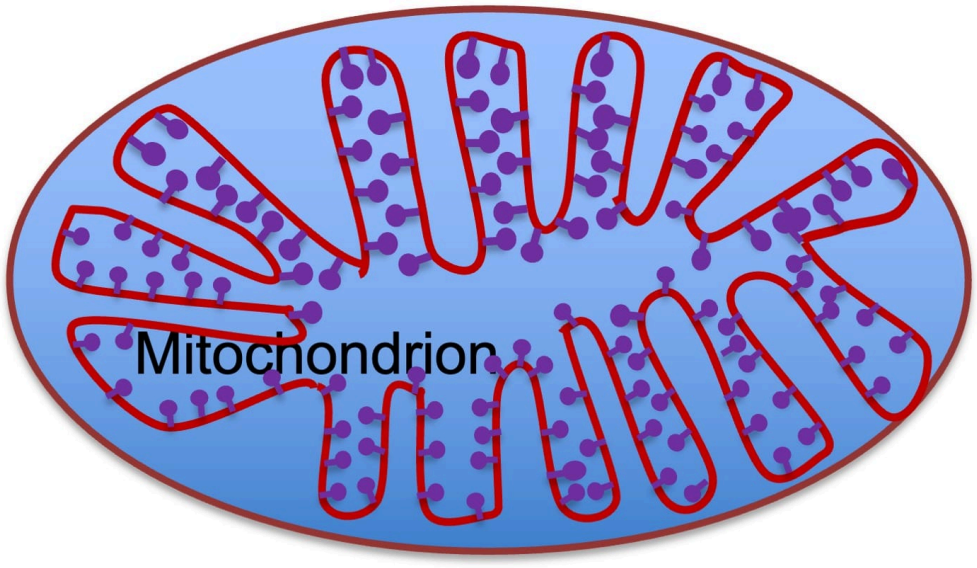


Figure 6A-6 Mitochondrial Structure. The mitochondrial reticulum has two membranes, internal (red) and external (brown). The internal membrane separates the intermembrane space from the matrix. The columns formed by the internal membrane are referred to as cristae.

There is a large number of proteins associated with the mitochondrion. These proteins fall into the classification of: structural, enzymes, channels and pumps. Some of these proteins are synthesized within the mitochondria, where the genes for these proteins are located, but many of them have their genes in the nucleus of the myocyte. One advantage of local synthesis is that it

avoids the difficult transport of the protein into the mitochondria.

Krebs or Tricarboxylic Acid Cycle

The Krebs Cycle is also known as the Citric Acid Cycle, because the first step in this cycle results in the formation of citric acid. When pyruvic acid enters the mitochondrion, it is decarboxylated to acetate. Acetate combines with Coenzyme A, forming acetyl CoA. Acetyl CoA reacts with oxaloacetate to form citric acid. The subsequent sequence of reactions take the 6-carbon citric acid and by removal of (2) CO_2, will form oxaloacetate. In this way, this metabolic pathway is a cycle, beginning with and ending with oxaloacetate. The enzymes and chemical reactions of the Krebs Cycle are illustrated in Figure 6A-7.

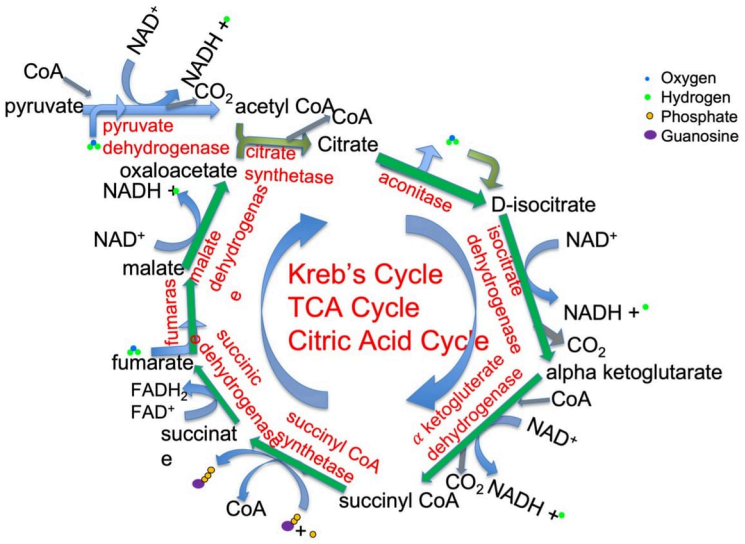


Figure 6A-7 The steps of the Kreb's Cycle. Enzymes are in red text. Arrows indicate direction of reaction (green) and input/output (blue and grey). Note the role played by water, CO2, NAD^+/NADH and H^+

The Kreb's Cycle, also known as the tricarboxylic acid cycle and the citric acid cycle, is a mitochondrial process associated with respiration, that takes pyruvate from glycolysis or acetyl CoA from fatty acid catabolism and generates CO_2, GTP, $FADH_2$ and NADH. The energy provided by mitochondrial metabolism is considered aerobic, because it relies on O_2 as the final acceptor of electrons in the electron transfer chain. The steps of the Kreb's Cycle follow:

- Pyruvate must be transferred into the mitochondria
- pyruvate dehydrogenase removes a CO_2 from pyruvate and adds CoA to make acetyl CoA, reducing NAD^+ in the process
- Citrate synthase combines acetate with oxaloacetate to make citrate, releasing CoA
- Aconitase rearranges a water making D isocitrate
- Isocitrate dehydrogenase lops off a CO_2, making alpha keto glycerate and reduces NAD^+ to NADH
- The formation of succinyl CoA requires a CoA and results in another CO_2 and NADH
- The removal of CoA forming succinate is combined with phosphorylation of guanosine diphosphate resulting in a nucleotide triphosphate (GTP) which can transfer energy to ADP, forming ATP
- Succinate dehydrogenase converts succinate to fumarate while reducing FAD to $FADH_2$
- Fumarase converts fumarate to malate
- Malate dehydrogenase converts malate to oxaloacetate while reducing NAD^+ to NADH

An important way to consider the Krebs Cycle is to observe what goes in and what comes out. It can be seen in Figure 6A-7 that several reactants are needed for activity of the Kreb Cycle. The cycle can proceed when the following are available: acetyl CoA, oxaloacetate, GDP (guanosine diphosphate), FAD and NAD^+. The Krebs Cycle reactions result in the formation of the following: oxaloacetate, NADH, $FADH_2$, CO_2, water and GTP. The GTP can be used to form ATP directly, but NADH and $FADH_2$ must undergo further reactions to make their energy available. Before we present the Electron Transfer Chain and phosphorylation, let's consider beta oxidation, another source of acetyl CoA for the Kreb's Cycle.

Fatty acids are stored within myocytes and are taken up easily from the blood into the muscle cells. Beta oxidation of fats occurs in the mitochondria. This process simply cuts a couple of carbon units off a fatty acid chain, forming acetyl CoA. This acetyl CoA can enter the Kreb's Cycle by replacing the acetyl CoA provided by pyruvate. Fatty acid metabolism is important for prolonged exercise, because glucose depletion can occur if fat is not mobilized and oxidized. Glucose is important for brain function, so it is important to preserve it.

Let's follow each of the substances provided by Kreb's Cycle, as ATP is regenerated for continued exercise. The oxaloacetate can react with another acetyl-CoA to keep the cycle going. The GTP can donate it's Pi to ADP, yielding ATP. H_2O is somewhat inconsequential, but metabolic production of water will delay the consequences of dehydration due to sweat loss. This is particularly relevant when glycogen loading has been accomplished because a noticeable amount of water can be released from the extra glycogen metabolism. The NADH and $FADH_2$ that are formed by the Kreb's Cycle, are important for stimulating the electron transfer chain and phosphorylation (see below). These are the processes that result in formation of ATP by oxidative metabolism. CO_2 must be removed from the cell and ultimately from the body. This process of removal is described in Chapter 7. It should also be noted that a rise in NADH concentration in the cytoplasm will stimulate lactate formation from pyruvate, thus making NAD^+ available for continued glycolysis.

Transferring Reducing Equivalents into the Mitochondria

NADH, produced in glycolysis can transfer reducing equivalents to the mitochondria via two shuttle systems: malate/aspartate shuttle and glycerol phosphate shuttle. These processes are described further in chapter 6B.

Electron Transfer Chain

The electron transfer chain, also known as the electron transport chain is a series of molecules that serve to harness the chemical energy made available from fat and carbohydrate metabolism. These molecules are located in the mitochondrial inner membrane, where they accept an electron from NADH, or $FADH_2$ and pass that electron along the sequence of cytochromes. The energy associated with this electron is used to transfer H^+ against it's concentration gradient, from the matrix into the mitochondrial intermembrane space. This process is described in more detail in Chapter 6B.

Integration of the Metabolic Response in Exercise

When we begin to exercise, molecular motors are engaged in our muscles to perform movement and/or force generation and work. This engagement requires energy in the form of ATP. ATP is hydrolyzed, forming ADP and the ATP must be regenerated. All three metabolic energy systems are activated, but the rate of ATP replenishment is initially greatest from creatine phosphate. The increased sarcoplasmic $[Ca^{2+}]$ that activates contraction also activates glycolysis in a feedforward control mechanism. The increased flux of glucose into glycolysis and the resulting formation of NADH and pyruvate will also accelerate the formation of lactate. Pyruvate will also be taken into the mitochondria for oxidative metabolism. Reducing equivalents will also be transferred into the mitochondria where phosphorylation will be accelerated, as soon as ADP is available. The increased rate of metabolism in the Kreb's Cycle and phosphorylation will increase the rate of formation of ATP (see Figure 6A-8 for a summary of the integrative metabolic systems).

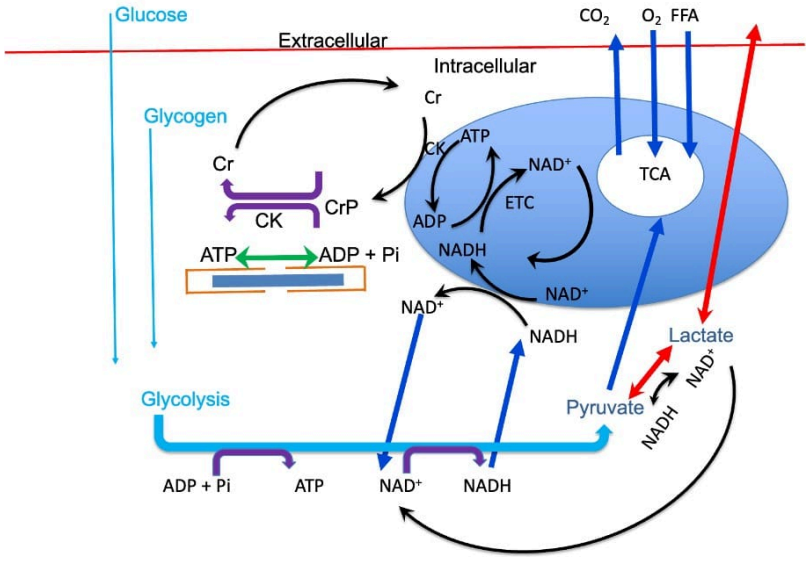


Figure 6A-8 Integrated Supply of ATP for Muscle Contraction Aerobic and anaerobic metabolic systems are illustrated here. The key message is that these systems communicate with each other. Use of ATP by the energy requiring processes in muscle results in rephosphorylation of ADP to ATP by creatine phosphate. This metabolic activity increases creatine concentration while it prevents a serious decline in ATP concentration. Glycolysis is activated by Ca^{2+} and by any decrease in [ATP]. Creatine diffused to the mitochondria where it gets rephosphorylated, increasing ADP concentration in the mitochondria and activating oxidative metabolism. This oxidative metabolism requires pyruvate from glycolysis, and uses the reducing equivalents from glycolysis in the electron transfer chain. Formation of lactate proceeds when pyruvate concentration increases and helps provide NAD^+ for continuation of glycolysis.

The homeostatic condition that existed at rest is disrupted by exercise. The action potentials conducted along motor axons and myocyte membranes will result in increased intracellular [Na^+] and decreased intracellular [K^+]. These ion concentrations will change in the extracellular space in the opposite direction. Heat will be generated within the working muscles and this heat will need to be distributed through-out the body and ultimately out of the body. Oxygen content of the venous blood will decrease and carbon dioxide content will increase. Glucose will be transported across the sarcolemma for use in glycolysis, so blood glucose should decrease. These changes are kept small by regulatory processes that are designed to minimize disturbance to homeostasis (see Chapter 9). In fact, both feed-forward and feed-back control systems are engaged during exercise and the potentially huge disturbance to homeostasis is avoided. A key element of this regulation involves the cardiovascular (Chapter 8) and pulmonary (Chapter 7) systems. Increased blood flow to the active muscles and increased ventilation serve to maintain arterial partial pressures of O_2 and CO_2 and increase the delivery of substrates to the active muscles while removing the products of metabolism.

Glycolysis and the Creatine Shuttle, Integrate with Oxidative Metabolism

When ATP use increases, ADP is formed. This increased concentration of ADP will stimulate glycolysis and CrP use. The increased [Cr] will stimulate oxidative metabolism. Rephosphorylation of Cr at the mitochondrial membrane (creatine shuttle) will activate oxidative metabolism. Stimulation of glycolysis will result in pyruvate and NADH formation. These products of glycolysis will also stimulate oxidative metabolism.

The Cori Cycle:

It was once thought that glucose, once it was in a muscle cell was trapped there and either used immediately in glycolysis or stored as glycogen. Glucose is released from glycogen intracellularly in its phosphorylated form and this is not easily transported out of the cell, because of the associated charge. Glucose phosphate must undergo glycolysis. However, the energy associated with glucose is not trapped in the cell. Lactate, one of the products of glycolysis, can be transported out of cells where it is produced, and appears in the blood. Blood lactate concentration rises, and this lactate is distributed throughout the body. The increase in blood lactate during exercise will result in transport of lactate into cells where lactate concentration is low. One such tissue is the liver, where lactate can be used as a substrate for gluconeogenesis. This recycling of lactate is called the Cori Cycle (Dashty 2013).

The Kinetics of Oxygen Uptake

When we transition from rest (or standing quietly) to exercise at a constant intensity, as with suddenly running on a treadmill at a constant velocity, oxygen uptake will rise quickly in three phases, known as phase I, phase II and phase III (Whipp and Wasserman 1972). The primary phase is the cardiodynamic phase. This is followed by a slower phase II or the fundamental phase and finally phase III which is either steady state or the what is known as the slow component of oxygen uptake (Poole et al. 1994). See Figure 6A-9 for a representation of the three phases of the rise in $\dot{V}O_2$. If it is assumed that total energy cost of the exercise rises immediately to some constant value, then clearly $\dot{V}O_2$ cannot provide all of the energy for exercise, at least to begin with. As $\dot{V}O_2$ increases, the anaerobic provision of energy decreases. In an oxygen-centric approach, the difference between the rate of energy use and the energy provided by VO_2 is referred to as the oxygen deficit. This is shown in Figure 6A-10.

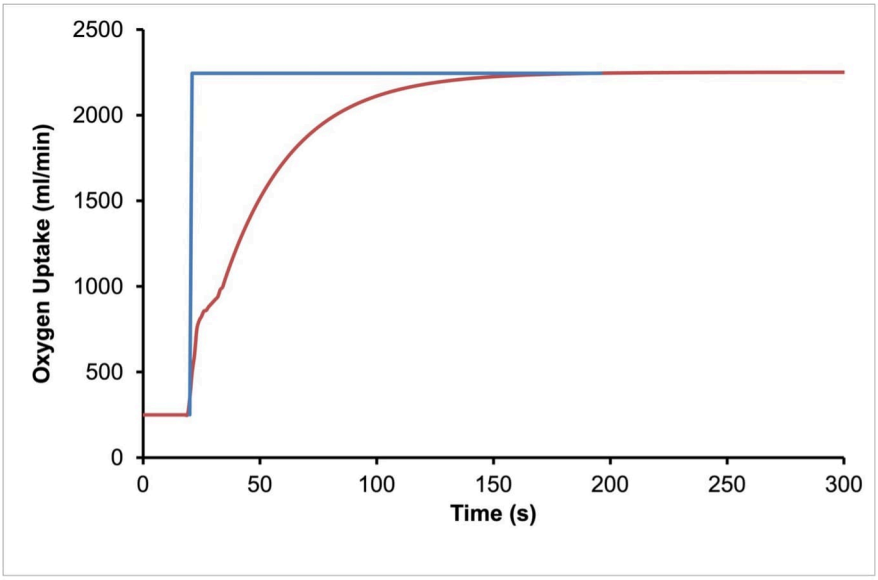


Figure 6A-9. The Kinetics of Oxygen Uptake The increase in oxygen uptake measured at the lungs (red line), requires time to develop, even when the energy cost of the exercise has suddenly increased to a high value. One reason for the delay at the beginning of exercise is the time it takes for blood leaving the muscles at the beginning of exercise to reach the lungs. The cardiodynamic phase an almost instantaneous rise in oxygen uptake. The graph shows the sudden rise in muscle oxygen uptake, followed by a delay then a slower rise because the measurement is being made at the lungs. This slower increase in $\dot{V}O2$ appears to be related to the slow increase in mitochondrial [ADP]. Oxygen uptake is stimulated by increased creatine concentration, but mitochondria need more ADP and NADH in order to increase the rate of use of O2. These changes take time, explaining why oxygen uptake does not instantaneously rise to the level needed to provide all ATP being used.

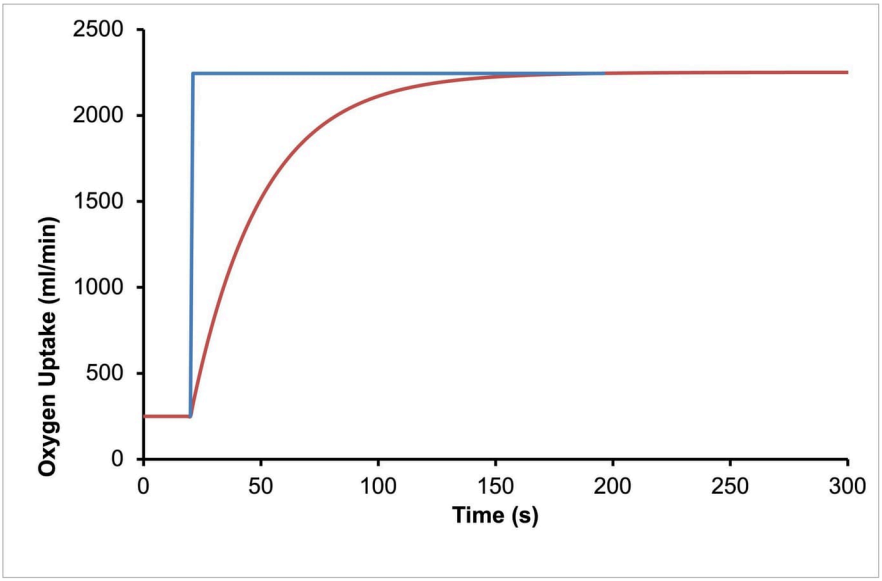


Figure 6A-10 The Oxygen Deficit During Exercise: The oxygen deficit represents the difference in energy requirement between total energy requirement and that provided by oxidative energy. Here, the oxygen deficit is the volume of oxygen (not used) between the blue line and the brown line. The blue line represents the oxygen cost of the exercise while the brown line represents measured oxygen uptake. Note that this "deficit" does not imply that there is a lack of oxygen.

Phase I of the Kinetics of Oxygen Uptake

The cardiodynamic phase is a rapid and small increase in $\dot{V}O_2$ that results from an increased blood flow to the lungs due to increased cardiac output. Although pulmonary blood flow increases, the oxygen content of the blood delivered to the lungs during the first 10-20 seconds of exercise is not different from that at rest. However, due to the increased blood flow, more oxygen can diffuse from the alveolae to the blood. The increased ventilation that accompanies the initiation of exercise will facilitate this increased uptake of O_2. After 10-20 s, the cardiodynamic phase decreases and phase II begins superimposing a rising $\dot{V}O_2$ on the declining cardiodynamic phase. Phase II is caused by the arrival of more desaturated blood in the lungs. This blood is at least partly coming from the exercising muscles, where the a-v O_2 content difference has increased.

Phase II of the Kinetics of Oxygen Uptake

Phase II of the rise of oxygen uptake on initiation of exercise is an exponential increase with a time-constant (t) of about 25-50 s, depending on familiarization with aerobic exercise. When exercise is no more intense than moderate exercise (at or below the aerobic threshold, see below), $\dot{V}O_2$ will reach a steady-state in 1.5-4 min. This phase II increase in $\dot{V}O_2$ represents the increased O_2 use in the exercising muscles and relies on further increase in cardiac output as well as increased a- v O_2 difference. The time constant for phase II can be shortened by aerobic training. With aging, the time constant is prolonged (DeLorey et al. 2004), but this prolongation also can be reversed by training (Grey et al. 2015).

Phase III of the Kinetics of Oxygen Uptake

As mentioned above, when the intensity of exercise is low enough, the $\dot{V}O_2$ levels off at a steady-state, SS, after about 4 x t. At these intensities of exercise, phase III is simply a constant oxygen uptake and is assumed to provide all the energy required for the exercise. Typically, the highest intensity of exercise for which a SS can be achieved is at the aerobic threshold. However, when exercise is at a higher intensity than moderate exercise, $\dot{V}O_2$ will either rise slowly to SS or continue to increase to$\dot{V}O_2max$ or until exercise is terminated due to the inability to continue exercising at the required intensity. This late slow increase in $\dot{V}O_2$ is referred to as the slow component of oxygen uptake.

The Slow Component of Oxygen Uptake

The slow-component of $\dot{V}O_2$ is identified as a slow increase of $\dot{V}O_2$ beyond the time when a SS would have been expected.

This was first described as a slow increase in $\dot{V}O_2$ that becomes evident after 3 min of exercise (Whipp and Wasserman 1972). Subsequently, fitting an equation to the data became popular and the slow component was identified with a third function in the equation describing the kinetics of $\dot{V}O_2$. This third function had a slower time-constant and a delay before starting. The mechanism of the slow component is not well understood, and only recently have viable mechanisms been proposed.

There are two current theories for the slow component of $\dot{V}O_2$ which has been confirmed to originate primarily in the active muscles (Poole et al. 1991). The first theory is the notion that as fatigue develops, there is an increased need for energy to be able to continue the exercise. This can be thought of as a fatigue-related inefficiency (Grassi et al. 2015). It certainly seems logical to think that muscles might become inefficient during fatigue, but the evidence for this is inconsistent. Two potential mechanisms of fatigue could lead to inefficiency: decreased Ca^{2+} sensitivity and decreased force per cross-bridge. Both of these mechanisms have been reported for isolated muscle, but the decreased Ca^{2+} sensitivity is much less likely at body temperature (see Chapter 13) and decreased force per cross-bridge appears to be most likely only in extreme acidosis (Edman and Mattiazzi 1981), which is unlikely to occur with exercise intensities below $\dot{V}O_2max$. Another way that fatigue might increase the energy cost of exercise would be if the fatigue led to recruitment of less efficient motor units. This idea has been proposed by several authors (MacIntosh and Holash 2000).

The second possible mechanism for the slow component of O2 is associated with the slow time-constant (tau, τ) for phase II $\dot{V}O_2$ when fast-twitch fibres are recruited. This theory was first proposed by O'Connell and colleagues (2017) and represents a slow transition from anaerobic to aerobic metabolic processes. It has been known for a long time that tau was longer for fast-twitch fibres, (Crow and Kushmerick 1982), but nobody had put the idea into practice.

To gain a further understanding of phase III dynamics, it is important to consider the metabolic boundary conditions described below. The slow component of O_2 only occurs above the intensity of exercise for which lactate accumulation continues beyond 3 min (but not necessarily beyond 10 min. This means that those who believe that fatigue causes the slow component must believe that fatigue does not occur below the first ventilatory threshold.

Metabolic Boundary Conditions

The intensity of exercise can be quantified by the rate of energy cost for the exercise. This can be expressed in absolute terms (J or Kcal per min) or relative terms (J or Kcal pr kg per min). However, it is important to understand that a given rate of energy use can have a very different effect on homeostasis in two different individuals. There are certain metabolic boundary conditions, based on the aerobic/anaerobic contributions to the energy cost of exercise, that help us understand these differences. Regular exercise (training) can influence these boundary conditions, but there is also a genetic predisposition that affects the intensity of exercise associated with a given metabolic boundary condition. Before we address the specific metabolic boundary conditions, it is worthwhile to consider the intensity-duration relationship.

The Intensity-Duration Relationship

A universal concept of exercise physiology is that the higher the intensity of exercise, the shorter the duration that the exercise can be sustained when it is continued until the limit of endurance. This idea is illustrated in Figure 6A-11. This concept is true, whether it is considered for exercise with small muscle groups (Monod and Scherrer 1965) or whole-body exercise (Moritani et al. 1981). When the exercise can be sustained no more than 15 min, results of 3-5 time-trials can be fitted to a hyperbolic equation, as shown in Figure 6A-11. A hyperbola has a shape that approaches an asymptote on both axes. It is generally accepted that the asymptote on the axis associated with power (or speed) is identified with the anaerobic threshold and is called the power (or critical speed when intensity is quantified by this measure). When time-trials are conducted within the time-constraints of 1 min to 15 min, 2 metabolic boundary conditions can be identified: oxygen uptake and critical power. Furthermore, the work or distance accomplished above the critical intensity is considered to be work or distance achieved using entirely anaerobic energy. The nature of a hyperbola is such that this distance (area within the rectangle in Figure 6A-11) will be a constant. Before we discuss these concepts further, it is worth elaborating a little on the metabolic interpretation of the parabolic relationship between intensity of exercise and the duration this exercise can be sustained.

The Vertical Asymptote of the Intensity Duration Relationship

It can be seen in Figure 6A-11 that extrapolation of the relationship between power and duration of exercise seems to indicate that at very short duration of exercise, power is not simply extremely high, but approaches infinitely. This cannot be true. From this relationship it is important to realize that extrapolation beyond the data obtained at this short end of the relationship is not

practical. Clearly, even if the exercise was only a millisecond in duration, nobody could generate anywhere near infinite power. In fact, somewhere up to about 1990 s, the concept of the intensity-duration relationship loses value of interpretation. This is because we are not capable of using all of the available anaerobic energy within this time. Success in athletic events lasting less than about 90 s is determined by something other than the total amount of anaerobic energy available. In very short duration events (high jump, long jump, 100 m, etc), success relates to the ability to generate speed or power.

Critical Intensity

Whether you have measured critical speed or critical power, the intensity of exercise you have identified is interpreted on a theoretical basis as the highest sustainable rate of aerobic metabolism. It is important to realize that although the mathematics would imply that this exercise intensity could be sustained indefinitely, this is obviously not the case. The intensity of exercise identified as critical intensity can typically be sustained for 30-60 min (Hill 1993). It is also important to realize that the longest duration of time-trial in the trials to determine critical speed affects this estimate of critical speed. Some investigators have indicated that exercise duration of the test trials can be up to 20 min, but others have stipulated that longer than 15 min is not appropriate (Drake et al. 2024). Regardless of the durations of exercise selected for the test, this is only an estimate of the anaerobic threshold.

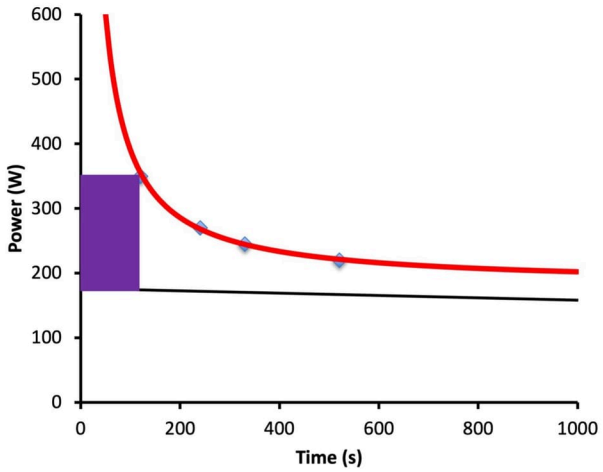


Figure 6A-11 The Intensity-Duration Relationship The results of time-trials conducted at constant power for as long as the participant can endure are illustrated as blue diamonds. Fitting a hyperbolic equation to the data allows estimation of the power at the horizontal black line (181 W) and the anaerobic work shown as the purple rectangle (20.1 kilojoules).

The asymptote for intensity appears to identify a power output that can be sustained indefinitely. This intensity has been assumed to represent a sustainable aerobic metabolism and has been called "critical speed" or "critical power". In reality, this intensity of exercise can be sustained for 30-60 min, so extrapolation of the data is not appropriate.

The area under the curve, but above power (purple rectangle in Figure 6A-11) represents a fixed amount of work. This has been assumed to be work that can be accomplished with a fixed amount of anaerobic energy.

Anaerobic Threshold

When the term "anaerobic threshold" was first used in a publication, it was with reference to the intensity of exercise that is identified with the first ventilatory threshold; the intensity of exercise during an incremental test when ventilation first increases proportionately more than $\dot{V}O_2$ (Wasserman et al. 1973). This intensity of exercise was thought to be associated with the transition to anaerobic metabolism. However, anaerobic glycolysis is present even at rest, so it is difficult to justify this definition. Furthermore, when exercising at an intensity identified as the first ventilatory threshold, a steady state for $\dot{V}O_2$ can be achieved, indicating that sustained anaerobic energy contribution is not associated with this intensity. Although many exercise physiologists still use the term anaerobic threshold with this intensity in mind, it is also often used to refer to a higher threshold. Considering that a threshold is "a border or transition to a different circumstance or condition", we define anaerobic threshold as the highest

intensity of exercise that can be sustained by aerobic metabolism (Svedahl and MacIntosh 2003) . Any exercise conducted above the anaerobic threshold must have a sustained anaerobic metabolic contribution when continued to the limit of endurance. This intensity of exercise, known as a metabolic boundary, is also measured by identifying the maximal lactate steady state (MLSS), though this is often imprecise, due to the limitations of measurement. The anaerobic threshold marks an intensity of exercise below which a small decrease in intensity allows a very large prolongation of the exercise.

Aerobic Threshold

The intensity of exercise that was first referred to as the anaerobic threshold is now known as the aerobic threshold. When Wasserman and Whipp were conducting incremental exercise tests, they attributed the increased ventilation above this threshold to the need to buffer the increased H+ in the blood; they thought they had detected the threshold beyond which anaerobic metabolism was required for the duration of the exercise. However, this was not the case. This intensity is associated with ventilation without a change in the ratio of ventilation to CO_2 output and has also been referred to as a boundary condition. The ratio of ventilation to $\dot{V}O_2$ still increases. This intensity corresponds with a mild increase in blood lactate, above the resting level during the incremental exercise test and when exercise is continued long enough, a steady state $\dot{V}O_2$ can be achieved, without continued contribution from anaerobic energy supply.

Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_2max$) is defined as the highest value for oxygen uptake per minute that can be achieved by an individual, usually noted for a given exercise. Essentially, when exercise is performed at an intensity sufficiently high, oxygen uptake will rise to $\dot{V}O_2max$ and will not go higher, even if the intensity of the exercise is increased. It is recognized that O2max can be different for different types of exercise, for example, $\dot{V}O_2max$ while cycling is generally less than that while running. This difference is thought to be due primarily to the mass of muscles involved. This notion is supported by the observation that $\dot{V}O_2max$ is even higher during cross-country skiing. However, cyclists are able to achieve a higher $\dot{V}O_2max$ while cycling than while running, so there may be another factor involved.

The limitations to $\dot{V}O_2max$ have long been of interest to exercise physiologists. A simplistic approach is to consider the Fick equation:

Fick Equation:

$$\dot{V}O_2 = \dot{Q} \cdot (a - \bar{v})O_2 \qquad \text{equation 4}$$

$\dot{V}O_2$ can increase if cardiac output increases or if arteriovenous oxygen content difference increases. Incr eased arteriovenous oxygen content difference could result from either higher arterial O_2 content or lower mixed venous O_2 content. These are the factors that must account for different $\dot{V}O_2max$ values for endurance athletes vs others. Cardiac output is the variable with the greatest potential change, so it has often been blamed as the limiting factor. However, regardless of who it is who is being evaluated, arteriovenous oxygen difference could be increased if needed and that makes this author believe that $\dot{V}O_2max$ is not limited by delivery, except in circumstances where cardiac output or arterial O_2 content are compromised.

Further consideration for the limits of $\dot{V}O_2max$ are beyond the scope of this textbook, but consider the duration that exercise of a sufficient intensity to reach O2max and the slow time-constant for the rise of $\dot{V}O_2$ for fast-twitch motor units. Is it possible that $\dot{V}O_2max$ rises only until exercise approaches the limit of endurance? Also, consider the possibility that $\dot{V}O_2$ rises in proportion to the fall in [ADP] and that anaerobic metabolic processes prevent the further fall of [ADP], possibly due to catecholamine-induced glycogenolysis. The combined metabolic processes are capable of providing the ATP that is needed during this high intensity exercise. This possibility can be discussed as part of the topics for discussion at the end of this chapter.

Exercise and Motor Unit Recruitment

During an incremental exercise test, we are able to increase the intensity of exercise by recruitment of additional motor units as power or speed of exercise increases. It is important to recognize this, and to realize that at the intensity of exercise when we reach $\dot{V}O_2max$, we have not yet recruited all of the available motor units in the primary muscles used for the activity in which we are engaged. Figure 6A-12. illustrates the EMG signal that reflects increasing muscle activation, including recruitment of motor units and rate coding of active motor units as exercise intensity increases. The magnitude of EMG signal can be much higher than that observed at $\dot{V}O_2max$,. This is consistent with the observation that cycling power output at $\dot{V}O_2max$, is merely 25-35 % of

the highest possible power output for cycling, such as that observed during the Wingate test. Of course, the highest power output can only be sustained for a few seconds, while power output at O2max can be sustained for 2-6 min.

The size principle governs the sequence in which motor units are activated; from small, slow-twitch units to progressively larger and faster units. Although there are exceptions to this orderly activation pattern, there is no reason to believe the size principle would be violated for incremental cycling. It could be that motor unit recruitment involves only slow-twitch units up to the intensity associated with the first ventilatory threshold (aerobic threshold). Any increase in intensity beyond this threshold may require recruitment of fast-twitch units. This would explain the rise in lactate when the first threshold is exceeded and would also explain the slow component of $\dot{V}O_2$. Considering that fast-twitch motor units have a slower time-constant for the rise of $\dot{V}O_2$, it would be expected that it would take longer to reach a steady state.

This graph shows the raw EMG signal in blue over time as power increases during a ramp incremental test. The EMG signal oscillates above and below zero with an increasing amplitude from the beginning of the test until the end.

Figure 6A-12. EMG Activity During a Ramp Incremental Test. This is a continuous record of the EMG activity of the vastus lateralis muscle during a cycling test where resistance is slowly increased throughout the test. To continue the test, the subject must continuously increase muscle activation. This occurs by recruiting new motor units and increasing the frequency of activation of already active motor units.

Submaximal Oxygen Uptake

During mild, moderate and vigorous exercise, oxygen uptake increases in three stages, as described above. It takes several seconds for the blood moving through the active muscles to get to the heart and subsequently to the lungs, so the fundamental phase is delayed by this time. The fundamental phase represents the resaturation of blood that has had more O_2 removed than was the case at rest. As cardiac output increases, more blood will be flowing through active muscles and subsequently returning to the right side of the heart where it will be sent to the lungs for gas exchange. Why do we measure oxygen uptake?

Oxygen Uptake and Metabolic Substrate Use

We measure to estimate the energy cost of exercise. However, $\dot{V}O_2$ does not provide the energy – nutrient substrates do. Our mitochondria oxidize fats and carbohydrates to provide the energy for muscle contraction. This energy comes in the form of adenosine triphosphate (ATP). It must be kept in mind that ATP can also be regenerated by nonaerobic metabolism, so typically the measure of $\dot{V}O_2$ to estimate energy cost is done at a steady-state. This necessitates that the energy requirement will not exceed the maximal lactate steady state.

Mitochondria can use fats, carbohydrate, and to some extent, proteins to replenish ATP by aerobic metabolism. The amount of O_2 used by someone during exercise can tell us how much substrate has been oxidized and therefore how much ATP has been produced by oxidative metabolism. The substrate mix is generally assumed to be fat and carbohydrate because under most circumstances, protein catabolism contributes a very small % of total substrate for aerobic metabolism. It is convenient to assume that only fats and carbohydrates are metabolized because the ratio of CO_2 produced to O_2 use can provide an estimate of the mix of these substrates. This works when it is assumed that only these two are providing the energy. In most circumstances, the amount of protein metabolized for ATP regeneration is sufficiently small that it does not make a huge difference to make this assumption.

The intensity and duration of exercise dictate the proportion of fats and carbohydrate that a given person will use for aerobic metabolism. When the exercise intensity is high, approaching maximal , carbohydrate is preferred (Romijn et al. 1993). At lower exercise intensities, the muscles use more fat (Brooks and Mercier 1994). A progressive increase in fat metabolism occurs as the duration of low intensity exercise increases (Mourtzakis et al. 2006). Prolonged exercise is only possible if the exercise intensity is relatively low. Considering that Jake will run most of his 10 km time-trial (see Chapter 16) above the intensity associated with his anaerobic threshold, he will metabolize predominantly carbohydrate with less than 30 % of the total energy cost coming from the metabolism of fat (Romijn et al. 1993).

The mix of carbohydrate and fat a person uses during exercise will dictate the amount of CO_2 he or she releases relative to the amount of O_2 they metabolize. When measured at the cellular level, this ratio is called the respiratory quotient (RQ). When carbohydrate is oxidized, the amount of CO2 released is equivalent to the amount of O_2 used (RQ is 1:1). When fatty acids are oxidized, this ratio is 0.7. It is difficult to measure the cellular use of O_2 and release of CO_2 as this requires the measurement of the amount of O_2 and CO_2 going into a given muscle and the amount of these gases coming out. The difference is the amount removed or added to the blood by the muscle cells. This exchange of gases can be measured by measurement of blood flow and O_2 and CO_2 content in arterial (a) and venous (v) blood. The Fick equation (see equation 16-1) is used to calculate $\dot{V}O_2$and $\dot{V}CO2$.

Fick Equation:

$$\dot{V}O_2 = \dot{Q} \bullet (a\text{-}v)O_2 \qquad \textbf{(Fick equation)}$$

$$\dot{V}CO_2 = \dot{Q} \bullet (a\text{-}v)CO_2 \qquad \textbf{(Fick equation)}$$

These measurements of blood flow as well as O_2 and CO_2 content require the isolation of the vascular system for a given muscle (Gladden et al. 1978). However, we can avoid this difficulty by getting an estimate of these gas exchanges at the cellular level by measurement of the exchange of O_2 and CO_2 at the lungs. RQ can be estimated by measurement of the respiratory exchange ratio (RER), which is the ratio of $\dot{V}CO_2 \cdot \dot{V}O_2^{-1}$ measured at the lungs. The difference between RQ and RER is that RQ represents actual metabolic production of CO_2 and metabolic use of O_2 while RER is the measured pulmonary exchange of these gases. When the rates of oxygen uptake and carbon dioxide output measured at the lungs are equal to the actual metabolic rates of use and production of these gases, then the RER is equal to the RQ. Under these conditions, there will be no change in the content of CO_2 or O_2 in the body during the period of measurement. That is, all of the CO_2 that is produced metabolically will be removed by the pulmonary system and all of the O_2 used in the cells of the body will be replaced by O_2 moving from the lungs into the blood. This condition is not met during the first 2-4 min of exercise nor during the first several minutes of recovery. RER is considered to be equal to RQ during steady-state exercise below the aerobic threshold. However, when the exercise intensity exceeds the aerobic threshold there is a clear ventilation that serves to reduce the CO_2 content of the body. This change in content violates the condition of constant content of CO_2 in the body.

Substrate use changes with intensity of exercise, but training status will also influence the mix of substrates metabolized. In general, as intensity of exercise increases, fat metabolism decreases and carbohydrate metabolism increases. There is an intensity of exercise where 50 % fat, and 50 % carbohydrate areis metabolized (Brooks and Mercier 1994). This intensity of exercise is called the cross-over intensity (see Figure 6A-13). Improved physical fitness is associated with greater mobilization and metabolism of fats. Thus, a higher fitness moves the crossover intensity to higher intensities of exercise. Jake will have a higher exercise intensity (metabolic rate) at the cross-over than the student described in Table 16.1. This is important for his performance of the 10 km time-trial but would be even more important for athletes who compete over longer distances like the marathon for which carbohydrate sparing is more relevant.

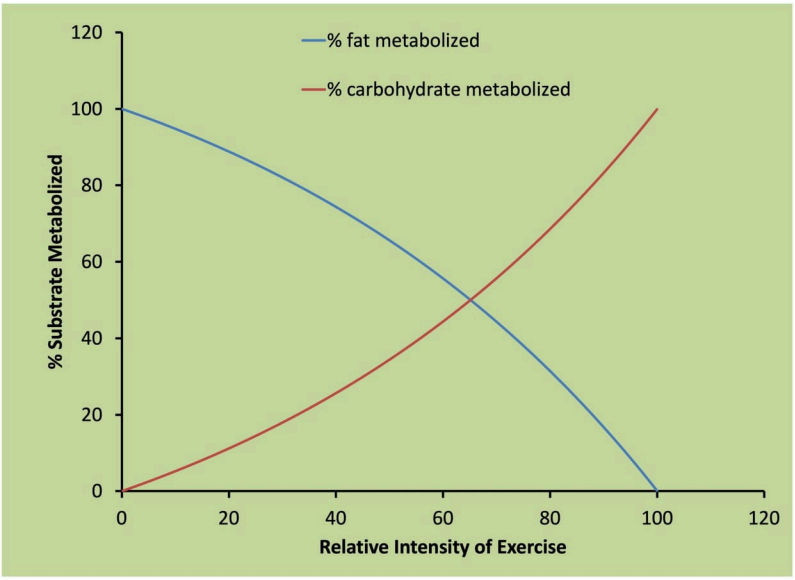


Figure 6A-13 Crossover concept of Brooks and Mercier. This graph shows the hypothetical proportion of carbohydrate, and fat metabolized relative to the energy cost of exercise at maximal oxygen uptake. The proportion of fat metabolized decreases as intensity of exercise increases. The proportion of carbohydrate metabolized increases as intensity of exercise increases. Adapted from Brooks et al.

During moderate intensity exercise below the aerobic threshold, oxygen uptake will level off at a constant rate, within a few minutes. Under these conditions, O_2, and CO_2 content in the body will remain constant and RER will be equal to RQ during the steady phase of oxygen uptake. The mix of substrates being metabolized is appropriately estimated by measurement

of pulmonary exchange of O_2, and CO_2. As the intensity of the exercise approaches and exceeds the anaerobic threshold, ventilation occurs. Hyperventilation results in continued net loss of CO_2 from the body, so RQ [1] RER. The substrate selection during exercise that is of such high intensity cannot be determined by estimation with measurement of RER because this ventilation results in decreases in total body CO_2 content. This means the measured release of CO_2 from ventilation exceeds the cellular metabolic release of CO_2 and RER > RQ. However, it is reasonable to assume that the majority of substrate metabolized is carbohydrate under these conditions..

Hormonal Control of Substrate Delivery

Skeletal muscle is very good at using substrates provided to it for metabolism. The preferred substrates are fats and carbohydrates, but protein is a very good substrate as well. Factors that will affect the substrate mix include the intensity and the duration of exercise. Hormones play an important role in providing the substrates for prolonged exercise duration.

Catecholamines

Both **epinephrine** and **norepinephrine** are catecholamines. They are both released into the blood from the adrenal medulla in response to activation of the **sympathetic nervous system**, with the quantity of epinephrine released being greater than that of norepinephrine. Norepinephrine is also released from peripheral nerve endings of sympathetic nerves and some of this norepinephrine will find its way to the blood, contributing to the exercise-associated increase in blood or plasma catecholamine concentration. The catecholamines have several functions, many of which are critically important during exercise. One of these important functions is mobilization of **substrates** for exercise-related increases in metabolism. Both epinephrine and norepinephrine react with sympathetic b receptors in the membranes of hepatocytes and kidney cells. The subsequent increase in intracellular cyclic adenosine monophosphate (cAMP) concentration results in activation of enzymes responsible for **gluconeogenesis**, the synthesis of glucose. Glycogenolysis is also activated in the liver and in skeletal muscles by b receptor activation and subsequent increase in cAMP concentration. This increased availability of glucose will be in proportion to catecholamine concentration, which in turn is proportional to the exercise intensity.

Table of approximate blood or serum values of catecholamines, growth hormone, glucagon, cortisol, glucose...

Substance	At Rest	Moderate Intensity	Maximal* Exercise Intensity
Glucose	4 mM	4 mM	4 mM
Growth Hormone (serum)	2 ng/mL	8 ng/ mL	15 ng/mL
Norepinephrine	130 pg/mL	700 pg/mL	2000 pg/mL
Epinephrine	20 pg/mL	130 pg/ml	200 pg/mL
Cortisol	450 nM	800 nM	1000 nM
			*Maximal refers to the intensity that elicits $\dot{V}O_2max$.

Muscles lack an important enzyme to allow glucose released from glycogen to leave the cell. Charged molecules are not fat-soluble, so they have difficulty passing through a lipid membrane. Glucose-1-phosphate is the product of glycolysis and it is a charged molecule. This means that any glucose released in a muscle cell from glycogen must undergo glycolysis in that specific cell. Even inactive muscle can have catecholamine-induced increases in glycogenolysis and glycolysis. This accelerated glycolysis may result in lactate production in reasonably inactive muscles. This lactate would make its way to the blood and be delivered to tissues where it can be used as an oxidative substrate. This means that inactive or mildly active cells will use lactate as an

oxidative substrate (Bergman et al. 1999). Even the heart can use lactate as a substrate for oxidative metabolism. Alternatively, this lactate can contribute, along with lactate coming from intensely active muscle, to gluconeogenesis in the liver and kidneys or to accumulation of lactate during exercise above the anaerobic threshold. The accumulation of lactate from inactive muscles with accelerated glycogenolysis could be a factor in determining the intensity of exercise associated with the anaerobic threshold.

Growth Hormone

Growth hormone is also known as somatotrophin. Although best known for the essential role in growth and development, somatotrophin is also instrumental in mobilizing substrates for exercise metabolism. This would explain why somatotrophin concentration in Jake's blood increases during exercise in spite of the fact that he is a full-grown adult. Somatotrophin is released from the anterior pituitary gland in response to a chemical signal (growth hormone releasing factor) from the hypothalamus. One of the key consequences of increasing somatotrophin concentration in the blood is increased lipolysis in adipose tissue. This lipolysis results in increased free fatty acid concentration in the blood and increased delivery of fatty acids to active muscle. Increased delivery of fats to the active muscles will result in carbohydrate sparing (use of fewer carbohydrates). The rate of use of glucose will decrease, provided the intensity of the exercise permits this. This change is not an important factor for Jake during his time-trial because his intensity of exercise is high enough that he will primarily use glucose during his run.

Glucagon

Glucagon has the opposite effect on cells of the body that insulin has. Glucagon is released from the pancreas when blood glucose concentration falls and will encourage an increase in blood glucose concentration. In contrast, insulin will cause blood glucose concentration to decrease. Glucagon stimulates liver glycogenolysis and gluconeogenesis. Activation of the sympathetic nervous system increases the secretion of glucagon.

Insulin

As indicated above, glucagon and insulin have opposing effects. Insulin is important in promoting a decrease in blood glucose concentration when ingestion of sugar-rich foods causes blood glucose to rise. Insulin is secreted from the pancreas in response to elevated blood glucose. An increase in insulin concentration results in a greater rate of transport of glucose into many cells of the body, including adipocytes and myocytes.

It is important to acknowledge that insulin is not required to promote glucose uptake in active skeletal muscle. The process by which glucose transport is augmented during muscle contraction is independent of insulin. During exercise, insulin concentration will decrease, even when glucose concentration is not changed from resting values. Muscle contraction has a mechanism to enhance glucose transport.

In the cytoplasm of myocytes, there are rafts of glucose transporter (GLUT 4) and signalling mechanisms will mobilize the transporter to the membrane and activate it to increase the rate of transport of glucose across the membrane. This increased transport can be initiated by either insulin or increased Ca2+ in the myoplasm (Richter and Hargreaves 2013). Details of this mechanism are presented in Chapter 6B.

Cortisol

Cortisol, like the catecholamines, comes from the adrenal gland. However, the catecholamines come from the adrenal medulla whereas cortisol comes from the adrenal cortex. Cortisol is considered to be a stress hormone. When the body is stressed, cortisol secretion will increase. Cortisol supports gluconeogenesis by inhibiting protein synthesis and increasing protein catabolism. The release of amino acids into the blood provides important substrates for gluconeogenesis in the liver. Cortisol also facilitates transport of amino acids into hepatocytes for subsequent gluconeogenesis.

Efficiency and Economy of Exercise

Efficiency, or more correctly, mechanical efficiency is the ratio of the work accomplished to the energy cost of doing that work. Economy is the energy cost of performing a task, like running from point A to point B. Efficiency is a unitless ratio, often expressed as a %. Economy is usually expressed as an energy cost per distance travelled, but considering it is the energy cost for a task, expression can have a variety of forms. A special case of economy is the economy of force maintenance. This is the energy cost

to maintain a given force or support a load when contractions are isometric. In all cases, the energy cost of the exercise must be estimated and should be expressed in joules, the ISI unit for energy. Energy may also be expressed in other units, like calories.

Efficiency: What is it Good For?

Skeletal muscles can be as efficient as internal combustion engines (the motors in nonelectric vehicles that use gasoline for fuel). That does not say very much, considering that the best an engine can do is about 25%. This means that about 25% of the energy use can be converted to work. The remaining 75% is dissipated as heat. The maximal efficiency of our muscles is typically about 25% when energy is considered to be supplied by fat and carbohydrate for oxidative metabolism. Measuring oxygen uptake and estimating the energy made available by oxidative metabolism is the most common way to estimate the energy cost of exercise. However, just like an internal combustion engine, the efficiency is dependent on the work done. Considering the force-velocity and corresponding power velocity relationship (see Figure 6A 15), there are circumstances when the muscles will contract and not produce any work or power (rate of doing work). This happens at each end of the power-velocity curve. This is kind of like revving the engine and not going anywhere, or trying to push an immobile wall (with your muscles or with your car). No work is done, so efficiency is zero.

During an isometric contraction, no work is accomplished. Also, when the load is zero, no work is accomplished. Realistically, the zero load condition is difficult to achieve, and truly isometric contractions are uncommon. When a muscle contracts with no motion of the joints, the muscle may shorten while the tendon elongates and force develops. This internal work may preserve energy for a short time, in the stretched tendon. However, if the muscle relaxes without joint motion, then no external work has been accomplished and efficiency is zero. For this reason, economy of force production is often used to quantify the effective energy cost of maintaining a force.

Different Ways to Calculate Efficiency

Quantifying efficiency when substantial work is done is a convenient way of comparing individuals and gaining an understanding of the energetic requirements of exercise. There have been several ways that efficiency has been calculated, and we will review those here. In all cases, calculation of efficiency requires measurement of energy cost and work (or rate of energy use and power). The ratio of these, each expressed in the same energy units will result in a unitless value which can be multiplied by 100 to express efficiency as a %.

The energy cost of exercise can be calculated by measurement of VO_2 and estimate of the caloric equivalent of the substrates metabolized. The amount of energy released with each liter of O_2 used in metabolism can vary, depending on the substrates used. It is generally assumed that oxidative metabolism relies on fats and carbohydrates, and the RQ indicates the mixture of these substrates that has been used. Respiratory exchange ratio (RER, VCO_2/VO_2 is a reasonable substitute for RQ when exercise is in a steady state.

The quantification is as follows:

Energy = RQ * 5153.3 + 15963

Where RQ is the unitless ratio of VCO_2/VO_2. This value obtained is the energy in joules (divide by 1000 to get kilojoules) per liter of VO2. If you multiply this by the oxygen uptake in litres, you will obtain the total energy made available by oxidative metabolism.

Gross Efficiency

When efficiency is calculated using the total measured oxygen uptake, and total work accomplished, then the value obtained by work/energy cost is the gross efficiency. No baseline has been subtracted. This calculation expresses to true cost for the human body to complete the work. This is the most common approach and arguably the most appropriate (MacDougall et al. 2022).

Net Efficiency

It is common to subtract the resting energy use from the total energy use and divide the work by this net energy cost. The resulting value is referred to as net efficiency. It is important to recognize that use of this approach assumes that the resting energy use continues to be used during the exercise, without contributing to accomplishment of the exercise . Although this may seem like a reasonable approach, it has not been proven that this assumption is correct.

Work Efficiency and Delta Efficiency

The term “work efficiency” has been used to describe a special baseline subtraction technique where energy cost for a zero work condition is subtracted from that for a condition where work is accomplished. For example, cycling at 80 RPM and no resistance and cycling at 80 RPM with some resistance. In the former situation, no work is accomplished. The assumption here is that the energy used for the zero work condition continues to be used in the work condition (when resistance is applied), without contributing to the completion of work. This cannot be assured, and although it seems like a logical approach, one circumstance would appear to violate this calculation. Cadence is kept constant for the trials at zero work and with work. It is assumed that velocity of shortening of muscles is therefore the same between the two conditions. If this was true, then it would seem logical that accomplishment of the additional work was achieved through recruitment of additional motor units and the extra energy was used to accomplish the extra work. Work efficiency would be considered an efficiency of the recruited muscles to achieve the added work. However, the velocity of shortening of muscles is not likely kept constant when resistance is added. The muscles must develop more force, and this will result in extra stretch of the tendons, which are in series with the active muscles. Considering that the muscle tendon unit is still moving at the rate needed to achieve whatever the cadence is, any variation in stretch of the tendon will alter the length change of the muscle fibres. A difference in length change will be reflected in a difference in average velocity of the fibres. Any change in velocity will affect the conditions of the cross-bridges that were assumed to have accomplished the zero work condition. The fundamental assumption has been violated.

Delta efficiency is an extrapolation of the case of work efficiency, and has often been proposed to be an estimate of muscle efficiency (Gaesser and Brooks 1975). To calculate delta efficiency, two or more trials at the same cadence, but different resistance will be completed and the energy cost quantified. Delta efficiency is the difference in work divided by difference in energy cost). The same argument above applies here. This has recently been defended (MacDougall and MacIntosh 2024).

Highlight Box

Calculating the power output of cycle ergometry, based on a standard Monark cycle ergometer. Cycle ergometry is often used in the study of the energetics of exercise. Calculation of work and power is relatively simple.

- Standard abbreviations
  - meter, m
  - joule, J
  - watt, W (note that watt, newton and joule are not capitalized when written out fully)
  - second, s
  - minute, min
  - kilogram, Kg
  - newton, N

Tension on the flywheel is often measured in Kg. Force or tension should be expressed in newtons.

$$1 \text{ kg} = 9.81 \text{ N}$$

Work is force times distance. The distance travelled by a point on the flywheel at the radius where the belt is in contact is 6 m per crank revolution. This estimate is based on the circumference of the flywheel associated with belt contact and the ratio of the chain ring and free wheel cog count (typically 52:14), indicating that the flywheel will rotate 52/14 times for each rotation of the crank.

$$1 \text{ J} = 1 \text{ Nm}$$

Power is work / time; expressed as watts (1 watt = 1 $J \cdot s^{-1}$)

When resistance is 9.8 N, work per crank revolution is 9.8N * 6m = 58.86 Nm per crank revolution

For a pedal rate of 80 RPM, this is 4708.8 J×min-1 or (dividing by 60 s), 78.48 J×s-1

1 joule×s-1 is 1 W so this is 78.48 W.

When a mass of 1 kg of resistance is applied to the belt on the flywheel, the power output at 80 RPM will be 78.48 watts.

Based on this approach, power can be calculated for different combinations of crank rate and resistance. Note that body weight is supported while cycling, so body weight is not a factor in the power output of cycling. Body weight is also not a factor in the energy cost of cycle ergometry, so the expression of energy cost is not expressed per kg of body mass, like running is.

Energy Transduction

It is important to realize that the first law of thermodynamics dictates that energy cannot be created or destroyed. When someone refers to "energy production" in the context of exercise physiology, they likely are referring to energy transduction. Energy can be transformed from one form to another. The forms of energy in the body include: chemical, heat, kinetic, and potential. External work can be accomplished by imparting kinetic or potential energy to an external object or increasing the potential energy of the body or a body part. Our muscles transduce chemical energy, releasing this as heat and work in a variety of proportions. Efficiency of mechanical work can vary from zero to about 26%. Conditions need to be optimal to achieve close to 26%.

Efficiency When Work is Optimized

The use of the term "efficiency" is associated with a variety of definitions and concepts. However, in terms of energetics of the body, efficiency or more specifically, mechanical efficiency, is the relative preservation of energy in the form of work, during muscular effort. Our muscles use chemical energy and produce work and heat. Efficiency is calculated as the ratio of useful energy out to total energy in (work / energy cost) where both quantities are expressed in the same units (typically, joules). To express efficiency as a %, this unitless ratio is multiplied by 100.

You might ask, so how efficient are our skeletal muscles? The answer is... "that depends". The answer depends entirely on the amount of work being done. During an isometric contraction, no work is done, so efficiency is zero. Similarly, if you can contract your muscles and allow shortening with zero force, no work would be accomplished and efficiency would be zero. So , between zero load and isometric force, work is generated and the muscles will have some efficiency. The magnitude of efficiency is closely related to the relationship between power and velocity of shortening. This is because force and velocity will determine the power of the relationship and the product of power and time is work.

The Force-Velocity Relationship and Power Output

As described in chapter 5, as the velocity of muscle shortening increases, the force that can be generated by a muscle decreases. This can be seen in Figure 6A.15 as the curvelinear fall in force as velocity of shortening increases. However, power output increases as velocity increases until a peak is reached, typically around one third of maximal velocity. This is also shown in Figure 6A.14. The energy cost of a muscle contraction also increases when shortening is allowed, but not as much as the power increases, so efficiency increases in proportion to the power output, reaching a maximal value at a velocity just less than the optimal velocity for power output. Beyond this velocity, the energy cost may continue to increase but the power output decreases so efficiency decreases.

This graph shows the relationships between force and velocity of shortening and between power and shortening velocity and finally between efficiency and velocity of shortening. The force-velocity relationship is hyperbolic, curving down from maximal force to zero force as velocity increases from zero to 1 (max velocity) for fast-twitch muscle. Slow-twitch muscle has a maximal velocity that is about 1/3 of that for fast-twitch muscle. Power is the product of force and velocity, so powerr will increase from zero at zero velocity to a peak value at about 1/3 of maximal velocity then decrease to zero at maximal velocity. This is true for both fast and slow-twitch muscle, but peak power is much higher for fast-twith muscle.

Figure 6A.14 Force-Velocity and Power-Velocity Relationships. *Here, these relationships are shown for full activation of fast-twitch and slow-twitch muscles. Vmax is 1 for the fastest fast-twitch motor unit and 0.38 for the slow-twitch units.*

The highest that muscular efficiency can be in converting chemical energy of fats and carbohydrates to work is ~30% (Stainsby 1982). Slow-twitch muscle is slightly more efficient while fast-twitch muscle is slightly less efficient at the maximal value. Efficiency depends on how much heat is released in converting the chemical energy of fats and carbohydrates to chemical energy in ATP. This efficiency is about 60%. Of the chemical energy preserved in ATP, about 50% of it can be released as work under ideal conditions (this would be at optimal velocity). Considering that the energy in ATP is already decreased relative to that which was available in the chemical substaratessubstrates, the overall efficiency is about 30% at the very best (0.6 X 0.5 = 0.3). When no work is done, the efficiency is zero and muscular efficiency can vary between zero and 30%. Considering that other body parts require energy (like the heart and ventilatory muscles) while exercise is going on, gross efficiency is never greater than about 25%, and some people cannot achieve greater than about 20%.

The maximum efficiency occurs when the power (work / time) is the highest it can be, or when velocity is about 1/3 of maximal velocity (this is dependent on curvature of the force-velocity relationship). Considering the difference in maximal velocity between fast-twitch and slow-twitch muscles, this relationship has a potential impact on efficiency of some physical activities (see Figure 6A.15). Cycling, for example is an activity for which the velocity of muscle shortening is dependent on pedallingpedaling frequency or cadence.

The Velocity Dependence of Efficiency

Considering the information presented in Figure 6A14, it can be seen that when the velocity is zero, or equal to maximal velocity, no work is done. For this reason, regardless of how many motor units are recruited, and how much energy is used, the efficiency (work/energy cost) must be zero. If only a small amount of work is done, then the efficiency will be very low. Only when the work or power is optimized will the efficiency approach 25%, and this depends on the motor unit recruitment required to accomplish the task. Motor unit recruitment depends on the fibre-type distribution in the muscles being activated. For example, cycling at 80 RPM and 200 watts, efficiency can vary from 16 to 24%. This efficiency is proportional to the proportion of type 1 muscle fibres in the vastus lateralis muscle, a primary muscle used in cycling (Coyle et al. 1992). It has been shown that at a given power output, efficiency varies with cadence (Sidossis et al. 1992). Cadence presumably affects velocity of shortening in the primary muscles contributing to the cycling exercise.

Cycle ergometry is a convenient way to quantify work and power and provides a stationary subject for measurement of VO_2. For this reason, considerable research has been done, evaluating efficiency of cycling. It should be kept in mind that in measuring efficiency of cycling, the measurement of includes the energy cost of all body parts, not just that of active muscles. For this reason, we use the term “gross efficiency” when has been used to estimate the energy cost of exercise without baseline subtraction. In some cases, resting has been subracted to yield “net” energy cost giving net efficiency. For cycling exercise, where the exercise can be considered whole-body exercise, this practise has been challenged (Stainsby et al. 1980) because it is not known if the energy used at rest continues to be used during exercise at the same rate. The only time when subtraction of resting metabolic demand can be justifiably used to estimate efficienct is when the exercise under consideration involves a small muscle group. In that case, resting metabolic rate is relatively large and would mask the true efficiency of performing that exercise.

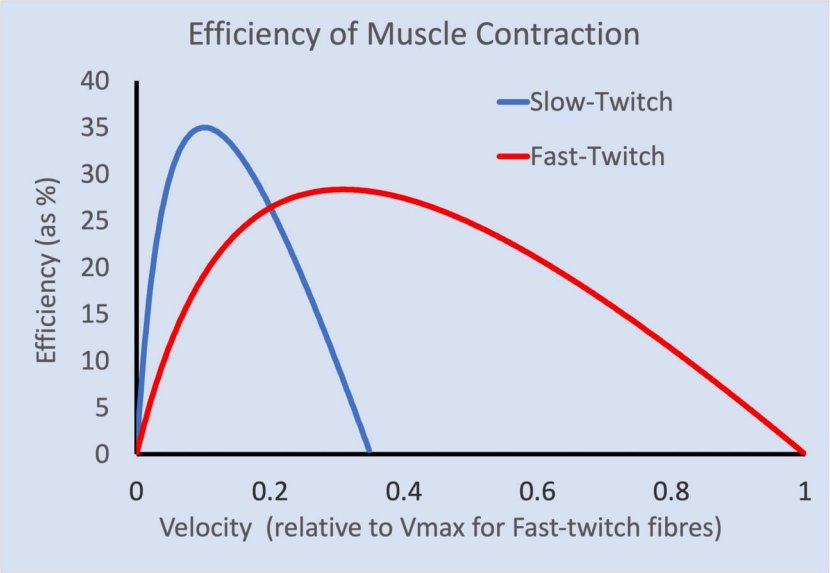


Figure 6A.15 Efficiency of motor units and velocity of contraction. Recognizing the very different maximal velocities of fast and slow-twitch motor units, and that maximal efficiency is achieved at near 1/3 of maximal velocity, the efficiency profile for fast and slow-twith motor units is quite different.

Economy of Locomotion is Dictated by Muscle Energetics

Economy of locomotion is defined as the energy cost of physically moving the body from one place to another by any means of locomotion (walking, running, skating, skiing, cycling...). The appropriate units are joules × kg^{-1} × km^{-1} when the form of locomotion is body mass dependent and joules × km-1 when the energy cost is not body mass dependent (like swimming and flat ground

cycling). Here, we consider the economy of running and cycling to illustrate the fundamentals of economy of locomotion. To measure the energy cost of locomotion, we typically measure $\dot{V}O_2$ and $\dot{V}CO_2$ during steady-state exercise and estimate the energy equivalent of the gas exchange, based on an estimated mixture of fat and carbohydrate metabolized. This approach typically works reasonably well for intensities of exercise associated with a true steady-state of $\dot{V}O_2$. In some cases, studying higher intensities has been accomplished by measurement of lactate accumulation (O'Connell et al. 2017) or by extrapolation from lower intensities. There is also a large body of literature that has simply presented $\dot{V}O_2$ as an estimate of energy cost of locomotion, and this is reasonable when precision is not necessary. This estimate is referred to as oxygen cost. Any factor that has been identified as affecting oxygen uptake of locomotion probably still has an impact if energy cost is considered. Fletcher and colleagues (2009) identified that consideration of the substrates used during metabolism, using RER, affects the estimate of energy cost and much of the work published since then goes on to calculate the energy equivalent.

Economy of Running

The economy of running has been of interest for decades. The body of literature associated with this topic is quite large. A review of the energy cost of running (Fletcher and MacIntosh 2017) puts a lot of this work into perspective, and emphasizes that changes in economy relate strongly to the need to change motor unit recruitment. If the task requires additional motor unit recruitment, then it is likely that it will require more energy. In .contrast, if the locomotion can be done with less motor unit recruitment, the energy cost will be less.

As indicated above, economy of running should be expressed as joules · m^{-1} or joules · kg^{-1} · m^{-1}. However, there is value in expressing running economy in Cal · kg^{-1} · km^{-1}. Many people are interested in knowing how many Calories they have burned when they have run a given distance. It is convenient and reasonably accurate to estimate about 1 Cal · kg^{-1} · km^{-1}. This equates to about 4.186 kJ · kg^{-1} · km^{-1}.

There are several factors that will influence the economy of running including: stride length, stride frequency, body mass distribution, surface properties and wind. Figure 6A.16 provides an illustration of the complex nature of the factors that can influence economy of running.

Although some research has indicated sex differences for running economy, it seems unlikely that there are real differences (Fletcher Jared et al. 2013). Differences between males and females have been observed when running on a treadmill at 1% grade. This slight incline, which is imposed in an effort to compensate for lack of air resistance, tends to penalize heavier individuals, leading to the conclusion that males are less economic while running than are females. Running on a treadmill with zero slope yields no difference between males and females. There is more variability between individuals than between the sexes.

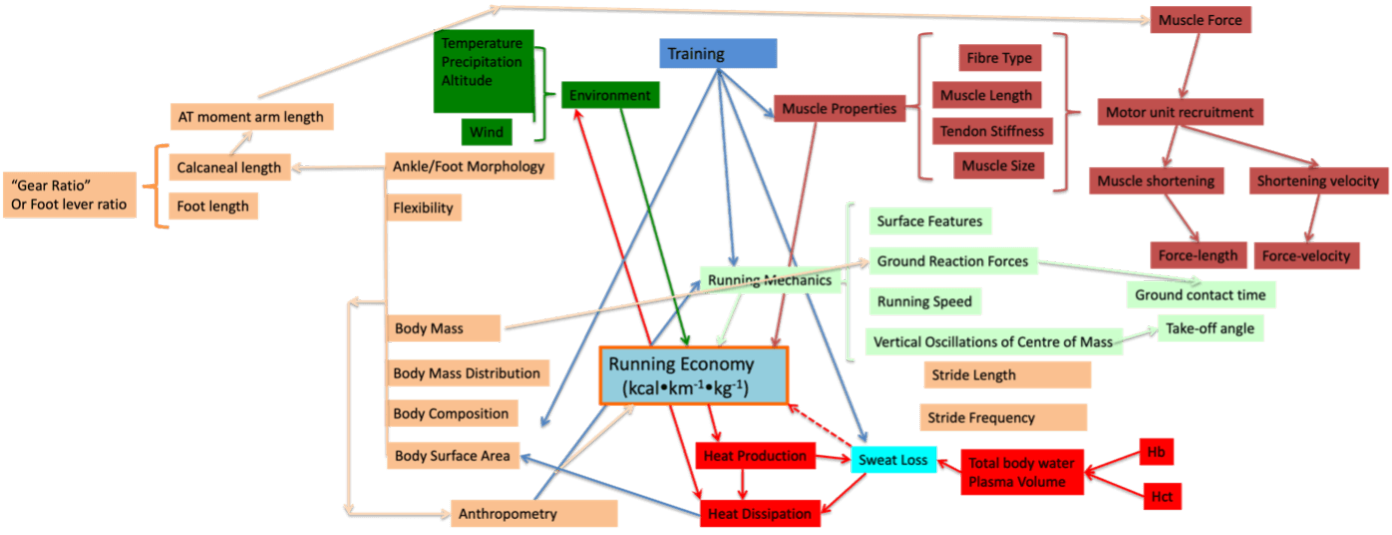


Figure 6A.16 Factors Affecting Running Economy: Running economy (near the middle, the blue box with red around it); is affected by several factors including muscle properties, body composition, environmental conditions and training.

Cycling

Although cycling efficiency is a well researchedwell-researched topic, it seems that cycling economy has been largely ignored. In spite of this, many advances in cycling performance have been gained by improvements in economy. For example, the use of aerobars for triathletes provides a substantial advantage in reducing air resistance, reducing power output and improving economy by decreasing energy cost for going a given speed. The truth is that power output is the primary determinant of the energy cost of cycling and the faster you can move at a given power output, the better the performance will be. The following equation (MacIntosh et al. 2000) gives the power output for cycling on a level surface, and consideration of the variables in the equation yields important factors affecting economy of cycling.

Power = ½ C_d ·A ·$(v-v_{air})^2$ · v +Cr · M · g

C_d is coefficient of drag, ai r resistance

A is frontal surface area

is air density

v is velocity of forward travel

v_{air} is velocity of the wind where headwind would have a negative value

C_r is the coefficient of drag for rolling resistance

M is body mass

g is acceleration due to gravity (typically 9.81 m s^{-1} · s^{-1})

Consideration of this equation reveals three factors that can be adjusted to affect the energy cost of cycling. Frontal surface area can be minimized by bending at the hip and keeping the elbows close to the body. Cd can be minimized by bicycle design, wearing tight fitting clothing, aerodynamic helmet and cycling shoes (or covers). Rolling resistance can be minimized by keeping the tires well inflated and cycling on a smooth hard surface.

Cyclists today not only have speedometers that inform them of their speed, but options to have devices that inform them of their power output. Although these devices are typically used to record the workout while training, they can be used to provide feedback on ways to minimize power output while travelling at a given speed. By reducing the power output at a given speed, the rider can reduce the energy cost for cycling at that speed.

Summary

It is the energy use in muscles during exercise that necessitates the physiological responses of the body's systems needed to maintain homeostasis. This energy is needed by the ATPases for ion pumping and molecular interactions of the muscles that generate force and accomplish mechanical work. The energy cost in a given muscle can increase nearly 100 fold during exercise. This increased energy need activates the metabolic anaerobic and aerobic pathways to regenerate ATP. ATP is regenerated by: phosphate transfer from creatine phosphate, glycolysis and oxidative metabolism. The use of creatine phosphate can be activated very quickly, and this increases creatine concentration in the myoplasm. A very small increase in [ADP] together with increased sarcoplasmic [Ca^{2+}] activates glycolysis. Increased creatine concentration activates aerobic metabolism. Greater oxidative metabolism results in a need for increased delivery of O_2 to the active muscles. Cardiac output increases and more oxygen is removed from the blood flowing through the active muscles. Ventilation increases to provide more oxygen to the blood and to allow more excretion of CO_2. Heat is released in the muscles accompanying ATP hydrolysis and ATP production by glycolysis and phosphorylation. This heat must be removed from the body by the evaporation of sweat or by conduction and convection. Skin blood flow increases to bring the added heat close to the surface, necessitating a further increase in cardiac output.

The amount of energy needed by the muscles during exercise depends on how many muscles are active and the magnitude of activation of the active muscles. Factors such as speed of locomotion, force of contraction, supported body mass and power output contribute to the energy cost. Exercise in the mild intensity exercise domain can be sustained by oxidative metabolism and

can be continued for hours. As exercise intensity increases, the duration that exercise can be sustained decreases. When the exercise elicits maximal oxygen update, the maximal duration of exercise is just a few minutes. When exercise requires all-out effort, the intensity can be maintained only for seconds. The energy cost of exercise can be quantified by measurement of oxygen uptake and lactate accumulation. Relating this energy cost to work accomplished permits calculation of efficiency. Economy of locomotion can be calculated with similar estimation of energy cost and relating this to the distance travelled by a given form of locomotion.

Research Highlight

The research presented in the article by O'Connell et al. (2017) illustrates how the energy cost of exercise in the severe intensity domain can be estimated, and provides an explanation for the slow component of . When intensity of exercise is above the anaerobic threshold, as is the case here, measurement of is not sufficient to allow calculation of the energy cost. Some of the energy at this intensity is provided by glycolysis, with accumulation of lactate. This research was done to address the question: is the slow rise in we call the slow component associated with constant or rising rate of lactate production. If the slow component was representative of a rising energy cost, as it most commonly is interpreted to be, then it would be expected that lactate production (accumulation) would continue at the same rate or a higher rate as the rose after 3 min of exercise at an intensity above the anaerobic threshold. Note that we define anaerobic threshold as the highest intensity of exercise that can be sustained with oxidative metabolism, so above the anaerobic threshold, lactate accumulation must occur.

The subjects in this study completed an incremental cycle ergometer test to determine lactate threshold and $\dot{V}O_2max$,. They then performed 3 constant intensity rides at 60% of the difference between anaerobic threshold and $\dot{V}O_2max$,. These rides, which were performed at approximately 88% of the power output at max were 3, 6 and 9 min in duration. At the end of the nine min trial, blood lactate was 13.9 mM, indicating a high level of exertion. Of interest, the accumulation of lactate from 3 to 6 min was 3.7 mM and from 6 to 9 min was 1.7 mM. This decrease in rate of accumulation was unexpected, and indicative that as rose, the energy yield from anaerobic glycolysis decreased. Taking into consideration the rising energy cost for ventilation, this decrease in energy yield from anaerobic glycolysis, the rise in associated with the slow component of did not represent an increase in energy cost of muscle contraction. Other than the small increase in energy cost for ventilation, the energy cost of the exercise remained constant through the 9 min of effort. In retrospect, this should have been expected, considering the slow time constant for the rise in for fast-twitch motor units. Figure 6A.17 illustrates this interpretation of the results of the study by O'Connell.

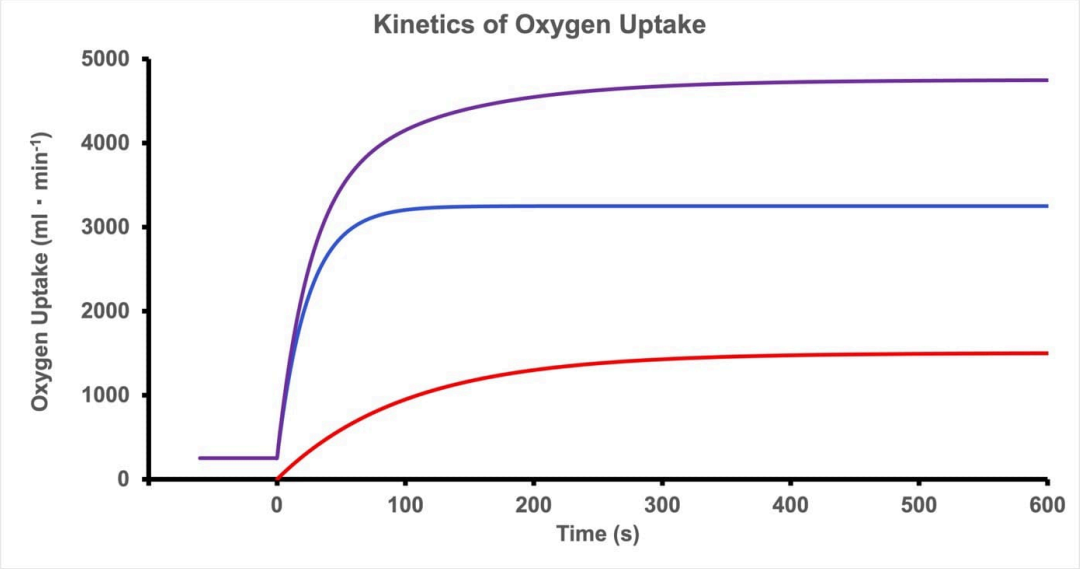


Figure 6A.17 Kinetics of Oxygen Uptake in the Severe Intensity Domain.

This figure shows the oxygen uptake on transition from rest to moderate domain exercise (blue line), the extra oxygen uptake in fast-twitch motor units (red line) for exercise in the severe intensity domain and the total oxygen uptake for this exercise (purple line). Note that the total oxygen uptake continues to rise after a steady state would otherwise be expected if only slow-twitch motor units were active. The slow component of slow component of oxygen uptake can be explained by the slow time constant for the kinetics of oxygen uptake in fast-twitch motor units. This would imply that the slow component would only be observed if fast-twitch motor units are required for the exercise.

Self-Assessment

Discussion Points:

Consider what is going on in the muscle fibres of an active motor unit and an inactive motor unit of the same muscle when exercise using that muscle is initiated.

Discuss the aerobic and anaerobic contributions during exercise in the mild, moderate, vigorous and hard intensity domains.

RQ and RER were explained in this chapter within the section titled “Substrate Use.” It was stated that when RQ = RER, total O_2 and CO_2 in the body would not change. Explain why the amount of O_2 and CO_2 in the body must not change for RQ = RER.

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Meet the Author

Dr. Brian MacIntosh obtained his undergraduate degree in Human Kinetics at the University of Guelph in 1975. He completed his PhD in 1979 at the University of Florida in Medical Sciences under the supervision of Dr. Wendell Stainsby. After a brief postdoctoral fellowship at Queens University in the Dept of Physiology, he held faculty positions at Concordia University (1980-1986), University of Saskatchewan (1986-1989) and the University of Calgary (1989-2019). He is now retired, but still pursuing research. During his career, Dr. MacIntosh published articles on a variety of topics: skeletal muscle contractile properties and fatigue, activity dependent potentiation, atrophy, running economy, critical power, slow component of oxygen uptake, force-velocity properties and power output.

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2.5: Chapter 7 - Pulmonary Function; Gas Exchange Between the Environment and Blood



Photo 9.1> – Gas exchange is required for the survival of all animals. Image by Myriams-Fotos under a Pixabay License

Learning Objectives

After reading this chapter, you should be able to:

- Describe the oxygen cascade; the physiological processes by which oxygen moves from room air to blood and what pulmonary adjustments must occur during dynamic exercise for this to occur in an effective manner.
- Identify the main components of the ventilatory control system during exercise.
- Visualize the processes of ventilation and perfusion in humans at rest and during exercise.
- Discuss the linkage between muscle metabolism and the pulmonary response to exercise.
- Describe how the cardiovascular and pulmonary systems interact during exercise.
- Explain what pulmonary limitations are present in some highly trained endurance athletes and how this can affect exercise performance.

Key Terms and Abbreviations

Pulmonary ventilation, pulmonary diffusion, inspiration, expiration, mixed venous oxygen content (CvO_2), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), mixed venous partial pressure of carbon dioxide ($PvCO_2$), cardiac output, alveolar ventilation ($\dot{V}_A$), upper airway, conducting zone, transitional zone, respiratory zone, anatomic dead space, pleural pressure, Fick's law of diffusion, hemoglobin (Hb), eupnea, tidal volume, ventilation, progressive exercise, minute ventilation ($\dot{V}E$), maximal oxygen uptake ($\dot{V}O_2max$), vital capacity, total lung capacity (TLC), residual volume (RV), forced vital capacity (FVC), homeostasis, central controller, sensory input, effectors, pontine respiratory group (PRG), dorsal respiratory group (DRG), ventral respiratory group (VRG), rostral ventral respiratory group (rVRG), caudal ventral respiratory group (cVRG), retrotrapezoid nucleus (RTN), Bötzinger complex, preBötzinger complex, chemoreceptors, metaboreceptors, mechanoreceptors, exercise hyperventilation, central locomotor command hypothesis, CO_2 flow hypothesis, locomotor muscle mechanoreceptor/metaboreceptor hypothesis, metabolic equivalent (MET), respiratory quotient (RQ), respiratory exchange ratio (RER), Bohr effect, shunt, physiologic dead space, ventilation-perfusion ratio, Fick's law, aenemia, polycythaemia, erythropoietin (EPO), mechanical interactions, preload, afterload, venous return, ventilatory sinus arrhythmia, metaboreflex, fatigue.

Case Presentation

Chris was born in Edmonton but moved to Victoria 5 years ago to train year round for cycling. He belongs to a team and has sponsorship from one of the large bike companies. With this income he is able to treat training like a full-time job; he does not have to hold a job to support himself. His coach has him doing one or even two workouts most days of the week. He has medaled in national and international road races and has set his sights on one of the large international, multi-day stage races. As part of his training his coach has enlisted Chris in an exercise physiologyresearch study. During one day of the study Chris performs an incremental cycle exercise test to exhaustion to determine his maximal oxygen uptake ($\dot{V}O_2max$) On another day Chris performed a constant load (85% of maximum) cycle test to exhaustion as a lab-based indicator of exercise performance. During the tests the researchers take arterial blood to examine how well Chris is able to transfer oxygen from room air to blood. At rest, Chris' oxyhemoglobin saturation (SaO_2) is 97%, whereas at maximal exercise it is 90%. In healthy individuals, SaO_2 is maintained at near-resting values but Chris, like some other highly-trained endurance athletes exhibit a fall in arterial oxygenation. The researchers are also interested if the main muscle of breathing, the diaphragm, can become fatigued during strenuous exercise. Both a reduction in blood oxygen content and diaphragm fatigue have measurable negative effects on exercise performance and emphasize that no organ system (the pulmonary system in this case) is without physiological limits. For further details on this, please see the now-classic work of Dr. Jerome Dempsey titled "Is the Lung Built for Exercise" (Dempsey JA 1986).

Introducing The Pulmonary System

The first major system involved in the oxygen transfer chain is the pulmonary system. It functions to move fresh air, rich in oxygen, from the external environment deep into the alveoli where oxygen diffuses into the blood stream. Carbon dioxide, which has been produced by the body's tissues, is also removed from the blood-stream and expired into the external environment. These two processes are referred to as pulmonary ventilation and pulmonary diffusion. Pulmonary ventilation specifically is the process of moving air into (inspiration) and out of the lung (expiration). Pulmonary diffusion is the oxygen and carbon dioxide gas exchange that occurs between the blood contained within the pulmonary capillaries and the air within the lungs. The respiratory system is well designed to face several major challenges to pulmonary diffusion that are present during exercise. These challenges include:

Decreased time for gas diffusion: Increases in muscle metabolism with exercise stress alveolar-to-arterial gas exchange. For example, at maximal exercise intensities, oxygen content of venous blood (CvO_2) falls below resting levels (about a 20% reduction) due to increased oxygen uptake ($\dot{V}O_2$) while increases in muscle carbon dioxide production (2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...z#v-%CC%87co2-">$\dot{V}CO_2$) increase the mixed venous partial pressure of carbon dioxide by as much as 40 mmHg. An increase in cardiac output ($\dot{Q}$) helps to deliver more oxygen to the working muscles but also dramatically reduces the time for gas exchange to occur in the pulmonary capillaries.

Maintenance of alveolar gas quality: In order to maintain the quality of alveolar oxygen and carbon dioxide partial pressure (Pao_2 & $Paco_2$), pulmonary ventilation, or more specifically, alveolar ventilation ($\dot{V}A$) must increase by as much as 20 times its resting level at maximal exercise intensities. Such an accomplishment requires significant force generating capabilities by the respiratory musculatures. However, the work of breathing must be restrained so as to conserve oxygen for the exercising muscles.

Ability to meet ventilatory muscle blood flow requirements: Like locomotor muscles, the respiratory muscles' demand for oxygen metabolism increases with increasing exercise intensity. In order to meet these demands, blood flow to the muscles that perform ventilation must increase. However, the increased blood supply to the respiratory muscles must be controlled effectively so as to not compromise the flow of blood to the exercising muscles.

Ability to match ventilation ventilation and metabolic demand: Ventilation during exercise must increase in a manner proportional to increasing whole body metabolism. If this did not occur arterial blood gas and pH would quickly deteriorate, dramatically affecting exercise performance. A complex respiratory control system composed of sensors throughout the cardiovascular, pulmonary, and skeletal muscle systems is capable of notifying a central pattern generator which integrates the mechanical and metabolic information and produces an appropriate motor output to the respiratory muscles.

The purpose of this chapter is to address several important physiological principles as they pertain to the pulmonary system of a healthy, young adult exercising at sea level. This includes description of the anatomical components of the respiratory system, the pattern of breathing during steady-state and progressive exercise, lung mechanics and energetics of respiratory muscle

contraction, control of exercise ventilation, pulmonary gas exchange, and cardiopulmonary interactions. Finally, the chapter will conclude with a discussion of pulmonary-related constraints to athletic performance in elite athletes.

The study of the pulmonary physiology of exercise has a number of abbreviations. Many of the more commonly used terms are presented in Table 7-1.

Table 7-1. Definition of terms commonly used in pulmonary exercise physiology.

Abbreviation	**Term**	**Typical Units**
$\mathbf{V_T}$	Tidal Volume	L or mL
b	Breathing Frequency	breaths·min^{-1}
$\mathbf{\dot{V}_e}$	Minute Ventilation	L·min^{-1}
$\mathbf{\dot{V}_a}$	Alveolar Ventilation	L·min^{-1}
$\mathbf{V_D}$	Dead Space	L or mL
$\mathbf{V_D/V_T}$	Ratio of Physiologic Dead Space to Tidal Volume	Unit-less
$\mathbf{Pao_2}$	Arterial Partial Pressure of Oxygen	mmHg
$\mathbf{Paco_2}$	Arterial Partial Pressure of Carbon Dioxide	mmHg
$\mathbf{Pao_2}$	Alveolar Partial Pressure of Oxygen	mmHg
$\mathbf{Paco_2}$	Alveolar Partial Pressure of Carbon Dioxide	mmHg
$\mathbf{Sao_2}$	Oxyhemoglobin Saturation	%
$\mathbf{AaDo_2}$	Alveolar-arterial Oxygen Difference	mmHg
$\mathbf{Cao_2}$	Arterial Oxygen Content	mL O_2·100mL^{-1}
$\mathbf{\dot{V}_{o_2}}$	Oxygen Consumption	L·min^{-1} or ml·kg^{-1}·min^{-1}
$\mathbf{\dot{V}_{co_2}}$	Carbon Dioxide Production	L·min^{-1}

RER	Respiratory Exchange Ratio ($V^{\cdot} co_2/V^{\cdot} o_2$)	Unit-less

Pulmonary System Anatomy

The pulmonary (respiratory) system is composed of the airways, the blood gas interface, the blood vessels, and the respiratory muscles (see Figure 7-1). In this section, the anatomical components of the respiratory system will be described in detail with reference to their function.

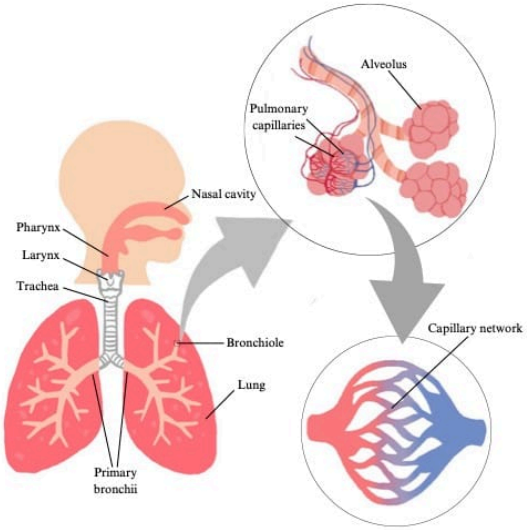


Figure 7-1 – A simplified view of the pulmonary system with an expanded view of alveolae and a capillary network. Image by Paulina Westergard.

Airways

The airways are the conducting 'pipes' through which the air flows, to reach the blood gas interface where pulmonary diffusion takes place. The first airways encountered are those of the upper airway. The upper airway consists of the nose, mouth, pharynx, and larynx. The nose is responsible for humidifying and warming the inspired air and is also a primary site of airflow resistance. The mouth can also be used for breathing and is involved in phonation and mastication. Both the mouth and the nose are connected into a single airway by the pharynx. Finally, the larynx contains the vocal cords and is therefore also responsible for phonation.

From the upper airways, the airways further divide like a branching tree, hanging upside down. From a single trunk, called the trachea, the airways branch into two main bronchi (one to each lung) and then each bronchus progressively branches, narrows, ending in short bronchioles and then terminal bronchioles. There are approximately 16 generations of branching that take place from the trachea to the terminal bronchioles and this accounts for the conducting zone. The conducting zone is composed of airways that are not involved in gas exchange and are simply responsible for the movement of air from the external environment to the transitional and respiratory zones. The volume of air found within the conducting zone is referred to as the dead space**.** Anatomic dead space refers to the conducting airways which contain no alveoli and do not participate in gas exchange. The volume of air in the dead space is approximately 150 ml at rest. However, the volume of the dead space increases during exercise, due to distention of the airways, increasing lung volume, and resulting negative pleural pressure. The transitional and respiratory zones. are composed of the respiratory bronchioles, the alveolar ducts, and the alveolar sacs. The transitional and respiratory zones. account for the next 7 generations of airway branching and these represent the main site for gas exchange. The volume of the transitional and respiratory zone is roughly between 2.5 and 3 litres in a resting adult.

The total cross sectional area of the lung increases exponentially from the first to the last generation. The cross sectional area of the trachea at functional residual capacity ranges from 2.0 to 4.7 cm^2(Dolyniuk and Fahey 1986), while airways within the

respiratory zonerange in cumulative cross-section from 200 to 1000 cm^2. Because of this feature (increasing cumulative cross-section) the velocity of gas flow is extremely slow in the vicinity of the alveoli thereby assisting with gas exchange. This is like a fast-flowing river slowing down as the width of the river increases.

Blood Gas Interface

The blood gas interface consists of the alveolar epithelium and the endothelial lining of the pulmonary capillary (see Figure 7-2). Important features of the blood gas interface include its extensive surface area (850 – 1000 cm^2) and its thinness (0.3 µm). These features are ideal for the diffusion of oxygen and carbon dioxide between the air and blood, which is governed by Fick's law of diffusion. It states that the amount of gas moving across a sheet of tissue is proportional to its surface area and inversely proportional to its thickness.

Oxygen in the air that is inhaled into the alveoli diffuses into the pulmonary capillary blood stream by crossing the alveolar epithelium, the interstitial space, the pulmonary capillary endothelium and the plasma, through the membrane and into the red blood cell. Oxygen then binds to haemoglobin, a protein found in the red blood cells. Carbon dioxide diffuses from the red blood cell or the plasma itself, across the pulmonary capillary endothelium, the interstitium, and finally the alveolar epithelium into the alveoli to be exhaled from the body.

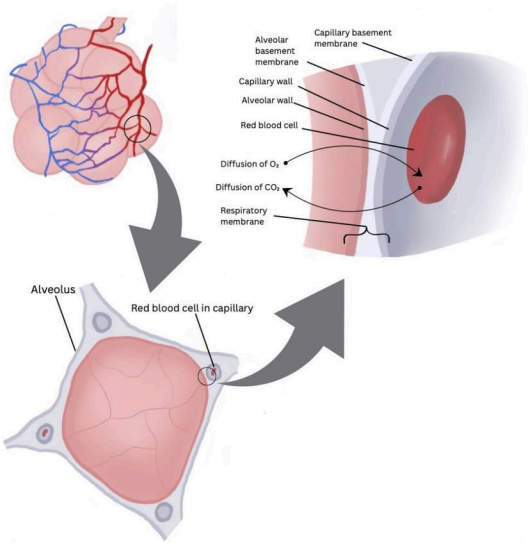


Figure 7-2. The Blood Gas Interface. This image illustrates the position of blood vessels on the alveolar walls with a close-up of the respiratory membrane. Image by Paulina Westergard.

Blood Vessels

The pulmonary blood vessels form a branching network that initially follows alongside the branching airways. Both vessels and airways bifurcate often, becoming smaller with each split. These arterioles and airways go deep within each lobe of the lung. Further downstream, a network of dense capillaries form in the region of the alveolar walls. The pulmonary veins, which return oxygenated blood to the left side of the heart, travel between the lobes of the lungs (rather than through their centres).

The pulmonary capillaries are sufficiently small in diameter (~10µm), just large enough to permit the passage of a red blood cell. This feature improves pulmonary gas exchange by reducing the distance for oxygen and carbon dioxide diffusion. Another important feature involves the vast network of the capillaries themselves, which forms nearly a complete sheet of blood in the vicinity of the alveoli. This large surface area is responsible for an amazingly small resistance to blood flow. Blood flow through each pulmonary capillary at rest is so slow that a red blood cell spends nearly 0.75 seconds in the capillary and traverses several alveoli, each with a diameter of roughly 200 µm.

These important features of the pulmonary circulation are responsible for nearly a complete equilibration of oxygen and carbon dioxide between the alveolar gas and the capillary blood. However, the thin and intricate array of the pulmonary capillaries also makes them quite weak and susceptible to damage. The entire cardiac output must travel through the pulmonary circulation.

Since the cardiac output can increase above resting levels by 5 to 6 times with high-intensity exercise, the high rate of flow and pressure in addition to mechanical strain caused by increased lung volumes can be responsible for capillary stress failure. In such an instance plasma and red blood cells may enter the interstitial space or alveoli and impair pulmonary gas exchange.

In addition to the pulmonary circulation, the respiratory system also has a bronchial circulation which is responsible for delivering oxygenated blood to the airways of the conducting zone. This includes supplying blood to the primary, secondary, and lobular bronchi, and the bronchioles.

Ventilatory Muscles & Muscles of the Upper Airway

The ventilatory muscles can be categorized into three different groups. These are the muscles of the upper airway and the bronchi, inspiratory muscles, and expiratory muscles.

The muscles of the upper airway include: nasal dilator muscles, tensor muscles of the soft palate, the genioglossus, and the geniohyoid. These muscles are involved in dilating and stiffening the upper airway thereby preventing its collapse as more negative intrathoracic pressures develop during inspiration. The activity of these muscles is phasic in nature and closely related to ventilation during regular breathing or eupnea. Although the activity of upper airway muscles is not well understood during exercise, there does appear to be some relation between their activity and the magnitude of inspiratory airflow. In addition to the muscles of the upper airway, the smooth muscle of the bronchi are also involved in controlling airway resistance.

Several muscles are involved in the process of inspiration. Airflow into the lungs requires that the volume of the thoracic cavity increase thereby reducing intrathoracic pressure. The pressure gradient generated between the airways and the external environment is responsible for the mass flow of fresh air into the alveoli. Expansion of the thoracic cavity is achieved by activity in the inspiratory muscles. This includes the external intercostals (which expand the rib cage), the diaphragm, the scalene muscles, and finally the sternocleidomastoids.

At rest, elastic recoil of the lung is responsible for the process of expiration. However, during exercise, as breathing frequency and tidal volumes increase, the accessory muscles of expiration are recruited. These muscles include the rectus abdominis, the internal and external oblique muscles, the transversus abdominis, and the internal intercostals. Contraction of the abdominal muscles helps to force the diaphragm upward thereby reducing the volume of the thoracic cavity. Activity in the internal intercostals draws each individual rib together and as a result decreases the volume of the thoracic cavity. A decrease in the volume of the thoracic cavity increases intrathoracic pressure and creates the pressure gradient necessary to expel air from the lungs.

Breathing Patterns During Exercise

Breathing at rest and during exercise is more complicated than simply ventilating the lung. Ventilation must be controlled appropriately such that the work of breathing is minimized and alveolar gas partial pressures are maintained. The control of breathing system is involved in maintaining appropriate breathing patterns and is described below. Variables involved in characterizing the breathing pattern include: *end-inspiratory* and *end-expiratory lung volumes* [the difference of which is the *tidal volume* (V_T)], *inspiratory and expiratory flow rates*, and breath timing [which includes *inspired time* (T_I), *expired time* (T_E), and the *frequency of breathing* (f_b)], and *duty cycle* [$T_i/(T_i+T_E)$]. The simplest method of assessing breathing patterns during exercise is therefore to measure f_b and V_T. Other approaches include measuring flow volume loops as discussed below. In this section, the basic characteristics of the breathing pattern during progressive exercise and during sub maximal exercise will be described.

Breathing Patterns During Progressive Exercise

Progressive exercise involves continuously increasing work of the locomotor muscles, such as a ramp protocol maximal exercise test. Other examples include a cycle exercise test with increasing resistance and a treadmill test with increasing speed and/or incline. Figure 7-3 illustrates the ventilatory response during incremental exercise. During this type of exercise, minute ventilation ($\dot{V}E$) increases with increasing intensity/($\dot{V}O_2$). At mild exercise intensities, the rise in $\dot{V}E$ is accomplished by increasing both f_b and V_T (see Figure 7-4). This is in contrast to moderate intensity exercise during which increases in $\dot{V}E$ are achieved primarily by increasing V_T while maintaining f_b. Increases in V_T are accomplished by increasing end-inspiratory lung volume and by decreasing end-expiratory lung volume. This is an ideal ventilatory exercise response because it increases $\dot{V}A$ and decreases dead space ventilation; it therefore has a positive effect on the quality of alveolar gases. During heavier exercise, further increases to V_T become too costly with respect to the work of breathing, therefore, V_T plateaus and increases in f_b are responsible for further

increases in . At maximal exercise intensity, V_T typically reaches about 50-60% of vital capacity.

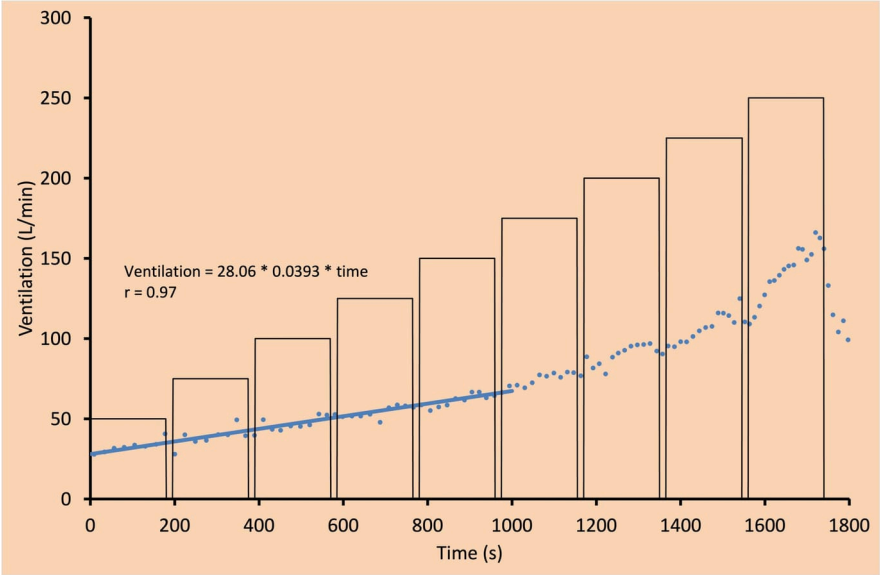


Figure 7-3 Ventilation During an Incremental Test. Each blue dot represents the average of 10 breaths during an incremental test that began with 50 watts power output and 25 watt increments (black boxes illustrate power, in watts). There was an interruption of 15 s after each stage of the test to obtain blood samples for lactate analysis. The regression equation represents the linear relationship over the first 1000 seconds of the test. Ventilation increases exponentially after this time.

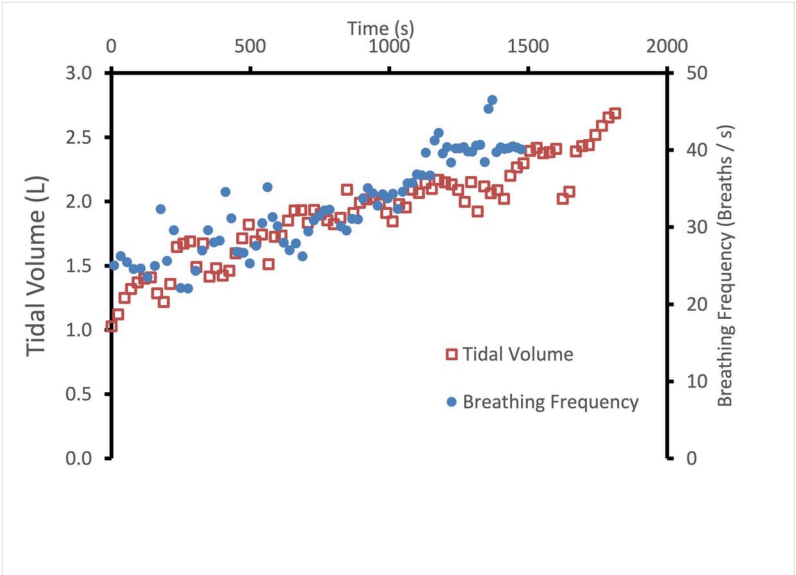


Figure 7-4 Pattern of Breathing Adjustment During Incremental Exercise. Initial changes in ventilation occur by increases in tidal volume, then by changes in breathing frequency as exercise intensity increases. Near the end of the test, tidal volume again dominates the change in ventilation.

Breathing Patterns During Submaximal Exercise

Submaximal exercise is typically an intensity of exercise that can be maintained in excess of five minutes. It may involve a steady state $\dot{V}E$ phase if the intensity is less than 70% of $\dot{V}O_2$max (in an untrained individual). Above this intensity $\dot{V}E$ may not reach a steady state but instead gradually increases.

$\dot{V}E$ during submaximal exercise can be characterized by three phases as illustrated in Figure 7-5. At exercise onset, $\dot{V}E$ increases abruptly and is referred to as *phase I*. Throughout the first 2-3 minutes of exercise $\dot{V}E$ slowly and gradually increases to a steady state. This slow, gradual increase in $\dot{V}E$ is called *phase II*. Finally, *phase III* is the steady state or the relatively constant period of $\dot{V}E$**.** Note that these phases are not the same as the 3 phases of the rise in $\dot{V}O_2$**.**

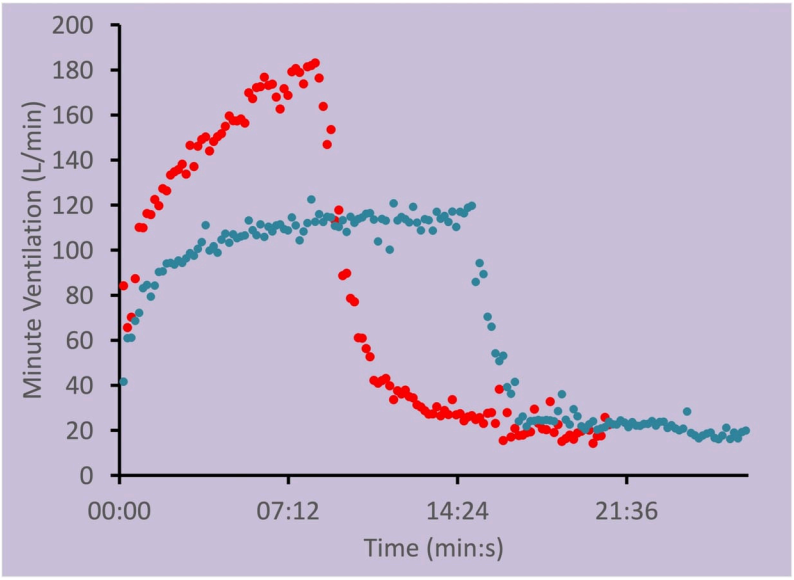


Figure 7-5 Rise in Minute Ventilation During Submaximal Exercise. The blue dots present minute ventilation during a constant intensity treadmill running task at 90% of the speed at 2nd lactate threshold for 15 min. A steady level of ventilation is achieved in about 7 min. The red dots present minute ventilation of the same subject running on a treadmill at a speed that was found to be just lower than the speed at which maximal oxygen uptake was reached in an incremental test. Ventilation continues to increase through-out the task.

Arterial Pco_2, Po_2, and typically do not change with exercise below ~70% of $\dot{V}O_2$ is illustrated in Table 7-2. Although above this exercise intensity it is not uncommon for hyperventilation to occur. Once this threshold is crossed, increases in plasma lactate, potassium, and norepinephrine concentrations drive $\dot{V}E$ out of proportion to $\dot{V}O_2$ and carbon dioxide production (2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...-%CC%87o2-peak">$\dot{V}CO_2$). As a result, alveolar Pco_2 decreases and alveolar Po_2 increases.

Table 7-2. Arterial Pco_2, Po_2, SaO_2 and pH at rest and at varying exercise intensities in healthy, recreationally active young adults.

		Mild	**Moderate**	**Heavy**	**Maximal**
	Rest	25-30%	55-60%	85-90%	100%
$Paco_2$ (mmHg)	40	38	36	33	31
Pao_2 (mmHg)	95-100	95	95	95	95
Sao_2 (%)	97	97	97	96	95
pH	7.40	7.38	7.34	7.29	7.28

Values from Romer, Sheel and Harms ; *The Respiratory System*.

Key Points

During exercise, pulmonary ventilation increases and there is a highly synchronized series of changes which serve to control the intra- and extra-thoracic airways. The patterns of breathing serve to minimize the work done by the inspiratory and expiratory

musculature.

Lung Mechanics During Exercise

Airway Caliber

During dynamic exercise, both inspiratory and expiratory flow rates increase in order to meet ventilatory demands. It is important that the caliber (diameter) of the airways increase with increasing ventilatory demands to prevent increases in airway resistance, which would place an intolerable load on the ventilatory muscles. Several key mechanisms serve to accomplish this. The upper airway, consisting of the nasal, pharyngeal and laryngeal airways, comprises most of the total respiratory system resistance to airflow in a healthy adult and is highly susceptible to narrowing during inspiration. During (and following) exercise it is known that the resistances of the nasal, pharyngeal and laryngeal portions of the upper airway are reduced in proportion to exercise intensity. In general, at approximately 20-40 $L \cdot min^{-1} \dot{V}E$ there is a change in the primary route of airflow from high resistance nasal routes (i.e. breathing through the nose) to the lower resistance oral route (i.e., mouth breathing).

During strenuous exercise, when ventilatory rates are high, the intra-thoracic airways are susceptible to narrowing via constriction of bronchiolar smooth muscle (bronchoconstriction). Inflammation may also narrow intra-thoracic airways during the hyperpnea of exercise, especially in the face of evaporative water losses from the airway mucosa or release of inflammatory mediators from mast cells lining the airway. However, in a healthy person exercising in temperate conditions the intra-thoracic airway resistance is reduced during and following exercise. This supports the concept of a strong exercise-induced bronchodilation during exercise, when compared to rest. The regulation of upper airway caliber during exercise is dependent upon three factors:

(1) vascular tone in the nasal mucosa;

(2) activation of key skeletal muscles of the upper airway, which stiffen the airway; and

(3) passive dilation of the airway. Each of these mechanisms serves to maximize the caliber of the airways.

Flow-Volume

During ventilation, the rate of movement of air and airway resistance are dictated by airway radius. As mentioned, there are important mechanisms in place that maximize airway radius in order to accommodate the substantial ventilatory load of exercise. The increase in ventilation occurs because of increases in breathing frequency and tidal volume. Tidal volume increases with increasing exercise intensity until approximately 50-60% of vital capacity is reached. Thereafter, any further increase in ventilation will be achieved by increasing breathing frequency alone at a constant tidal volume. *Maximal expiratory flow-volume loops* are used to graphically present the relationship between maximum possible flow and lung volume across the range of volume from total lung capacity (TLC) to residual volume (RV). This volume is also referred to as forced vital capacity (FVC). In healthy individuals, these expiratory curves have a distinctive shape resulting from a rapid rise to maximal expiratory flow with the onset of expiration from TLC, followed by a steady reduction in flow rate with falling lung volume. The maximal flow volume defines the limits of the airways and ventilatory muscles to produce flow and change volume during exercise. By examining these loops (see Figure 7-6) one can see that the mechanical properties of airways and lungs for flow and volume appear ideally designed for exercise. The maximal flow-volume loop (i.e., capacity) is much larger than the peak flow rate and tidal volume reached at maximum exercise (i.e., demand) in a healthy person.

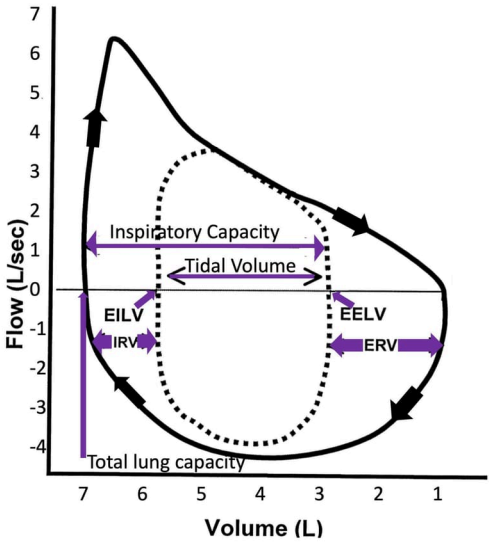


Figure 7-6 Flow Volume Loop. The dottted line represents the flow-volume relationship during a breath (in and out) while performing exercise at or near maximal oxygen uptake. EILV end inspiratory Lung Volume; EELV End expiratory lung volume; IRV, Inspiratory reserve volume, the volume of air you could exhale after a normal expiration; ERV, expiratory reserve volume (the volume of air you could breathe out after a normal expiration. Total lung capacity is the volume of air in the lungs after inspiring as much as possible. Adapted from Guenette and Sheel "Physiological consequences of high work or breathing during heavy exercise in humans. Journal of Sciences and Medicine in Sport. 10: 341-350, 2007.

Ventilatory Muscle Energetics

Homeostasis of respiratory gases in the blood is reliant upon the coordinated changes that link tissue metabolism, alveolar ventilation, cardiac output and peripheral blood flow. The pulmonary system in the young, healthy adult responds to dynamic exercise with remarkably precise regulation of alveolar ventilation that is matched to metabolic demand. Even during strenuous sea-level exercise the arterial partial pressures of oxygen and carbon dioxide and arterialpH remain close to resting values indicating that the neuromechanical regulation of alveolar ventilation is highly effective. Exchange of air between the atmosphere and the alveoli is dependent, in part, upon the mechanical properties and interactions between the lung, the surrounding anatomy including the chest-wall, the abdomen, and the ventilatory muscles that act upon them. The ventilation that accompanies exercise requires contraction of the ventilatory pump muscles. Contraction of these muscles permits increases in V_T and f_b during exercise and thus appropriate pulmonary gas exchange. Like the contraction of skeletal muscle there is an energy cost associated with the work of breathing. At rest, the O_2 consumption of the ventilatory muscles is approximately 3-5% of $\dot{V}O_2$. At maximal exercise this can increase to 8-10% of $\dot{V}O_2$max in healthy individuals and as much as 13-16% $\dot{V}O_2$max in highly trained endurance athletes (Aaron et al. 1992). The work of breathing can be divided into two categories:

- elastic work, which involves altering the shape of the anatomical structures involved, and
- resistive work, which is necessary to overcome the resistance to airflow in the airways.

In general, the ventilatory response to exercise is thought to be governed by the principle of "minimal effort" (Macklem 2002). This concept is supported in two ways. First, models describing the work of breathing indicate that the ventilatory patterns naturally observed during exercise are the least costly in terms of energy expenditure. Second, ventilation during exercise occurs within a range of lung volumes for which total lung compliance is greatest. This means that the amount of work performed on the lungs and chest wall to achieve a given tidal volume is minimized compared to higher or lower lung volumes.

The total work of inspiration and expiration is substantially higher during exercise than at rest because f_b and V_T are increased. Elastic work increases substantially as tidal volume increases relative to rest. Once V_T reaches a plateau, elastic work decreases with increasing f_b because more of the elastic energy that is stored in the chest wall and lung during inspiration is recovered during expiration. The resistive work of breathing increases significantly as flow-rate increases because of increases in turbulent airflow.

As one would expect, the work of breathing will increase when $\dot{V}E$ increased, and therefore, the recruitment of motor units in the ventilatory muscles is increased and energy demand placed on the ventilatory muscles is increased as well. It has been shown

that the metabolic and circulatory costs of a high work of breathing during maximal levels of ventilation amount to 10% of $\dot{V}O_2$max in the untrained person, and up to 15-16% of $\dot{V}O_2$ at maximal cardiac output in the highly-trained person (Aaron et al. 1992; Harms et al. 1997). This difference between trained and untrained individuals occurs because the trained person must achieve a greater $\dot{V}E$ to support the higher $\dot{V}O_2$max.

The ventilatory muscle oxygen cost at similar minute ventilations is greater in females and is increased by age. An older, male, of average fitness has a higher work of breathing compared with a younger male of average fitness. Ageing is associated with a loss of lung elastic recoil and the consequences of this include a reduction in maximal expiratory flow rate and an increase in functional residual capacity. The greater oxygen cost of breathing in females compared with males occurs because women have smaller airways, lung volumes, and maximal expiratory flow rates relative to men even when matched for lung size (Mead 1980; Sheel et al. 2009). Female athletes develop expiratory flow limitation (i.e., expiratory flow during tidal breathing intersects the maximum flow-volume envelope) more frequently than male athletes and have an increase in end-expiratory and end-inspiratory lung volume at maximal exercise. This pattern of lung inflation is called dynamic hyperinflation.

Key Points

The muscles of breathing are heavily recruited during exercise and there is a significant metabolic cost associated with this muscular contraction.

Control of Exercise Ventilation

The control of exercise ventilation has been studied extensively but still remains highly controversial and poorly understood. Before undertaking our discussion of the control of exercise ventilation we must understand the components of the basic respiratory control system and normal breathing at rest (eupnea).

Overview of the Ventilatory Control System

The ventilatory control system is schematically presented in Figure 7-7. It consists of three main components: central controller, sensory input and effectors.

The first component is referred to as the central controller. The central controller is made up of groups of neurons located within the medulla and the pons that work together to integrate sensory information and to produce efferent outflow to the ventilatory muscles. These groups of neurons are therefore responsible for generating the ventilatory rhythm and pattern. They determine the length of inspiration and expiration, the rate of inspiration and expiration, and finally the volumes of inspiration and expiration. Since the ventilatory system is affected by sleep/wake state, phonation/speaking, emotion, body temperature, locomotion, learning and experience, it also receives inputs from higher brain structures such as the hypothalamus. This information allows breathing to occur automatically during a variety of activities and states, yet allows voluntary override when the need arises. We do not have to consciously alter our breathing during tasks like speaking, coughing, chewing, and swallowing which all involve the same airway and ventilatory muscles. Throughout these activities the ventilatory system is capable of regulating arterialPO_2 and PCO_2 within a narrow range (±1-2 mmHg).

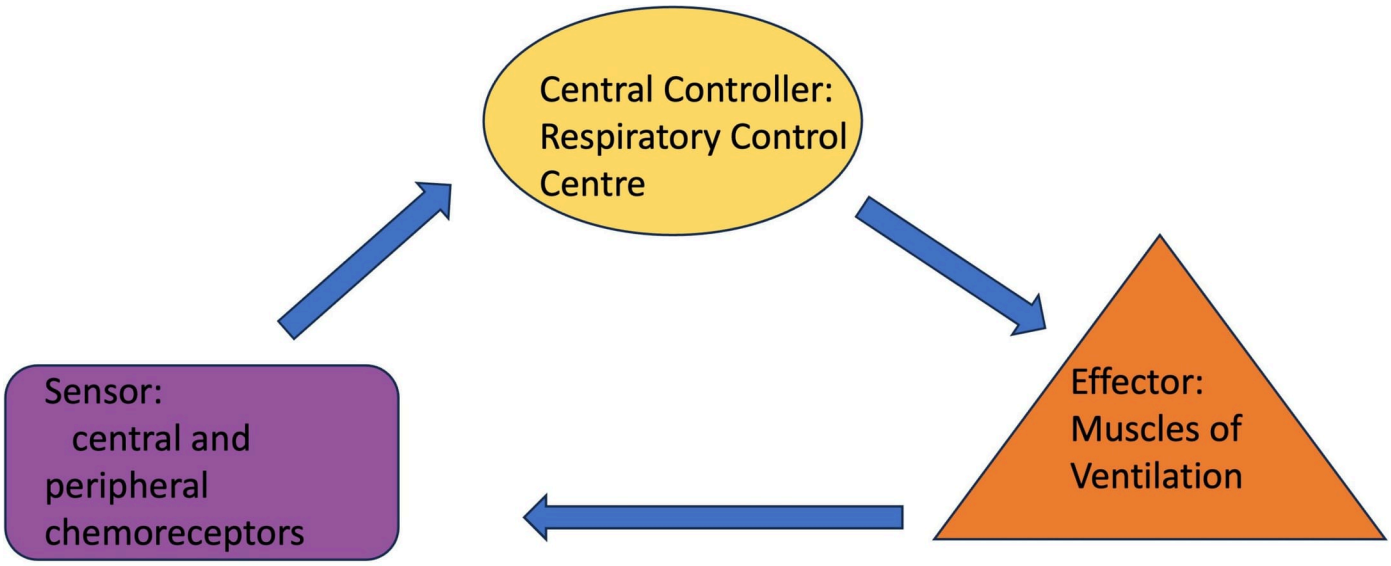


Figure 7-7 Schematic Control System. A control system must have 3 components: Sensor(s), Controller (decision maker) and effector (means of changing what is being sensed).

The second component of the ventilatory control system is the sensory input. Sensory inputs include peripheral and central chemoreceptors, mechanoreceptors and metaboreceptors of the lung and skeletal muscle. These receptors provide information regarding the chemical or humoral state of the blood, mechanical changes such as distention or compression of muscles, blood vessels, or the lung wall, and metabolic changes in the muscles of both the ventilatory and locomotor muscles.

The third component of the ventilatory control system is the motor output or effectors. The effectors include the neural connections leaving the central controllerand the ventilatory muscles that they stimulate. The motor output from the central controller activates with synchronization of the appropriate ventilatory muscles. In the following sections, each component of the ventilatory control system will be further discussed.

Central Controller

The central controller involves neurons located throughout the *ventral lateral medulla*, and consists of pacemaker neurons that generate the intrinsic oscillations required for the basic pattern of breathing. An extensive neuronal network is also present and is responsible for pattern generation and fine-tuning breathing by integrating sensory and supramedullary inputs. Figure 7-8 shows a lateral view of the brainstem and highlights several distinct areas of ventilatory neurons: the *pontine respiratory group* (PRG), the *dorsal respiratory group* (DRG), the *ventral respiratory group* [divided into the rostral (rVRG) and caudal (cVRG) ventral respiratory group], the *retrotrapezoid nucleus* (RTN), the *Bötzinger complex*, and the *preBötzingercomplex*. Nuclei within the PRG receive vagal afferent inputs that provide information relating to lung volume. These neurons are therefore important for limiting the rate and depth of breathing. The DRG receives bulbospinal inspiratory neurons and afferents from the peripheral chemoreceptors. It is likely an important site for sensory integration. The RTN contains both inspiratory and expiratory neurons that project to neurons within the rVRG. The importance of the RTN is not well understood but it may serve as a site of central chemoreception. The cVRG contains bulbospinal expiratory neurons that excite internal intercostals and abdominal motor neurons during expiration. The rVRG contains bulbospinal expiratory neurons that excite inspiratory muscles such as the diaphragm. The Bötzingercomplex contains expiratory bulbospinal premotor neurons and excitatory interneurons. Finally, the preBötzingercomplex contains pacemaker neurons that generate the basic ventilatory rhythms.

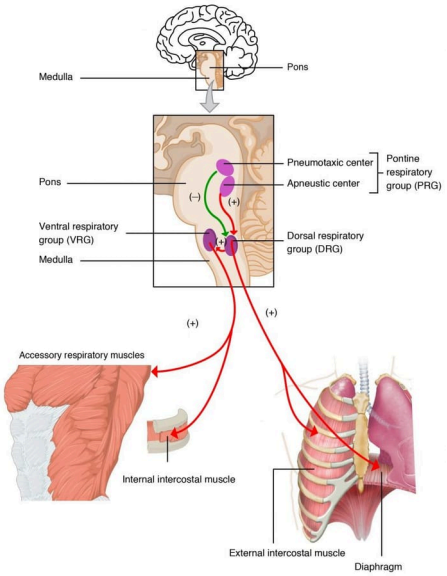


Figure 7-8 Control of Ventilation. A control system requires sensors, controller and effectors. central controller for ventilation is located in the pons and medulla of the brainstem. Here, a collection of centres provide modulation of the ventilatory response by activation of the muscles of ventilation, shown in the lower part of the image. Image is from Anatomy and Physiology by Authors: J. Gordon Betts, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix

Sensory Inputs

Sensory inputs to the central controller provide information about the chemical and metabolic status of the blood and muscles, and mechanical information such as stretch of the lung. This section describes the *peripheral chemoreceptors*, *central chemoreceptors*, *metaboreceptors*, and *mechanoreceptors*.

Peripheral Chemoreceptors

The chemoreceptors are located bilaterally at the bifurcations of the common carotid arteries. They are highly vascularized and are sensitive to changes in arterial Po_2, Pco_2, and potassium ion concentration. The sensory activity from the peripheral chemoreceptors is projected to the brainstem medullary respiratory neurons through the carotid sinus nerve where it synapses with neurons located within the nucleus of the solitary tract.

The peripheral chemoreceptors are the only receptors in the human body responsible for stimulating ventilation in the presence of hypoxia. There is a curvilinear relationship between ventilation and arterial Po_2 in hypoxia, as would be experienced on going to altitude (see Figure 7-9). This relationship becomes linear when ventilation is plotted against arterial oxyhemoglobin saturation, showing that the relationship between . The slope of this relationship is generally referred to as the *hypoxic respiratoryresponse*. This response is blunted (i.e. slope more shallow) if the level of arterial Pco_2 is held below the resting level (hypocapnic) and augmented (i.e. steeper slope) if the arterial Pco_2 is held above the resting level (hypercapnic). This modulation of the respiratory response provides evidence that both O_2 and CO_2 are detected and impact ventilation.

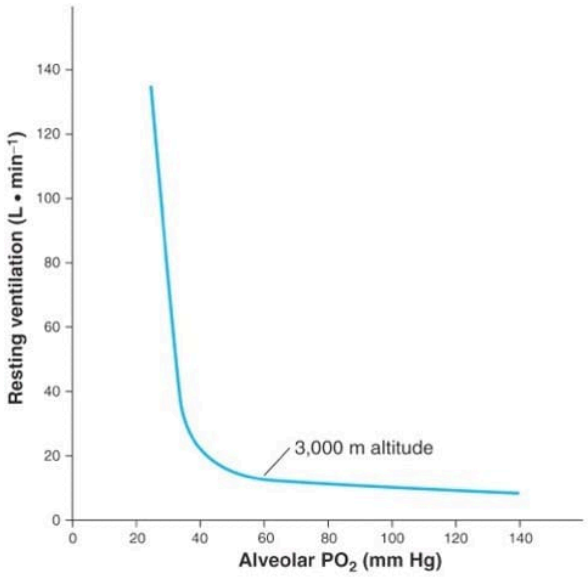


Figure 7-9 Hypoxia Stimulates Ventilation. Consider that arterial PO2 will be considerably less than alveolar PO2. Note that arterial PO2 can decrease to just below 60 mm Hg before substantial changes in arterial oxygen content occurs.

The ventilatory response to increases in arterial $Pco_2$is illustrated in Figure 7-10 and is a linear relationship. The slope of this relationship is typically referred to as the *hypercapnic ventilatory response*. The level of arterial Po_2also affects this response such that the slope of the response is decreased with hyperoxia and increased with hypoxia.

Finally, the peripheral chemoreceptors stimulate increases in ventilation when there are increases in potassium ion concentration and when pH decreases. With heavy exercise, potassium ion concentration increases and pH decreases; these changes may contribute to the hyperventilationthat occurs with heavy exercise.

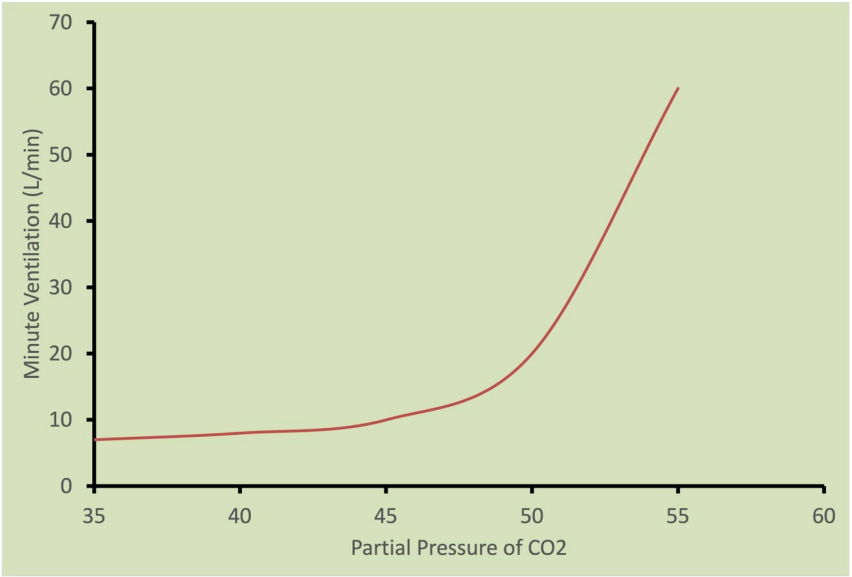


Figure 7-10 Increased Arterial PCO_2 increases Minute Ventilation. When CO_2 is increased in arterial blood, ventilation increases. The increased CO_2 is detected by peripheral chemoreceptors.

Central Chemoreceptors

Central chemoreceptors are located throughout the ventral lateral surface of the medulla. Some important locations identified to contain central chemoreceptors include the rostral ventral surface of the medulla in the vicinity of the retrotrapezoid nucleus, the ventral medullary raphé, the rostral aspect of the ventral respiratory group, the nucleus of the solitary tract, and the locus ceruleus. The central chemoreceptors are sensitive to changes in of the interstitial brain fluid that result with changes in arterial Pco_2. The

ionic composition of cerebral spinal fluid is closely regulated by the blood-brain barrier. However, changes can occur rapidly in the brain because CO_2 is able to quickly cross the blood brain barrier and quickly reacts with H_2O to form carbonic acid. Carbonic acid then dissociates to form bicarbonate and H^+ ions thereby decreasing pH. The ventilatory response to hypercapnia is due to stimulation of both peripheral and central chemoreceptors. Generally, the peripheral chemoreceptors contribute the most to the initial response, as they are fast to respond while the central chemoreceptors contribute more to the steady state response.

Metaboreceptors

are located throughout the ventilatory and locomotor muscle vasculatures. Specifically they are found in the muscle interstitium in close proximity to blood vessels. Metaboreceptors provide feedback to the central controllerthrough type IVafferents regarding the metabolic state of the skeletal muscles. The firing rate of type IV afferents increases with increases in the concentration of hydrogen and potassium ions. This information has a stimulating effect on ventilation.

Mechanoreceptors

Mechanoreceptors provide feedback to the central pattern generating neurons regarding the mechanical state of the lung, airways, and locomotor muscles. Feedback is sent to the central control system through type IIIafferents. In the lung, mechanoreceptors are found in the parenchyma and respond to lung stretch corresponding with increased volume. The firing rate of these afferents increases with increasing lung volume and inhibits ventilation.

Mechanoreceptors are also found in airway skeletal muscle fibres and respond to pressure and airway wall deformation. This information is important for directing activity to pharyngeal and laryngeal musculatures for abducting and stiffening the airway. This is important to protect upper airway patency and prevent airflow limitation.

Efferent Output

Once the central controller has processed sensory information an appropriate response is prepared and sent to the ventilatory muscles. This efferent activity can be described during the three phases of ventilation: Inspiration, post-inspiration, and expiration. Discharge to the diaphragm through the phrenic nerve increases progressively during inspiration. During the post-inspiratory phase, phrenic neural activity dramatically drops and slowly tapers off. Phrenic discharge is silent during expiration. The 10th and 11th thoracic spinal motor nerves innervate the internal intercostal muscles. Excitation of the internal intercostals muscles acts to draw the ribs down and together thereby compressing the thoracic cavity. This increases pleural pressure and assists in expiration. During resting ventilation activity of the internal intercostals would be low as expiration is passive. But during exercise the activity of these muscles becomes very important to assist with expiration. The 5th and 6th thoracic spinal motor nerves innervate the external intercostal muscles. Excitation of the external intercostal muscles acts to lift and expand the rib cage. This has the effect of decreasing pleural pressure and thereby enhances the pressure gradient for air to enter the lungs.

Exercise Hyperpnea

Now that we have a basic understanding of the control of breathing it is possible to consider how breathing is controlled during exercise. How does the central controller know to increase ventilation during exercise? The increase in breathing with exercise is referred to as exercise hyperpnea because arterial Pco_2 is typically maintained. During strenuous exercise, ventilation may increase out of proportion to carbon dioxide production (2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...z#v-%CC%87co2-">$\dot{V}CO_2$) and arterial PCO_2 decreases below resting levels. This is referred to as exercise hyperventilation.

The increase in ventilation with exercise must meet two specific demands. First, increases in $\dot{V}_A$ must be proportional to the increase in metabolic use of O_2 by the working muscles. Such increase in $\dot{V}_A$ must meet the guidelines set by the alveolar gas equation. Second, the work and metabolic cost of increasing ventilation should be minimal such that O_2 delivery and cardiac output are conserved for the locomotor muscles.

Relationship Between Alveolar Gas and Metabolic Requirements

The increase in ventilation with exercise is related to the increase in metabolic demand. The alveolar gas pressures for O_2 and CO_2 (PAO_2 and $PACO_2$ respectively) can be related to $\dot{V}O_2$ and 2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...z#v-%CC%87co2-">$\dot{V}CO_2$ by variants of the alveolar gas equation. The relationship between, $\dot{V}_A$, $\dot{V}O_2$ and $PAco_2$ is:

$PACO_2$ = 2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...z#v-%CC%87co2-">$\dot{V}CO_2 \cdot \dot{V}_A^{-1} \cdot K$

where $PAco_2$ is the alveolar partial pressure for carbon dioxide (in mmHg), $\dot{V}CO_2$ is carbon dioxide production (in $ml \cdot min^{-1}$), $\dot{V}_A$ is alveolar ventilation (in $L \cdot min^{-1}$) and K is a constant (equal to 0.863).

The relationship between $\dot{V}_A$, $\dot{V}O_2$and Pao_2 is:

$PAO_2 = PIO_2 - \dot{V}O_2 \cdot \dot{V}_A^{-1} \cdot K$

where Pao_2 is the alveolar partial pressure for oxygen (in mmHg), Pio_2 is the inspired partial pressure for oxygen (in mmHg, 150 mmHg at sea level), $\dot{V}O_2$ is oxygen consumed (in $ml \cdot min^{-1}$), $\dot{V}_A$ is alveolar ventilation (in $L \cdot min^{-1}$) and K is a constant (equal to 0.863).

Example: An athlete has a resting oxygen consumption of 300 $ml \cdot min^{-1}$ and a resting carbon dioxide production of 240 $ml \cdot min^{-1}$. At sea level the athlete has normal alveolar gas pressures of 40 mmHg for CO_2 and 100 mmHg for O_2. During exercise, the athlete increases their metabolic rate six times and alveolar gas pressure for oxygen increases to about 110 mmHg. What is the alveolar ventilation at rest and during exercise? What is the $Paco_2$ during this exercise?

Based on the above data you should be able to determine that the alveolar ventilation at rest is 5 $L \cdot min^{-1}$ and during exercise is 39 $L \cdot min^{-1}$. If alveolar ventilation during exercise is 39 $L \cdot min^{-1}$ and the carbon dioxide production is 1440 $ml \cdot min^{-1}$ then the alveolar partial pressure for CO_2 during exercise is 32 mmHg.

The matching of metabolic demand and alveolar ventilation is essential. This is the first line of defense in the oxygen transport system. Alveolar ventilation is capable of increasing rapidly and precisely to meet the body's oxygen demand. Alternatively, alveolar ventilation must control arterial carbon dioxide within a narrow range so as to maintain arterial blood acid base homeostasis

Exercise Hyperpnea Control Hypotheses

What drives ventilation during exercise? The mechanisms involved in controlling the ventilatory response to dynamic exercise have been studied for over a century and there remains controversy over what causes the onset of increased ventilation and what controls its level afterwards. In this section, three hypotheses will be briefly described and include:

- the central locomotor command hypothesis,
- the *CO_2flow hypothesis*
- the *locomotor musclemechanoreceptor/metaboreceptorhypothesis*.

It is likely that all three hypotheses are simultaneously involved during exercise. The contribution of each hypothesis to the ventilatory phases of submaximal exercise will also be described.

Central Locomotor Command Hypothesis

Unlike the CO_2 flow and muscleafferents hypotheses, the central command hypothesis is a *feed-forward* pathway rather than a *feed-back* pathway. With this hypothesis ventilation is stimulated directly by supramedullary locomotor centre neurons. These

neurons are found in regions of the hypothalamus, the diencephalons of the midbrain, and in the premotor cortex. Excitation of exercise and respiratory circuits is parallel and simultaneous and ventilation would therefore increase concurrently with the beginning of locomotion (Eldridge et al. 1985). This hypothesis likely contributes extensively to the phase 1 ventilatory response to exercise.

CO2 Flow Hypothesis

The CO_2 flow hypothesis states that exercise ventilation is influenced byafferents sensing CO_2 flow in the lung or in the right side of the pulmonary circulation. This hypothesis is represented by the equation:

$$CO_2Flow = \dot{Q} \cdot CvCO_2$$

where $\dot{Q}$ is pulmonary blood flow in $L \cdot min^{-1}$ and $CvCO_2$ is the CO_2 content of mixed venous blood in mL CO_2 per 100mL of blood. A close relationship exists between increases in alveolar ventilation to CO_2 production with steady-state exercise (Phillipson et al. 1981). Also, for this reason, this hypothesis is thought to contribute the most to the control of ventilation during the third phase of sub maximal exercise. This hypothesis is attractive because typically during exercise there is no change in arterial Pco_2 and increases by only a small amount. Therefore, it is otherwise unlikely that the peripheral chemoreceptors could be involved in exercise ventilation. However, CO_2 flow to the lung is not the sole contributor to exercise ventilation. Contribution from locomotor receptors and central command is also important.

Locomotor Muscle Mechanoreceptor/Metaboreceptor Hypothesis

Feedback from working locomotor muscles is another hypothesis thought to contribute to the control of exercise hyperpnea. With this hypothesis, mechanical stimuli such as stretch, pressure, and tension of skeletal muscle and tendons is sensed by type III nerveafferents and metabolic stimuli such as and bradykinin is sensed by type IV afferents (Kaufman and Forster 2011). This information is sent to the central controller and influences ventilation. Information from type III and IV afferents plays an important role in stimulating the initial phase 1 ventilatory response to exercise and also is involved in the slower increase in ventilation toward steady state or the phase 2 response.

Regulation of Ventilation During High-Intensity Exercise

The regulation of ventilation during high-intensity exercise remains a topic of debate. During submaximal exercise blood is near-normal but with heavier exercise there is significant lactacidosis and increases in other blood substances (e.g., potassium, catecholamines). Exercise-induced changes in these substances within arterial blood are known to excite the carotid chemoreceptors suggesting that they contribute to the hyperpnea of heavy exercise. Indeed many experimental approaches have yielded impressive correlative data linking a given humoral stimuli and exercise ventilation. On the other hand, when the carotid body is removed in experimental animals the ventilator response to exercise remains intact (Pan et al. 1986). The general consensus is that the carotid bodies are not the primary transducer of the hyperventilatory response. Rather, they may serve to ‘fine tune’ the regulation of ventilation during heavy exercise.

Key Points

Our understanding of the mechanisms that control ventilation during exercise remains incomplete. It is difficult, if not impossible, to identify a given mechanism as the ‘primary driver’ of exercise hyperpnea. It is likely that in the intact state (i.e., whole organism) the integrated ventilator response incorporates both feed-forward and feed-back mechanisms and that there is considerable redundancy in control mechanisms.

Pulmonary Gas Exchange

Demands of Exercise

As mentioned in the introduction to this chapter, exercise places unique demands on the body that must be accommodated by the ventilatory system. During exercise, the metabolic rate can increase 10-20 fold over resting values. As such, both oxygen delivery and carbon dioxide elimination must increase to meet these demands. It is the job of the ventilatory system (in conjunction with

the cardiovascular system) to ensure adequate oxygen delivery and removal of waste CO_2 at all intensities of exercise. In the healthy exercising human, even at maximal exercise, CO_2 levels in the blood do not rise and in the majority of people O_2 levels remain constant, demonstrating the effectiveness of the ventilatory system in meeting these demands.

When we talk about the amount of physiological work done by the exercising human we talk about metabolic rate. Metabolic rate is typically expressed as a measure of oxygen consumption. Physiologists usually express oxygen consumption in $L \cdot min^{-1}$ or $mL \cdot kg^{-1} \cdot min^{-1}$. The former unit is used for absolute oxygen consumption, whereas the latter is used for relative oxygen consumption, taking body mass into account. It is appropriate to use absolute when the energy cost of the exercise is independent of body mass (like swimming or cycling on an ergometer) and relative when the exercise is dependent on body mass (like running and walking). In contrast clinicians use a different unit (called the MET) to measure metabolic rate. One MET approximates resting metabolic rate and is equivalent to 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$. During exercise if an individual is exercising at 10 METs, then their oxygen consumption is equivalent to 10 times their resting metabolic rate. Very fit athletes will be able to perform up to 20 METs of work at maximal exercise (the intensity that elicits maximal oxygen uptake).

To interpret gas exchange during exercise, we not only assess oxygen consumption, ($\dot{V}O_2$), but also carbon dioxide production (2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...-%CC%87o2-peak">$\dot{V}CO_2$). The ratio of carbon dioxide production to oxygen consumption depends on the fuels being utilized. Each of the primary fuels for exercise (carbohydrate, protein and fat) produce slightly different amounts of carbon dioxide for a given amount of oxygen consumed. This ratio of carbon dioxide production to oxygen consumption ($\dot{V}CO_2/\dot{V}O_2$) is called the respiratory quotient (RQ) when it represents the true metabolic gas exchange. For example in the metabolism of glucose we see the following reaction:

$C_6H_{12}O_6 + 6\ O_2\ 6\ CO_2 + 6\ H_2O$

Six molecules of O_2 are consumed, and 6 molecules of CO_2 are produced, giving a of 6/6 or 1.0. Conversely, when palmitic acid (a fatty acid) is metabolized we get the following equation:

$C_{16}H_{32}O_2 + 23\ O_2\ 16\ CO_2 + 16\ H_2O$

Twenty-three molecules of O_2 are consumed and only 16 molecules of CO_2 are produced, giving us a of 0.7. By comparison, the RQ of protein metabolism is typically in the range of 0.8-0.9. When we calculate the RQ, we are using it to reflect the specific gas exchange that is occurring at the tissue level. In exercising humans, we cannot easily measure these tissue values, so instead we look at the ratio of whole body 2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...z#v-%CC%87co2-">$\dot{V}CO_2$ and $\dot{V}O_2$ measured across the pulmonary system. This whole body ratio is called the respiratory exchange ratio (RER), and represents the ratio of whole body $\dot{V}Co_2/\dot{V}o_2$. During rest and low and moderate intensity exercise we can use the RER to estimate the relative contributions of and carbohydrate to oxygen consumption. For example, we notice at lower intensities, that individuals typically have values below 0.85, reflecting a relative preference for lipid metabolism. As exercise intensity increases, RER gets closer to 1.0, indicating a transition to carbohydrates as the predominant fuel source.

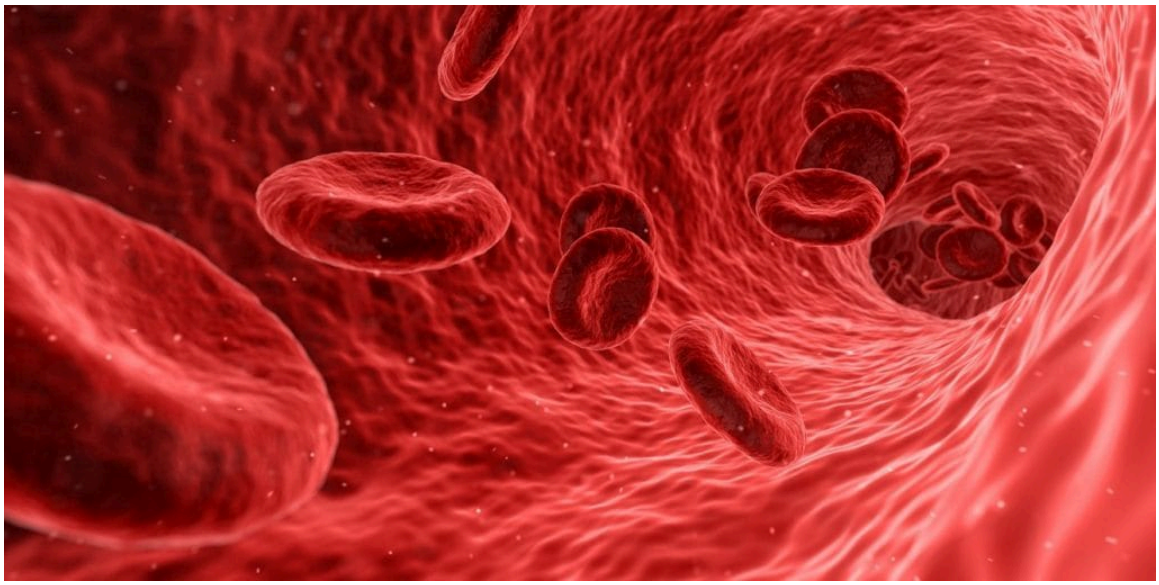


Photo 7-4 – Red blood cells, contain haemoglobin, which is utilized to maximize oxygen transport. Image by qimono under a Pixabay License.

Oxygen Transport

Oxygen is relatively insoluble in bodily fluids. For example for a partial pressure of oxygen in the alveolus (Po_2) of 100 mmHg, only 3 mL of oxygen dissolves in the blood for each litre of blood. With this oxygen carrying capacity, the cardiac output would have to be (3.5 $ml \cdot min^{-1}$* 60 $kg \cdot (3ml \cdot litre^{-1})^{-1}$ =70 $litres \cdot min^{-1}$ for a 60 kg person (assuming total extraction). The capacity of dissolved oxygen in fluids is clearly inadequate. Instead, humans use haemoglobin(Hb) to boost the oxygen carrying capacity of the blood. Haemoglobin is an iron-containing metalloprotein pigment in the erythrocytes (red blood cells) that enhances oxygen carrying capacity of the blood by approximately 70-fold. At rest, the 60 kg individual mentioned above would have a cardiac output of about 4 $litres \cdot min^{-1}$ with extraction of only 25% of the available O_2. Each haemoglobin molecule can bind up to 4 oxygen molecules and the binding of Hb to O_2 is directly related to PO_2. At a high arterial PO_2 (100 mmHg for example) the saturation of Hb is nearly 100%. As PO_2 drops, then the number of O_2 binding sites that are occupied by O_2 decreases. Typically Hb is 50% saturated with O_2 at a PO_2 of 60 mmHg. When haemoglobin is saturated with oxygen molecules, it is called oxyhaemoglobin, conversely, desaturated Hb is referred to as deoxyhaemoglobin. The binding of oxygen to haemoglobin demonstrates cooperative binding. This means that each oxygen molecule that binds to one of the four sites on the haemoglobin increases the affinity for binding of subsequent oxygen molecules. This behaviour explains the sigmoidal shape of the haemoglobin oxygen dissociation curve (Figure 7-11).

The affinity of Hb for O_2 also varies based on tissue conditions. Circumstances influence binding of O_2 to Hb; 2,3 diphosphoglycerate (2,3 DPG), CO_2, and temperature affect binding. These circumstances allow a higher Hb-O_2 affinity at the lung where is preferred, and enhanced dissociation at the level of exercising tissue where the O_2 unloading is preferred. The factors that favour enhanced dissociation are all present in exercising muscle. These are a low pH, a high PCO_2, high temperature, and an increase in the concentration of 2,3 DPG. 2,3 DPG is a 3-carbon molecule that is present within the erythrocytes due to glycolysis. It acts by binding to deoxyhaemoglobin and stabilizing it in its deoxygenated state, thus promoting oxygen dissociation. Conversely when the haemoglobin returns to the lung, these conditions are reversed, favouring enhanced binding of O_2 to Hb. This shifting of the Hb-O_2 dissociation curve is termed the Bohr effect (Figure 7-11).

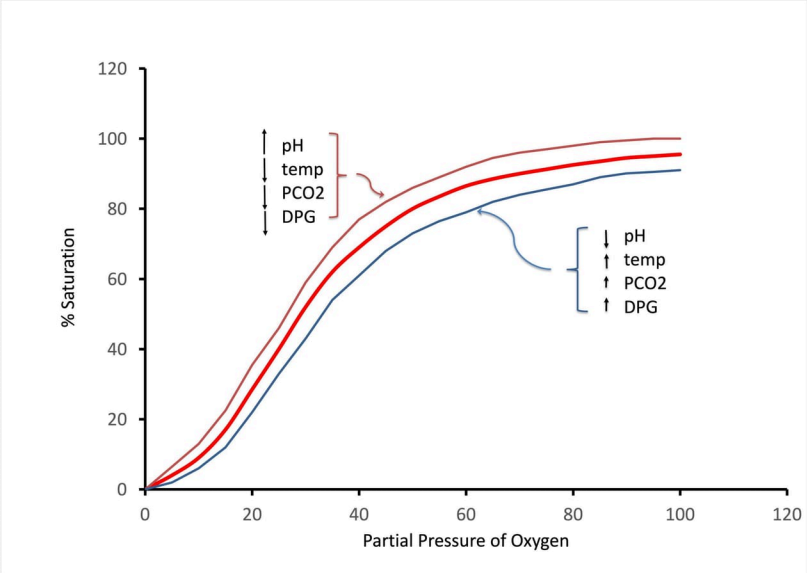


Figure 7-11. Oxygen Dissociation Curve. This graph shows the relationship between Haemoglobin saturation and partial pressure of O2. The middle (red) line represents the control situation (temperature 37 degrees, pH 7.4, PCO2 40 mm Hg.

Within the muscle cells, oxygen transport is facilitated by myoglobin, another iron-containing globular protein, with a similar function to haemoglobin. In contrast, each molecule of myoglobin can only bind one molecule of oxygen instead of four. Since each myoglobin only binds to a single oxygen molecule it does not exhibit cooperative binding, and therefore it has neither a sigmoid dissociation curve like haemoglobin, nor does it exhibit the Bohr effect.

Ventilation-Perfusion

Gas transport relies on adequate lung ventilation to bring new oxygen to the alveoli and to remove CO_2. Likewise, blood has to be pumped to these same alveoli in order to take up the oxygen and transfer the CO_2 to the alveoli. Matching of these two processes (ventilation and perfusion) is key to effective gas exchange. When ventilation and perfusion are not adequately matched the phenomena of *shunt* and *dead space* occur. *Shunting* refers to blood that travels from the right side of the heart to the left side of the heart without exposure to ventilated alveoli, whereas dead space refers to inspired air that is exhaled without exposure to perfused alveoli. Shunt and dead space will now be described in detail.

Shunt

Shunt can occur within the pulmonary system or the heart. Intracardiac shunting occurs when blood travels directly from the right side of the heart to the left side of the heart through a direct communication such as a patent foramen ovale, or a ventricular septal defect. The foramen ovale is a portal between the right and left atria which is open during embryonic development, but which is meant to close soon after birth. However, in 25% of the population the foramen ovale fails to close completely, allowing some shunting from the right atrium to the left atrium. A ventricular septal defect is a direct communication between the ventricles that remains open due to an abnormality during development. Ventricular septal defects occur much less frequently than patent foramina ovale and cause more substantial shunts.

Shunt can also occur in the pulmonary circulation. Certain individuals with a condition called hereditary haemorrhagic telangiectasia (also called Osler-Weber-Rendu Syndrome) have direct interfaces between the arterial and venous circulations within the lung. These connections are called arteriovenous malformations. One of the clinical findings in people with pulmonary arteriovenous malformations (AVMs) is that they demonstrate platypnea, which means that when they sit up they become more short of breath. This platypnea occurs because as they sit up, a greater proportion of their cardiac output is shunted through the lower regions of the lung where the AVMs occur, leading to low levels of arterial oxygen (hypoxaemia) and increased levels of arterial carbon dioxide (hypercarbia). The hypoxaemia and the hypercarbia cause the sensation of shortness of breath (dyspnea).

A potential intrapulmonary *shunt* has also been demonstrated in athletic individuals without any medical condition. Termed exercise-induced intrapulmonary shunt, researchers have shown that an intrapulmonary shunt seems to occur in the majority of athletic individuals during exercise. Using a technique called contrast echocardiography, researchers inject agitated saline that

contains small bubbles (called microbubbles) that are easily visualised with a cardiac ultrasound (echocardiogram). To look for shunt, these microbubbles are injected on the venous side of the vascular system and visualised as they travel through the right side of the heart. If the microbubbles are immediately visible on the left side at the same time or soon after they appear on the right side of the heart, an intracardiac shunt is suspected. If instead, the bubbles appear on the left side after a delay, then it is suggested that the shunting occurred outside the heart but somewhere in the pulmonary vascular system (an intrapulmonary shunt). This intrapulmonary shunt has been shown to be more common during exercise in hypoxic conditions, and seems to be preventable with hyperoxia.

Dead Space

Anatomic *dead space* has already been discussed previously in the chapter and is different from physiologic dead space. Instead of referring to an anatomic subsection of the lung in which no gas exchange takes place, physiologic dead space is a functional definition. It includes parts of the lung that are not perfused at all, but will also comprise areas that are poorly perfused, providing an assessment of the gas exchange capacity of the lung. In healthy individuals, anatomic and physiologic dead space are very close in value, whereas individuals with lung disease can have a much larger physiologic than dead space.

Physiologic *dead space* is calculated using Bohr's method:

$$V_D \cdot V_T^{-1} = (Paco_2 - Peco_2) \cdot Paco_2^{-1}$$

Where V_D and V_T represent *dead space* and tidal volume, respectively. $PAco_2$ and $PEco_2$ represent alveolar and mixed expired partial pressures of CO_2, respectively. Often arterial Pco_2 is substituted for alveolar Pco_2 in this equation, because they are nearly equivalent in healthy individuals. The partial pressure of end-tidal CO_2 ($PETCO_2$) can be used as a measure of $PAco_2$ and eliminate the need for arterial puncture or catheterization.

Distribution of Ventilation

Ventilation is not homogenous across the lung. There are regional differences in ventilation of the lung, mostly due to the effects of gravity. Because of the weight of the lung, the intrapleural pressures are more negative in the upper parts of the lung than in the lower parts of the lung. This difference causes the alveoli in the lower parts of the lung to have a smaller resting volume than the upper parts of the lung. Said differently, this means that the base of the lung is relatively compressed in the resting state but expands more on inspiration than the apex. During inspiration, the lower parts of the lung take up a greater proportion of the inspired air than the upper areas. This relationship varies depending on the degree of lung inflation. In fact, at very low lung volumes, the upper regions of the lung are better ventilated than the lower regions.

At the end of expiration when the volume in the lung is low, not all of the air is allowed to leave the alveoli. Respiratory bronchioles can close before the alveoli are empty, leading to gas trapping or airway closure. This occurs at only very low lung volumes (not normally found during exercise) in healthy young people. With age, healthy people slowly lose the elastic recoil in their lungs. This loss of elasticity causes intrapleural pressures to be less negative, and lead to airway closure at higher lung volumes. As the loss of elastic recoil becomes more apparent, airway closure can occur above functional residual capacity, leading to impairment in gas exchange.

Distribution of Perfusion

As with ventilation, perfusion is also not uniformly distributed. The pressures exerted on the arterial and venous components of the pulmonary vasculature vary in different regions of the lung. Gravity affects the perfusion pressure of the lung such that perfusion pressures are higher in the dependent (lower) regions of the lung, and lower in the upper regions of the lung. These pressure differentials are affected by posture and body position during exercise. For example, during supine exercise such as recumbent cycling the posterior parts of the lung would be dependent and demonstrate higher perfusion pressures whereas during road cycling (leaning forward) these same areas would show a relative decrease in perfusion pressure. In certain situations there may be a region in the lung where arterial pressure is lower than alveolar pressure. In this situation, the alveolar pressure occludes the pulmonary capillary and there is no perfusion at that alveolus. This particular phenomenon leads to dead space. Figure 7-11 displays the regional differences in lung perfusion.

Ventilation-Perfusion Matching

To strive for optimal gas exchange, the body attempts to match ventilation-perfusion ratio to perfusion. The relationship between ventilation and perfusion on a whole body level is described by the ventilation-perfusion ratio. For example, at rest, average ventilation would be 4.2 $L \cdot min^{-1}$, while perfusion (cardiac output from the right ventricle) would be 5 $L \cdot min^{-1}$. This situation gives us a ventilation-perfusion ratio of 0.84. This ratio remains essentially unchanged during light exercise, but during heavy exercise, as ventilation increases disproportionately to oxygen consumption, the ventilation-perfusion ratio can increase substantially. It is not uncommon for ventilation during heavy exercise to be in the range of 150 $L \cdot min^{-1}$ for a corresponding perfusion of about 30 $L \cdot min^{-1}$, giving a ventilation-perfusion ratio of 5.

We have already covered the regional differences in both ventilation-perfusion ratio and perfusion as a result of the effects of gravity and lung mechanics on various areas of the lung. Typically, ventilation increases as you move from the top of the lung to the bottom of the lung. Similarly, perfusion also increases but in a much greater magnitude of change. This situation can lead to significant variation in ventilation-perfusion ratio in different regions of the lung. One strategy used to somewhat mitigate this potential for variation is hypoxic pulmonary vasoconstriction (HPV). The smooth muscle in the walls of the small pulmonary arterioles can constrict in response to hypoxic conditions, increasing pulmonary vascular resistance by up to 300%. Interestingly, this phenomenon occurs primarily in response to alveolar and not arterial hypoxia. Alveolar hypoxia presumably causes vessel wall hypoxia, which is sensed in the vessel smooth muscle wall, causing contraction and vasoconstriction. The effect of this response is to decrease blood flow to poorly ventilated areas of the lung, diverting it to the better-perfused areas. In contrast, at high altitude the entire lung becomes hypoxic, leading to a global hypoxic pulmonary vasoconstriction and resultant rise in pulmonary artery pressure. High altitude pulmonary oedema (HAPE) is a potentially lethal condition that can develop in highly sensitive visitors to high altitude (approximately 2500 meters above sea level or higher). These susceptible individuals develop a form of exaggerated hypoxic pulmonary vasoconstriction, which is presumed to cause leakage of fluid from the pulmonary capillaries into the alveoli. This build-up of fluid in the alveoli leads to impairment in gas exchange, causing significant hypoxaemia, illness, and often death. HAPE is exacerbated by exercise, presumably as it increases cardiac output, and therefore pulmonary artery pressure, which would increase the potential for leakage of fluid into the lung. The ultimate treatment for HAPE is descent back to a lower altitude that has higher partial pressure for O_2, where the condition resolves spontaneously within a couple of days.

Diffusion

Diffusion of a gas through a tissue is governed by Fick's law (see below). Diffusion is the process where a substance goes from an area of higher concentration to an area of lower concentration. It is a passive process that that does not require energy. In respiratory physiology, diffusion refers to the movement of gas across the distance and barriers between the alveoli and the blood. The rate of diffusion is proportionate to the area of the membrane, and the difference in partial pressure of the gas across the membrane. Diffusion is inversely proportional to the thickness of the membrane. The area of the blood gas interface in the lung is approximately 70 square metres, and it is as thin as 0.3 m. Solubility of each particular gas is also important. For example CO_2 diffuses about 20 times more rapidly than O_2 across the blood alveolar interface due to its much higher solubility in body fluids.

The rate of transfer of gas across the barrier between the alveolus and the capillary is not only modulated by the direct tissue barrier. Resistance to diffusion also comes from the path that the gas molecule (such as O_2 or CO_2) takes through the capillary plasma and erythrocyte cytoplasm to ultimately bind with the haemoglobin molecule. Resistance comes from both the distance of diffusion through the blood as well as the rate of reaction between the CO_2 and O_2 molecules with the haemoglobin molecule. Typically the process of diffusion is regarded as a two-component process, with the two components being the membrane component and the blood component. The membrane component comprises the process of diffusion from the alveolus, across the respiratory membrane (including the diffusion through the plasma and the erythrocyte cytoplasm). The blood component comprises the reaction between the gas molecules and the Hb molecule.

The diffusing capacity of the lung is described by the equation:

$$D_L = \dot{V}gas \cdot (P_1\text{-}P_2)^{-1}$$

Where D_L represents the diffusing capacity of both lungs, $\dot{V}_{GAS}$ represents the flow of the gas, and P_1-P_2 represents the difference in partial pressure from one side of the tissue to the other (i.e., alveoli-to-blood).

The diffusing capacity can be subdivided into it's constituent components as:

$1{\cdot}DL^{-1} = 1 \cdot DM^{-1} + 1 \cdot \Theta^{-1} \cdot V_C$

Where D_L represents the diffusing capacity of both lungs, D_M represents the membrane component, and represents the blood component with V_C as the capillary blood flow, and as the rate of reaction of O_2 with Hb. We can therefore see that diffusing capacity can be affected by changes in the membrane or in the blood component. Examples of membrane changes would be pulmonary fibrosis (where scarring increases the resistance to diffusion across the membrane) or pulmonary oedema (where water impairs the transmission by increasing the distance). Examples of blood component changes that affect diffusing capacity would include anaemia. Anaemia is a term describing a number of conditions that cause a decrease in the red cell content of blood. Anaemia is one potential medical cause of poor performance in the athlete, and it is one of the first conditions to be screened for in the athlete presenting to medical care for unexplained poor performance or fatigue. Conversely, some people can develop a rare condition called polycythaemia, which causes an increase in the number of red blood cells, and thus Hb in the pulmonary vasculature, leading to an increase in diffusing capacity. Athletes can also cause spurious polycythaemia by blood doping or taking erythropoietin (EPO). In blood doping, an athlete increases their red cell mass by adding extra blood to their vascular system, either their own blood that has been previously removed and stored, or blood from a compatible donor. Erythropoietin is a hormone that signals the body to make more red blood cells.

During exercise, pulmonary blood flow increases dramatically, causing diffusing capacity to rise proportionately. Following intense exercise, this elevated diffusing capacity may take some time to return to baseline levels, due to an increase in post-exercise cardiac output.

Cardio-Pulmonary Interactions

The respiratory and cardiovascular systems interact extensively with each other. Not only do they share close quarters within the thoracic cavity, but also, they must work together to support oxygen delivery and carbon dioxide transport. There are two types of interactions that occur between the cardiovascular and respiratory systems. The first is mechanical interactions. Mechanical interactions occur due to the pressure changes that occur within the thoracic cavity due to breathing. Mechanical interactions can affect cardiac preload,afterload, and venous return. The second type of interaction is reflexive in nature and results from an integration of the cardiovascular and ventilatory control systems in the medulla. Such reflexes affect heart rate (ventilatory sinus arrhythmia), muscle sympathetic nerve outflow, and blood flow to the ventilatory muscles and limb muscles (metaboreflex). These mechanical and reflexive interactions will be described in the following section.

Mechanical Interactions between the Cardiovascular and Pulmonary Systems

Inspiration generates substantial negative pressures (with respect to pressure measured outside the body) within the thoracic space. This increases the transmural pressure gradient across the walls of the ventricles, increases cardiac preload, and improves ventricular filling. During inspiration, right atrial pressure is reduced and the pressure gradient for returning venous blood to the heart is increased. With expiration, the opposite effects impede ventricular filling. During expiration the pressures within the thoracic space are increased and the pressure gradient responsible for ventricular filling. is reduced. Similarly, the return of venous blood is reduced because its pressure gradient is also reduced. There is an effect of lung surface pressure upon the heart that can limit the facilitating effects of inspiration on ventricular filling. This occurs during exercise when larger lung volumes result and the cardiac fossa becomes less compliant.

Increases in venous return during inspiration and reductions in intrathoracic pressure can also be countered by an increase in abdominal cavity pressure caused by the descent of the diaphragm. Diaphragm descent can compress the abdominal inferior vena cava and hinder venous return from the lower extremities (Miller et al. 2005a, 2005b).

Although, negative thoracic pressure during inspiration increases venous return to the right heart, it does not necessarily lead to increased stroke volume from the left ventricle. There are two forces opposing left ventricular output during inspiration. The first is a reduction of left ventricular volume due to ventricular interdependence. The increased volume of the right ventricle shifts the interventricular septum and encroaches upon the left ventricle thereby reducing its compliance and its volume. Left heart output is also reduced during inspiration because of an increase inafterload. Afterload is increased because the pressure gradient that the left ventricle must overcome to eject blood is much greater during inspiration.

Reflexive Interactions between the Cardiovascular and Pulmonary Systems

Breathing has significant influences on sympathetic vasoconstrictor outflow. Sympathetic nervous system activity in a resting

muscle vascular bed is reduced during the late inspiration and early expiration. It rises and peaks during mid expiration. This reflex is controlled by a neural pathway that senses stretch of the lung parenchyma providing feedback to the nucleus of the solitary tract, where input is integrated by a group of cardiopulmonary interneurons and efferent sympathetic nerves. The lung stretch is sensed by pulmonary stretch receptors found in the lung parenchyma.

Another reflex pathway dependent upon ventilation is the within-breath variation in heart rate. This is commonly referred to as ventilatory-sinus arrhythmia. This pathway is vagally mediated and is dependent upon tidal volume. Pulmonary stretch receptors sense the stretch of the lung and during inspiration as lung stretch increases there is an increase in heart rate. Alternatively, during expiration as lung stretch decreases the heart rate also decreases. Ventilatory sinus arrhythmia may improve ventilation-perfusion matching and/or minimize cardiac work (Ben-Tal et al. 2012). During inspiration when good air is entering the lungs the heart rate increases to increase perfusion of the lung. During expiration there is a lack of useful ventilation, heart rate decreases, and lung perfusion decreases.

The ventilatory muscle metaboreflex is important because it causes blood to preferentially perfuse the ventilatory muscles over exercising muscles as the ventilatory muscles become fatigued (Dempsey et al. 2003). Metaboreceptors within the ventilatory muscles sense the accumulation of metabolic byproducts and this reflexively increases sympathetic nervous system output to muscle vascular beds. The ensuing vasoconstriction diverts blood away from the exercising muscles to the fatiguing ventilatory muscles. In terms of exercise performance this limits the delivery of oxygen to the working peripheral muscles and limits overall performance.

Key Points

During exercise there are important cardiorespiratory interactions whereby the act of breathing can influence venous return, cardiac output and blood flow distribution.

Lessons from Elite Athletes

To this point we have presented the pulmonary system as a complex system but one that is capable of meeting the ‘challenges’ of exercise. The maintenance of homeostasis of oxygen in arterial blood is generally not a problem because of a lung and chest wall that are generally “overbuilt” with respect to maximum metabolic demands for gas transport. On the other hand, evidence is accumulating that the healthy pulmonary system in some humans may not be so “overbuilt” as fitness level increases, because the lung diffusion surface and airways, and perhaps even ventilatory muscles, do not adapt to the “training stimulus” anywhere near to the same extent as do other links in the oxygen transport scheme. The result is that the now relatively “underbuilt” pulmonary system in the fit subject contributes significantly to the limitations of exercise performance for two specific reasons: (i) diaphragm and (ii) exercise-induced arterial hypoxaemia (EIAH).



Photo 7-5 – Cyclists such as Chris, will experience diaphragm fatigue and exercise-induced arterial hypoxaemia. Photo by T B from Pexels

Diaphragm Fatigue

The human diaphragm is a large dome-shaped muscle that separates the abdominal and thoracic cavities and is the primary muscle driving active inspiration. Other muscles of inspiration include the external intercostals and accessory muscles (i.e., scalenes and sternocleidomastoid), which become recruited to a greater degree as ventilation increases. The diaphragm must sustain extremely high levels of force output and requires a high proportion of cardiac output during intense exercise. Given the significant demand for O_2 and the high work of breathing that occurs during maximal exercise, it seems possible that the diaphragm, like other skeletal muscle, can be susceptible to (Johnson et al. 1993).

Fatigue has been defined as any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained. However, due to the potential clinical significance of ventilatory muscle fatigue, a more appropriate definition is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and which is reversible by rest. Although the techniques used in the assessment of diaphragm fatigue are indirect, there is sufficient evidence to suggest that the muscles of inspiration (primarily diaphragm) can be fatigued with high levels of ventilatory muscle work. For fatigue to occur, the diaphragm must sustain extremely high levels of force output and during heavy endurance exercise, the magnitude of fatigue and the likelihood of its occurrence increases as the relative intensity exceeds 85% of $\dot{V}O_2$max. Measurement of diaphragm fatigue is done by stimulating the phrenic nerves via electrical or magnetic stimulation while measuring the pressure difference between gastric and esophageal pressure (i.e., transdiaphragmatic pressure) before and after exercise. Several studies utilizing this technique in healthy individuals have shown that the diaphragm fatigues during heavy endurance-type exercise.

Does diaphragm fatigue influence $\dot{V}O_2$max and exercise performance? To test this hypothesis, cyclists performed time to exhaustion cycle exercise at 90% of $\dot{V}O_2$max work of breathing was increased or decreased by ventilatory muscle loading and unloading respectively. The increased work of breathing by ventilatory muscle loading caused a 15% reduction in time to exhaustion performance compared to controls. This detrimental effect on exercise performance was attributed to the associated reduction in leg blood flow, which enhances the onset of leg and also the intensity of leg and ventilatory muscle effort perceptions. When the ventilatory muscles were unloaded, there was a reduction in $\dot{V}O_2$ a reduced rate of change in dyspneic and limb discomfort sensations, and improvements in time to exhaustion performance by 14%. Exercise-induced diaphragmatic has important relevance to the athlete and causative mechanisms relate to interactions among the ventilatory muscles, the autonomic nervous system and the cardiovascular system.

Case Presentation Continued and Focus on Exercise Physiology Research

Question: why do you think that performance can be improved by removing diaphragm fatigue? What are the physiological mechanisms?

Chris's coach is seeking a practical way to prevent or reduce diaphragm fatigue. There are commercially available devices which can be used to train the muscle of breathing. These so-called ventilatory muscle training devices have gained popularity and many athletes incorporate their use into their training regime. If we assume that the muscles of breathing can respond to a training stimulus like any other muscle (i.e., increased fibre size, capillarity, mitochondrial density etc.) it is possible that these changes could potentially reduce diaphragm and positively influence exercise performance. However, there remains controversy and debate within the scientific literature as to whether or not training the muscles of breathing can indeed improve performance. For an in depth perspective on this topic see Cross-Talk Debate (Ta and Mcconnell 2012; Patel et al. 2012).

Exercise-Induced Arterial Hypoxaemia (EIAH)

The level of oxygenation in arterial blood during exercise is defined by measures of PaO_2, SaO_2, and CaO_2. Traditionally, all three measurements were thought to be maintained at all levels of exercise. However, an SaO_2 of 3-15% below resting levels have been observed to occur at or near maximum exercise intensities. EIAH has been reported most frequently in fit young males, as sedentary males do not experience EIAH. It has been estimated that approximately 50% of very fit endurance athletes develop EIAH when exercising at sea level whereas untrained individuals do not. Studies of smaller numbers of fit females claim higher prevalence of EIAH and that it occurs at lower levels of $\dot{V}O_2$max than in young adult males. In our view, there is insufficient data to know the true prevalence of EIAH and the effects of fitness level or gender. Larger studies with direct blood gas measurements

are required. Furthermore, it is not known if the mechanisms mediating EIAH are the same between men and women; nor is it known why some untrained (but healthy) women develop EIAH while their male counterparts do not.

What causes EIAH? Mechanisms to explain EIAH remain controversial. Pao_2 is reduced below resting levels due to a widened alveolar-arterial O_2 difference ($AaDO_2$) and/or an insufficient increase in PAO_2. Decreases in SaO_2 are further exaggerated by a rightward shift of the HbO_2 dissociation curve due to metabolic acidosis and increased temperature. An excessively widened $AaDO_2$ during exercise is the most consistent contributor to EIAH. Hyperventilation in heavy exercise is a major compensatory mechanism—not only to minimize the degree of metabolic acidosis but also to prevent arterial hypoxemia. Thus this compensatory ventilatory response is often insufficient in the face of a widened $AaDO_2$ and therefore contributes to EIAH. The precise causes of either of these deficiencies are not known but some promising mechanisms are currently under study. For example, exercise-induced ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality most likely contributes to a widened $AaDO_2$; especially in view of the onset of EIAH during sub maximal exercise in some subjects. At least some of this proposed $\dot{V}_A/\dot{Q}$ inequality may be due to the release of inflammatory mediators in the lung and their effects on the small airways and/or arterioles in the lung periphery. At maximum exercise, a diffusion limitation and perhaps even “stress-failure” of the alveolar-capillary interface remain plausible, but evidence for their existence is indirect in exercising humans. Recent studies imply that exercise-induced intrapulmonary arteriovenous shunting may play a role in EIAH but this has not yet been directly tested. This could simply be due to the fast transit time of the blood. The time needed for equilibration between alveolar and capillary blood PO_2 is greater than the time that a drop of blood is in the capillary.

Does EIAH affect $\dot{V}O_2$max and exercise performance? Preventing O_2 desaturation by having athletes breathe a mildly hyperoxic gas (F_IO_2: 26%) shows that there is a 1% drop in $\dot{V}$ $o_2$max for every 1% drop in SaO_2 at any SaO_2 beyond 92-93%. Although EIAH affects $\dot{V}O_2$max, it is important to recognize that an individual’s maximalaerobic capacity is simply one of many factors that influences endurance performance. Recent work in male subjects has shown that peripheral muscle during strenuous exercise is greater when arterial O_2 content is reduced by breathing hypoxic gas versus normoxic and hyperoxic gases, lending support to the idea that gas exchange impairment may adversely influence exercise performance.

Summary

The primary purpose of the pulmonary system is to provide the body with oxygen and dispose of CO_2. The oxygen cascade illustrates the pathway for oxygen delivery to the muscles. Partial pressure of O_2 decreases as you move from ambient air (PO_2=159 mm Hg) to alveolae (PO_2 = 105 mm Hg), to arterial blood (PO_2=98 mmHg to tissue (PO_2 =2-40 mm Hg and venous blood (PO_2=20-40 mmHg. Our ventilation responds during exercise by increasing quickly at the onset of exercise, and levelling off at a rate that is proportional to the exercise demand for O_2. As exercise intensity approaches $\dot{V}O_2$max, ventilation increases disproportionately. This hyperventilation assists with buffering H^+ by ridding the body of CO_2. The control of ventilation is complex and includes both feedforward ad feedback mechanisms. Feedforward involves output from the motor cortex directly into the ventilatory control system. Feedback involves central and peripheral chemoreceptors and mechanoreceptors providing input to the ventilatory control system.

For most of us, our lungs are overbuilt for the demand that we can place on them; able to ventilate more than is needed even at maximal oxygen uptake. For highly trained athletes, however, this may not be the case. The inability to fully saturate arterial blood for those with exceptionally high $\dot{V}O_2$max is an indication that the lungs do not adapt to training.

Assignments

1. Using the terminology from this chapter, describe an example of the process by which the brain receives information from the body, process the information, and initiates changes in breathing. Place your example in the context of a real-world scenario.

2. Consider the idea of physiologic dead space. a) How does it differ from dead space? b) How is it calculated? c) How is physiologic dead space affected in a person with respiratory illness?

3. Using the categories discussed in this chapter, place the following muscles into the correct group of ventilatory muscles. Also, briefly touch on their function.

Nasal dilator muscles

External intercostals

Sternocleidomastoids

The genioglossus

Tensor muscles of the soft palate

Rectus abdominis

Scalenes

Internal and external oblique muscles

The diaphragm

Transversus abdominis

Internal intercostals

Geniohyoid

4. Describe how the ventilatory system meets the demands of rising minute ventilation during a) light, b) moderate, and c) intense exercise.

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2.6: Chapter 8 - The Circulatory System Response to Exercise and Training

This chapter is in preparation.

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2.7: Chapter 9 - Homeostasis And its Disturbance During Exercise



Photo 9-1. Running in a hot environment can disrupt homeostasis. Photo by 12019 from Pixabay.

Learning Objectives

After reading this Chapter, you will:

- Explain how the integrated responses amongst physiological systems deal with challenges to homeostasis
- Describe the nature of water and electrolyte imbalances that can occur during exercise
- Describe the basic thermoregulatory responses to exercise, and how this affects body fluid balance
- Describe the basic concepts describing acid-base regulation in blood and muscle during exercise.

Key Terms

acid-base balance, acid-base state, dehydration, diuresis, electrolyte balance, euhydration, fluid balance, heat balance, heat strain, heat stress, homeostasis, osmolality, strong-ion difference, thermoregulation, ventilation

Introduction of Homeostasis and the Challenge of Exercise

The purpose of this chapter is to describe and discuss three interdependent aspects of exercise that pose physiological challenges to maintaining homeostasis. These are thermoregulation, fluid / electrolyte regulation and acid-base regulation. The relationships between these may not be readily evident, so by way of introduction let us consider Figure 9-1. Thermoregulation, the ability to regulate core body temperature involves integrating the inputs from many physiological systems that participate in heat generation, heat sensing, heat flow, and heat dissipation. The most effective way to dissipate heat during periods of heat stress, i.e. exercise, is through sweating. There is a strong relationship between fluid / electrolyte balance and thermal stress during periods of moderate to vigorous intensity exercise because the need to cool the body is achieved in large part through increased sweating rates. Our sweat is dilute compared to the electrolyte composition of our body fluids, so prolonged sweating with inadequate fluid and electrolyte intake can lead to life threatening imbalances. Exercise also results in disturbance of acid-base balance arising from electrolyte imbalances, dehydration, metabolic CO_2 production (and lactate accumulation at higher exercise intensities), and ventilatory CO_2 elimination. Therefore exercise, whether prolonged, low intensity, or short-term

high intensity, results in regulatory responses to mitigate thermal stress, dehydration and electrolyte imbalance, and acid-base imbalance. We will examine some of these physiological responses to low- and high-intensity exercise and discuss strategies for optimizing health and well-being during exercise.

This chapter will first consider challenges to fluid **/** electrolyte balance, and this will directly lead to a description and discussion of thermoregulation during exercise. The final section of the chapter will be on challenges to acid-base balance, with foci on short-term high intensity exercise and long-term exercise with dehydration / water imbalance.

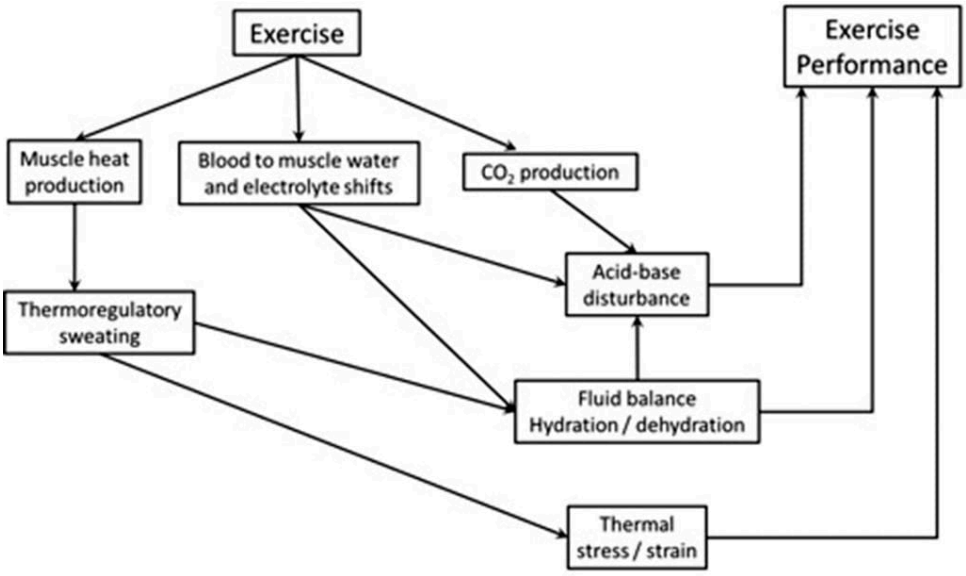


Figure 9-1 Relationships between fluid / electrolyte balance, thermoregulation and acid-base balance during exercise and their potential influences on exercise performance.

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Case Presentation: Hyponatremia in an Ultradistance Event

An ultradistance event, for runners, is one in which the distance is greater than the marathon (42 km) and, in Canada, these are typically called ultramarathons. Canada boasts the 430 mile (692 km) Yukon Arctic Ultra that is organized in February of even-numbered years. Runners, mountain bikers and cross-country skiers traverse from Whitehorse to Dawson City along the route of the Yukon Quest trail, the same trail taken by participants of the world's toughest sled dog race. Most ultradistance events are of much shorter distances and occur under relatively mild ambient conditions of temperature and humidity. Regardless of the distance and the environment, one of the key challenges of ultra-events is to be able to maintain fluid and electrolyte balance within the body. Even when running in cold conditions, sweating can occur at high rates and can lead to pronounced and life-threatening dehydration.

Endurance based events can occur in a variety of environments, as such, it is important to understand the unique physiological demands experienced in different environments. Whether it is the Yukon in February or a desert in July.

Blake Jacque (BJ) Shellaque has decided that he will run an 80 km ultramarathon. The event is being held in April in central Ontario. In order to prepare himself for the sweat losses of fluid that will occur during the first 16 km, BJ consumed 1 litre of water during the 2-hour period prior to the start of the race. He had to urinate prior to race start, and then is ready to go. There are drink stations set up at 5 km intervals where cups of water and Gatorade® are handed out to the runners as they pass by. BJ knows that it is important to maintain hydration during this event. The ambient temperature ranges from 14 to 21C (relatively humidity ~60%) and he is maintaining a steady rate of sweating of about 1.5 L per hour. BJ manages to consume adequate amounts of fluids along the way but he drinks water because he does not know about the benefits of drinking an electrolyte supplement. By 4 hours into the run, at about the 50 km mark, BJ has consumed a total of 5 litres of water, which replaces 83% of the fluid lost through sweating (6 L). At this time, BJ experiences some lightheadedness and

mild nausea. He is thinking that if he does not start feeling better soon, that he is going to have to stop. He keeps going for a short distance but is feeling bloated and tired and starts to get some muscle cramping. He stops and, because of his condition, receives medical attention within minutes.

Let us examine what has happened. The level of dehydration itself was not pronounced, and certainly not life threatening. However, consider the effect of the water that was imbibed prior to the race and during the 4 hours of exercise. When water is consumed, without electrolytes, then dilution of fluid compartments will occur and can create complications that may be just as profound as dehydration. The kidneys respond to the lowered plasma [Na^+] and osmolarity by increasing the excretion of water, but can only accomplish this by also excreting ions. This results in an ongoing loss of electrolytes with the 'excess' water.

- Drinking water
- dilution of body fluids
- impaired cellular function
- increased renal excretion of water with ions.

Hyponatremia, or low plasma sodium concentration ([Na^+]), is a pathophysiological condition that results from dilution of body fluids. The normal range for plasma [Na^+] is 135 – 145 mmolL^{-1}. The condition is caused, usually, from drinking water that is devoid of, or very low in, sodium. Putting this information into the context of ultradistance running, it should be evident that drinking water during such events can lead to hyponatremia. BJ's total body water in the euhydrated condition before the race was 40 L, with 1/3 of this present as extracellular fluid (13 L), of which 1/5 (2.7 L) is plasma. BJ lost 6 L of fluid through sweating and an additional 1 L as urine for a total of 7 L (Table 9-1). Six liters of this fluid was replaced by drinking water, leaving a deficit of 1 L and a TBW (Total Body Water) of 39 L. Also, the 6 L of water that was consumed essentially diluted 33 L of body fluid (40 L TBW – 7 L sweat and urine). Assuming that 1/3 of the water (2 L) remained in the extracellular fluid compartment (ECF), which is presently 12.5 L, then pure water diluted ECF by about 16% (2 L / 12.7 L). With consideration that sweat is a dilute filtrate of plasma, then ion concentrations in plasma should have decreased by ~10%) lowering plasma [Na^+] from 140 mmol · L^{-1} to 126 mmol · L^{-1}. This low level of Na^+ is life-threatening, and treatment requires immediate electrolyte therapy. Without treatment, the diuresis resulting from decreased plasma [Na^+] and the corresponding low plasma osmolality will cause the loss of 2 L of urine, which partially restores plasma [Na^+] (Table 9-1).

Table 9.1 Changes in body fluid compartment and sodium during BJ's run drinking only water.

Time	Volume of drink consumed (L)	TBW (L)	ECFV (L)	PV (L)	Sweating rate (L×h-1)	Sweat + urine fluid loss (L)	Plasma [Na+] (mmol×L-1)
Before start	1.0	40	13	2.7	0.1	0	140
1 to 4 h	+5.0				1.5		
At 4 h	5.0 total	39	12.7	2.5	1.5	6 + 1	126
At 1 h of 'recovery'		37	12.0	2.4	0.5	Diuresis of 2 L	133

Excessive intake of water results in dilution of body fluids and the life-threatening condition known as hyponatremia (natrium is Latin for sodium, and hypo mean low). Clinically, hyponatremia is defined as having a plasma [Na^+] of less than 135 mmoles · L^{-1}. Because hyponatremia represents a dilution of body fluids, other ion imbalances within extracellular fluid and intracellular fluid (ICF) are also often present. Mental signs of hyponatremia include headache, irritability, general fatigue, confusion, hallucination and in severe conditions loss of consciousness and coma. Other signs include nausea, vomiting, muscle weakness, muscle spasms and cramps (Siegel et al. 2008). In contrast, in adequate intake of fluids, or excessive intake of electrolyte solutions, results in elevated concentrations of ions in body fluids, and these also result in performance and health detriments (Siegel et al. 2008). It is clear that optimizing health and performance during prolonged activities requires careful consideration of fluid ingestion.

Take Home Message

The only way to maintain hydration is to maintain an adequate and balanced intake of electrolytes with water. This is why beverages such as Gatorade® were developed and are effective.

Fluid Balance

As noted in the endurance running example described above, fluid balance is important for performance and for thermoregulation (see below). Fluid balance, through its effects on the concentrations of ions, proteins, and metabolites in plasma and body fluids, is also an important contributor to acid-base balance – this will be discussed in the final section. In order to appreciate the demands of exercise on fluid balance, we also need to understand fluid needs in the individual at rest.

When a body is euhydrated it is in a state of ideal fluid balance such that there are no deficits (dehydration) in any fluid compartments, and also no excesses of fluid or electrolyte that would result in increased urine production. When we are in fluid balance the oral ingestion of fluid and electrolytes meets the losses occurring through the feces (~5%), respiratory tract (~10%), the skin (~50%), and the kidneys (~35%). Healthy men and women at rest need to consume 3.7 L and 2.7 L, respectively, of water daily in order to meet these losses (Sawka et al., 2005). An appreciable amount of this water is consumed in the foods that we eat, while the remainder is consumed in various beverages. Sweat losses can approach 2 L per day for individuals at rest in hot, humid environments, although a sweat rate of 5 L per hour has been reported for an individual exposed to hot conditions. This can only be achieved when skin blood flow is maximal and not in competition for blood flow to muscles.



Photo 9-2 Rehydrating during training/competition is crucial for athletes when experiencing high sweat rates. Photo by Greenfinger from Morguefile.com

Increases in activity resulting in increases in core temperature result in proportionate increases in sweating and respiratory fluid losses. Respiratory fluid losses are increased as a result of the increased depth (tidal volume) and frequency of breathing. Sweating fluid losses during activity are much higher than those occurring from the respiratory tract. High levels of activity can increase sweat losses by more than 4 L per day, such that total fluid losses may be 6 L per day or higher. Typical sweat rates during moderate intensity exercise are 1 – 2 L per hour, and these sweat rates can be sustained only as long as individuals do not lose too much fluid, i.e. there is ongoing rehydration.

The highest recorded sweat rate during exercise is 3.7 L per hour, reported for Roberto Salazar when training for the 1984 Olympics. Sweat rates greater than 3 L per hour can only be sustained for over an hour when hydration is maintained through consumption of electrolyte-containing beverages (Sherriffs et al., 2007). It is very difficult to consume more than 2 L of fluids per hour during exercise. Therefore, when sweat rates are very high it is clearly not possible to drink fluids at a high enough rate to prevent dehydration from occurring. Therefore, strategies have been developed and used that minimize dehydration and its negative effects on performance, thermoregulation, and health.

A number of strategies are used to try to maintain hydration during exercise. These include achieving euhydration prior to the start of exercise and during exercise to ensure adequate intake of water, electrolyte solutions, or sports gels. Gels are increasingly being used by athletes because they are less bulky and provide electrolytes and energy; however, caution must be used with these because adequate water ingestion is required to provide the needed balance between ingested electrolytes and water.

Another strategy is to try to hyperhydrate prior to exercise by ingesting compounds that will 'hold' water within the body for some time; glycerol has been used and well-studied in this regard. Hyperhydration using glycerol or any compound must be performed carefully, and for novices should be tried at lower loading amounts than recommend. Inappropriate use can lead to headaches, blurred vision, and gastro-intestinal upset. When using glycerol, 1 to 1.5 grams of glycerol per kg body weight is mixed into 25 $mlkg^{-1}$ body weight of water, and this should be consumed over a 1-hour period 60-90 minutes before starting exercise (Robergs, 1998). For a 70 kg person, this equates to 70 – 105 g of glycerol in 1.75 L of water (or electrolyte solution). While some of this fluid will be rapidly lost through the kidneys, total body water will be increased by about 500 ml, which may benefit cardiovascular function, skin and muscle blood flow during exercise, and skin blood flow to meet needs for thermoregulatory sweating.

Composition of Effective Rehydration Solutions

Electrolyte concentrations in human sweat are much lower than those of the body fluids (Table 9-2). This is because the fluid excreted into the sweat gland is altered by the selective reabsorption of Na^+ and Cl^- by active ion transport process by cells within the tubular epithelium. The human eccrine sweat gland has evolved as a means of retaining valuable salts within the body (Baker and Jeukendrup, 2014). The composition of effective electrolyte solutions for ingestion during and following exercise can thus be estimated from the composition of sweat.

Table 9-2 ***Plasma and sweat ion concentrations and composition of sports drinks. There can be considerable variability in sweat ion concentrations between individuals, and within individuals over time, including during periods of prolonged exercise.***

	Plasma	Sweat[1]	Sports drinks[2]
Carbohydrate ($g \cdot L^{-1}$)	0.7 – 1.5		60 – 80
Sodium (Na^+, $mmol \cdot L^{-1}$)	136 – 145	7 – 96	10 – 35
Potassium (K^+, $mmol \cdot L^{-1}$)	3.5 – 5.0	3 – 8	3 – 5
Calcium (Ca^{2+}, $mmol \cdot L^{-1}$)	2.2 – 2.6	0.2 – 0.5	0 – 2
Magnesium (Mg^{2+}, $mmol \cdot L^{-1}$)	1.5 – 2.4	0.04 – 0.1	0 – 2
Chloride (Cl^-, $mmol \cdot L^{-1}$)	98 – 106	7 – 91	10 – 12
Osmolality ($mOsm \cdot kg^{-1}$)	275 – 295	100 – 200	280 – 380

[1] Data from Lara et al., 2016; Ely et al., 2013; Baker et al., 2011

[2] Data from Baker and Jeukendrup, 2014; Proactive Nutrition (proactivenutrition.net)

In the 1960s, researchers and staff working with the University of Florida Gators football team developed the first recognized electrolyte solution for fluid replacement during exercise, Gatorade®. This was necessary because the high sweat rates occurring in individuals working at moderate to high intensities while wearing protective football equipment for extended durations in hot and often humid conditions, resulted in numerous cases of heat strain. Heat strain occurs when mechanisms for dealing with heat stress are exceeded, and in the extreme can result in catastrophic failure of thermoregulation, renal function, and death.

Because sweat is relatively dilute compared to body fluids, a consequence of sweating dehydration is an increase in the concentrations of Na^+, Cl^-, other ions, and proteins in the plasma and extracellular fluid (ECF). This feature of human ion regulation results in increased plasma osmolality, which serves as an important stimulus to the thirst mechanism. The concentrating effect of sweating on plasma/ECF ion concentrations can be countered by drinking water in adequate amounts to restore ion balance. However, because ion losses occur with sweating, ingesting sufficient water to restore plasma/ECF ion balance will not fully rehydrate the individual. The only way to effectively accomplish this would be by also taking in adequate amounts of electrolytes to replace those lost in sweat.

The types of fluids ingested for the purpose of maintaining hydration and optimizing water and ion concentrations in the body has received much study in the past 50 years. Because the main electrolytes lost in sweat are Na^+ and Cl^-, these are the main electrolytes found in effective oral electrolyte solutions (Proactive Nutrition, 2018). There should also be appropriate amounts of K^+, Ca^{2+}, and Mg^{2+}. In order to accommodate taste and gastrointestinal (GI) function, the osmolality of the solution is typically about half that of body fluids (i.e. ~150 mOsmol $\cdot$ L^{-1}), contains some dextrose to enhance intestinal absorption of water and electrolytes, as well as flavouring agents. Ideally, small amounts (~250 ml) should be consumed frequently (15 to 30-minute intervals prior to the start of exercise) during exercise and during the immediate post-exercise recovery period.

The presence of electrolytes in post-exercise rehydration beverages is very important for effectively restoring hydration. In 1994, Maughan and coworkers studied the effects of electrolytes in the recovery period after exercise. Subjects underwent dehydration by 1.8% of body mass with intermittent cycle ergometry. Between 30 and 60 minutes after exercise, subjects drank 1 of 4 solutions at a volume equal to the body water loss. Solution A, comprising 90 mmol $\cdot L^{-1}$ glucose only (no electrolytes), resulted in increased urine output and a net negative fluid balance (still dehydrated) the following morning. Therefore, the ingested volume effectively diluted the concentrations of ions in the blood and body fluids, which was sensed by the body as a volume overload, although the volume was equal to that lost. The kidneys respond to this signal by increasing the excretion of water, which can only be accomplished by reduced tubular reabsorption of ions. The result is that there is no effective rehydration and that dehydration could, in fact, worsen. In this recovery 'rehydration' study, there were no differences among the three other solutions with respect to urine production and fluid balance. As expected, recovery of Na^+ balance was enhanced when Na^+ was present in the solution, and recovery of K^+ balance was better with K^+ containing beverages. Additionally. the presence of Cl^- in the solution improved the recovery of cation balance. It can be concluded from studies such as this that it is important that the electrolytes present in rehydration solutions are physiologically balanced to meet the needs for optimal fluid recovery.

Summary

Prolonged exercise heat stress results in loss of water and electrolyte through sweating. Sweat rates of 1.5 L $\cdot$ h^{-1} are normal and can be twice as high in acclimated athletes. Prolonged sweating, without fluid supplementation, will result in life-threatening dehydration and electrolyte imbalance. Replacing sweat losses with only water results in a dilution of body fluids, which can make the electrolyte imbalance worse and which will result in a diuresis to try to restore plasma [Na^+] and osmolality. Replacing sweat losses with well-designed electrolyte solutions, consumed at a rate to match sweat rate, will prevent dehydration and electrolyte balance, and enhance exercise performance and ability to thermoregulate.

Exercise Heat Stress Results in Dehydration to Meet the Needs of Thermoregulatory Cooling

The efficiency of muscular contraction, expressed as the conversion of chemical energy to the mechanical energy of locomotion, ranges from 0-25%, but for cycling is typically 16-23% (Coyle, et al. 1992). The chemical energy refers to those compounds (e.g. free fatty acids, glucose, amino acids) that cells can metabolize, thus liberating energy from the bonds between atoms. Most of the chemical energy that cannot be used for generating ATP is released as heat (refer back to Figure 9.1). It is essential that heat is removed from muscle as rapidly as possible during periods of contraction because temperatures above 43°C result in conformational changes in muscle proteins (i.e. some proteins start to denature or cook). At 42°C, mitochondrial uncoupling occurs, resulting in without corresponding rephosphorylation of ADP (Jarmuszkiewicz et al., 2015). This uncoupling will further increase heat production. The most important means of removing heat from muscle is by convective flow of blood. This is accomplished by maintaining a high rate of blood flow through the muscles – this is one key demand for the increased cardiac output required during exercise. Blood perfusing contracting muscles is transported initially to the lungs and skin where heat dissipation can occur. Heat is also transferred via blood to all tissues of the body, resulting in an increase in body heat storage which results in an increase in core body temperature.

Exercise heat production and storage thermoregulatory cooling increased sweating fluid loss from all compartments dehydration.

Case Presentation: Heat Stress in a Distance Event

Our budding athlete, BJ, has learned an important lesson and uses electrolyte solutions when training and competing so as to avoid electrolyte imbalance and dehydration. He has entered into a half-marathon race in early May. Training conditions through April and early May were relatively cool, with the highest ambient temperatures at 20°C. From training in these conditions he has learned that his sweating rate is about 1.5 L per hour, at a running speed of 12 km · h^{-1}, and he now religiously consumes 1.5 L of Gatorade® during each hour of running.

Race day morning weather conditions are very fine and temperatures are predicted to reach 25°C during the race, with relative humidity (RH) pushing 80%. BJ is thinking "nice – I'm going to have a great run today". Temperature at the start of the race is 21°C, and with the excitement of the start, BJ goes out hard and his speed for the first 2 km is 13 km · h^{-1}. He feels great, he feels that he is in for a good run, and he decides to maintain this pace. His legs are moving well, his breathing is good. What BJ is not appreciating, however, is that with the increased running speed he is also experiencing an increased rate of body heat storage. He pushes on, past 5 km, maintaining his intake of fluids. As he approaches 10 km he realizes that his breathing has become heavier than normal, and his breathing rate is faster than usual. He also notices that he seems to be sweatier. He attributes these physiological responses to increased running speed. He is on a personal best pace and he is highly motivated to continue at or close to this pace.

Let us now examine the physiological responses to running in warm (25°C and RH 80%) conditions, compared to 'normal' conditions (20°C and RH 60%). We have already learned that the increased running speed results in a more rapid generation of heat by contracting muscles, leading to an increased rate of body heat storage and core temperature rises (Figure 9-2). The body responds to the increase in core temperature (sensed by the hypothalamus) by increasing blood flow to the skin (convective and radiative cooling) and by increasing the rate of sweating in order to provide thermoregulatory cooling through evaporation of sweat. In general, sweat rate is directly proportional to core body temperature (Figure 9-3). When BJ was running in the warmer ambient conditions, both skin and core temperatures were greater than when he trained at cooler ambient conditions, resulting in a greater increase in core temperature and greater sweat rates. I think that now you can appreciate that BJ is headed for some physiological difficulties. If he tries to keep going at this pace, he will crash.

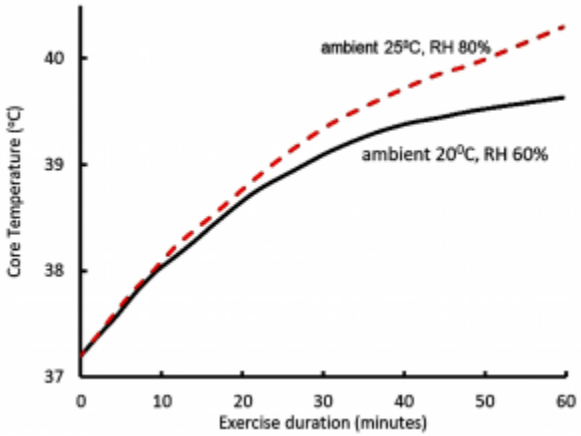


Figure 9-2 Increase in core temperature with prolonged submaximal (~70% of $\dot{V}O_2$peak) exercise in neutral and warm, humid conditions. Adapted from Brengelmann et al., 1977; Adams et al., 1992; Kenny et al., 2003a.

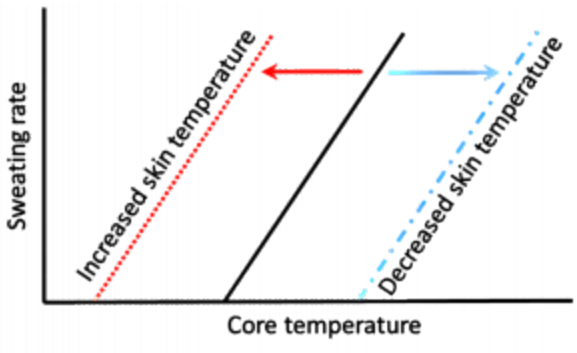


Figure 9-3 Sweating rate is directly proportional to core temperature and is influenced by skin temperature. Increases in skin temperature augment the sweating rate at any given core temperature. Adapted from Nadel et al., 1971.

Muscle Contraction Generates Heat; Increases Sweating Rate and Reduces Blood Volume

Due to the increase in BJ's core temperature his sweating rate has increased to 2 $L \cdot h^{-1}$, although fluid intake remains at 1.5 $L \cdot h^{-1}$. Respiratory rate has also increased, resulting in additional respiratory fluid loss of 0.5 $L \cdot h^{-1}$. The increased fluid loss during the first hour of the race is thus 1 L, with a significant part of this borne by the extracellular fluid (ECF) compartment, and so ECF volume is reduced from 13 L (at rest) to 12.3 L. Blood volume (2.6 L at rest) comprises about 20% of extracellular fluid volume and therefore blood volume is proportionately reduced (140 ml). Blood volume has also been reduced 5% (260 ml) due to a net osmotic transfer of fluid into contracting muscle that occurred with the rest to work transition, such that the total reduction in blood volume is presently 400 ml (15% of initial blood volume).

The reduction in blood volume means that the heart needs to work even harder to meet the demands of increased blood flow to contracting muscles, to the lungs, and to the skin. Cardiac output ($\dot{Q}$) is the product of heart rate (HR) and SV, (the volume of blood pumped with each contraction of the left ventricle) and thus $\dot{Q}$=HR SV. SV is indirectly proportional to blood volume (BV), therefore when BV is reduced by 15% then SV will similarly be reduced. Therefore the only way to maintain $\dot{Q}$ is to increase HR, thus increasing the work of the heart. Now let us consider the demands for $\dot{Q}$:

- increased $\dot{Q}$ demanded by contracting muscles to provide oxygen and fuel and to remove heat the metabolic products such as CO_2;
- increased $\dot{Q}$ demanded by the skin for thermoregulatorycooling;
- increased blood flow to the lungs for gas and heat transfer.

Each of these three processes results in profound vasodilation of the vascular beds in these tissues, reflecting both the needs of the tissues and of the whole body.

Let us summarize:

- BJ decides to run faster.
- It is warmer outside.
- It is more humid outside.
- BJ's core body temperature increases faster than usual.
- BJ's sweating rate is greater than usual, and exceeds his rate of fluid replacement.
- His blood volume is reduced at a time when high $\dot{Q}$ is needed to meet tissue and body needs for metabolism and cooling.

Is this a scenario for heat injury? We have not yet considered the impact of elevated relative humidity on the ability to dissipate heat. BJ does notice that he is more sweaty than usual, and attributes this to increased running speed, which is partially correct. The increased humidity has also significantly reduced the rate at which sweat can evaporate, and therefore more sweat is dripping off than evaporating. It is the evaporation that provides the cooling effect, so when humidity is high, evaporative cooling is diminished. This in turn reduces the ability to dissipate heat by the skin and contributes to the higher rate of body heat storage

experienced by BJ, and this in turn increases the sweating rate. But this is not beneficial at this point.

- Heat dissipation is not adequate to match the rate of heat generation.
- Most of the sweat produced does not evaporate, sweating rate is increased, contributing to dehydration, loss of blood volume, and increase in HR**.**

At this point BJ knows that something is not right. He is not able to maintain the pace and slows down. There is some fairly immediate relief, but this is short lasting. Sweating rate remains high, core temperature and heart rate continue to increase. Heart rate is maximal, but no longer adequate to meet needs, and blood pressure drops. Then BJ stumbles, steps off the course onto the grass, falls to his knees and collapses.

- Heat syncope has occurred.
- BJ receives immediate medical attention, with fluid and cold therapy, and feels much better within an hour.
- Thermoregulation

The scenario with BJ described above provides an example of a number of disturbances to homeostasis that occur during prolonged, moderate intensity exercise. These include muscular heat production and whole body heat storage initiating the need for thermoregulatory cooling, the production and secretion of sweat that allows for evaporative cooling at the skin, increased demand for cardiac output to meet the need for increased blood flow to move heat from contracting muscles to the skin, resultant decreases in intracellular fluid volume, extracellular fluid volume, circulating blood volume, and total body water. These, in turn, further influence blood pressure and cardiovascular function. Attempts to limit the dehydration, by drinking only water, results in dilution of ion concentrations, which additionally affects functioning of all cells of the body.

Thermoregulation refers to the mechanisms involved in the control of body and tissue temperatures. Figure 9-4 shows the reasons for the increase in body heat storage during exercise and the main ways in which heat can be dissipated. When body heat storage is increased, heat balance is maintained through various heat dissipation routes including evaporation of sweat, convective heat loss from the skin by movement of air, radiation of heat to the ambient environment (assuming air temperature is cooler than skin temperature), and conduction of heat to solid surfaces (usually minimal).

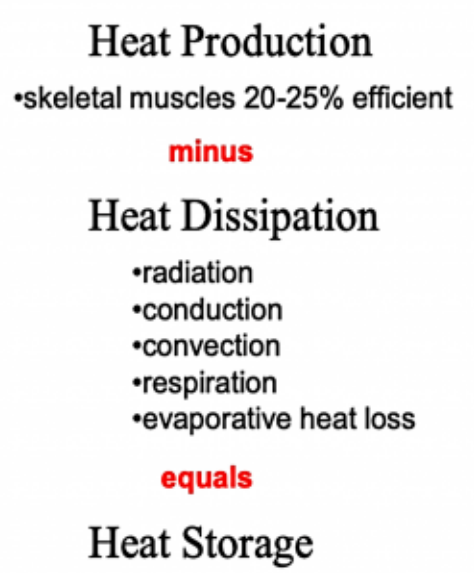


Figure 9-4 Heat balance during periods of heat stress such as exercise.

Body heat storage (S) can be calculated from measurements of core body temperature (T_{core}), mean skin temperature (T_{skin}), boy mass (m) and height (h) using equation 9-1 (Tikuisis et al., 2001).

$S\ (kJ) = 3.55\ kJ \cdot kg^{-1} \cdot T_b \cdot BSA^{-1}$ **equation 9-1**

where $T_b = 0.65 \cdot T_{core} + 0.35 \cdot T_{skin}$ **equation 9-1a**

and $BSA\ (cm^2) = 128.1 \cdot m^{0.44} \cdot h^{0.60}$ **for men equation 9-1b**

BSA (cm^2) = 147.4 · $m^{0.4}$ · $h^{0.55}$ **for women equation 9-1c**

Detecting Changes in Temperature

The body is endowed with thermal sensors at the hypothalamus and in the skin (Figure 9-5). The hypothalamus is a small multifunctional integrating organ in the mid-region of the brain. As warmed blood perfuses the hypothalamus, an increase in blood temperature is detected by temperature sensitive neurons. The hypothalamus controls skin blood flow and sweat production. Mild increases in blood temperature (e.g. less than 0.2°C) have no effect on skin blood flow and sweating because there is a temperature setpoint or threshold that must be reached before signals are sent from the hypothalamus to the skin to change vascular resistance and initiate sweating. In most individuals an increase in circulating blood temperature of ~0.2C results in adequate stimulation of heat-sensitive neurons in the hypothalamus to initiate a sweating response.

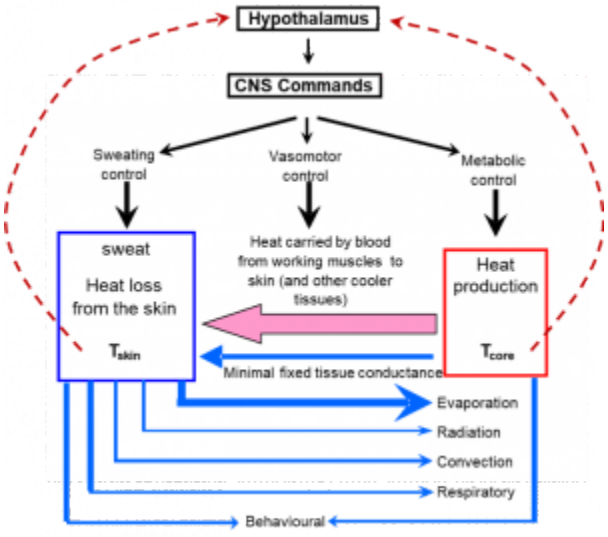


Figure 9-5 Hypothalamic sensing and central response to increased core and/or skin temperature. The hypothalamus is the central sensor of body heat, and it controls the response to changes in body heat storage including sweating and possible changes in heat production or heat loss through the skin.

Heat Dissipating Mechanisms

The main ways that we can lose heat to the environment are sweating with evaporative cooling, convection of air over our body, radiation of heat into the environment, and conduction to solid surfaces (Figure 9-5). Heat loss through the respiratory system (combination of evaporation, radiation, and convection within the pulmonary system) can also be substantial in cool conditions with low relative humidity. Conduction and convection can also play important roles for heat transfer when the body is immersed in water because water has a greater heat capacity than air.



Photo 9-3 Ovens and microwaves use convection and radiation in order to heat our food, these same principles are used to regulate body temperature. Photo by jackietrains at Morguefile.com.

Respiratory heat loss

We lose heat from our bodies through the process of breathing. Not only do we warm up the air we inhale (to body temperature), we also fully saturate this inhaled air. The evaporative heat energy is lost from the body. When at rest and dressed appropriately, between ambient temperatures of -20 to 20°C, ventilatory heat loss corresponds to about 25% of the whole-body metabolic rate. This magnitude of heat loss may be undesirable when in cool conditions for extended periods of time and could lead to a decrease in T_{core}. In situations of heat stress (exercise, over-clothed, heat exposure) an increase in core temperature of about 1°C is accompanied by an increase in breathing frequency without increase in tidal volume. This is called a thermal hyperpnea, thermal tachypnea or panting, and is similar (but much less obvious) to what is seen in dogs and other mammals during periods of thermal stress (White, 2006). With exercise, ventilatory heat loss as a fraction of metabolic rate diminishes, such that at work rates greater than 200 W the ventilatory heat loss represents about 15% of the metabolic rate (Cain et al., 1990). In conditions of $\dot{Q}$ this represents a favorable loss of heat from the body. There are corresponding increases in heat loss through evaporative sweating and radiation as work rate increases.

When heat loss through non-ventilatory mechanisms is inadequate, thermal tachypnea may contribute to an acid-base imbalance termed a ‘respiratory 2. Ventilation removes CO_2 from the body and when more CO_2 is removed than is produced by metabolism, this removal results in decreased [H+] (alkalosis) because of the following reaction is driven to t” href=”https://kinesiology.ucalgary.ca/maci...tory-alkalosis–“>alkalosis’ . Because the ventilatory system is important in gas exchange and acid-base regulation, thermal tachypnea will increase the rate of ventilatory CO_2 elimination, thus lowering plasma PCO_2 and [HCO_3^-] and raising [H^+] (plasma alkalosis). At some point, peripheral and central chemoreceptors will be sensitive to the changes in plasma PCO_2 and pH and decrease the drive to ventilate. Therefore, there can be a conflict in control of breathing with heat driving an increased breathing frequency and chemoreceptors driving a decreased breathing frequency (Kenny et al., 2014). The thermal effects on plasma ventilatory and acid-base variables are easily measured when someone is at rest. During exercise, however, it is difficult to separate the thermal effects on acid-base balance from those imposed by exercise.

Increased Skin Blood Flow, Sweating and Evaporative Heat Loss

Sweat production is required for evaporative cooling. This is recognized by the term evaporative requirement (E_{req}), which is the sum of the metabolic heat production (H) and the radiative (R) and conductive/convective (C) heat exchanges (Brotherhood, 2008). Therefore, to achieve thermal balance and control of body temperature the net heat load arising from

$$H \pm R \pm C$$

must be balanced by evaporative cooling (E), such that

$$E_{req} = H \pm R \pm C.$$

Note that E_{req} only provides an estimate of sweat requirement; thermal balance can only be achieved if sufficient sweat is produced AND evaporated to meet E_{req}. Any sweat dripping off the body cannot contribute to evaporative cooling. The rate of evaporation is also affected by the ambient humidity such that evaporation is reduced at high relative humidity. Also, the rate of heat transfer from the skin to the environment by convection and radiation depends on the temperature gradient between the skin and the environment. Heat transfer by radiation is a function of body surface area and remains constant with changes in core temperature and air speed. In contrast, heat transfer by convection increases as a function of increases in core temperature. Also, increasing air speed from 0.2 to 3.0 ms^{-1} doubles the rate of convective heat transfer.

Heat loss at the skin is dependent on the flow of blood to the skin – an increased blood flow during times of elevated T_{core} moves heated blood to the skin to allow for heat transfer through tissues and also to provide the fluid required for sweating. The increase in blood flow to the skin is largely passive and results from cutaneous vasodilation and recruitment of capillaries – the latter two of which are under neural control. In order to maintain central blood pressure, the cutaneous vasodilation must be met by an increase in cardiac output. This need for increased skin blood flow is thus in competition with the need for cardiac output directed towards contracting muscles, particularly as the cardiac output approaches maximal levels. Thus, beyond this passive component, there is also a complementary neural drive to increase heart rate.

In 1977 Rowell and colleagues examined the relationship between skin temperature (T_{skin}), exercise, esophageal temperature (a measure of T_{core}), and skin blood flow (Brengelmann et al., 1977). Subjects performed submaximal leg cycling exercise and when T_{skin} was elevated to 38°C by means of water-perfused suits, there was a small transient increase in skin blood flow between 6 and 10 minutes, (measured as forearm blood flow – lower panel, Figure 9-6).

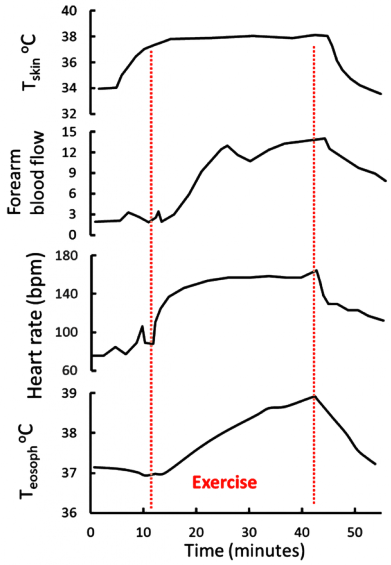


Figure 9-6 Responses to elevated skin temperature (6 to 12 minutes) and added submaximal leg cycling exercise (~123 W from 12 to 42 minutes). Data from Brengelmann et al., 1977.

This indicates that thermal sensors in the skin responded by inducing a short-lasting vasodilation of the skin. The increase in blood flow was associated with the expected increase in heart rate between 6 and 12 minutes. Subjects then exercises at 86-147 W for 17-30 min while T_{skin} was held at 38°C. Core temperature increased by 1°C during the first 13 minutes of exercise, then continued to increase until 2 minutes after the end of the 30-minute exercise period. Heart rate had peaked 8 minutes into the exercise (top panel), however skin blood flow continued to increase for an additional 5 minutes, that is until 13 minutes of exercise (lower panel). This indicates a loss of association between heart rate and skin blood flow after the initial increases. Also, the fact that skin blood flow did not increase after the initial 13 minutes of exercise, despite T_{core} increasing by 2°C over the exercise period, suggests that near-maximal vasodilation of the skin, and cutaneous thermoregulatory potential, occurs with relatively small increases in T_{core}. This is beneficial for heat dissipation during even brief periods (less than 10 minutes) of submaximal intensity exercise.

Johnson and coworkers (1984) further demonstrated the relationships between T_{core}, T_{skin}, skin blood flow, and sweat rate. They also used water-perfused suits to rapidly elevate T_{skin} during exercise. There was a small increase in sweat rate with the 0.5°C

increase in T_{core} occurring at the onset of exercise. In contrast, gradually increasing T_{skin} by 4°C during exercise resulted in early and pronounced increased in skin blood flow and sweat rate. The results are consistent with a dominant role for T_{skin} in the reflex regulation of both skin blood flow and sweat rate. This interplay between central (hypothalamic) and peripheral (skin) thermal sensors in thermoregulatory sweating is exemplified in Figure 9-3. Changes in T_{skin} alters the set point (threshold) at which sweating will occur. When the threshold is reached, sweat rate increases as a function of increases in T_{core}.

In summary, increases in core and skin temperatures are involved in the regulation of skin blood flow and sweat rate. However, increases in T_{skin} appear to play the dominant role in regulating blood flow and sweat rate.

Heat Loss by Radiation, Conduction, and Convection

We will now consider the minor routes of heat loss by radiation of heat from surfaces, conduction between masses, and convective cooling by the movement of air over the skin. Adams and coworkers (1992) studied the cooling effects of convective air movement (wind) over the body's surface at ambient temperatures of 24°C and 35°C during submaximal leg cycling exercise. Increasing air speed from 0.7 to 10.8 $km \cdot h^{-1}$ resulted in a significant reduction in sweat loss at both ambient temperatures, but without change in sweatevaporative rate at the lower temperature. Therefore, increased air speed reduces sweat rate, an effect mediated in part by a reduction in skin temperature (see above). At the higher temperature sweat evaporative rate was increased only during the first 30 minutes and this resulted in a 20% reduction in sweat rate at the higher temperature (i.e. evaporative cooling of the skin resulted in a reduced rate of sweating). Convective heat loss was minimal at the higher temperature at both air speeds. When exercise was performed at 24°C increased air speed rapidly decreased T_{skin} (Figure 9-7) and augmented convective heat loss by 20% compared to still air. However, contrary to what might be expected, increasing air speed from 0.7 to 10.8 $km \cdot h^{-1}$ actually increased the rate of body heat storage during the first 30 minutes of exercise (Figure 9-8) and reduced the rate of evaporative heat loss. This occurred because the decrease in T_{skin} that occurred with air speed 10.8 $km \cdot h^{-1}$ at ambient T of 24°C (Figure 9-7) resulted in increased heat transfer coefficients and a reduced skin-to-ambient temperature gradient. In contrast, when exercise was performed at 35°C, the increased air speed resulted in a decreased rate of heat storage and increased rates of evaporative sweating and evaporative heat loss, which enhanced skin dryness. At 35°C, because of the very small difference between air and body temperature, convective and radiative heat loss was minimal. The decreased rate of heat storage during exercise indicates a significant convective heat loss. Taken over the 60-minute exercise duration of this experiment the main heat exchange values were as follows, using the formula:

$$S = (M - W) - E + R + C \quad \textbf{equation 9-2}$$

where S is heat storage, M is metabolic free energy production, W is work, E represents whole body evaporative heat loss, R is the radiation heat exchange, and C represents the convective heat exchange, with heat exchange unit of $W \cdot m^{-2}$.

24°C with air speed 0.7 $km \cdot h^{-1}$

35 = (345) – 210 – 46 – 52

24°C with air speed 10.8 $km \cdot h^{-1}$

21 = (345) – 196 – 24 – 65

35°C with air speed 0.7 $km \cdot h^{-1}$

53 = (345) – 306 – 1 – 1

35°C with air speed 9.8 $km \cdot h^{-1}$

29 = (345) – 352 + 7 + 20

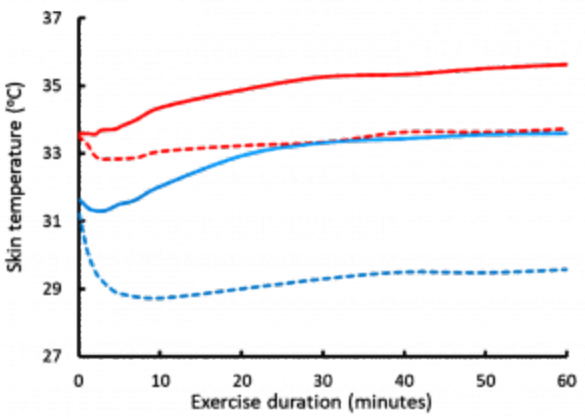


Figure 9-7 Skin temperature as a function of air speed (solid line 0.7 km · h^{-1}; dashed line 10.8 km · h^{-1}) at ambient temperatures of 24C (blue) and 35C (red) during leg cycling exercise at ~56% of $\dot{V}O_2$peak. Data from Adams et al., 1992.

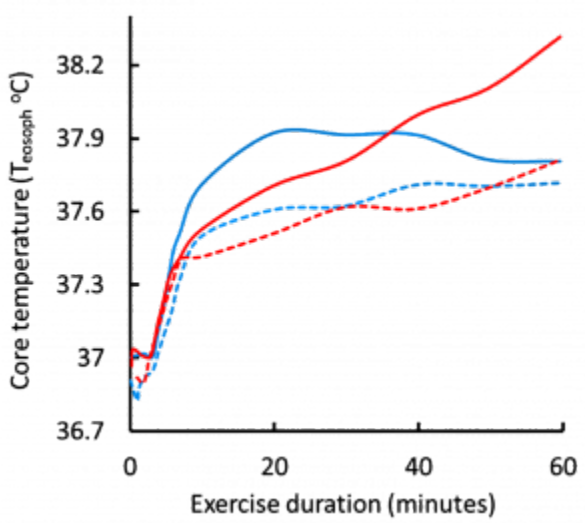


Figure 9-8 Core temperature (measured as esophageal temperature, Tesoph) as a function of air speed (solid line 0.7 km · h^{-1}; dashed line 10.8 km · h^{-1}) at ambient temperatures of 24°C (blue) and 35°C (red) during leg cycling exercise at ~56% of $\dot{V}O_2$peak. Data from Adams et al., 1992.

While the differences in convective heat loss may appear small, when exercise is prolonged then the increase in air velocity is positively and linearly correlated with the exercise time to exhaustion (Figure 9-9). Increasing the air speed to 30 km · h^{-1} resulted in a doubling of exercise time to exhaustion (Otani et al., 2018).

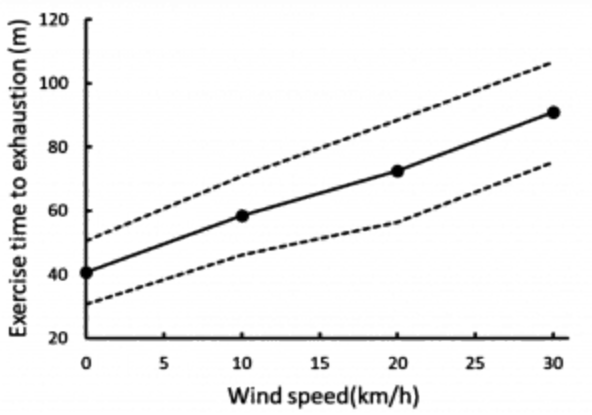


Figure 9-9 Eight subjects performed leg exercise on a stationary cycle ergometer at 4 air speeds until voluntary exhaustion. Solid line is the mean, dashed lines are the upper and lower standard deviations. Data from Otani et al., 2018.

Heat Stress and Heat Injury

Our budding athlete BJ has experienced excess whole body heat storage which has resulted in heat syncope. Heat syncope is dizziness or fainting as a result of overheating. It is relatively mild on the continuum of heat injuries. As heat storage increases in the body, specific terms are used to describe the status of the body's response: heat stress, heat strain, heat injury, and heat stroke. Let us consider what is normal as well as what is abnormal and dangerous. Recall from above it was noted that some proteins in our cells begin to denature at temperatures close to 43°C, which is readily achievable in contracting muscle if care is not taken.

Heat stress is a normal part of exercise

At this point we have an appreciation that heat stress is a normal part of exercise and cannot be avoided. Ambient conditions also contribute to the heat stress associated with exercise. Moderate to elevated ambient conditions reduce the thermal gradient for radiating heat away from the surface of the body, thus exercise in warm or hot conditions results in a greater rate of body heat storage during exercise. High humidity has a similar effect on heat storage because the greater the humidity the smaller the water vapour pressure that allows for evaporation of sweat. Thus, under conditions of high humidity, very little sweat evaporates but rather may drip off in large amounts. This, in essence, is 'wasted' sweat because there is minimal associated evaporative cooling. The movement of air over the skin (convection) can be an effective cooling agent, particularly during prolonged exercise when ambient conditions are both cool and dry. When one is exercising at moderate intensity to high intensity and is wearing clothing or protective equipment, i.e. hockey players, the clothing effectively prevents or minimizes heat loss through evaporative cooling, radiation and convection – the rate of heat storage can exceed 1.5 times that without protective clothing (Noonan, 2006). If one is not careful, the rate and amount of heat storage can be too great, resulting in heat strain (Table 9-3). In contrast, under cool conditions with low relative humidity and high air flow the resultant 'wind chill' creates a significant challenge to keep in the heat. In addition to these exercise and ambient influences on the body's ability to regulate temperature, body temperature is also influenced by inflammation of injured tissues and by fever (illness). Thus, many factors can contribute to the heat stress that one experiences during periods of exercise. While heat stress is normal and, indeed, provides beneficial adaptations to occur over time (heat acclimatization), excessive heat stress will result in heat strain with risk of severe thermal injury.

Table 9-3 Metabolic Heat Stress and Potential for Thermoregulatory Strain in Sport

Body mass (kg)	70	95	65	75
$\dot{V}O_{2peak}$ (L $O_2 \cdot min^{-1}$)	4.2	5.2	4.9	4.1

Exercise intensity (%$\dot{V}O_{2peak}$)	60	75	85	80
Metabolic heat production (W)	880	1330	1410	1380
Sweat evaporation required for heat balance ($L \cdot h^{-1}$)	1.3	2.0	2.1	1.8
Predicted steady state T_{core}	38.4	39.2	39.7	39.5
Rise in T_{core} without heat loss ($C \cdot h^{-1}$)	9.4	14.5	22.5	480

Source s : Brotherhood , 2008 ; Noonan , 2006; Noonan et al. , 2007; Green et al. , 1976; Montgomery , 2000 ; Palmer and Spriet , 2008 ; Palmer et al. , 2010.

Physics, physiology, behavior, and the environment influence the ability to thermoregulate. These factors can be assessed in order to determine those conditions under which we will not be able to effectively thermoregulate. While the main indicator of heat stress is elevated core body temperature, other indicators may include increased heart rate, increased ventilation, increased blood flow to the skin (cutaneous vasodilation), and sweating. There is a continuum in these normal physiological responses as one approaches heat strain until one or more of the following indicators of heat strain (with impending injury) are reached: core temperature of 41°C, heart rate continues to increase despite no increase in work load or power, increased frequency of breathing (panting), and sweat rate may decrease considerably (indicating profound dehydration). When indicators of heat strain occur, immediate steps should be taken to cool the person and try to restore hydration. Heat injury will occur when tissue temperature exceeds 43°C (i.e. in contracting muscles), when the body has lost the ability to produce sweat and when dehydration is greater than 5% body weight. Thus, heat injury is often associated with hypotension (lower than normal blood pressure), nausea, and renal failure if dehydration and muscle injury are severe. It is therefore important to recognize and understand the signs of heat stress and heat strain in order to maintain health and to prevent injury.

Exercise Training and Heat Acclimatization

As one progresses from a sedentary or less active lifestyle, to a more active one (exercise training) there can occur a number of physiological adaptations that improve the interplay between muscle energetics, pulmonary gas exchange, and thermoregulation. From the perspective of thermoregulation, exercise is itself a cause of heat stress. The ability of the body to adapt to daily (or nearly so) repeated bouts of heat stress is termed heat acclimatization. Imposing additional heat stress to exercise, such as repeated bouts of exercise in warm or hot conditions, results in additional heat acclimatization responses beyond that seen with exercise training alone (Roberts et al., 1977). For example, with respect to sweat rate**,** exercise training results in a small decrease in the setpoint for sweating onset, and an increased slope of the esophageal temerature – sweating rate relationship, or enhanced sweating response for a given increase in esophageal temperature. With subsequent heat acclimatization there is minimal further increase in sweat rate at a given Tes, however there is a pronounced (up to 0.5 °C) decrease in the hypothalamic thermal setpoint for onset of sweating.

Heat acclimatization results in decreased core temperature at rest, increased plasma volume, decreased heart rate during exercise, a decreased thermal setpoint for onset of sweating (thus earlier cutaneous vasodilation and onset of sweating = increased sweating sensitivity), increased sweat rate, and decreased sweat and urine sodium losses (Armstrong and Maresh, 1991). The increase in plasma volume occurs within 3-7 days and is beneficial to meet the demands of increased cardiac output during exercise in the heat. The full spectrum of complete adaptations requires at least 14 days of regular exercise.

Summary of Thermal Responses during Exercise

Evaporation of sweat is the predominant means for eliminating metabolic heat from the body during exercise. When there is a high temperature gradient between skin and the ambient air, then convective and radiative heat losses make a significant contribution, particularly when exercise is performed for prolonged periods of time. A practical caveat is when running or cycling against the wind, maintaining constant velocity requires increased expenditure of energy. As always, it is imperative that the athlete finds a good, operational balance between heat loss and metabolic energy expenditure during training and competition in order to avoid heat injury situations. Heat acclimation increases sweat rate and lower the thermal setpoint at which sweating is initiated. While heat acclimation confers many beneficial adaptations, it is very important to use effective strategies to replace fluids and maintain heat dissipation.

Acid-base Balance

In traditional terms, acid-base balance refers to regulation of the acidity of plasma and other body fluid compartments, as can be assessed from measures of the 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure of CO_2 and pH. The relationship between these two variables and bicarbonate is provided by the Henderson-Hasselbalch equation:

$pH = pK + \log ([HCO_3^-] / sPCO_2)$ **equation 9-3**

where pK is the log of the dissociation constant (Kc) for the CO_2 to $[HCO_3^-]$ pseudo-equilibrium; and 's' is the solubility coefficient for CO_2 in aqueous solutions. The log transform can be removed to express the relationship in terms of $[H^+]$:

$Kc\ sPCO_2 = [H^+] [HCO_3^-]$ **equation 9-4**

This carbon dioxide view of acid-base balance is very limiting in terms of quantifying the factors that contribute to changes in acid-base state, because changes in the concentrations of many other substances contribute to changes in acid-base state.

A more encompassing description of acid-base balance is provided by the physico-chemical approach described by Peter Stewart (1981; Lindinger and Heigenhauser, 2012). The approach recognizes that changes in the concentrations of strong and weak ions, as well as CO_2, contribute to acid-base balance. Strong ions are those that are fully (or nearly so) dissociated in physiological solutions, and include Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and the metabolites lactate**(**lactate$^-$**)** and phosphocreatine**(**PCr^{2-}**),** which have dissociation constants of 1.9 and 3.9, respectively. The total concentration of weak ions (primarily proteins, some amino acids, and phosphate) is encompassed by the term **[**Atot**]**. The dependence of $[H^+]$ and $[HCO_3^-]$ on the independent variables are shown in Figures 9-10, 9-11 and 9-12.

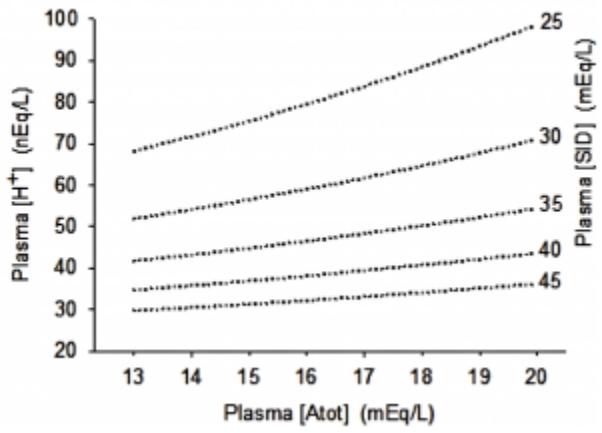


Figure 9-10 The dependence of plasma $[H^+]$ on [Atot] and the strong ion difference ([SID]) when PCO_2 is constant at 40 mm Hg.

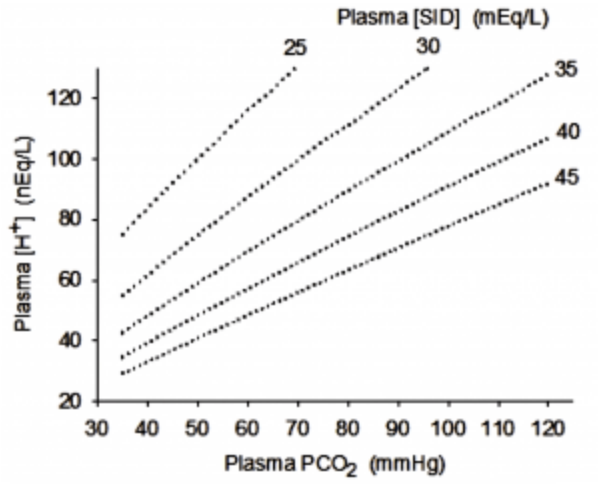


Figure 9-11 The dependence of plasma $[H^+]$ on PCO_2 and [SID] when [Atot] is constant at 16 mEq · L^{-1}.

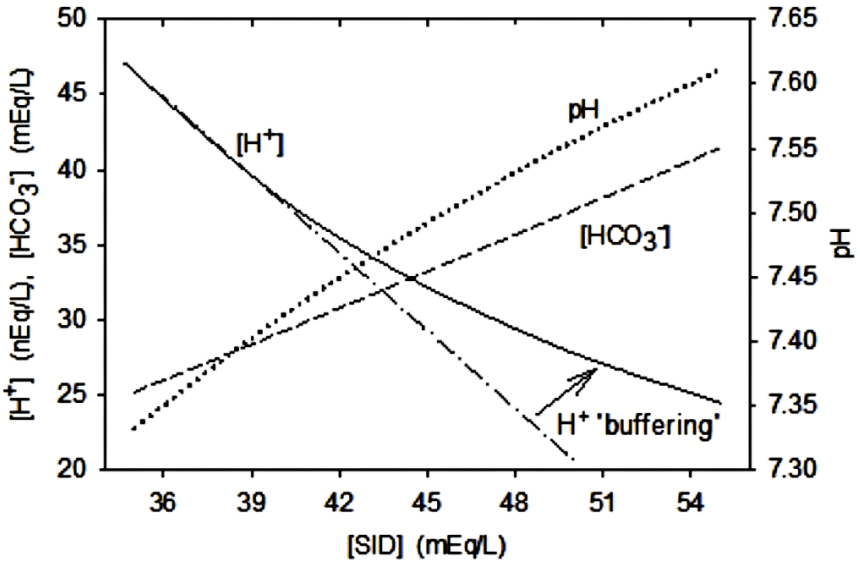


Figure 9-12 Relationships showing the dependence of plasma pH, $[H^+]$, and $[HCO_3^-]$ on plasma [SID] when PCO_2 is held constant at 40 mm Hg and [Atot] is held constant at 16 mEqL-1. Note the decreasing slope in the [SID] : $[H^+]$ relationship with increasing [SID], indicating increased ability to remove ('buffer') H^+ from solution. For comparison, the dashed – dotted line extrapolates a linear decrease in $[H^+]$ with increasing [SID]; increasing [SID] from 39 to 45 mEq · L-1 has the effect of 'buffering' ~3 nEq · L-1 of H^+.

The physico-chemical approach is capable of quantitatively assessing acid-base balance in a variety of normal and pathophysiological conditions. Physico-chemical characteristics refer to those properties and reactions that are physical and chemical in nature; they are capable of proceeding in the absence of enzymes and life, and occur as a result of the physical and chemical properties of the solvent and solute molecules (although they are facilitated in vivo by numerous enzymes). Accordingly, the physical and chemical mass action laws governing the reactions between molecules within aqueous solutions must be obeyed. These are:

- the law of conservation of mass (the mass of atoms is conserved as molecules undergo physical and biochemical reactions);
- there is a dynamic equilibrium state between water and weak electrolytes, as defined by their equilibrium constants; and
- the law of electroneutrality of solutions (any solution is comprised of molecules that in total have an equal number of positive and negative charges).

The maintenance of electroneutrality refers to the fact that aqueous solutions are always electrically neutral, that is, the sum of all negatively charged ion concentrations equals the sum of all positively charged ion concentrations: – + [weak base cations] – [weak acid anions] + $[H^+]$ – $[HO^-]$ = 0 **equation 9-5**

From this equation we can separate out the contributions from strong ions. The difference between the sums of the concentrations of strong cations (positively charged) and anions (negatively charged) is termed the strong ion difference, or **[**SID**]**, where the square brackets denote concentration units.

[SID] = – **equation 9-6**

The main weak ions in plasma is inorganic phosphate and the protein albumin. The total concentration of weak acids in solutions is denoted as **[**Atot**]**.

With this background, we can see that the acid-base state of a solution can be described in terms of the PCO_2, the **[**SID**]** and the **[**Atot**]**. The 5 equations describing mass action and one equation describing maintenance of electroneutrality are thus:

Water dissociation:

$K_w = [H^+] [^-OH]$ **equation 9-7a**

Weak electrolyte system:

$K_A [HA] = [H^+] [A^-]$ **equation 9-7b**

$[A_{tot}] = [HA] + [A^-]$ **equation 9-7c**

Carbon dioxide system:

$K_cPCO_2 = [H^+] [HCO_3^-]$ **equation 9-7d**

$K_3 [HCO_3^-] = [H^+] [CO_3^{2-}]$ **equation 9-7e**

Electrical neutrality:

[SID] + $[H^+]$ – $[HCO_3^-]$ – $[A^-]$ – $[CO_3^{2-}]$ – $[^-OH] = 0$. **equation 9-8**

It is noteworthy that $[H^+]$ appears in each of these equations and its dependence on the concentrations of strong and weak acids/base and CO_2 is evident. These six equations can be combined into a single equation that may then be solved for $[H^+]$:

$[H^+]^4 + \{K_A = [SID]\} [H^+]^3 = \{K_A ([SID] - [A_{tot}]) - (K_CPCO_2 + K'_w)\} . [H^+]^2 - \{K_A (K_C PCO_2 + K'_w) + K_3 K_C PCO_2\} [H^+] - K_A K_3 K_CPCO_2 = 0$

Values for the constants depend on the solution being assessed and can be found in Lindinger and Heigenhauser, 2012. This equation, and variations of it, can be solved using available software (acidbase.org).

Acid-base Summary

The independent acid-base variables are **[**SID**],** **[**Atot**]**, and PCO_2.

The dependent acid-base variables are $[H^+]$, pH, $[OH^-]$, and $[HCO_3^-]$.

The following are changes in independent variables that contribute to acidosis:

- decrease in [SID]; (decrease in $[Na^+]$, increase in $[lactate^-]$, increase in $[Cl^-]$)
- increase in [Atot]; (dehydration)
- increase in PCO_2; hypoventilation

The following are changes in independent variables that contribute to alkalosis:

- increased in [SID]**;** (increase in $[Na^+]$, decrease in $[lactate^-]$, decrease in $[Cl^-]$)

- decrease in [Atot]; dilution of plasma – excessive fluid intake
- decrease in PCO_2; hyperventilation

Disturbances to Acid-Base Balance: Prolonged Endurance Exercise

The 'theoretical' concepts of acid-base balance described above can be applied to any physiological situation, including exercise, as shown in Figure 9-13.

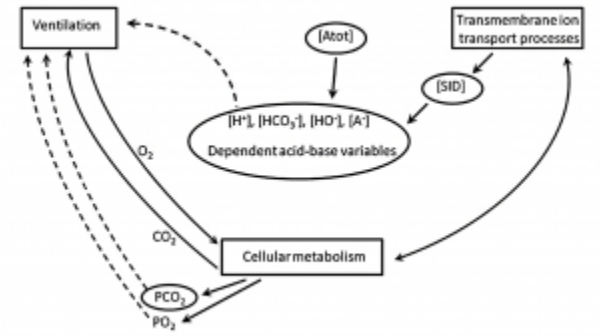


Figure 9-13 Interrelationships between ventilation, acid-base variables, and cellular processes. The dashed arrows indicate pathways through peripheral and central chemoreceptors that drive ventilation according to the acid-base status of the individual. Fluid shifts due to exercise, and fluid changes due to sweating are represented by changes in [Atot] and in ion transport processes.

Using the example of the ultra-endurance exercise described above, our runner (BJ) lost 7 L of fluid through sweating and urine production and had replaced 4 L of this by drinking water. Analysis of a blood sample showed a mild acidosis that one may attribute to the fact that the person was exercising. This would be an error, however, as endurance exercise is seldom associated with a plasma acidosis because plasma [lactate] remains low, PCO_2 normal, and [Atot] reflects the balance between sweating and water drinking.

Our runner had hyponatremia with a plasma [Na^+] of 130 mmol · L^{-1}, 10 mmol · L^{-1} lower than normal. Plasma [Cl^-] would decrease too, but not as much (let's say by 5 mmol · L^{-1}) because of partial replacement from intracellular fluids. The result would therefore be a decrease in the **[**SID**]** of 5 mmolL^{-1}, because changes in the concentrations of the other ions are very small and the positive and negative charges cancel out. The decrease in [SID] has an acidifying effect and therefore contributes to an increase in [H^+] (decrease in pH). The effect of decreasing [SID] by 5 mmol · L^{-1} increased [H^+] from a normal resting value of 40 mmol · L^{-1} (= 7.40) to 48.2 nmol · L^{-1} (pH = 7.32).

While drinking water also diluted plasma protein concentrations, the sweating-induced dehydration had resulted in increased plasma [protein]. Therefore, the water consumption would bring the increased plasma **[**Atot**]** close to normal. Thus, there would be minimal contribution of [Atot] to plasma acid-base balance.

The effects of the hyponatremia on ventilation, and therefore the plasma PCO_2, are probably minor. Severe hypernatremia causes respiratory depression and affected individuals would thus under-ventilate, which would increase $_{PCO_2}$ which, in turn, would contribute to an increase in plasma [H^+]. This runner's ventilation was unaffected, and $_{PCO_2}$ was normal with therefore no contribution to the altered acid-base state.

In summary, with the water-drinking-induced hyponatremia**,** a decrease in plasma [Na^+] of 10 mmol · L^{-1} and plasma [Cl^-] of 5 mmol · L^{-1} contributed to a decrease in [SID] of 5 mmol · L^{-1}. This decrease in [SID] increased plasma [H^+] from 40 to 48 nmol · L^{-1} (decrease from 7.40 to 7.32). The mild acid-base disturbance could have been prevented by drinking a balanced electrolyte solution during the period of exercise.

Disturbances to Acid-Base Balance: Short Term, High Intensity Exercise



Photo 9-4 Short, sprint-based events lead to an accumulation of lactate and leads to acidosis.

It is well known that short term, high intensity exercise results in an acidosis within contracting skeletal muscle and in blood. There is evidence that the acidosis, once thought to contribute to but does not, plays beneficial roles in maintaining muscle excitability and contractility during contractionin vivo (see Chapter 13). It is also widely believed, erroneously, that the accumulation of lactate within contracting muscle and in blood is a major contributor to the acidosis and to fatigue. In this section we will use the physico-chemical principles outlined above to show that the acidosis of exercise is multifactorial both in muscle and in blood (Figure 9-14).

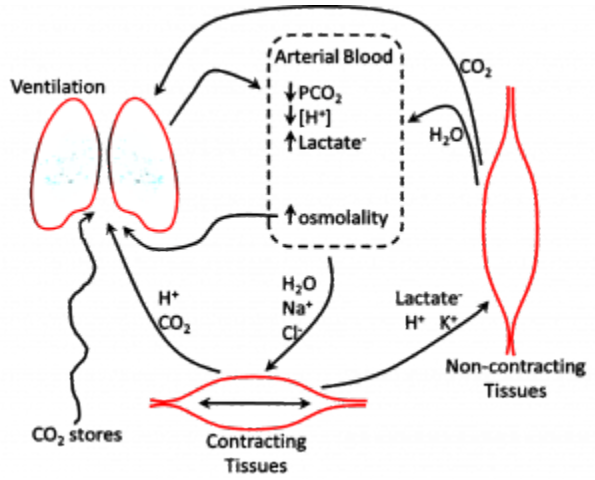


Figure 9-14 Schematic of whole body acid-base interactions during high intensity exercise.

For our example we will use a subject that is performing 30 seconds of a very high intensity leg bicycling exercise. The intensity is similar to what would be experienced with a 30 s sprint running uphill on a 15% slope. Energy for muscular ATP production is initially coming from the breakdown of PCr^{2-} and, over the 30 s period, there are increasing contributions of glycolytic and also aerobic ATP production. As stated above, PCr^{2-} is considered a strong acid anion in muscle so its hydrolysis results in a decrease in [PCr^{2-}] and hence contributes to a decrease in muscle **[**SID**]** and therefore a decrease in muscle [H^+] (i.e. an alkalinizing effect). This reflects what has been measured in muscle during the first 10-15 s of high intensity exercise.

Changes in Independent Variables and [H+] Within Contracting Muscle

In order to determine changes occurring within muscle during 30 s of high intensity exercise a muscle biopsy and blood samples

from the femoral and radial arterial were obtained within the first 30 s of recovery (Kowalchuk et al., 1988a; 1988b). Muscle **[**SID**]** decreased by 50 mmol · L^{-1} due mainly to the increase in [lactate$^-$] and decrease in [K^+] (Figure 9-15, Table 9-4); the decrease in [SID] directly contributed 61% to the increase in [H^+]. A measured femoral venous plasma PCO_2 of 96 mm Hg indicates that muscle PCO_2 was at least 100 mm Hg; this contributed 13% to the increase in [H^+]. Muscle **[**Atot**]** also increased due to the accumulation of weak acid metabolites; it can be calculated that the increase in [Atot] directly contributed 26% to the increase in muscle [H^+]. Thus, the increase in muscle [lactate$^-$] contributed not more than 50% to the muscle acidosis of high intensity exercise.

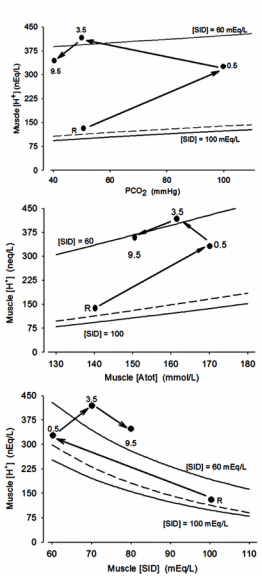


Figure 9-15 The relationships between muscle [H^+] and each of the independent variables PCO_2, [Atot], and [SID] in response to 30 s of very high intensity exercise and subsequent 9.5 minutes of recovery. The time course of change is indicated by the arrows. = resting; 0.5 = 0.5 minutes of recovery; 3.5 = 3.5 minutes of recovery; 9.5 = 9.5 minutes of recovery. The solid lines indicate [H^+] isopleths at resting [SID] of 100 mEq · L^{-1} (with KA of 1.64 10-7 Eq · L-1) and [SID] of 60 mEq · L^{-1} which occurred at 3.5 min of recovery (with Ka of 1.98 10-7 Eq · L^{-1}. The dashed line indicates the resting [H^+] isopleth but using the exercise KA of 1.98 x 10-7 Eq · L^{-1}.

Table 9-4 Independent and Dependent Acid-base Variables at Rest and After 30 Seconds of Very High Intensity Leg Bicycling Exercise in Arterial Plasma and Skeletal Muscle

Dependent variables	**Arterial plasma**		**Skeletal muscle**	
	rest	**exercise**	**rest**	**exercise**
[H^+] nanoEq · L^{-1}	40	49	100	170
pH	7.40	7.31	7.0	6.77
[HCO_3^-] mEq · L^{-1}	28	19	10	3
Independent variables	**rest**	**exercise**	**rest**	**exercise**

Dependent variables	Arterial plasma		Skeletal muscle	
PCO_2 mm Hg	40	37	45	110
[SID] mEq · L^{-1}	40	35	110	60
[Atot] mEq · L^{-1}	12	15	140	170
Strong Ions				
[Na^+] mEq ·L^{-1}	140	146	15	40
[K^+] mEq · L^{-1}	3.7	5.5	140	110
[Cl^-] mEq · L^{-1}	105	110	10	20
[$lactate^-$] mEq · L^{-1}	1.0	10	1.5	45
[PCr^{2-}] mEq · L^{-1}	na	na	15	5

Source: Data from Lindinger & Heigenhauser, 2012; Stickland et al., 2012.

Changes in Independent Variables and [H^+] Within Arterial Plasma

Arterial plasma is a reflection of numerous ion, metabolite, and gas exchange processes that occur between extracellular fluids and cells, including those of the lungs and non-contracting tissues (Figure 9-16). Arterial plasma thus has a very different composition than that of venous plasma, draining contracting skeletal muscle and draining non-contracting tissues (Figure 9-17). Arterial plasma thus has a different acid-base state than that of femoral venous plasma and antecubital venous plasma. Because arterial blood is blood that has returned from the lungs and not yet perfused tissues, it has been re-oxygenated and important for acid-base regulation, the CO_2 has been removed. The PCO_2 of arterial plasma is typically lower with high intensity exercise than at rest due to the hyperventilation of exercise; this demonstrates how well the lungs eliminate excess CO_2 arising from high rates of aerobic production within contracting muscles. The lower PCO_2 at the end of 30 s of very high intensity exercise contributed 4 nmol·L^{-1} to a lowering of [H^+]. In this example, arterial plasma [$lactate^-$] is 10 mmol·L^{-1}, less than in femoral venous plasma (13 mmol·L^{-1}) due to diffusion of $lactate^-$ into red blood cells and other tissues. The simultaneous changes in plasma strong ion concentrations results in a **[**SID**]** that is decreased by 5 mmol·L^{-1}, which contributed 8 nmol·L^{-1} to the increase in [H^+]. An osmotic fluid shift from plasma into contracting muscle results in an increase in plasma **[**Atot**]**, which contribute 5 nmol·L^{-1} to the increase in [H^+]. The net effect of CO_2 (- 4 nmol·L^{-1}), [SID] (+8 nmol·L^{-1}) and [Atot] (+5 nmol·L^{-1}) was 9 nmol·L^{-1}.

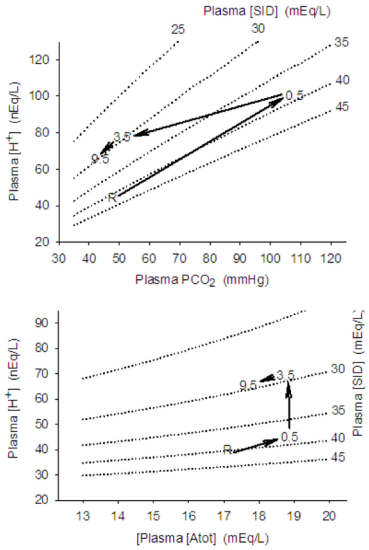


Figure 9-16 Plasma [H^+] as functions of PCO_2 and [SID] (top) and [Atot] and [SID] (bottom). The arrows show the time course of change going from rest (R) to 0.5 min after 30 s of very high intensity exercise, then to 3.5 and 9.5 minutes of recovery. Data from Kowalchuk et al., 1988b.

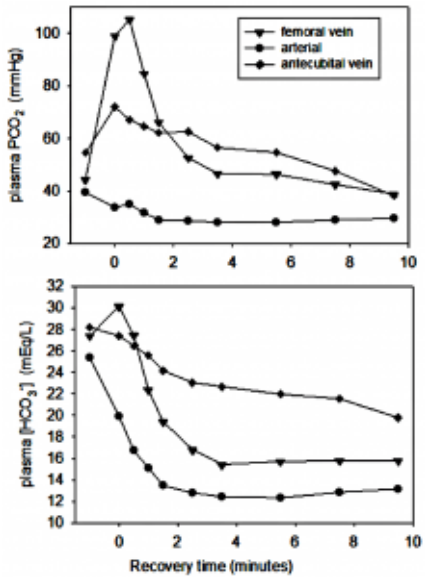


Figure 9-17 Time course of plasma [H^+] (top panel), PCO_2 (middle panel), and [HCO_3^-] (bottom panel) in humans that performed 30 s of very high intensity leg bicycling exercise. Data from Kowalchuk et al., 1988a, 1988b.

Summary

We used examples of prolonged, low intensity exercise and of short-term high intensity exercise to show that the factors contributing to acid-base state are multifactorial. We also showed that the contributions from each of the independent acid-base variables can be determined, and that the contributions differ depending on the intensity and duration of exercise. With prolonged, low intensity exercise, dehydration and excessive water ingestion result in altered plasma water and electrolyte balance, and hence acid-base balance. The fluids ingested prior to, during, and after exercise of this type should be balanced fluids with respect to water and electrolyte contents. This will not only reduce acid-base disturbances, but facilitate maintenance of hydration and thermoregulation. With short-term high intensity exercise the increase in muscle and plasma [$lactate^-$] contributed at best to about 50% of the acidosis. The muscle acidosis of exercise also has important contributions from decreased muscle [K^+], increased PCO_2 and increased **[**Atot**]**. The arterial plasma acidosis of exercise has its main contributions from decreased **[**SID**]** associated with increased [$lactate^-$] and from increased [Atot]**.**

Exercises or Topics for Discussion

- Read the labels for four different electrolyte products (from the store or from websites) and tabulate the concentrations of ingredients so that you can easily compare the composition of the different products.
- Which product would you use and recommend as the most effective product to replace fluid (water and electrolyte) losses due to sweating?
- Provide a few good reasons for your answer.

- For each, water and Gatorade, estimate the plasma ion concentrations after 4 hours of exercise using the parameters provided in the case presentation. Refer to Table 9.1 to guide you in your calculations.
- How would running in the rain influence BJ's ability to dissipate heat when running for an hour in warm conditions?
- In the first scenario describing BJ running for 4 hours and drinking only water, describe the effect of combined sweating and drinking water on plasma [Atot] and [SID]. Based on the change in each of these two independent variables, state the direction of change in $[H^+]$ and $[HCO_3^-]$.

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Michael Lindinger is classically educated in comparative animal physiology and has strong research interests in exercise physiology (Jones, Heigenhauser, Sutton group at McMaster University), skeletal muscle physiology with focus on water and electrolyte balance, muscle biochemistry and whole body fluid balance, hydration and thermoregulation. More recent interests include the effects of nutraceutical ingredients on joint health and muscle performance. After a 25-year career as a professor at the University of Guelph he left in 2013 to own and operate an equine research farm and The Nutraceutical Alliance with Dr. Wendy Pearson. He currently owns and is president of The Nutraceutical Alliance in which role he helps clients design effective, science-based nutraceutical supplements, and designs and implements research projects. He continues to be active in research and publishing. He presently serves on the editorial board of several scientific journals including the European Journal of Applied Physiology, Scientifica Physiology, and Animals.

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1. Data from Lara et al., 2016; Ely et al., 2013; Baker et al., 2011 ↵
2. Data from Baker and Jeukendrup, 2014; Proactive Nutrition (proactivenutrition.net) ↵

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2.8: Chapter 10 - Measuring Metabolic Rates and Capacities

This chapter is in preparation.

Authors are: Brian R. MacIntosh

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2.9: Chapter 11 - Nutrition and Energy Balance in Active People



Photo 11-1 Fruits and Vegetables. photo by Brian R. MacIntosh

Learning Objectives

After reading this chapter, you should:

- Identify the three macronutrients and describe their function, requirements, and roles in energy metabolism.
- Identify each of the fat-soluble and water-soluble vitamins and list one major function for each.
- Argue for or against supplementation above the RDA with vitamin or mineral supplements for a physically active population.
- Define energy balance and describe how this relates to energy requirements in the context of physical activity and athletic performance.
- Identify specific fluid and nutrient requirements for endurance and strength/ training. Include pre-event, during event, and post-event needs.
- Develop a dietary strategy for an athlete competing in a marathon (42.2 km road race). Include pre-race, race, and post-race fluid and energy requirements.

Key Terms

acceptable macronutrient distribution range (AMDR), adequate intake (AI), amenorrhea, amino acids, antioxidant, blood glucose, caloric equivalent, carbohydrate, protein, dehydration, dietary reference intake (DRI), electrolyte, energy balance, energy availability, ergogenic aid, essential nutrient, fat, triad, free radical, glycemic index (GI), glycogen, hyponatremia, kilocalorie (kcal), macronutrient, mineral, non-essential nutrient, nutrition periodization, osteopenia, osteoporosis, phytochemical, postprandial, protein, recommended dietary allowances (RDA), resting metabolic rate (RMR), sports drink, sweat rate, thermic effect of food (TEF), tolerable upper limit (UL), vitamin, water balance

Case Presentation

Multi-Stage Events: Highlighting Nutritional Needs for Cyclists in the Tour de France

The Tour de France is one of the most challenging cycling races in the world. It began in 1903 by a sport newspaper called L'Auto and has increased in popularity ever since. In July of every year, athletes pedal 3500 km through France and neighbouring European countries, competing to win the yellow jersey. Over three weeks, these athletes race 21 different stages, ranging from shorter time-trial to gruelling hill climbing days. On the longer days, competitors will cycle for more than 200 km over high mountain passes. All of this with only two days of rest!



Photo 11-1 – A rider training on a time-trial bike, which are used commonly by athletes in the Tour de France on time-trial stages. Such bikes are worth more than 2 years of tuition. https://pixabay.com/en/workout-racing-bike-bicycle-bike-713658/

The difference between winning and losing is measured in seconds, and proper nutrition and hydration can make or break the race (Saris, van Erp-Baart et al., 1989). These athletes need to consume thousands of kilocalories (kcal) each day and drink enough to replenish fluids and electrolytes; all while riding a bike for hours. Once the current day's stage is completed, they need to recover and prepare for the next day. Chris is an international level cyclist who is competing in the Tour de France for the first time. Let us follow Chris as he prepares for and completes today's ride and recovers for tomorrow.

The Importance of Nutrition for Physical Performance

One of the most important nutritional considerations for athletes is their energy needs. All of the body's energy for physical activity comes from the macronutrients: carbohydrates, fat, and protein. Athletes in the Tour will need between 6000 and 7000 per day. Chris knows that if he doesn't consume enough carbohydrates his blood glucose levels will drop. When this happened to him in the past, he felt dizzy, confused, irritable, and tired and couldn't finish his race. Athletes often call this bonking. Chris is also aware that he has to match his water and electrolyte intake with his sweat rate. In a previous race, he did not hydrate properly and became dehydrated. Consequently, he had a very poor performance and developed heat exhaustion. We will discuss all of the nutrients required for physical performance later in the chapter but let's take a look at Chris' needs right now.

Pre-Event

Chris' goal with his pre-event nutrition is to optimize his body's carbohydrate and fluid levels to ensure that he has enough energy to finish the race and avoid dehydration. He also wants to make sure that the food he eats is easily digestible and familiar to him. He doesn't want to end up with stomach cramps or digestive distress from trying all sort of new local cuisine. In previous training sessions, he developed routines for his meals and has tested everything to make sure it works for him. This is not the time to experiment with deep-fried frog legs!

Pre-Event Energy and Fluid Intakes

Chris knows that he needs to maximize glycogen, the body's carbohydrate stores, at every opportunity. Three hours before the start of today's stage, Chris will eat a full meal that is high in carbohydrates and contains some protein. About an hour before the race starts, he is also going to have a pre-race snack including some carbohydrates and fluids. Meal timing is very important, if he waits too long, he won't have enough energy for the race, but if he eats too close to the start time, all of that undigested food could cause an upset stomach.

Chris has checked the weather forecast and knows that the temperature on the course tomorrow will range from 20-30°C. He has also looked at the racecourse and estimates that it will take him 5 hours to finish. He has been drinking water and sports drinks as often as he can since he finished riding yesterday and has been adding extra salt to his meals. He's making sure that he is well hydrated prior to starting the race and can confirm his hydration status by checking that his urine is pale yellow and voluminous.

During Event

Nutritional intakes during a long-distance endurance event are extremely important. Even with the best pre-event nutrition, it is not possible to exercise for hours without giving your body some additional carbohydrates and fluids. Chris has carefully prepared all of the food and fluids that he will be able to pick up along the way. Chris will try to match his fluid intakes with his sweat rate, however, knows this can be challenging, so is aiming to avoid losing greater than 2% body weight. Additionally, he will consume up to 90g carbohydrate per hour of endurance exercise. Including some protein in combination with his carbohydrate intake may also be beneficial. Therefore, Chris will consume a maximum of 450 g of carbohydrate (1800 kcal) during the event.

During Event Energy and Fluid Intakes

While racing, Chris will have a sports drink that provides him with water, electrolytes, and contains 6-8% carbohydrates. During the race, Chris will alternate between drinking water and a sports drink. Liquid forms of energy digest quickly and easily and will provide him with immediate energy. The carbohydrates and electrolytes in the sports drink will also help his body absorb the water more effectively. He will also eat some easily digestible solid foods containing some protein or sports gels and wash them down with plenty of water. In multi-day events, it is especially important to consume carbohydrates during exercise, as your body stores are continually being depleted as you compete.

Post Event

After today's sprint to the finish, Chris knows that no matter how tired he is he must start thinking about tomorrow's stage. He has a small window of opportunity to maximize his recovery. Exercise increases sensitivity and depletes muscle glycogen, which means after exercise Chris will be better able to refuel his muscles. He can use the increased insulin sensitivity to maximize glucose and amino acid delivery to the muscles, helping replenish the muscles' energy and aiding in rebuilding of the tissue. He should be sure to consume lots of carbohydrates and some protein in the 4 hours after exercise to maximize this effect. After that, the second phase of recovery begins and he should be sure to eat a healthy meal high in carbohydrates with protein. If he does not follow this recovery plan, he will not be able to optimize glycogen re-synthesis and give his body the protein it needs to build and repair muscles.

Post Event Energy and Fluid Intakes

Immediately after his race, Chris is going to have some fluid, carbohydrates, and protein in the form of a recovery drink. In the next couple of hours, he is also going to eat a full meal that is high in carbohydrates and contains protein.

Chris has been drinking throughout the day but knows that with a long ride, in the heat, he has likely not replaced all of the fluid and electrolytes he's lost. After his race, he is going to weigh himself and compare with his prerace weight to determine how much body water he has lost. He will continue to drink until he has made up the lost water weight. He will also consume some sports drinks or electrolyte drinks and salty foods to replace his electrolytes.

This case study has provided a general overview of nutrition and meal timing for athletes engaged in multi-day endurance events. In this chapter, we will go into much more detail and provide specific guidelines for athletes and individuals who are physically active.

Introduction

Since the beginning of competitive sports, athletes have recognized the relationship between nutrition and performance. Dating as far back as the ancient Olympics, there are numerous accounts of athletes consuming foods and beverages to specifically improve their performance. Milo of Croton, a great wrestler who won his events at 5 consecutive Olympics (532-526BC), was said to eat 20 pounds of meat, 20 pounds of bread, and 18 pints of wine *per day*! Although the validity of this is questionable (~55,000 kilocalories per day!), it highlights the long-standing and ever-changing fascination with nutrition and athletic performance. More recent examples of athletes' use of nutrition to improve performance are plentiful. In more modern Olympic times (early 1900s), there is documented evidence of the consumption of 22 glasses of beer and a half bottle of wine by a German 100km walker during his race. Reports of marathon runners who consumed cognac, prior to and during their event, seem bizarre in the context of our modern-day sport nutrition principles! Although slightly different in nature, there are many familiar examples of current nutritional practices for improved performance. Fitness enthusiasts and athletes alike consume various whole foods and natural health products in an attempt to optimize wellness and performance. Examples of current popular nutritional ergogenic aids include creatine, antioxidants, caffeine, fish oils, and consumption of protein drinks (Grandjean, 1997).

Throughout history, the number of anecdotal and in some cases factual examples of nutritional practices intended to boost performance has been plentiful. Given the barrage of advertisements and 'free advice' given to athletes, it can be challenging to confidently identify the best dietary choices for improving performance. Importantly, the science of sport nutrition has grown tremendously in recent decades and recommendations based on scientific evidence can now be provided to athletes – both professional and amateur. This chapter will emphasize evidence based nutritional guidelines and best practices for both physically active populations and athletes to help them reach their full athletic potential.

The purpose of this chapter is to introduce the field of nutrition in relation to healthy active living and peak sports performance. Herein we will briefly describe the physical activity-specific role of carbohydrates, protein, water, vitamins, and minerals and then highlight special nutritional requirements for active living and optimal athletic performance. This chapter has been split into two defined sections. The first section will provide foundational information about nutrition and discuss nutrition in the context of 'healthy active living' for the fitness enthusiast. The second half of the chapter will be geared towards the competitive amateur to professional athlete and provide specific guidelines for nutritional practices that optimize performance.



Photo 11-2 – A daily pill that contains vitamins and minerals that may be missing from one's diet. Image by Steve Buissinne from Pixabay

The Nutrients: Fuel for Performance

The foods and beverages that we consume are composed of six categories of nutrients that are critical for life that include carbohydrates, protein, vitamins, and minerals, and water. These are classified as essential nutrients and we cannot survive without adequate consumption of each category. The six essential nutrients provide us with energy; allow for growth and development; maintenance of body homeostasis; prevention of disease; as well as many other critical bodily functions. In the context of physical activity and athletic performance, essential nutrients provide the energy and chemicals to promote optimal physical functioning as well as appropriate adaptation to training.

In the human body, we have many varied sources of energy for physical activity. Carbohydrate energy is largely in the form of blood glucose and liver and muscle glycogen; a large reserve of stored energy in the form of fat is found in adipose tissue and intramuscular fat; and while we would prefer not to use body protein for energy, certain amino acids can be converted to glucose when needed and thereby provide energy for exercise. Understanding the macronutrient composition of our foods is critical in understanding how dietary energy is used and converted to physical energy. Following digestion, absorption, and assimilation of nutrients, we convert carbohydrates, protein, and fat into a usable form of energy – adenosine triphosphate (ATP) – via various metabolic pathways. We have two primary energy systems that allow us to perform work: the anaerobic system and the aerobic system. While both systems are typically active simultaneously, the intensity and duration of the exercise, the fitness level of the individual, and the environmental temperature will influence which system preferentially supplies the majority of fuel and the mixture of substrates that will be used. The immediate, short-term and long-term energy systems and the fuels required are described below.

Energy Systems and Nutrient Use

The direct role that specialized nutrition plays in modifying theATP –creatine phosphate system (ATP-CP), also known as the immediate energy system, is likely small. The best way to increase available ATP from the ATP-CP system is likely via a power-specific training program and adequate overall nutrition. However, a popular dietary supplement, creatine has been demonstrated to improve repeated sprint performance.

The other energy systems: glycolysis, tricarboxylic acid cycle (TCA), and the electron transport chain (ETC) all require adequate nutrition for production. In order for glycolysis to occur, adequate carbohydrates (blood glucose and muscle glycogen) must be available. Glucose can be degraded to pyruvate and then acetyl CoA which is a frequently-used substrate for the TCA. Acetyl CoA, the starting substrate for the TCA, can also be generated from fat and protein (Figure 11-1). Protein is broken down into amino acids, deaminated or transaminated, and then the remaining keto-acid enters the TCA. Likewise, fatty acids are broken down into two carbon units via beta oxidation, and enter the TCA. Consequently, the TCA is a highly integrative pathway that incorporates all substrates (carbohydrates, protein, and fat) to produce usable ATP. In addition to macronutrients, the TCA requires vitamins, and minerals to function adequately. Certain micronutrients, including the B-vitamins, magnesium (Mg^{2+}), and iron (Fe^{+}) are critical in the production of ATP (Figure 11-1).

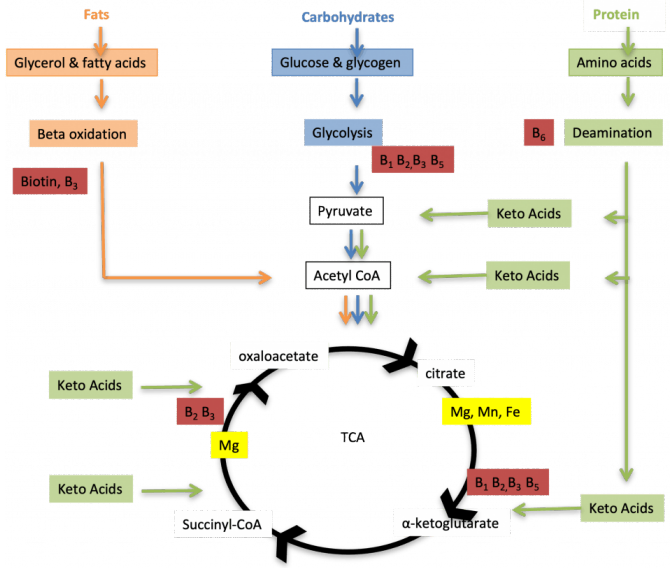


Figure 11-1 The assimilation of macro and micronutrients in energy transduction. Carbohydrates, protein and fat have separate pathways for production of ATP. Vitamins and minerals are also essential for energy production.

How the Energy Systems Work Together

As an individual begins to exercise, all three energy systems begin replacing ATP-CP (immediate), glycolysis, leading to the formation of lactate (short-term energy system), and aerobic metabolism (long-term energy system). These systems are described further in Chapter 6. As exercise continues, there is an increase in breathing and heart rate, supporting the increase in aerobic metabolism. At lower intensities of physical activity, when the duration of exercise is prolonged, the preferential fuel for the

TCA is fat. The complete oxidation of, for example a common fatty acid, palmitic acid will yield 106 ATP (Darvey, 1998). The potential energy from each substrate can also be expressed as the caloric equivalent, which for fat is ~4.65 kcal· L^{-1} of oxygen and represents the energy available per litre of oxygen consumed. As the intensity of exercise increases, the body uses a greater proportion of carbohydrates. The complete oxidation of glucose to carbon dioxide and water yields 30 to 36 ATP depending on the shuttle used to oxidize NADH. The potential energy from carbohydrates expressed as a caloric equivalent is ~5 kcal · L^{-1} of oxygen consumed. While there is not a great deal of variation between the substrates, the caloric equivalent values do indicate that carbohydrate is the most efficient in the use of oxygen to provide energy. In summary, a physically active individual requires a calorically adequate and balanced diet to fuel activity and to achieve optimum athletic performance. Specific macronutrient and micronutrient requirements are provided in the subsequent sections.

Macronutrients

Carbohydrates, protein, and are the three essential, energy-providing macronutrients. These macronutrients provide energy in the form of a kilocalorie (kcal**)**. A is a measurement of food energy and is equivalent to the amount of heat required to increase the temperature of 1 kg of water by 1°C. We must consume a certain amount of kcal from a combination of these macronutrients to ensure adequate overall energy for physical activity and for optimal athletic performance. Energy needs of individuals vary greatly and depend on sex, age, physical activity levels, body composition, height, and genetics. Over consumption or under consumption of any macronutrient can be detrimental to wellness and performance. Moreover, it is important to consider the type of each macronutrient that is consumed, as there are various qualities of carbohydrates, protein, and fat that can invariably influence health and athletic capability. The following section will examine each macronutrient and how consumption can influence physical activity and optimum sports performance. The recommendations for physically active individuals will be provided first while the specific nutritional recommendations for peak athletic performance will be addressed during the second half of the chapter.

What are you Eating?

Food labels are an excellent way to determine the nutrients you are consuming (Figure 11-2). In Canada, all foods and beverages, excluding fresh meats and produce, must contain information on a defined set of nutrients (Canada, 2018). Many different dietary patterns can provide the energy and nutrients an individual needs for health and performance. One option is *Canada's Food Guide* (CFG), which provides guidance on food choices for all Canadians and can easily be adapted for physically active and athletic populations. Another more detailed method of determining what you are eating is to use dietary analysis software. There are many software programs available that allow you to enter the foods and beverages you consume and determine the nutritional breakdown. The Dietitians of Canada provide a free program at eaTracker.ca that is useful in personal dietary assessments.

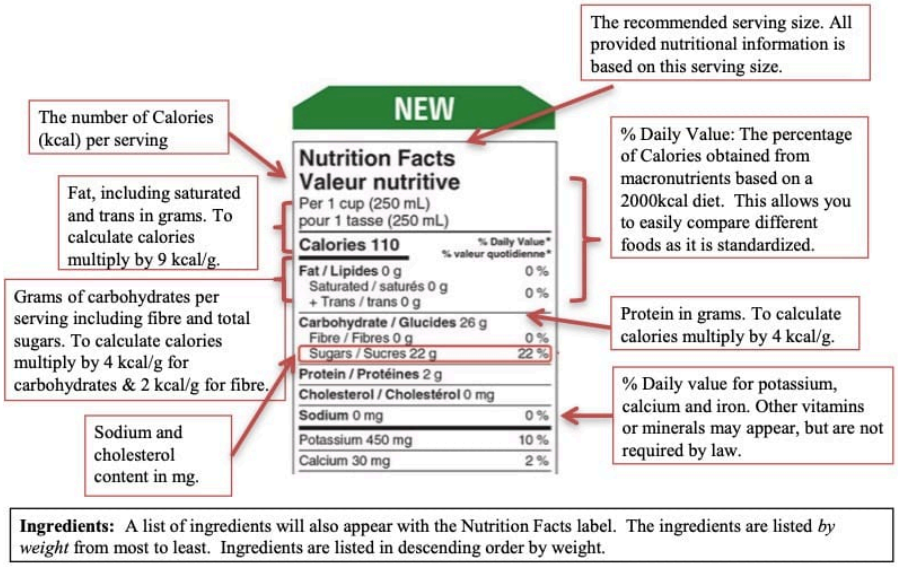


Figure 11-2 How to interpret a food label. A food label contains a 'Nutrition Facts Panel' and the ingredient list. This provides the consumer information about the product. It allows you to understand what you are eating and to learn more about your dietary choices. For more information, refer to Health Canada at www.hc-sc.gc.ca.

Carbohydrates

Dietary carbohydrates, (4 kcal/g) are the primary source of fuel for most people – both sedentary and active. The average Canadian consumes approximately 50% of their energy in the form of carbohydrates (Canada, 2017). The acceptable macronutrient distribution range (AMDR) represents a range of intakes that are associated with reduced risk of chronic disease while providing all theessential nutrients. For carbohydrates, this acceptable range is 45-65% of total dailycalories. Adequate intake of carbohydrates is critical for both health and optimal performance because of their key role in meeting energy requirements, protein sparing, and for fueling the central nervous system. Rich sources of carbohydrates include grains, starchy vegetables, legumes, juices, fruits, and sports drinks. Dietary fibre, an indigestible form of carbohydrate is also required in an amount of 38 g · d^{-1} for males aged 19-50 and 25 g· d^{-1} for females aged 19-50 years. In addition to promoting digestive system function, consuming adequate fibre has also been shown to help prevent certain chronic diseases such as type 2 diabetes and cardiovascular diseases (Slavin, 2013).

Carbohydrates can be divided into two categories, based on chemical structure: simple and complex. Simple carbohydrates come in two forms: monosaccharides (glucose, fructose, and galactose) and disaccharides (sucrose, maltose and lactose), whereas a complex carbohydrate is a polysaccharide [polymer of >2 carbohydrate molecules (starch and dietary fibre)]. Dietary carbohydrates are a key energy source for physical activity. When we consume carbohydrates – either simple or complex – digestive enzymes in the mouth, stomach, and small intestine break them down into absorbable monosaccharides such as glucose and fructose. Monosaccharides cross the intestinal wall and are transported to the liver via the hepatic portal system. Once at the liver, monosaccharides other than glucose are converted to glucose. Then glucose is either stored as glycogen or released into the systemic blood circulation. This causes a rise in blood glucose that will gradually decrease back to baseline levels as working tissues such as the brain, kidneys, muscle, and heart utilize the glucose. To gain entry into these cells, a glucose transporter (GLUT) must transport glucose across the cell membrane. Once in the cell, glucose has one of two fats – immediate energy use or storage. In muscle, liver, and heart, glucose can be stored as glycogen or converted to fat for storage as adipose tissue. In all other tissues, excess glucose is converted to fat and stored as adipose.



Photo 11-3 – Pasta, a common source of carbohydrates. Image by PublicDomainPictures from Pixabay

Fuel for muscle contraction is particularly important for physically active individuals and athletes; therefore, we will examine the fate of glucose in a muscle cell. After a meal, circulating blood glucose enters skeletal muscle via GLUT1 or GLUT4. Once in the cell cytosol, hexokinase converts glucose to glucose-6-phosphate (G6P). G6P can either be channeled to glycolysis and TCA or be used as the starting product of glycogen synthesis. Therefore, during periods of immediate energy need (i.e. physical activity), glucose can be used for production of for muscle contraction, but in times of recovery, glucose can be stored as glycogen for future energy demands. The ability of the body to store extra glucose in the form of glycogen is important for fueling future physical activity. However, we have only finite capacity for glycogen storage and once those depots are at capacity [80g-100 g (320 kcal-400 kcal) in the form of liver glycogen and 300g-400 g (1200 kcal-1600 kcal) as muscle glycogen] extra glucose is converted to fatty acids and stored as fat if the body does not need the glucose to meet energy needs (Burke, Hawley et al., 2011). During exercise, blood flow to the muscle increases and GLUT4 translocates to the muscle surface membrane. As the exercise continues, blood glucose or the stored muscle glycogen can be utilized for production. Glycolysis and subsequent β- oxidation

represent the major fate of glucose in the muscle (Rose and Richter, 2005).

Glycemic index

Glycemic index (GI) is a tool used to classify carbohydrates according to their impact on blood glucose. The concept of was developed by a Canadian researcher and classifies foods based the rate at which postprandialblood glucose increases when compared to 50 g of glucose (Table 7.1) (Jenkins,Wolever et al., 1981). In general, 50 g portions of each test food are used to make this comparison. Foods with a high GI cause higher levels of postprandial blood glucose, whereas foods with a low GI result in lower postprandial blood glucose. Generally, foods that contain simple sugars tend to raise blood glucose more rapidly and those that contain complex carbohydrates tend to raise blood glucose more slowly due to the slower rate of digestion and absorption (Mondazzi and Arcelli, 2009, Qin,Wang et al., 2017). The GI can be important to athletes and physically active individuals because it influences both blood glucose and glycogen storage capacity. Athletes and physically active individuals can use the GI to optimize their performance. For example, during an event an athlete would want to choose a food that is high on the GI because this will immediately replace glucose that is being used for physical activity (Gretebeck, Gretebeck et al., 2002). Another example of when an athlete would want to eat a high GI food is after exercise to replace the glycogen stores in the muscle and liver. However, prior to exercise, low GI foods would be recommended to stabilize blood glucose levels (Burdon, Spronk et al., 2017, Heung-Sang Wong, Sun et al. 2017). On a day-to-day basis, however, everyone – athlete or not – should try to eat foods lower on the GI to provide their body with a stable supply of glucose and reduce their risk for chronic diseases such as type 2 diabetes.

Table 11-1 The Average GI for Some Common Foods

Food Group	Food	Glycemic index
Grains		
	Cornflakes	81
	Instant oatmeal	79
	White bread	75
	Whole wheat bread	74
	White rice	73
	Couscous	65
	Muesli	57
	Porridge (large flake rolled oats)	55
	White spaghetti	49
	Corn tortilla	46

Food Group	Food	Glycemic index
Fruits and Vegetables		
	Boiled potato	78
	Watermelon	76
	Boiled sweet potato	63
	Pineapple	59
	Banana	51
	Orange Juice	50
	Orange	43
	Boiled carrots	39
	Apple	36
Dairy and Dairy Substitutes		
	Rice milk	86
	Ice cream	51
	Fruit yogurt	41
	Skim milk	37
	Soy milk	34
Legumes and Nuts		
	Lentils	32
	Chickpeas	28

Food Group	Food	Glycemic index
	Cashew nuts	25
	Kidney beans	24
Sweeteners		
	Table sugar	65
	Honey	61
	Fructose (fruit sugar)	15
Sports Products		
	Clif Bar (Cookies and Cream)	101
	Gatorade	89
	PowerBar (Chocolate)	83
	PowerAid	65
	Cytomax	62
	Allsport	53

≤55 Low GI, 56-69 Medium GI, ≥70 High GI. Generally, grain products have the highest whereas legumes, nuts, and vegetables have lower GI. Based on Atkinson et al. (Atkinson, Foster-Powell et al., 2008) and Gretebeck et al. (Gretebeck, Gretebeck et al., 2002)

Carbohydrate Requirements for Physically Active Individuals

The timing of carbohydrate intake is critical for all physically active individuals as it influences carbohydrate fuel availability. It is important to consume carbohydrates prior to exercise to ensure adequate glycogen storage in the liver and muscles. As well, if exercise duration is over 1-2 hours, it is important to consume carbohydrates during exercise to maintain blood glucose levels and reduce fatigue. It is important to note that liver glycogen and muscle glycogen have different fates. The primary substrate responsible for maintenance of blood glucose during fasting or exercise is liver glycogen. This occurs via a series of hormonal controls that regulate release of liver glycogen into the blood to maintain normal blood glucose. In contrast, *muscle*glycogen is only used as a fuel for production in the skeletal muscle.

As you recall, the AMDR for carbohydrate is 45-65% of dailycalories, however, recommendations for athletes based on their body

weight are thought to better reflect their needs. Specifically, athletes should strive for 3-12 g of carbohydrates per kg of body weight to ensure adequate energy for training and performance. The range reflects variations in duration and intensity of activity. In general, as the intensity and duration increase there is a greater need for carbohydrates (Thomas, Erdman et al., 2016). Overall, a diet rich in carbohydrates derived from complex, unprocessed sources is most likely to improve health while still providing appropriate fuel.

Problems of Inadequate Carbohydrate Intake

A typical North American diet will provide sufficient carbohydrate to fuel moderate to high intensityphysical activity lasting up to 2 hours. However, the length of time that an athlete can perform at a given intensity is related to the size of glycogen stores and is affected by previous nutrition and exercise patterns. The point at which muscle glycogen stores are depleted during physical activity is sometimes referred to as 'hitting the wall'. When an individual hits the wall, they feel fatigued and must slow the intensity of their exercise in order to switch to a greater proportion of for fuel. If an individual continues to exercise after hitting the wall, without replenishing carbohydrates, they will eventually 'bonk'. Bonking refers to the point when both muscle and liver glycogen stores are depleted, and the athlete cannot continue with exercise. Endurance athletes may try to achieve glycogen supercompensation, maximizing glycogen storage in the muscles, by a process called carbohydrate loading. Specific carbohydrate loading protocols are outlined at the end of this chapter. As expected, carbohydrate loading is generally only applicable to activities that are longer than 2 hours. Athletes performing short, high intensity activities usually will not benefit from carbohydrate loading and may actually be hindered due to water retention. The temporary weight gain associated with carbohydrate loading is the consequence of water retention related to the storage of ~3 grams of water with each gram of glycogen.

Conclusions

In conclusion, a physically active individual requires a diet that contains 45-65% of their dailycalories fromcarbohydrates to fuel the activity. Specific carbohydrate requirements for athletes in heavy training for peak performance and competition will be discussed at the end of this chapter.

Protein

Protein intake is arguably one of the most controversial topics in sports nutrition. There has been long-standing interest in the consumption of protein for optimal performance, with many athletes believing that more is always better. The purpose of this section is to provide information about protein use in the body and include evidence-based recommendations for protein intake.



Photo 11-4 – A well-seasoned source of protein. Image by gate74 from Pixabay

Dietary proteins consist of chains of amino acids and provide 4 kcal · g^{-1} of energy. There are 20 amino acids; 9 are essential and 11 are considered nonessential**.** Nonessential amino acids can be synthesized in the body, whereas essential amino acids cannot be synthesized, so they need to be consumed. Dietary protein has many functions in the body including energy supply and production of proteins (hormones, transporters, enzymes, muscle, hair, etc.). Upon digestion and absorption, amino acids

are mainly used to build structural and functional proteins in the body but can also be metabolized for energy. The nitrogen-containing amino group is removed from the amino acid (deamination) and the remaining carbon skeleton (keto-acid) enters the TCA (Figure 11-1). Depending on the specific amino acid, they enter the TCA at various levels and result in aerobic production. As with excess carbohydrate intake, excess amino acids can be converted to and eventually get stored as adipose tissue. During rest, approximately 5% of energy is derived from protein. The magnitude of protein's contribution to energy needs during exercise depends on the intensity and duration of the activity as well as how much fuel in the form of carbohydrate and fat is available.

Protein Requirements for Physically Active Individuals

The adult AMDR for protein is 10-35% of daily energy intake or can be calculated based on body weight using a value of 0.8 grams protein per kg body weight. For example, a sedentary individual who weighs 80 kg should aim to consume 80 kg·0.8 g/kg = 64 g of protein per day. The daily dietary protein requirements of a physically active individual will vary depending on their level of physical activity and type of activity. Protein needs are increased with exercise for three primary reasons:

- increases to muscle mass following heavy strength training;
- for muscle recovery and repair;
- to compensate for protein used as energy during training when carbohydrates are limited.

As with carbohydrates, protein recommendations based on body weight are thought to best match an athlete's needs. Athletes require 1.2-2.0 g of protein · kg^{-1} body weight depending on their training and energy needs (Thomas, Erdman et al., 2016).

Dietary Sources of Protein

The quality of a protein source depends on the amino acids and digestibility. Animal sources of protein generally provide the full complement of essential amino acids and are easily digestible, thus they are classified as complete and high-quality proteins. Animal proteins include milk, eggs, meat, poultry, cheese, and fish. Protein is also available from plant-sources and includes legumes, beans, and grains. In general, plant-based proteins are considered incomplete because they do not contain sufficient quantities of one or more of the essential amino acids such as lysine, methionine, or tryptophan. Grains generally do not contain adequate lysine and legumes do not contain adequate methionine or tryptophan. If an athlete is consuming a vegetarian diet or a diet that primarily consists of only plant-based proteins, it is important to combine a grain and a legume to ensure that a complete array of amino acids is consumed. These foods are referred to as 'proteins'. For example, together chickpeas (hummus) and pita bread provide complete protein and are complementary; likewise, rice and beans, or lentil soup and bread. For a vegetarian, it is important to consume proteins over the period of a day – the sources do not need to be at a single meal. It is perfectly healthy to be a vegetarian athlete, however, care must be taken to ensure adequate intake of all essential amino acids (adequate protein) and other at-risk nutrients such as iron, zinc, vitamin B_{12}, vitamin D and calcium among others (Melina, Craig et al., 2016).

Protein and Amino acid Supplementation

The use of protein supplements (i.e. whey protein or soy protein shakes) and individual amino acids as ergogenic aids is very popular with both recreational and professional athletes. The use of protein supplements to achieve adequate amounts of protein intake is well supported, as whey and soy are both high quality proteins. However, most Canadians – both male and female – do not require protein supplementation given that protein intake as part of our whole-foods diet generally exceeds recommended amounts. Moreover, there is no evidence to suggest that a diet with excess protein is necessary or beneficial. The specific timing and intake recommendations are highlighted in the second half of this chapter. Furthermore, scientific evidence does not currently support the use of individual amino acids as ergogenic aids for athletes or fitness enthusiasts. Supplementation with single amino acids can disrupt the balance of essential amino acids and inadvertently result in deficiency (Phillips, Moore et al., 2007).

Fats

Dietary s are the most energy dense macronutrient at 9 kcal · g^{-1} and fat storage in the body provides humans with our largest reservoir of energy. As recommended by the AMDR, the optimal diet contains approximately 20-35% of energy from fats with no more than 10% from saturated fat. Dietary fats are critical for many functions including an important energy reserve, a source of energy at rest and during exercise, protection for vital organs, thermoregulation, a source and carrier of vitamins (vitamins A, D, E, and K) and other fat-soluble phytochemicals, hormone synthesis, and satiety.

Fats and oils are classified according to chemical structure and the two primary forms are unsaturated and saturated fats. Unsaturated fats are generally liquid at room temperature and often derived from plants such as canola, safflower, and olive. Unsaturated fats confer many health benefits such as reducing low-density lipoprotein (LDL) cholesterol levels when consumed as part of a balanced, low fat diet. Canadians eat diets that contain foods rich in two types of unsaturated fats: polyunsaturated (e.g. sunflower and corn oils) and monounsaturated fats (e.g. olive and canola oils). There are two essential fatty acids required by the body that are both unsaturated. Linoleic acid is an omega-6 fatty acid, which refers to the location of its double bond, whereas linolenic acid is an omega-3 fatty acid. Researchers are interested in the ratio of these fatty acids in our diets because evidence suggests that omega-3 have anti-inflammatory properties while omega-6 promote inflammation. The second major type of fat, saturated fats come primarily from animal fats and are solid at room temperature (e.g. meat, cheese, butter, coconut oil). Hydrogenation is a process that takes an unsaturated fat and converts it into a fat that is more saturated and contains '*trans* fat'. Trans fats are naturally found in some ruminant animal products but can also be manufactured industrially via hydrogenation for enhancement of food texture and shelf life. Industrial trans fats increase the risk of cardiovascular disease by increasing LDL cholesterol ("bad" cholesterol) levels and decreasing HDL cholesterol ("good" **c**holesterol) levels. For this reason, it is recommended that people avoid consuming industrial trans fats. Recommendations for consumption of total fat (20-35%), and saturated fat (<10%) are the same for all people, regardless of physical activity levels. Dietary fats are used first for physiological functions after which the excess is stored as adipose tissue.



Photo 11-5 – Butter, the secret to good baking, also a source of fat. Image by congerdesign from Pixabay

In addition to saturated and unsaturated, we consume animal products that contain dietary cholesterol. Cholesterol is not anessential nutrient as our liver is able to make all the cholesterol we need. Cholesterol is required for many functions including hormone production and cell structure. Contrary to what you might expect, dietary cholesterol is not the only dietary factor to influence blood cholesterol levels. Individuals who are concerned about their cholesterol also need to consider their saturated fats, dietary fibre, and trans fat intakes. Nonetheless, intake of cholesterol should be limited to 300 mg for all individuals – both sedentary and active.

During physical activity, use is mostly dependent on carbohydrate availability and intensity of exercise. When carbohydrates are readily available, one can perform exercise at a higher intensity due to ease of production; however, upon depletion of carbohydrate stores, the intensity of exercise must be reduced, and fat utilized for energy. Fatty acids undergo beta oxidation to be broken down into 2-carbon units for entry into the TCA (Figure 11-1). Although the body has a vast reserve of stored energy in the form of fat, the conversion of fat into ATP uses more energy than the conversion of carbohydrates to ATP in TCA. Furthermore, fats can only be used as a fuel source in the presence of oxygen. Therefore, the intensity of exercise must be reduced, as fat metabolism cannot supply ATP at the same rate as carbohydrate metabolism. As the body adapts to training, a greater percentage of fat can be used for fuel at a given submaximal intensity of exercise.

The Micronutrients: Vitamins and Minerals

Vitamins

The effective provision of energy and regulation of metabolic processes requires both chemical energy (carbohydrates, protein, and and a balance of vitamins and minerals. Vitamins are essential organic substances required for life and for optimal performance. Vitamins play many roles in the body including metabolic processes that release energy from food; regulation of

tissue synthesis; and protection of cell membranes (Table 11-2). There are two classifications of vitamins: fat soluble (A, D, E, and K) and water-soluble (C and B's). The fat-soluble vitamins do not dissolve easily in water or blood and require dietary fat for transport and storage. If taken in excess, fat-soluble vitamins can build up in fatty tissue and become toxic. The water-soluble vitamins in contrast readily dissolve in water and are easily transported in the blood. However, due to their water solubility, they are not stored to any great extent and turn over rapidly. Regular intake of vitamins is therefore necessary for health and performance. To understand how much of each vitamin we require, The National Academy of Medicine provides dietary reference intakes (DRI). The DRI provides information regarding recommended dietary allowance (RDA), the adequate intake (AI), and tolerable upper limit (UL) of nutrients**.** The RDA or AI are provided for most vitamins and represent the minimum recommended amount of each vitamin to consume on a daily basis. Some vitamins also have a UL, which is the maximum amount that one should not exceed daily. It is challenging to determine whether athletes and physically active individuals require vitamin supplementation. The vitamins that are most often a concern for athletes are the B vitamins, vitamin D, and the antioxidants (C and E). However, deficiencies are often only seen in those who consume poor, unbalanced diets or restrict their calories. Daily RDA and AI can often be achieved through consumption of a healthy and adequate-energy diet. Vitamin supplements should not be used to compensate for a poor diet, as they will not ensure adequate intake of the macronutrients, fibre, fluid and antioxidant s. Given that athletes are often consuming a large volume of food, their vitamin intake should be sufficient, if they are making healthy choices. One exception is the need for a vitamin D supplement when sunlight exposure is inadequate (winter, indoor training, etc.). Vitamin supplements do not improve performance in those who consume nutritionally adequate diets. It is recommended that individuals who would like to supplement one or more single vitamins consult with a health care professional knowledgeable in sports nutrition prior to beginning any vitamin program.

Table 11-2 Vitamins

Vitamin	Dietary Source	Major Function in Physical Activity
Water Soluble		
Thiamin (B1)	Whole grains, oatmeal, sweet potato, pork, fortified cereals	Carbohydrate metabolism, links glycolysis and the 2 and NADH" href="https://kinesiology.ucalgary.ca/maci...ric-acid-cycle">citric acid cycle, converts pyruvate to acetyl-CoA; critical for proper functioning of the central nervous system (CNS).
Riboflavin (B2)	Ground beef, poultry, eggs, mushrooms, tofu, dairy foods, whole grains, fortified cereals	Aerobic energy production during TCA and the ETC. The coenzyme FAD contains riboflavin.
Niacin (B3)	Liver, poultry, tuna, salmon, pork, portabello mushrooms, pumpkin seeds, tempeh fortified cereals	Energy production, the coenzymes NAD+ and NADP+ contain niacin.
Pantothenic Acid (B5)	Chicken, beef, oat cereals, whole grains, sunflower seeds, broccoli, mushrooms	Key in aerobic energy production as it is a component of coenzyme A
Vitamin B6	Beef, poultry, pork, salmon, banana, potato, avocado, chickpeas, sunflower seeds, fortified cereals	Component of >100 enzymes responsible for processes such as: (1) glycogenolysis (2) production of hemoglobin (3) neurotransmitter production (4) transamination

Vitamin	Dietary Source	Major Function in Physical Activity
Vitamin B12	Liver, fish, meats, dairy products (only found naturally in animal products); fortified soy foods, fortified cereals	Neurological function; lipid metabolism; red blood cell formation, DNA synthesis
Folate (Folic acid)	Liver, lentils, dried beans and peas, dark green leafy vegetables, avocado, orange juice, fortified grains	Facilitates muscle repair and red blood cell formation, DNA synthesis
Biotin	Egg yolks, salmon, cheese, nuts, dark leafy green vegetables, almonds, beans and peas	Acts as a cofactor for the aerobic metabolism of macronutrients and required for gluconeogenesis
Vitamin C	Peppers, broccoli, Brussels sprouts, asparagus, citrus fruits, kiwi, and strawberries	Acts as an antioxidant and responsible for collagen tissue formation (bones, tendons, ligaments), promotes iron absorption
Fat Soluble		
Vitamin A (Beta-carotene)	Liver, fish, egg yolks, yellow and orange fruits and vegetables, dark green leafy vegetables, fortified dairy products	Epithelial cell repair and function; immune function; vision
Vitamin D	Salmon (including bones), egg yolks, beef liver, fortified milk and milk alternatives, fortified cereals, fortified orange juice	Regulates calcium levels for bone health; immune function, responsible for and maintenance of skeletal muscle and nervous tissue.
Vitamin E	Cooked spinach and Swiss chard, wheat germ, sunflower seeds, vegetable oils, nuts (almonds, hazelnuts)	Antioxidant
Vitamin K	Cabbage family vegetables, soybeans, liver, eggs, dairy products	Blood clotting and bone health

Minerals

Minerals are inorganic substances (atoms or elements) required for life in relatively small amounts. There are two classifications of minerals: major minerals and minor minerals. The seven major minerals are:

- calcium (Ca^{2+}),
- chloride (Cl^{-}),

- magnesium (Mg^{2+}),
- phosphorus (P),
- potassium (K^{+}),
- sodium (Na^{+}),
- sulphur (S)

For a mineral to be classified as major, intakes of greater than 100 mg per day are required. There are 14 minor minerals, which include chromium (Cr), copper (Cu), fluoride (F), iodine (I), iron (Fe), manganese (Mn), selenium (Se), and zinc (Zn). A minor mineral is required in amounts less than 100 mg per day. All minerals are consumed in our diet and then stored in our bodies. Minerals are required for matrix structures (bone/teeth); regulation of metabolism via use in enzymes and hormones; maintaining homeostasis in functions such as muscle contraction, neural function, heartbeat, and acid-base balance. A complete list of functions critical to sports performance is provided in Table 11-3. Similar to vitamins, the supplementation of single minerals is not recommended. The RDA of most minerals can be obtained from consuming a nutritionally balanced, energy-sufficient diet. The most likely minerals to be deficient in an athlete's diet are zinc, iron, and calcium. However, as with low vitamin status, low mineral status often arises due to unbalanced diets or caloric restriction. Individuals wishing to supplement minerals should consult with a sport medicine physician prior to consumption.

Of special interest to athletes and physically active individuals, are the minerals referred to as electrolytes such as Na^{+}, K^{+}, Ca^{2+}, and Cl^{-}. These minerals are electrically charged particles (ions) that are critical for ensuring proper electrochemical gradient across cells, regulation of acid-base balance, and regulation of blood volume and blood pressure. Most individuals consume sufficient quantities of these minerals; however, care should be taken if there are large fluctuations in body water – both in intake (drinking) and output (urine, sweat, breathing, and feces). Recommendations for these minerals combined with fluid intake are provided below.

Table 11-3 Minerals

Mineral	Dietary Source	Major Function in Physical Activity
Major		
Calcium	Dairy products and milk alternatives (soy milk, almond milk), salmon with bones, tofu, dark leafy green vegetables	Growth and maintenance of bone; muscle contraction; nerve signaling
Chloride	Table salt	Fluid and electrolyte balance
Magnesium	Legumes, whole grains, dark green vegetables, seafood	Energy production from carbohydrates, protein, and fat; muscle, nerve, cardiovascular, and immune function
Phosphorus	Dairy products, meats, seafood, whole grains, oats, beans, lentils, nuts, potato	Component of and CP; deficiency is very rare
Potassium	Fruits and vegetables especially potato, banana, spinach, and orange juice	Nerve function; muscle contraction; blood pressure regulation; fluid and electrolyte balance
Sodium	Soy sauce, table salt, canned and processed foods, soups	Nerve function; blood pressure regulation; fluid and electrolyte balance

Mineral	Dietary Source	Major Function in Physical Activity
Minor		
Copper	Seafood, legumes, nuts, whole grains	Energy production in ETC; helps form hemoglobin
Fluoride	Drinking water, topical use of toothpaste	Mineralization of bones and teeth
Iodine	Iodized salt, dairy products, eggs, seafood	Component of thyroid hormone thyroxine
Iron	Red meat, lentils, shrimp, enriched cereals, liver, sunflower seeds, legumes, dried fruit	Oxygen transport via myoglobin and hemoglobin; energy production
Manganese	Plant based foods such as legumes, grains, and vegetables	Energy production; antioxidant; bone health
Selenium	Meats, fish, seafood, grains, Brazil nuts, beans, peas	Antioxidant; DNA synthesis
Zinc	Meat, poultry, seafood, enriched cereals, chickpeas, cashews, kidney beans, peas	Immune function; DNA and protein synthesis; enzyme production; cardiovascular function

Research Box: Antioxidants

- You have probably heard of antioxidants and think that they are beneficial for your health, but do you know how antioxidants work? Do you know which foods are high in antioxidants? Do athletes benefit from taking supplements?
- Antioxidants are compounds that can protect cells against the harmful effects of free radicals. Free radicals are chemically unstable molecules that attack cells and have been linked to many different chronic diseases. For example, it is thought that when free radicals interact with a cell's DNA it can promote cancer development. Alternatively, when free radicals interact with LDL cholesterol they can cause cholesterol to deposit along the walls of the arteries. Over time this blocks the arteries and increases the risk of heart disease and stroke. There are many diseases that are linked to free radicals and it is important for the body to be able to defend itself against them.
- Free radicals are produced in the body during normal metabolic reactions, for example, breaking down food to provide energy for exercise (oxidative metabolism). They are also found in the external environment, for example when you are exposed to sunlight or chemical toxins. Antioxidants neutralize free radicals and stabilize them, thus preventing them from attacking cells. When antioxidants neutralize free radicals they are used up, therefore, it is important for the body to have a continuous supply. Fortunately, the body naturally produces antioxidants and can extract them from the foods that you eat.
- Fruits and vegetables are a rich source of dietary antioxidants. Scientists have discovered that there are likely thousands of different substances in plants that can act as antioxidants such as vitamin C and vitamin E, as well as selenium and manganese. Plant foods also contain phytochemicals, biologically active compounds found only in plants, many of which have properties. You have probably heard that dark chocolate and red wine have health benefits. This is likely due to the phytochemicals found in these foods. There is some truth to this; however, the alcohol in the wine and high sugar and content of the chocolate might offset the health benefits!

Initially, researchers noticed that people who ate a diet with plenty of fruits and vegetables rich in antioxidants were at the lowest risk of developing many free radical-related diseases. This led the researchers to examine individual phytochemicals, vitamins, and minerals in supplement (pill) form to see if they would also prevent disease. Unfortunately, the overwhelming majority of such studies do not find that taking a single supplement, such as vitamin or vitamin C, has any measurable health benefit. In fact, beta-carotene supplements had just the opposite effect. It had been shown that people who smoked yet ate foods that were rich in beta-carotene, one of the phytochemicals found in dark green and orange vegetables, had lower risks of lung cancer than those who did not eat the beta-carotene rich foods. Researchers then hypothesized that a beta-carotene supplement should decrease the risk of lung cancer in people who smoked. Surprisingly, the supplement increased the risk of cancer in smokers and the studies had to be stopped (Goralczyk, 2009).

- It is not completely understood why diets high in antioxidant rich fruits and vegetables are protective against these diseases when individual supplements are not. However, there are important differences between eating whole foods and taking a supplement. Whole foods refer to eating the complete food as opposed to extracting a specific nutrient or nutrients from the food and taking them in supplement form or eating an overly processed and refined product. When you eat broccoli, you are getting a whole range of phytochemicals as well as protein, carbohydrates, vitamins, minerals, fibre and water. This is very different from taking a beta-carotene pill, where you simply get one phytochemical. There are also a lot of unknowns surrounding the phytochemicals in foods. Researchers do not know all of the different types of phytochemicals, the amounts they are found in the foods (and therefore the dose to recommend with a supplement), or if they need to be taken with other phytochemicals or nutrients to be effective and beneficial. Also, although antioxidants are grouped together, they are not all the same and do not all have the same benefits for the body. This means that we should eat a wide variety of whole foods to get antioxidants rather than consume a supplement that provides only one or a few antioxidants.
- What about antioxidants for athletes? Powers et al. (Powers, Nelson et al., 2011) have reviewed the literature surrounding free radical production and supplementation in athletes. They found that many athletes take supplements based on a belief that free radicals increase muscle fatigue. Exercise does increase free radical production in the muscles, and in theory, can contribute to fatigue. However, a well-trained athlete also has higher endogenous production. Therefore, there is little evidence to suggest that common supplements can improve performance. If anything, the research suggests that supplementation might have a negative effect on physical performance (Paulsen, Cumming et al., 2014). The exercise-induced free radical production occurring as a result of exercise signals the muscle to produce enzymes. However, when supplements are consumed this training adaptation is attenuated. Considering this, athletes should not use supplements, but rather focus on consuming a balanced diet with plenty of plant-based foods naturally high in antioxidants.

Water

The human body consists of about 65-75% water. Variations in body water – either increases or decreases can lead to impairment of physiological function and in the extreme, death. Body water is vital for many functions including transport of nutrients, removal of waste, temperature regulation, and cushioning of joints. Water balance describes the flow of water into and out of the body. Intake of water comes primarily from consuming beverages and foods, but also is produced during metabolism as a byproduct. Water output is affected by losses in the urine, feces, and sweat, as well as from evaporative loss from the skin and the ventilatory system. When the losses of body water exceed the input, this leads to dehydration**.** Dehydration leads to decreased performance when there is a loss of body water equivalent to 2% or more of total body weight. Symptoms of dehydration can include headache, dizziness, fatigue, tachycardia, unconsciousness, and in extreme cases death. In order for an individual to determine water status, it is recommended that immediately prior to exercise and immediately following exercise, an individual weigh themselves. The change in body weight is an excellent determinant of changes in body water. In contrast, a small percentage of athletes suffer from the opposite problem and actually over-hydrate resulting in a condition called hyponatremia**.** Hyponatremia can result from consuming too much water without replacing electrolytes**.**

It is recommended that physically active individuals and athletes consume fluids prior to exercise, during exercise, and after exercise. The volume required depends on many factors including sweat rate, environment (humidity, temperature and altitude), genetics, and personal fitness levels. Drinking to thirst is often insufficient for athletes competing at high intensities in warm-hot environments. In general, in the 2-4 hours prior to exercise, individuals should consume a volume of water equivalent to 5-10 mL·kg^{-1} body weight (Thomas, Erdman et al., 2016). For example, a 60 kg person should consume about 300-600 mL of fluid. This amount of fluid maximizes hydration status and reduces the risk of having to urinate during exercise. During exercise, sweat rates can vary from 0.3 to 2.4 L · kg^{-1} and can contain variable amounts of Na^+ and K^+. Therefore, it is recommended that individuals consume fluids at a rate that maintains body weight or minimizes changes in body weight. If an event or training session is to

last more than 1 hour, it is recommended that fluids (such as sports drinks) containing 6-8% carbohydrates and electrolytes (Na^+, K^+) be consumed instead of plain water. After exercise, it is recommended to consume 1.25 L to 1.5 L fluid for every kilogram of body weight lost during exercise for rehydration (Thomas, Erdman et al., 2016).

Energy Requirements for a Physically Active Population

Consuming enough total energy is important for all physically active individuals. In competitive sport, meeting energy needs is a key factor in optimizing athletic performance. Daily energy requirements can fluctuate widely depending on individual characteristics and physical activity levels. An athlete like Chris in the Tour de France can easily expend over 4000 per day in exercise alone, whereas a person with largely sedentary behaviour may only burn a few hundred kcal per day due to physical activity. Without adequate energy intake, the ability of the body to maintain body weight, replenish glycogen stores, and provide adequate protein to build and repair tissue is compromised. In fact, the benefits of training can be negated if adequate energy is not consumed. In female athletes, persistent low energy intake can lead to the triad, a serious health problem that involves disordered eating, amenorrhea (loss of menstruation) and low bone mass.



Photo 11-6 – Swimmers, similar to cyclists, log many hours of training, this training will greatly increase the energy requirements of such athletes. Image by H. B. from Pixabay

One of the major reasons that individuals increase or decrease their energy intake is to change their body weight or more specifically their body composition. Weight management through exercise is a chief goal of many fitness enthusiasts. For example, Paula is in her first year of university and finds that she has gained a couple kilograms of weight during her first semester. While she hasn't really changed her eating habits very much compared to when she was in high school, she finds that she is less active throughout the day sitting in class and studying in the evenings. Paula decides that she is going to keep her dietary habits fairly similar but burn more energy by walking to university each day. Paula will change her energy balance by increasing her energy expenditure and keeping her energy intake relatively stable. If Paula is 66 kg when she starts walking to and from university every day, she will expend approximately 5.9 $kcal \cdot min^{-1}$ if she walks at a pace of 4.0 miles per hour (6.4 $km \cdot hr^{-1}$). Her walk takes 60 minutes total each day resulting in 354 $kcal \cdot day^{-1}$ energy usage. If she is persistent, Paula might expect to lose approximately 1 pound (0.6 kg) of body weight after approximately 10 days according to popular thinking about energy deficits. However, the body likes to protect a higher body weight and may make metabolic adaptations so that weight loss is not guaranteed in a linear manner with an energy deficit. Even if Paula does experience some weight loss, it is critical to realize that weight loss will not continue indefinitely because as Paula's weight drops, the cost of doing the same exercise goes down. Therefore, if she has not reached her goal weight when the weight loss plateaus, she will have to increase the duration or intensity of her walk or consume fewercalories to continue to create an energy deficit.

For athletes, the incentive to change their overall energy intake or individual macronutrient intake is often linked to a desire for less mass and greater lean mass. Achieving what is perceived as an optimal body composition is often undertaken in hopes of gaining a competitive edge. Consuming enough energy is critical if these compositional changes are to take place in a positive direction. For example, David thinks that if he could increase his muscle mass and decrease his fat mass he would be more competitive in triathlons. David decides he will consume more protein to help build up muscle, but restrict his overall energy intake in hopes of losing fat. This strategy could end up working against David. When overall calories are restricted too severely, both fat and lean tissue can be used as a fuel by the body (Stiegler and Cunliffe, 2006). For example, if a person simply restricts

their calories, the weight loss that results is approximately 75% adipose tissue and 25% fat free mass. If the person also exercises while they restrict their calorie intake, the loss of fat free mass can be reduced to 12% (Weinheimer, Sands et al. 2010). If David restricts his eating too much, the lean tissue he was hoping to build up may be used as a fuel source by his body to meet its daily energy needs. This loss of lean tissue can compromise many processes in his body including his immune, endocrine and musculoskeletal function and result in loss of strength and endurance.

You can recognize the importance of understanding what the energy requirements of the body are. Knowing how to accurately estimate your energy needs is key to understanding how to achieve or maintain a healthy and optimal body weight.

Energy Needs: What, Why, and How They Change

Energy balance occurs when energy intake equals energy expenditure. Body weight reflects energy balance and will remain stable when an individual is in energy balance; it will increase when a person is in positive energy balance; and it will decrease when a person is in negative energy balance. Energy intake is simply reflected in the kilocalories a person consumes throughout the day. If you recall, carbohydrates and protein supply the body with 4 $kcal \cdot g^{-1}$ while provides 9 $kcal \cdot g^{-1}$ and alcohol 7 $kcal \cdot g^{-1}$ Food records, where a person records all foods and beverages consumed over a 3 or 7-day period, and 24-hour dietary recalls are common ways of estimating a person's energy intake. The energy intakes of athletes tend to be higher than sedentary individuals to balance the higher energy expenditure associated with their training.

Energy expenditure is the second component of energy balance. The major components of energy expenditure include resting metabolic rate (RMR), physical activity, and the thermic effect of food (TEF) (Figure 11.3) (Levine, 2005). RMR is synonymous with resting energy expenditure and is usually the largest portion of daily energy expenditure. RMR is the energy required to fuel basic physiologic functions in the body, including circulation, respiration, nervous system function, and organ function. RMR is measured usually after 4 hours of resting. For most individuals, RMR will account for about 60-75% of total daily energy expenditure. Higher levels of lean body mass in athletes are often associated with higher RMR largely because lean tissue is more metabolically active than adipose tissue. Many factors can increase or decrease RMR (Figure 11-3).

- For most individuals, the energy cost of physical activity is the second largest contributor to energy expenditure. For some athletes their training can be so extensive that the energy they expend in physical activity can actually equal or exceed their RMR. The energy cost of performing activity is influenced to a large extent by body weight. For example, while a 57 kg person running at 9.6 $km \cdot hr^{-1}$expends 568 in an hour, a 91 kg person would expend 909 kcal running at the same speed (Ainsworth, Haskell et al., 2000). Although there is some variability, due to differences in economy, the energy cost of running can be estimated as 1 $kcal \cdot kg^{-1} \cdot km^{-1}$.

The body also uses energy to digest, absorb and metabolize the foods we eat. This is called the thermic effect of food (TEF) and it accounts for approximately 10% of total daily energy expenditure. This means that if a person consumes 3500 $kcal \cdot day^{-1}$, approximately 350 will be used to process the food they eat. There is some difference in the TEF between the macronutrients and it requires more calories to assimilate protein and carbohydrates than fat.

Gender Feature: Female Athlete Triad

Rachel is a runner who competes at an international level. As an elite athlete, Rachel has had the opportunity to have coaches, physiologists, and a sports dietitian to assist with training and dietary needs. Last year, Rachel began studies at university and for the first time ever did not have a staff of trainers overseeing her food intake or the strict regime of training for international events. The change in lifestyle and environment resulted in her gaining about 4 kg during the school year. During the summer, she changed her eating habits and increased her training to lose this extra 'freshman' weight. She is currently 22 years old, 172 cm (5'6") tall, and 51.2 kg (113 lb). Her body percentage is 10.4% and her 30)" href="https://kinesiology.ucalgary.ca/maci...y/5bx-dea#bmi-">body mass index (30)" href="https://kinesiology.ucalgary.ca/maci...y/5bx-dea#bmi-">BMI) is 17.3 $kg \cdot m^{-2}$. Rachel recently noticed that her menstrual cycle had become very irregular and she was diagnosed with a stress fracture in her tibia last week.

Rachel's symptoms are likely due to the triad (Otis, Drinkwater et al., 1997, De Souza, Nattiv et al., 2014). The triad is a group of three related conditions that is often diagnosed in young female athletes. The three conditions include low energy availability, possibly due to disordered eating, menstrual dysfunction, and low bone mineral density (BMD). Left untreated it can lead to eating disorders, amenorrhea and osteoporosis (De Souza, Nattiv et al., 2014). Disordered eating can include many different behaviors, but commonly in the triad it involves caloric insufficiency due to reduced food intake combined with high intensity, long duration

training. This creates a reduction in energy availability. When energy availability drops below 30 kcal·kg^{-1}·day^{-1} of free mass, there are consequences for both reproductive and skeletal health. For example, when there is low energy availability, body fat stores decrease, sex hormone function changes, and frequently the menstrual cycle is altered or ceases. When the menstrual period is absent for at least 3 months, a diagnosis of amenorrhea may be made (Meczekalski, Katulski et al., 2014). The amenorrhea is thought to occur in response to low energy availability and an interruption in the normal function of the hypothalamus-pituitary-ovary axis. The disruption to this axis can lead to decreased production of estrogen by the ovaries. Lowered estrogen is undesirable because it contributes to a decrease in bone mineral density (BMD) via alterations in bone modeling regulation. Loss of BMD is intensified by the caloric restriction, as a calorically inadequate diet usually does not provide sufficient calcium, vitamin D, or other minerals required for bone mineralization. Over time the reduction of BMD results in osteopenia and/or osteoporosis.

It is recommended that for any female who presents with the characteristics of the triad to be referred to a health professional for treatment, in addition to increasing energy availability by decreasing exercise and increasing caloric intake (De Souza, Nattiv et al., 2014).

Equations for Calculating Energy Needs

Several methods are available to estimate daily energy expenditure. The most accurate is through the use of direct calorimetry, which directly measures the body's heat production in a small room, called a calorimeter. Because these chambers are expensive and not readily available outside of research settings, indirect calorimetry is an acceptable option in real life situations. Indirect calorimetry is based on equations that predict energy expenditure based on the input of variables such as age, weight, and height. Three equations are presented below. The Harris-Benedict equation is commonly used to predict resting energy expenditure and has distinct equations for males and females (Figure 11-4) (Harris and Benedict, 1919). Beyond estimates of RMR, specific activity factors can be used to arrive at total daily energy expenditure. For example, the Dietary reference intakes (DRI) Method uses an estimate of RMR plus a physical activity factor to arrive at an estimate of 24-hour energy needs (Figure 11-4) (Lupton, Brooks et al., 2002). For athletes it is important to remember that these equations were developed with the general population and may not apply specifically to athletes. The equations provide a good estimate of energy requirements, but athletes will have to do some fine-tuning to arrive at their optimal energy needs. This is because athletes often have higher RMR due to increased lean body mass and for the DRI Method, the physical activity component may be much higher than expected in an athletic population (Ainsworth, Haskell et al., 2000). It is also important to note that physical activity often varies from day-to-day in an athlete's training and their energy intake needs to fluctuate accordingly. Finally, to compensate for differences in individuals with overweight or obesity, a different equation called the Mifflin-St. Jeor has been shown to be more accurate for predicting RMR adults with overweight or obesity (Figure 11-4) (Frankenfield, Roth-Yousey et al., 2005).

Figure 11-4

Indirect c alorimeter m etabolic r ate c alculations .

Harris-Benedict Equation

Adult Females:

Resting energy expenditure = 655 + 9.6 ·(weight in kg) + 1.8 ·(height in cm) – 4.7 ·(age)

Adult Males:

Resting energy expenditure = 66 + 13.7 ·(weight in kg) + 5.0 ç(height in cm) – 6.8 ·(age)

Dietary reference intake (DRI) Method

Adult Females:

354 – 6.91 · (age) + (9.36 · [weight in kg] + 726·[height in meters])

Where Physical activity (PA): Sedentary 1.0, Low active 1.12, Active 1.27, and Very active 1.45

Adult Males:

662 – 9.53 · (age) +·(15.91 · [weight in kg] + 539.6·[height in meters])

Where Physical activity (PA): Sedentary 1.0, Low active 1.11, Active 1.25, and Very active 1.48

Mifflin-St. Jeor Equation

Men: (9.99·kg) + (6.25·cm) – (4.92·years) + 5

Women: (9.99·kg) + (6.25·cm) – (4.92·years) – 161

How to Incorporate an Active Lifestyle for Weight Loss/Maintenance for Populations with Obesity

Obesity rates continue to rise worldwide and place an ever-increasing burden on health care systems. Treatment programs aimed at increasing energy expenditure and decreasing energy intake are very often effective at helping individuals lose weight but maintaining that weight loss is continually problematic. Several research studies have tried to determine what it is about successful weight loss maintainers that allows them to succeed when so many regain the weight they lost. Researchers found that being able to persist in key behaviour changes, including reducing calorie intake, increasing physical activity and monitoring their weight, were all important to keeping the weight off (Wing and Phelan, 2005). Other researchers have looked at psychological and behavioural factors that help weight loss maintainers succeed and found the following (Soleymani, Daniel et al., 2016):

- Physically active for an average of 1 $hr \cdot d^{-1}$
- Low-calorie, low diet
- Self-monitored physical activity and diet
- Ate breakfast
- Weighed themselves at least once a week
- Watched <10 hr of television per week

Nutrition for Athletic Performance: Specific Timing Requirements and Recommendations for Optimal Performance

Overview

For peak performance, athletes need to make important decisions regarding the types and timing of food intake as well as the use of supplements. Just as an athlete needs to periodize their physical training, they need to periodize their nutrient intakes to match their daily training, a concept called nutrition periodization. Sport performance and recovery is enhanced with optimal nutrition. It is essential for every athlete to eat a calorically adequate and balanced diet, consisting of a variety of whole foods, on a daily basis. The guidelines presented above for physically active populations are appropriate for elite athletes, however, some specific additional needs for high-performance athletes will be examined in greater detail for the remainder of the chapter.

Canadian Registered Dietitians, with specialized training in sport nutrition, have developed a number of resources for athletes and physically active populations to optimize their nutrition. These tips for training diet, sport specific tips, weight control tips and others are available through the Coaching Association of Canada. To explore these great resources, check out the website at https://www.coach.ca/sport-nutrition-s14783.

When designing meals for athletes, it is important to consider not only what they are eating and the nutrients the foods provide but also the timing of their meals. An athlete who pays attention to meal timing will have sufficient energy to push their limits during a workout and maximize their recovery. They will get the utmost benefit out of every training session and perform their best in competition. Athletes who neglect to pay attention to the timing of their meals often feel tired, lethargic, and experience digestive problems and dehydration. It is important to consider what to eat *before*, *during* and *after* each work-out. Designing the optimal diet plan takes into consideration a variety of factors including the individual athlete, their age, the environment and the type and duration of physical activity they will be performing. It's important to note that everyone is slightly different and that the guidelines provide a starting point. The guidelines presented have extensive scientific evidence backing them however, trial and error is necessary to find the optimal nutritional strategy for the individual athlete, which considers both the workout and environmental conditions they will be performing in. In all cases, this trial and error process should occur in training sessions, not during competition. Recommendations for endurance activities will be provided first, followed by recommendations for strength

and activities.

Endurance Exercise

Endurance exercise has specific requirements with respect to nutrition due to their high caloric needs. Athletes participating in endurance-exercise perform long bouts of moderate to high intensity exercise and can only do so by carefully planning what they eat before, during, and after their event or training session. Even the leanest of endurance athletes will have sufficient and protein stores to sustain them throughout their physical activity; thus, their primary concern is being able to meet the body's carbohydrate needs. Energy needs will vary depending on the duration of exercise, the intensity of the exercise, and the athlete's training and fitness. Protein is primarily important for the recovery, or post-event period.

Pre-event Nutrition

A pre-exercise meal should provide enough energy for the workout without causing any digestive discomfort**.** Research has shown that eating before exercise improves performance compared to exercising in the fasted state. In the ideal situation, an endurance athlete should have a pre-exercise meal 1-4 hours before their event or training session. Endurance athletes should aim to consume between 1-4 $g \cdot kg^{-1}$ BW of carbohydrates in their pre-exercise meal to maintain blood glucose levels and maximize the body's glycogen stores (Thomas, Erdman et al., 2016). Athletes will need to adjust their pre-exercise meal to match their work-out or competitive event. A longer training session or event will require that the athlete use the high end of the 1-4 $g \cdot kg^{-1} \cdot$ BW range. For a shorter work-out or event, athletes should use the low end of the recommended range. Additionally, the athlete's glycogen stores must be considered. If their glycogen stores are depleted due to a previous work-out, they will be required to use the higher end of the range. The meal should be low in fat and fibre as these nutrients take longer to digest and high intakes have the potential to cause digestive distress. Excess fibre may cause gas production, constipation, bloating and laxative effects. There is some evidence that adding protein to the meal will improve performance in longer endurance events, however, the optimal amount remains to be determined (Jager, Kerksick et al., 2017). Furthermore, the protein content of the meal should be moderate as excess amounts are hard to digest and could promote dehydration. To metabolize protein, the body must cleave the nitrogen containing amino group and eliminate it through the urine. The increased urination increases the risk of dehydration. Finally, it is also important that the pre-exercise meal contains sufficient amounts of fluid as described below.

In the event that a full meal prior to a workout or competition is not possible, as would be the case for an early morning workout, it is essential that the athlete have a complete meal the evening before and an easily digestible snack prior to exercising. Exercising on a full stomach is not recommended; thus, as the time to exercise diminishes the meals should become smaller and easier to digest. Liquids are optimal in this case as they digest more quickly than solid foods and work equally well to promote glycogen resynthesis (Kerksick, Arent et al., 2017). Items like smoothies, sports drinks and meal replacement drinks are very useful and many were developed specifically for athletes. In the event of suboptimal carbohydrate stores pre-exercise, carbohydrate intake during exercise becomes extremely important.

For events lasting longer than 2 hours, athletes can also use carbohydrate loading protocols to maximize their glycogen stores. There are several different protocols for carbohydrate loading; yet, the general technique is a decrease in physical activity and an increase in dietary carbohydrate intake. Many protocols are carried out over a week, but a simpler protocol of 36-48 hours of 10-12 g carbohydrate/kg body weight/24 hour, while tapering training has been found to be equally effective at maximizing muscle glycogen storage (Thomas, Erdman et al., 2016). For athletes undergoing carbohydrate loading, it is important that they also increase their fluid intake because as the body stores additional carbohydrate, it will also store water. As with all sport nutrition, the athlete should test their body's response to carbohydrate loading prior to their event. For some athletes, carbohydrate loading will make them feel bloated and the benefits of the extra glycogen are outweighed by the weight gain. These athletes may prefer to focus on consuming sufficient carbohydrates during exercise. Athletes exercising for less than 1.5 to 2 hours do not need to carbohydrate load, as they will have sufficient glycogen stores from their normal dietary carbohydrate intake.

Pre-event Hydration

The importance of adequate hydration and electrolyte balance cannot be overstated. Experts agree that a relatively small loss of 2% of body weight can negatively impact physical performance. Realistically, many athletes find it challenging to maintain their hydration status and most cannot consume sufficient amounts of fluid to match their losses when exercising. With this in mind, athletes should ensure adequate hydration prior to commencing a workout. It is recommended that athletes consume 5-10 ml/kg body weight of water or a sports drink 2-4 hours before exercise (Thomas, Erdman et al., 2016). Recommendations based on body weight are much more accurate than providing a universal fluid level for all athletes. The 2-4 hour time period is to optimize

hydration status while ensuring that excess fluid can be voided, thereby, preventing the need to urinate during competition. The use of a sports drink will also provide athletes with carbohydrates and electrolytes. Another benefit to a sports drink is that the salts, flavour, and sweetness encourage higher fluid intakes. The use of carbohydrate-electrolyte beverages to stimulate adequate fluid intakes is particularly important during a workout or competitive event. In all cases, consuming a carbohydrate-electrolyte beverage can be a useful strategy for athletes who struggle to consume the recommended amounts of fluid. When planning a hydration schedule, it is imperative to recognize that fluid needs are highly variable and will depend on the athlete and the environmental conditions. All of these factors must be considered and intakes adjusted accordingly.



Photo 11-7 Practicing good hydration habits is key for optimum physical activity. Image by Gary G from Pixabay

During Event Nutrition

Regardless of how carefully an endurance athlete plans their pre-exercise meal, it is not possible to physically exert oneself for hours without providing additional nutrients. The general consensus is that any bout of exercise longer than one hour requires supplementary nutrition. As with pre-event nutrition, the focus is on carbohydrates, fluids, and electrolytes as these are the nutrients most likely to limit physical performance when inadequate amounts are available.

Consuming carbohydrates during exercise can vastly improve physical performance. This is critical when an athlete is going into an event or workout with low glycogen stores; this is likely to occur in stage races, tournament situations, or anytime there are repeated exercise bouts with minimal recovery time. For periods of exercise lasting longer than one hour, endurance athletes should consume 0.7 g CHO · kg^{-1} · hr during the exercise. For most athletes this works out to 30-60 g CHO · hr^{-1}. For ultra-endurance exercise, continuous exercise for greater than 2.5 hr, intakes of up to 90 g CHO · hr^{-1} are recommended. In this case, the athlete should start consuming carbohydrates shortly after beginning to exercise and approximately every 10 minutes thereafter (Thomas, Erdman et al., 2016, Kerksick, Arent et al., 2017). This schedule is more effective than consuming a single large dose of carbohydrates later in exercise, as it allows for greater stability in blood glucose and maintenance of glycogen stores, as well as minimizing gastrointestinal distress.

There are many ways to obtain adequate carbohydrates during exercise. Athletes should experiment with various strategies during training, to optimize their nutrition for competition. Options include sports drinks, solid food and water, sports gels and water or a combination of these. A sports drink that contains 6-8% carbohydrate is advised, as lower concentrations will not provide enough carbohydrates and higher concentrations will draw water into the gastrointestinal tract from the body. This can lead to both dehydration and abdominal cramping. For this reason, soft drinks, sodas, juice, or other sugar-sweetened beverages are not appropriate choices for fluids during exercise. Importantly, if solid food is to be used, the focus should be on foods that are easy to carry, consume, and digest. It has been suggested that consuming protein during exercise may also be beneficial in endurance events, however, further research is required to confirm the optimal dosage (Jager, Kerksick et al., 2017).

During Event Hydration

For all athletes it is important to hydrate during the event. Given the wide range of environmental and physiological factors that affect an individual's sweat rate, it is highly recommended that athletes use a personalized fluid replacement strategy rather than a global guideline. Athletes should frequently weigh themselves pre and post exercise to determine their sweat rates and develop appropriate fluid replacement strategies. The goal is to have less than 2% change between baseline body weight and post-exercise body weight (Figure 11-5). Finally, intake of cold fluids (0.5^{o}C) may help reduce core body temperature when athletes are competing in the heat (Thomas, Erdman et al., 2016).

Athletes can determine their approximate sweat rate by weighing themselves (without clothing), exercising for one hour and then weighing themselves after exercise (without clothing so that the weight of sweat in the clothing doesn't interfere with the determination). They will also need to keep track of how much they drink during exercise. They can then calculate their sweat rate using the formula below. Recall 1 kg = 2.2 lbs.

Figure 11-5. Sweat rate calculation. Modified from Skolnik and Cherpass, Nutrient Timing for Peak Performance.

Determine pre and post exercise weight

Pre-exercise weight (kg) – post exercise weight (kg) = kg lost

kg lost

1 000 (1kg = 1000 ml) = ml lost

Add amount of fluids consumed during exercise

ml lost + ml consumed = ml sweat lost

This is your sweat rate per hour

*If the athlete urinated during that time, they will need to subtract that amount. It is also important to know that an individual's sweat rate will change depending on the environmental conditions and the test should be repeated in a variety of conditions.

In events longer than 1 hour, it is recommended that athletes consume fluids that contain electrolytes to ensure adequate replenishment. Specifically, the presence of Na^{+} in the fluid will help stimulate thirst and promote fluid retention. A person can lose up to 1g of Na for every liter of sweat, although this can vary greatly depending on the individual (Sawka, Burke et al., 2007). Athletes need to choose beverages with appropriate electrolyte concentrations to counteract Na^{+} loss in sweat. Practically, an athlete should also be aware of symptoms such as headaches, dark urine, and low urine output, which indicate either a lack of fluid, electrolytes or both (Von Duvillard, Braun et al., 2004). Finally, it is important to note that in some cases it will not be possible for an athlete to consume sufficient fluids during exercise. Typically, the sweat rate exceeds the body's ability to absorb the required amounts of fluids. In these cases, adequate pre and post hydration are crucial.

Recovery Nutrition

Recovery nutrition depends, not surprisingly, on conditioning, as well as the length and intensity of the exercise session and when the next intense bout of exercise is scheduled. Athletes will have a window of opportunity where they can most effectively recover from their exercise. For speedy refueling, defined as less than 8 hours before the next workout, athletes should aim for 1-1.2g of carbohydrates · kg^{-1} body weight · $hour^{-1}$ for the first 4 hours followed by their regular meals. Furthermore, maximum glycogen re-synthesis occurs when carbohydrates are consumed within 30 minutes after a workout. Unless the muscles are severely damaged, regular meals and reduced training should restore glycogen levels within 24 hours. It is also important for endurance athletes to consume protein after their workout to provide essential amino acids for muscle repair. For optimal recovery, carbohydrate and protein should be consumed in combination. Ideally, the foods and beverages selected for recovery will provide a carbohydrate, fluid, electrolytes, and protein. See Figure 11-6 for examples of foods and drinks to recover after a workout.

Figure 11- 6

Recovery foods**.** Foods eaten after exercise should provide fluids, carbohydrates, protein and electrolytes

Stage 1: within 30 minutes after exercise

Banana, yogurt, juice

Peanut butter sandwich, strawberries, milk or juice

Flavoured milk, granola bar, apple and water

Sports drink, cheese strings, grapes, juice or water

Low-fat muffin or bagel, homemade smoothie (blend milk, yogurt, fruit, juice and ice)

Protein bar, orange, pretzels and juice or water

Meal replacement drink (Boost™, Ensure™, etc.), carbohydrate sports bar, apple, water

Stage 2: 1-2 hours after exercise

Meat or cheese submarine sandwich loaded with veggies, milk/juice

Chicken and vegetable stir-fry with brown rice, milk/juice/water

Whole wheat pasta with meatballs, vegetable salad, milk/juice/water

Grilled salmon, quinoa or whole wheat couscous, raw veggies with light dip, milk/juice/water

Bowl of cereal with yogurt or milk, fresh fruit, water/juice

Scrambled eggs with cheese and diced peppers, whole wheat bagel, milk/juice/water

Lentil soup, whole wheat bun, Greek yogurt/regular yogurt, fruit salad, water/soy beverage/milk

Pasta salad tossed with chopped vegetables, canned tuna or chicken breast, milk/juice/water

Cottage cheese or Greek yogurt, fruit salad, low-fat muffin, milk/juice/water

Recovery Hydration

It is not uncommon for athletes to fail to consume sufficient fluids during exercise. To effectively recover from a workout, athletes should weigh themselves pre and post exercise and drink 1.25 L to 1.5 L for every 1.0 kg lost. Aiming to consume this amount of fluid will replace those fluids that are lost through sweating and compensate for fluid lost in urination. It is also advisable with moderate to severe water losses to consume rehydration beverages containing sodium chloride or salty foods to help the body absorb fluids and replace lost electrolytes (Thomas, Erdman et al., 2016).

Strength and Power Training

Strength and activities have specific nutritional requirements that differ from endurance exercise. Carbohydrate needs will be unique and most often lower than endurance activities. Strength and power training also tends to focus more heavily on protein intake with a goal of building and repairing a greater amount of muscle tissue. With all of this in mind, however, it is important to note that carbohydrate intakes are still important during strength workouts and that the average North American diet provides enough protein to meet their needs. With respect to the recommendations, there is overlap in the guidelines for endurance and power training. For example, although strength training will likely have lower rehydration requirements, the process of calculating sweat rates and consuming fluids to replace losses is the same as for endurance activities.



Photo 11-8 – Weight training can be an example of both a strength or power activity, depending on the number of reps and load. Photo by patrisyu from freedigitalphotos.net

Pre-event Nutrition

Strength training pre-event nutrition should provide sufficient energy to complete the workout or event while not causing any gastrointestinal discomfort. Both foods and fluids are required. The recommendation for a meal consumed 1-4 hours prior to the workout or event that provides carbohydrate at 1-4 $g \cdot kg^{-1}$ in combination with some protein is applicable. Carbohydrate intake is still highly relevant, as an athlete that goes into a workout in a state of carbohydrate depletion, will have to rely on other fuels to provide the energy required. A strength training athlete will want to preserve as much muscle mass as possible and does not want muscle protein being metabolized to provide the energy for their workout. For this reason, they will need to consume sufficient carbohydrate to fuel their workout. With respect to protein, whole foods and protein supplements will both be effective as long as high-quality proteins are being consumed. Many athletes choose protein supplements, but there is little to no evidence that they are more effective than protein-containing foods. Supplements also carry with them the risk of contamination with banned substances, which could put competing athletes at risk. Many supplements are also very costly.

During Event Nutrition

Athletes doing a strength and work-out should calculate fluid needs based on their estimated sweat rate (as discussed above). Carbohydrate intakes during resistance exercise are beneficial. Evidence regarding the benefit of a combination of carbohydrates and protein, especially the essential amino acids, is still controversial. Studies do show some benefits however, if adequate carbohydrate is consumed, the additional effect of adding protein is minimal (Jager, Kerksick et al., 2017). Excessive amounts of protein do not enhance muscle and will not digest well causing digestive upset. Excess protein also increases the risk of dehydration due to the need to excrete the unusable nitrogen released with protein breakdown. Furthermore, intakes need to be matched to the amount of energy that is expended during the workout. Regular monitoring of body weight is an effective way to assure energy intake and expenditure are matched. Importantly, excess carbohydrates and protein will result in a gain of mass, not muscle mass.

Recovery Nutrition

A focus on recovery nutrition is essential to achieve maximum benefit from strength workouts. Often the primary goal of a strength workout is to stimulate muscle protein synthesis (MPS), and studies show that exercise will promote MPS for at least 24 hours. Consequently, during the 24 hours post workout athletes will have increased sensitivity to protein intakes. A recovery snack or meal should be consumed as soon as possible after a training session or competitive event. The 30-minute rule mentioned for endurance exercise also applies here. For optimal MPS 0.25 to 0.3 $g \cdot kg^{-1}$ BW should be consumed within 2 hours. It is also recommended that protein intakes be spaced out every 3-5 hours and in multiple meals. Protein sources should be high-quality and supplements can be used, if intakes cannot be achieved through whole foods.

Supplements

For optimal performance, athletes are required to be in perfect health and physical fitness. The margin of error between winning and losing is very small and the pressure to win is extreme. As you can imagine, athletes are very interested in any supplement with the potential to enhance their athletic performance and increase their chances of winning. Inherent in a large number of athletes, is the belief that dietary supplements are required to give them a competitive edge and that a "normal" diet will not meet their needs.

Evidence suggests that most legal dietary supplements or ergogenic aids do not improve performance. However, there are a few exceptions to this. The most conclusive evidence exists for the use of creatine in short-power events, and caffeine during endurance events. There is also some evidence that sodium bicarbonate can be beneficial due to its ability to offset the decrease in blood pH, which occurs with physical activity. However, sodium bicarbonate is also associated with adverse gastrointestinal side-effects including diarrhea. Finally, dietary nitrates may enhance muscle function and increase blood flow. Other supplements such a carnitine, chromium, coenzyme Q10, and oxygenated water have not been found to enhance physical performance (Maughan, Burke et al., 2018).

Another concern with athletes and supplement use is the risk of inadvertently consuming a substance that is on the banned substance list. In this case, it could be deliberate or accidental. In either circumstance, the athlete is blamed and their awards can be withdrawn and sanctions imposed. Doping is a serious offense for an athlete and can be career-ending. It is extremely important for all athletes to be aware of the rules and make sure they follow them. This is difficult if they are consuming a product with unknown composition. You can get more information on doping regulation by going to the Canadian Centre for Ethics in Sport website: www.cces.ca.

Dietary and sport supplements can be beneficial for many athletes, particularly if the athlete has a nutrient deficiency that needs to be corrected. Products like sports bars and drinks are specifically designed to meet the athlete's needs and are easy to carry and drink or eat. They do tend to be expensive, however, and in most cases a well-planned diet can meet most of the athlete's needs. All athletes must be sure that the products they consume are permitted in their sport and that they are not contaminated with any banned substances. Several studies have tested the contamination of supplements and find that between three and 25% have steroids or stimulants not listed on the label (Judkins, Teale et al., 2010). Product purity can be ensured by using supplements that have been evaluated by an independent laboratory that certifies them as contamination free and appropriate for athlete use. One supplement company that verifies their product via independent testing is NSF International. NSF International has a NSF Certified for Sport Program. More information can be found at their website: www.nsfsport.com.

Summary

Physically active individuals and athletes alike require adequate intake of the sixessential nutrients: carbohydrates protein, , vitamins, minerals, and water. This ensures that all bodily processes are maintained, and adequate energy production can occur. The AMDR recommends 45-65% of kilocalories come from carbohydrates (4 kcal/g) and that athletes should strive for 3-12 g · kg^{-1} of body weight from carbohydrates depending on exercise duration and intensity. This ensures adequate energy for storage as blood glucose and glycogen. When carbohydrate intake is insufficient, individuals do not have adequate energy for intense physical activity. Protein (4 kcal/g) is required for energy supply and for replacement/production of bodily proteins. The AMDR for protein is 10-35% of daily energy intake or specifically 0.8-2.0 g· kg^{-1} of body weight depending on activity levels. Most Canadians consume adequate protein with their daily diet and do not require protein or amino acid supplementation. The third macronutrient, fat (9 kcal· g^{-1} is recommended to provide 20-35% of energy intake with no more than 10% from saturated fats. Dietary fat is required for many functions including energy production during low intensity physical activity. In addition to the three energy-providing macronutrients, we also require vitamins and minerals for wellness and optimal performance. Vitamins are organic substances required in relatively small amounts. For physically active individuals and athletes, the B vitamins, vitamin D, and the antioxidants (C and E) are particularly important. The B vitamins are critical in energy metabolism; vitamin D is important for bone health; and the antioxidants help to maintain balance with free radicals. Similar to vitamins, minerals are also required in small amounts, but are inorganic substances. Physically active individuals and athletes should be most concerned with adequate intake of zinc, iron, calcium and the electrolytes, sodium, potassium, and chloride. When individuals consume a calorically adequate and balanced diet, supplementation with vitamins and minerals is generally not recommended. A supplement will not compensate for a poor, insufficient diet and there is little evidence that high-dose vitamin or mineral supplementation will improve performance, in the absence of a deficiency. Water is the sixth essential nutrient and is critical for performance. Individuals should maintain water balance during physical activity to prevent dehydration-induced deterioration of performance.

Understanding energy requirements is critical in optimizing athletic performance. This includes both energy balance and the timing of specific nutrient intake. Energy balance occurs when energy intake is equal to energy expenditure, over a fixed period of time. A negative energy balance results in weight loss, whereas positive energy balance results in weight gain. Negative energy balance can result in conditions such as the triad and a positive energy balance can result in excess gain. By understanding energy needs, one can estimate how to achieve a healthy body weight and maintain or obtain a body weight that optimizes athletic performance. In addition to consuming adequate amounts of nutrients, athletes should be aware of when they are consuming foods and fluids. The pre-race nutritional strategies of athletes can involve many unique strategies such as carbohydrate loading, pre-event meals, and pre-event snacks. During an event, an athlete must consider both energy requirements and fluid/electrolyte needs based on duration, intensity, and other personal factors. Finally, after training or a competitive event, athletes require adequate recovery nutrition to ensure that they will be ready to perform at subsequent events.

Exercises or Topics for Discussion

- Design a dietary strategy for a 25-year-old male (70kg) who is completing his first marathon (42.2km road race). Include strategies for pre-race preparation, during race requirements, and post-race recovery. Ensure that both fluids and energy requirements are met.
- If this was a multi-stage event where the athlete was required to run a total of 250 km over 5 consecutive days, how would the dietary strategy for optimum performance be changed?
- Discuss the safety and efficacy of ergogenic aids in sports performance.
- Discuss how the 6 nutrients work together to provide an athlete with sufficient energy for physical activity. What can happen with a diet that is calorically inadequate or nutritionally unbalanced?

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Photographer: Riley Brandt
University of Calgary, 2012

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3: INTEGRATION OF EXERCISE PHYSIOLOGY

3.1: Chapter 12 - Body Composition; the Stuff We Are Made of

3.2: Chapter 13 - Potentiation and Fatigue, the Consequences of Repetitive Activation of Muscle

3.3: Chapter 14 - Molecular Basis of Exercise Training Adaptations in Skeletal Muscle

3.4: Chapter 15 - The Immune System Response to Acute and Chronic Exercise

3.5: Chapter 16 - Physiological Determinants of Athletic Performance

3.6: Chapter 17 - The Child- Responses and Adaptations to Physical Activity and Training

3.7: Chapter 18 - The Role of Physical Activity and Lifestyle in the Elderly

3.8: Chapter 19 - What are the Health Benefits of Regular Physical Activity?

3.9: Chapter 20 - High Altitude Physiology- Climbing Earth's Highest Peak

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3.1: Chapter 12 - Body Composition; the Stuff We Are Made of

This chapter is in preparation

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3.2: Chapter 13 - Potentiation and Fatigue, the Consequences of Repetitive Activation of Muscle



Photo 13-1 Tired boxer on break from exercise and training on the floor of a gym.

Learning Objectives

After studying this chapter, you should be able to:

- Describe the various forms of activity dependent potentiation
- Discuss the mechanisms of activity dependent potentiation
- Identify the difference between central and peripheral fatigue
- Discuss the potential causes and mechanisms of central and peripheral fatigue
- Illustrate changes in Ca^{2+} sensitivity and discuss the possible mechanisms
- Describe the metabolic changes in fatigued muscle
- Describe the changes in contractile properties associated with muscle fatigue

Key Terms:

activity dependent potentiation, calcium sensitivity, calmodulin, fatigue, central fatigue, peripheral fatigue, history dependence, myosin light chain kinase, postactivation potentiation, posttetanic potentiation, staircase potentiation, time-trial, twitch, postactivation performance enhancement

Introduction

Skeletal muscle has several properties that are considered history dependent properties. This means that muscle “remembers” that it has been active, or in some cases that length has changed, and this memory has very specific consequences with respect to the subsequent contractile response. This history dependence can be divided into three characteristic features: 1) potentiated (enhanced) contractile response due to recent contractile activity; 2) attenuated contractile response due to recent contractile activity and 3) enhancement or diminishment of isometric force by stretch or shortening respectively. The last of these will not be presented in this textbook. In the case of potentiation and fatigue, the magnitude of contraction for a given stimulation depends on the influence of these two processes, and the contribution of these depends on how much contractile activity has occurred in

the recent past and how long ago that contractile activity occurred.

Case Presentation: Does Warm-up Cause Neuromuscular Fatigue?

For the case presentation in this chapter, we will present the results for one subject in a study that was recently published in Journal of Applied Physiology (Tomaras and MacIntosh 2011). The name of the subject cannot be revealed due to confidentiality requirements, but we will assume this subject was “Andrew” (see Character Profiles). The study was conducted to determine whether or not the usual warm-up procedures followed by sprint cyclists in preparation for a flying 200 m time-trial are appropriate.

It was surprising to find out that sprint cyclists warm-up for 45 min prior to this sprint event, which takes about 10 s to complete. Their traditional warm-up typically consists of an aerobic component that involves progressive increase in exercise intensity over 30 min from 60 % of maximal heart rate to 95 % of maximal heart rate. This is followed by a series of 3-4 sprints, each of which lasts only 8 s. Each sprint is followed by a recovery ride for 1.5 min at low intensity and 6.5 min rest. In contrast with this warm-up, an alternative warm-up was designed by the study authors. The alternative warm-up was intended to prepare the cyclist for a competitive event, without overdoing it. This alternative warm-up, referred to here as the experimental warm-up involved 15.5 min of aerobic cycling, while increasing exercise intensity to 70 % of maximal heart rate and this was followed by just one 8 s sprint.

Andrew was asked to come to the lab on four separate occasions, but here we will describe the first two lab visits, and we will focus on the muscle contractile measurements that were made. On each of the two visits, Andrew had twitchcontraction measurements made prior to and after doing one of the two warm-ups completed in random order. A twitch is the contractile response to a single activation. In this case the single activation was applied to all motor units of his quadriceps muscles. Figure 13-1 shows the results of the twitch measurements for Andrew on each of these two visits.

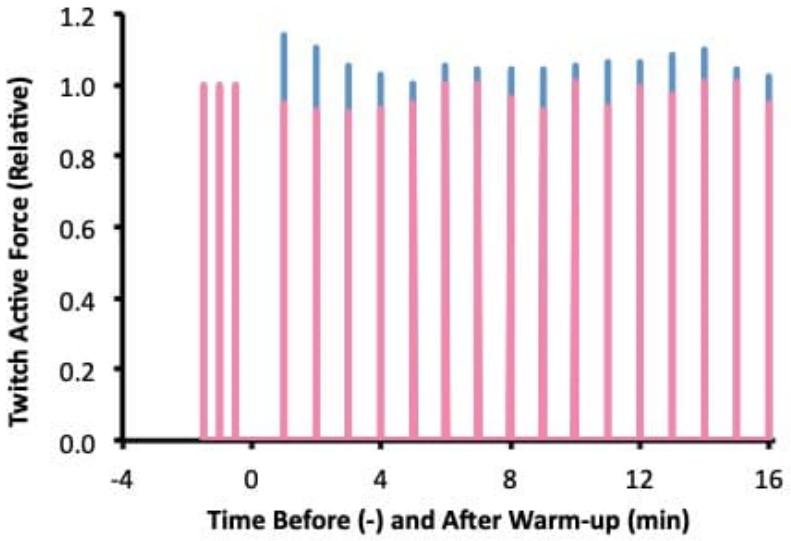


Figure 13-1. Twitch Contractions Before and After Warm-up. Three twitch contractions were obtained prior to and at one min intervals after either the traditional warm-up (pink) or the experimental warm-up (blue). Potentiation (enhanced contractile response) is evident after the experimental warm-up but is not obvious after the traditional warm-up.

Following each warm-up, the twitchcontractions undergo some dramatic changes, demonstrating postactivation potentiation and fatigue. The amplitude of the twitch at 1 min after the traditional warm-up was clearly less than 1.0. For the next two min, the twitch amplitude decreases, indicating that although fatigue was present, postactivation potentiation was also present, and this potentiation dissipates, revealing additional fatigue. The contraction was greater than 1.0 after the experimental warm-up, and decreased in amplitude over the next few minutes, illustrating the dissipation of this potentiation. Fatigue is not apparent in Andrew’s quadriceps muscles after the experimental warm-up. The twitch amplitude does not decrease below 1.0.

According to these results, Andrew would have an advantage if he did the experimental warm-up, but would be fatigued if he did the traditional warm-up. The performance results on the next two visits confirmed this advantage, as his power output on a cycle ergometer was higher when he did the experimental warm-up than when he did the traditional warm-up. His results were typical of the subjects in this study. The research confirmed that fatigue results from the traditional warm-up and higher power output

was achieved after the experimental warm-up.

Activity Dependent Potentiation:

Prior contractile activity results in enhanced contractile response which can only be adequately quantified with controlled activation. The most consistent way to detect this enhanced contraction is with electrical stimulation (MacIntosh et al. 2012c). This enhanced contractile response is referred to as activity dependent potentiation.

There are three forms of activity dependent potentiation: staircase potentiation, posttetanic potentiation and postactivation potentiation. The mechanism for activity dependent potentiation is common between these forms of potentiation. This mechanism is primarily dependent on regulatory light chainphosphorylation, as described below. Before we get to this mechanism, the contractile response associated with each of these forms of potentiation will be described.

Staircase

Repeated stimulation of muscle at a low frequency, resulting in discreet twitchcontractions or intermittent submaximal (incompletely fused) tetanic contractions, will result in a progressive increase in amplitude of these contractions (Figure 13-2), at least for the first few seconds. Staircase potentiation was first observed in isolated animal muscle, but the first report in human muscle was by Brown and Tuttle (1926). Staircase and is typically observed in research studies (Close 1967; Krarup 1981; MacIntosh and Gardiner 1987; Rassier and MacIntosh 2000).

The shape of the twitchcontraction gives some clues to the cellular mechanism associated with staircase. The twitch increases in amplitude, but contraction time is not longer (see Figure 13-3). This observation relates to the mechanism. The ways in which a twitch contraction can be affected in amplitude are illustrated in Figure 13-4. It can be seen here that an increase in amplitude of the twitch is dependent on the rate of rise of force and/or the duration of the rise in force. In the case of activity dependent potentiation, it is the rate of rise of force that determines the magnitude of the twitch contraction. This implies that potentiation is a property of intensity of activation, not duration.

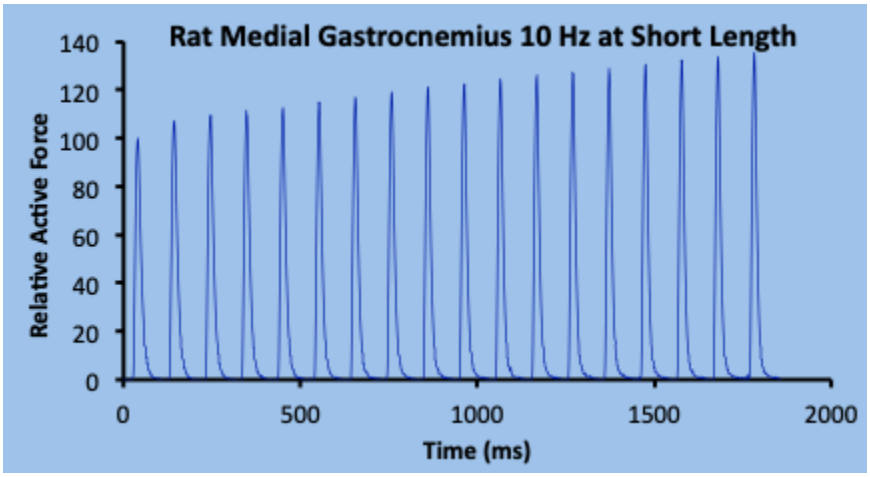
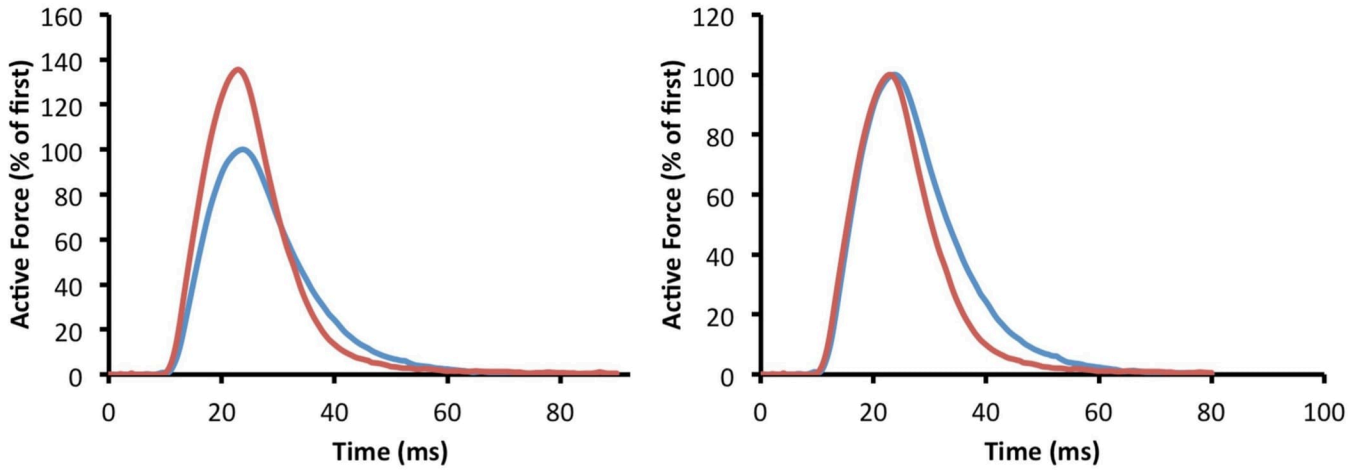


Figure 13-2 Staircase response in rat medial gastrocnemius muscle. Typical staircase in intact skeletal muscle is a progressive increase in amplitude for sequential contractions. The increase is sustained for several seconds before decline in force occurs. Sometimes the staircase is preceded by a slight decline in active force, but this is more likely in an isolated single fibre preparation.



13-3 Twitch contractions early and late in staircase illustrated in Figure 13-2. On the left, the first twitch in the sequence showing staircase is the smaller of the two contractions. You can see that staircase has resulted in a much larger twitch contraction, and that the contraction time (time from start of the twitch to the peak force) is minimally affected, but relaxation is accelerated. These differences are more obvious when the amplitudes of the two contractions are normalized to the same amplitude as shown on the right.

On the left, the first twitch in the sequence showing staircase is the smaller of the two contractions. You can see that staircase has resulted in a much larger twitch contraction, and that the contraction time (time from start of the twitch to the peak force) is minimally affected, but relaxation is accelerated. These differences are more obvious when the amplitudes of the two contractions are normalized to the same amplitude as shown on the right.

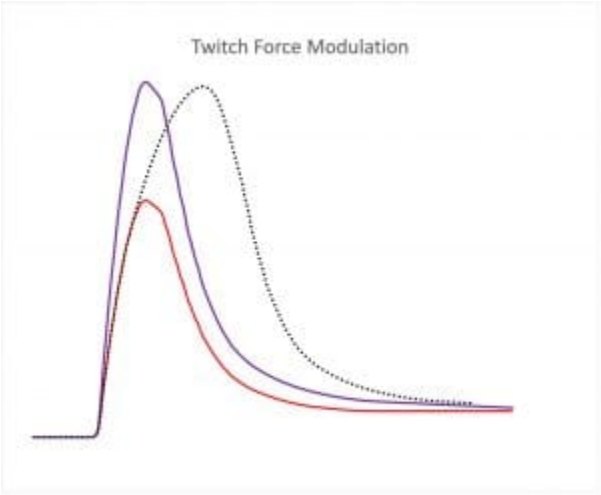


Figure 13-4 Modulation of Twitch Amplitude. The active force of a twitch contraction can be changed by changing rate of force development or by changing the time taken to rise to the peak of the contraction, often called the contraction time. Here, the red twitch is the control condition and the other two show how force can be increased by increasing the rate of rise of force or prolonging the time that force is increasing.

The progressive rise in force associated with staircase continues for several seconds. With consecutive contractions, active force reaches a peak, then begins to decrease as stimulation continues. This decrease clearly relates to fatigue, and the question that comes to mind with this change is “when did the fatigue begin”? Considering that when active force first begins to decline, the force is still above the initial contraction, so potentiation and fatigue coexist. It is possible that factors causing fatigue were present much earlier than the time when force first begins to decline. This issue of coexistence of fatigue and potentiation has been addressed in several publications dealing with activity dependent potentiation (Fowles and Green 2003; Green and Jones 1989; MacIntosh and Bryan 2002; Rankin et al. 1988; Rassier and MacIntosh 2000), and will be addressed further after fatigue is presented, later in the chapter.

Posttetanic Potentiation

A twitch or submaximaltetanic contraction will be enhanced following a tetanic contraction, relative to what it was prior to that tetanic contraction (see Figure 13-5). In these circumstances, the tetanic contraction that has caused potentiation is referred to as a conditioning contraction; that is, the tetanic contraction affects the contractile response of subsequent contractions, or it has altered the conditions under which subsequent contractions occur. When the following contraction is a twitch, similar to staircase, the twitch is increased in amplitude, but the time-course of the twitch is not prolonged. This implies that the mechanism of potentiation is associated with an intensification of the activation, not a prolongation of activation. The magnitude of enhancement varies with the duration of tetanic contraction, and is also dependent on the frequency of activation within the tetanic contraction. O'Leary and colleagues (O'Leary et al. 1997) reported nearly 50% increase in twitch contraction amplitude after 7 s tetanic stimulation at 100 Hz; in human subjects.

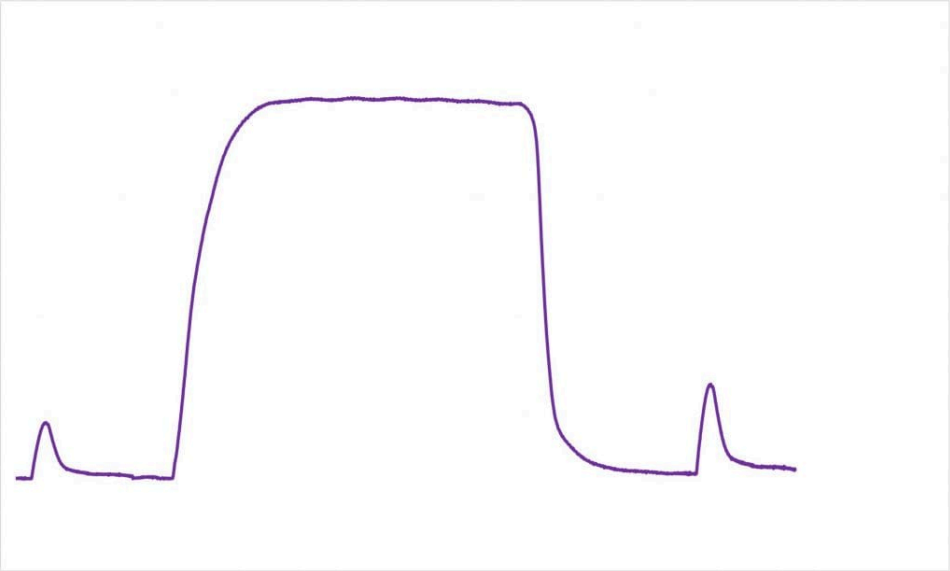


Figure 13-5 Posttetanic potentiation. The rat medial gastrocnemius muscle was used to obtain this sequence of twitch, tetanus and twitch to illustrate posttetanic potentiation. Following the tetanic contraction the twitch is much stronger than the original twitch obtained prior to the tetanic contraction.

Postactivation Potentiation:

When the conditioning contraction is a voluntary contraction, the subsequent enhanced contractile response is called postactivation potentiation (PAP). Typically,PAP has been measured as an enhanced twitch following a maximal voluntary contraction (Baudry and Duchateau 2007). However, PAP can occur following submaximal contractions (MacIntosh 2012). PAP can only be confirmed with electrical stimulation, to be sure the motor unit involvement is the same. There has been a recent glut of papers in the past 10 years that have used the term PAP without confirming that there was an enhanced contractile response for a given stimulation. For this reason, the term "postactivation performance enhancement" has been introduced (Cuenca-Fernández et al. 2017). This novel aspect of potentiation will be discussed below.

It is interesting to consider howPAP affects neural control of contraction. If the twitch is enhanced as a result of PAP, and submaximaltetanic contractions are also enhanced, then as PAP develops, the frequency of activation needed to achieve a given amplitude of contraction will change. This has been examined in a series of papers by Klein and colleagues. Young healthy subjects performed a 30% MVC isometric contraction before and after a 75% MVC conditioning contraction. The postactivation potentiation induced by the conditioning contraction was associated with a significant reduction in motor unit firing rate (Klein et al. 2001). When the same experiment was performed in older adults, the conditioning contraction resulted in a comparable amount of PAP but only a modest reduction of motor unit firing rate that was no longer correlated with the amount of PAP (Klein et al. 2002). We do not know what signal the central nervous system uses to modify the firing rate of a given motor unit to elicit the desired force when the force response obtained is changing so drastically. Researchers have altered the duration of the twitch contraction by either cooling the muscle or changing the muscle length which should change the force-frequency relationship. However, the motor unit discharge rate needed to duplicate the force of a control contraction did not necessarily change in concert with the changing contractile speed. Although not experimentally-proven, the central nervous system receives feedback on the amount of tension produced by the muscle and this feedback could be used to reduce the drive sent to the motoneuron

pool in situations where constant force is required. Whatever the signal is, it would appear to be negatively affected by age.

Now that we know what the various forms of activity dependent potentiation are, it is time to consider the mechanism of this history dependent property of muscle. Several possible mechanisms have been proposed over the years, but at the current time, only one mechanism is considered to be responsible for activity dependent potentiation. This mechanism relates to myosin regulatory light chain (RLC) phosphorylation, as described below. A second possible mechanism is also presented below.

The Mechanism of Activity Dependent Potentiation

Protein phosphorylation is one of the main forms of posttranslational modification of proteins. The addition of a phosphate group to a protein often activates it or modifies the tertiary structure of the molecule, changing its function in the process. Each myosin head contains a pair of light chains, one of which is phosphorylatable. This phosphorylatable light chain is called theRLC, because phosphorylation permits the RLC to alter the function of the myosin head. Figure 13-6 shows the location of the RLC on the myosin head.

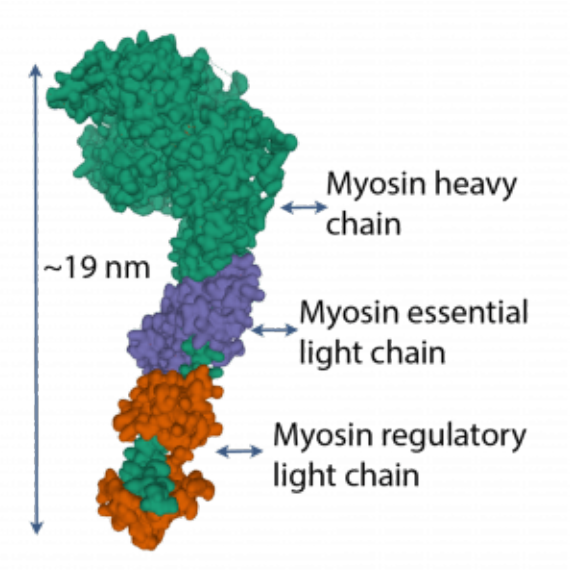


Figure 13-6 Model of myosin head. Each Myosin Head Contains Two Light Chains. Essential light chain and regulatory light chain which is phosphorylatable.

Phosphorylation and Dephosphorylation of Regulatory Light Chains

Before we consider how phosphorylation alters the myosin head function, we will discuss how theRLC gets phosphorylated. Phosphorylation is achieved by the enzyme, myosin light chain kinase (MLCK), which is inactive when the muscle is in a resting state.

When a muscle has been inactive for 6 min or longer, the light chains of myosin are minimally phosphorylated (about 10%). In this state, the contractile response is not potentiated. However, any muscle contraction will result in activation of the MLCK and this will result in an increase in light chain phosphorylation.

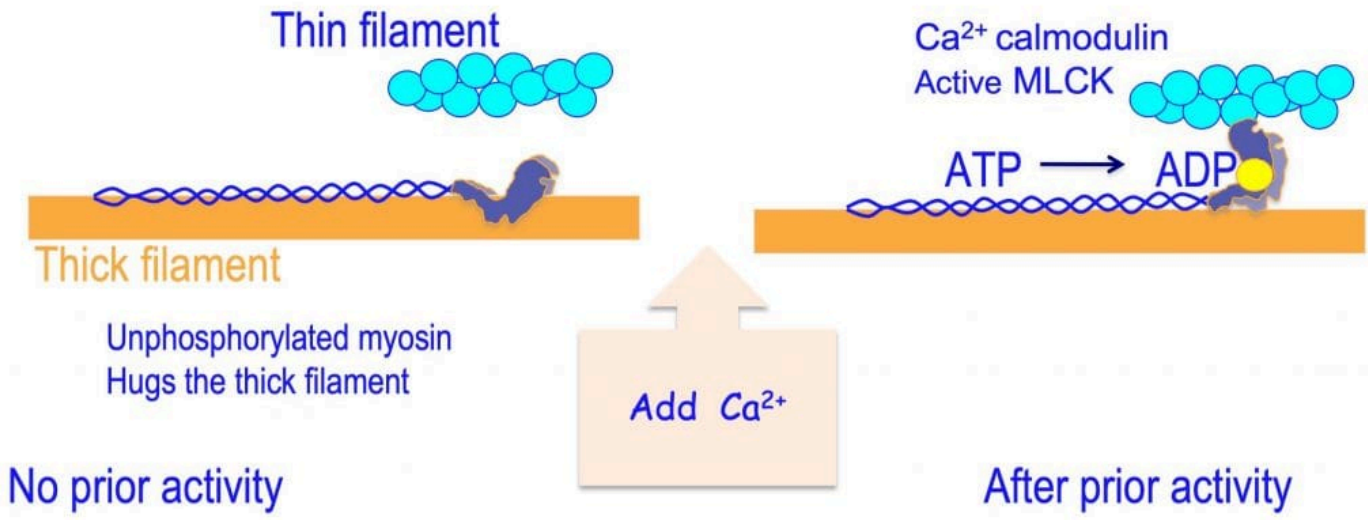


Figure 13-7 Regulation of Myosin Light Chain Kinase and Phosphorylation of Regulatory Light Chains of Myosin. On the left is shown a myosin molecule, lying tightly against the thick filament (note that there are two heads of myosin per molecule). When Ca^{2+} is added, as in activation, Ca^{2+} will bind to calmodulin and the Ca^{2+}-calmodulin complex will bind to myosin light chain kinase (MLCK), activating this enzyme. When MLCK is activated, it phosphorylates the regulatory light chains of myosin and this phosphorylation results in increased mobility of the myosin heads, allowing the myosin heads to become more disperse. This increases the number of myosin heads that are close to the actin thin filaments.

As you are aware, activation of muscle results in a rise in intracellular [Ca^{2+}]. Calmodulin is a Ca^{2+}-binding protein that functions in the activation of a number of proteins. One of these proteins that is activated by calmodulin is MLCK. When [Ca^{2+}] rises, Ca^{2+} binds to calmodulin and the Ca^{2+} – calmodulin complex binds to MLCK, activating it. The activity of MLCK depends on the [Ca^{2+}], so during contractions that are obtained with relatively high frequency of activation and therefore high [Ca^{2+}], the activity of MLCK will be high. This scheme of activation of MLCK is illustrated in Figure 13-7. This figure also illustrates the consequences of this phosphorylation.

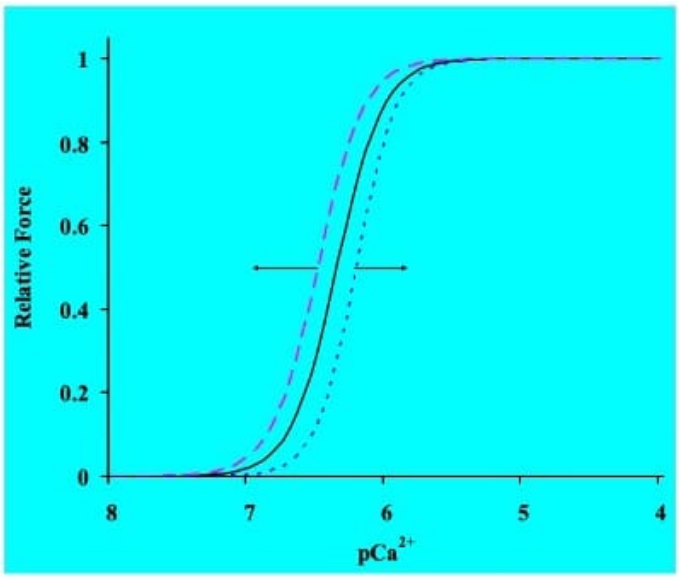


Figure 13-8: Calcium Sensitivity and Myosin Regulatory Light Chain Phosphorylation The control force-Ca^{2+} relationship is sigmoidal in shape and is shown in black. Here, [Ca^{2+}] is expressed as the negative log (pCa^{2+}), similar to the pH scale. A lower number is associated with a higher concentration. The fuscia coloured dashed line represents increased sensitivity to Ca^{2+}. This shift to the left would be expected with phosphorylation of a substantial proportion of regulatory light chains. Here, more force is developed for any given [Ca^{2+}]. The dotted blue line represents decreased Ca^{2+} sensitivity. Note that maximal force is not affected by Ca^{2+} sensitivity.

Factors Affecting Activity Dependent Potentiation

The magnitude of potentiation obtained following a conditioning contraction is dependent on several factors, including: the magnitude ofRLCphosphorylation, sarcomere length, temperature, test stimulus frequency, and fatigue. The interaction of these factors is presented in a review (MacIntosh 2003), but here we will briefly describe how these factors affect the magnitude of potentiation, and introduce how they interact. The nature of the conditioning contraction affects the potentiation by two mechanisms: it determines the level of activation of MLCK and the conditioning contraction can result in fatigue, a regulatory process that opposes potentiation (MacIntosh et al. 2012b) when energy resources in the cell are limited (see later in this chapter).

Magnitude of Light Chain Phosphorylation

The magnitude of RLC phosphorylation is dependent on the activities of two enzymes: MLCK and light chain phosphatase. As indicated above, MLCK is activated by increased [Ca^{2+}]. Light chain phosphatase is apparently unregulated, and has a low but continuous level of activity.

At rest, about 10 % of the light chains are phosphorylated. With each muscle activation, the enzymeMLCK is activated. When the interval between activations is short, the level of enzyme activation will accumulate, decreasing only slightly between contractions. It takes a few seconds for MLCK activity to decrease to the resting level. When MLCK activity is above the resting level, there will be an accumulation of phosphorylation of the RLC. When the MLCK activity is low, the light chain phosphatase activity will predominate, and the level of RLC phosphorylation will decline exponentially over time, to the resting level.

The magnitude of potentiation observed at a given level of phosphorylation is dependent on a number of factors. Most of these are described below. One such factor that is not presented below is the impact of [Ca^{2+}]. Take another look at Figure 13-8. At low [Ca^{2+}], the relative increase in force is large for a given increase in Ca^{2+} sensitivity. At high [Ca^{2+}] the relative increase in force is much less.

This consideration assumes that [Ca^{2+}] remains constant from one contraction to the next. A change in [Ca^{2+}] can contribute to potentiation or diminish its effect. It was shown recently that in a series of submaximal contractions, [Ca^{2+}] does not remain constant (Glass et al. 2021). In fact, the second and third contractions have increased [Ca^{2+}], and this increase will contribute to potentiation. This aspect of the mechanism of activity dependent potentiation has been given very little consideration.

Fibre Type:

You will recall from Chapter 4 that human skeletal muscle has three primary fibre types and rat skeletal muscle has four. The primary determinant of fibre-type is theATP isoform. Hybrid fibres with more than one ATP isoform do exist, meaning that not all fibres can be classified into the discreet fibre types. The myosin isoform composition of muscle can affect activity dependent potentiation in at least two ways.

In general, it can be said that a higher level of light chain phosphorylation is achieved in fast-twitch fibres than in slow-twitch fibres. This occurs as a result of differences in MLCK activity and differences in phosphatase activity. Fast-twitch fibres have higher MLCK activity, and lower phosphatase activity than slow-twitch fibres. For this reason, a given stimulation will result in a higher rate of regulatory light chainphosphorylation in fast-twitch fibres than in slow-twitch fibres. When stimulation has stopped, the rate of dephosphorylation will be slower in the fast-twitch fibres (Grange et al. 1993).

The second factor that affects fibre type difference for activity dependent potentiation is fatigue. Slow-twitch fibres tend to be more fatigue resistant than fast-twitch fibres. Any conditioning contraction will cause some fatigue and some potentiation. The resulting contractile response after the conditioning contraction will reflect the balance of fatigue and potentiation. In spite of the lower amount of fatigue, slow-twitch fibres still have less activity dependent potentiation than fast-twitch fibres. However, it has been observed that endurance trained individuals demonstrate more twitch potentiation than control subjects or resistance trained individuals (Hamada et al. 2000). This reported difference does not consider actual fibre type differences between these groups of individuals, and the reported difference in potentiation could be dependent on less fatigue in the fast-twitchtype IIa fibres.

Sarcomere Length

It has been known for some time now that the magnitude of potentiation obtained from a given conditioning stimulation is greater at short muscle length than at long length. In fact, it has been shown that even when twitch potentiation is evident at short sarcomere lengths, the same conditioning contraction will cause fatigue when measured by twitch contraction at long sarcomere lengths (Rassier and MacIntosh 2002). Rassier et al. (1997) showed that the length dependence of potentiation was not due to differences in magnitude ofRLCphosphorylation, so greater potentiation was evident at short sarcomere lengths than at long sarcomere lengths, for a given level of light chain phosphorylation.

The proximity of the myosin head to actin is also affected by sarcomere length. At long sarcomere lengths the filaments are closer together. The distance between the filaments is affected by the diameter of the fibre, and as the fibre is stretched, the diameter becomes smaller. This occurs because the volume of the fibre remains constant.

The proximity of the filaments, as sarcomere length increases, also increases the probability of myosin head interaction with actin, and increases Ca^{2+} sensitivity (Stephenson and Williams 1982). Obviously, light chain phosphorylation and long sarcomere length have similar effects. The two mechanisms are not additive when one of these mechanisms has optimally potentiated the muscle, the other mechanism can no longer enhance the contraction. For this reason, the magnitude of potentiation with a given level of light chain phosphorylation is greater at short sarcomere length, and much less at long sarcomere lengths where increased mobility of the myosin heads has less effect on probability of actin myosin interaction.

Temperature

The temperature of the muscle can affect the magnitude of potentiation for a given level of RLC phosphorylation. At room temperature, relatively little potentiation is observed when RLC phosphorylation increases from resting level to 50-60 % . However, the same increase in phosphorylation will result in considerably more potentiation at 37◈C, normal human body temperature. At colder temperatures, the magnitude of potentiation decreases even more (Gossen et al. 2001).

The mechanism for the temperature dependence of activity dependent potentiation is unknown, but MacIntosh has proposed a theory (MacIntosh 2003). It has been reported that the mobility of the myosin heads increases at cold temperatures (Xu et al. 2003), similar to the increased mobility observed with regulatory light chainphosphorylation. The absence of potentiation at low temperatures when the light chains are phosphorylated can be explained by the fact that Ca^{2+} sensitivity is already increased by this temperature dependent enhanced mobility, and cannot be increased further. The myosin heads are already more mobile, so light chain phosphorylation does not increase mobility and has no effect on Ca^{2+} sensitivity.

Test-stimulus Frequency and Duration

Historically, the presence of potentiation and measurement of its magnitude has been done using single pulse stimulation. Twitch contractions are the most sensitive way to evaluate potentiation, particularly when tested at a short sarcomere length. However, it is of interest to know the impact of activity dependent potentiation on contractions that are obtained with low frequency activation (stimulated or voluntary). This range of frequencies would have the most relevance for voluntary activation.

Warm-up Effects of Postactivation Potentiation

It has been suggested that postactivation potentiation can enhance brief maximal effort contractions (Sale 2002). This suggestion is based on the fact thatPAP increases the peak rate of force development, so early in a maximal effort contraction, the force will rise faster. When the contraction is so brief that maximal voluntary force cannot be reached, the potentiated contraction will be of greater magnitude than the nonpotentiated contraction. This is illustrated in Figure 13-9, where it can be seen that force rises faster in the potentiated state, so when the contraction is very brief, a greater active force is obtained than before the conditioning contraction (nonpotentiated state). The suggestion that maximal effort performance should be enhanced by a prior conditioning contraction set off a series of research studies to test this idea. This notion is like taking a practice golf swing, then stepping up to address the ball. Keep in mind that potentiation might increase the possible force of the swing, but other factors, like coordination will dictate the direction the ball goes.

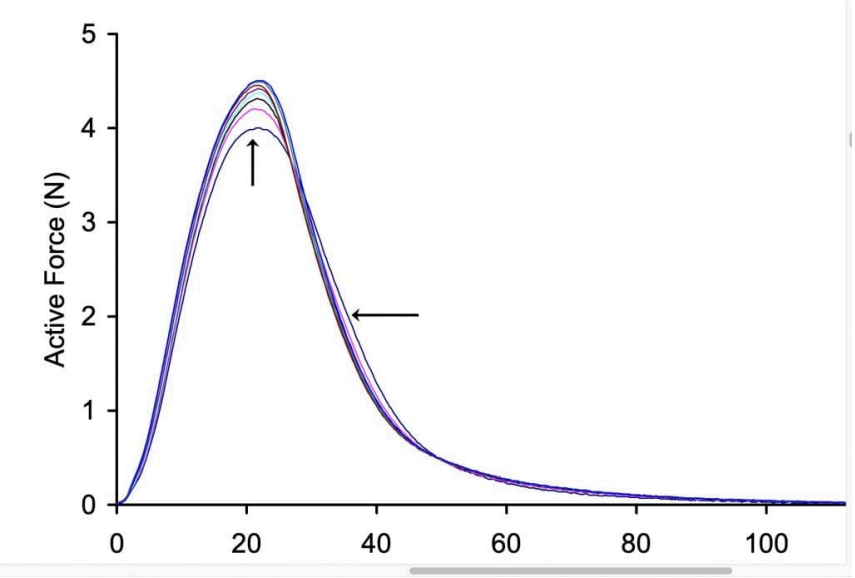


Figure 13-9 A potentiated brief tetanic contraction will be stronger. Here, a sequence of high frequency doublets (200 Hz) is shown for rat medial gastrocnemius muscle (MacIntosh et al. 2008). Note that peak rate of force development increases, in spite of the fact that 200 Hz stimulation gives a maximal steady state force (see Figure 13-5).

In spite of considerable interest in this concept ofPAP assisted performance, it has been difficult to prove that PAP can contribute to the warm-up in a way that enhances subsequent performance. Early attempts to demonstrate this aspect of warm-up were successful at demonstrating the importance of fatigue in impairing subsequent response (Gossen and Sale 2000). This is consistent with work described in the case study (see beginning of chapter) that has confirmed that some athletes do too much warm-up (Tomaras and MacIntosh 2011). However, in spite of a large number of attempts, it has not been clearly demonstrated that high intensity conditioning contractions as part of the warm-up can enhance subsequent high intensity performance by PAP. The difficulty is that even when performance enhancement is observed, it has not been possible to confirm that PAP is the determining factor. In fact performance enhancement after a conditioning contraction appears to follow a different time-course than PAP. For this reason, the term “postactivation performance enhancement” (PAPE) has been introduced (Cuenca-Fernández et al. 2017). This is a more general term that can be used for any mechanism that enhances performance following one or more high intensity conditioning contraction(s).

Several studies have investigated what they call PAP, but have not confirmed the presence of PAP. These studies have typically investigated the impact of a high intensity warm-up on subsequent performance, and several such studies have confirmed that the high intensity effort during the warm-up is associated with improved performance. In many cases the performance was evaluated at a time when it would not be expected that PAP was present. Typically, performance assessment is made 8 min or longer after the conditioning contraction. However, this research does not rule out some other factor, like temperature actually causing the improved performance. Regardless of whether or not PAP does allow enhanced maximal effort performance, it would only make a difference within the first few contractions of a performance. Eventually, the effort itself will result in PAP, then fatigue. The ideal situation would be if you could induce PAP by a conditioning contraction that resulted in very little fatigue. Then the first few maximal effort contractions would be enhanced by the increased maximal rate of force development.

As mentioned above, PAP can coexist with fatigue. This can occur because the mechanisms that cause fatigue can coexist with or counter the mechanisms that cause PAP (Rassier and MacIntosh 2000). Now we will turn our attention to fatigue; what is it and what are the mechanisms?

Skeletal Muscle Fatigue

Definition of Muscle Fatigue:

The term “muscle fatigue” is used in a broad range of contexts. For this reason, it is a term that often needs to be interpreted from the context of its use (see discussion of definitions in Chapter 1). Fatigue can be used in a general sense to refer to a state ofmental tiredness. Fatigue is also used to refer to solid structures that are failing due to use. However, in this chapter we will use the term “fatigue” to refer to a short-term depression of contractile response that is attributable to prior exercise.

Traditionally, fatigue has been defined as an exercise-induced reduction in the ability of muscle to produce force or power whether or not the task can be sustained(Bigland-Ritchie and Woods 1984; Søgaard et al. 2006). When performing maximal voluntary contractions, it is pretty easy to observe the failure of force production. However, there are relatively few activities, even in competitive sport, that require the maintenance of maximal force or power for any length of time. Instead, most of our activities require the maintenance of submaximal force or power, intermittently over time. Although someone may be able to maintain the target force or power, it doesn't mean that they are not becoming fatigued. In the same way, just because maximal isometric force is not depressed does not mean fatigue is absent.

A valuable way to evaluate fatigue is to stimulate all motor units of a muscle with a known frequency of activation. This can be as simple as a single pulse, or a series of activations with a range of frequencies. This approach has been particularly valuable in detecting low-frequency fatigue. When fatigue is defined as a reduction in maximal force, low-frequency fatigue is not detected. Typically, to accurately quantify fatigue, stimulation is applied to the motor neurons, and the muscle force is measured. Alternatively, the stimulation could be applied directly to the muscle of interest. In both of these cases, the detection of fatigue relies on what is going on in the periphery. The central nervous system is bypassed. This approach to detection of fatigue can only detect peripheral fatigue (see below). Furthermore, this approach requires special equipment (stimulator and force measuring device) that is not universally available.

Low-Frequency Fatigue

It is important to remember that muscle fatigue can exist, even when maximal force is not decreased! When the force depression following exercise persists only at lower frequency of stimulation and maximal force has recovered, it is called low-frequency fatigue. This is illustrated in Figure 13-10. Low-frequency fatigue is typical of postexercise fatigue and can persist for more than 24 hours (Edwards et al. 1977).

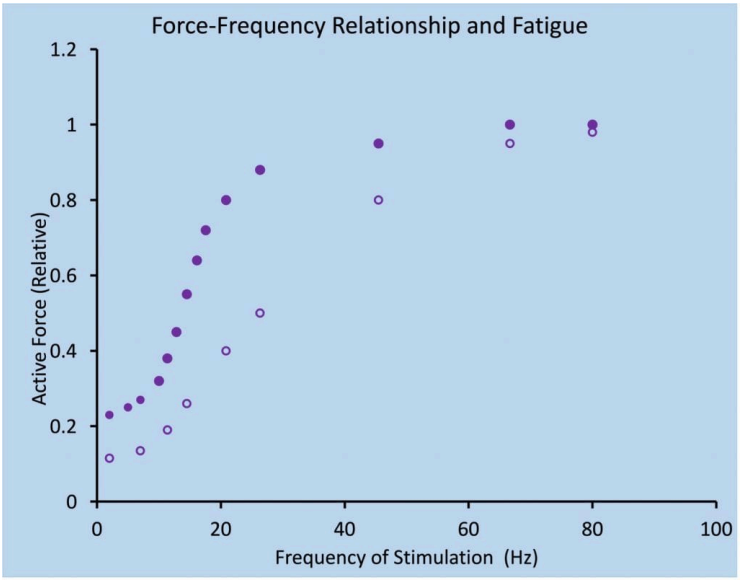


Figure 13-10. Low-frequency fatigue is greater depression of force at low frequency. The solid symbols represent control muscle and the open symbols represent active force measured after 20-40 min of recovery. Force is more depressed at low frequencies, but approaches the prefatigued level at higher frequencies. In some cases, maximal voluntary force may be no different than prior to the exercise

Low-frequency fatigue is detected by stimulating the muscle at low and high frequencies in order to determine if the depression of force is greater at the lower frequency. Alternatively, the low frequency response can be compared with a maximal voluntary contraction which is assumed to represent a high-frequency response. There are many publications that describe low-frequency fatigue as the consequence of repetitive low-frequency stimulation, but this is not the true definition of low-frequency fatigue. The frequency of activation during the exercise is not relevant to the development or observation of low-frequency fatigue.

Low-frequency fatigue is very relevant to those who engage invigorous intensity exercise on a regular basis. Recovery from low-frequency fatigue is very slow, so subsequent exercise performance can be compromised, even 24 hours later. Most training programs consider this and never put two hard workouts on successive days. Low-frequency fatigue is a common consequence of a bout of lengthening contractions (Keeton and Binder-Macleod 2006).

Mechanisms of Fatigue

In order to address the mechanisms of fatigue, the pathway for motor command must be considered. This pathway is illustrated in Figure 13-11. Here, it can be seen that to exercise, or maintain a constant force or power output, one must engage the neural pathway from motor cortex to spinal motor neurons. The final structure in this pathway is the skeletal muscles. Fatigue could be a consequence of failure at any point along this motor command pathway. This pathway can be divided into two areas: central and peripheral; representing the central nervous system and the peripheral nervous system and muscles.

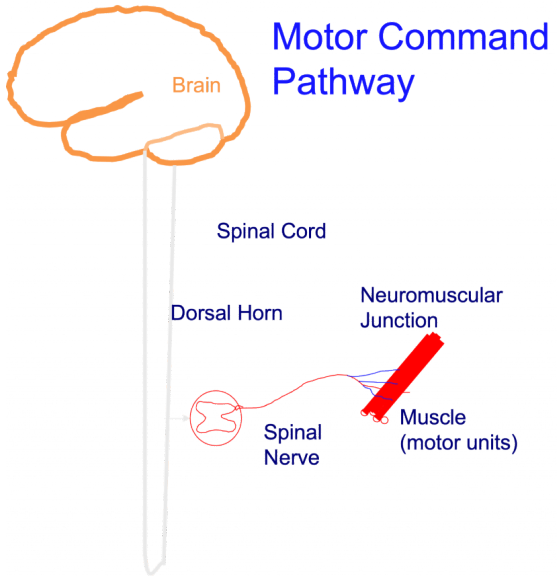


Figure 13-11. Motor Command Pathway The motor command pathway encompasses all structures from the motor cortex to the myocytes. Failure at any point along this path can result in impaired force, detected as fatigue. When failure occurs within the central nervous system (brain and spinal cord, it is considered central. When failure occurs outside the central nervous system (motor axons, neuromuscular junction, myocytes) it is considered peripheral.

Central fatigue is failure of force production because the activation of the motor nerves is impaired. This can be a failure of descending voluntary drive to the motor neuron pool, or failure of the motoneuron(s) to discharge. Failure beyond this point is considered peripheral. Peripheral fatigue includes failure of the signal to transmit along the motoneuron axon or across the neuromuscular junction (which are not really factors except in disease), and failure in the steps of excitation-contraction coupling. Peripheral fatigue occurs primarily when excitation-contraction coupling fails: the action potential fails to conduct along the muscle fibre membrane, or down the t-tubules, there is inadequate Ca^{2+} release or the contractile apparatus fails to produce the required or expected force. Peripheral fatigue during exercise is heavily dependent on the chemical state of the muscle. However, in recovery there appears to be less Ca^{2+} released with each activation in spite of recovery of homeostasis. Whether central or peripheral fatigue is present is highly dependent on the task being performed: static vs. dynamic; intermittent vs. sustained; high force vs. low force. There is also a difference when a given force is maintained by maintenance of position or maintenance of force, using feedback of these parameters. These task dependencies will be discussed later but first we present an overview of central and peripheral fatigue.

Peripheral fatigue is potentially due to one of the following: a lower [Ca^{2+}] achieved during activation, decreased Ca^{2+} sensitivity or less force per cross-bridge. There is considerable evidence for all of these mechanisms, but the actual cause of the decreased [Ca^{2+}] or decreased Ca^{2+} sensitivity is not as clear.

Does Fatigue Represent Regulation of Activation?

It has been suggested that fatigue, a decreased contractile response for a given stimulation, is a regulatory process designed to prevent depletion ofATP (MacIntosh et al. 2012b). This explanation of fatigue seems very logical and evidence is obvious. The first line of evidence relates to the fact that ATP concentration is strongly defended, typically falling to 60-70% of the resting value only after exhaustive exercise (Harmer et al. 2000). This is important, because the ratio of the concentrations of ATP andADP give the energy charge for processes using the energy from ATP. When [ATP] decreases or [ADP] increases, the energy available for cellular processes decreases. There are several ways that decreasing [ATP] can affect excitation of the myocyte: depolarize

the membrane with inhibition of the Cl^- and K^+ channels, and impair Ca^{2+} release by the ryanodinereceptor. It has also been suggested that glycogen depletion might regulate Ca^{2+} release, contributing to a regulated fatigue process (Ørtenblad et al. 2011).

Central Fatigue:

Central fatigue is evaluated through the estimation of voluntary activation. The most common technique, because of its simplicity, low cost, and low risk, is called the interpolated twitch technique. This was first developed by Merton (1954) and popularized by Belanger and McComas in the early 80s (1981; 1989). There has been a commentary in the Journal of Applied Physiology debating the accuracy of the technique (de Haan et al. 2009; Taylor 2009). The technique involves superimposing a supramaximal electrical stimulus to the peripheral nerve innervating the contracting muscle group. The premise is that if the voluntary contraction is truly maximal, then the addition of an electrical stimulus ought to evoke no more force than that already being produced. If anything, the additional stimulus results in a period of electrical silence in the muscle and a corresponding drop in force. On the other hand, if the voluntary contraction is not maximal, the increase in frequency of firing of active motor units or the recruitment of additional motor units will produce a brief increment in the force production. This interpolated twitch has been quantified, by dividing the incremental force by the peak force of a potentiated twitch evoked at rest immediately after the MVC. Equation 1 presents the method of calculating voluntary activation ratio (VAR) and Figure 13-12 illustrates this technique.

VAR = 1 – (Twi/Twp) Equation 1

Where VAR is voluntary activation ratio, Twi is interpolated twitch amplitude and Twp is potentiated twitch amplitude.

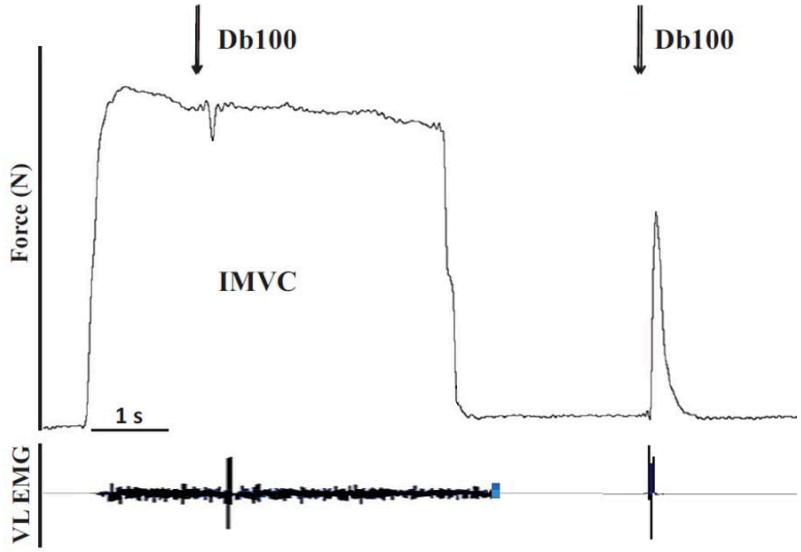


Figure 13-12. Doublet Superimposed on Maximal Voluntary Effort. EMG is shown below force and doublet stimulation is evident during the maximal voluntary contraction and a few seconds after. The force response to the stimulation during the maximal voluntary contraction is very small, but is very large when stimulation is given during rest. Db100 is doublet at 100 Hz. IMVC is isometric maximal voluntary contraction. 1s indicates 1 second,. VLEMG is vastus lateralis electromyogram.

It is recommended to use the potentiated twitch because the voluntary contraction will cause activity dependent potentiation so the interpolated twitch will likely be potentiated. The use of a nonpotentiated twitch in the equation would result in underestimation of the VAR. On the other hand, if the interpolated twitch results primarily from recruitment of inactive motor units, these should not be potentiated.If the voluntary contraction is close to maximal, it can be quite difficult to detect the small increment in the force production when the extra stimulus is applied. There are different ways to try and improve this detection. One method is to superimpose a doublet (two pulses with a short inter-impulse interval – less than 10 ms) instead of a single stimulus. This creates a bigger force, and hence improves the resolution of the force difference when superimposed on the voluntary force. To make the proper calculation, the potentiated twitch must also be obtained with doublet stimulation.

It has been reported that true maximal force is more easily achieved in some muscles than others (Shield, 2004 #18056). However, in a noninjured limb that is free of pain, most individuals are capable of near maximal activation. This allows the use of this technique to detect central fatigue. If voluntary activation, as calculated using equation 1, decreases as a result of physical

effort, then central fatigue is present.

Mechanism of Central Fatigue

We have just dealt with one easy way to measure central fatigue. The causes of central fatigue can be placed in three categories: (A) insufficient descending drive to the motoneuron from central sources; (B) inhibition of the motoneuron at the spinal level; (C) changes to the motoneuron intrinsic properties that make it difficult for the motoneuron to be repetitively active (see below).

The interpolated twitch technique cannot differentiate between central fatigue that is occurring at the level of the spinal cord or the cortex. Magnetic stimulation can be applied to the cortex (transcranial magnetic stimulation, TMS) and an increment in torque evoked by TMS during an attempted MVC suggests that the neural drive from the motor cortex was suboptimal to activate and/or drive the motor units maximally despite maximal voluntary effort (Gandevia et al. 1996; Søgaard et al. 2006). Although spinal sources of the central fatigue cannot be excluded (because the signal passes through the spinal cord and would be influenced by inhibition occurring at that level), an increment in torque following cortical stimulation suggests that motoneurons could be activated with additional descending drive. Thus, suboptimal output from the motor cortex contributes, at least in part, to the failure in voluntary activation. Unlike the interpolated twitch technique, the contribution of failure of cortical drive to the overall decrease in voluntary activation is problematic to quantify using TMS because the amplitude of the superimposed twitch evoked by TMS cannot be expressed as a fraction of the twitch evoked by the same stimulus in the relaxed muscle. The excitability of the cortical and spinal motoneurons is substantially lower in the resting state so typically it is not possible to get a twitch contraction in most relaxed muscles (apart from the hand where direct corticospinal projections are prevalent). To get around this problem, the TMS evoked twitch is obtained with different levels of voluntary activation (i.e. 50, 75 and 100% effort) and linear regression is used to estimate the amplitude of the potentiated twitch (Todd et al. 2003).

Case Study: An Example of Central Activation Failure

I will use Joseph as a case example to illustrate the clinical application of the interpolated twitch technique. Before Joseph moved from Toronto, he used to work at Ford Motor Company in Oakville, a job that required him to repetitively take objects from one conveyor belt and place them on another. Over time, this rotational activity flared up an old hockey injury in his knee. Xray confirmed quite advanced osteoarthritis and cartilage breakdown, requiring him to have surgery. Return to work required him to rebuild his quadriceps strength. This progressed quite slowly and he was off work for nearly a year. As part of the return to work evaluation, his strength was tested with administration of the interpolated twitch technique. The presence of a superimposed twitch led to concerns that he was not putting his full effort into his rehabilitation program. His voluntary activation ratio was 0.72. The trouble with using the interpolated twitch to make such judgments is that the interpolated twitch tells you that he has central failure of voluntary activation but it doesn't tell you why.There are several factors that can lead to such a result. First, a period of immobilization has been shown to influence voluntary activation. Experiments that immobilized a healthy limb are helpful because they separate the impact of immobilization per se from pain and/or tissue damage that would be present in real life. Seki and colleagues immobilized a hand muscle for 6 weeks and found a reduction in the maximal discharge rates of the motoneuron. It is possible that there were changes in the intrinsic properties of the motoneuron (Kernell 1966) resulting from disuse (C). Immobilization has also been shown to reduce the descending drive (Sale) (A).

Second, the presence of persistent pain can inhibit the spinal motor neurons through the small diameterafferent neurons (B). There is extensive literature to demonstrate that small diameter afferents activated by mechanical or chemical stimuli can inhibit the motoneuron. A number of paradigms have been used to evaluate this pathway. In animal models, chemical byproducts of muscle contraction have been injected and the motoneuron was inhibited. In human models, when small diameter afferents were blocked and unable to provide input to the spinal motoneurons, there was no inhibition of the H-reflex. The H-reflex is an electrical analogy of the stretch reflex; stimulation of afferent neurons will reflexly activate alpha motoneurons.

Third, a failure to voluntarily activate the muscle may be a motor control issue. Persistent pain can result in abnormal co-contraction of muscles about the joint – a way of "bracing" the joint. This reduces the net force and makes it more difficult to produce a maximal contraction. In addition, after an extended period of relative disuse, the highestthresholdmotor units may be difficult to recruit (use it or lose it problem).

Thus, while the interpolated twitch is very useful at detecting failure of voluntary activation and central fatigue, it does not give the practitioner license to assume the patient is simply not trying hard enough.

Peripheral Fatigue:

Skeletal muscle fatigue has often been studied in isolated muscles. This approach can be conducted from single fibre to whole muscle level. To understand the changes in contractile properties of muscle, work on whole muscle has been most revealing. Below, we will present observations on the contractile properties of whole muscle when fatigue has been imposed on the muscle. Following this, the consequences of peripheral skeletal muscle fatigue on whole body exercise will be presented.

Symptoms of Skeletal Muscle Fatigue

The development of fatigue is a process that occurs with a speed that is dependent on the exercise intensity of the individual muscles involved in an exercise. Fatigue is often quantified by measurement of the maximal voluntary force, and this is one of the early symptoms of fatigue. However, while maximal voluntary force is declining, the force elicited with submaximal frequencies may actually increase, before they decrease. This increase is associated with two potential factors: activity dependent potentiation and slowing of relaxation. The decrease in force is associated with less force for a given activation. If the fatiguing task requires maintenance of a submaximal force (continuous or intermittent), eventually additional motor units will need to be recruited to allow continuation with the task at the same force or power output. This will manifest as an increasing magnitude ofEMG and corresponds with a perception that the task is more difficult.

The Force-Frequency Relationship

The force-frequency relationship is sigmoidal in shape and is obtained by stimulating the muscle briefly with a variety of stimulation frequencies, such that force varies from a twitch level to maximal force. For human muscle, this requires a range of frequencies from 1 to about 70 Hz. The resolution of the relationship depends on how many frequencies are tested. Figure 13-13 illustrates the force-frequency relationship for fast and slow-twitch muscle.

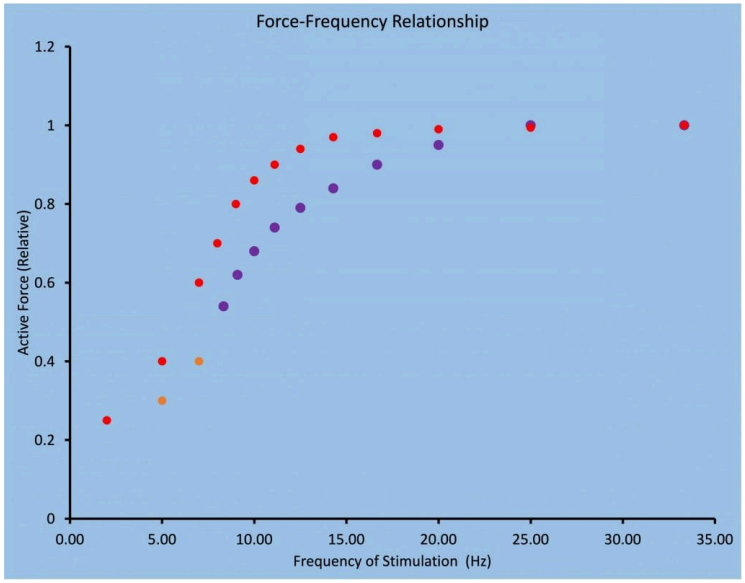


Figure 13-13; Force-frequency relationship for fast-twitch and slow-twitch muscle. This graph shows the force-frequency relationship for fast- and slow-twitch motor units (normalized to the maximum force). Note that slow-twitch motor units rise to maximum force at a lower frequency than fast-twitch motor units However, fast-twitch motor units are typically larger than slow-twitch units, so maximum force will be lower in slow-twitch than in fast-twitch motor units.

As fatigue develops, force for low-frequency stimulation will actually increase due to activity dependent potentiation, bur force for high-frequency stimulation will simply de crease (MacDougall et al. 2020). Figure 13-14 illustrates the change in force expected for 3 frequencies of stimulation (1, 10 and 50 Hz) for the triceps surae muscle during a fatiguing task. Measurements are presented at the times that voluntary force decreases from 100% to 80%, 50% and 25%. Note that at 1 Hz and 10 Hz, the decrease in the stimulated responses is not as great as the decrease in voluntary force generation. In fact, when voluntary force has decreased by 20%, stimulated responses are potentiated at 1 and 10 Hz. In contrast, the 50 Hz stimulated responses follow the voluntary force fairly well.

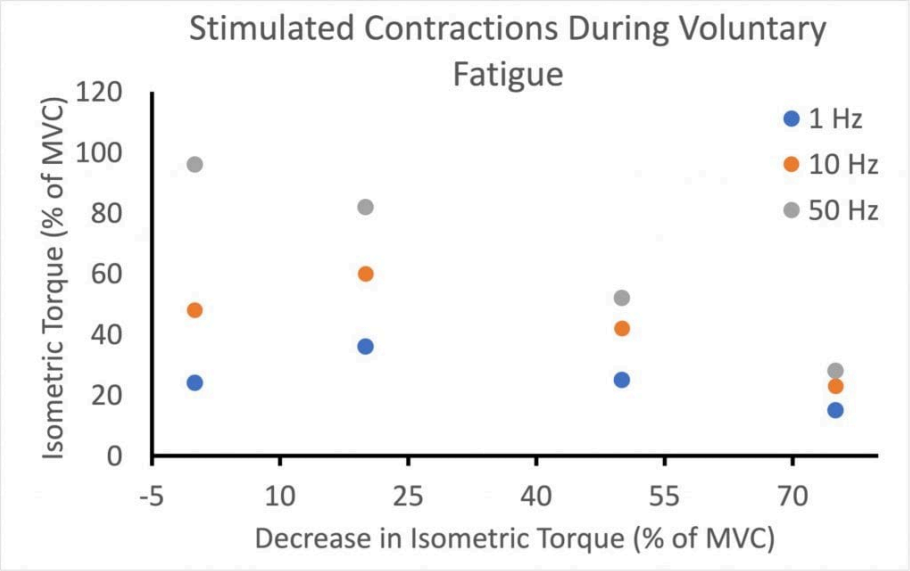


Figure 13-14; Change in stimulated force during fatigue. As maximal voluntary force decreases, stimulated force at low frequency (1 and 10 Hz) first increases, then declines. The increase is a consequence of activity dependent potentiation and the decrease is a consequence of fatigue.

The Force-Velocity Relationship in Fatigue

As presented in Chapter 5, the force-velocity relationship can be defined by maximal isometric force, maximal velocity and the curvature of the relationship. In fatigue, all three of these parameters can change. There is a decrease in isometric force and maximal velocity and an increase in curvature (Kristensen et al. 2020). However, in some cases the curvature actually decreases, which is thought to preserve power (Devrome and MacIntosh 2018). Less curvature means force does not decrease as much as would be expected in the middle range of the force-velocity relationship.

The force-velocity relationship is thought to be important in determining power output during cycling. In this case, the relationship between torque and angular velocity is for multijoint movement, not a single muscle. The torque, angular velocity relationship of cycling cannot be obtained over the full range of velocities, because the crank limits the time available for application of force against the pedals before the range of movement dictates a necessary change in direction of movement. For this reason, the relationship is linear, not curvilinear (See Figure 13-15). This relationship is obtained by measurement of torque and angular velocity during an acceleration where measurements are made during each crank revolution. Making this measurement after a Wingate test (30 s all-out on a cycle ergometer) results in a nearly parallel shift in this relationship. When power is considered, it can be seen that peak power decreases and the optimal conditions for peak power also shift to the left.

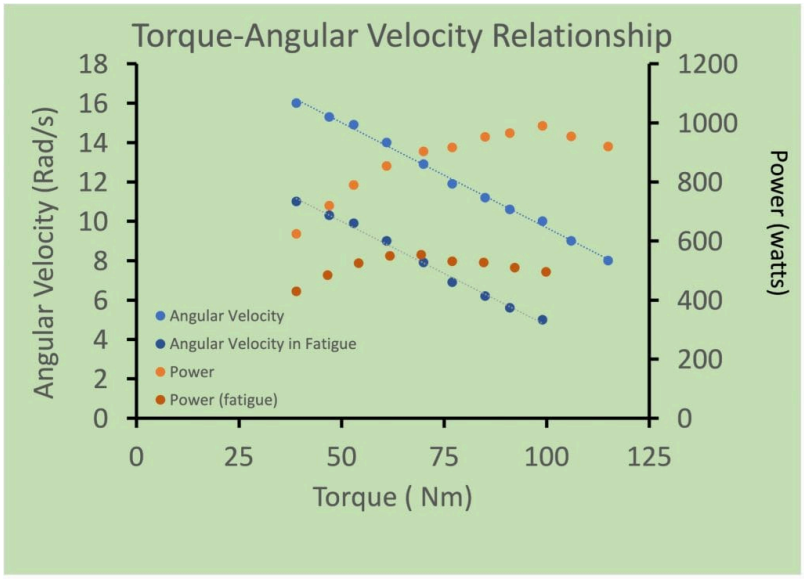


Figure 13-15: Torque-angular velocity relationship for cycling before and after a Wingate test. This graph illustrates the torque-angular velocity relationship and the corresponding power-angular velocity relationship measured prior to and after a Wingate test.

Fatigue and the Force-Length Relationship

There are a few publications that illustrate greater fatigue at shorter length than at longer length, similar to that illustrated in Figure 13-16. However, it was demonstrated that this length dependence of fatigue was a consequence of inappropriate calculation of active force. Traditionally, Active force has been calculated by subtracting the passive force measured prior to a contraction. However, when a muscle contracts (fixed end contraction) the force of contraction stretches the tendon. When the contraction begins at a relatively long length, the passive force will decrease as the tendon stretches and the fascicles shorten. When active force is properly calculated (see Figure 13-17) there is a parallel shift down in active force across all lengths.

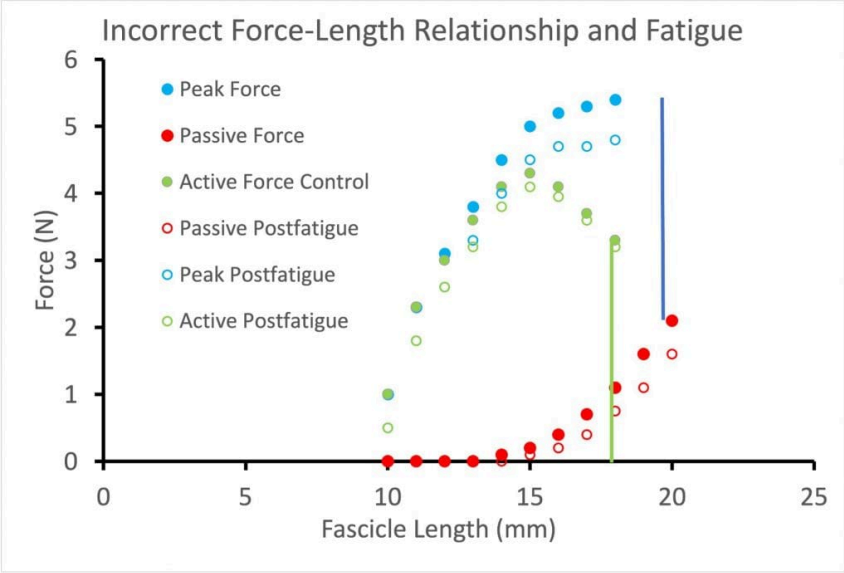


Figure 13-16 Incorrect calculation of active force. Active force decreases more due to fatigue at short length than at long length when active force is estimated with the passive force measured prior to the contraction. This yields an incorrect active force and less apparent fatigue at long lengths. The vertical blue line represents the difference between passive force measured prior to the contraction and peak force. The vertical green line is the same length as the blue line, showing the calculated active force.

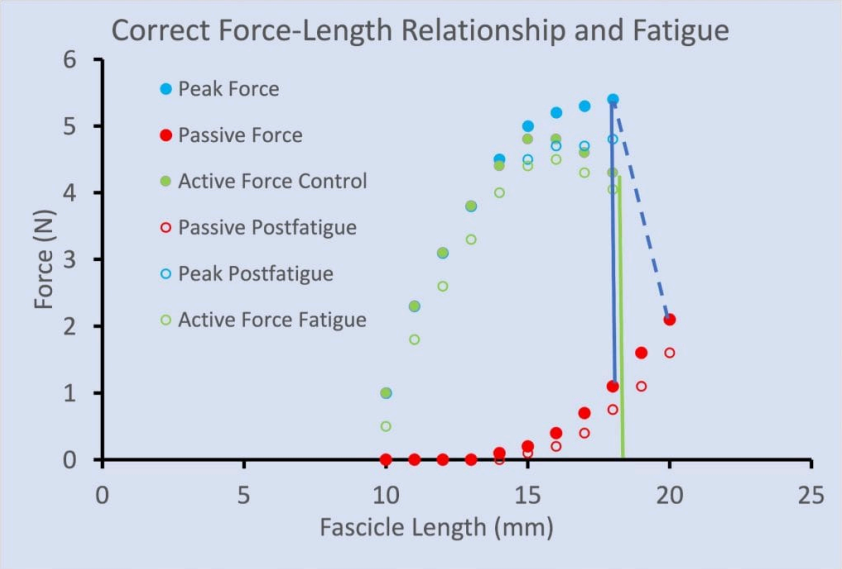


Figure 13-17 Correct calculation of active force: When the passive force is estimated for the fascicle length achieved at the peak of contraction, the correct active force is obtained and fatigue results in similar decrease of active force across all lengths. The dashed blue line represents the change in force during a contraction. When the passive force estimated at the peak of the contraction is subtracted from the peak force (solid blue line), a more accurate active force is obtained (solid green line).

Metabolic Changes with Peripheral Fatigue

When exercise is initiated, the active motor units will experience increased use of ATP, resulting in an increase in [ADP]. However, this change in concentration ofADP is small because the metabolic control systems are geared to replenishATP almost as fast as it is used. As a consequence of the increased metabolic replacement of ATP, the following will increase in concentration in the active myocytes: creatine, inorganic phosphate (Pi), H^+, lactate and other intermediates of the glycolytic pathway. Glycogen concentration will decline in proportion to the intensity of exercise and the duration of exercise.

Considerable research has been directed towards finding the metabolic change that causes muscle fatigue, but this has been challenging. One long-standing theory of muscle fatigue is that lactate orpH are important determinants of fatigue. This theory was supported by skinned fibre measurements of inhibition of force generation caused by decreased Ca^{2+} sensitivity when pH was decreased (Fabiato and Fabiato 1978). It has subsequently been shown that this impairment is evident only at cool temperatures, but not at body temperature of a large mammal (Pate et al. 1995). This work illustrates how important the external validity of a study is. Lactate itself has been shown to enhance contractile response (Pannier et al. 1970), an outcome that might surprise some, but considering that lactate is as suitable a substrate as glucose for oxidative metabolism, it should not be surprising. It is now generally agreed that accumulation of lactate and/or a decrease in intracellularpH are not factors contributing to muscle fatigue in human exercise (Westerblad et al. 2002).

Accumulation of inorganic phosphate (Pi) has also been identified as a potential cause of muscle fatigue. Due to the net breakdown of creatine phosphate, intracellular Pi can increase from resting concentrations (< 10 mM) to over 30 mM. Skinned fibre experiments at room temperature consistently demonstrate decreased Ca^{2+} sensitivity with 25-30 mM Pi (Cooke and Pate 1985; Coupland et al. 2001; Nelson and Fitts 2014), and results at 30 show less impairment, but impaired contraction is still present. Evaluation of increased Pi at human body temperature has not been done.

Another important metabolic change associated with exercise, that has often been associated with fatigue is glycogen depletion (Bergstrîm et al. 1967). However, depletion of glycogen alone does not weaken muscles (Fitts et al. 1982). It has been suggested that low glycogen stores may have control over Ca^{2+} release from the sarcoplasmic reticulum (Hargreaves 2004). The suggestion that the mechanism of muscle fatigue may be a consequence of regulation in the muscle has been elaborated by MacIntosh and colleagues (MacIntosh et al. 2012a). This mechanism may be the reason that fatigue occurs with minimal disturbance to [ATP] when blood flow is maintained.

For the metabolites to accumulate in the muscle, there must be some degree of compromise of the muscle perfusion. Thus, if the force is low (approximately 20% MVC or less) the perfusion is sufficient to flush away the metabolites as they are produced.

However, with higher forces, the intramuscular pressure increases and this restricts blood flow. Even in submaximalcontractions, there is motor unitrecruitment to offset any fatigue that is being experienced by the active motor units. With more and more of the muscle being recruited, the activity is perceived as more challenging and the reserve contractile capability gets smaller.

Special Considerations in Fatigue

The Task Dependency of Fatigue

Isometric Contractions – Low versus High Force

Much of the early work on muscle fatigue in humans was performed using maximal voluntary contractions. In classic work by Bigland-Ritchie and colleagues, both force and the electromyographic (EMG) activation declined in parallel. This observation, and others by Merton, led to the muscle wisdom hypothesis which spurred on a decade of investigation. The theory of muscle wisdom was proposed when it was discovered that 80Hz electrical stimulation was sufficient to produce the same force as a maximal voluntary contraction, fatigue occurred more quickly than a sustained maximal voluntary contraction. It was proposed that the firing rate of motor units must decrease during a maximal voluntary contraction and this was considered to be a clever way for the muscle to minimize the rate of fatigue (see below). However, it is extremely difficult to measure rate of activation of motor units during maximal activation, so this can only be considered speculation.

The muscle wisdom hypothesis stated that as the muscle fatigues, it produces less force and it produces this force more slowly. With the slowing of the muscle contractile properties, there is more fusion of the twitches at a given submaximal frequency of activation. This fusion allows better summation of forces with lower firing rates of the motor units. Thus, the nervous system can be more effective by lowering the firing rate of motor units to match the slowing of the contractile properties.

The mechanism underlying the matching of motor unit firing rate to contractile slowing with fatigue is believed to be sensory feedback from the metabolites building up in the muscle. The small diameterafferents in the muscle respond to the chemical and mechanical events in the exercising muscle and these afferents have been shown to inhibit spinal motoneurons. It is not the slowing of the muscle per se that mediates the muscle wisdom but the metabolites that are causing the slowing. For instance, cooling the muscle resulted in a slowing of the twitch but did not result in failure of voluntary activation. This suggests that slowing of the twitch, without the activation of the small diameter afferents, would not evoke muscle wisdom.

Muscle wisdom hypothesis does not hold up so well in submaximalcontractions. In submaximal isometric contractions, the firing rates are much slower than in maximal voluntary contractions. Fuglevand and colleagues illustrated with computer modeling, that when motor units discharge at rates typical of submaximal contractions (30 Hz) and then slow down to 15Hz, the force produced by the muscle dropped. The muscle wisdom hypothesis predicted that the slowing of discharge rate would preserve force, which was not borne out. Several others performed experimental studies that showed that muscle wisdom applied to high-force contractions but less so to low-force contractions. The central fatigue in low-force contractions actually exacerbated the force loss. Muscle wisdom was less evident in fatiguing arm movements as well, in which a reduction in firing rate was not witnessed as fatigue developed. It was thought that muscle spindle activation from the arm movement added excitation to the motoneuron pool. This notion has been supported by an experiment in isometric contractions in which transient vibration of the muscle (vibration is known to inhibit the muscle spindle) offset the reduction of firing rates typically seen (Griffin et al.). Thus muscle wisdom is likely a phenomenon restricted to isometric conditions.

High force isometriccontractions, e.g. greater than 75% of maximal voluntary contraction, experience less central fatigue than low-force contractions. The low-force contractions can be sustained for longer durations. This requires a sustained voluntary drive and it would appear that the central nervous system experiences difficulty in maintaining full voluntary activation for prolonged periods of time. You can imagine that it is much easier to maintain your concentration and motivation for short periods but this wanes with longer periods.

Many researchers have studied sustained contractions out of convenience. Whereas the classic fatigue protocol of Burke (1973) for mammalian muscle preparations, was an intermittent protocol that was able to distinguish fatigue-resistant from fatiguable motor units. In humans, intermittent contractions allow better perfusion of the muscle, thereby making the experiments much longer. And the longer the experiment, the more central fatigue. This is not only because of concentration issues as stated previously but issues of increasing discomfort in the apparatus and temperature in the restrained limb can decrease. To avoid these complicating factors, many researchers have either used sustained contractions or have performed the intermittent contractions under ischemic conditions. Neither sustained contraction nor ischemic intermittent contractions are commonly experienced in daily life. When you see Bruce Willis dangling from a ledge with only a hand hold for minutes, believe me, there is

considerable artistic license in that depiction. Many a Hollywood star would have plunged to their death in real life. First, we don't have the strength and second we would fatigue very quickly under those conditions.

Isometric Contractions: Position versus Force

Another illustration of the task-dependency of fatigue, even in isometriccontractions, is the much longer times to task failure in "force tasks" versus "position tasks". In force tasks, the subject is restrained in a device and exerts an isometric force against a transducer to match a force target. In position tasks, the subject holds a weight that requires the production of the same net torque but the limb is unrestrained and the subject tries to keep the limb in the same position. Even though the torque requirements of the task are the same, people fatigue much faster in the position task. The mechanism of increased fatiguability in the position task is thought to be neural or central fatigue. That is, the main difference between the two tasks is that subjects produce much higherEMG and earlier motor unitrecruitment in the position task. This is thought to be a result of excitatory muscle spindle input from small fluctuations in position. Also the postural requirements of the position task recruits additional synergists which would exacerbate the fatigue over the force task. Therefore, the motor control strategies of performing a task must be considered with fatigue. That is, people can learn to be less fatiguable in certain tasks by changing the way the brain activates muscles to perform the task, rather than make changes within the muscle itself.

Dynamic Contractions:

Most of our activities involve dynamic contractions. Contractions, in which the limb is moving, produce power (force X velocity) and can be limited more by a slowing of the velocity of the contraction than the absolute force produced. This is especially noteable in aging and in conditions like stroke. These have been studied in isokinetic mode, meaning the velocity or angular velocity of the movements is kept constant, or in isotonic mode, meaning the force of the movement is kept constant. Dynamic movements, like the position task above, are influenced by muscle spindles because the length of the muscle is changing. Furthermore there is much better perfusion to the muscle because of the rest periods. The reduction in power (through reduced velocity) is implicated in falls in the elderly, a serious health issue.

Sex Differences

There are sex differences in low-force sustained isometriccontractions, with men having shorter endurance times than women when maintaining the same relative contraction intensity (Hunter review). This sex difference is diminished when subjects are matched for strength, suggesting that much of the difference has to do with the absolute force maintained and the larger intramuscular pressures and restricted blood flows in subjects that can generate more maximal force. However just as the mechanisms for fatigue are task-dependent, so the sex differences depend on the fatiguing task. That is, studies have found no differences between the sexes in times to fatigue with dynamic contractions. Yet, when isometric contractions are intermittent, the sex differences resurface even when the sexes are matched for strength, yet cannot be solely attributed to blood flow because blood flow is not a limitation when rest is provided between contractions. Contractile properties are thought to contribute the sex difference, given that men have more fatiguable Type II muscle fibres than women. The sex-related differences in fatigue also depend on the muscle group. While both men and women experience central fatigue in low-force contractions, the amount of central fatigue is not different between sexes in the elbow flexors but is in the knee and ankle flexors. Bottom line, you cannot assume that men and women will behave similarly in fatiguing tasks!

Diseases and Fatigue

In many diseases, muscle fatigue is a common problem. It is difficult in some cases to separate the cause of the increased fatigue between the disease or the corresponding disuse. Here, we will discuss the fatigue associated with disuse, and consider a couple of disease conditions, to illustrate how disease can selectively add to the fatigue that is experienced.

Cancer –

Cancer– related fatigue is defined as a state of exhaustion that lasts longer than the activity would be expected to precipitate. This is rather common after chemotherapy and/or radiation. It is not known the extent to which neuromuscular and cardiovascular factors play a role in the fatigue. Certainly, there is a high probability for the "vicious circle", in that fatigue leads to a reduction in activity, which can in turn lead to depression and deconditioning which can further reduce activity and increase fatigue. Cancer-related fatigue has been reported to be accompanied by a failure to voluntarily activate the muscle. However, our data show that

central fatigue is prevalent in women after chemotherapy and/or radiation for breast cancer, irrespective of whether they exhibit cancer-related fatigue (Neil et al. 2013).

Neurological Conditions – Stroke:

Stroke refers to a disruption in the blood supply in the brain, either from a blockage in a vessel or from hemorrhage. Fatigue is a common symptom after stroke but this fatigue is often defined as a state of tiredness. This "tiredness" certainly has a neuromuscular component. In our study, we found that there is increased intracortical inhibition during and after a fatiguing contraction. This inhibition, is overcome by an increase in central excitation in healthy subjects and on the non-paretic side of stroke patients. When exercising with the paretic muscles, there is no increase in central excitation so the inhibition results in central fatigue. Failure to voluntary activate the muscle might be expected if the sensorimotor cortices are damaged. However, we have found central fatigue in people whose stroke occurred in sub-cortical regions of the brain. Thus the effects of fatigue are not simply caused by damage to the descending motor pathways.

After stroke, and many other neurological conditions like Multiple Sclerosis or Parkinson's Disease, there are impairments in motor coordination and muscle weakness that make functional movement more difficult. These impairments can often make the cardiorespiratory cost of even a simple task like walking quite high. There is considerable attention being paid now to the cardiovascular deconditioning that takes place with neurological impairments. Often slow walking can actually be using quite a high percentage of their $\dot{V}O_2$max. So again, the vicious circle. The more difficult it is for the brain to control the muscles and movements, the more sedentary people become. Indeed, even in rehabilitation, where people are most likely to be active, the number of steps taken per day is about 10% of age-matched norms.

The restricted activity patterns in stroke results in atrophy of their fast twitch muscle fibres. After stroke, there is a tendency for the muscles to have slower contractile properties. You would think this would make the muscles less fatiguable. While the type 1 fibres remain fatigue resistant, the trouble is that the poor coordination results in an inordinate amount of motor unitrecruitment, including co-contraction reducing the effectiveness. Thus the amount ofEMG produced for a given force is higher in people after stroke. Considering the sense of effort is related to the descending command, these people have the perception of having to work harder to produce the required force. This leads to the central fatigue.

Conclusions

The consequences of prior activity can vary from enhanced contraction due to activity dependent potentiation to decreased force response due to fatigue. The outcome depends on several factors including sarcomere length, temperature of the muscle and the intensity and duration of the prior activity. There are three types of activity dependent potentiation: staircase potentiation, posttetanic potentiation and postactivation potentiation. Postactivation performance enhancement may or may not include enhanced contractile response. Fatigue can be central, due to failure within the central nervous system or peripheral due to failure in the peripheral nerves or the muscles themselves. Failure within the muscles may be due to disturbance to ion distribution homeostasis, or due to regulation of excitation-contraction coupling associated with an energy shortage. Fatigue is often exacerbated by disease conditions.

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3.3: Chapter 14 - Molecular Basis of Exercise Training Adaptations in Skeletal Muscle



Photo 14-1. Strong, wellness couple doing kettlebell weight exercise, workout or training inside a gym. Resistance exercise activates specific genes in our muscles. Photo by peopleimages.

Learning Objectives

- Understand the concept of adaptation as it relates to changes in gene expression;
- Appreciate the divergent signals and pathways that lead to adaptation in exercising muscle;
- Comprehend the details of gene expression and be able to converse about how changes in muscle adaptations apply to a real training setting.

Key Terms

muscle adaptation, gene expression, transcription, translation, protein synthesis, myosin heavy chain, mitochondrialbiogenesisbiogenesis, fibre types, electron transport chain, isoforms, NuGEMPs, transgenic, hypertrophy, endurance training, resistance training training, proteins, satellite cell, myonuclear domain, slow twitch, fast twitch, receptors (DHPR), creatine kinase (CK), myoglobin, heat-shock protein (HSP)-70, ROS, PGC-1α, Nuclear Respiratory Factor-1 (NRF-1), mTOR, nuclear factor of activated T-cells (NFAT), S6Kinase, IGF, SERCA, $\dot{V}O_2$max, ADP.

Case Presentation: A Look Inside the Muscle: The Metabolic Benefits of Training

Andrew is a 26-year-old university graduate who has never been an elite athlete. In fact, he was recreationally active in only a few sports during high school and university, preferring to focus on his studies and academic achievements. His girlfriend Erin is sports-minded, and always participated in track and field in her youth. Now she finds running the occasional 10 km race rewarding since her track career has ended. Erin has convinced Andrew that his fitness level is on the low end of average, and that starting a training regimen (jogging and running) with the goal of completing a running race together might be a way to spend time together as well as to get fit. In fact, through her university connections, she has arranged a complete “work-up” and analysis of Andrew’s fitness, from the level of the muscle to hisaerobic capacity. During a pre-test,$\dot{V}O_2$max would be assessed and micro-biopsy samples would also be taken to analyze the metabolic

changes within the muscle during exercise before and after the training period. Erin has set up a progressive training program appropriate for Andrew's starting fitness level beginning about 10 weeks prior to the race. Andrew underwent a graded exercise stress test before and after the training period in which and muscle biopsy samples are taken at various workloads.



Photo 14-2 A group of researchers assess the aerobic fitness of a male subject like Andrew. By Fretamales [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0) or GFDL (http://www.gnu.org/copyleft/fdl.html)], from Wikimedia Commons

The results of Andrew's training are illustrated in Figure 14-1. They are typical of changes from a previously untrained state to that of a more physically fit individual who faithfully adheres to a well-designed endurance training program. Andrew's $\dot{V}O_2$max increased by about 10% and the proportion of his type IIa fibres increased at the expense of type IIx fibres. His proportion of type I fibres did not change, as expected. Typically, a transition to more type I fibres would take a much longer period of training (see later in this chapter). During graded exercise, Andrew displayed the beneficial metabolic adaptations of training, corresponding to improved endurance performance. Andrew used less glycogen during exercise and produced less lactate during the submaximal portion of the stress test. He also spared his use of phosphocreatine and the level ofadenosine diphosphate (ADP) was reduced. This lowerADP concentration was a reason for the lower level of glycolytic stimulation. Mitochondrial marker succinate dehydrogenase was elevated, indicating that the training program increased mitochondrial content within the trained muscle. This adaptation would account for a better use of lipid as a substrate during exercise and contribute to the preservation of carbohydrate (COH) fuels like glycogen which must be preserved in order to perform well in endurance events. Andrew's muscles have a higher oxidative capacity because they have more mitochondria. They also have more capillaries surrounding each muscle fibre which provide energy substrates and oxygen to the mitochondria. His endurance time is much more prolonged, and he is ready to run his race with Erin!

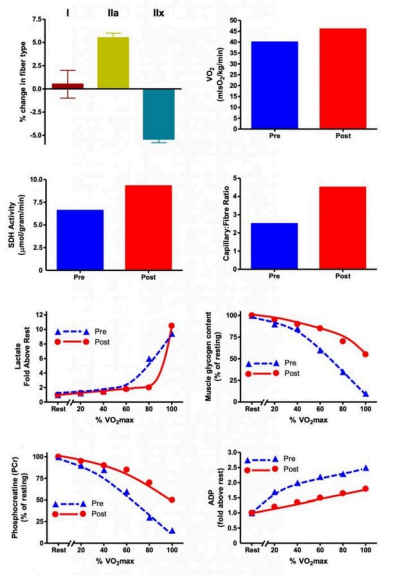


Figure 14-1 (Top) Changes in muscle fibre type, $\dot{V}O_2$max, muscle succinate dehydrogenase (SDH) activity and capillary: fibre ratio pre- and post-training. Line graphs illustrate the changes in metabolites (lactate, glycogen, phosphocreatine (PCr) and ADP) in muscle during graded exercise up to $\dot{V}O_2$max both pre- and post-training.

Gender BOX: Battle of the Sexes? It's a Molecular Matter!

There is no denying that males and females differ vastly in their muscle structure, size, and ability to undergo hypertrophy in response to training. Males feature a greater free mass, a bigger muscle cross-sectional area, and more fast-twitch type IIA muscle fibres when compared with their female counterparts (Miller et al. 1993). Females, on the other hand, display superior resistance (Wüst et al. 2008) and a greater reliance on for energy production (Roepstorff et al. 2006). It has been postulated that these discrepancies are due to inherent hormonal differences between the two genders where men have 10-30-fold greater resting levels of testosterone while women are well-endowed with estrogen. Testosterone has the ability to enhance protein synthesis, ultimately contributing to muscle hypertrophy, while estrogen activates the synthesis of burning machinery. Does this mean that men adapt better to exercise training than women? Not necessarily! Several studies indicate that men and women undergo the same level of protein synthesis following an acute bout of resistance exercise despite dramatic differences in testosterone levels (West et al. 2012). Men and women also adapt similarly to high intensityinterval training (Astorino et al. 2011). However, if the two sexes display similar adaptations to resistance training what accounts for the extensive increase in muscle size observed in men? Other than the hormonal differences, there also appears to be variations in gene expression between the two genders. The muscle transcriptome is vastly different between the two sexes both at baseline and following an acute bout of resistance exercise (Liu et al. 2010). The time course of the transcriptional modulation is also sex-dependent wherein males experience prolonged changes in gene expression while females exhibit rapid transitions (Liu et al. 2010). Thus, in addition to the hormonal divergence, transcriptional regulation might be at the root of the differential adaptations observed between the sexes following exercise training at the same relative intensity.

Introduction to the Types of Exercise Training

Exercise can be classified in a number of ways. Acute exercise refers to a single bout which can either be short (i.e. seconds) or long (several hours), and can vary in intensity from being mild, as in a light jog, to supramaximal, like a 100-meter sprint at top speed. A single acute exercise bout produces physiological and metabolic changes in the working muscle that, if repeated many times, can ultimately lead to an "adaptation". When acute exercise bouts are repeated over and over again, this is referred to as exercise *training*. In order for exercise training to be effective, certain *training principles* must be adhered to. These include:

- the frequency of exercise per week;
- the duration of each exercise bout in minutes;
- the intensity of exercise, usually expressed in terms of %$\dot{V}O_2$max, or %max heart rate;
- the length of the training period in weeks or months.

These training principles should be applied regardless of the type of training employed. Traditionally, three forms of training have been recognized for many years. As reviewed below, these are:

- endurance training;
- resistance training;
- interval training;

Endurance Training

This type of training usually refers to repeated bouts of acute endurance exercise which employs a large fraction of available muscle mass. Commonly accepted exercise dosage for adults aged 18-64 years is to engage in moderate-to-vigorous intensity aerobic exercise (65-75% $\dot{V}O_2$max) for 30-40 minutes at a frequency of 3-5 days per week. More recently, the Canadian Society for Exercise Physiology has revised these guidelines to indicate that adults should aim to accumulate 150 minutes of exercise per week in bouts of 10 minutes or more. From a health perspective, this helps reduce the risk of chronic pathological maladies such as heart disease, stroke, obesity, type 2 diabetes and osteoporosis. Typical examples include brisk walking, jogging, running, swimming, cycling and cross-country skiing. These types of exercise produce transient increases in heart rate, cardiac output and peripheral muscle oxygen and substrate extraction, leading to an acute increase in above rest to a steady-state level which can be sustained for a prolonged period. When this is repeated 3-5 times per week for several weeks, endurance training benefits such as improved whole-body endurance and an increase in max, will accrue. The increase in endurance is a result of muscle adaptations to exercise, as outlined in this chapter.

Resistance Training



Photo 14-3 Resistance exercise involves resisting body movements, often using weights. Generally, this type of exercise is repeated 3-4 times per week, with a rest day in between sessions. Exercise is performed using specific muscle groups, such as the biceps, pectoral muscles, or quadriceps, for example. Typically, 3 “sets” of exercise are performed, with each set consisting of 8-20 repetitions of the same motion (e.g. biceps curl) with a given weight. The lower number of repetitions (i.e. 8) generally employs a higher load in order to maximize strength gains, while the higher number of repetitions uses a smaller load and leads to greater improvements in muscular endurance. The load chosen is usually expressed as a percentage of the 10 Repetition Maximum (10RM), or the maximum load that can be moved in ten repetitions of the exercise. Resistance exercise performed over the course of several weeks to months leads to an increase in size and strength of the specific muscle groups that are trained. Improvements in muscle mass are directly related to improving quality of life, especially in the elderly population where muscle frailty often leads to falls and a subsequent dependence on others to perform simple daily tasks. The increase in muscle mass is due to adaptations brought about by the high forces generated within the fibres recruited during the resistance training. These adaptations are different from those observed with endurance training, as described below.

Interval Training



Photo 14-4 Interval training involves repetitive bouts of intense aerobic exercise followed by periods of rest.

This type of training has been well recognized for many years, and it has regained some popularity recently because of the adaptations that can be observed within muscle. Interval training usually entails the performance ofvigorous or supramaximal intensity exercise over short intervals of time. An example of such training is repeated 400-meter sprints at a pace of 60 seconds (6.7 metres·s^{-1}), done with a rest interval of 2 minutes between sprints. This represents a “work-to-rest” ratio of 1:2. Various work-to-rest ratios can be employed depending on the fitness of the subjects. Many, many different types of intervals can be imagined, tailored to the specificity of the sport or activity. A longer rest interval may permit a higher intensity in the next interval. During high intensityinterval training, it is more likely that the rarely used Type IIx motor units within the muscle will be recruited. The fibres within these motor units adapt readily to exercise because they have a very low endurance to begin with. Not only are muscles and motor units within them heavily activated by such high intensity exercise but so are the respiratory and cardiovascular systems. High heart rates are common, and if the rest interval is short enough, the heart rate remains high even during the recovery period between bouts. This maximizes the cardiovascular benefits of such exercise. Known for its difficulty, interval training has recently seen a revival of interest from exercise physiologists who wish to minimize time spent training and maximize the benefits of high intensity exercise.

Subcellular Systems that Adapt to Training

Like most cell types in the body, muscle cells contain the organelles responsible for cell survival including a nucleus, ribosomes, endo- and sarcoplasmic reticulum, lysosomes, cytoskeletal elements and a cytoplasm with an abundance of proteins. The specialized elements within muscle cells that distinguish them from many other cell types include

- multiple myonuclei;
- a well-developed calcium handling system that responds with every action potential**;**
- myofibrillar proteins that produce force;
- three energy systems that provide rapid and sustained for muscle contractions**.**

Myonuclei

During embryonic development, stem cells commit themselves to form muscle cell precursors called myoblasts. Myoblasts have a single nucleus and lack protein**s**. Myoblasts then fuse together to form myotubes which are elongated immature muscle cells. When many myoblasts fuse together, they donate their individual nuclei to the growing, elongated myotube, forming a multinucleated muscle cell (Figure 14-2). As progresses, these nuclei express muscle-specific

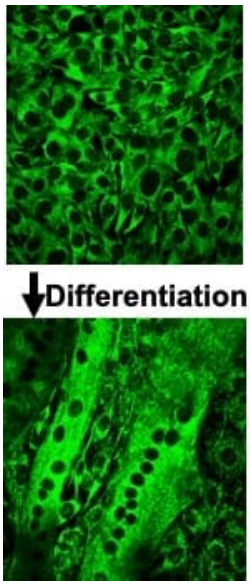


Figure 14-2 Image of myoblasts (Top) and differentiated immature muscle cells (myotubes) grown in cell culture. The dark circles represent individual myonuclei within the cells. Myoblasts have fused together to produce multi-nucleated myotubes in the lower figure.

genes, such as and myosin, and the cell gains the ability to contract. Nuclei are necessary all along the muscle fibre as a single nucleus is only able to provide the DNA and building blocks necessary to sustain a certain volume of the cell. This volume is known as the myonuclear domain and it corresponds to the volume of cytoplasm governed by each individual nucleus (Figure 14-3). Multiple nuclei are necessary to provide sufficient machinery to support the full length of the muscle fibre. Thus, unlike most cells in the body which possess only one nucleus, mature muscle fibres have many. As we discuss muscle adaptations to exercise, we will continually refer to the genes within these nuclei and how these genes are “expressed” to give rise to specialized adaptations that we observe with training. In addition, as discussed below, the number of myonuclei in muscle can be altered by training, giving the cell the potential to increase gene expression to better support the needs of a growing muscle.

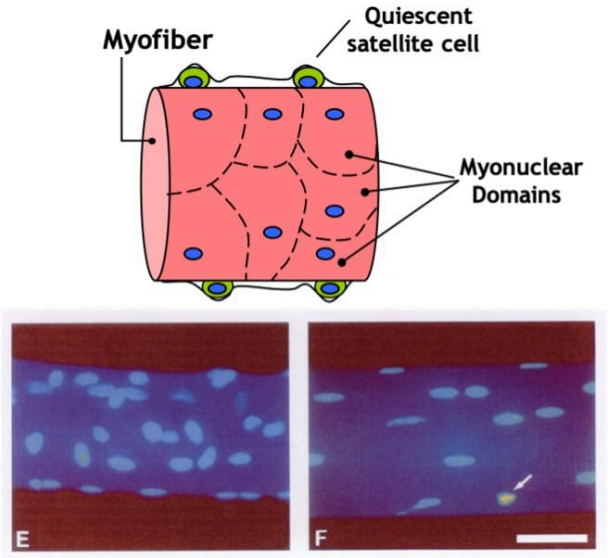


Figure 14-3 (Top) Illustration of a segment of a muscle fibre with its theoretical myonuclear domains, along with adjacent quiescent satellite cells. (Bottom) Photograph of fibre segments with small (left) and large (right) myonuclear domains; a rare apoptotic myonucleus is stained yellow (arrow). Adapted from Saleem A. et al., in Reed J. and D. Green, Eds. Apoptosis: Physiology and Pathology. New York: Cambridge, 2011, p. 318.

Myofibrillar proteins

Within the cytoplasm of muscle cells are organized bundles of proteins called myofibrils . These myofibrils contain

- proteins,
- structural proteins,
- cytoplasmic proteins,
- regulatory proteins.

Contractile proteins generally refer to and myosin, while structural proteins include titin, z-line proteins and nebulin. Regulatory proteins are those which “control” the contraction process. These include troponin and tropomyosin (Figure 14.4**)**. Both the contractile and regulatory proteins exist as multiple “isoforms” within muscle fibres. Isoforms are variants of the same protein, but with a slightly different primary amino acid sequence. This gives them a different physiological capability within the cell. Some physiologically-relevant isoforms that exist within muscle are listed in Table 14-1.

Mammals possess four genes that encode MHC isoforms that are expressed in adulthood. These are the MHC Type I, IIa, IIx and IIb genes (Figure 14-5). The MHC isoforms were discovered based on their different molecular weights when they are separated using a technique called *electrophoresis*, which distinguishes proteins based on their size. It is now known that only three of these four genes are expressed in adult human muscle and that the fourth, the MHC Type IIb, is only expressed in smaller mammals, like rabbits, rats and mice. The abundance of these proteins in muscle fibres can be very high, giving rise to the idea that muscle “fibre types” can be classified based on how much of each isoform is present. For example, a type IIa fibre contains mostly MHC IIa. Because MHC IIa is a fast isoform of MHC, this means that a type IIa fibre is a fast-twitch fibre. In contrast, a fibre composed of mostly MHC I is a slow-twitch fibre because this MHC has a slow rate of breakdown. The abundance of these isoforms is typically detected using *histochemistry* which yields a qualitative analysis of the muscle fibres (Figures 14-5, 14-6). However, more quantitative analyses based on single fibre electrophoresis reveals that many muscle fibres, referred to as hybrid fibres, express multiple MHC isoforms. Our classification of Type I, IIa and IIx fibres is really an oversimplification of what really exists in muscle. Nonetheless, the classification into these three fibre types remains useful in general.

A question that often arises in exercise physiology is “Can fibre types be changed with training”? To do this, one would have to train at a sufficient exercise intensity, duration and frequency, and for a long period of time to induce a change in the expression of the MHC genes. Once we learn about the gene expression pathway (below), this fascinating topic will be considered once again.

Sarcoplasmic Reticulum (SR) Proteins

As discussed in earlier chapters on muscle contraction, when an action potential within a muscle fibre occurs, the change in voltage across the plasma membrane propagates along the plasmalemma and down the t-tubule which is continuous with the plasmalemma (Figure 14-4). Embedded in the t-tubule membrane are proteins called dihydropyridinereceptors (DHPR). These are voltage sensitive and alter their conformation when an action potential occurs. The DHPRs physically interact with the calcium release in the SR, also called the ryanodine receptors (RyR). An action potential causes conformational changes in these two proteins including the opening of the RyR to permit a burst of calcium to be released into the cytoplasm. When action potentials cease, calcium release channels close and the calcium in the cytoplasm is taken back up into the SR in anATP-dependent process catalyzed by the sarco**/**endoplasmic reticulum calcium- ATPase **(**SERCA**)** which, like MHCs, also exist in different isoforms. SERCA1a is the primary isoform present in adult fast-twitchskeletal muscle whereas SERCA2a is highly expressed in slow-twitch muscle and heart. SERCA3 exists in many cells of the body. SERCA-mediated calcium uptake allows cytoplasmic calcium to return to resting levels and causes the muscle to relax (Figure 14-4).

A number of these proteins have the potential to adapt to training though the study of SR proteins is not as advanced as for the myofibrillar or metabolic proteins. Endurance exercise training appears to reduce SR calcium uptake and release. Several proteins involved in SR calcium cycling undergo alterations resulting in this effect. For example, decreases in the content of the fast isoform SERCA1a and the RyR protein have been noted, which would tend to reduce the speed at which calcium is handled within endurance-trained muscle.

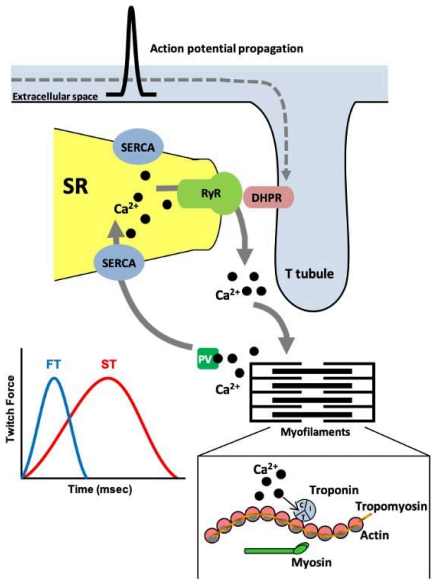


Figure 14-4 Review of the contractile response to an action potential. Voltage sensor proteins such as the DHPR change conformation in response to an action potential and cause the calcium release (Ryanodine receptor; RyR) to open, allowing calcium to escape the sarcoplasmic reticulum (SR). Calcium diffuses to the myofilaments where it interacts with the Troponin-C, allowing tropomyosin to remove its inhibition of the myosin-binding site on actin, allowing for actin-myosin interaction, breakdown, and crossbridge cycling. When the action potential terminates, calcium is no longer released and cytoplasmic calcium can diffuse back the SR, aided by the transport protein parvalbumin (PV), thus promoting muscle fibre relaxation. The sarco-, endoplasmic reticulum calcium ATPase pump facilitates calcium uptake into the SR in an ATP-dependent manner.

Table 14-1 ***Example of important protein isoforms in muscle and their associated functions.***

Protein	Isoforms	Functions	Distinctions
Myosin heavy chain (MHC)	MHC I MHC IIa MHC IIx	Catalyze the breakdown of ADP during the crossbridge cycle, when myosin is bound to actin	MHC I has a slow rate of breakdown, whereas isoforms IIa and IIx catalyze fast breakdown
Actin	Alpha-actin Gamma-actin	α- is a protein involved in the crossbridge cycle, whereas γ- is a cytoskeletal protein involved in maintaining the shape of the cell	

Lactate dehydrogenase	M-LDH H-LDH	M-isoform catalyzes the reaction of Pyruvic acid + NADH Lactic acid + NAD+	**The H-isoform catalyzes the reaction in the opposite direction**
Sarcoplasmic-endoplasmic reticulum ATPase	SERCA 1 SERCA2	Catalyze the uptake of calcium back into the sarcoplasmic reticulum following the contraction phase. This uptake produces muscle relaxation	SERCA1 is found in fast-twitch, Type IIa and IIX fibers. SERCA2 is found in slow-twitch f ibers

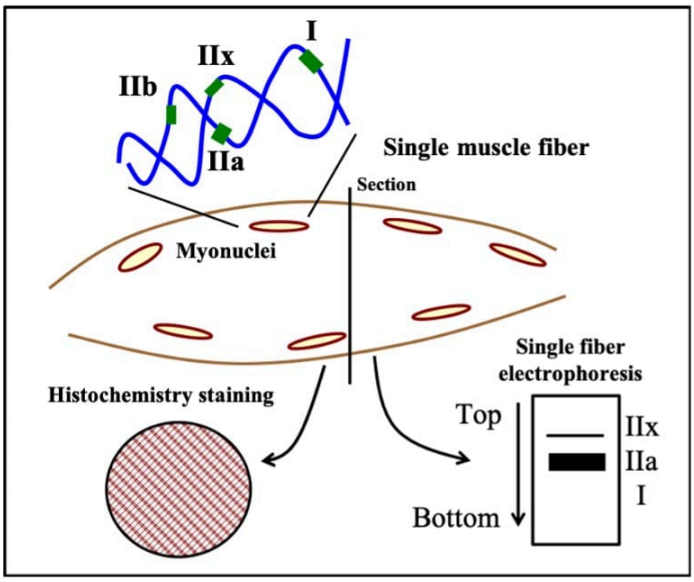


Figure 14-5 Multinucleated single fibers have genes encoding all four MHC isoforms. Only the type I, Iia and Iix isoforms are expressed in humans. The gene that is expressed the most will lead to the greatest abundance of MHC isoform within the fiber, and this can be determined by histochemistry staining. Alternatively, single fiber electrophoresis can provide a more quantitative description of the relative expression of each gene, sometimes revealing the co-expression of an alternative isoform within the same fibre.

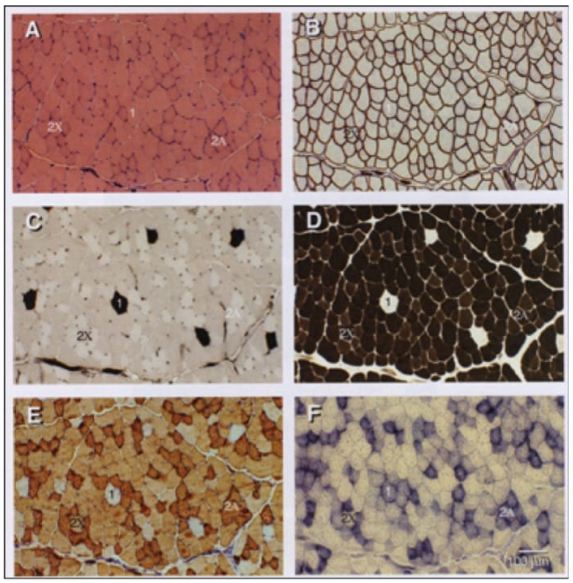


Figure 14-6 Serial cross-sections of rabbit tibialis anterior muscle under various staining conditions. The identical fiber can be traced through each section to compare the properties of fibers. (A) Hematoxylin and eosin, demonstrating general muscle fiber morphology. (B) Dystrophin immunohistochemistry showing the subsarcolemmal nature of this protein (brown deposits represent protein). (C) Myofibrillar ATPase under acid preincubation conditions. Under these conditions, slow fibers stain darkly as do the extracellular capillaries while fast fibers stain lightly. (D) Myofibrillar ATPase under alkaline preincubation conditions. Under these conditions, slow fibers stain lightly while fast fibers stain darkly. Note that in both panels C and D, fast fiber staining intensity occurs at two levels. (E) Immunohistochemical reaction for fast myosin heavy chain antibody. In rat skeletal muscle, this stains type 2A fibers darkly and type 2X fibers more lightly and is negative for types 2B and 1 fibers. (F) Succinate dehydrogenase (SDH) used to demonstrate muscle fiber mitochondrial content. Note that the slow fibers (Samples fiber labelled with a "1") as well as the type 2A fast fibers (sample fiber labelled with a "2A") have higher oxidative capacity compared to the type 2X fibers (sample fiber labelled with a "2X"). Adapted from Lieber, RL. Skeletal Muscle Structure, Function and Plasticity, 3Ed., Philadelphia: LWW, 2010.

Cytosolic Proteins

There are a number of different types of proteins within the cytoplasm but the most studied are those which are involved in energy metabolism, particularly enzymes of glycolysis or the metabolism of phosphocreatine (i.e. ATP + Creatine" href="https://kinesiology.ucalgary.ca/maci...l-czz#creatine">creatine phosphokinase, or CPK). These enzymes have a very high specific activity in muscle fibres, much higher (10-fold!) than those enzymes devoted to oxidative metabolism in the mitochondria, for example. A large number of studies have been conducted which have evaluated the effects of training on the activity of these enzymes and most indicate very little effect, regardless of whether endurance, sprint or resistance training methods are employed.

In addition to metabolic enzymes, two other proteins which serve a "chaperone"-like role are responsive for changes in muscle activity. These are parvalbumin, a calcium binding protein, and myoglobin (Mb), a protein which binds oxygen. These proteins are chaperones in the sense that they facilitate the transport of their ligands (i.e. calcium or oxygen respectively) to the site of where they are needed. For example, parvalbumin facilitates the diffusion of calcium to the SERCA pump for removal from the cytoplasm. This protein is considered to be important for the relaxation phase of muscle contraction and it is very high in concentration in fast-twitch muscle fibres and low in slow-twitch muscle fibres. Myoglobin, on the other hand, helps to transport oxygen from the periphery of the muscle fibre to the where it can be used in phosphorylation, the aerobic production of ATP. Myoglobin is highly abundant in slow-twitch and Type IIa fibres. These fibre-types have a red colour due to the presence ofMb which contains the red pigment, heme. In response to chronic endurance training, parvalbumin tends to decrease in the cell while Mb is usually found to increase (Figure 14-7).

A third class of proteins are referred to as stress proteins, typified by the heat-shock protein-70 (HSP-70). These proteins are induced very rapidly in response to a variety of stressors including exercise. Their main function appears to be in protein refolding. Any protein that is denatured, or unfolded, during a stressful cellular condition loses its function. This undermines the health of the cell. HSP70 has an active role in preventing cellular death by helping to restore protein shape and function.

Mitochondrial Proteins

Mitochondria are the “powerhouses” of the cell because they are the source of most of the that is used to fuel muscular contraction. The proteins within are those involved in the oxidation of pyruvic acid, derived from glycolysis, and **β** oxidation, the breakdown of fatty acids from triglycerides derived from within the muscle cell itself or originally found within adipose tissue. The proteins ultimately responsible for this metabolism are the enzymes of Krebs’ Cycle and the electron transport chain (ETC) as described earlier (Chapter 6). One of the most dramatic adaptations to regularly performed exercise training is the uniform increase of many enzymes involved in β-oxidation, Krebs’ Cycle and the ETC. This occurs in the muscle fibres that are recruited, or used, during the training period. For example, in response to training of relatively mild intensity (i.e. jogging), the muscle fibres that are predominantly used during this exercise will adapt and produce more mitochondrial proteins. These fibres would include type I and IIa, but probably not the Type IIx fibres which are only activated during intense exercise bouts. It is also important to realize that mitochondrial adaptations are lost rather rapidly once a training regime ceases (Figure 14-8). Since mitochondrial adaptations closely correlate with endurance performance and measures of aerobicfitness, it is important to maintain a level of physical activity to avoid losing these adaptive changes.

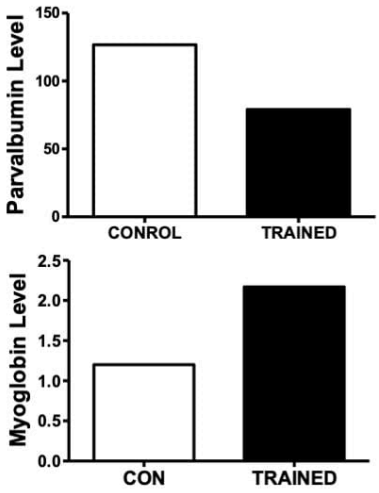


Figure 14-7 Typical endurance training-induced changes in the cytsolic proteins, parvalbumin and myoglobin in muscle.

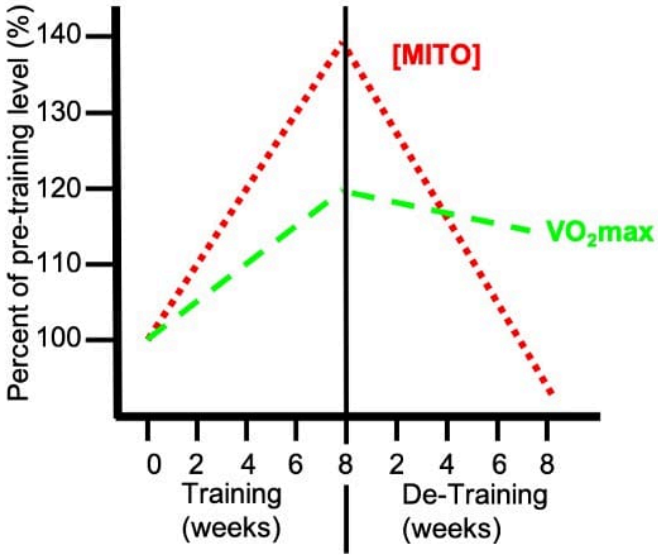


Figure 14-8 Typical changes in $\dot{V}O_2$max and muscle mitochondrial enzymes (MITO) induced by 8 weeks of endurance training and followed by de-training for 8 weeks. Modified from Henriksson, J. and Reitman J.S. Acta Physiol. Scand. 99: 91-97, 1977.

There are many benefits of mitochondrialadaptation including an improvement of lipid metabolism and a reduction in the reliance

on COH as energy sources during prolonged exercise. This is important because of the limited (gram) quantities of COH stores within our muscles and liver. In contrast, an increase in allows us to take greater advantage of the (kilogram) quantities of stores within our adipocytes and muscle cells. In addition, having more means that we can rely less on glycolysis and phosphocreatine as energy sources during intense contraction conditions. This reduced reliance on these pathways means that we produce less lactic acid during exercise, glycogen is used at a slower rate, and phosphocreatine breakdown is diminished. These adaptations have important benefits for endurance performance. A perfect example of this is shown in the Case Study at the start of this Chapter. Traditionally, this kind of adaptation has been observed with endurance training, but more recently it has been shown to occur with different forms of sprint training, which produce adaptations in type IIx fibres as well.In order to understand how these adaptations in muscle occur, it is important the review the pathway of gene expression and how it is activated in response to different exercise stimuli. Gene expression is the precursor to protein synthesis; therefore, both processes are crucial for muscle adaption with exercise.

Highlight BOX: The “Secret” of Muscle

Within the last 10-15 years, numerous studies have shown that muscle tissue is capable of producing and releasing hundreds of different proteins (Bortoluzzi, (2006). The ability of skeletal muscle to secrete factors provides a method for communication. The signaling molecules that are released have been called “myokines” (Pedersen, 2008). These secreted signals can travel in the blood and affect other tissue types, well known as an endocrine effect. Secreted myokines may also remain local and work to cause changes within the muscle itself. This is known as an autocrine o r paracrine effect. While not all of the proteins secreted from muscle have been identified yet, the IGF (insulin-like growth factor) family, IL-6 (interleukin-6), and most recently irisin (named after the Greek messenger goddess , Iris), have all been accepted as myokines.

The IGF family consists of many proteins.In skeletal muscle, IGF-I and IGF-II can be secreted and act back on the muscle in an autocrine/paracrinemanner.IGF-II seems to promote the formation of muscle during development (Florini , 1991).In adults, IGF-I is capable of increasing muscle size (i.e. hypertrophy) as well as promoting muscle repair through the activation of satellite cells (Barton, 2006).

IL-6 was among one of the first- ever myokines to be identified. It was discovered that IL-6 was released from muscle during exercise, and that plasma blood levels could increase up to 100-fold! (Steensberg, 2002). This increase in IL-6 depends on both the exercise intensity and duration. Increased muscle-derived IL-6 triggers breakdown (lipolysis) and utilization (fat oxidation) in other tissues. Mice that lack IL-6 become obese and resistant (Pedersen, 2008).

The latest myokine to be identified is irisin. Irisin production is regulated by a protein called PGC-1 α which is a critical factor for exercise adaptations in skeletal muscle (Boström , 2012). It is very well known that PGC-1α and circulating levels of irisin both increase with exercise. Once released from the muscle, irisin is able to travel to the adipose tissue where it will stimulate the to increase energy expenditure which will be released as heat. Administration of irisin to rodents is also shown to stimulate weight loss and prevent insulin resistance. Thus, production of the myokines IL-6 and irisin are important signals from the muscle that coordinate the beneficial adaptations to regular exercise such as weight loss and resistance to metabolic disease.

The Gene Expression Pathway that Mediates Muscle Adaptations to Exercise

One way to produce an adaptation within a tissue in response to a stimulus is to either activate or inhibit the gene expression pathway (Figure 14-9). This usually means that the stimulus has to initially modify gene transcription. The mRNA that results is translated into protein which contributes to changing the “phenotype” or appearance of the muscle cell. For example, if the transcription of MHC Type I is increased, then the muscle will become slower in its contractile properties. If the transcription of a mitochondrial lipid oxidation enzyme is increased, increased protein levels of the enzyme will cause the muscle to begin to favour lipid over COH metabolism.

What are typical *stimuli* that result in adaptations within skeletal muscle? Exercise is one, of course, but muscle also responds to conditions such as 2 in the arterial blood or a part of the body is less than adequate” href=”https://kinesiology.ucalgary.ca/maci...ossary/gra-max”>hypoxia, hibernation, heat and cold exposure, altitude, muscle disuse, and nutrient deprivation, to name a few. Indeed, muscle is considered to be highly “plastic”, meaning that it adapts readily to a number of external stimuli. In

this chapter, we will consider only the adaptive response to exercise. While adaptations to any stimulus take time, you may be surprised to learn that even the first exercise bout can initiate the adaptation process.

There are several levels of "control" over this pathway, generally classified into

- transcriptional; and
- post-transcriptional regulation.

Transcriptional control is exerted within the nucleus, while post-transcriptional regulation can take place in the nucleus, cytoplasm or within organelles of the cell.

The Signals Involved in Triggering Muscle Adaptations to Exercise

The adaptation process begins with the response of muscle cells to the first seconds of an acute bout of exercise. Signals are transmitted from one protein to another via physical interactions which lead to changes in protein shape (i.e. conformational changes). Often these interactions arise because of the actions of an enzyme like a kinase that phosphorylates a protein or a phosphatase which removes a phosphate group (Figure 14-10). This is a very common method of transmitting a signal within a cell in response to a stimulus, like exercise, or hormone treatment, for example.

There are six possible signals to be considered that occur in muscle at the start of each exercise bout (Figure 14-11**):**

Voltage-sensitive proteins

When a motor unit is recruited and muscle cell membranes are depolarized, a voltage signal travels across the plasmalemma. Many proteins within the muscle membrane system are voltage-sensitive (e.g. Na+ channels, receptors) and their conformation is altered in response to differences in voltage. When that happens, they can often interact with other proteins to begin a signaling cascade.

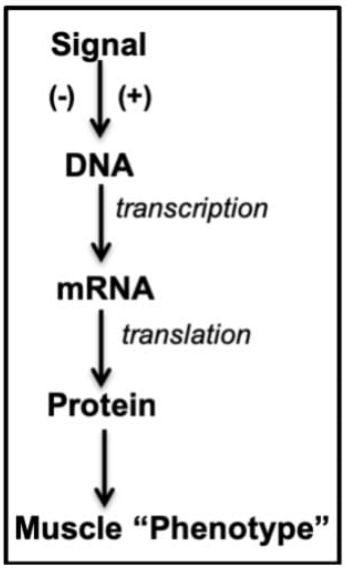


Figure 14-9 Exercise produces intracellular "signals" which alter the gene expression pathway within myonuclei. These signals promote selective gene transcription, and the mRNA product is then translated into protein. The change in specific protein concentration within the muscle cell alters the appearance and function of the muscle fibre (i.e. changes the fiber phenotype).

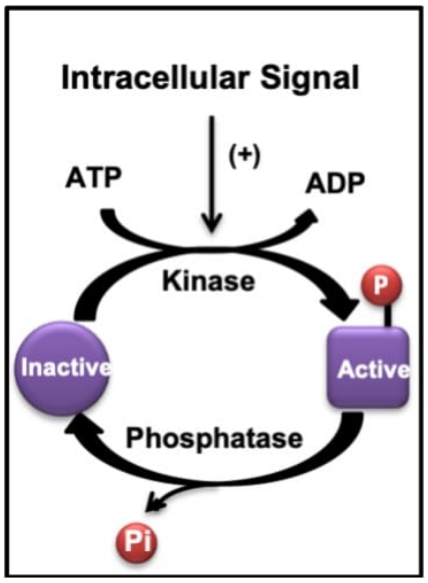


Figure 14-10 The first step in signal transduction in response to exercise is often via the activation of specific proteins such as transcription factors by phosphorylation. Repression of transcription factor activity can be achieved via de-phosphorylation. The enzymes responsible for this are kinases and phosphatases, respectively

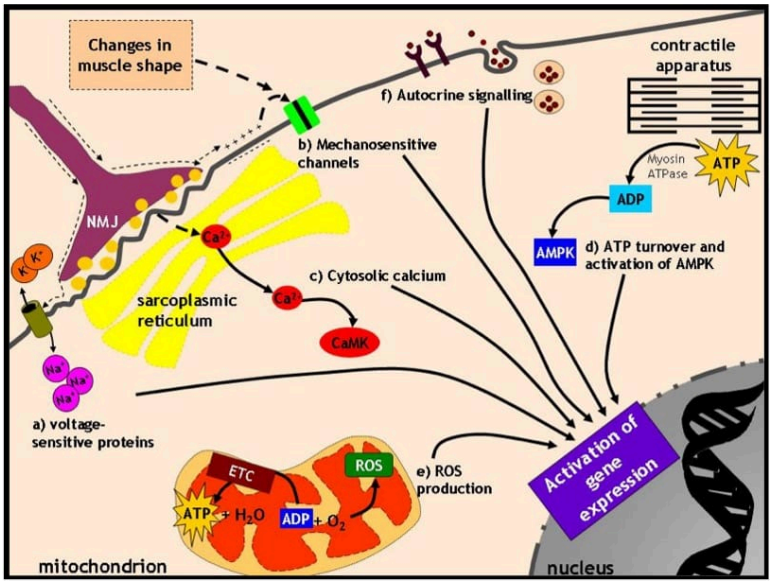


Figure 14-11 Summary of the cellular events occurring during muscle contraction which could activate signals leading to changes in the gene expression pathway. See the text for details.

Mechanosensitive proteins

When a muscle cell contracts, a number of protein**s** are activated in response to changes in the shape of the muscle cell. In other words, they respond to mechanical deformation and trigger further protein activation “downstream”.

Cytosolic calcium

The propagation of the action potential causes the release of calcium from the SR. While calcium is important for mediating the contraction process, it is also a powerful activator of a number of kinase and phosphatase enzymes that can modify proteins by phosphorylation or dephosphorylation.

ATP turnover and the activation of AMP kinase

When calcium binds to troponin and permits and myosin to interact, is broken down to ADP and some ADP is further converted to AMP. AMP is an allosteric activator of the enzyme AMP kinase (hence its name!) which phosphorylates a number of transcription factors or other proteins which regulate transcription processes within the nucleus by binding to DNA in a sequence-specific manner.

Reactive O_2 Species (ROS) production

ADP is the most important activator of phosphorylation (i.e. O_2 consumption and production in the mitochondria). When O_2 consumption is increased, a small percentage of the O_2 forms reactive oxygen species (ROS) instead of being converted to water. These molecules can be damaging when present in excess or beneficial when produced in moderate amounts since they can serve to oxidize and activate proteins.

Secreted proteins acting in *autocrine fas hion*

When a muscle cell contracts, a number of myokines are secreted from the muscle cells into the extracellular space. These molecules may act on specific receptors on the surface of the muscle cell which secreted them, termed autocrine signaling. The binding of the myokine to its receptor triggers a series of signaling events, usually phosphorylation reactions, which activate proteins to modify gene expression. An excellent example of this is the secretion of insulin-like growth factor-1 (IGF-1) from muscle cells, which then triggers protein synthesis in muscle cells. Some newly discovered myokines that are released upon exercise include interleukin-6 (IL-6) and irisin. These circulate in the blood and can have metabolic effects in other tissues. Thus, muscle not only produces molecules that have autocrine effects, but can act as an endocrine organ as well! (See the Highlight Box for additional details).

Gene Expression and Splicing

The activation of proteins by any one of these six mechanisms can lead to a change in their shape and location within the cell. In the case of proteins such as transcription factors, random movements within the cell can allow them to be translocated from the cytosol to the nucleus. There, these transcription factors bind DNA within the control region of genes in a sequence-specific manner. The particular sequence to which a transcription factor binds is called the response element or transcription factor-binding site (Figure 14.12). Recall that the structure of genes includes DNA which is “coding” (i.e. exons) and that which is non-coding (introns). Upstream of these gene segments is the control region called the promoter of the genes. It is usually within this upstream region that transcription factors bind to either facilitate or inhibit, the activity ofRNA polymerase, the enzyme that actually transcribes the DNA into mRNA. Additional proteins such as co-activators and co-repressors work in tandem with the transcription factor to activate or repress the expression of the gene of interest. Co-activators and co-repressors do not directly bind to the DNA, but instead interact with the transcription factor itself to affect its action on gene expression. Thus, the ability of the signals described above to activate or inhibit transcription factors, and the consequent effects on genes within the nucleus, are the key elements of transcriptional control of the gene expression pathway.

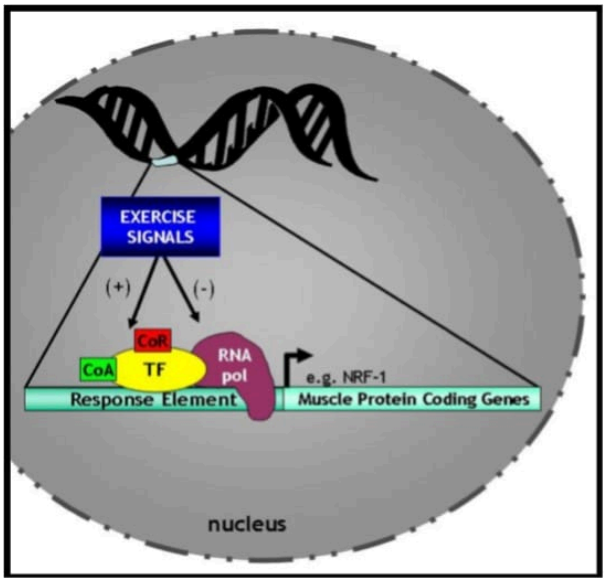


Figure 14-12 Exercise signals gene transcription. At the level of the DNA within each myonucleus, cellular signals provoked by exercise lead to the binding of transcription factors (TF) to the response element (DNA) upstream of the coding region of a gene. The action of the TF is often aided or inhibited by coactivator (CoA) or corepressor (CoR) proteins, respectively. TF activity facilitates RNA Polymerase (RNA Pol) to transcribe the gene into mRNA for subsequent translation. Nuclear-respiratory factor-1 (NRF-1) is a typical protein which helps promote the synthesis of in muscle in response to repeated exercise bouts.

Once a gene has been transcribed, the mRNA is referred to as the primary transcript. This transcript still contains intronic regions of the gene and is subject to the process of *splicing* within the nucleus to remove these non-coding regions. This activity is controlled by splicing proteins. Different cell types (e.g. liver or heart or muscle) can splice a primary transcript differently depending on the activity of these splicing proteins. This can lead to mature mRNA sequences which differ from one another in different tissues, thereby coding for tissue-specific variations in the protein derived from that gene. This is a mechanism of producing divergent isoforms of proteins as discussed earlier in the chapter. Thus, one gene does not always encode one protein; different isoforms can represent more than one gene product from the same gene. Some isoforms arise from different genes (e.g. myosin heavy chain genes) while others can be derived from the same gene. An example of this is the fast myosin light chain gene within muscle (Figure 14-13).

mRNA Stability and Translation

The mature mRNA, once formed in the nucleus, is exported via nuclear pores into the cytoplasm where it can follow a number of paths. It can be protected, stabilized and then translated into protein. Alternately, it can be subject to degradation by RNAses within the cytoplasm. Thus, the fate of an mRNA molecule is a result of competition between stabilizing and degradative factors in the cytoplasm of the cell **(**Figure 14-14**)**. Assuming that the translation process wins out, the initiation of translation is the "rate-limiting" step in the formation of a protein. Translation initiation is mediated by factors which require activation by signals similar to those described above for transcriptional activation. It involves the assembly of the ribosomal subunits around the mRNA and the start of ribosome movement down the mRNA molecule. The ribosome "reads" the mRNA one triplet codon at a time and permits the insertion of charged tRNAs to enter with their corresponding amino acid at each mRNA codon. This is the elongation phase of translation. Ribosomal proteins then assemble the growing polypeptide chain, one amino acid at a time, as the ribosome moves along the mRNA. When the termination codon is reached, no new tRNA is attached, and the polypeptide chain is released as a newborn protein molecule.

Protein Trafficking and Assembly

New proteins can be inserted as they are made into the endoplasmic reticulum (ER) of cells for further modification. This is called co-translational trafficking. The ER contains enzymes which can post-translationally modify proteins to increase their activity. These modifications include the cleaving of inactive regions of the protein or adding COH residues to the protein (i.e. a glycosylation reaction), to name a few. Alternatively, the newly-made protein can be bound by chaperone proteins which serve to traffic the protein to its correct location. An example of this is the movement of a protein from the cytoplasm to the mitochondrion (see below). Chaperones are bound to this newly synthesized protein at specific locations within the polypeptide sequence and they serve to target the protein to its correct location based on the amino acid sequence found within it. Thus, a chaperone

acts like a taxi cab, serving to direct a protein to its correct location within the cell while the “driver” of the cab is the targeting sequence found on the protein which tells the taxi, or chaperone, where to go.

Examples of Exercise-Induced Adaptations in Muscle

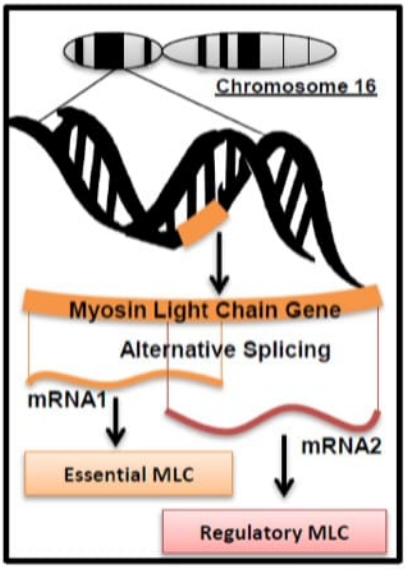


Figure 14-13 Arrangements of the genes encoding MHC isoforms (Top) and myosin light chains (MLC; Bottom). MHC isoforms are encoded by different genes on chromosome 17, whereas MLC isoforms are generated by transcription of the same gene, but the mRNA product are spliced in different ways to produce two different proteins.

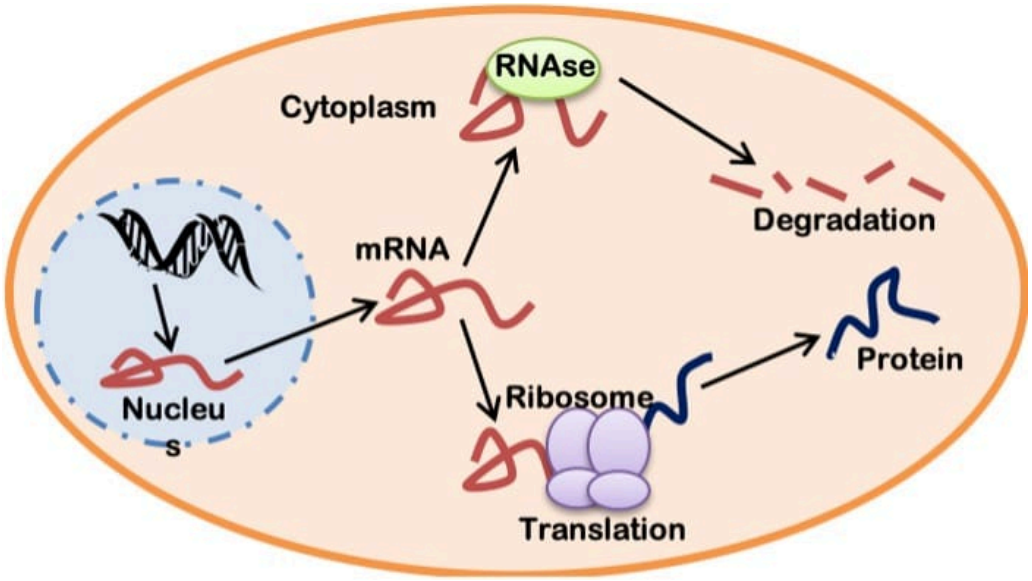


Figure 14-14 mRNA molecules emerging from the nucleus following transcription can be translated into protein by the action of ribosomes, or they can be degraded by the interaction of RNAses within the cytoplasm. The length of time that an mRNA molecule remains intact in the cytoplasm prior to degradation can determine how much protein is translated from the specific mRNA molecule.

Myosin Heavy Chain Isoform (MHC) Expression and Muscle Fibre-Type Conversions

As noted earlier, myosin heavy chains exist in several predominant isoforms within muscle. These include the MHC Type I, IIa and IIx, and they are so abundant in muscle that their expression determines the muscle fibre types of the same name. MHCs are large proteins of approximately 200 kDa in size. They are encoded by separate genes within the genome which lie in tandem beside each other on chromosome 17 (Figure 14.13). The factors that determine the expression of these genes are of great interest to exercise physiologists and fitness buffs alike. If we knew how to activate the expression of these genes, we could potentially switch fibre types and improve performance, or muscle health, at will.

What is the evidence that exercise can produce an adaptation in MHC gene expression, and therefore in muscle fibre types? There is plenty of evidence, but the result may not be what you expect. Recall that there are three main muscle fibre types, Type I (slow-twitch), Type IIa (fast-twitch) and Type IIx (also fast-twitch). These are so named because of the abundance of MHC isoforms (of the same name) within these fibres as detected by histochemical staining. In order for a fibre type "switch" to occur as result of training, the expression of the predominant MHC isoform within that fibre has to be reduced while that of another MHC isoform has to be increased.

Evidence from histochemical studies reveals that both endurance and resistance exercise training result in the same fibre type shift. The abundance of the Type IIx fibres is reduced and that of Type IIa fibres increases (Figure 14-15). There is very little evidence for conversion of fast- to slow-twitch fibres with the regular training regimens imposed on human muscle, though a few exceptions to this general rule have been documented in the literature. That being said, plenty of evidence for a slow-to-fast fibre type conversion exists in other mammals subjected to artificially-imposed chronic electrical stimulation for up to 24 hours per day. In those cases, the workload that is imposed on the muscle is much higher than we, as humans, impose on our muscles. In those cases, the result is a successful conversion to slow muscle fibres due to a change in the expression of the MHC genes. This suggests that it may ultimately be possible in humans as well. Note that opposite conversion, that of Type IIa to Type IIx fibres, can occur in humans, and this is generally observed under conditions of chronic muscle disuse such as that brought about by immobilization, denervation, or prolonged inactivity.

Why is it then that superb, elite endurance athletes (e.g. high level marathoners) have a high proportion of slow-twitch fibres, and that elite performers (e.g. Olympic-caliber sprinters) have a large fraction of fast-twitch fibres in their locomotory muscles? These endowments were not brought about by training but are a result of "genetics". While these athletes have the same complement of genes as normal healthy non-athletes, the expression of those genes has differed for those athletes ever since they were born. These athletes have a different pattern of gene expression than most other individuals either because of

- subtle differences in the sequence of DNA that controls gene expression (i.e. in the promoter region); or
- differences in the sensitivity of the gene expression pathway, at any of the levels that we have discussed above, to intracellular signals.

This was likely inherited to a large degree and modified slightly by training and environmental influences. Hence, we refer to this difference as "genetic".

Mitochondrial Biogenesis and Endurance Performance

Early findings

In the late 1960s, John Holloszy and his colleagues at Washington University in St. Louis were the first to show that endurance training produced an increase in mitochondrial content within muscles that had been recruited during the training period. This pioneering study led to an outpouring of research in this field, and it is now a well-known fact that the mitochondrial adaptations to training have a large number of performance benefits. These include a better use of lipid as a fuel during long-term exercise and the sparing of COH stores as well as a lesser production of lactic acid, leading to an improved endurance performance.

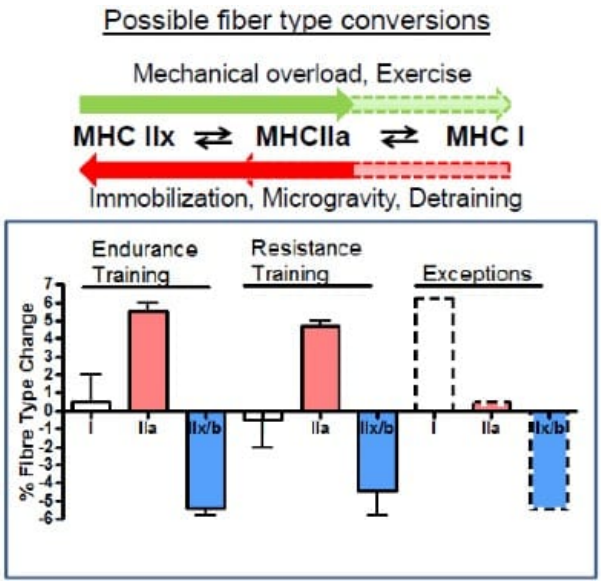


Figure 14-15 Typical (and exceptional) changes in muscle fibre type determined by histochemistry as a result of chronic muscle use (eg. exercise). The vast majority of studies illustrate that both resistance and endurance training program produce similar changes in muscle fibre type, with an increase in Type IIa, and a decrease in the proportion of Type IIb fibers. Type I fibre proportion is usually unchanged, but a few studies (Exceptions) report modest increases in Type I fibers in response to endurance training. In response to chronic muscle disuse such as microgravity or immobilization, most research indicates that the fibre conversion is the opposite to that of training, with increases in Type IIx, and decreases in Type IIa fibres. The dashed lines in the arrowheads indicate the rarity of the fibre type conversion involving Type I fibres.

Molecular basis for these changes

Figure 14-16 illustrates the complexity of the process of mitochondrialbiogenesisproduced by exercise.This process requires the coordinated synthesis of over 1500 proteins to expand the mitochondrial network within muscle cells. Mitochondria are unique in that they possess their own DNA, termed mitochondrial DNA (mtDNA). This genome is very small, encoding only 13 proteins. Thus, the remainder (about 1487 proteins!) must be coded for by nuclear DNA and synthesized in the cytoplasm via translation and then imported via specific channels into the mitochondrion. These imported proteins include Krebs' cycle enzymes, proteins within the electron transport chain (ETC), and many others that the organelle requires to makeATP. Imported proteins, along with those derived from mtDNA, are then assembled to form multi-subunit complexes which are required for the to function. Exercise is known to increase the transcription of nuclear genes encoding mitochondrial proteins (NuGEMPS), and to increase the transport of newly synthesized proteins into the mitochondrion. Exercise also increases the number of copies of mtDNA within the organelle, thereby increasing the capacity for mitochondrial biogenesis.

How does exercise do this? The signals evoked by exercise provoke an increase in the expression and activity of PGC-1α (Figure 14-16). PGC-1α is considered to be a "master" regulator of mitochondrial synthesis. It facilitates the transcriptional activity of a large number of transcription factors in the nucleus including Nuclear respiratory factor-1 (NRF-1). NRF-1 transcribes a whole host of NuGEMPs, and the mRNAs encoded then escape the nucleus and are translated into protein in the cytoplasm. Some examples of these proteins include cytochrome c and subunits of the electron transport chain.

The importance of PGC-1α in mediating these adaptations in muscle is evident from animal studies in which mice are genetically engineered to have too much PGC-1α (i.e. Transgenic overexpressing animals), or too little (i.e. Knockout mice). These types of genetic manipulations in animals have proven to be extremely useful in medical science research. In the transgenic overexpressing animals, the muscle mitochondrial content is much higher than normal and so is the endurance performance. In contrast, in the knockout animals' mitochondrial content is reduced and performance is impaired. Thus, it is clear that an understanding of how PGC-1α works in the cell can have a big impact on our knowledge of muscle adaptations.

Muscle Hypertrophy

Muscles enlarge in our bodies by undergoing hypertrophy as a result of an increase in the size of each individual muscle cell. Muscles typically do not divide or multiply, a process termed hyperplasia -they simply enlarge. The growth of individual muscle cells commonly occurs with resistance training that is performed with an appropriate intensity and duration as discussed earlier.

The hypertrophy occurs as a result of two major types of events:

- anabolic processes; and
- satellite cell activation, fusion and donation of new myonuclei.

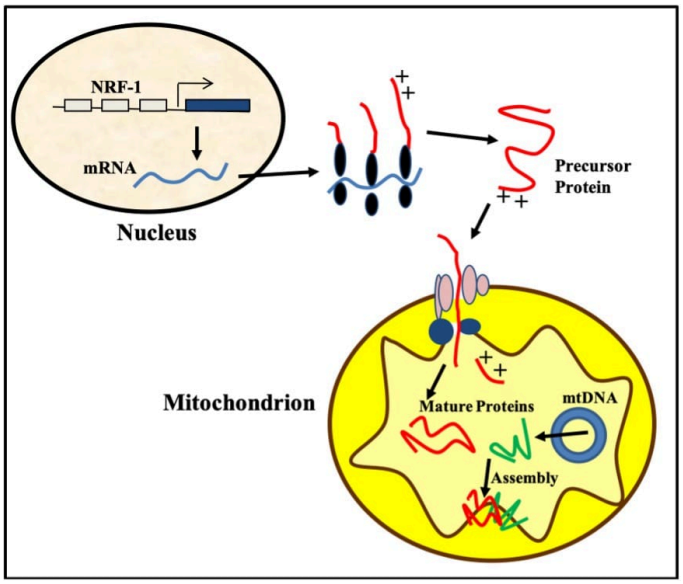


Figure 14-16 Mitochondrial biogenesis in muscle occurs as a result of chronic exercise. First, gene are transcribed in the nucleus via the action of transcription factors like NRF-1. The mRNA is translated in the cytoplasm into a precursor protein with a positively charged targeting sequence which helps direct it to the mitochondrion import channel. The protein is imported into the organelle, the targeting sequence is cleaved, and the mature protein is refolded to act as an enzyme or assembled as a component of the electron transport chain.

The result is an increase in the number of contractile myofibrils as a consequence of increased expression of myosin, and regulatory protein genes that comprise the majority of the proteins within muscle cells. This muscular hypertrophy causes myofibrils to thicken and then divide, making more myofibrils. The increase in mass and cross-sectional area of a muscle is directly proportional to its ability to produce force.

Anabolic Pathways

These pathways are activated by resistance exercise and lead to an increase in protein synthesis. They involve a number of important signaling proteins. One of these proteins, called mTOR (mammalian target of rapamycin), plays a crucial role in the formation of new proteins. The mTOR protein is a kinase which phosphorylates and activates proteins such as S6Kinase and 4E-BP1 to activate translation (Figure 14-17). Calcium is also an essential player for skeletal musclehypertrophy. With the release of calcium from the SR with every muscle contraction, calcium can activate a protein phosphatase called calcineurin. In contrast to mTOR, calcineurin removes phosphate groups from other proteins, particularly the nuclear factor of activated T-cells (NFAT), a name derived from the cell type in which it was originally discovered. When the phosphate group is removed from NFAT, it becomes free to enter the nucleus and increase the transcriptional activation of genes important for muscle growth like α- and IGF-1.

Satellite Cell Activation

Satellite cells (SC) are normally small dormant cells which reside adjacent to and within the basal lamina but outside of the plasmalemma of the much larger muscle cells (Figure 14.18). When skeletal muscle is exposed to an overload stimulus, factors such as Insulin-like Growth Factor-1 GF-1.are released which act on the neighboring satellite cells, causing them to become activated as well. Once activated, SC can divide to form “daughter” SC or fuse to the mature muscle cell and donate their nuclei and cytoplasm to that much larger muscle cell. Thus, the number of nuclei within a muscle cell can be altered by resistance training. This fusion and donation of nuclei by SC is an important adaptation which leads to muscle cell hypertrophy in response to this form of training. In fact, experiments have shown that if neighboring SC are destroyed prior to the start of training, very little hypertrophy will occur! It stands to reason that if a muscle cell gains a myonucleus and that nucleus continues to be active in gene expression, then the gene products (i.e. proteins) will contribute meaningfully to the size of the cell.

In contrast to muscle growth and hypertrophy of muscle fibres, disuse conditions such as casting, space flight, loss of innervation,

or prolonged bed rest produce atrophy of fibres and of the whole muscle. This is likely due to a combination of a decrease in myofibrillarprotein synthesis and an increase in protein degradation. In these situations, the number of myonuclei remains constant while the muscle fibre shrinks (Figure 14-18**)**. Maintaining the same number of nuclei in light of a decrease in muscle mass allows for more rapid recovery. This may help explain the phenomenon of muscle “memory”, in which re-adaptations following injury or disuse are more rapid than they were originally when training first began. It should be noted that this is a highly studied area of research, and some controversy still exists in the field.

Research Box: Myonuclear Domain Theory

The myonuclear domain (MND) theory, originally conceptualized by Cheek and colleagues in 1971 (1985), has been widely accepted in research until very recently when it gathered a storm of controversy. Simply put, the theory postulates that each nucleus in a myofibre is responsible for a theoretical amount of cytoplasm and that this nuclear-to-cytoplasmic ratio adapts to changes in muscle size. During muscle hypertrophy, the muscle grows in size either by increasing the cytoplasmic domain size per nucleus or by augmenting the number of myonuclei thereby keeping the MND size constant. Conversely, the theory posits that under conditions ofatrophy as the myonuclei are targeted for destruction, there is an accompanying yet relatively greater loss of cytoplasmic volume and the MND size is reduced.

Much of the work in the field has been conducted by Edgerton and colleagues (1991) who have rigorously studied myonuclear number and domain size during muscle hypertrophy and atrophy Earliest reports suggested an elevation in the number of myonuclei commensurate with an increase in fibre size during muscle hypertrophy wherein the nuclear-to-cytoplasmic ratio remains unchanged. However, it was later illustrated that increases in muscle size can occur independently of changes in nuclei count. In such cases, the domain size has been proposed to increase to a 2000μmthreshold ceiling subsequent to which an increase in nuclei number is necessary for further muscle hypertrophy (Allen, 1999). Furthermore, MNDs increase in size during maturational muscle growth and are fibre-type dependent, with the smallest domains found in type I and the largest in type IIB/X fibres. Thus, the literature supports the existence of a constant or increasing size of nuclear domains with muscle hypertrophy.

A multitude of studies have suggested that myonuclei are targeted for degradation and the subsequent loss of MNDs explains the observed muscle atrophy during conditions such as disuse, denervation, neuromuscular disorders and mechanical unloading (Bruusgaard et al., 2012). This notion was recently challengedvigorously by Gundersen and colleagues (Bruusgaard and Gundersen 2008, Gunderson, 2011) who illustrated that these studies had failed to distinguish between the muscle nuclei and nuclei from surrounding cells undergoing apoptosis such as stromal and satellite cells. Using time lapse imaging of a single fibre in vivo, they illustrated no loss of myonuclei despite a 50% reduction in fibre size. Even during aging, a clear pattern has emerged that myonuclei are not lost despite substantial atrophy. In fact, some studies even report an increase in myonuclei per muscle fibre (Petrella, et al., 2006). Clearly, the data are in direct opposition to the MND theory as they reflect that muscle atrophy occurs independently of the loss of myonuclei and is therefore irrespective of the principle of a nuclear-based control over cytoplasmic domains.

Despite the evidence presented by Gundersen et al. (Bruusgaard and Gundersen 2008, Gunderson, 2011) in recent years that challenges the MND theory, it would be premature and unwise to discount the plethora of studies published over the last 30 years that show otherwise. Differences in methodology and study design can account for some of the variability observed. Clearly, this area of research certainly warrants the attention it is currently receiving and may result in a universally agreed upon adjustment to the MND theory and its role in muscle size.

Summary

Muscles are composed of different fibre types which adapt differently depending on the type of exercise imposed. Resistance training typically leads to muscle fibre hypertrophy, thereby increasing strength, while endurance training leads to metabolic adaptations in mitochondrial function, producing greater endurance. The bases for these adaptations reside in exercise-induced modifications of the gene expression pathway, consisting of signaling, gene transcription, mRNA processing, translation, and post-translational modifications and trafficking. A single acute bout of exercise can initiate the adaptation process by activating this pathway. Repeated bouts of exercise (i.e. training) can lead to the accumulation of gene products (i.e. proteins) that result in an alteration in muscle phenotype, and improved function. Understanding how the gene expression pathway works and how exercise can modify it is the basis for our comprehension of exercise adaptations.

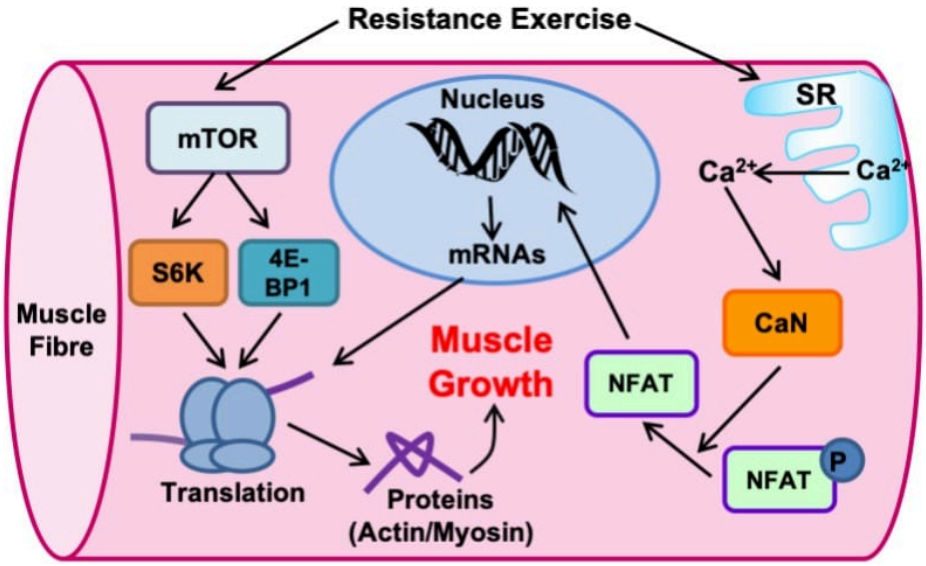


Figure 14-17 Resistance exercise activates two pathways which signal muscle growth (or hypertrophy). First, the kinase mTOR is activated to phosphorylate two proteins required for translation: S6K and 4E-BP1. Once activated these proteins trigger the process of protein synthesis, including and myosin. In addition, contraction causes the release of calcium which binds to calcineurin (CaN) to dephosphorylate the transcription factor nuclear factor of activated T cells (NF-AT). This protein promotes the transcription of the and myosin genes to provide the mRNA for translation.

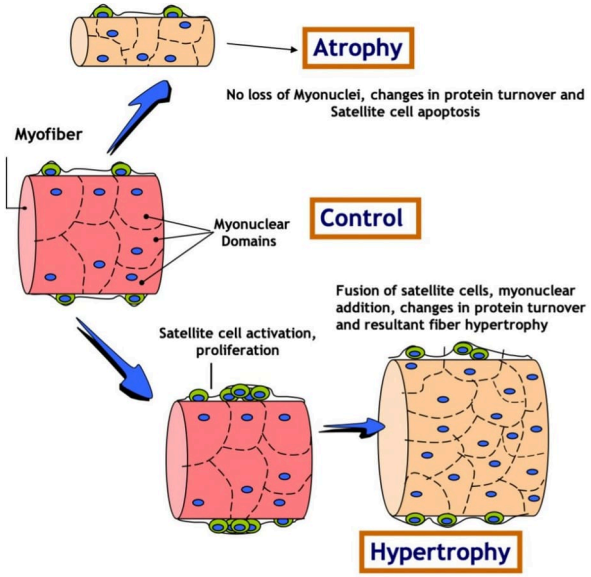


Figure 14-18 Muscle fibers atrophy in response to chronic disuse, and hypertrophy as a result of resistance training. See text for details. Adapted from Saleem A. et al., in Reed J. and D. Green, Eds. Apoptosis: Physiology and Pathology. New York: Cambridge, 2011, p. 318.

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Examine your adaptations to endurance training

Resources to have available:

- Exercise facility with a calibrated bicycle ergometer or treadmill;
- Portable blood lactate analyzer;
- Heart rate monitor;
- A partner to help with heart rate (HR) or breathing rate (f).

Purpose: to examine your individualized adaptations to endurance training

Methods:

- Design your own endurance training regimen in which you exercise using a modality of your choice (e.g. Jogging, swimming, cycling) 3-4 times/week, at 60-90% of your maximum HR for at least 6 weeks. This program needs to be in addition to your current level of activity. Prior to starting this additional training, test your currentfitness level using an indirect, submaximalfitness test (e.g. Astrand-Rhyming test). At a standardized, absolute workload, measure your HR and breathing frequency (f; here is where a partner could help). If possible, donate a finger prick blood drop for lactate analysis.
- Complete the fitness training program.
- Repeat your measurements again after 6 weeks of training, using the same test workload as in the pre-test.

Expected Results:

- A lower HR and f are expected at the same absolute workload after training.
- Reduced blood lactate concentrations are also expected, reflecting less lactic acid production by the working muscle. This is probably a result of an improved mitochondrial content (and therefore aerobic system energy provision) as an adaptation to training. This adaptation means that there is less reliance on anaerobic glycolysis for synthesis post-training, and greater endurance.

Introducing the Authors



D.A. Hood, ,, , , School of Kinesiology *and Health Science, Muscle Health Research Centre, York University, Toronto ON.* David A. Hood is a Full Professor and Tier I Canada Research Chair in Cell Physiology in the School of Kinesiology and Health Science at York University. His research investigates the role of exercise and disuse on mitochondrial turnover in skeletal muscle.

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Nashwa Cheema is a postdoc in Dr. Rox Anderson's lab in Harvard Medical School at Massachusetts General Hospital (HMS/MGH) and has been working on a project to enhance muscle performance and mitigate injuries with the application of photobiomodulation, the process of near-infrared light treatment. She obtained her PhD in 2017 at University of Alberta, Canada, in Physiology, Cell and Developmental Biology where her thesis was focused on sarcopenia, loss of muscle mass and function, in aged rats. Prior to joining HMS/MGH in 2020, Nashwa was a postdoc in Dr. David Hood's laboratory at York University, Canada, a pioneer in the field of exercise physiology. Her project in his lab was focused on treatment strategies for mitochondrial health in isolated fibroblasts from patients with mitochondrial mutations.

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Ayesha Saleem, received her PhD degree from the School of Kinesiology and Health Science at York University in 2013.
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Heather Carter –



Heather Carter received her PhD degree (2017) from the School of Kinesiology and Health Science at York University

She is now enrolled as a student at OISE, University of Toronto

Anna Vainshtein –Director, Craft Science Inc.



Dr. Anna Vainshtein is currently the director of Craft Science Inc., a science communications consulting firm based out of Toronto, Canada. She earned her B.Sc. (Hons), MSc. and Ph.D. at the School of Kinesiology and Health Science at York University, Toronto, Canada. During her academic journey, Dr. Vainshtein discovered and cultivated a profound passion for mitochondria, autophagy, muscle biology, and cellular bioenergetics. Seeking to deepen her understanding of mitophagy's intricate roles in skeletal muscle, she pursued a fellowship at the Venetian Institute for Molecular Medicine in Padova, Italy. Subsequently, she completed her postdoctoral training at the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas, USA, where she expanded her expertise to encompass the genetic regulation of the autophagy-lysosome system. Dr. Vainshtein's journey reflects a relentless pursuit of knowledge and a commitment to advancing the frontiers of biomedical science on an international stage.

Olga Ostojic



Olga Green (née Ostojic) completed both a Bachelor's (2010) and Master's (2012) degree from the school of Kinesiology and Health Sciences at York University. She then went on to complete her Doctor of Dental Surgery degree at the University of Toronto. She partook in several dental outreach initiatives, including a rotation within a hospital-based clinic in Moose Factory, Ontario, where she worked with underserved First Nations populations. She now works as a general dentist in Toronto.

S. Iqbal



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3.4: Chapter 15 - The Immune System Response to Acute and Chronic Exercise

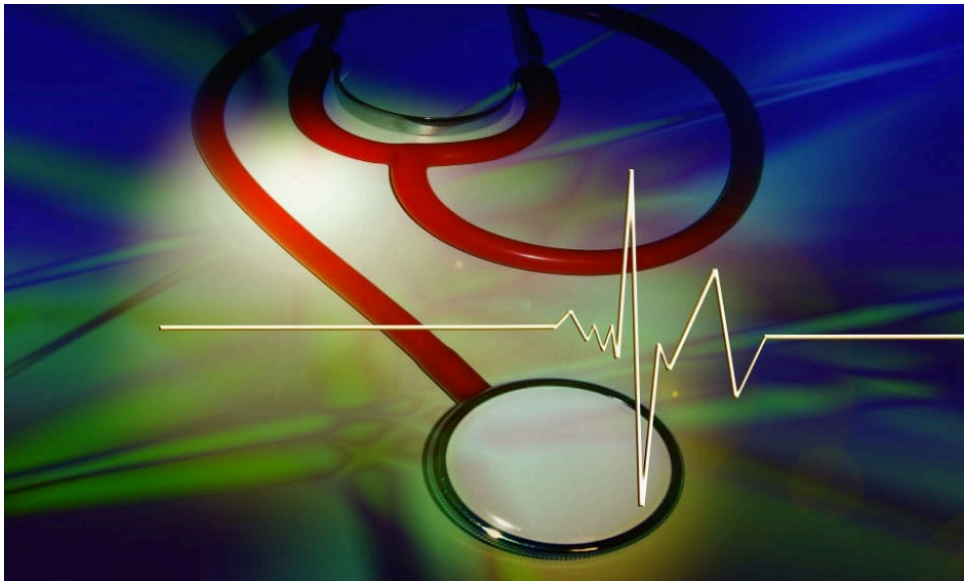


Photo 15-1. Exercise and health are intricately related.

Learning Objectives

After reading this Chapter, you should be able to:

1. Describe the basic components of the immune system including the lymphatic system, the major immune organs, and the primary physiological barriers.
2. List and describe the common cells and signaling molecules of the immune system.
3. Compare and contrast the innate versus acquired immune systems.
4. Describe the components of the immune system that are modified by exercise.

Key Terms

acute phase proteins, allergic immunity, antibodies, antigen presenting cells, antibody mediated, anti-microbial, anti-viral, apoptosis, B memory cells, C-reactive protein, cell-mediated immunity, cluster of differentiation, complement system, haematopoiesis, humoral immunity, immunology, immunosurveillance, innate/acquired or adaptive, lipopolysaccharide, lymphocytes, opsonisation, pathogens, pattern recognition receptors, phagocytes, pathogen-associated molecular patterns, plasma cells, receptors, toll-like receptors,

Case Presentation: Heavy Training can Compromise Your Immune System

Jake, who you have met earlier, and Jerry are close friends. They grew up together, were highly active through elementary and high school, and even wound up attending the same university to compete in track and field. Jerry, however, quickly found himself unable to balance his academic and athletic careers and chose to cut his university running career short. Even though he left the team, he did not stop running, and found himself enjoying the freedom to train when and where he wanted without the pressures of performance times and team practices. He also started to take up new forms of exercise, such as yoga, with a young woman he met while out on a leisurely jog. Jake, on the other hand, enjoyed a year of success and even won “Freshman of the Year” at the end of his first season. He seemed to revel in the competitive aspect of the sport and

took his training to new heights over the summer, increasing his training intensity and volume such that he was without peer in practice runs. Towards the middle of the first semester in second year, there came to be a dramatic difference in the 2 young men. Jerry's grades improved so that he was no longer in danger of being kicked out of his program, he noticed his runs were feeling easier, and his attitudes about life and health were at all-time highs. Jake, on the other hand, was still the top sophomore runner, but he never approached his performance times of the year before, and as the season progressed his performance seemed to decline every week. Jake assumed this was a function of inadequate training and reasoned that if he could only train harder and longer, he would regain some of his first-year prowess. Unfortunately, over the course of the year Jake found himself sick more often than he could remember and this significantly hindered his ability to train and perform. Even though they were roommates, Jerry seemed to enjoy a sort of immunity from the colds and flues that plagued Jake all year. One day when Jerry was heading out to the yoga studio with his girlfriend, he noticed Jake sniffling away on their beat-up dormitory lounge chair.

"Don't worry, Jake," he shouted just before leaving the cramped dorm room. "I'm sure you'll be better tomorrow."

What is it about exercise that can cause a young varsity athlete to become confined to his "beat-up old dormitory couch", seemingly more susceptible to minor "colds and flues" as Jake described them? Further, what is it about exercise in other forms that actually appears to fortify the body against a host of potential stressors? Answers to these questions require an understanding of the immune system and the strategies employed to protect your body against disease and infection. In the next chapter, we will first learn about the important components of the human immune system including the transport vessels, cells, chemical messengers, and the functional integration of these different components to make up the fast acting innate and slow acting but powerful acquired branches of the immune system. Then, you will be introduced to how exercise affects the immune system with special emphasis on the importance of exercise dose (intensity and duration). Knowledge of these effects can be used by athletes and recreationally active individuals alike in an attempt to keep their complex but vital immune systems as healthy as possible. Small organisms and chemical molecules that originate from outside the body can initiate massive physiological defense responses when they enter our interior environment. This response is a necessity for life, but, depending on the stress, can become an energy and resource glutton and render the rest of the body almost helpless against the physical stresses that present themselves every day such as getting up and walking. Think about your energy levels when you've had a cold or flu like Jake in the example above. Again, depending on the severity of the sickness, exercise or movement is likely the furthest thing from your mind. This fatigue and lethargy is not typically a result of the foreign invader itself, but rather directly related to your body devoting energy to the immune system to rid yourself of the harmful invader. In a common but extreme example of the importance of the immune system, the human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS) by destroying a vital component of the immune response, helper T Cells, and in so doing renders the body defenseless against the onslaught of bacterial and viral invaders we normally face each day. In fact, most individuals unsuccessfully treated against HIV usually succumb to AIDS opportunistic infections (Collaboration 2010) such as Pneumocystis pneumonia (PCP), a potentially fatal fungal infection that you likely carry in your lungs right now but which your healthy immune system can easily keep under control.

Introduction

The Nobel Prize in Physiology and Medicine in 1908 was given jointly to doctors Ilya Mechnikov and Paul Ehrlich as pioneers in the study of the immune system. Dr. Mechnikov noticed that groups of cells that could engulf and devour foreign bodies would congregate at a puncture site in the skin of sea star larvae. Meanwhile, Dr. Ehrlich theorized that cells, when invaded by a toxin releasing substance, possess the capability to neutralize these toxins by producing specific receptors to the toxins. Dr. Mechnikov went on to name those specialized cells phagocytes (from the Greek meaning *devouring cells*) and Dr. Ehrlich's side chain receptors form the basis for how we now understand antibodies to function. While they did not possess the capabilities we now do, their findings were also the bases behind the inherent and acquired immune responses that we now know are much more complex.

We live in a world of microbes whose primary biological purpose, much like our own, is to propagate the survival of their genetic information. Unfortunately for us, we and other animals are excellent incubators for microbes to thrive, develop, and achieve their life's purpose with great success. However, it is to our benefit that many of these microbes can achieve this goal without mortal consequences to us. In fact, we co-exist with several bacteria that aid in the proper function of our physiology. For example, it is estimated that there are approximately 10^{12} microorganisms and their associated viruses per gram of contents that line the intestinal walls and are necessary for proper digestion and protection (Garrett et al. 2010). For example, it is estimated that there are approximately 10^{12} microorganisms and their associated viruses per gram of contents that line the intestinal walls and are necessary for proper digestion and protection (Garrett et al. 2010). However, it is important to be aware of the fact that there are

a significant number of harmful pathogens (any agents that cause infection or disease) that require a continual upgrade of our body's defense throughout evolution. This challenge has been referred to as a biological arms race between us and the multitude of the ever-evolving pathogens that fill our environment. The body is a well-fortified system with very limited access to what Dr. Claude Bernard, a prominent French physiologist and one of the forefathers of the concept of homeostasis, described as the milieu interieur (internal environment or fluids that surround all of our cells). It is easy to imagine, however, that when dealing with the likely thousands of attacks the body has to deal with every day, there are bound to be at least a few perpetrators that penetrate into our internal environment. As a consequence, and thankfully for us, our bodies employ multiple levels of defense that include physical barriers and mucosae (mucus membranes), non-specific chemical and cellular defenses, and specific systems targeted towards learned and recognized threats to fend off invading pathogens. Combined, these defenses make up what is known as the immune system.

Highlight Feature: Edward Jenner and the Smallpox Vaccination

Before anything was known about antibodies and phagocytes, Edward Jenner, an English country doctor, cleverly introduced to the world what we now know as immunization. Jenner, who himself underwent variolation against smallpox at a very young age (i.e. deliberate infection with smallpox in an effort to protect against full blown smallpox later on), observed, as did many others, that milkmaids who suffered from cowpox (a bovine variant of the smallpox disease) were protected against smallpox. Because cowpox was symptomatically different than the more deadly smallpox, these milkmaids benefited from protection against smallpox without any of the side effects experienced in variolation. Jenner, using this knowledge, inoculated (injected) cowpox into the arm of a young boy. The boy became mildly ill with cowpox and then recovered. Several years later, he introduced smallpox to the young boy. Lucky for the boy that Jenner's theory proved correct, he did not succumb to it. This was the first indication of vaccination (from the Latin word *vacca* for cow), and subsequently adopted by Louis Pasteur for the immunization against any disease. Most of us have undergone several vaccinations in infancy which required only a few doses to make us immune to what would have otherwise been life threatening diseases. This fact speaks to the remarkable memory of the immune system.

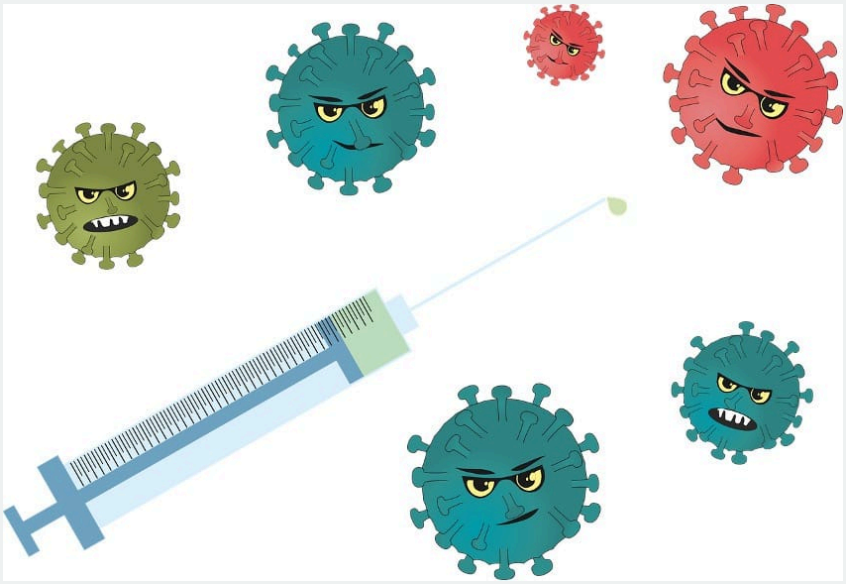


Photo 15-2 Vaccines help the body to acquire immunity against harmful pathogens

The Immune System and Immunology

The word "immune" stems from the Latin *immunis(im*-not; *munus*-duty). It literally means exemption from military service, taxes or other public services, but has taken on more general ("you are immune from further persecution" or "immune from being voted off the island") and medically specific ("immune from disease") meanings. The immune system actually consists of the second and subsequent lines of defense in our fortified biological systems. In the true sense of the word "system", these defenses employ a coordinated effort of different organs, cells, and molecules that function to keep us healthy. Likely one of the most important concepts in the field of immunology is that the body must be able to distinguish the billions of cells and molecules that make up each individual's own body from an almost endless possibility of foreign invaders. As such, immunology has been defined as the

science of the selective differentiation of self from non-self (Klein 1999). How does your body recognize the bacterium that causes strep throat (group A streptococcus) and destroy it, but not set the same defenses against the cells of the upper respiratory tract where these bacteria are most likely to infect? This concept is described in further detail in Highlight Feature 15-2 and highlights the problems that can occur when this distinction is not clearly made. Nonetheless, it does allude to the importance of the primary defense system (physical barriers) that prevent a need for immune action. In order to understand how exercise modifies immune system function, it is first important to learn about the important components of the defense system.

Examples:

Highlight Feature: Self Versus Non-self

In the evolution of multicellular organisms, the ability to separate what is foreign (non-self) from what is of host origin (self) became paramount. At one extreme, if your body cannot distinguish foreign cells from your own, it would be easy for bacteria to proliferate in the ripe conditions your body works so hard to maintain. Similarly, with an immune system that cannot distinguish what is of host origin, there would be indiscriminate attack of all cells, greatly taxing survival. In fact, several current diseases are manifest in the body's altered recognition of self versus non-self. For example, several types of arthritis originate in the destruction of the synovium (i.e. lining of the joints) by the body's immune system. Similarly, Type 1 diabetes begins with the attack of pancreatic beta cells by host immune cells. These are known as autoimmune (auto meaning "self") diseases, and represent a difficult and active area of research in those and other diseases. The difficulty lies in the fact that in order to prevent the disease, portions of the hosts immune system must be disabled.

Sir Frank Macfarlane Burnet, an Australian virologist, formally introduced the discussion of "self" into the field of immunology. His theory of immunological tolerance stated that the cells and biological material that made up the host organism (i.e. self) were ignored or "tolerated" by the immune system, whereas the foreign, genetically alien cells (i.e. non-self) were destroyed. Burnet's theories were central to the understanding of immune reactivity and portions of his work jointly won him and Sir Peter Brian Medawar, who experimentally studied the concept of immune tolerance, the 1960 Nobel Prize in Physiology or Medicine. In his Nobel lecture, Burnet asked a question that has intrigued immunologists since his time, "How can an immunized animal recognize the difference between an injected material like insulin from another species and its own corresponding substance?" For example, several drugs we currently inject are tolerated by our immune systems even though they are of foreign origin. Consequently, it may be more appropriate to think of the "self", "non-self" or for that matter, immunogenic, as categories defined by the immune system that could include foreign or non-foreign structures rather than simply of the body or not. Indeed, Dr. Charles Janeway later theorized that the "self/non-self" categories were defined by the innate immune system using evolutionary conserved pathogen-associated molecular patterns. This has become known as Pattern Recognition Theory, and is generally accepted as a bridge between innate and adaptive immunity in mammals. However, Dr. Polly Matzinger proposed a theory in which the immune system does not care so much for "self/non-self", but which is concerned with preventing insult to the bodily tissues. Having at least some recognition of "self" best allows the system to determine what is dangerous, but is not the deciding factor in generating an immune response. Nonetheless, while "self/non-self" is taught in every immunology class, the question asked by Dr. Burnet is still actively investigated to this day.

Physical and Chemical Barriers

The skin acts as the first line of defense in the battle to protect the body from foreign invasion. A structural protein in skin cells, keratin, makes them highly resistant to many forms of bacterial attack. Further, sebaceous cells located predominantly in the face, head, and hairy regions of the body, secrete an acidic oily substance (sebum) that contains chemicals to inhibit and destroy many pathogens. Further, all cavities open to the exterior (remember, the respiratory, gastrointestinal, and urogenital tracts are all exposed to the internal environment) are lined with mucous membranes whose sticky mucus can trap foreign particles. This is supplemented by the mechanical actions of coughing, sneezing, crying (tears), urination, and the chemical actions of enzymes and other anti-microbial or anti-viral substances to keep invaders out. These physical, mechanical, and chemical barriers are listed in Table 15-1.

Table 15-1 Physical Barriers and Chemical Defenses

	Function
Physical Barriers	
The skin and interior epithelium	• Most important physical barrier. • Tight junctions between epithelial cells cannot be penetrated by most organisms unless damaged (e.g. cuts, scrapes, etc.). • Skin cells contain keratin, a structural protein that is resistant to weak acids and bases and many bacterial enzymes and toxins. • The gastrointestinal, respiratory, urogenital tracts contain tight epithelial barriers that, like the skin, prevent most bacterial penetration.
Mucous membranes	
Mucus	• Made up of several glycosylated proteins called mucins; sticky mucus traps pathogens; may contain anti-microbial proteins and immunoglobins to help prevent infection.
Gastrointestinal tract	• Saliva traps pathogens in the mouth.
Urogenital tract	• Mucus traps pathogens; while urination expels pathogens.
Respiratory tract and lungs	• Tiny hairs in the respiratory tract moving in the direction of the mouth and nose expel pathogens by a process termed ciliary action. • Sticky mucus traps tiny particles and organisms; pathogens are forcefully expelled by the actions of coughing and sneezing.
Chemical Defenses	

pH	• Acidic skin secretions (called sebum) prevent the growth of bacteria. • Lactic acid in the urogenital tract and hydrochloric acid in the stomach kill foreign pathogens.
Enzymes	• The sebum (oily skin secretions) contain chemicals that are toxic to bacteria. This sebum is secreted by sebaceous cells found predominantly around the face, head, and hairy regions of the body. As such, areas not covered by hair are more susceptible to bacterial growth which is a concern for some athletes and exercisers; as noted in Highlight Feature 15.4 regarding Athlete's Foot. • Saliva (in the mouth), tears (coating the eyes), breast milk, and mucus contain lysozyme, an enzyme that destroys bacteria. • Proteases in the gastrointestinal tract digest proteins.

Typically, these barriers are sufficient to prevent infection, and it should be easy to see why the risk of infection rises substantially when those barriers are broken. For that reason, physical exercise in which close physical contact and the increased potential for scrapes, cuts, bruises, and bleeding to occur increases the potential for infection and transmission of respiratory and blood-borne pathogens. This presents a difficult issue for athletes, parents, coaches, and sports officials given that many individuals might not know if they are infected with a disease at the time of athletic competition. To highlight this difficulty, in 1991, one of the greatest basketball players in the world, Earvin "Magic" Johnson held a press conference to announce that he had tested positive for HIV and would retire from the National Basketball Association (NBA). However, Magic was voted into the all-star game for that season (1991-1992). Several players indicated their discontent, especially given their unawareness of how diseases were spread. Nonetheless, several physicians cleared him to play and amid large public debate, he did compete and won the MVP for that contest. While the other players' concerns were warranted, today, several organizations present guidelines about minimizing the spread of infectious diseases during sport and one of the most notable findings is that the risk of serious blood-borne disease spreading during athletic competition is slim. A summary of the recommendations by the American Academy of Pediatrics and National Athletic Therapists Association are presented in Highlight Feature "Position Statement on HIV and Other Blood-Borne Viral Pathogens in the Athletic Setting"

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High-light Feature: Position Statement on HIV and Other Blood-Borne Viral Pathogens in the Athletic Setting

The American Academy of Pediatrics (www.AAP.org) has established recommendations for individuals participating in sport, including athletes and the staff of athletic programs, who may be at risk of exposure to human blood. The Committee on Sports Medicine and Fitness, a subcommittee of the Academy given the task of preparing the position statement, noted that the risks of infection were small, primarily because bleeding wounds are not particularly common and most blood-borne diseases require some access point to the blood in the non-infected person and require prolonged exposure to large amounts of infected blood. Nonetheless, a brief summary of the report's recommendations are listed below:

1. Athletes infected with HIV, Hepatitis B (HBV), and Hepatitis C (HCV) which are collectively the more serious blood-borne viruses, should be allowed to participate in all competitive sports.
2. Infection status of athletes should remain confidential.
3. Athletes should not be tested for infectious diseases.
4. Physicians should council athletes infected with HIV, HBV, or HCV that they have a low risk of infecting others, but should take precautions against the spread of disease.
5. Athletes and their parents should be made aware that the sport organization is operating under these recommendations.

6. Clinicians and athletic staff should encourage all individuals related to sport get immunizations against HBV.
7. All coaches and trainers must receive training in first aid and emergency care and in the prevention of transmission of blood-borne pathogens in the athletic setting.
8. Coaches and athletic staff should educate athletes about the recommendations and precautions outlined in this position stand.
9. While not required, it is a recommendation that athletic programs comply with Occupational Safety and Health Administration regulations of the region.
10. Sports in which the risk of direct contact with an athlete's blood is increased (e.g. wrestling or boxing) should take additional precautions to minimize the risk of pathogen transmission. Though the risk of transmission can never completely be eliminated, these precautions include:
    - Existing cuts, abrasions, wounds, and other areas of broken skin should be covered and dressed appropriately in all participants in the athletic event. This includes, athletes, coaches, officials, trainers, etc. ...
    - Disposable, waterproof latex or vinyl gloves should be worn whenever addressing a wound or handling any blood-soiled clothing, bandages, or other materials.
    - Athletes should be advised to report injuries and wounds in a timely fashion before or during competition.
    - Contaminated equipment, clothing, and playing areas should be disinfected or replaced. Disinfection should include contact with an appropriate germicide or freshly-made bleach solution (1-part bleach in 10 parts water) for at least 30 seconds.
    - Emergency care must not be delayed because protective equipment is not available.
    - Breathing bags and sterile oral airways should be available at sporting events and be used preferably to mouth-to-mouth resuscitation.
    - These precautions extend to equipment handlers, laundry personnel, and janitorial staff who must be trained in the proper handling and disposal of blood contaminated materials.

These guidelines are furthered by the National Athletic Trainers Association (www.nata.org) in their guidelines on how to prevent the spread of communicable and infectious diseases in secondary school sports:

- Immediately shower after each practice or competition.
- Wash all athletic clothing worn during practice or competition daily.
- Clean and disinfect gym bags and/or travel bags, if the athlete is carrying dirty workout gear home to be washed and then bringing clean gear back to school in the same bag (note: instead of disinfection, using disposable bags for practice laundry could be introduced).
- Wash athletic gear (such as knee or elbow pads) periodically and hang to dry.
- Clean and disinfect protective equipment such as helmets, shoulder pads, catcher's equipment, and hockey goalie equipment on a regular basis.
- Do not share towels or personal hygiene products with others.
- All skin lesions should be covered before practice or competition to prevent risk of infection to the wound and transmission of illness to other participants; only skin infections that have been properly diagnosed and treated may be covered to allow participation of any kind.
- All new skin lesions occurring during practice or competition should be properly diagnosed and treated immediately.
- Playing fields should be inspected regularly for foreign objects and debris that could cause cuts or abrasions.
- Playing fields should be inspected regularly for animal droppings that could cause bacterial infections of cuts or abrasions.
- Athletic lockers should be sanitized between seasons.
- Rather than carpeting, locker or dressing rooms should have tile floors that can not only be cleaned, but also sanitized.
- Wrestling and gymnastics mats should be sanitized daily.
- Weight room equipment – including benches, bars, and handles – should be cleaned and sanitized daily.

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Functional Organs of the Immune System

The Lymph System

If you are asked to indicate the part of your body most responsible for glucose homeostasis, you might say the pancreas (because of its glucose regulatory hormones) or liver (because of its role in gluconeogenesis and secretion of glucose). Now think about

what organs are important to the immune system. Likely, the first thing to come to mind is not an organ at all, but rather components of the immune system including inflammation, white blood cells, or antibodies. This is because the cells of the immune system can be found in nearly all regions of the human body. In many instances these locations correspond with sites of potential pathogen entry (e.g. tonsils at the entry to the throat), but this is not a requirement. The lymph system is actually made up of the lymphoid tissue, vessels, and lymph fluid. The word lymph is of Latin and Greek origin (lymph meaning water) and refers to a clear, transparent, sometimes yellowish fluid that circulates around the body in lymphatic vessels. Lymph contains primarily white blood cells, lipids and lipid-soluble vitamins, and other material collected from the extracellular space through-out the body. Lymph drains into the venous blood system at the thoracic and right lymphatic ducts. Lymphoid tissue is rich in cells named lymphocytes, but also contains accessory immune cells such as macrophages and reticular cells (a type of fibroblast). Lymphocytes and macrophages are described in more detail later in the chapter. The lymphoid system (see Figure 15-1) consists of the lymph vessels, the primary organ of the thymus gland, as well as the adenoids, tonsils, appendix, spleen (located at the upper left of the abdomen), lymph nodes (bundles of lymphoid tissue located along the lymphatic vessels with concentrations in the neck, armpits, abdomen, and groin), and Peyer's patches (bundles of lymphoid tissue located along portions of the intestines). The thymus is located in front of the aorta and behind the sternum and varies considerably in size, such that in newborns and children, the thymus is relatively large, but progressively decreases in size into adulthood. The secondary lymphoid tissues are located close to anatomical sites in close contact with the external environment (e.g. throat and intestines) where they can best intercept pathogens before they enter the blood.

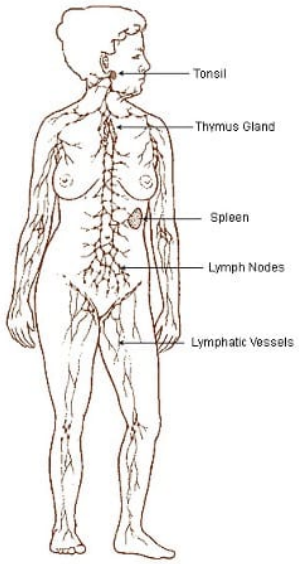


Figure 15-1 The Lymph System.

Bone Marrow

Lymphocytes typically mature in the thymus and other lymph tissues but originate in the bone marrow, the primary site of undifferentiated precursor cells called bone marrow stem cells (BMSC). As such, the bone marrow is considered one of the primary anatomical sites of the immune system. It is for this reason there is such concern with diseases that affect the normal functioning of BMSCs (e.g. leukemia, a type of cancer that causes excessive production of white blood cells) or therapies that may destroy the bone marrow, such as radiation or chemotherapy used to fight some cancers.

The Blood and its Constituents

In addition to the lymph, the blood, blood cells, and the vascular system are important components of the immune system. Human blood is composed of the plasma, red blood cells, platelets, and white blood cells. The plasma makes up approximately 60% of whole blood, is predominantly water-based and acts as a carrier for all blood-borne substances. As you have learned in previous chapters, the blood vessels provide the conduits through which the blood, and hence blood cells, travel. White and red blood cells are products of haematopoiesis (from the Greek: haima for blood and poiein to make) or the making of blood cells in the bone marrow. The red blood cells (erythrocytes) contain haemoglobin and thereby carry oxygen throughout the body. The platelets (thrombocytes) are cell fragments important to the clotting process whereby open wounds in the vasculature are sealed to prevent blood loss and maintain the integrity of the first line of defense against invading pathogens. The white blood cells or leukocytes

compose the buffy coat or middle layer of centrifuged whole blood and are the cells most directly involved in immune system action. For this reason, standard blood tests examine the white blood cell count and use this measurement as an indication of immune health, infection, or stress. The typical complete blood count (CBC) is presented in Table 15-2. Standard tests of health typically include some portion of the CBC.

Table 15-2. Blood Cells

Cell Type	Count (K/uL)	% of Whole Blood	% of WBC Count	Time in the blood
RBC (erythrocytes)				Months
male	4700-6100 K/µL	41-50%		
Female	4200-5400 K/µL	36-45%		
Platelets (thrombocytes)	147-347 K/µL			days/weeks
WBC (leukocytes)	3.3-8.7 K/µL	~1%		
Granulocytes				
Neutrophils			54-62%	1 day
Eosinophils			1-6%	d
Basophils			<1%	days
Agranulocytes				
Monocytes			2-8%	days
Lymphocytes			25-33%	years

Note: these are typical ranges only and you should be aware that they may vary depending on the lab in which a blood test is done. Normal counts are thousands of cells per cubic millimeter or microliter of blood (K µ L $^{-1}$).

Platelets Mediate Clotting

The primary function of the platelets is to prevent blood loss from the vasculature through the coordinated actions of coagulation and clotting (i.e. the grouping together of platelets into thick globs that seal blood vessel breaches). This role can be both external (think about the scabs you see on a young soccer player's knees) or internal (you might have heard about the danger of blood clots that are only detectable with more invasive devices). As noted above, the platelets or thrombocytes (Greek: *thrombos* meaning clot and *cyte* meaning cell) are actually cell fragments that originate from megakaryocytes formed in the bone marrow. The importance of the thrombocytes to normal physiological function, especially during athletic activity, cannot be overstated. For example, in a survey of 66 NCAA Division I team physicians, 64% noted that they would not allow an athlete with severe haemophilia, a genetic disease that prevents the clotting process, to participate in non-contact sports. An overwhelming majority (all of the physicians who responded to that question, ~83%) would not allow haemophiliacs to participate in contact sports (Fiala et al. 2003). While the dangers of a disease such as haemophilia are not directly immune related, not being able to seal any breaches to the vascular system could lead to life-threatening losses of blood.

Normal Flora

It is likely that you have heard the claim that the majority of the cells in your body are not human. If not, consider this: the human body is composed of approximately 10^{13} cells. However, in nearly every region of our bodies that are exposed to the external environment including the skin, oral and nasal cavities, gastrointestinal and urogenital tracts, vagina, and upper respiratory tract, we are normally colonized by a variety of micro-organisms that benefit our health. In fact, there are approximately 10^{12} bacteria that live on the skin and a whopping 10^{14} bacteria (over 400 separate species) that colonize the large intestine (Berg 1996). These bacteria provide several beneficial functions such as aiding in the motility of foodstuffs through the intestines, maintaining the integrity of mucosal tracts, and promoting the acidity of the vaginal tract through metabolism. With respect to the immune system, normal flora typically out-compete pathogenic bacteria for specific niches in the body. To this effect, they produce and release antimicrobial enzymes and substances into their local environment which can disrupt and destroy foreign bacteria. In healthy individuals, the normal gut flora periodically translocate across the intestinal barrier but are quickly neutralized by the host immune system. This may serve to prime the host immune system for quicker action (Berg 1996) and is important to normal immune system maturation (Marshall 1998).

When the immune system is weakened or compromised, or when the normal flora enter the body in excessive amounts through breaks in the epithelial barrier, an immune response may be invoked. Further, when the normal gut flora are eliminated, such as due to antibiotic drug treatments, unprotected niches may be opened up to more harmful pathogenic microorganisms. Interestingly, it has been hypothesized that during strenuous exercise when blood flow is redirected away from non-essential organs such as the intestines, the gut may experience transient periods of ischaemia (i.e. inadequate blood flow, and hence inadequate oxygen, nutrient, and waste removal/supply to an area). Because of this ischaemia, the gut mucosal and epithelial barriers, and the gut-associated lymph tissue, may be compromised allowing bacteria and their toxins into the body. Consequently, this may be part of the gastrointestinal discomfort and whole body inflammation (a standard immune response to infection) experienced during exercise (Marshall 1998; Pedersen et al. 1998). Evidence to support this hypothesis will be presented later in the chapter.

Immune Signaling Molecules

While foreign pathogens typically present their own danger signals, there are 3 types of chemical messengers that have a multitude of functions around the body including vital signaling and propagation of both a healthy and dysfunctional immune system. These chemical messengers fall within the ever-growing families of cytokines, eicosanoids, and chemokines.

The Cytokines

The cytokines (Greek: cyto for cell and kinos meaning movement) are important for intercellular communication and trafficking. While cytokines have predominantly been associated with inflammation and the immune system, they have recently been implicated in other physiological processes including exercise (described later in this chapter). The cytokines are predominantly glycoprotein chemical messengers, originally termed monokines and lymphokines because of their association with monocytes and lymphocytes, respectively. When it was determined that other cell types could synthesize and release these molecules, they were given the more inclusive name, cytokines. Now it is clear that nearly all cell types can secrete cytokines, but their roles in inflammation and immune cell signaling remain predominant. The individual molecules making up the cytokines do not have a

distinct nomenclature and consequently many were named according to their observed function (e.g. tissue necrosis factor alpha, TNFα), their cell targets, and/or their origins (e.g. interleukin-1, IL-1). This nomenclature may be confusing given the multitude of roles observed today for any given cytokine, many of which are portions of complex signaling networks that may be redundant, synergistic, or even counteracting. While the cytokines can be grouped according to structural similarity based on amino acid sequence homology (Sprang and Fernando Bazan 1993), there are 7 functional families (Liles and van Voorhis 1995) of most major cytokines, including: the haematopoietic growth factors – which stimulate the proliferation and differentiation of blood cells.

- interferons – primarily anti-viral ("interfering" with the ability of viruses to replicate themselves).
- lymphokines – primarily produced by T-lymphocytes, these cytokines activate and signal other immune cells.
- monokines – cytokines produced by monocytes and macrophages.
- chemokines – involved in the chemical attraction and activation of immune cells (chemotaxis) (described below).
- other cytokines – in which roles cannot be distinctly defined.

Though not exhaustive, Table 15-3 lists many of the cytokines important to immune function and gives their primary roles in inflammation and immunity. The cytokines are primarily involved in local (autocrine and paracrine) intercellular communication and invoke responses by binding to specific membrane spanning receptors on target cells. During immune system activation and inflammation, cytokines levels can increase dramatically around the site of infection but also in the blood. It is important to note that while the plasma concentration of most cytokines is very low or undetectable, the observation of cytokines in the blood under some non-infection related conditions implicates them in more systemic or whole body responses. Naturally, from a diagnostic standpoint, cytokine profile blood tests can be used to characterize the state of the body with respect to stress or inflammation.

Table 15-3 Cytokines Important to Immune Function

	Pro-inflammatory			Anti-inflammatory	Involved in Acute Phase Response	Modified by Exercise
	Cell-Mediated Immunity	**Humoral Immunity**	**Allergic Immunity**			
Interleukin (IL)						
IL-1	•	•			•	
IL-2	•	•				
IL-3			•			
IL-4	•	•	•	•		
IL-5		•	•	•		
IL-6	•	•		•	•	•
IL-7	•					

IL-8					•	•
IL-9			•			
IL-10	•	•		•		•
IL-11	•					
IL-12	•	•				
IL-13		•	•	•		
IL-15	•	•				
IL-16	•					
IL-17	•					
IL-18	•					
IL-19				•		
IL-20				•		
IL-21	•	•				
IL-22				•		
IL-23	•					
IL-24				•		
IL-25		•	•			

IL-26				•		
IL-1ra				•		•
Tissue Necrosis Factor (TNF)						
TNFα	•				•	•
TNFβ	•					
Interferons (IFN)						
IFNα	•					
IFNβ	•					
IFNγ	•		•		•	
Transforming Growth Factor (TGFβ)		•			•	
Stem Cell Factor (SCF)			•			
Colony Stimulating Factor (CSF)			•		•	

While all of the cytokines play important roles in immune function, the chemokines are sometimes considered their own class of molecules. Chemokines (Greek meaning “chemical” and “movement”) are usually small cytokines that are important because they cause immune cell migration towards the area of highest chemokine concentration, a process called chemotaxis. Chemotaxis is the primary chemical event that coordinates the congregation of immune cells at the site of infection. Some of the interleukins are chemokines, but many chemokines possess unique names that can be grouped by their structural identities.

Physical exercise is a multifaceted stress, and not surprisingly, is a potent modifier of the cytokines that often mimics the response to other stresses. In the plasma of exercising individuals, the cytokines and chemokines are elevated in an exercise dose-dependent manner. These changes can have both positive and negative effects as we will see later in this chapter.

Some Cytokines Activate the Acute Phase Response

The local response to a tissue injury or infection by pathogen involves the release of cytokines in a coordinated sequence of events. However, during this acute phase of infection or inflammation, a host of other proteins (called acute phase proteins) can be observed to increase (>25%) in the plasma, thereby regulating a more global immune response. Some cytokines, produced by early responding immune cells such as macrophages, are highly associated with activation of the acute phase response. They are noted in Table 15-3. These cytokines can induce the liver, the primary site of proteins, to increase hepatocyte metabolism and initiate secretion of proteins. Interestingly, a cytokine profile response similar to that seen with infection and other trauma such as burns or surgery is observed after intense exercise or after eccentric contractions. This is part of the evidence of the power exercise has on modification of the immune system. One notable protein is called C-reactive protein (CRP). CRP may be both pro-inflammatory and anti-inflammatory but appears to be a key marker of pathophysiologic inflammation, hence its use as a diagnostic tool of disease severity, including heart disease. Other proteins play roles in activation of the complement system, (see below) coating of bacterial walls to target them for immune reaction in a process called opsonisation, and wound healing/tissue repair. Note that the proteins constitute one part of the acute phase response, which also includes more observable physiological changes such as fever and fatigue.

The Eicosanoids

The eicosanoids are a large group of fatty acid molecules that, like the cytokines play important roles in local cell-to-cell communication and, in particular, inflammation. In mammals, eicosanoids are primarily synthesized from the naturally occurring arachidonic acid, which itself is a product of enzymatic modification of released cell membrane phospholipids. The enzyme responsible for the production of arachidonic acid is called phospholipase A2. Phospholipase A2 appears to be the rate limiting step in eicosanoid synthesis and physiological expression given that eicosanoids can diffuse through the cell membrane. Arachidonic acid is the precursor to all 3 families of the functionally active eicosanoids: the prostaglandins, thromboxanes and leuokotrienes. These names stem from their respective origins of first discovery. The prostaglandins were first observed in the seminal fluid (originating from the prostate gland), the thromboxanes were platelet derived factors that had key roles in thrombosis (clot formation) and the leukotrienes were initially characterized as leukocyte derived signaling molecules. The prostaglandins and thromboxanes are collectively termed prostanoids and synthesized subsequent to the enzymatic modification of free arachidonic acid by the enzyme cyclooxygenase. If you have ever taken the drug Aspirin™ to reduce the pain associated with an injury, you have targeted this eicosanoid synthesis pathway. Cyclooxygenase is the primary target of Aspirin™ and related non-steroidal anti-inflammatory drugs (NSAIDs) which cause inhibition of the enzyme. Ibuprofen, another common NSAID, reversibly competes for the arachidonic acid binding site in cyclooxygenase, thereby accomplishing the same goal: inhibition of pro-inflammatory prostanoid synthesis. In order to generate leukotrienes, free arachidonic acid is modified by the enzyme lipoxygenase. The nomenclature for the eicosanoids is more unified than the cytokines and this can be observed in Table 15-4. The eicosanoids are extremely short-lived with half-lives in the seconds to minutes and have predominantly autocrine and paracrine roles. Consequently, they are expressed in extremely low plasma concentrations (10-9 M) in healthy individuals. Much like the cytokines, however, physical exercise can increase the expression of many eicosanoids that have important physiological functions such as vasoconstriction/dilation (sciencedirect.com). The eicosanoids primarily act on membrane spanning g-protein coupled receptors and have target cells from nearly every organ in the human body. Like the cytokines, the eicosanoids perform a multitude of diverse functions, making classification by this route difficult. For example, some eicosanoids may be associated with bronchodilation whereas others are highly correlated with bronchoconstriction. As a result of exercise, a change in the amount of broncho-constricting eicosanoids released from immune cells may be a factor in exercise-induced bronchoconstriction and asthma (Hallstrand et al. 2005). Nonetheless, for the purposes of this chapter, the important functions of the eicosanoids lie in their ability to influence local immune cell congregation, inflammation.

Table 15-4 Eicosanoid Nomenclature and Biological Function

Eicosanoid						Major Biological Activities	

Family	Name	Major Site(s) of Synthesis	Vasodilation	Vasoconstriction	Vascular Permeability	Bronchoconstriction	Platelet Aggregation
Prostaglandins and Prostacyclins(PG)							
	PGD2	mast cells	↑				↓
	PGE2	kidney, spleen, heart	↑				↑
	PGF2α	kidney, spleen, heart		↑		↑	
	PGH2	many sites		↑			↑
	PGI2	heart, vascular endothelial cells	↑				↑
Thromboxanes(TX)							
	TXA2	platelets		↑		↑	↑
	TXB2	platelets		↑			
Leukotrienes (LT)							

	LTB4	immune cells			↑		
	LTC4	immune cells	↑		↑	↑	
	LTD4	immune cells	↑		↑	↑	
	LTE4	mast cells and basophils	↑			↑	

Complement Proteins

Complement refers to a large number of plasma proteins and cell surface proteins that function as enzymes, binding proteins and immune cell activating molecules. Complement proteins recognize some pathogens and infected cells and bind to them. This binding typically results in bacterial destruction by one of two methods:

- Several complement proteins congregate on the infected cell forming a membrane attack complex that forms channels or pores in the infected cell's membrane leading to cell death.
- Complement coated cells attract immune cells to target the infected cell for destruction.

Complement proteins typically circulate in the blood plasma in inactive form but are activated by pathogenic material. The cascade of component activation and congregation occurs in an ordered fashion to accomplish the actions listed above. The proteins are given the names C1, C2, C3, etc. which represents the order of activation.

Cells of the Immune System

All Immune Cells are Leukocytes

The leukocytes (leukos, Greek for white), or white blood cells, is the family name of nearly all of the cells of the immune system. They are so named because of their distinctly colourless or white appearance relative to the erythrocytes (red blood cells) found in the blood. Leukocytes are formed by the process of haematopoiesis in the bone marrow from a common blood cell precursor. Figure 15-2 shows the various lineages of the common white blood cell lines. It is also important to note that while they are found predominantly in the blood, this is primarily a vehicle of a transport for the leukocytes. In fact, many of the functions of the leukocytes occur outside of the blood vessels and are due to a special ability of the white blood cells to exit blood vessels through small pores in the capillary endothelium. The leukocytes are not, however, a homogeneous mix of cells and consequently their nomenclature requires further characterization. Leukocytes are generally classed by the nuclear and granular expression in each cell. Leukocytes may either be mononuclear containing a single round nucleus or polymorphonuclear containing a varied shape nucleus that may appear divided. Granules are small secretory vesicles located in the cell cytoplasm that contain chemical molecules (e.g. lysing enzymes and cytokines) that are released upon stimulation in a process referred to as degranulation. Some leukocytes have many granules and are consequently considered granulocytes, while other leukocytes contain few to no granules and are therefore considered agranulocytes. While each cell type can usually be further classified as belonging to either the innate or acquired immune systems, their coordinated actions are a requirement of proper immune health.

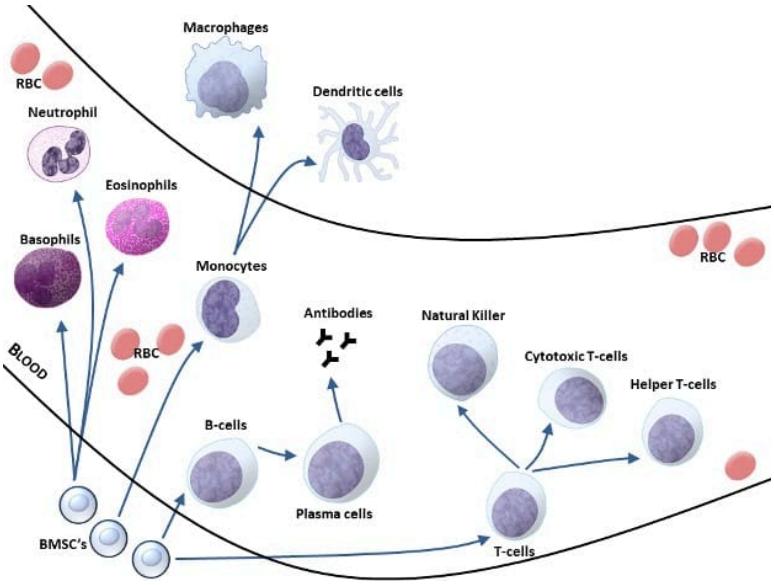


Figure 15-2 Blood Cells and their Roles in Immune Response. Various lineages of the common white blood cell lines. Bone marrow stem cells are the progenitors to all white blood cells (leukocytes). The polymorphonuclear granulocytes consist of the neutrophils, eosinophils, basophils, and mast cells (not pictured). These cells contain granuoles that contain bacteria and virus fighting substances, immune stimulating proteins, and inflammatory molecules. They are found in the blood, but can also migrate to various tissues of the body. Monocytes are found in the circulation, but differentiate into macrophages and dendritic cells in response to local tissue factors. Macrophages and dendritic cells can also enter the bloodstream and travel to remote locations. The granulocytes and macrophages are important in innate immunity. The lymphocytes consist of B and T-cell populations. In response to activation by cytokines, eicosanoids, and antigen presentation, B-cells can differentiate into plasma cells and memory cells (not pictured). Plasma cells are the main effectors of antibody secretion which provide humoral immunity. T-cell differentiation elicits helper T-cell, cytotoxic T-cell, natural killer cell, and memory T cell (not pictured) populations. B and T-cell differentiation can occur in the blood, but much happens in the lymph tissues. In the latter case, differentiated lymphocytes can then enter the blood stream and travel to remote locations. The lymphocytes, except natural killer cells, are important to acquired or adaptive immunity. Natural killer cells are typically considered effectors of innate immunity. RBC = red blood cell.

The Granulocytes

The granulocytes are so named because of the appearance of granules (small particles that contain various enzymes, proteins, and signaling molecules) that pock mark the cytoplasm of this type of leukocyte. It is the pattern of histological staining of the granules with acidic and basic dyes that gives each subsequent class of granulocyte its name. The neutrophils, the most abundant of the leukocytes, exhibit neutral pink staining of the cytoplasm while the eosinophils (acid-liking) exhibit brick red staining and the basophils (basic-liking) exhibit a dark blue colour after hematoxylin (blue) and eosin (red) staining. All of the granulocytes can undergo degranulation in which the contents of the granules are released to the surrounding extracellular area.

Neutrophils

In the innate defense against pathogens, tissue embedded neutrophils [also called polymorphonuclear neutrophils (PMN) or polys for short] are typically the first responders to react after detection of certain chemoattractants. These chemoattractants can include the membrane proteins of certain bacteria, bacterial toxins, or host cellular proteins such as cytokines, chemokines, and eicosanoids or inorganic ions such as calcium. Nonetheless, these signals typically denote foreign invasion or the disruption of host cellular integrity. Movement to the areas of high chemical attractant by neutrophils is known as chemotaxis (chemo-, chemical and taxis, Greek for arrangement or order) and allows many neutrophils to amass at a site of infection. If the early arriving neutrophils are insufficient to defend against the attack, circulating neutrophils can exit the blood vessels through tiny gaps by a process termed diapedesis (pedesis is Greek for movement). After congregating at the site of infection by chemotaxis, the neutrophils defend against foreign bodies by adhering to, engulfing, and ingesting the pathogen (e.g. shown in Figure 15-3). This process is termed phagocytosis (phagein is Greek for eat) and is common to the other granulocytes as well as monocytes and dendritic cells, consequently providing another grouping for cells with this specialized ability as phagocytes. Phagocytosis results in the containment of foreign matter inside a packaged vacuole which can fuse with lysosomes containing degrading enzymes inside the phagocyte, leading to pathogen digestion. Activated neutrophils undergoing degranulation can release proteases that aid in the digestion of foreign particles or other chemoattractants such as chemokines, eicosanoids, and cytokines that signal other immune cells to the area (Wright et al. 2010). The critical part of this entire process is that the neutrophils recognize

the pathogen based on a standard set of chemoattractants. If the pathogen does not possess a known attractant, it can evade destruction – often providing enough time for reproduction and spread of the infection.

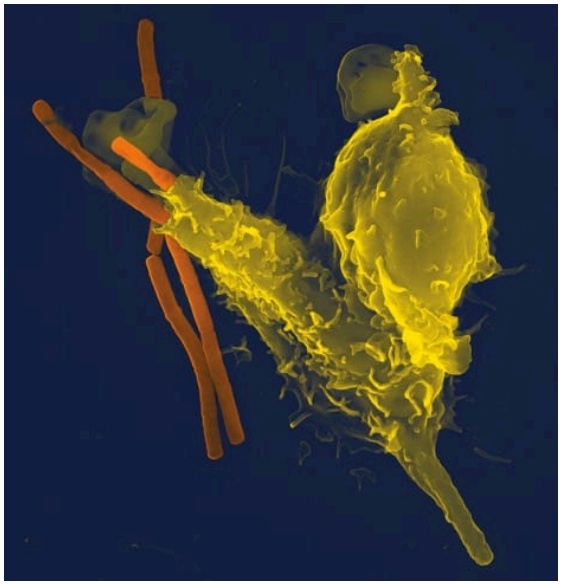


Figure 15-3 “Neutrophil engulfing Bacillus anthracis”. PLoS Pathogens 1(3): Cover page. DOI:10.1371. Retrieved on 2009-01-04. Volker Brinkmann – (November 2005).

Eosinophils

Eosinophils possess the ability to detect and destroy foreign invaders through phagocytosis; however, they circulate in much smaller concentrations than the neutrophils but last several days longer. In addition to phagocytosis, activated eosinophils can release or secrete a host of chemoattractants as well as granule proteins that can degrade surrounding biological material (Kita 1996). Another important difference between the eosinophils and neutrophils is that the eosinophils are not typically detected in the esophagus, lungs, skin, and some internal organs whereas the neutrophils can be found in the blood and tissues all over the body. In fact, when eosinophils are detected in these locations, it is usually a sign of disease. For example, in individuals who experience exercise-induced asthma, a higher concentration of eosinophils are detected in the lungs. This will be discussed later in this chapter. Nonetheless, because eosinophils and the basophils described below typically mediate allergic responses, they can be grouped into an arm of the immune system known as allergic immunity. See Figure 15-4 for a micrograph image of eosinophils.

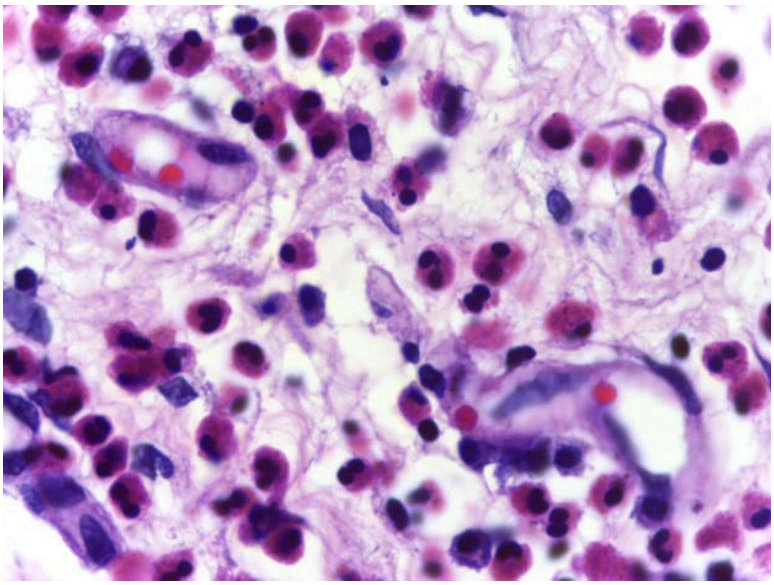


Figure 15-4 Micrograph of eosinophils. By Department of Pathology, Calicut Medical College – Calicut Medical College, CC BY-SA 4.0, https://commons.wikimedia.org/w/inde...curid=36651693

Basophils and Mast Cells

In contrast to the neutrophils and eosinophils, basophils travel in the circulation but are relatively rare during normal circumstances. Basophils are very similar to mast cells (they are granulocytes that originate from the same precursor cell) but the latter typically congregate in the connective tissue of the skin, lungs, and gastrointestinal tract where they can stop and neutralize pathogens that breach these areas. These granulocytes bridge actions in both the innate and acquired immune systems, either by interaction with antibodies produced by T-lymphocytes of the acquired immune system (see below) or through direct detection of some bacteria and pathogens. They can release histamine, heparin, proteases, cytokines, and eicosanoids that are important mediators of inflammation and the immune response, but also can change blood vessel tone and smooth muscle contraction in the gut and vasculature (Galli 2000). Interestingly, Basophils and mast cells are often considered the “bad guys” in the immune response because of their roles in allergic disorders including anaphylaxis and asthma in which the immune system is considered hypersensitive. In this regard, histamine is one of the key mediators of allergic reactions and if you or anyone you know typically suffers from allergies, you will be familiar with the role of anti-histamine drugs to combat a hypersensitive immune system.

Monocytes (Macrophages and Dendritic Cells)

Monocytes, like all leukocytes, originate in the bone marrow, but are more similar to the lymphocytes as they are mononucleated. Monocytes can be released into the circulation where they can spend hours to days before differentiating into macrophages or dendritic cells (Figure 15-5). In most body tissues this replenishes basal macrophage numbers but can also increase the number of WBC in response to pro-inflammatory immune signals. Circulating monocytes can be classified based on the expression of certain antigenic markers standardly named cluster of differentiation (CD) markers. Most monocytes specifically express large amounts of CD14 (therefore they are considered CD14+) but it is the relative expression of antigenic proteins, chemokine receptors, and the local extracellular milieu that determine whether monocytes will differentiate into macrophages or dendritic cells. Further, both macrophages and dendritic cells are heterogeneous groups of cells whose phenotype and function is dependent on their local environment (Gordon and Taylor 2005).

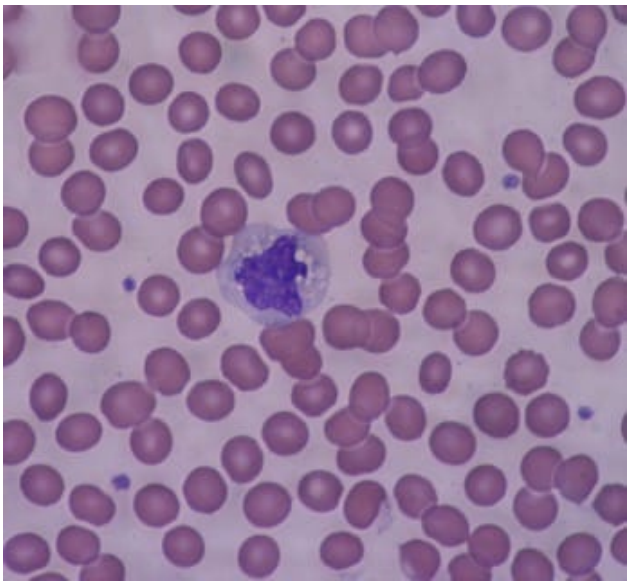


Figure 15-5 A monocyte surrounded by red blood cells. By Bobjgalindo [GFDL (http://www.gnu.org/copyleft/fdl.html) or CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0)], from Wikimedia Common

Macrophages

Once differentiated, macrophages contribute to host innate immune responses by engulfing pathogens (phagocytosis) but also aid in healthy tissue maintenance and repair by clearing away dead cells and cellular material. For example, novel and/or intense exercise, primarily resistance or eccentric type training, is associated with skeletal muscle damage on both micro and macro scales (Smith 1991), leading to the consequent symptoms of delayed onset muscle soreness (DOMS). Clearing of these damaged myocytes (muscle cells) and other cellular debris is primarily accomplished by local macrophages and is an important component of muscle recovery and repair (Butterfield et al. 2006). This will be discussed further later in this chapter. Mature macrophages can be fixed to certain locations or mobile throughout specific tissues, actively patrolling for dead cells or foreign invaders. While smaller in number, the phagocytic activity of macrophages is much greater than the circulating neutrophils. Further, because these immune cells function without the aid of antibodies, this type of immunity is known as cell-mediated immunity. The granulocytes, macrophages, natural killer cells, and cytotoxic T cells (described below) all play a part in cell-mediated immunity.

Dendritic Cells

Dendritic cells are so named because of their large cellular extensions much like the dendrites of nerve cells (Figure 15-6). When monocytes differentiate into dendritic cells, they do not typically remain at the site of tissue injury, inflammation, or infection. Dendritic cells can ingest (phagocytose) foreign and host cellular material but differ from macrophages in that they can re-enter the circulation and migrate to lymph nodes where they act as antigen presenting cells (APCs) for T-lymphocytes of the acquired immune system. Antigen presenting cells digest foreign material and then express parts of the digested cells on their surface, typically proteins. These proteins (“antigens”) can then be “presented” in a way that cells of the acquire d immune system can recognize them and become activated. Macrophages and other cells can act as APCs, but do not circulate back to the lymph organs for cell priming. As an unfortunate yet ingenious method of infection, this is the method by which the HIV virus infects and consequently is able to disable the cells of the immune system.

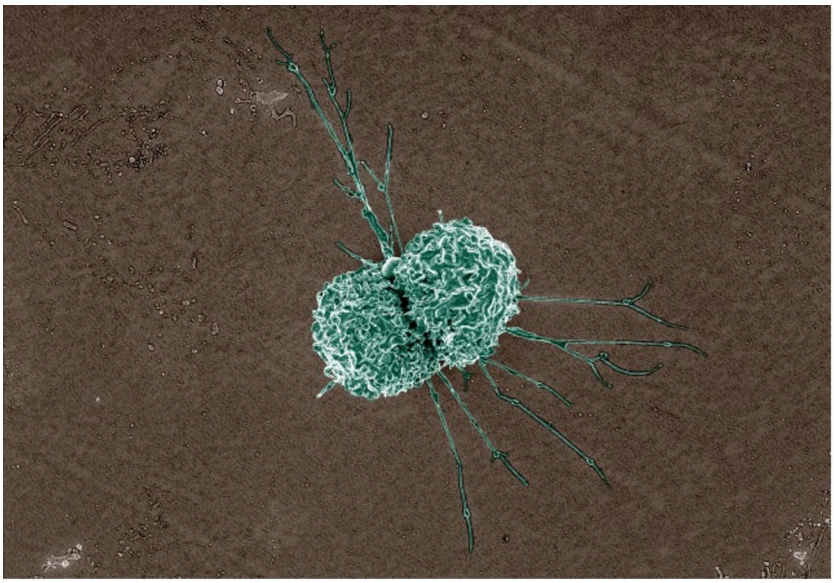


Figure 15-6 Dendritic macrophage. By NIAID (Macrophage) [CC BY 2.0 (https://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons

Lymphocytes

The lymphocytes are mononuclear cells that typically lack the granular expression of the immune cells previously mentioned. They include the B-lymphocytes and T-lymphocytes which play large roles in the ability of the immune system to “remember” certain pathogens and respond in greater amount after a second exposure.

B-Lymphocytes

The B-lymphocytes (or B cells) were so named because they were observed to originate from the Bursa midura in birds and, coincidentally, the bone marrow in mammals. Recall that all leukocytes originate in the bone marrow so this is not really a distinguishing feature. B-cells are specialized lymphocytes that possess antibodies on their cell surface and can produce and secrete antibodies into the blood. When B-cells are activated due to antigen binding, they begin to divide and separate into 2 cell types:

- plasma cells that produce antibodies.
- B memory cells that are important to the immune system‘s ability to “remember” specific antigens.

Antibodies, also called immunoglobins (Ig), are Y-shaped proteins (Figure 15.7) that possess antigen specific binding sites and can be used to target and flag pathogenic bacteria and other material. Because antibodies are released into the blood and around tissues, the B cells give rise to what is known as antibody mediated or humoral (“in the blood or body fluid”) immunity. The ability of B cells to generate antibodies against specific antigens and store this information is a key component of the acquired immune system. However, once produced, some antibodies (IgM, IgA) are involved in immediate responses to pathogen. For example IgA and IgM antibodies form part of the mucosal and salivary defenses in the linings of the gut, urogenital tract, respiratory tract, nose, and mouth where they assist in pathogen antigen recognition, aggregation, and destruction (Bouvet and Fischetti 1999; Gleeson and Pyne 2000)

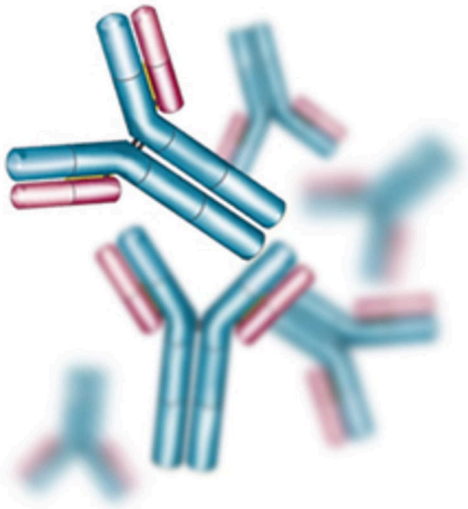


Figure 15-7 Antibodies.

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Highlight Feature: Tinea Pedis (Athlete's Foot)

Tinea Pedis is a non-life threatening fungal infection caused by dermatophytes (fungi that require keratin for growth) infection (Crawford 2009). This infection is more common in individuals who partake in sports, hence its more common name, athlete's foot. It does not appear that its prevalence is higher in any particular type of sport, but rather it has been reported that athletes of all types show almost double the prevalence as the general population (Field and Adams 2008). The feet provide a favourable location for dermatophytes to thrive. This is because there are few host anti-fungal defenses in the feet. Also, in particular to the athlete, there is a greater chance that the feet:

- may be wet or damp due to sweating;
- are occluded by athletic footwear increasing heat and anaerobe favouring conditions;
- may be damaged due to athletic activity; and
- may come into contact with the fungi in communal showers and change rooms.

Athlete's foot is highly infectious and scales from infected skin can remain infectious for several months. It is characterised by itching, flaking, and fissuring of the skin. It may manifest in three ways: the skin between the toes may appear macerated (white) and soggy; the soles of the feet may become dry and scaly; and the skin all over the foot may become red, and vesicular eruptions may appear (Crawford 2009).

The dermatophytes responsible for athlete's foot are primarily of the type, *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and with few exceptions, this appears to be similar in athletes although symptoms may be more robust (Auger et al. 1993). The general population may often come in contact with the fungi that cause athlete's foot, however, it may not be able to manifest itself unless the immune system is weakened. In the case of the athlete, a depressed immune system as a result of high intensity high volume training can further increase the risk of fungal infection (Brenner et al. 1994).

While athlete's foot is non-life threatening, it is important to treat the infection and prevent the possibility of it becoming systemic through more invasive cuts or abrasions. As presented in this chapter, once an infection becomes systemic (in the blood), other host defenses are called into play, presenting a more significant challenge for the individual. Athlete's foot, like many superficial infections, can be successfully treated with topical creams or powders containing anti-fungal and anti-bacterial agents under most conditions, with the addition of corticosteroids when more severe.

Prevention includes both personal (changing socks, allowing athletic footwear to dry out, the use of preventative powders) and environmental (proper sanitation of communal areas) methods.

Table 15-5 Antibody Classes and Function

Immunoglobin (Ig)	Typically Observed	% of Total Body Ig	Function
IgG	blood + extracellular fluid	75-80%	secondary immune response and acquired immunity; activates complement system
IgA	nose, mouth, respiratory, urogenital, reproductive, and digestive tracts in external secretions (breast milk, gastrointestinal mucus, saliva, tears, etc.)	10-15%	disable pathogen before internal entry; consequently primary immune defense and innate immunity; activates complement system
IgM	B cell membrane + extracellular fluid (lymph, blood)	5-10%	activate the complement system and therefore, are involved in primary immune responses
IgE	extracellular fluid (lungs, skin, and mucous membranes)	~1%	stimulate mast cells during allergic responses
IgD	primarily B-cell membrane	<1%	activate B-cells, basophils, and mast cells

T-Lymphocytes

The T-lymphocytes (T cells) are so named because a large proportion of these cells are found in the thymus. Like all lymphocytes, T cells originate in the bone marrow but migrate to the thymus where they develop further and differentiate into subsets. These include Helper T (T_H) cells, cytotoxic T (T_C) cells, and the granular natural killer cells. In contrast to B cells and antibodies, T cells recognize infected cells and cannot bind free pathogen. In this regard they, along with the macrophages, are key components of cell-mediated immunity. Recognition of infected cells is accomplished by receptors on the T cells that interact with antigen in combination with major histocompatibility complexes (MHC). The MHCs are a family of cell surface proteins that hold portions of host cellular proteins or digested pathogen proteins in a conformation that can be recognized by T cells. While every nucleated cell in the body expresses related MHC proteins, non-immune cells typically only express MHC Class I (MHC-I) molecules on their cell surface. It is the totality of MHC-I- antigen expression that dictates whether host cells will be considered normal, abnormal, or infected. In contrast, “professional” APCs, such as the dendritic cells described above, typically express both MHC-I and MHC Class II (MHC-II) membrane proteins. The MHC-II proteins “present” antigen to T cells to induce immune action. You could think of the MHC and antigen presentation like a bar code on each cell. T cells can scan the barcode to determine if that cell “belongs” in the body. When infected or if the cell becomes abnormal, the T cells do not recognize the barcode and subsequently target that cell for destruction. This is a key method by which the immune system regulates dysfunctional cells in addition to infected cells. It should also be apparent to you that a dysfunctional immune system, such as one that cannot recognize normal from abnormal cells or one that is hyperactive and does not discriminate in the attack of cells, could become problematic.

Helper T Cells (CD4+)

Helper T (TH) cells are a major driving force of the immune system but they do not destroy cells. Instead, TH activate B cells and

cytotoxic T cells after coming in contact with infected cells. In particular, TH cells are activated by APCs with MHC-II membrane proteins that "present" the TH cells with antigens specific to a processed pathogen. Simultaneously, APCs and other immune cells release cytokines, eicosanoids, and other signaling molecules that help to activate the TH cells, induce further TH cell differentiation, and stimulate the immune system. Activation can lead naïve TH cells (i.e. undifferentiated) to become one of 4 further subtypes, including:

- T_H1 cells – that activate macrophages and natural killer cells (members of the innate immune system and cell-mediated immunity) and promote memory cell antibody (IgG) responses.
- T_H2 cells – that predominantly increase B cell activity for antibody or humoral immunity, and eosinophil activity involved in allergic inflammation. They also suppress macrophages and cell-mediated immunity.
- T_H17 cells – that recruit neutrophils and macrophages to infected tissues through the secretion of the cytokine Il-17.
- Regulatory T (T_{reg}) cells – that suppress allergen induced T-cell activation as well as suppress mast cells, basophils, and eosinophils. T_{regs} and the cytokines they secrete are typically considered anti-inflammatory.

Each subset typically secretes a distinct set of cytokines and other immune signaling molecules that control immune action. For example, the cytokines released by the T_H1 cells are termed T_H1 cytokines while T_H2 cells secrete T_H2 cytokines. Consequently, T_H1, T_H2, or T_H17 cytokines will be referred to later in the chapter but you should be aware that they ultimately result in the process listed above.

Cytotoxic T Cells (CD8+)

In contrast to T_H cells, cytotoxic T (T_C) cells are the "soldiers" of this lymphocyte population. TC cells can destroy infected cells when antigen is presented by MHC-I surface proteins. They accomplish this by releasing enzymes to disrupt and breach the cell membrane and induce programmed cell death (apoptosis). Apoptosis is a controlled method of destroying a cell, similar to the coordinated implosion of a building. In the case of a condemned building analogy, specialized crews go into the building to salvage materials that still hold value and then explosives are placed at designated sites to limit the amount of damage to neighbouring structures when the structure is destroyed and falls upon itself. In this regard, apoptosis is a method of pruning or eliminating specific abnormal cells.

Natural Killer Cells

Natural killer (NK cells) cells make up about 5 to 16 percent of the total lymphocyte population and are an important component of the immediate immune response to cancerous or pathogen-infected host cells. They are named "natural killer" cells because of their ability to destroy infected and malignant cells upon their first exposure to them (within hours) without presentation by typical pathogen related surface signals. NK cells possess similar actions to the cytotoxic T-cells; however, unlike the other lymphocytes, they express cytosolic granules in similar number to the granulocytes described earlier. Formed in the bone marrow and released into the circulation, NK cells can be recruited to different areas of the body by chemokine signals. Further, they can also migrate between body areas and perform their functions in several places. Like T cells, NK cells will interact with MHC-antigen expression on host cells, but they will also recognize when MHC-I- antigen molecules are altered or missing in stressed cells (Shi et al. 2011). This is an important component of the recognition of self and presents a method by which NK cells can remove cancerous cells.

The roles of NK and TC cells in addition to macrophages in monitoring cell activity is termed immunosurveillance because they patrol the body for cells that are abnormal, destroying and inhibiting the multiplication of cells that are deemed so. Consequently, an increase in the activity or amount of these cell types could potentially increase the removal of abnormal, often cancerous cells. Interestingly, with some forms of moderate intensity exercise basal levels of NK cell function, but likely not number, are elevated (Nieman et al. 1990; MacNeil and Hoffman-Goetz 1993). It has recently been suggested that this may be partly responsible for the reduction in some forms of cancer with regular exercise (Rogers et al. 2008).

The Immune System Employs Two Types of Defense

In order to successfully protect the body against pathogens that can take on almost endless identities, the immune system has evolved two separate but functionally linked branches. Nonspecific defenses are inherent to our biology and therefore passed on through genetic information. Specific defenses provide the ability to ward off and eliminate specific invading pathogens and are acquired or for which the host defenses adapt to the specific pathogen. Rather fittingly, these defense systems are referred to as innate and acquired or adaptive immunity, respectively, and vary in the speed and specificity of responses. Both types of immunity rely on their ability to:

- detect and identify foreign material
- signal and coordinate the actions of other immune cells
- contain, suppress, and/or destroy the pathogen

When invading pathogens make it past the skin, chemicals they secrete (known as toxins) can enter the blood or lymphatic vessels where they may then infect other areas of the body. Not surprisingly, the more global the infection, the more of a danger it is to the body. Consequently, the immune system attempts to limit this spread.

Innate Immunity: Defenses You Were Born With

Once past the physical and chemical barriers of the body, the second line of host defense against foreign pathogens involves the action of phagocytes. Remember that these are the devouring cells that Dr. Ilya Mechnikov observed gathering at a wound site following skin puncture and primarily include the neutrophils and macrophages upon first exposure. At the most basic level, these cells are responsible for recognizing, engulfing, and subsequently destroying foreign microbes. This is accomplished by a group of receptors on the cell membranes of phagocytes that recognize a large number of pathogen-associated molecular patterns (PAMPs) which may include biological material such as proteins, lipids, carbohydrates, and nucleic acids associated with the foreign agent. Of particular note is a type of PAMP called lipopolysaccharide (LPS) that is an endotoxin present on certain bacteria that induces massive immune responses and is used quite frequently in research studies to examine immune health. Not surprisingly, the immune cell receptors that recognize these PAMPs are called pathogen-associated pattern recognition receptors (PRR) that initiate an intra- (“inside”), and subsequently inter- (“between”), cellular signaling cascade leading to the secretion of cytokines, chemokines, and other anti-microbial or inflammatory substances. These events also lead to the congregation of immune cells at the site of infection. A superfamily of PRRs includes the toll-like receptors (TLR), so named because of their similar structure to a protein named Toll in fruit flies that is important to the immune response of those organisms. These receptors are found in all cells of the innate immune system but also infat cells, liver cells, and muscle cells and are typically considered pro-inflammatory. s have only been characterized within the last two decades, but recent evidence suggests tha t exercise training can reduce the expression of TLRs in muscle and some leukocytes, thereby reducing the inflammatory process (see Research Box 15-1).

Research Box 15-1Heat Shock Proteins and Immunity: Potential Link to Exercise-Induced Anti-Tumor Immunity

The Canadian Cancer Society reports that 35% of all cancers can be prevented by being physically active. Further, the Center for Disease Control indicates that physical fitness along with reduced body weight is an important method of preventing several of the most common forms of cancer The mechanisms behind this relationship are unclear, but some of those mechanisms may include immune system modification. In particular, an increase in immunosurveillance and cytotoxic ability of the innate immune system may provide this link.

Recall that some immune cells can recognize abnormal host cells and target them for destruction. This process is known as immunosurveillance and is particularly accomplished by differentiated monocytes and NK cells. You have learned that toll-likereceptors (TLR) are a type of pattern recognition receptor found on the cell membranes of leukocytes involved in innate immunity including neutrophils, monocytes (macrophages and dendritic cells), and NK cells. There are at least 10 isoforms of the TLRs with both independent and redundant functions (Takeda et al. 2003). In particular, TLR-4 is significant because it was the first pattern recognition receptor found to bind with lipopolysaccharide (LPS), a common bacterial toxin. Upon binding LPS or some other ligand, and together with other cell surface proteins such as CD14, TLR -4 signalling induces pro-inflammatory cytokine release from its host cell. Other TLR ligands that have recently gained interest are members of the heat shock protein (HSP) family.

HSPs are molecular chaperones that have several intra- and inter-cellular functions. Primarily these are:

- to prevent intracellularprotein denaturation and aggregation
- to assist in the proper folding of newly synthesized and misfolded proteins
- to aid in the transport of proteins through various intracellular compartments

HSPs are also expressed on cell surface membranes and in the extracellular fluid and plasma where they may be free or bound to other peptides. These types of HSPs are known as extracellular HSPs (eHSPs). Some extracellular HSPs are ligands for TLR-2 an d TLR-4. These include the highly inducible 70 kDa HSP, HSP-70, and 60 kDa HSP, Hsp60. When HSP-70 binds to TLR-2 or TLR-4, they activate the immune cell possessing those receptors. Activation can cause increased activity of that cell and the release of TH1 or pro-inflammatory cytokines that initiate other immune responses (Asea et al. 2002).

NK cells possess TLR-2 and TLR-4 in sufficient quantities to be major targets of HSP-70 and Hsp60. Cell surface HSP-70 binds TLR-4 o n NK cells and enhances NK cell cytolytic activity in the presence of CD14. In this chapter, you learned that NK cells are integral in the removal of cancerous cells in the body. As such, an increase in NK cell cytolytic activity could potentially increase this ability.

Monocytes also interact with eHSP-70 including eHSP-70. This observation links eHSPs to antigen presentation of both foreign and endogenous cell material (think non-self versus self). Recall that circulating monocytes are precursors to macrophages and dendritic cells which possess the ability to phagocytose material and act as antigen presenting cells. Because HSP-70 binds with other proteins, antigen bound HSP-70 can interact with monocyte TLRs, be phagocytosed and then “presented” to lymphocytes of the adaptive immune system (Calderwood et al. 2008). Primarily, this results in activated cytotoxic T-cells that can then destroy the abnormal cells.

Given the role of HSPs in increased NK cells and T-cell cytolytic ability and antigen presentation, it is not surprising that some tumor derived HSPs are now included in anti-cancer vaccines and medications with successful outcomes. Further, it is likely that the use of different HSPs in future treatments will occur (Murshid et al. 2011).Intense exercise causes a significant increase in eHSPs, HSP-70 in particular (Febbraio et al. 2002; Lancaster et al. 2004). This extracellular HSP-70 appears to originate from the contracting skeletal muscle and brain during exhaustive exercise (Febbraio et al. 2002; Lancaster et al. 2004). The role of exercise-induced eHSP-70 is unknown, but given those functions listed above, it may increase immunosurveillance and anti-tumor immunity. Indeed, there is a concomitant increase in eHSP and NK cell associated HSP-70 after strenuous exercise (Horn et al. 2007). As such, exercise-induced eHSP, TLR-2 signalling, and immune function may provide one link between exercise and the reduced risk of cancer.

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Interestingly, PRRs also recognize host-borne danger signals that are found when cells are damaged and release their intracellular contents. This should remind you that the innate immune system is not only to keep invaders out but also to clean up damaged cells and help in the repair of the body’s own tissues. Key components of the innate system include that:

- immunity is passed on from generation to generation and is present in individuals from birth (hence innate).
- the recognition and destruction is non-specific such that anything possessing the right type of PAMP will be targeted.
- this is a relatively fast acting response because all of the necessary components are present at the time of invasion.

Think about your body like a large factory with expensive equipment and materials in the warehouse and confidential documents in the offices. Thieves could steal your resources and competitors could steal your documents to make their products better. You fortify the factory with fences and gates and lock all of the doors at night. These are sufficient to keep out most unwanted visitors, but for enhanced protection you have also installed an alarm system that will alert you and the authorities if any entry point is breached and you have employed a night watchman who patrols the factory and offices. Now your factory is well guarded against all but the most sophisticated and/or overwhelming threats. An important component of this system is that you and your trusted employees are able to get into the factory. For this, you give them all pass keys that open most doors, and photos of your most trusted employees are memorized by the security guards. Think about the series of events that will occur if someone cuts through your outer fences and manages to pry open one of the windows. First of all, if your alarm system is working, a loud siren will sound and indicate to the central watchman where a breach has occurred. Simultaneously, this alarm will contact the local authorities, but it will be some time before they reach the factory. The sound and location of the alarm will cause nearby security guards to rush to the spot to investigate whether there has been an actual break-in. If they cannot handle the threat (say there are several burglars at the scene), they will signal to other security guards for back-up. At that time, there will be a congregation of burglars and security guards at the point of entry while the alarm continues to sound. This is a close analogy of how your innate immune system functions. Once physical barriers such as the skin are breached, cellular contents, bacterial toxins, cytokines, and other molecules can all act as alarm signals. The complement system is activated destroying some bacteria but also signaling and activating immune cells to the site (acting as the security guards on-site who call for more back-up). Patrolling macrophages and other phagocytes congregate at the area to clear damaged or infected cells while at the same time releasing cytokines themselves that signal to other immune cells that help is needed. The innate immune system in action can be observed as the redness and swelling (hallmarks of inflammation) that occur when someone has an allergic reaction to a substance. These symptoms are a

direct result of the accumulation of white blood cells (forming pus) at the area, increased blood flow and permeability of blood vessel walls, and the release of histamine by activated basophils and mast cells that allows additional leukocytes and fluid entry at the infected site (swelling/redness). Leukocytes continue to the site while some cytokines activate the acute phase response if the infection is major. If it has been successfully suppressed, macrophages and some white blood cells remain at the site to clean and repair damage, but eventually the immune response returns to normal. All of this happens whether you have been exposed to the pathogen or not; but as you can imagine, a depressed ability of the innate system to respond would result in greater time for infection to take hold and spread.

Recall Jake from the case presentation at the beginning of this chapter (see Case Study). For some reason, he seemed to be getting small colds more often than his roommate Jerry. One of the reasons why individuals can catch a cold or flu several times a year is that there are several hundred strains of the cold or flu viruses and mutations during reproduction generate new ones each year. Antibodies generated against specific cold viruses will not work as effectively on new viruses. As a consequence, the ability to fight off the common cold is largely dependent on innate immune system. We can then suspect that, for some reason, Jake's innate immune system is suppressed allowing these viruses to infect and multiply in his body, thereby causing more pronounced symptoms.

On the other hand, an enhanced innate immune system would result in more speedy suppression of infection and faster healing. Given that Jerry and Jake are roommates and are therefore likely exposed to similar pathogens, again we can suspect that there is something about Jerry's innate immune system that is more active than Jake's. Interestingly, with both acute exercise (i.e. a single bout) and chronic (long term) exercise training, the innate immune system is predominantly affected.

Recall, however, that dendritic cells can migrate to the site of infection by chemotaxis, phagocytose foreign material as part of the innate response, and then re-enter the circulation to finally "present" the digested antigenic material to immune cells in the lymph tissue. This, other APCs, and a more global spread of pathogens can activate B and T lymphocytes that mount more long term, sustained, and in some cases, lifelong defenses.

Acquired Immunity: Adaptation to Specific Threats

While all of the components of the acquired immune system are present in the body at all times, they are not functionally capable of successfully combating a pathogen until they "learn" about that threat. This learning and memory are important and distinguish the acquired from the innate system. Immune reactivity through the acquired immune system occurs in 3 stages:

- Recognition
- Amplification
- Memory

Recognition occurs when IgM antibodies on select circulating B cells (called clones) bind with free pathogen or when both B and T cells are presented with antigen from APCs.

In the case of B cells, antigen binding leads to their transformation into antibody secreting plasma cells which then divide and "expand" the clone of cells so that more antibodies against the specific pathogen can be made. This amplifies the response to the pathogen. Some B cells become memory cells that remain dormant but expand that specific clone of B cells for future use and the system is then deemed to have memorized the response to that antigen. In a subsequent infection, the B cell antibody response will be swifter, eliminating that threat sooner. The process of B cell differentiation and expansion takes several days, but the memory cells can last in the body for a lifetime.

While B cells primarily respond to free pathogen, T cells respond to infected host cells. Activation of both B and T cells normally occurs at the same time. As such, several days typically pass before the cell-mediated immunity of T cells can come into effect. Nonetheless, once infected cells are recognized by specific T cell clones, immune stimulating molecules (typically cytokines) activate these cells to expand and differentiate into TC cells and TH cells. TC cells disable and destroy infected cells as described earlier, while TH cells orchestrate a coordinated action of all parts of the immune system in the attack of the pathogen. These actions include stimulation of B cells, increased activity of TC cells, chemokine secretion to influence phagocyte migration and stationing at the site of infection, and stimulation of eosinophils in allergic responses. In this regard, TH cells are like the quarterbacks of the immune system and their proper functioning is vital to immune health. Some activated T cells also become memory T cells that are stationed around the body to elicit faster responses upon secondary exposure to that specific pathogen.

The ability to learn and remember foreign invaders is a powerful characteristic of the acquired immune system that allows us to mount defenses in a world where threats may be ever changing. As we shall see in the next section, exercise can have profound

effects on the immune system. It is for this reason that the scarcity of research on exercise and acquired immune responses is surprising. Nonetheless, let's now take a look at specific effects of exercise on immunity.

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Gender Box: Females Have More Active Immune Systems

Interestingly, females of reproductive age tend to have more active immune systems including greater TH2 cytokines, more T lymphocytes, and a greater percentage of active neutrophils and macrophages. This may account for lower mortality rates after acute infection related inflammatory events, but higher rates of autoimmune diseases such as Lupus, Multiple Sclerosis and Rheumatoid Arthritis (Pennell et al. 2012). While estrogen has been linked to this sex dimorphism, other factors likely act in concert with it. Nonetheless, given the higher activity of the immune system in females, it is to prudent to ask what will exercise do to this response. While the research in this area is limited, it appears that at least some portions of the immune response are modulated by exercise. In particular, pubertal and post-pubertal women show increased NK cells immediately following moderate intensity exercise (Timmons et al. 2006). However, after an acute bout of moderate exercise (70% V O2max) pre-pubertal girls exhibit a blunted leukocytosis.

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Exercise Affects the Immune System

Strenuous exercise in the animal world typically involves life or death circumstances. The lion must eat and the buffalo must not be eaten, but for the lion and buffalo the possibility of torn skin, tissue damage, broken bones, and consequent susceptibility to disease or infection are dangers the body must prepare for. When the physiological effects of exercise are examined from this point of view, it is easy to see their importance. While it is no longer a requirement that we exercise vigorously under the auspices of mortal danger, the potential for injury is still inherent and the physiological responses that occur in modern day humans are the same nonetheless. In the following sections we will describe how exercise modifies the immune system components discussed previously. What may be most interesting is that these effects can at times be immune stimulating and at others immune inhibiting. Moreover, because exercise carries inherent risks of injury and close physical contact with others, recognition of infection probability is important. Nonetheless, the wealth of data on this subject would tend to support observation that light to moderate intensity exercise training improves immune function, especially that of the innate immune response. It appears that moderate exercise (walking 35-45 min per day in elderly men and women (Nieman 2008) or 60-80 min per week of moderate exercise in middle-aged adults (Matthews et al. 2002)) can significantly reduce the incidence of cold and cold symptoms, compared to sedentary people.

Contrast this with one of the most classic examples of the effects of over-training on the immune system and overall health of the body: the case of former American and World marathon record holder, multiple-time New York and Boston marathon winner and current USATF coach, Alberto Salazar. In the early 1980's, Alberto Salazar was one of the most prolific marathoners in the world. After several years of intense training and a particularly grueling victory in the 1980 "Duel in the Sun" Boston marathon where Salazar required medical attention after the race, Alberto began training for the 1984 Olympic marathon. Salazar's training regimen leading up to the event was reported to be several hundred miles of intense running every week. However, within this time Salazar also reported that he developed 12 colds in the 12 months of over-training. In fact, Salazar may not have known by what mechanisms this was occurring but he was quoted as saying "my immune system was totally shot as a result of my training". This is a sentiment anecdotally shared by many high-performance athletes and has been found in the relevant research both in Olympic athletes as well as after a single prolonged and intense bout of exercise.



Photo 15-3 Alberto Salazar was one of the world's most prominent marathoners in the 1980's. He now serves as head coach of the Nike Oregon Project elite track and field club. Photo by Cal Hopkins / Cal Hopkins at en.Wikipedia – Transferred from en.Wikipedia to Commons by User:Kafuffle using CommonsHelper. Public Domain, https://commons.wikimedia.org/w/inde...curid=16015855.

How can exercise at these two intensities differ so much in its effect on the immune system? As proposed by Dr. DC Nieman and others, the immune-modulating effects of exercise exist on a J-shaped curve with exercise intensity (Figure 15-8) such that moderate intensity exercise is more beneficial than light or no activity against infection, but intense exercise can actually be detrimental. The following sections highlight the components of the immune system that are modified by exercise in this regard.

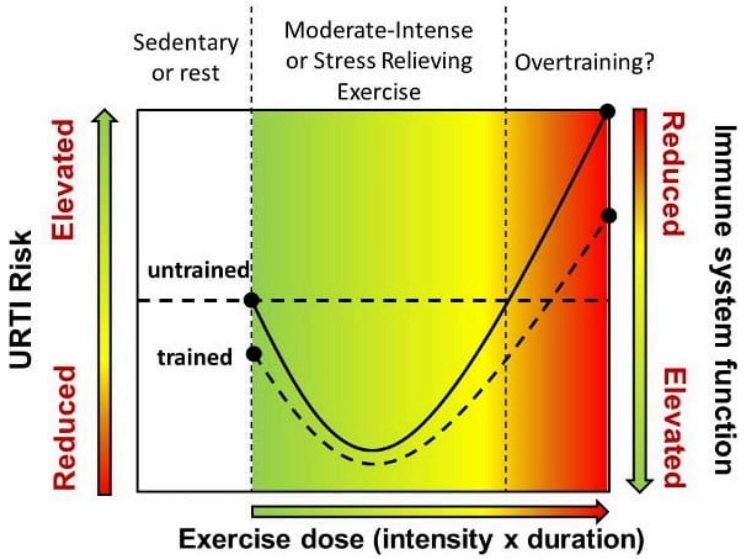


Figure 15-8 J-Shaped curve illustrating relationship between quantity of exercise and risk of upper respiratory tract infection. Adapted from Neiman, 1997.

Exercise and Primary Barrier Support (Clotting)

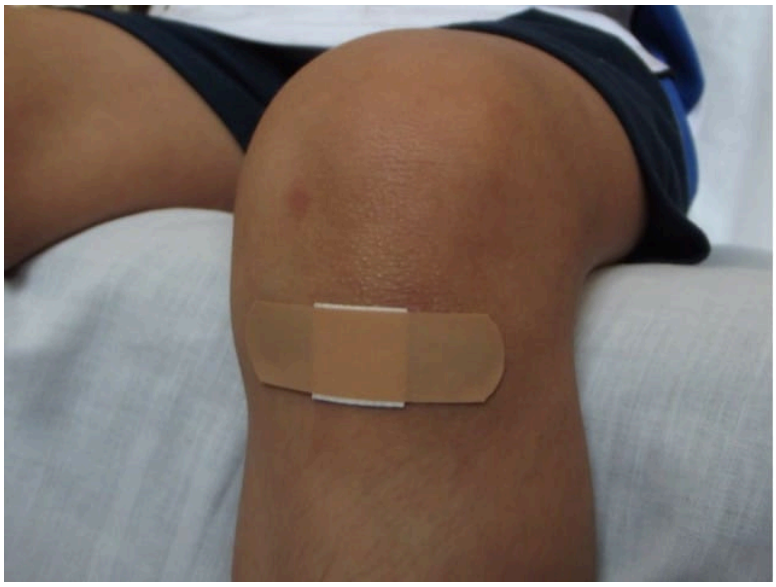


Photo 15-4 Scrapes and cuts allow pathogens to breach the body's primary barrier – the skin.

Think about all the times you have ever scraped your knee or received a blow that broke the skin. Likely you were involved in some form of physical activity (playing tag in the schoolyard, a fall while skating or at the extreme end, a grueling boxing match, for example). Abrasions, blisters, and cuts/lacerations combined make up the largest percentage of injuries for individuals involved in running activities (Gosling et al. 2010). This is an inherent risk in physical activity, and while these injuries are typically considered minor, they do break the skin which we will recall is the primary barrier in the defense against foreign pathogens. In response to exercise of various intensities, there is an increase in the overall coagulation and thrombin generation potential of the blood (Menzel and Hilberg 2011) which is sustained for some period after exercise (Ikarugi et al. 2003). These results are primarily due to the sympathoadrenal catecholamines, epinephrine, and norepinephrine (Ikarugi et al. 1999) which are key mediators of the body's fight-or-flight response during exercise. Further, catecholamine-stimulated platelet activation is augmented by a blood flow mediated increase in blood vessel shear stress that occurs with elevated cardiac output during exercise (Goto et al. 1996). This shear stress acts synergistically with the catecholamines to increas e platelet activation and increase clotting potential after exercise (Goto et al. 1996). Further, maximal intensity, short duration (90 sec) exercise may increase platelet activation (i.e. priming for response to some stimulus) (Hilberg et al. 2003), while moderate and strenuous exercise over an hour appears to increase the release of platelet and neutrophil derived microparticles (i.e. fragmented portions of the plasma membrane that can activate and recruit other leukocytes) in addition to platelet activation (Hilberg et al. 2002; Chaar et al. 2011). Interestingly, trained individuals show as much or a greater response of the microparticle increase (Sossdorf et al. 2011), but it appears that exercise training reduces the exercise induced shear stress related increase in procoagulation potential (Wang et al. 2005). The latter indicates the importance of exercise training in contrast to the effects of an acute exercise bout. Given that the intensity of exercise is important to the magnitude of procoagulation change (Hilberg et al. 2008), training may act to reduce the relative intensity of any given exercise bout and consequently reduce the catecholamine and shear induced increase in clotting potential.

Interestingly, the conjugation of platelets and leukocytes has also been observed after various exercise intensities (Hilberg et al. 2002, 2003). The meaning of this is unclear at this time, but this is an intriguing find, given that platelet-leukocyte conjugates are primarily observed at times of cardiovascular stress such as after ischaemic stroke (Marquardt et al. 2009) and acute coronary syndromes such as myocardial infarction (heart attacks) where they may increase vascular obstruction at plaque sites (Sarma et al. 2002).

As noted in the opening paragraph to this section, an increase in the clotting potential of humans undertaking physical exercise seems intuitive when viewed from the perspective of the fight-or-flight response. While exercise today is not typically performed under the auspices of life or death, the physiological responses are conserved from the times when it was. Scratches, gashes, and bites were to be expected, and these wounds could potentially result in significant blood loss and would also expose the body to potentially dangerous microbes. An enhanced ability to seal these wounds is a benefit. However, this increased clotting ability has also been theorized to be a cause of cardiovascular complications after exercise (https://www.ncbi.nlm.nih.gov/pubmed/12959620 Nonetheless, it is not uncommon to observe significant increases in the fibrinolytic potential of humans after exercise, and this result has been theorized to counter the potentially dangerous effects of a hyper-reactive clotting system (Weiss et al. 1998). Further, after multi week training programs of moderate intensity, fibrinolytic potential is improved in both young and old

men and women but men tend to show a more pronounced response (Kulaputana et al. 2005). The reasons for this are unclear but may be due to differences in body and body composition changes as a result of exercise.

Exercise and Upper Respiratory Tract Infections

You may be asking yourself, “but I always thought exercise was good for you. The harder the better, right? No pain, no gain.” While a progressive increase in training intensity is a hallmark of inducing further physiological adaptations, the increase in training intensity does have it limits. With respect to exercise and immune function, the consequences of immunosuppression observed with prolonged high intensity exercise are notable. One of the most common medical conditions affecting Olympic athletes is succumbing to common upper respiratory tract infections (URTI). Olympic athletes and in particular those athletes who compete in the longest duration type events (e.g. marathon or triathlon) show a significantly elevated risk of URTI above sedentary individuals (https://www.ncbi.nlm.nih.gov/pubmed/26568028).

Exercise-Induced Asthma and Exercise-Induced Bronchoconstriction



Photo 15-5 Asthma medicine is taken to open airways during periods of bronchiospams, such as during exercise. Photo by Тетяна Фіонік [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)], from Wikimedia Commons.

Asthma is defined as a chronic inflammatory condition of the air passageways in the lungs. The lining of the airways may become inflamed, produce more mucous, or narrow due to tightening of the muscles surrounding the airways. The difficulty manifested by these physiological occurrences is obvious: a person experiencing asthma-like symptoms will find it difficult to move air into and out of the lungs. In individuals with asthma, triggers may either induce inflammation or tightening of the surrounding muscles around already inflamed tissue. While pollens, dust mites, mould, viral infections, and other air pollutants may be triggers for inflammation, exercise happens to be a major trigger of bronchiole muscle tightening (bronchospasms). In fact, while the term “exercise -induced asthma” (EIA) is still used today, referring to this event as exercise -induced bronchospasms (EIB) is more correct and inclusive of all individuals experiencing symptoms (Gotshall 2002). As a consequence of EIB, some individuals may experience extreme difficulty breathing during, after, and as a result of exercise, a time when unrestricted air transport is even more vital. Symptoms of EIB usually become greater with increased exercise intensity and duration, but it is important to note that this may not be the same as the increased ventilation (heavy breathing) or dyspnea (shortness of breath) you may have experienced during intense activity that returned to normal a short time after exercise was completed. Exercise induced asthma is a much more severe and longer lasting respiratory distress and is actually a leading cause of asthmatic patients first presentation to a medical professional (Parsons 2010). Nonetheless, while exercise-induced asthma is common in individuals who have been clinically diagnosed with asthma (40-90% of asthmatics (McFadden and Gilbert 1994; Parsons et al. 2011), this is not a requirement. It has been reported that approximately 26% of non-asthmatic people report symptoms (shortness of breath, wheezing, coughing, difficulty inhaling, or chest tightness) that are consistent with EIB after exercise (Parsons et al. 2011). These incident rates should not be taken lightly. In one of the only studies to examine exercise and asthma related deaths, it was determined that over a seven-year period (1993-2000) in the United States, 61 deaths of individuals competing in athletic activity could directly be attributed to EIA or EIB while another 202 may have been associated with EIB symptoms (Becker et al. 2004).

Exercise Increases Concentration of Circulating White Blood Cells

As early as 1893, the increased concentration of white blood cells (leukocytosis) was observed to occur in humans undergoing strenuous work. A slew of articles in the next few decades examined this phenomenon and were summarized nicely, along with additions, in a paper by Doctors. H.T. Edwards and W.B. Wood out of the Harvard Fatigue Laboratory (Edwards and Wood 1932). Summarizing the effects of vigorous physical activity in soldiers, football players, marathoners, 400 m sprinters, and hockey players on leukocytosis, it was shown that this effect occurred in both trained and untrained individuals and was dependent on exercise duration on exercise duration and intensity. Further, approximately one hour after exercise there was a marked decline in plasma lymphocyte expression (below normal) that appeared to be due to storage of these cells rather than loss. These results have been repeated since this time.

An important consideration here is that vigorous exercise involves significant water loss and consequently plasma volume loss which would tend to concentrate the other constituents of blood independent of new secretion. This potentially confounding factor was addressed early on but ruled unlikely given the lack of a correlation between mass and water loss and the extent of leukocytosis. Currently, it is clear that this exercise induced leukocytosis is the result of newly secreted leukocytes, primarily as a result of adrenal catecholamines. Not only are the immune cells increased in concentration in the plasma after exercise, but they also appear to be primed such that they will respond to the same stressor with greater activity (Degerstrøm and Østerud 2006).

In this regard, it is important that hormonal responses occurring during exercise and their effects on immunity are presented here.

Exercise Related Hormones and Cytokines Affect Immune Cells

Neuroendocrine *C hemical M essengers M ediate I mmune S ystem C hanges D uring E xercise*

The sympathoadrenal, hypothalamus-pituitary adrenal and growth hormone axes, and some natural opiates are all elevated in an intensity and duration dependent manner during exercise (Luger et al. 1987). Together these hormones include the catecholamines (norepinephrine and epinephrine), cortisol, growth hormone, prolactin, and β-endorphin. The increase in these hormones, especially the catecholamines, prior to any observed leukocytosis or cytokine release is indicative of their roles in immune function. Each hormone has different physiological roles during exercise including the elevation of cardiac output, regulation of blood distribution, maintenance of glucose homeostasis, and regulation of metabolic substrate availability and use. These hormones cause physiologic changes that resist the multitude of stresses that may occur during exercise. Hormones exert their effects by working on receptors in target cells. Consequently, if a particular cell possesses a receptor for some hormone, it can respond to that particular hormone.

The C atecholamines

The sympathetic nervous system (think fight-or-flight response) innervates most organs and tissues of the immune system (Mignini et al. 2003). In fact, lymphoid tissues and all leukocytes possess adrenergic receptors that respond to catecholamines released from the sympathetic nervous system or adrenal catecholamines in the circulation (Elenkov et al. 2000). Catecholamine stimulation causes movement of white blood cells out of the circulation and aids in activation of these cells. The difference in the densities of the different types of adrenergic receptors on immune cells dictates their responsiveness to catecholamine stimulation. For example, NK cells have a higher proportion of β2-adrenergic receptors than T-cells, and consequently, NK cells show greater changes (i.e. increased movement into the circulation and enhanced activity) in response to catecholamine stimulation (Elenkov et al. 2000). During moderate activity, sympathetic norepinephrine primarily stimulates leukocytosis, but epinephrine becomes the predominant mechanism during intense exercise. Nonetheless, acute exposure to the catecholamines stimulates leukocytosis and enhanced immune function (Krüger et al. 2008).

Cortisol

Cortisol, the primary glucocorticoid, is a powerful glucoregulatory steroid hormone. It is also an anti-inflammatory steroid. Cortisol invokes its anti-inflammatory actions by:

- increasing the amount of anti-inflammatory molecules and

- decreasing the transcription of pro-inflammatory eicosanoids, cytokines, and chemokines

Cortisol also inhibits immune function by:

- causing a redistribution of circulating cells to the bone marrow;
- •reducing lymphocyte movement from peripheral lymph tissues to the circulation;
- inhibiting NK cell function; and
- inducing B and T cell apoptosis (supraphysiological doses)

Because of these roles, it is not surprising that many athletes receive glucocorticoid injections in the form of hydrocortisone injections or topical creams to relieve joint inflammation. In fact, exogenous glucocorticoids are a type of the most commonly detected substances in high level athletes by the World Anti-Doping Agency. Cortisol is a steroid and many of its actions work on the genome, making them slower responding than those of the catecholamines. Further, cortisol is primarily elevated during prolonged exercise or when blood glucose levels drop significantly. For these reasons, the actions of cortisol on the immune system are likely more predominant during the recovery period after exercise. Indeed, its immunosuppressive roles would fit with the decrease in circulating lymphocytes observed after an acute bout of exercise.

Growth Hormone

One of the most potent inducers of an increase in plasma growth hormone is physical exercise. Like the other hormones, it is elevated in an exercise dose (intensity x duration) manner where it provides additional metabolic support by increasing peripheral availability/use and helps in repair. Unlike the adrenal catecholamin es, growth hormone typically peaks near the end or even after strenuous exercise. Thus, its roles are more delayed. Nonetheless, growth hormone also contributes to leukocytosis through growth hormone receptors on most cells of the immune system. To this effect, growth hormone stimulates or enhances:

- neutrophil differentiation
- •lymphocyte proliferation, activation, and migration
- macrophage activation

While growth hormone is primarily secreted by the anterior pituitary gland, it is now apparent that most immune cells can secrete it as well (Clark 1997). As such, growth hormone is thought to act in local immune signalling either directly or through the mediator of growth hormone action, insulin-like growth factor (IGF-1). Further, several cytokines act on the hypothalamus and pituitary gland to modify growth hormone production.

Endogenous O piates

The more common opiates you might have heard of are exogenous analogs such as morphine or illegal drugs such as heroin. When you think about what these drugs are used and abused for, it should not be surprising that the opiates are analgesic and may cause feelings of euphoria. The common endogenous opiates are the endorphins and enkephalins of which β-endorphin is most commonly studied during exercise. The exact role of β-endorphin in exercise is not entirely clear, but it is associated with an extreme euphoric sensation some runners experience during prolonged or intense exercise known as the runner's high. The time-course of increase in β-endorphins tends to match that of cortisol because it is synthesized from a large pro-hormone that also contains the tropic hormone for cortisol release. Like many of the hormones, an immunomodulating role for β-endorphin has been observed in vitro, but this is not as clear inside the body. Nonetheless, the endogenous opiates have both immunostimulating and immunosuppressive effects on lymphocyte activity. For example, high levels of β-endorphin are directly correlated with increased NK cell activity while high enkephalin appears to suppress it at rest (Mozzanica et al. 1991). Further, the lymphocyte changes in response to increases in the endogenous opiates is small (Carr and Serou 1995), but they cannot be fully discounted as playing a role in the exercise-induced changes in the immune system.

Glutamine Availability

Glutamine, an abundant non-essential amino acid, is a key substrate used by lymphocytes and monocytes for energy and cell proliferation. Lymphocytes utilize glutamine several folds greater than glucose to meet their energy demands. In fact, glutamine supplementation has an extensive history in boosting the immune system in clinical populations (Ziegler 1992; Estívariz et al. 2008). Skeletal muscle is the largest source of plasma glutamine (Newsholme and Parry-Billings 1990). Further, strenuous exercise has been shown to reduce muscle and plasma glutamine levels (Kargotich et al. 2005) in a timeframe similar to reduced immune system function. Not surprisingly, it has been theorized that the maintenance of plasma glutamine would prevent

immunodepression with exercise. Indeed, some reports have shown improved immune function in athletes supplementing with either glutamine (Castell and Newsholme 1997) or branch chain amino acids that prevented a fall in glutamine during strenuous exercise (Bassit et al. 2000). However, it has also been shown that maintenance of glutamine levels is not sufficient to maintain immune function in all cases (Mackinnon and Hooper 1996; Delgado et al. 2006), though this does not preclude glutamine availability as one of many factors that affect immune function.

Delayed Onset Muscle Soreness After Exercise: Role of the Immune System

Exercise, especially intense or eccentric type activity, may induce significant muscle fibre damage including disruption to the myofibre sarcolemma, proteins, cytoskeleton, and structural components between the myofibres (Fridén and Lieber 2001). Attracted by the products of protein degradation and inflammatory cytokines released by damaged cells, neutrophils followed by macrophages invade the damaged area to clear cellular debris and help in the repair and regeneration of damaged skeletal muscle (Tsivitse et al. 2003). Indeed, there is a concomitant increase in plasma leukocytes (neutrophils, macrophages, and NK cells) and skeletal muscle neutrophils, macrophages, and activated satellite cells in the days following an acute damaging exercise bout and multiple biopsies alone (Malm et al. 2000). Either muscle cells or infiltrating leukocytes may then release inflammatory cytokines (predominantly IL-1, IL-6, and/or TNFα) that act as chemotaxic signals for other immune cells. Indeed, exercise associated with significant myofibre damage invokes a low grade inflammatory response that includes increased circulating cytokines and leukocytes for up to several days later although these immune changes do not always correspond with the common feelings of delayed onset muscle soreness (Kuipers 1994). The time-course of change after muscle damage is shown in Figure 15-9.

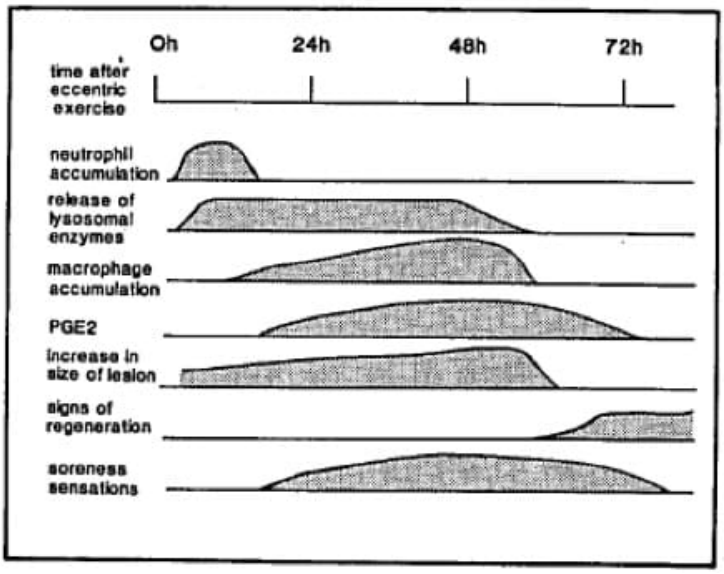


Figure 15-9 Time course of immune cell appearance and activity, muscle regeneration and perception of soreness following eccentric exercise.

Exercise and Endotoxemia

As noted above, we normally live in a symbiotic relationship with a variety of beneficial bacteria. The greatest concentration of these bacteria is found in the large intestines. The reason these bacteria are not normally pathogenic is because we maintain adequate physical (mucosal and cellular) and immunological (intestinal lymph nodes) barriers to their entrance into the body. These barriers are maintained by a healthy physiology. Under stress (for example in burn or shock victims) where there is a reduction in splanchnic blood flow, there is the potential for the gastrointestinal mucosal barrier to succumb to ischaemic injury. Lack of oxygen and nutrient rich blood may lead to cell death. Once this barrier is compromised, normal flora may be able to penetrate into the body's circulation invoking systemic inflammatory responses directed against the bacteria and/or their toxins (endotoxemia). During exercise, blood flow is redirected away from non-essential organs such as the intestines in order to satisfy the nutrient and gas needs of working muscle as well as essential organs like the brain and lungs. It has been theorized that this exercise induced blood redirection may be a source of intestinal ischaemic injury and subsequently endotoxemia (Marshall 1998; Pedersen et al. 1998). These theories are supported by the gastrointestinal distress symptoms commonly observed in athletes participating in long duration high intensity exercise. For example, symptoms such as dizziness, stomach cramps,

nausea, vomiting, and diarrhea (with and without blood in the stool) are all highly reported in marathon runners (Riddoch and Trinick 1988), ultramarathon runners (Rehrer et al. 1992), triathletes (Peters et al. 1999), and Ironman triathletes (Pfeiffer et al. 2012). Further, endurance athletes show increased plasma concentrations of endotoxins and anti-endotoxin IgG immediately after exercise and these observations are significantly correlated with magnitude of gastrointestinal distress symptoms (Brock-Utne et al. 1988). However, even though splanchnic blood flow has been shown to be reduced during exercise, several reports show a disconnect between this reduced blood flow and symptomology (Wright et al. 2011). Consequently, there are likely other factors that cause, independently or in conjunction with reduced blood flow, the gastrointestinal symptoms observed in some athletes.

Exercise and the Acute Phase Response

Training reduces plasma C reactive protein (CRP) levels in healthy adults (Lakka et al. 2005). In fact, one of the strongest correlates with reduced CRP is maximal oxygen uptake suggesting that one of the adaptations associated with fitness is a reduction in whole body stress. Because this protein is associated with many chronic diseases including Type 2 diabetes and heart disease (Lakka et al. 2005), reductions in CRP with training could account for portions of the reduction in Type 2 diabetes and CVD risk as a result of exercise.

Interestingly, Dr. BK Pedersen has shown over a series of studies that the clinical syndrome known as the systemic inflammatory response syndrome, essentially a global, highly negative inflammatory state, is reproduced very closely by vigorous exercise. What should be questioned here is, why do stresses such as trauma, burns, and serious infection result in life threatening immune response, while exercise with a similar cytokine and immune profile typically does not?

The answer to the question above is that while the cytokines and activated immune cells are similar during exercise and other pathological stresses, the magnitude and duration of the immune response is much less as a result of exercise. These changes are shown in Figure 15-10. For example, the exercise-induced increase in plasma IL-6 is not even elevated to a tenth of the level associated with mortality during sepsis (~40pgml^{-1} after strenuous exercise (Ostrowski et al. 1998a) versus ~280-950 pgml^{-1} during sepsis causing 50% mortality (Casey et al. 1993). Further, in contrast to serious infection, the cytokine response to strenuous exercise (e.g. marathon running at ~75% of V O2max) favours anti-inflammatory molecules. Plasma levels of the inflammatory cytokines TNFα and IL-1 are minimally changed after prolonged strenuous exercise (Ostrowski et al. 1998a) and the levels do not approach those observed in sepsis (Casey et al. 1993). Moreover, IL-10, IL-1 receptor antagonist (IL-1ra) and soluble TNF- receptor are elevated subsequent to the increase in IL-6 (Ostrowski et al. 1998a, 1999). The cytokine IL-10 is a potent anti-inflammatory cytokine while IL-1ra and sTNFα-R decrease the signalling capabilities of the pro-inflammatory cytokines, IL-1, and TNFα by limiting their ability to interact with receptors on other immune and non-immune target cells.

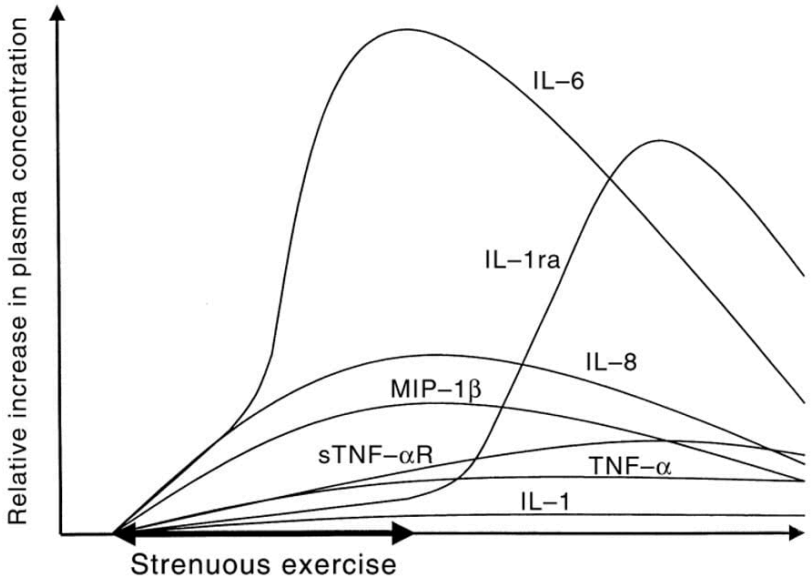


Figure 15-10 Cytokine profile associated with vigorous exercise. Typical course of cytokine appearance in the plasma following strenuous exercise. Changes in cytokine concentration are relative. Unlike sepsis, the pro-inflammatory cytokines, TNFα and IL-1, may only minimally be elevated following exercise. IL-1, interleukin-1; IL-1ra, interleukin-1 receptor alpha; IL-6, interleukin-6; IL-8, interleukin-8; MIP-1β, macrophage inflammatory protein-1b; TNF-α, tissue necrosis factor alpha; sTNFα-R, soluble TNF- α receptor. See text for more details.

Although the purpose of an increase in IL-6 is not completely known, its apparent source during exercise is contracting skeletal

muscle (Steensberg et al. 2002) rather than circulating immune cells. This increase tends to both correlate with (Bruunsgaard et al. 1997) and occur independent of (Ostrowski et al. 1998b; Toft et al. 2002) markers of significant muscle damage. However, in addition to its role in inflammation, exercise-induced plasma IL-6 functions like a muscle derived hormone to increase hepatic glucose output and assist in muscle adaptation (Pedersen et al. 2003). With respect to the former, this is partly due to the IL-6 stimulated increase in the glucoregulatory and anti-inflammatory hormone, cortisol (Steensberg et al. 2003). As such, glucose feeding during intense exercise can reduce the IL-6 increase (Febbraio et al. 2003).

Further evidence for a differential effect between exercise and severe infection is that exercise does not appear to affect the complement system (Córdova et al. 2010). Consequently, the cascading physiological responses of the immune system to infection (e.g. fever associated with the acute phase response) do not tend to occur with exercise.

Summary

It is quite apparent that exercise has profound effects on the immune system. These effects are dependent on exercise intensity, proper training regimens (i.e. the avoidance of over-training), and likely good nutrition. Exercise is a physiological stress and the repeated disturbance to homeostasis of several physiological variables as a result of exercise training may lead to adaptations that fortify the body against those stresses. When exercise training is accomplished from the standpoint of health promotion, these adaptations are overwhelmingly positive. This includes stimulation and priming of the immune system observed in low-to-moderate intensity training. However, competitive athletes often walk a fine line between training that will induce positive adaptations and over-training. With respect to immune system dysfunction, it is the high training intensities with little rest and elevated stress hormone levels (i.e. cortisol and epinephrine) that appears to be detrimental to immune function. Immune suppression can be observed after as little as a single bout of intense and/or prolonged exercise and last for days to weeks. While not isolated to the competitive athlete, suppression of the immune system is exacerbated by psychological and other physiological stresses (e.g. Olympic athletes exhibit poorer quality of sleep than age and sex matched controls (Leeder et al. 2012)) that are likely to be higher in elite athletes. In particular, this immune suppression is associated with the increased risk of upper respiratory tract infection in elite athletes, one of the most common medical conditions in Olympic level athletes. Consequently, it is important for both the recreational and elite athlete to be aware of the potential immune system suppression of intense prolonged exercise, so that they may take the appropriate measures to try to limit these negative effects.

Review Questions

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Meet the Author

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3.5: Chapter 16 - Physiological Determinants of Athletic Performance



Photo 20-1 High Jumper

High jumping is a skill that requires a high degree of motor coordination, a high percentage of fast-twitch motor units in the leg muscles and physical height.

Learning Objectives

After studying this Chapter, you can:

1. Describe the integrated physiological response during long-distance running.
2. Describe the intensity-duration relationship.
3. Compare the intensity-duration relationship for an elite athlete with yourself (or a reference student).
4. Identify the five physiological properties that permit world-class athletic performance.
5. Describe three factors that permit a high running economy.
6. Summarize the physiological characteristics of an elite athlete in a quantitative way.
7. Compare the determinants of success in long distance running with the determinants of success in sprint running.

Key Terms

adenosine triphosphate, aerobic, aerobic capacity, aerobic inertia, anabolic steroids, anaerobic capacity, anaerobic threshold, autoregulation, blood lactate, body composition, carbohydrate loading, cardiac output, catecholamines, cortisol, critical speed, cross-bridge turnover, economy of locomotion, endurance, excess postexercise oxygen uptake, glucagon, glycogenolysis, glycolysis, growth hormone, haemoglobin, histochemical, homeostasis, hyperaemia, intensity-duration relationship, maximal accumulated oxygen deficit, maximal oxygen uptake, monocarboxylate, motor units, myoglobin, myosin ATPase, nitric oxide, non-aerobic, oxygen deficit, phosphocreatine, power, slow component of oxygen uptake, somatotropin, strength, substrate, substrate mobilization, supramaximal, tendon compliance, tendon stiffness, tidal volume, time-trial, tolerance, ventilation

Case Study: Volunteer for a Research Study

Jake has volunteered to participate in a research project that requires him to complete an incremental test to exhaustion. He has done this before, so he is not apprehensive about the test. He follows the brief instructions prior to the test and shows up in the lab at the required time. Jake completes a 10 min warm-up of easy jogging, then sits for 10 min before beginning his test.

Preparation for the test included having a heart rate transmitter placed on Jake's chest and a nose clip was put on his nose. He inserted the mouth piece into his mouth and took several breaths while the technician checked things out. Everything was working, so the test was initiated. Jake had been straddling the treadmill, so to begin running he simply supported his weight on his arms and started placing his feet on the moving treadmill belt. The speed of the treadmill was initially 281 $m \cdot s^{-1}$, and the slope was 0%. The protocol required Jake to run for two min at each speed, and a blood sample was taken from a finger-tip while he stopped running for 30 s at each speed. The speed increased until Jake was no longer willing to run. The treadmill was stopped, and a final blood sample was taken for measurement. Results of this test are shown in Figure 16.1a and 16.1b.

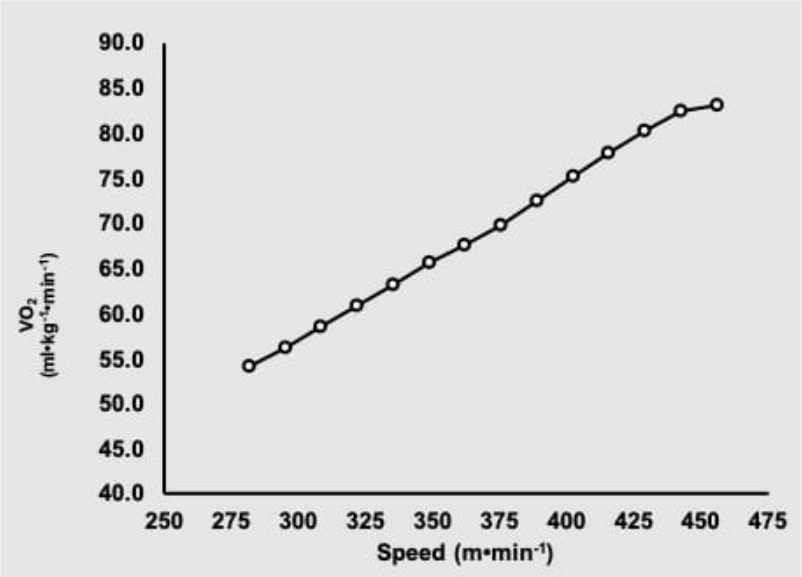


Figure 16-1a Oxygen Uptake during incremental test.

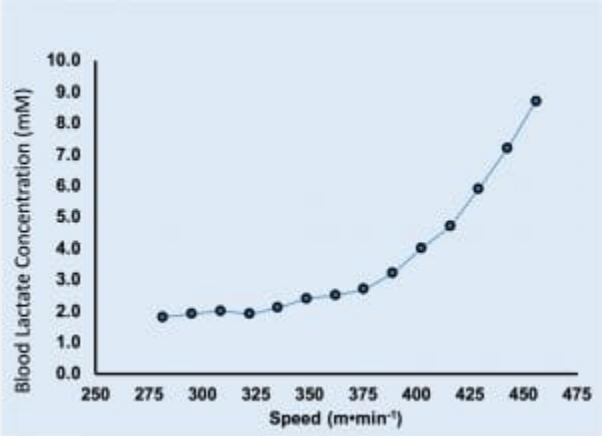


Figure 16-1b Blood lactate during incremental test.

Overview

One way to show how exercise physiology relates to real life situations is to examine the body's responses during an extreme physical challenge and evaluate the physiological properties that permit elite athlete performance. The primary example we will use is running a 10 km time-trial, but comparisons will be made between this and other athletic events as well. Jake has been selected for careful study throughout this chapter. You will recall that Jake is one of the fictitious characters described in Appendix F. Following our description of Jake below, we will present a few general considerations related to the physiological determinants of success in athletic events. This includes: a description of the importance of physiology, considerations for differences in sprint vs endurance events, and a brief description of male vs female characteristics. Following this presentation, Jake's physiological responses while running a 10 km time-trial will be presented. This includes: oxygen uptake , substrate use by his muscles, mobilization of substrates, cardiovascular response, heat generation and dissipation, ventilatory response, blood concentration changes, and other disturbances to homeostasis. This information will allow you to see how the various physiological systems described in Part II of this textbook integrate to permit Jake to achieve world-class performance in distance running.

Following this description of physiological response, pacing strategy is discussed, in the context of the intensity-duration relationship. This relationship puts the 10 km effort into perspective and gives a framework for consideration of the true physiological determinants of athletic success: maximal oxygen uptake, fraction of oxygen uptake that is sustained for a long time, economy of locomotion, and anaerobic capacity. These parameters relate to the ability to provide energy for the task at hand. In addition to these primary determinants, we will give consideration to the secondary physiological determinants that influence athletic performance: strength, body composition, and the ability of Jake to tolerate a disturbance to homeostasis. Homeostasis is the tendency of the body to keep things constant. Temperature, ion concentrations and gradients, and blood glucose are examples of things for which there are control systems to maintain homeostasis in the body.

Jake Specializes in Running 10 km

You will have met Jake in some of the previous chapters. Recall that he is a 29 year-old distance runner who has competed internationally with some success. His recent intense training and disciplined lifestyle have allowed him to approach the world record for his specialty, the 10 km race. Some physical and physiological characteristics of Jake are presented in Table 16.1 in comparison with a healthy male of similar age (Andrew). Female counterparts (Rachel the runner and Julia) are also presented for comparison. Take some time to evaluate the table and contemplate the differences in these measures between these individuals.

Table 16-1 Physical and Physiological Characteristics

	Jake	**Rachel**	**Andrew**	**Julia**
Age (years)	29	28	26	20
Height (cm)	177	175	175	188
Weight (kg)	61	56	87	79.4
$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	84	75	40.5	42.1
Critical Speed ($m \cdot s^{-1}$)	5.93	5.40	4.00	3.50
Q_{max} ($l \cdot min^{-1}$)	28.84	26.50	25.00	21.00

HR_{max} ($beats \cdot min^{-1}$)	188	190	203	197
% body fat	4.5	8.2	19.5	27.2
RE* ($kcal \cdot km^{-1} \cdot kg^{-1}$)	0.96	1.01	1.13	1.14

*RE is running economy

This chapter will focus on energy delivery as the major determinant of success as is the case in an endurance event such as the 10 km race example. Other athletic events like field events (high jump, javelin etc.), and team sports like hockey (ice or field), soccer, volleyball, and basketball will have differing physiological determinants of success depending on the demands of the activity. Because of their easily quantifiable distances and speeds, race events are most easily described in terms of rate and magnitude of energy delivery and use.

Regardless of the type of exercise, energy use in muscles is in the form of . There are three primary sites of ATP use: actin-myosin-ATPase for muscle contraction, Ca^{2+}ATPase for muscle relaxation, and ion pumping for the restoration of Na^{+} and K^{+} gradients across muscle and nerve membranes. Although the focus here is on energy delivery, any reduction in ATP demand will potentially result in performance enhancement. This topic is addressed later within the section “Economy of Locomotion.”

The Importance of Physiology

Physiology is the field of study associated with understanding how the body functions. Optimal physiology, or body functioning, is an important determinant of success in most athletic events, but the role of physiology is most easily demonstrated as a determinant of success for race events. In race events, the objective is to cover a specified distance in the shortest possible time. This is the goal, regardless of the type of exercise: running, skiing, skating, swimming, or cycling. Success in race events, or the shortest time to complete the required distance, is dictated by the energy an athlete needs to cover a specific distance, also referred to as economy of locomotion, and the rate at which he or she expends energy for the duration required to complete the race. The ability to provide energy for long distance events relates to the physiological systems of aerobic energy delivery and supply including: ventilation, cardiac output, distribution of blood flow, and mitochondrial capacity to use oxygen in the active muscles.

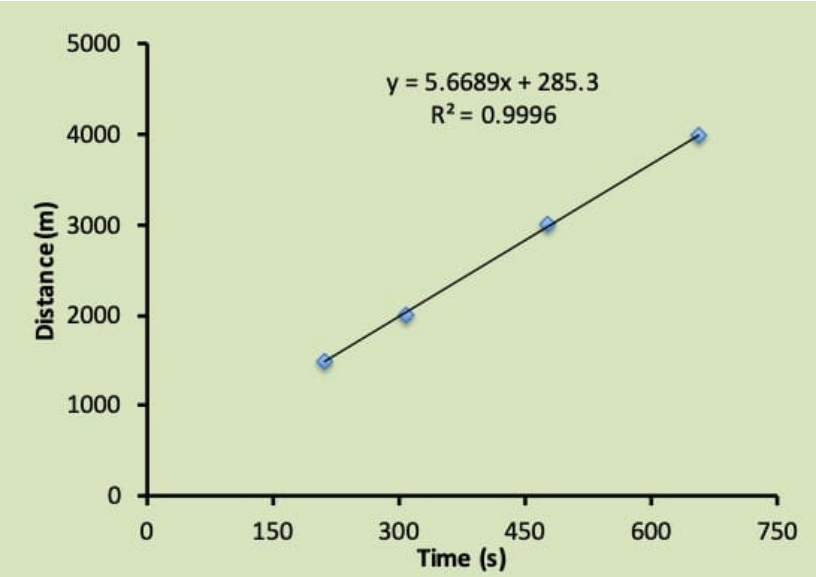


Figure 16-2 Critical speed test results for Jake. Jake completed 4 time-trials, completing the test distance in as short a time as possible. Typical results of such a test gives a straight-line relationship as indicated in the figure. The slope of the line (5.67 m·s-1) yields the critical speed. The intercept, 285.3 m gives the distance that can be covered by only anaerobic energy. This is one way the intensity-duration relationship can be illustrated.

Non-aerobic energy sources include PCr, adenosine triphosphate(ATP), and glycolysis, which results in formation. Non-aerobic energy systems can also play a role in endurance events, but these contribute a relatively small proportion of the total energy needs in such events. Of greater importance, but often neglected as a physiological factor affecting endurance performance, is tolerance for disturbance to homeostasis. This is particularly relevant when the race is above the intensity associated with the . Races at this intensity will be shorter than 45 min.

The concept of limits of energy delivery is most easily illustrated using the intensity-duration relationship (see below). The duration of an event dictates the relative importance of the various energy delivery systems. The various physiological responses of the body serve to provide the energy needed for the task and minimize the disturbance to homeostasis that would otherwise occur during this exercise.

Aerobic energy delivery involves several steps to get oxygen from the atmosphere all the way to the mitochondria. Substrates (primarily fats and carbohydrates (COH) are also needed for energy metabolism. This delivery of oxygen involves an integration of pulmonary, cardiovascular, mitochondrial, and regulatory physiological systems that involve neural and hormonal input. Given that aerobic energy supply is essential to endurance performance, physiology is the major contributor to success when the objective is to complete a given distance in as short a time as possible.

Although physiology is considered the major contributor to success in race events, the emphasis in terms of which specific physiological system serves as the dominating factor will change according to the nature of the competition. Most often, the major consideration under these circumstances is the duration of the event.

Physiological Determinants of Success in Endurance Events

In order to understand the physiological adjustments that Jake will go through in completing his 10 km time-trial, it is of value to get to the main topic of this chapter: the determinants of success in such an endeavour. To be successful in an endurance event, an athlete must have a high maximal oxygen uptake ($\dot{V}O_2max$), a low energy cost of locomotion, and a high . All of these factors will contribute to a high critical speed which is an important predictor of success in distance running, especially the 10 km distance. This high accuracy of prediction is because critical speed incorporates all three of these important determinants of success:

A high maximal oxygen uptake

A low energy cost of locomotion

A high threshold (which allows a high fractional use of $\dot{V}O_2max$)

Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_2max$) is the highest rate at which oxygen is taken up, distributed, and used by the body during whole-body exercise (Bassett and Howley 1997). The determinants of $\dot{V}O_2max$ and the apparent factors that limit it are addressed in Chapter 10. $\dot{V}O_2max$ is an important determinant of success in endurance events (Foster et al. 1978; Karlsson and Saltin 1971). Male elite endurance athletes will have a $\dot{V}O_2max$ of more than 75 $ml \cdot kg^{-1} \cdot min^{-1}$. The very highest values recorded for males are just over 90 $ml \cdot kg^{-1} \cdot min^{-1}$. Females typically have slightly lower values with elite female athletes scoring above 60 $ml \cdot kg^{-1} \cdot min^{-1}$ and extreme values just over 80 $ml \cdot kg^{-1} \cdot min^{-1}$. Although $\dot{V}O_2max$ represents the upper limit of aerobic metabolism, exercise at this intensity already has substantial non-aerobic contribution. It is thought that there is a finite amount of non-aerobic energy available, so once this energy is expended, this intensity of exercise can no longer be sustained. The limit of endurance at $\dot{V}O_2max$ is just 5-7 minutes (Billat et al. 2000). In Figure 16.2, this duration would correspond with the 2000 m time-trial for Jake (305 s), who has a oxygen uptake of 84 $ml \cdot kg^{-1} \cdot min^{-1}$.

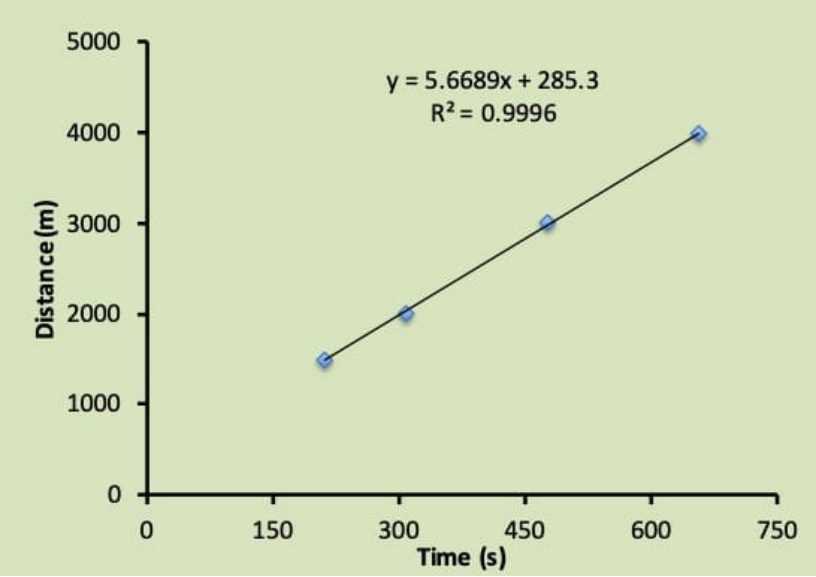


Figure 16-2 Critical speed test results for Jake. Jake completed 4 time-trials, completing the test distance in as short a time as possible. Typical results of such a test gives a straight-line relationship as indicated in the figure. The slope of the line (5.67 m·s-1) yields the critical speed. The intercept, 285.3 m gives the distance that can be covered by only anaerobic energy. This is one way the intensity-duration relationship can be illustrated.

Clearly, Jake's success in running the 10 km distance is not because he uses his high $\dot{V}O_2max$ during the event. However, he can run the full 10 km time-trial using a high fraction of his $\dot{V}O_2max$, so having a high $\dot{V}O_2max$ allows him to maintain a high rate of production by aerobic metabolism at this high fraction of his $\dot{V}O_2max$.

A high $\dot{V}O_2max$ is dependent on a high maximal cardiac output and a large arterio-venous oxygen difference. These criteria for a high $\dot{V}O_2max$ can be inferred from the Fick equation, which is based on the principle that the amount of substance taken up by an organ (or organism) is equal to the amount delivered minus the amount coming out" (see equation 16.1). Since oxygen uptake ($\dot{V}O_2$) is the product of cardiac output and arterio-venous oxygen difference, Jake must have a high maximal cardiac output and be able to extract oxygen from his blood in order to achieve a high arterio-venous oxygen difference. Although some physiologists would use this equation to support the notion that cardiac output limits

$\dot{V}O_2max$, it is important to realize that a high capacity to use O_2 is also dependent on what is going on in the muscles as well. Jake must have a high mitochondrial volume in his skeletal muscles to be able to use the oxygen that his circulatory system can deliver. $\dot{V}O_2 = \dot{Q} \cdot (a\text{-}\bar{v})O_2$ **Equation 16-1**

Where a and $\bar{v}$ represent arterial and mixed venous O_2 content and $\dot{Q}$ is cardiac output.

Considering the broad range of values for oxygen uptake in the human population $\dot{V}O_2max$ is clearly a distinguishing feature that assists in identifying potential elite endurance athletes (see Figure 16.3). However, among a group of elite runners $\dot{V}O_2max$ is not a distinguishing characteristic (Saunders et al. 2004). This lack of apparent relationship is because all elite endurance athletes will have a high $\dot{V}O_2max$ and one of the important contributors to a significant correlation is a wide range of values in the corresponding variables. Running economy and oxygen uptake at have greater predictive capabilities (Costill et al. 1973; Coyle et al. 1992; Xu and Montgomery 1995). These two parameters of athletic performance are described next.

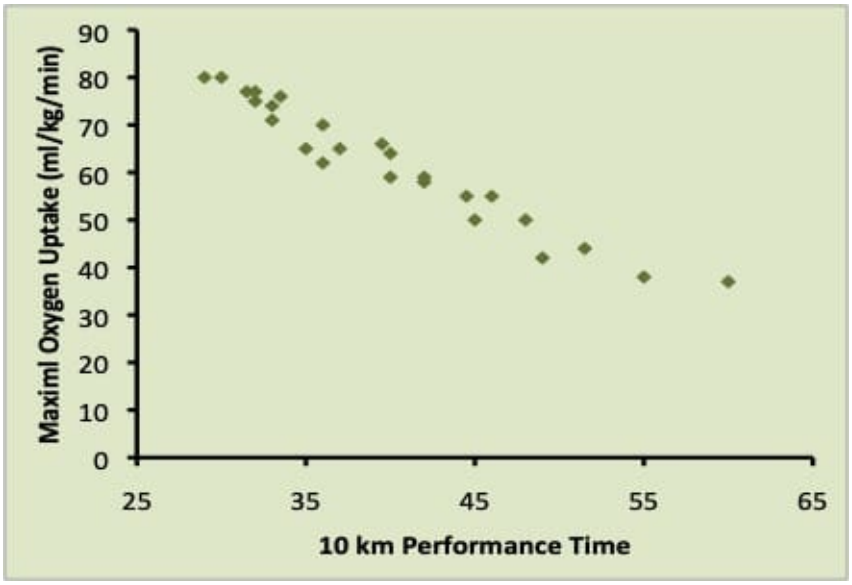


Figure 16-3 Relationship between $\dot{V}O_2max$ and 10 km performance. Subjects ran a time-trial and had maximal $\dot{V}O_2$ measured. You would expect to find a strong correlation between these variables. The higher the $\dot{V}O_2max$, the faster their performance will be. However, variability exists. Some subjects with a high $\dot{V}O_2max$ may not run as well as others with a similar $\dot{V}O_2max$. This is because other factors are important in addition to $\dot{V}O_2max$.

Economy of Running

Economy of running is a measure of the energy cost to travel a given distance or the rate of energy use while running at a given speed. It is easy to imagine that body mass would be a factor that would influence running economy. A simple analogy is to compare the energy cost of driving a small car versus a full-sized pick-up truck. The pick-up truck requires more gas to travel a given distance. Economy of automotive travel is expressed in terms of litres (of gas) per 100 km (or miles per gallon). The truck might require 12 litres per 100 km while the small car can travel for 6.5 litres per 100 km. This difference in economy would be reduced if the fuel use was expressed relative to mass, but there would still be differences. Part of the reason for the difference in fuel economy is due to size of the vehicles but other factors contribute – the size of the engine, shape of the vehicle etc. Similarly, the economy of running is affected by body size and other factors (see below). It makes sense to express economy of running in units of energy per distance travelled per kg of body mass, but this approach is not always used.

It is common to measure oxygen uptake to obtain an estimate of the energy used by an athlete. Often the calculation of oxygen uptake is as far as the estimate is taken, and economy is expressed as $ml \cdot min^{-1} \cdot kg^{-1}$ while running at a given speed. However, this expression of economy has 2 problems:

- Comparison between individuals requires that they run at the same speed
- The energy yield per volume of oxygen can vary as the substrate mix changes

The first of these problems can be overcome by expression of the economy as or $ml \cdot km^{-1} \cdot kg^{-1}$ but this does not solve the second problem. To address this second issue, it is necessary to express economy as $kcal \cdot km^{-1} \cdot kg^{-1}$ (Fletcher et al. 2009). Arriving at this estimate still requires measurement of oxygen uptake and carbon dioxide output to facilitate calculation of the energy yield per litre of oxygen used. Normal values for economy of running range from 0.95 to 1.25 $kcal \cdot km^{-1} \cdot kg^{-1}$.

The factors that affect economy of running are not well understood, but this situation is changing (Fletcher and MacIntosh 2017). Some of the factors that affect economy of running include the following: muscle fibre-type distribution, tendoncompliance, limb

length, stride length, and stride rate as well as speed and load (body weight, and mass distribution). Each of these factors can increase or decrease the energy cost of muscle contractions required for running. Below, we will see how these factors influence running economy. Figure 16.4 illustrates the impact of several factors on running economy. Some of these factors are obvious and will not be discussed here. Others including muscle fibre types, muscle efficiency, and tendon compliance require some explanation.

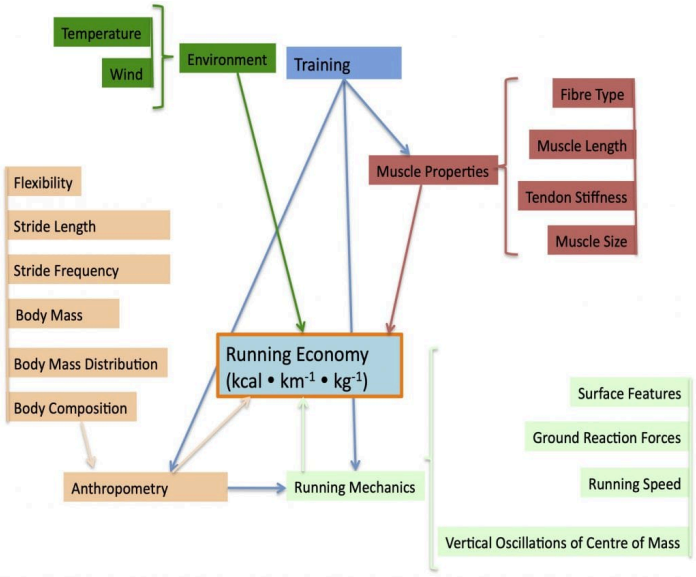


Figure 16-4 Determinants of running economy. This diagram illustrates the complex interactions of several factors that influence running economy. Arrows indicate the connections between various factors that can influence running economy. The general categories of these factors can be divided between environment (dark green), surface (light green), body shape and limb lengths (beige), and skeletal muscle properties (red). Training (blue) can influence several of these factors, as shown by the connections, but not all of them.

Muscle Fibre Types

Muscle fibre types were presented in Chapter 5. In that chapter, it was indicated that muscle fibre types can be categorized on the basis of contractile, histochemical, and proteinisoform properties. Adult human muscle has three categories of fibre type (type I fibres, type IIa fibres and type IIx fibres), but it is recognized that intermediate types do exist in the form of hybrid fibres. Foster et al. (1978) evaluated biopsies from 26 runners with a broad range of skill and found that % slow-twitch fibre composition was significantly related to endurance running performance. Furthermore, they present data from previous studies that confirm this relationship. Jake is a highly successful endurance runner so it would be expected that he would have a high proportion of type I muscle fibres in his legs. If we were to take a biopsy of his gastrocnemius muscle, we would likely see >75% slow-twitch muscle fibres. The remaining fibres would be hybrid Type I-Type IIa, and Type IIa. He would likely have very few if any Type IIx fibres.

It could be asked whether this high proportion of slow-twitch fibres is genetically endowed or a consequence of training. Although there is a long history of belief among exercise physiologists that muscle fibre type cannot change with training, this belief has been successfully challenged. It has been known for quite a long time that muscle activation pattern is primary determinant of myosinisoform expression and that cross-reinnervation (Buller et al. 1960; Luff 1975) or imposed electrical stimulation of the appropriate pattern (Pette and Staron 2000) will induce a change in myosin isoform expression. However, these are artificial ways of modifying muscle fibre type. The relevant question is whether voluntary activation associated with training can achieve the same fibre type transformation.

Coyle et al. (1992) reported that % slow-twitch muscle fibres was correlated with years of endurance training and Rusko (1992) has demonstrated that endurance training can cause a shift towards slow-twitch muscle fibres in elite cross-country skiers. This latter study presents rather convincing evidence for a training-induced change in fibre type expression.

Rusko (1992) evaluated muscle biopsy samples from elite cross-country skiers before and after 8 years of high training volume. He observed an increase of type I muscle fibres of 11% over the eight years, nearly 1.5% per year. Athletes who retired at the time of the initial measurement were also measured 8 years later and they were found to have decreased in type I fibre proportion. The implications of this research are clear. Fibre type can and does change with training, but the changes occur very slowly. It takes

years of high-level training to achieve a noticeable change in fibre type composition. The fact that this fibre type transformation is very slow provides an answer for why most research studies lasting 8-20 weeks find no significant change in fibre type.

How can fibre type affect the energy cost of running? Understanding the energetics of skeletal muscle is complex. There are some generalizations that will make this understanding of energetics easier. The easiest way to consider the advantage of slow-twitch fibres is to consider isometriccontractions. Slow-twitch muscle fibres contain a myosin isoform that has a relatively slow rate of use. This slow rate ofATP use relates to the fact that crossbridge of slow-twitch muscle fibres remain attached longer than crossbridges of fast-twitch muscle fibres. This longer time of attachment causes the slower rate of ATP use. The same force is maintained for a lower energy cost in slow-twitch fibres. During fast velocity shortening, this advantage is lost in that cross-bridge turnover increases in proportion to velocity of shortening. The force generated by slow-twitch fibres decreases more than the force generation of fast-twitch fibres due to the force-velocity relationship (see Chapter 5). Fast-twitch fibres become an advantage when shortening velocity is fast, but when shortening velocity is slow, then slow-twitch fibres still retain an advantage over fast-twitch fibres. This advantage becomes clearer when efficiency of contraction is considered.

Efficiency of Muscle Contraction

Mechanical efficiency is defined as the mechanical work accomplished divided by the total energy used. Efficiency can also be quantified as the power output divided by the rate of energy input. Either way, this calculation is essentially an expression of the relative conservation of energy in a useful form. When the work accomplished and the energy used are both expressed as kcal, or joules the ratio has no units. Efficiency is typically expressed as a % by multiplying this unitless ratio by 100.

Efficiency is easy to calculate for tasks like cycle ergometry where whole body exercise results in substantial work. The total energy input is estimated by measurement of $\dot{V}O_2$ and the appropriate consideration of the substrate that was metabolized as discussed earlier in this chapter. However, efficiency is not easy to calculate when work or power is not easily quantified, as is the case in running. Once Jake reaches a relatively constant running speed, the work he is doing is the work to overcome air and ground resistance. This impediment to forward motion is a combination of the resistance due to motion through the air as well as the intermittent resistance associated with each foot-strike. The energy associated with this work is a small proportion of the total energy input which is calculated from the measurement of the and production. The “efficiency of running” is typically very low and is probably meaningless because “work” is not the objective, locomotion is.

It is a curiosity that running at a fast speed requires considerable energy, but output is not very high. This low power output is because lateral translation of a body requires very little work. In fact, if we add work to the task of locomotion by increasing the vertical oscillations of the centre of mass with each stride, the energy cost of running will increase, even if speed of forward movement is not changed. Jake has a nice smooth running style with very little vertical oscillation of his centre of mass. Paradoxically, one way to improve economy of locomotion is to reduce power at a given speed. This applies not only to the idea that vertical oscillation of the centre of mass needs to be minimized, but also relates to modes of locomotion like skating, swimming, and cycling where resistance to forward locomotion is substantial. Reducing the resistance to forward locomotion while maintaining speed will reduce the power output but improve economy. This concept is further described in the next paragraph.

Measurable power output increases considerably when the speed of locomotion is substantial, like in cycling. Imagine someone cycling at a given speed in an upright position versus a more streamlined position at the same speed. Air resistance is greater in the upright position, so power output (resistance velocity) will be higher in this position. By bending over to a more streamlined position, air resistance will decrease and so will power output at the same velocity. Energy cost (rate of energy use) will also decrease, but not proportionally as much as power output. Reducing power in this way should reduce the energy cost to travel a given distance because speed is the same in both cases. Efficiency would go down, because power has decreased more than the energy cost, but economy would be improved. This interesting contrast between efficiency and economy is more relevant in race events with higher speed and therefore greater air resistance like cycling or speed skating. However, economy is still more important in running than efficiency is.

Tendon Stiffness/Compliance

It was recently revealed that energy cost of running was negatively correlated with Achilles tendon stiffness, and positively correlated with patellar tendon stiffness (Karamanidis and Arampatzis 2006). Stiffness is a quantitative measure of the force needed to stretch something (like a tendon). Stiffness is expressed as $N{\cdot}mm^{-1}$. Compliance is the inverse of stiffness: $mm{\cdot}N^{-1}$. The energy cost of running will decrease as Achilles tendon stiffness increases and will increase as patellar tendon stiffness increases. This observation reveals that tendon stiffness is an important determinant of energy cost, but the relationships are

complex. In some cases, stiffness is better for reducing energy cost and in other cases a more compliant tendon is desirable. The actual mechanism by which these differences can help keep the energy cost of running low is not clear, but probably relates to the increasing energy cost of a muscle contraction as velocity increases (Fletcher et al. 2013b). This concept dictates that if you keep the velocity of contraction low, you will minimize the energy cost.

How can high compliance in one tendon and high stiffness in another tendon decrease the energy cost of running? Every muscle that contracts during running will have an impact on the energy cost. Any structural property that can decrease the energy cost of a muscle contraction will contribute to an improved economy and lower energy cost per distance travelled. In general, an isometric contraction has a lower energy cost than a contraction that involves shortening, if the number of motor units and number of activations remain constant.

There are very good reasons that high tendon compliance in one muscle group (quadriceps), and low tendon compliance in another muscle group (triceps surae) will reduce energy cost of running. In both cases, these tendon properties influence the velocity of shortening, and therefore will also influence the energy cost of muscle contraction. The key is to recognize that these muscles behave differently during running.

In the case of the quadriceps muscles, the muscle-tendon unit is stretched at the beginning of the stance phase of running and shortens late in the stance phase. A compliant tendon is stretched during the early phase and shortens later, allowing the muscle fibres to remain at a relatively constant length during the whole stance phase. This mechanical response has the potential to conserve energy in two ways: 1) lower velocity of length change of the muscle will reduce energy cost, and 2) energy stored in the stretched tendon is released during the latter part of the stance phase, as force decreases, and this shortening tendon contributes to forward locomotion. This latter property represents a conservation of potential energy and is often referred to as energy transfer.

The gastrocnemius muscle does not likely have a stretch phase prior to shortening, so the discussion above does not apply to the muscles of the triceps surae. In this case, it is important to recognize that even during an isometriccontraction, muscle fibre shortening will occur if the tendon is compliant. Actual muscle fibre shortening can result from altered joint configuration (plantar flexion in this case), and from shortening to compensate for elongation of a tendon. A more compliant tendon will stretch more, requiring more shortening of the muscle fibres in a given time (greater velocity of shortening). In this case, a stiff tendon can reduce the need for shortening, and therefore reduce the energy cost of the muscle contraction (see Figure 16.5).

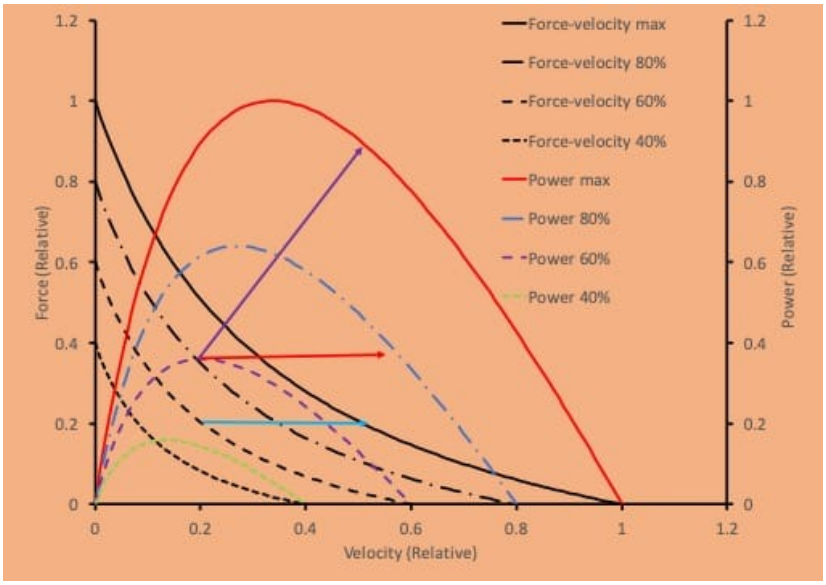


Figure 16-5 Force-velocity and power-velocity relationships. Four levels of the Force-velocity relationship and the corresponding power-velocity relationship are shown. As motor unit recruitment increases, maximal isometric force increases and so does maximal velocity of shortening. Maximum (product of force and velocity) also increases, and so does the velocity at which maximum power output occurs. The straight purple line shows the consequence of power output as motor unit recruitment increases from 60% to 100%, corresponding to changes in the force-velocity relationship shown in the straight blue line. The horizontal red line shows the need for recruitment if power output is to remain constant as velocity increases. Note that recruitment would also increase to change from an isometric contraction at 0.4 of maximum isometric force to shortening with the same load (straight dashed line). Increased motor unit recruitment will increase the energy cost of muscle contraction.

In addition to reducing the velocity of contraction, a stiff tendon will also restrict the magnitude of shortening needed by muscle

fibres, permitting the muscle to remain at a sarcomere length close to the optimum. This function of the tendon permits the force generating capabilities of the muscle to remain high, according to the force-length relationship of muscle.

Economy of locomotion, the energy cost to travel a given distance, is an important determinant of success in endurance running. When a runner can go a given distance using less energy, they maintain a given speed with a lower rate of energy use. Among other factors, economy is affected by muscle fibre type, tendon compliance, and efficiency of muscle contraction. Jake's regular run training will have brought about favourable changes in each of these factors, as well as other factors like stride length and frequency. All of these adaptations will contribute to his outstanding performance of the 10 km run.

Fractional Use of Maximal Oxygen Uptake

The term "fractional use of $\dot{V}O_2max$" is often given as a determinant of success in enduranceevents. If the closest competitor to Jake could maintain a higher % of his$\dot{V}O_2max$ at his (say, 88%), then he should be able to perform better than Jake. However, this statement would only be true if all other factors were equal between these two competitors. If his $\dot{V}O_2max$ was lower than that of Jake (perhaps 75 $ml \cdot kg^{-1} \cdot min^{-1}$), it would be fair to say that Jake would still be the better runner. An even more revealing way to use threshold would be to express it as a speed. The term critical speedis a term that takes this notion into consideration. In fact, the critical speed incorporates the metabolic rate that can be sustained for a long time and the economy of locomotion into one term, making this the best predictor of success in a 10 km run. To fully understand the determinants of success, it is important to consider these parameters independently and yet to understand that they all work together to dictate the best performance an individual is capable of.

Anaerobic Capacity

Understanding that the term "anaerobic" means "without the use of oxygen", it is useful to imagine that the term "anaerobic capacity" refers to the total amount of energy that can be derived without the use of oxygen. In practical terms, anaerobic energy refers to the energy that comes from net degradation of , and PCr, and from glycolysis leading to formation of or pyruvate that accumulate in the body. It is generally assumed that there is a constant (fixed) amount of energy that can be provided by these mechanisms for a given individual.

Maximal Accumulated Oxygen Deficit

In contrast with supra-threshold exercise, one of the unique features of the is that it represents a pseudo-steady-state. At or below this intensity of exercise, the physiological response is able to keep several blood and muscle constituents at a constant level. For example, blood and oxygen uptake remain constant. However, when the exercise intensity exceeds the threshold, an unsteady-state exists. The body will accumulate lactate and the oxygen uptake may continue to increase even if the speed of running does not change. Once he begins running at a speed greater than his critical speed, Jake is tapping into his limited non-aerobic energy reserves. Considering these energy reserves are limited, there is only a finite distance that he can run at a speed greater than the critical speed. This finite distance is equivalent to the intercept of the linear relationship between distance and duration shown in Figure 16.2. In this case, Jake can travel a distance of 285 m using exclusively non-aerobic energy. This anaerobic capacity is quite low in comparison with sprinters or even average active students; however, it is typical of highly trained distance runners. Knowing his economy of locomotion (see below), this distance can be used to calculate a finite amount of energy. This energy would be his anaerobic capacity.Anaerobic capacity can also be determined with the test described in this chapter's Research Feature.

It is important to realize that the energy associated with anaerobic capacity is over and above the aerobic energy associated with critical speed (or threshold). Consider the following example to see how these energy sources work together.

Jake has an anaerobic capacity(distance) of 285 m and has run most of his time-trial at his critical speed. If he has used only half of this capacity during parts of the race, he will have half of this anaerobic capacity still available for a finishing kick (142.5 m). Although non-aerobic energy would have been required during the initial minute or two (oxygen deficit), this energy is not considered part of the anaerobic capacity determined by the critical speed test. If Jake picks up the pace by 2 m·s-1 over the final 71 s, he could completely deplete his non-aerobic energy by the end of the time-trial and finish the time-trial in less time than if he had maintained his critical speed to the finish. The ability to increase the pace during the final stage of a race is dependent on whether or not the runner has expended their anaerobic capacity during the race. If no anaerobic energy is left, then an increase in pace is not possible.

Sprint Versus Endurance Performance

Automobiles designed for drag racing have different physical characteristics than those designed for longer duration events such as Formula 1 racing or the 24 hours of Le Mans Grand Prix. Similarly, the physical features of sprinters and endurance runners are quite different. For our purposes, a sprint event could be considered any race that is completed in less than 60 s. In sprint events, raw and maximizing the rate of energy delivery are critical. Power is defined as the rate of doing work (force·distance·time^{-1}). In endurance events which last longer than 60 s (and sometimes several hours or even days!), economy of locomotion and maintenance of a steady-state at a high sustainable rate of energy delivery are more critical. It is not surprising that the physical appearance and physiological characteristics of sprint runners (see Photo 16.3) are quite different from those of endurance runners. Sprinters require large powerful muscles while endurance runners want to minimize body mass. There are also qualitative differences. For example, sprinters have a large proportion of muscle fibres that are fast-twitch while endurance runners have a greater proportion of slow-twitch muscle fibres. A detailed description of these fibre-types was presented in Chapter 4. The implications of these fibre types will be described later in this chapter.



Photo 16-3 Sprinters look very different from distance runners. Looking at world-class runners who focus on sprints reveals very muscular and lean athletes. Height is a benefit, but apparently only to a limited extent. You rarely see sprinters who would likely excel at basketball. Distance runners, in contrast with sprinters, have very little muscle mass. Small muscle fibres allow diffusion exchange with the vascular system to a very short distance. Height is not an advantage, but long legs are. Pictured above on the left is Yohan Blake, the second fastest man ever over 100 m and 200 m. Above right is Eluid Kipchoge, the fastest man to ever cover the marathon distance, running 2:00:22 in the Nike Sub-2 project. Left photo by Nick Webb from London, United Kingdom (Yohan Blake Uploaded by Kafuffle) [CC BY 2.0 (https://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons. Right photo by Paul Hudson from United Kingdom (London Marathon 2018) [CC BY 2.0 (https://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons.

The greatest physiological differences between a sprinter and an endurance athlete can be summarized as the difference between an athlete who relies primarily on non-aerobic energy sources and one who relies on aerobic energy sources. The sprinter needs to provide at a very high rate for a short duration of time. This can be achieved most effectively by non-aerobic metabolism: glycogenolysis, glycolysis, and PCr hydrolysis, which provide energy very rapidly. All of these processes happen within the active muscles themselves. In contrast, the endurance athlete must rely primarily on aerobic metabolism. The maximum rate that energy can be made available with aerobic metabolism is just a fraction of the rate that can be attained with non-aerobic metabolism, but aerobic metabolism can be sustained for a much longer period of time. This is why the endurance athlete has a big heart, a highly developed vascular system, and a greater relative volume of in their muscles. Another physical difference between the two athlete-types is that endurance runners have a larger surface area-to-mass ratio than sprinters. This provides an advantage in heat dissipation, as described later in this chapter. Heat dissipation is not as important for sprinters because they do not sustain their intense exercise for as long as endurance runners do and are therefore at a much lower risk of overheating.

Oxygen Uptake Pattern in Ice Hockey

We have seen that the pattern of during a race or time-trial event has three phases: transition, steady level, and recovery. The pattern of oxygen uptake would be very different from this for an intermittent activity like that expected during an ice hockey game

(see Figure 16.6). In hockey, the players take turns participating in the game, and these bouts of physical exertion are separated by periods of rest while team-mates get their turn. While a player is on the ice, intensity of exercise is quite high, often in excess of the intensity associated with maximal oxygen uptake. When the metabolic cost of exercise exceeds the maximal oxygen uptake, it is referred to as supramaximal. This supramaximal exertion in hockey continues for 30-60 s and is commonly followed by a rest of 1-4 min. Remembering that oxygen uptake takes time to rise following an increase in exercise intensity (the transition phase), $\dot{V}O_2$ is unlikely to rise all the way to its maximum during the 30-60 s on the ice. The time to reach maximum is typically in excess of 60 s, and the player would normally be back on the bench before their $\dot{V}O_2$ reaches the maximal level. Alternatively, when a player does stay on the ice more than 45 s, the supramaximal intensity is not typically maintained, and $\dot{V}O_2max$ is not required. In this circumstance, it would be expected that $\dot{V}O_2$ would oscillate at a higher level, as in the third increase in $\dot{V}O_2$ shown in Figure 16.6. While sitting on the bench, the player's would fall exponentially towards the resting level, but would not reach resting oxygen uptake in the 2-4 min available before the next bout of exertion. This declining $\dot{V}O_2$ is called recovery $\dot{V}O_2$. The resulting oscillations in $\dot{V}O_2$ for the hockey player would look something like that shown in Figure 16.6. Note that the concepts of aerobic inertia andEPOC (excess postexercise oxygen consumption) apply to the hockey player, just as they do for Jake (see below). However, there is no "steady level" phase of $\dot{V}O_2$, and no discernible slow component of oxygen uptake. These are absent because the hockey player does not stay on the ice long enough to develop these.

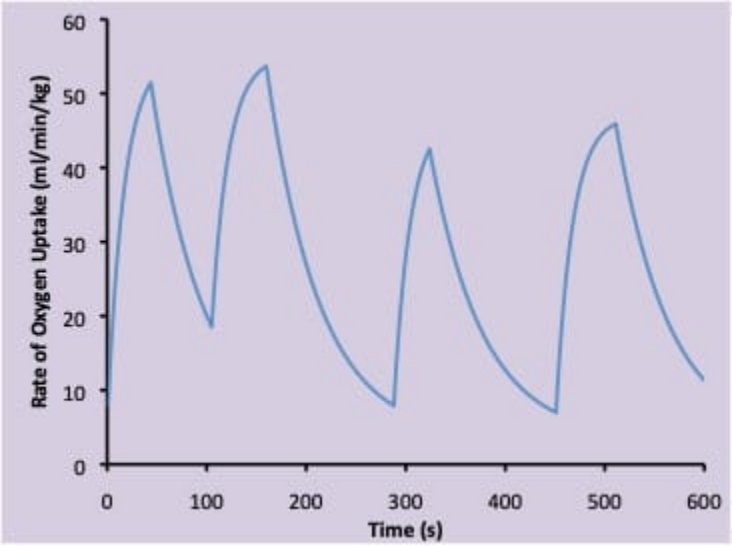


Figure 16-6 $\dot{V}O_2$ during a few shifts of hockey. This graph shows the rate of that would be expected for a hockey player with a oxygen uptake of 55 ml·kg^{-1}·min-1 (Ferland et al. 2021). The time constant for increase in $\dot{V}O_2$ is faster than the time constant for decrease. However, this hockey player does not stay on the ice long enough to reach $\dot{V}O_2max$, and does not stay on the bench long enough for $\dot{V}O_2$ to return to resting. For these reasons, $\dot{V}O_2$ increases continuously while the player is on the ice and decreases continuously when they return to the bench. The average $\dot{V}O_2$ for this 10 min period of time is just 27.7 ml·kg^{-1}·min^{-1}.

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Gender Feature: Male Versus Female Endurance Performance

When we are considering the determinants of success in athletic events, it is also relevant to consider other factors that determine male vs female differences in exceptional performance.

During the 1980's, experts predicted that women would surpass men in performance of long-distance events like the marathon, a running race that covers 42.2 km. This prediction was based on extrapolations of the history of marathon performance records. Figure 16.7 illustrates the history of world records for males and females for the marathon. It is obvious that prior to the 80's, marathon records of males and females were converging very quickly. This convergence was due to the rapid improvement of records for females, whereas the male world records improved at a much slower rate. It is easy to see how someone looking at the records in the 80's might surmise that females will one day overcome males in this sport. However, this extrapolation of information from thegraph (Figure 16.7) can obviously be misleading.

Since the 1980's, the rate of improvement of records for females has changed to a rate that is not substantially different from the rate of change of records for males. Although their performances are much more similar now than they were

just 30 years ago, it seems much less likely that females will eventually beat the males. While it is speculative to indicate why these rates of change have evolved in the way they have, it is worth considering what might have allowed females to improve much more quickly than males during the early 80's. The main reason is most likely sociological. As more females participate in sports events, there will be more great performances. You will notice that the world records for females in the marathon started in the 1950's, but men were doing the marathon much longer than that. Women were not allowed to compete in this distance until well after the men had achieved respectable performances. It is important to understand background relationships like the time course of world records before useful extrapolations of this data can be done.

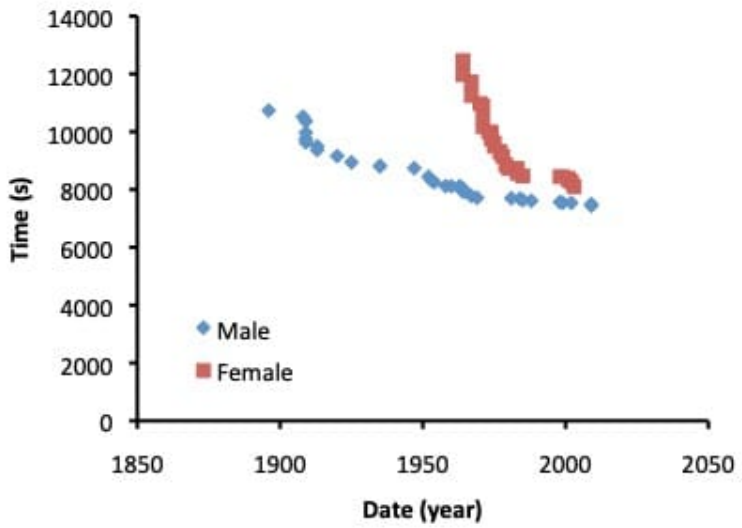


Figure 16-7 World records over the years for the marathon distance for males and females. The early apparent convergence of records has been replaced by a slow parallel slope towards better performance. The fact that there were no records for females before the early 1960's is an indication of social factors that restricted the distances that females were allowed to run.

In contrast with the comparison of male and female endurance runners, comparisons of top performances (not simply records) for male and female sprinters have revealed that the difference between the sexes is actually increasing. The increasing difference in performance is actually due to slowing of top performances of women in the past few years. This anomaly has been proposed to be a function of the decreased use of anabolic androgenic steroids among the world's top female sprinters. Anabolic steroids are in a class of drugs that promo

ynthesis, leading to increased muscle mass. These drugs are illegal to use without a medical prescription and are banned by the World Antidoping Agency, due partly to the unfair advantage obtained but also because of side effects with serious health implications.

This interesting speculation on changing drug use is described in detail at sportsci.org. Additionally, an interesting analysis of Masters records for a variety of distances is given at eliteracingsystems.com.

There are several key physiological differences between males and females that will always contribute to the differences that are evident in Figure 16.7. The principal factors that make males faster than females relate to sex-specific differences in muscle mass and mass. Females typically have more body and less muscle than males, though this difference is much smaller in elite distance runners than in the general population. In the case of a marathon race, having less fat is an advantage because fat does not contribute to the success in the event, rather, extra body fat increases the absolute energy cost of locomotion. Although females can add muscle mass with weight training, the use of anabolic steroids has been a tempting option for some. The recent move to eliminate this practice has resulted in slowing of sprint performances in world class female sprinters over the past several decades.

It is interesting to note that there appear to be no significant differences in running economy between males and females (Fletcher et al. 2013a). However, some investigators still claim that females have better economy than males (Mendonca et al. 2020), this observation relates to the inappropriate use of a slight grade on the treadmill in an attempt to simulate over-ground running, which has a slightly higher energy cost than running on a treadmill. This modification penalizes those with higher body mass, so males tend to have a higher energy cost of running than females when this is done.



Photo 16-4 Body and muscle mass are two major physical differences between male and female athletes. This contributes to lower aerobic capacity, strength, and in females compared to males of a similar training status. Trained females may outperform untrained males in these areas.

Aerobic capacity (maximal oxygen uptake), one of the key physiological determinants of success in endurance events, is typically expressed per kg of body mass. Muscle tissue contributes to the capability to use oxygen, but fat does not. For a given mass of muscle, a body with more fat will have a lower relative $\dot{V}O_2$max. This is evident in Table 16.1 when you compare Jake with Rachel. Note that Rachel's $\dot{V}O_2$max is less than Jake's, but still higher than Andrew's. As well, females typically have a smaller lung volume than their male counterparts, which results in a lower maximal absolute $\dot{V}_E$.

Now that we have considered some of the sex-specific differences and the differences between sprinters and endurance athletes, it is time to proceed with a discussion of the physiological responses during an incremental exercise test. This information will help put the determinants of success in perspective. The description of the physiological responses that is given below is presented with consideration for Jake's physical and physiological characteristics that are presented in Table 16.1.

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Physiological Response During a 10 km Time-Trial

This part of the chapter will focus on the physiological responses that would be expected for Jake if he were to begin the time-trial by accelerating to the speed that he hopes to maintain for the duration of the event and holds that pace until the finish. This is the strategy, called "even-splitting", that will permit Jake to complete the distance in the shortest possible time. It is important to realize that there are three distinct physiological phases to the race, deemed the transition, steady pace, and recovery phases. The physiological responses in the body are quite different during these three phases. In reality, a fourth phase might be relevant -the "end-spurt" or "kick", where competitors finish a race or time-trial with an increase in speed above the average speed maintained through-out the race.

Oxygen Uptake

Oxygen is necessary for aerobic metabolism. Oxygen is taken into the body via and pulmonary gas exchange (see Chapter 7) and is delivered via red blood cell circulation to the tissues throughout the body. Oxygen is needed in the for phosphorylation. Oxidative phosphorylation is a process that provides adenosine triphosphate**(**ATP**)** to meet the increased demand for energy by the active muscles. The rate of phosphorylation relies on the availability of oxygen. At rest, the body needs about 3.5-4.0 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ of to satisfy all energy requirements. When metabolic rate increases due to muscle contractions during exercise, there must be increased delivery of oxygen to the muscle cells. The measurement of $\dot{V}O_2$, and the various phases associated with the kinetics of oxygen uptake were presented in Chapter 6. These are relevant to the current chapter.

At the beginning of his time-trial, Jake is still in the recovery phase from his warm-up. His oxygen uptake at the start line will possibly have returned to his usual resting state. One of the key benefits of a warm-up is that the kinetics of oxygen uptake are accelerated by prior exercise (Burnley et al. 2002). This faster rise in rate of oxygen uptake will reduce the amount of energy that must come from non-aerobic metabolism during the transition phase following exercise onset. We will see from the determinants of performance described below that any time we can provide energy via oxidative metabolism rather than from non-aerobic metabolism, there is a benefit. This is particularly true during the transition to the steady pace because this reduces the oxygen deficit – the cumulative difference between total energy required and the energy provided by aerobic metabolism. This energy, referred to as the oxygen deficit**,** is provided by non-aerobic metabolism, and it is thought that there is a limited supply of non-aerobic energy. Any delay in using this limited supply can permit better performance later in the time-trial.

Supply and Demand

It is important to realize that in the skeletal muscles, there are two important factors that dictate the relative contributions of aerobic and non-aerobic metabolism: energy demand vs energy supply. Keep in mind that both metabolic systems are attempting to replenish as fast as it is used. We know that [ATP] does not decrease substantially during endurance exercise, so this balance is maintained by replenishment (via both aerobic and non-aerobic metabolism) matching ATP hydrolysis by the three keyATPase enzymes: actin-myosin-ATPase, Ca^{2+}ATPaseand Na^{+}–K^{+}ATPase. Skeletal muscle contraction dictates the demand, or rate, of ATP usage, and oxygen delivery and mitochondrial capacity determine the supply of aerobic energy. When [ATP] remains constant, non-aerobic pathways provide the additional ATP.

Transition Phase

At the beginning of his time-trial, Jake will accelerate to the speed that he wants to maintain for the majority of the distance. This acceleration will take only a few seconds which means his actual energy requirement will increase rapidly relative to the speed he is running, with extra energy needed for acceleration. In contrast, will have slower kinetics. The rate of $\dot{V}O_2$ will increase from just slightly greater than a normal resting level to a level that would nearly support the metabolic demand for energy after about 1-2 min. This increase in oxygen uptake is illustrated in Figure 16.8. The fact that oxygen uptake require s a minute or more to reach the steady-state is called aerobic inertia, but the mechanism of this slow increase is not clear.

Following exercise onset, it can take several minutes for oxygen uptake to reach a steady-state in a less well-trained individual. One view on the reason for this aerobic inertia is that the rise in oxygen uptake occurs slowly because non-aerobic energy pathways are activated more quickly, and these processes replenish nearly as fast as it is required in the muscles (Lanza et al. 2005). Alternatively, the more traditional view is that rapid acceleration by Jake to the speed that he will maintain during the time-trial will use ATP faster than aerobic metabolism can initially replenish it. The difference between these explanations is subtle. In one case, the slow rise in $\dot{V}O_2$ is due to the slowed decrease in [ATP], due to contributions from non-aerobic pathways. In the other case, the activation of non-aerobic metabolism is thought to compensate for a slow delivery of oxygen. Non-aerobic metabolism will make up the difference in either case, preventing much decrease in ATP concentration. Non-aerobic metabolism includes hydrolysis of PCr, and glycolysis leading to the formation of lactate. There is also some non-aerobic energy provided by a small net breakdown of ATP. However, the concentration of ATP within a cell is never permitted to decrease very much, as the cell's viability depends to a great extent on the availability of ATP. The non-aerobic energy makes up the oxygen deficit.

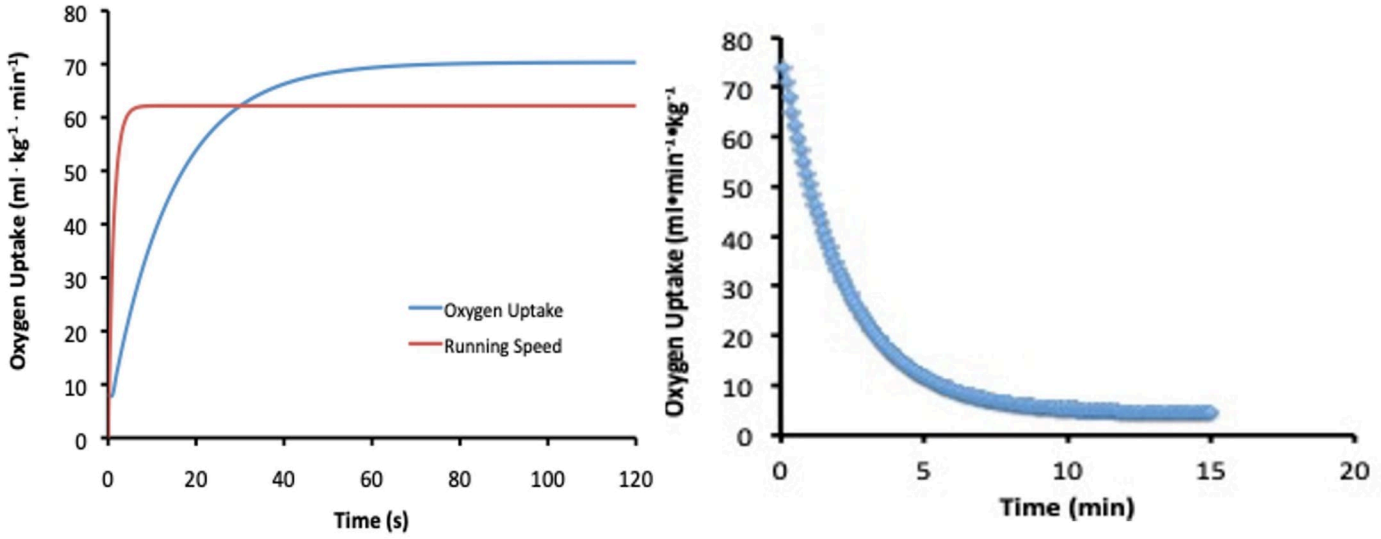


Figure 16-8 Oxygen Uptake during and following Jake's 10km Time-Trial. In this figure, Jake's is shown in blue and his speed ($m \cdot s^{-1}$*10) is shown in red (divide by 10 to get $m \cdot s^{-1}$). In the graph on the left, we see that his speed increases early and levels off before his oxygen uptake during the first 2 min. This graph shows that oxygen uptake is slow to rise to the level expected for the exercise. In the graph on the right, the first few min of the recovery period are shown. Once Jake stops running, his oxygen uptake decreases exponentially over the next several minutes. The approach to resting rate of oxygen uptake is very slow after 10 min.

As increases, the rate at which ATP is provided from the non-aerobic pathways is slowed, and concentration in the active muscles is maintained at a concentration just slightly lower than the resting value. Phosphocreatine (PCr) concentration decreases substantially during the time that oxygen uptake is increasing. This decrease is evidence that PCr hydrolysis contributes to the energy needed for the exercise. If the pace was slow enough to permit oxidative metabolism to provide all of the energy at steady-state, the oxygen deficit would only accumulate during the time that oxygen uptake was rising. However, since Jake will be running at a pace that is above his , the oxygen deficit will continue to accumulate throughout the time-trial, and by the finish should have reached what would be his oxygen deficit (see Chapter 13).

Steady Level Oxygen Uptake and the Slow Component

It should be kept in mind that the changes in and phosphocreatine concentration will only be in the motor units that are active. Running at his race pace will not initially require Jake to activate all of his motor units in the muscles that can be used for running. Also, of the active motor units, only a few will be maximally or near-maximally activated. For most of the time-trial, Jake will maintain a nearly constant oxygen uptake while running at his race pace which is just slightly faster than his critical speed (see intensity-duration relationship, illustrated in Figure 16.2). However, in spite of the constant pace, there will be a continued slow increase in oxygen uptake for the first 10-15 min. This slow increase in $\dot{V}O_2$ is due to the slow component of oxygen uptake. The slow component of oxygen uptake is the reason that the initial value for $\dot{V}O_2$ in the graph on the right side of Figure 16.8 begins at a higher value than indicated by the end of the graph on the left. The concept of the slow component of slow component of oxygen uptake was covered in Chapter 13 The actual mechanism responsible for this increasing $\dot{V}O_2$ is not fully understood. It could represent a decreasing non-aerobic contribution that is compensated for by an increasing $\dot{V}O_2$, 2017b) Most exercise physiologists believe the slow component is associated with fatigue, and the need to recruit less efficient (or in this case, less economical) motor units, and/or support an increasing minute ventilation, which is typical of continued exercise at an intensity above the . However, this seems unlikely.

During his time-trial, Jake is running at a pace just above the threshold. He will be hyperventilating and blowing off more CO_2 than his cells are producing. However, based on studies using radioactive-labeled substrates and understanding his level of training, it is reasonable to assume that he will provide no more than 30 % of his total required energy with oxidation of fats. Fats and/or COH can be labelled with radioactive carbon or hydrogen to allow monitoring of the amount of these substrates oxidized during exercise. This technique is not affected by the that alters pulmonary CO_2 output, so it offers precision even above the threshold.

When the mix of substrates metabolized and the 2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ are known, then the total amount of COH metabolized can be estimated. This is important because the total amount of COH available in the body can be a limiting factor in performance of endurance events (Karlsson and Saltin 1971). The

total amount of COHs that Jake needs for this time-trial (nearly 220 g; see Highlight Feature 16.1) would represent approximately 70-80% of the total COH stores (muscle and liver glycogen as well as free glucose) available to Jake prior to the time-trial. There would be no need for him to undergo procedures for "carbohydrate loading" or to consume COH during the event. Carbohydrate loading is a training and dietary procedure that is intended to enhance the total COH content of the body by increasing muscle glycogen storage (James et al. 2001; Nakatani et al. 1997).

Some of the substrates metabolized in Jake's muscle will come from stores within the active muscle cells, but some will be taken up from the blood flowing through the capillaries adjacent to these cells.

In order for Jake to get the substrate needed for oxidative metabolism into the blood where they can be delivered to and taken up by his active muscles, it is necessary to remove the and COH from storage sites in his body. Although Jake is very lean (see Table 16.1), fat is stored in Jake's adipose tissue in the form of triglycerides. Carbohydrate is stored in muscle and liver in the form of glycogen. Substrate mobilization, the process of getting these substrate**s** out of storage and into the blood, is triggered by hormones. Catecholamine, growth hormone, glucagon, and cortisol are critical hormones that perform this function. The concentration of these hormones in the blood can be increased in response to a decline in blood glucose. During exercise, the concentration of these hormones also increases in anticipation of Jake's need for more fuel for the time-trial. This is an example of a feed-forward control system.

The hormonal response during Jake's time-trial will permit him to use a mix of COH and as fuel for his run, without depleting his muscle stores of glycogen. He will experience increases in epinephrine, norepinephrine, glucagon, growth hormone, and cortisol in his blood. The response of these various hormones will be moderate, since the exercise intensity will be just slightly higher than his intensity at anaerobic threshold. The increases will be less than in a less trained individual running at the same speed. The consequences of the increase in catecholamine, cortisol, glucagon, and somatotropin concentrations will be an elevated rate of output of glucose from the liver such that Jake will not deplete his glycogen stores in the primary muscles used for running. However, glycogenolysis will still be going on in those muscles. Glycogenolysis will also be occurring in his inactive muscles, stimulated by the increased sympathetic nervous system. Since oxidative metabolism in these muscles is relatively low, will be produced and will move into the blood, contributing to the increase in blood lactate concentration.

In this example, we are assuming that Jake will run almost the entire time-trial at a constant speed. An alternative strategy would be for him to run at a slightly slower speed for much of the time-trial and pick up the pace near the finish. If he did this, he would experience a rise in oxygen uptake near the end of the time-trial. His$\dot{V}O_2$ can rise no higher than his maximal oxygen uptake, so his non-aerobic energy pathways must help replenish theATP that he uses, not only during the time that oxygen uptake is rising, but also after that if his demand exceeds the rate of his aerobic ATP replenishment.

The shape of the graphs in Figure 16.8 would be very similar for a female distance runner (like Rachel). However, the speed of running would be slower and the magnitude of $\dot{V}O_2$ would be correspondingly lower. There are several reasons contributing to the slower running for Rachel, some of which are not fully understood. One factor that contributes to the slower running is that Rachel has a higher energy cost of running than Jake has, shown in Table 16.1. Rachel requires 1.01 $kcal \cdot kg^{-1} \cdot km^{-1}$ whereas Jake can run while using just 0.96 $kcal \cdot kg^{-1} \cdot km^{-1}$. This means that even if they could maintain the same relative $\dot{V}O_2$ for the duration of a race, Jake would be going faster than Rachel. Rachel will also most likely have a higher body content than Jake. This means that her muscle mass represents a slightly smaller proportion of her body than Jake's muscle mass of his body. Since muscle mass is a primary determinant of absolute $\dot{V}O_2max$, this smaller relative muscle mass contributes to a lower $\dot{V}O_2max$.

Recovery Oxygen Uptake

The graph on the right in Figure 16.8 shows that Jake's $\dot{V}O_2$ begins to decrease once he completes the time-trial, but the decrease does not go immediately to his resting level. If Jake were to completely stop at the finish line, and lie down, his oxygen uptake would still not immediately return to a resting level. Even simply walking around, Jake's oxygen uptake would take considerable time to return to a steady rate that would resemble the $\dot{V}O_2$ at rest. This is evident when watching racers gasp for air after finishing a race. Jake's $\dot{V}O_2$ would decrease exponentially after exercise and would take 20-60 minutes to reach a constant level (Short and Sedlock 1997). Some research indicates that it would take even longer than this duration. The total oxygen uptake used by Jake's body once he completes the time-trial is called the recovery (also known as "excess postexercise oxygen consumption" orEPOC). $\dot{V}O_2$ does not return immediately to the resting level, because energy is needed during the recovery period that is greater than that normally needed at rest, and oxygen stores that were used during the exercise need to be replaced.

Several factors contribute to Jake's recovery including: returning oxygen stores (haemoglobin and myoglobin) to a resting state, resynthesis of ATP , PCr, and some glycogen, and restoration of ion gradients across cell membranes. The haemoglobin that

needs replacement is primarily that which is in the venous circulation. Arterial blood will have the normal amount of O_2 for the duration of the time-trial**.** At rest, Jake will have a venous oxygen content of about 15 ml of oxygen per 100 ml of blood. At the end of the time-trial, much of his venous blood will have an oxygen content of about 5 ml of oxygen per 100 ml of blood. Considering the venous circulation contains about 60% of the total blood volume and Jake's blood volume will be slightly greater than the normal 8% of body mass, perhaps 9%. It can be estimated that Jake has a venous blood mass of: $0.6 \cdot 0.09 \cdot 61$ kg or 3.29 kg. Here, 0.6 represents 60% of total blood volume and 0.09 represents 9% of body mass. Normally, blood is expressed as a volume and it can be assumed that blood has a density of 1.0, so 3.29 kg would be equal to 3.29 litres. The difference in oxygen content that needs to be replenished is 10 ml of O_2 per 100 ml of blood, or 100 ml of O_2 per litre. The total amount of oxygen uptake needed to replenish oxygen stores in the blood is 3.29 litres of venous blood 100 ml of O_2 per litre of blood or 329 ml of O_2.

A similar calculation could be made for the O_2 needed to replenish depletion of O_2 bound to myoglobin. Myoglobin is an oxygen-binding protein in muscle which is similar in many ways to haemoglobin. Myoglobin is also the molecule that gives meat a red colour. A few assumptions are necessary for this calculation. To estimate how much oxygen is needed to restore the resting state of O_2 bound to myoglobin, we need to know how much muscle is involved in the task, what the concentration of myoglobin is in the active muscles, and how much oxygen was associated with this myoglobin. Human muscles have about 2 mg of myoglobin per g of muscle. This value would be a little higher in Jake because there is more myoglobin in muscle fibres with a higher oxidative capacity, and Jake, as an elite endurance athlete, has a higher proportion of type I and type IIa fibres than most people. The total amount of oxygen stored in Jake's active muscle would be about 0.17 mmoles per kg of muscle. If we assume that Jake has 20 kg of active muscle during his run, then this amount of muscle would have about 3.4 mmoles of oxygen. This is equivalent to 75 ml of oxygen. Since myoglobin typically loses about 70% of its oxygen during vigorous exercise, Jake would probably require just 50 ml of oxygen to replenish his myoglobin oxygen stores.

It takes several minutes for to return close to the resting level, so the metabolic needs of the ventilatory muscles would also contribute to EPOC. Similar to ventilation, cardiac output slows gradually. Extra energy is needed to maintain this extra work of the heart. The elevation in body temperature may also contribute to the elevation of during the recovery period. One of the factors that could contribute to a prolonged elevation of post exercise oxygen uptake is the need for energy to restore tissue structures that might have been damaged during the exercise. This restorative energy requirement could include muscle as well as other tissues. The repair process takes hours to days to complete but raises metabolic rate such a minor degree that it may be difficult to detect. Resynthesis of glycogen to the pre-exercise level requires dietary consumption of COH and may take 24-48 hours to fully compensate for the glycogen used during the time-trial.

Pacing Strategy



Photo 16-5 Pacing strategy is of extreme importance in distance running races. Though maintaining a steady pace (as Jake does in this example) is the most metabolically efficient way to run a race, in reality there are often many fluctuations as leaders change, strategy and race tactics are employed, and athletes accelerate with a finishing "kick".

For the example shown in Figure 16-8, Jake maintains a constant speed for the duration of the time-trial. This strategy is not a typical pacing strategy. Often, 10 km races are run with variable pace such that the metabolic rate is not constant but rises and

falls with the pace. The leader of the race may change several times. For any runner to be able to do their best, it is important that they not allow the pace to fall below the critical speed, which is considered to be the speed that is supported by aerobic energy. This inappropriate strategy (slower than critical speed) would represent a loss of energy that would otherwise contribute to completing the race. The major difference between aerobic and non-aerobic energy is that the former represents a potential maximal rate, and the latter represents a fixed amount of energy. Brief excursions to a higher intensity that uses more non-aerobic energy results in less of this energy being available for later. However, any running at an intensity that is less than critical speed results in a lost opportunity to use energy that cannot be recovered (Fukuba and Whipp 1999).

Another important point of strategy is to realize that the energy cost to run 10 km relies on running *just* 10 km, which requires running exclusively on the inside lane of the track. Any running outside the inner lane will result in running a longer distance. Considering the energy cost is expressed "per km", any increased distance in a real-life scenario will represent a requirement for more energy.

The minimum time for Jake to run 10 km can be estimated from his critical speed test. This estimation is illustrated in Figure 16.9. Here, the blue line represents his hyperbolic fit to the results of his critical speed trials (same as in Figure 16.2). The brown line depicts the time needed to cover 10 km at a given speed. The intersection represents the fastest speed that Jake can maintain long enough to complete 10 km. This speed is the pace he should use for his time-trial. Kindly note that any measurement of a threshold or critical speed will have some error. This means that the intersection here is simply an estimate and is not expected to be precise.

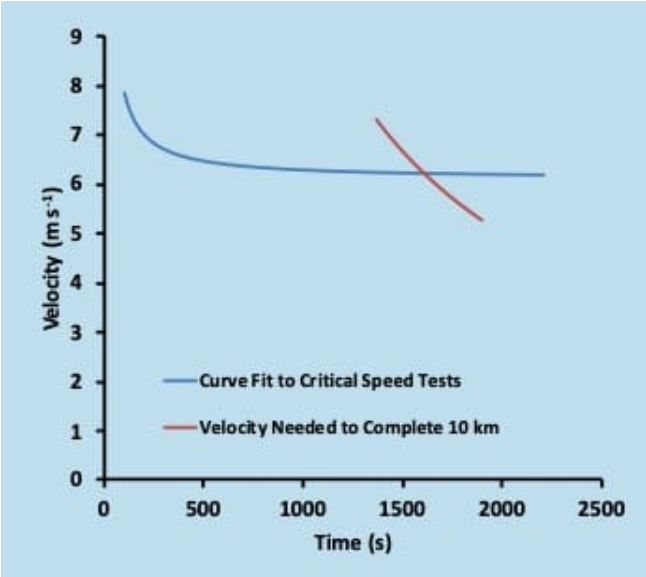


Figure 16-9 Prediction of best pace. The blue line represents the fit of a hyperbola to Jake's critical speed test results. The brown line is the time to complete 10 km at the corresponding speed of running. The intersection represents the best performance that Jake can achieve. This intersection corresponds with a time of 26.8 min.

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Highlight Feature: Calculating Carbohydrate Needs

The total amount of COH required for Jake's time-trial can be calculated, because we know the energy cost per km. In this example, it is assumed that 70% of the energy is coming from COH metabolism.

Jake has an economy of 0.96 $kcal \cdot km^{-1} \cdot kg^{-1}$. We know that he weighs 61 kg, and the time-trial distance is 10 km. Therefore:

$$\text{Total energy required} = 0.96\ kcal \cdot km^{-1} \cdot kg^{-1} \cdot 10\ km \cdot 61\ kg = 585.6\ kcal \quad \textbf{Equation 16-2}$$

Some of this energy will come from non-aerobic sources. The total (determined by integration of the oxygen uptake shown in Figure 16.8 and multiplying by body mass) would be 114.04 litres. This cumulative oxygen uptake with a corresponding respiratory quotient (RQ) = 0.91 would require 95.11 grams of COH, and 18.25 grams of for the aerobic energy. This amount of COH would come primarily from muscle glycogen, but some would come from blood glucose. Blood glucose would be replenished by liver glycogenolysis, and gluconeogenesis. The fat would come from a mix of intramuscular fat and plasma free fatty acids. Plasma free fatty acids will have been mobilized from adipose tissue, and/or the liver.

Considering an anaerobic distance of 285 m, the non-aerobic supply of energy would account for (285 m/10000 m 585.6 kcal) 16.7 or only 2.85% of total energy cost. Assuming this energy comes from PCr hydrolysis, and glycolysis leading to formation, Jake would require additional glucose. This glucose would come primarily from muscle glycogen.

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Cardiovascular Response

In order to deliver the oxygen that is required in Jake's exercising muscles and to remove the CO_2 that is produced, it is necessary that his cardiac output increase well above the resting level. This greater cardiac output is achieved by increases in heart rate and stroke volume. The time course of increase in cardiac output parallels the increase in oxygen uptake that is shown in Figure 16-8. However, the magnitude of increase in Jake's cardiac output is considerably smaller than his increase in oxygen uptake. While oxygen uptake increases about 20-fold from the true resting level, cardiac output increases only 7-fold. This increase in cardiac output will allow the greater increase in because the arterio-venous oxygen difference also increases (approximately 3-fold). In addition to increasing the cardiac output, there is a redistribution of blood flow that allows most of the extra cardiac output to go to the exercising muscles. These concepts were presented in Chapter 8.

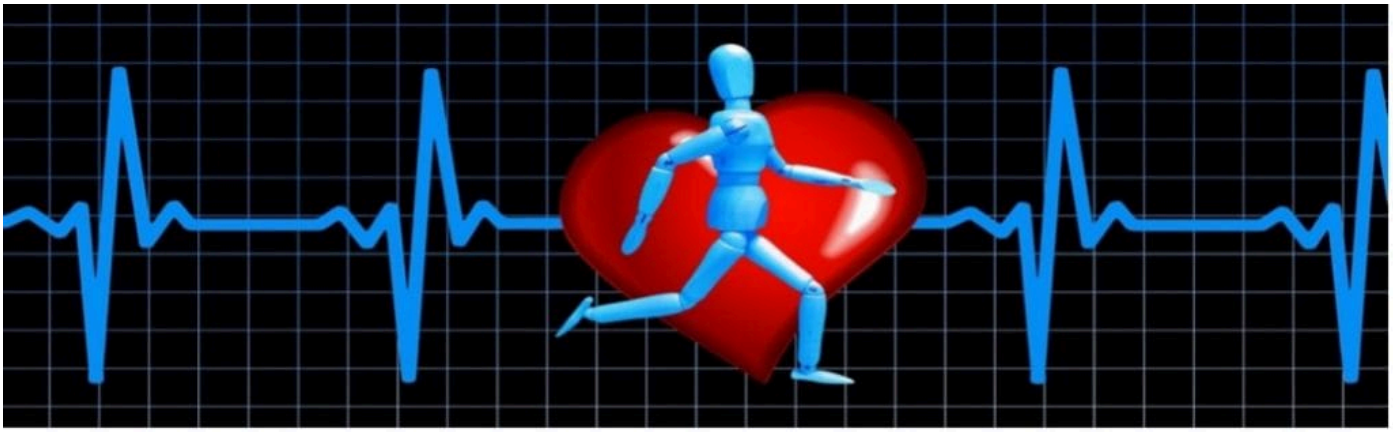


Photo 16-6 Heart rate is greatly affected by movement. Not only will exercise elevate heart rate, but also anticipation of exercise due to sympathetic nervous system activity. This helps to provide appropriate blood flow quickly following exercise onset.

Heart Rate

At the start line of his time-trial, Jake will very likely have a heart rate much higher than his normal resting value of 45 beats·min^{-1}; perhaps about 90 beats·min^{-1}. This elevated heart rate can be attributed to a combination of an anticipatory response and incomplete recovery from his warm-up. The sympathetic nervous system has already kicked in, causing the heart rate to be elevated. Once the time-trial begins, his heart rate will increase further to reach a rate of 170 beats·min-1. His heart rate will gradually increase to nearly 180 beats·min^{-1} at the end of the time-trial in spite of the constant pace he will maintain. This gradual increase is called the cardiac drift (see Chapter 8).

It should be noted that Table 16.1 indicates that Jake will have a lower maximal heart rate than the reference male student. This lower heart rate is not simply because Jake is older. It is not unusual for a highly trained athlete to have a relatively low maximal heart rate. The reason for this lower maximal heart rate is not known. In spite of the lower maximal heart rate, Jake can achieve a higher maximal cardiac output than Andrew because he has a larger heart and therefore can eject a larger stroke volume.

Stroke Volume

At rest, Jake has a cardiac output of 4.2 L·min^{-1}, and a heart rate, (HR) of 45 beats·min^{-1}. Therefore, his stroke volume (SV) would be 93.3 ml·beat^{-1} (see equation 16.3). Early in the time-trial, his stroke volume will have risen to 140 ml·beat^{-1}. Stroke volume would remain fairly constant at this level for the remaining duration of the time-trial. During this time, as$\dot{V}O_2$ rises to nearly a maximal level, stroke volume may stay the same or increase only slightly.

$$\text{Cardiac Output } (\dot{Q}) = SV \cdot HR = 4.2 \text{ L} \cdot \text{min}^{-1} = 0.0933 \text{ litres} \cdot \text{beat}^{-1} \; 45 \text{ beats} \cdot \text{min}^{-1} \quad \textbf{Equation 16-3}$$

The increase in stroke volume is accomplished primarily by an increase in the ejection fraction, which is compensated for by an increased rate of filling. The ejection fraction is the proportion of the end-diastolic volume (EDV) that is ejected, or stroke volume (SV) divided by EDV. For example, if at rest his end-diastolic volume is 148 ml he would have an ejection fraction of:

$$\text{Ejection Fraction} = SV \cdot EDV^{-1} = 93.3 \cdot 148^{-1} = 0.683. \quad \textbf{Equation 16-4}$$

During the time-trial, Jake's ejection fraction would increase to nearly 1. Ejection fraction is illustrated in Figure 16-10.

Figure 16-10. Ejection fraction is the difference between end-diastolic volume and end-systolic volume. Here two hearts are shown; one is at end-diastole and the second one is at end-systole.

While running at a speed of 6.22 m $\cdot$ s^{-1}, Jake will be generating a lot of heat which must be dissipated in order to avoid a dangerous situation like heat stroke. This heat comes from the chemical reactions that occur in his muscles to provide the energy for crossbridge formation, force generation, and ion pumping. Some of the heat comes from the reactions associated with glycolysis and oxidative metabolism, and some comes at the time each is hydrolyzed. The total heat generated can be estimated with a few basic assumptions. This estimation of heat generation during exercise is shown in Highlight Feature 16-2. This calculation shows that if there was no heat loss from the body, Jake's body temperature could increase to above 46C! Jake could not survive with a body temperature this high, so it is imperative that he has a way to get rid of this extra heat.

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Highlight Feature: Calculation of Heat Generation During Running

The total heat generated in the body can be estimated with a few known facts. We will illustrate this heat generation, with what we know about Jake. Jake has a running economy of 0.96 kcal·kg^{-1}·km^{-1}. Some of this energy is used to overcome friction (track and air), but most of it is released as heat within the body. The total available energy would be his economy times body mass times distance:

$$0.96 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{km}^{-1} \cdot 61 \text{ kg} \cdot 10 \text{ km} = 585.6 \text{ kcal} \quad \textbf{Equation 16-5}$$

The definition of a is "the energy required to increase the temperature of 1 kg of water from 14°C to 15°C". Assuming the body is like water, and ignoring the absolute temperature condition, the effect of this much energy transduction is calculated. The first calculation below assumes that all energy is converted to heat. The total change in temperature of Jake would be the total energy (kcal) divided by his mass:

$$585.6 \; 61 \text{ kcal} \cdot 1°\text{C} \cdot 61\text{kg}^{-1} = 9.6°\text{C} \quad \textbf{Equation 16-6}$$

If all energy used during the time-trial contributed to heat accumulation, and assuming Jake started the race with a core body temperature of 37°C, Jake would have a body temperature of 46.6°C at the end of the time-trial. This estimation assumes he cannot dissipate the heat that is generated and that any warm-up he performed prior to the time-trial did not increase body temperature above resting body temperature. Of course, this body temperature (46.6°C) would prove to be lethal, and we know that running a 10 km time-trial is not lethal, so it is unrealistic. In reality, the total heat generated will be less than this estimate, but not by much. However, Jake is also capable of releasing heat to the atmosphere, preventing this diabolical increase in body temperature.

> In reality, some of the energy associated with running is used to accomplish work, but that would be very small during level ground running. This "work" would be the force needed to overcome air and ground resistance. Taking this work into consideration, efficiency might be 2-3%, so the total heat generated would be just 2-3% less than the total given above. In this case, it would be between 567.5 and 568.0 kcal. It has been pointed out that running requires oscillations in velocity and in height of the centre of mass. Both of these circumstances can be calculated as work. However, they are oscillations, meaning that any increase in the centre of mass is countered by a decrease; work done is balanced by work done on the body by gravity. For this reason, the net mechanical work associated with oscillation in centre of mass and velocity during running is zero.

Environmental conditions will dictate the ability to lose the heat that is generated within the body. These mechanisms of heat dissipation are described in Chapter 9 and include: radiation, conduction, convection, and evaporation. Factors that will affect the magnitude of involvement of these mechanisms include the following: air temperature, relative humidity, sources, and sinks for radiative heat loss or gain, sweat rate, body surface area, and body mass. Any heat generated that is not lost from the body will cause an increase in body temperature. This increase in body temperature would amount to 1-2C during Jake's 10 km time-trial but could be as high as 4C during a marathon.



Photo 16-7 Sweating is one of the primary mechanisms of heat dissipation. Sweat evaporation helps to cool the body; however, care must be taken to avoid dehydration from loss of fluids.

The amount of sweatevaporation that Jake needs to lose the extra heat he is producing can be estimated. The heat of evaporation of water is 540 $kcal \cdot kg^{-1}$. Jake would have to evaporate just a little over 1 litre of sweat to lose this heat. If we assumed that he could dissipate half of the heat by conduction and convection, then only half of the heat would have to be lost by evaporation. However, some of the sweat will drop from his body or remain in his clothes at the end of the time-trial, and this sweat will contribute to fluid loss but not heat loss. He may still need to lose a litre of sweat to lose the excess heat generated in his muscles. This rate of sweat loss is within Jake's capability.

In shorter duration events, heat dissipation is less of a problem even though heat is produced at a higher rate. For a 100 m sprint, heat may be generated at a rate that is 3-4 times greater than during the 10 km run, but this high rate of heat generation is sustained for just 10 s. The total heat generated would be sufficient to increase body temperature of a larger sprinter (80 kg) by less than 1 degree. During this sprint, muscle temperature would increase more than 1 degree because there would not be time during the time-trial for blood flow to redistribute this extra heat. The heat dissipating mechanisms are illustrated in Figure 16-11.

Blood flow is an important component of the temperature regulation process. The increased muscle blood flow that Jake would have during the time-trial is important not only for providing O_2 and removing CO_2, but also for removing this excess heat that is generated in the active muscles. The blood in the veins leaving his leg muscles will have been warmed by the passage through the heated muscles. Heat losing mechanisms rely on getting some of the warmed blood to the skin. The skin will be warmed by this blood flow and cooled primarily by convection and evaporation. A large body surface area to mass ratio will facilitate this heat dissipation.

Sweating to facilitate heat loss from the body would result in relative dehydration. If Jake was sweating at a rate of 2 litres per hour, he would lose 1.5% of his body mass during the time-trial. This fluid loss could compromise his performance and his ability to regulate temperature, so it would be important for Jake to take advantage of water stations during the time-trial.

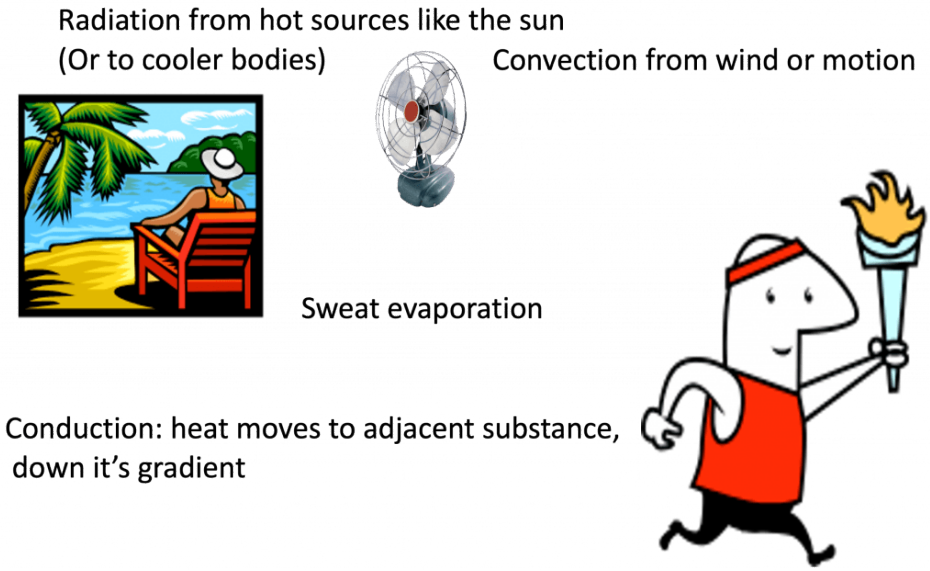


Figure 16-11 Integration of heat dissipating mechanisms. Heat is lost or gained by four primary mechanisms: radiation, conduction, convection, and evaporation. The most important mechanisms during exercise are convection and evaporation. Radiation and conduction can result in gaining heat from the environment.

In this section of the Chapter, we have been reminded that one of the byproducts of exercise is the generation of heat. During the 10 km time-trial, Jake will generate nearly 580 kcal of heat energy. Heat is produced in the muscles in conjunction with metabolism. The excess heat must be transported from the muscles to the skin by blood flow, and dissipated to the environment by convection, conduction, evaporation, and radiation. Of these mechanisms, evaporation is the most important for keeping Jake at a safe temperature.

Ventilatory Response

We breathe to keep the partial pressure of carbon dioxide fairly constant within the alveolar spaces of the lungs. These partial pressures allow exchange of O_2 and CO_2 between the air and the blood. As increases and cardiac output increases, there will be a need to increase to maintain these partial pressures of O_2 and CO_2.

Jake would have a resting ventilation of about 5-6 litres. Integration of heat dissipating mechanisms. This ventilation would involve a tidal volume of about 500 ml and a breathing frequency of 10-12 breaths·min^{-1}. The ventilatory response in exercise and its regulation was presented in Chapter 7. Prior to the time-trial, his ventilation would still be elevated due to his warm-up, but not by much. Jake would experience an increase in ventilation, immediately on initiating the time-trial, and a further increase would occur in conjunction with the increase in $\dot{V}O_2$ (see Figure 16-8). By the time his oxygen uptake had reached 4.3 litres·min^{-1}, his ventilation would be well over 100 litres·min^{-1}. This ventilation would be achieved with a tidal volume of about 2.0-2.5 litres, and a breathing frequency of 50-55 breaths·min^{-1}. This rate of ventilation is more than adequate to provide the O_2 Jake needs. Hyperventilation, then, will result in a rate of removal of CO_2 from the body that exceeds the metabolic production of CO_2. Total body content of CO_2 will decline. The decline will assist with buffering of H^+ (see Chapter 9).

Blood Lactate

Lactate is formed in muscles as a consequence of glycolysis. The enzyme dehydrogenase converts pyruvate to and at the same time converts NADH to NAD^+. This oxidation of NADH actually permits glycolysis to continue because glycolysis requires NAD^+. Any time there is formation of pyruvate, there will be formation of lactate in proportion to the concentration of pyruvate. Lactate is transported out of muscle cells by a monocarboxylate transporter, and H^+ is co-transported with lactate. From the extracellular

space, lactate can get into adjacent muscle cells or can get picked up by capillaries. An increased rate of glycolysis will result in increased production of lactate and increased appearance of lactate in the blood.

At rest prior to the time-trial, Jake will likely have a blood lactate concentration that is slightly higher than the concentration usually detected at rest. A normal resting level would be less than 1 mM, but Jake would have a value that was 2-3 mM. This level of "resting" blood lactate would not be due to inadequate oxygen delivery, but due to the increased sympathetic tone that would accompany the anticipation of his impending time-trial. It was presented in Chapter 6 that circulating epinephrine will activate glycogenolysis, and this increased glycogenolysis will lead to increased glycolysis. An increased rate of glycolysis will result in an accumulation of blood lactate.

Once the time-trial begins, the rate of glycolysis will be further increased, and non-aerobic metabolism will provide the additional energy needed while increases to the steady level. Blood lactate will continue to increase throughout the time-trial because Jake would be running at an intensity just above his threshold. The muscular production of lactate results in appearance of lactate in the blood. Some lactate will be taken up in less active tissue and oxidized. This process contributes to removal of lactate from the blood. However, the rate of appearance of lactate in the blood would just slightly exceed the rate of removal, so lactate will accumulate in the blood throughout the time-trial. Figure 16.12 illustrates the factors that contribute to or reduce the accumulation of lactate in the blood. By the end of the time-trial, Jake's blood lactate concentration would be about 8 mM.

Factors that add lactate to the blood. Factors that remove lactate from the blood

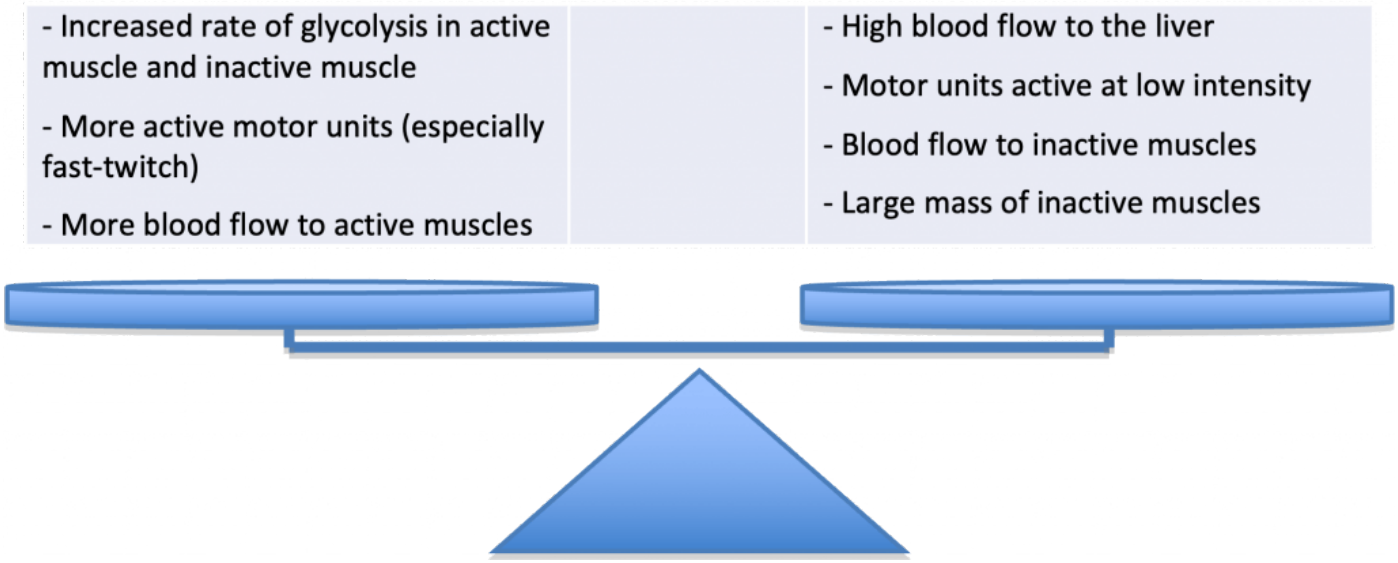


Figure 16-12 Lactate balance in the blood. Factors that determine the balance of lactate in the blood. When the rate of appearance of lactate in the blood is equal to the rate of disappearance from the blood, blood lactate concentration will remain constant.

Disturbance to Ion Homeostasis

There are three key ions that are particularly important in the body and are affected by exercise: H^+, Na^+, and K^+. Each of these is critical for homeostasis and important in the ability to continue exercising. The concentrations of these can vary substantially during Jake's 10 km time-trial. The general scheme of ion exchange during exercise is illustrated in Figure 16-13. This diagram illustrates the concentrations gradients for the major ions, and the direction of transfer between the muscle cells and the extracellular space. Further exchange must occur between the extracellular space and the vascular system, across capillary walls. In Figure 16-13 an active muscle cell is shown along with an inactive muscle cell.

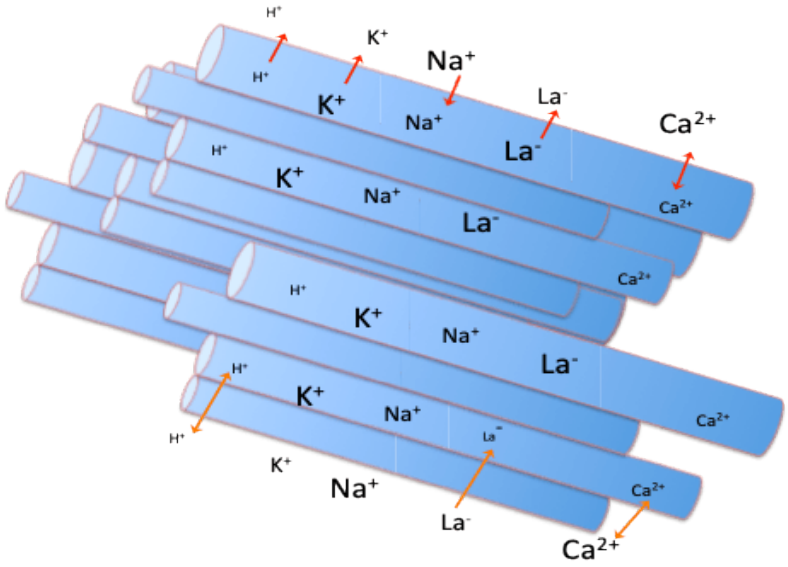


Figure 16-13 Ion exchange during exercise. This diagram presents muscle fibres (tube-shaped structures) and extracellular space. Ion concentrations are crudely represented by the size of the letters. The top muscle fibre represents the situation in a very active muscle fibre: K+ moves out, down it's concentration gradient; Na+ moves in down it's concentration gradient; Lactate (La-) moves out down it's concentration gradient, taking H+ with it (against its very small concentration gradient). Most of the Ca2+ movement in muscle occurs between sarcoplasmic reticulum and cytoplasmic space. This exchange is not shown. There may also be some net loss of Ca2+ from active muscle but this has not been studied in detail. The muscle fibre near the bottom is an inactive fibre. This fibre is taking up La- and H+.

H+

During repeated contractions as would occur during high intensity running, muscle cells become acidotic. Muscle pH can decrease from a resting value of about 7.0 to 6.5 or lower, depending on the intensity and duration of exercise. During the 10 km time-trial, Jake's leg muscles that are used for running might experience a decrease in pH to about 6.7. There is some uncertainty about the source of H^+ that causes this acidity, but the general consensus is that it arises as a result of glycolysis and accompanies production of lactate.

The consequence of acidosis is also a controversial issue. For decades now, muscle and exercise physiologists have believed that acidosis was a primary cause of muscle fatigue. There is certainly a strong correlation between muscle acidosis and fatigue, but correlations can be misleading. A correlation can indicate a cause and effect relationship but can also occur if there is a third (or more) related variable(s). For example, consider the strong relationship between lightning and thunder. It could be that lightning causes thunder, or some other event causes both. In the case of lightning and thunder, it is another event that causes both.

Early research on the effects of acidosis on muscle revealed that Ca^{2+}sensitivity is decreased by acidosis (Fabiato and Fabiato 1978). This means the force exerted by a muscle cell will be lower when the same [Ca^{2+}] is achieved. This was very strong evidence that acidosis contributed to fatigue in skeletal muscle. However, more recently it has been shown that this decreased Ca^{2+} sensitivity is temperature dependent. At room temperature or lower, Ca^{2+} sensitivity is decreased by acidosis. When the muscle is warmed up to above 30C (a more physiological temperature), acidosis has little or no effect on Ca^{2+} sensitivity (Pate et al. 1995) In a genuine twist to the story of acidosis and muscle contraction, it has recently been suggested that acidosis may help delay the fatiguing consequences of repetitive muscle contractions (Pedersen et al. 2005). This delay is thought to be accomplished by an acidosis-induced opening of Cl^-channels. The increased membrane permeability to Cl^- permits the cell membrane to be kept in a polarized state, opposing the depolarization that would otherwise occur with the decreased K^+ gradient described below.

Na+ and K+

With each activation of muscle and nerve, there is an exchange of Na^+ and K^+, such that there is a tendency for extracellular K^+ to increase in concentration and [Na^+] to decrease. Intracellular concentrations of these ions will change in the opposite direction. Activity of the Na^+/K^+ pump + pump will minimize the impact of action potentials on these concentration changes. However, there

are other K^+channels, in addition to the fast K^+ associated with action potential repolarization, which may open during repetitive muscle contractions. This will lead to loss of K^+ from active muscle cells, and accumulation of K^+ in the extracellular space. This increased extracellular K^+ will result in increases in plasma [K^+]. An accumulation of K^+ in extracellular spaces will result in depolarization of muscle and nerve membranes and decreased excitability. Excitability is necessary for continued activation, so accumulation of K^+ in the extracellular space may contribute to the decreased muscle activation that is known as fatigue.

Summary of Physiological Responses

During much of the 10 km time-trial, Jake is able to maintain an that is 83.7% of his $\dot{V}O_2$max. He achieves this oxygen uptake with a of 110 L·min^{-1} and a heart rate of 170 beats·min^{-1}. This exercise intensity corresponds with an intensity just greater than his . Blood would gradually increase through-out the time-trial. He generates considerable heat but is able to dissipate most of it by convection and evaporation. During the repeated muscle contractions associated with running, Jake will generate H^+ within his exercising muscles, and some of this H^+ will be lost from the cell, contributing to a general acidosis. Some of this H^+ will be buffered in the muscle cells, and some will be buffered in the blood or by CO_2 loss from the body. Jake will also lose K^+ from his muscles cells, and this will result in increased extracellular and plasma [K^+]. There is also a potential muscle cell gain of Na^+. According to Figure 16.2, Jake completes the 10 km in 26.8 min.

In this chapter, we have seen the impact of running this time-trial on the physiological responses, and we have discussed what factors have given Jake the ability to complete this distance in such a short time. The focus of this discussion was on the ability to deliver energy to the muscles and mechanisms that keep the energy cost low. These are the physiological determinants of athletic performance. An overview of the consequences of the ability to deliver energy can be obtained by consideration of the intensity-duration relationship. Many of these principles apply to a number of sports.

Summary

Jake is a highly trained athlete. He has trained long hours for several years, and this training in combination with his favourable genetic background allow him to perform at a very high level. He has a high and low energy cost of running. His Achilles tendons are stiff, and his patellar tendons are compliant. He has a high proportion of slow-twitchmotor units contributing to his high $\dot{V}O_2$max and favourable economy of running. His body has a very low proportion of and this contributes to his very good economy. Jake is able to run the 10 km distance at a high fraction of his $\dot{V}O_2$max and he can tolerate a substantial disturbance to his homeostasis. The one determinant of success in athletic events that is not well developed for Jake is his anaerobic capacity. This is a common issue for endurance athletes and represents a trade-off for a higher proportion of slow-twitchmotor units.

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3.6: Chapter 17 - The Child- Responses and Adaptations to Physical Activity and Training



Photo 17-1 Children, while they may dress like tiny adults, should not be viewed as tiny adults by exercise physiologists.

Learning Objectives

After reading this chapter, you will be able to:

- Understand the rationale and methods used in scaling physiological responses to body size;
- Describe the integrated physiological responses to aerobic activity and endurance training in children and adolescents;
- Describe the physiological responses and adaptations to intense activity and recovery from intense exercise in children and adolescents;
- Describe the physiological responses and adaptations to resistance training in children and adolescents;
- Describe the thermoregulatory responses of children during exercise in the heat;
- Summarize the effects of physical activity on bone strength during childhood and adolescence;
- Discuss the interactions between training and normal growth and development.

Key Terms

aerobic exercise, allometric scaling, anaerobic performance, central (or cardiac) response, development, endurance training, growth, maturation, morphological adaptations**,**muscle composition, strength, neurological adaptations, neuromuscular activation, oxygen uptake, peak bone mass**,** peripheral (or vascular) response, puberty, recovery, ratio standards, resistance training, thermoregulation.

Introduction

This chapter describes the responses and adaptations of children to exercise and training. The pattern of these responses, for the most part, is similar to that of adults. The magnitude of these responses, however, may differ due to the effects of growth and maturation on body structures, and differences in body size and proportions. Physiologically, children are not small adults. This chapter highlights the quantitative and qualitative differences between children and adults in their responses to acute exercise and to aerobic training, including cardiovascular, pulmonary and metabolic changes. It then discusses the responses to anaerobic activity and resistance training from both the metabolic and neuromuscular perspective, highlighting new issues related to

children's neuromuscular activation and motor unitrecruitment. The child-adult differences in the physiological responses during exercise in the heat, and their implications are also discussed. Special attention is paid to the effects of athletic training on growth, and the positive effects of exercise on bone accretion in children and adolescents.

Case Presentation

Rachel has lived her whole life in Vancouver. She learned in elementary school that she could run better than most of the boys. This information provided her with sufficient motivation to pursue a career in long distance running. She has never tried any other sport. She has competed internationally, representing Canada, for the past 12 years. Last year, she returned to her goal of completing university. She is studying Kinesiology at UBC. While in University she volunteered to participate in a study that compared the physiological responses to moderate, prolonged exercise between girls and women of similar fitness level. Rachel was matched in terms of fitness (size-adjusted maximalaerobic capacity) with Anna, an 11 years old girl, and both were asked to run for 30 min on a treadmill at a constant speed of 8 $km \cdot hr^{-1}$. The results indicated that Rachel's average rate of oxygen consumption during the run was higher than Anna's (1.5 $L \cdot min^{-1}$ versus 1.3 $L \cdot min^{-1}$, respectfully), reflecting that Rachel used more energy to run at the same speed as Anna. However, Anna was the one who had trouble completing the exercise bout. Her heart rate was higher, and her breathing was much "harder". Apparently, Anna was working a lot harder than Rachel. That is, at same submaximal speed, Anna was working much closer to her maximal oxygen uptake. There is an easy explanation for these results. When the results were adjusted to reflect the difference in body mass, Rachel's energy cost of running was 1.09 $kcal \cdot km^{-1} \cdot kg^{-1}$, corresponding to 40% of her maximal oxygen uptake while Anna was using energy at a normal rate for a young female runner (1.7 $kcal \cdot km^{-1} \cdot kg^{-1}$) corresponding to 77% of her maximal oxygen uptake. This speed of running would be an easy jog for Rachel, but a difficult challenge for Anna.

In the above example, a child and an adult were asked to complete an identical task. Although both individuals were considered good runners, the child had difficulty completing the task, while the adult completed it without any trouble. This example illustrates that when examining the physiological response to exercise in children and adults, size differences must be taken into account.

Accounting For Differences In Body Size

Children's response to exercise differs from that of adults largely, although not only, because of this size difference. This chapter highlights the child-adult differences in the response to exercise, which are *beyond* that due to differences in body size. But in order to do that, one must somehow account for size differences. That is, in order to adequately compare the physiological response to exercise between children and adults, or longitudinally during growth and development, one must "normalize" for variation in body size.



Photo 17-2 Children of different body size; a factor that must be considered by exercise physiologists.

There are different approaches to account for differences in body size but unfortunately, there is no one ideal, optimal or "correct" method. The method used will depend on the question asked.

The most commonly used approach to scaling in pediatric exercise physiology is the ratio standards. Its common use is attributed mainly to its simplicity. That is, the physiological variable of interest (e.g.,$\dot{V}O_2$peak), is divided by a measure of body size (e.g., mass). A variety of anthropometric measures of body dimensions have been used as the denominator in ratio standards. For example, when comparingaerobic capacity between individuals of different sizes, body mass is often used in the denominator of (see case above). However, when comparing aerobic capacity between lean and obese individuals, it is preferable to use fat-free mass as the denominator, because the extra body does not contribute to oxygen uptake. Jumping ability is determined mainly by leg power. Therefore, when comparing jumping ability between individuals of different body size, body mass is often used as the denominator for leg power. However, when comparing strength between individuals, it is preferable to express strength relative to muscle cross-sectional area (see Section on strength later in this chapter). Body surface area is often used when adjusting metabolic rate for body size. The rationale for this is related to thermoregulation. That is, since animals of widely differing body size are characterized by the same body temperature, and since body heat loss is related to body surface area, it makes sense to relate resting metabolic rate, which controls body heat production, to body surface area (see section on thermoregulation later in this chapter). Likewise, the cardiovascular measures (cardiac output and stroke volume) have also traditionally been expressed relative to body surface area. This approach is based on empirical data of the cardiovascular response to exercise in children, although its biological rationale is not clear (see section on cardiovascular response later in this chapter).

Ratio standards, while simple to use and to conceptualize, are arguably, not always appropriate. The underlying assumption in using ratio standards is that the physiological variable of interest is linearly related to the denominator. Often, this is not the case (see (Rowland, 2005)(Nevill, 1997; Welsman and Armstrong, 2008) for details). Allometric scaling is recommended when the physiological variable of interest is related to body size in a *non*-linear fashion. For example, Welsman and Armstrong (2000) demonstrated that in their sample of children, $\dot{V}O_2$peak was related to body mass to the of 0.66 ($mass^{0.66}$), rather than to mass to the of 1 ($mass^{1}$), which is the commonly used normalizing factor. Allometric scaling involves using the equation $Y=aM^b$, where a is the physiological variable of interest, M is the body dimension (e.g., mass), and b is the scaling exponent. Y is the normalized physiological variable of interest. The main limitation of allometric scaling, besides its mathematical and conceptual complexity relative to ratio standards, is the fact that scaling exponents for a given physiological variable calculated in different data sets vary widely. For example, empirically derived scaling exponents for VO_2peak in children vary from 0.37 to 1.07, depending on the sample size, body composition, training status, etc. (Rowland, 2005). Moreover, it is not clear what exponent actually reflects the "true" biological relationship between VO_2peak and body mass. Therefore, while the use of allometric scaling in pediatric exercise physiology is increasing, the use of ratio standards is still prevalent. The optimal way to account for, or "normalize" for body size is yet to be determined. Therefore, for the most part, ratio standards are used in order to compare between children and adults. The body dimension used in the denominator varies in accordance with the physiological variable and the question of interest.

Aerobic Exercise and Training

Aerobic exercise Aerobic exercise and endurance training have long been associated with multiple health-related physiological outcomes in adults. It is assumed that in children, as in adults, aerobic exercise is associated with short- and long-term health outcomes. Therefore, the physiological responses to prolonged exercise and to aerobic training in children are of particular interest. Generally, the pattern of responses and adaptations to aerobic exercise and training in children are similar to those of adults. The magnitude of these responses is, however, different due to the effect of growth and maturation of body structures, and differences in body size. This section presents the main physiological responses associated with aerobic activities, *highlighting the differences in response between children and adults*.

Cardiovascular Responses

The role of the cardiovascular system during exercise is to deliver blood to the working muscles**,** providing O_2 and removing CO_2 from the muscles, transporting nutrients and hormones**,** retaining osmotic and acid-base balance and regulating the body's core temperature (see Chapters 9 and 11). Traditionally, the cardiovascular response to exercise has been studied via the Fick equation:

$\dot{V}O_2 = \dot{Q} \cdot (a - \bar{v})O_2$ difference or $\dot{V}O_2 = SV \cdot HR \cdot (a - \bar{v})O_2$ difference **Equation 17-1**

Where $\dot{V}O_2$ is the rate of oxygen uptake, $\dot{Q}$ is the rate of cardiac output, which is determined by the stroke volume (SV) and heart rate (HR), and $(a\text{-}\bar{v})O_2$ is the arterio-venous oxygen difference. The central (or cardiac) response is reflected by changes in $\dot{Q}$, SV, andHR, while the peripheral (or vascular) response at the level of the tissue is reflected by changes in $(a - \bar{v})O_2$ difference. The central and peripheral factors determining $\dot{V}O_2$ have been previously described in detail in the commentary by Bassett and Howley (Bassett and Howley, 2000).

In children, as in adults, all components of the Fick equation increase during exercise, reflecting the fact that as exercise intensity increases, the body makes central and peripheral adjustments in order to supply its energy needs. However, the magnitude and the rate of change in the cardiovascular response differ between children and adults.

Cardiac Response

In an elegant study by Turley and Wilmore (Turley and Wilmore, 1997), children's cardiac response to different exercise intensities was compared to that of adults. This study demonstrated that at an exercise intensity requiring a given

$\dot{V}O_2$, children's stroke volume was lower and heart rate was higher than in adults. This makes sense, since the heart of the child is smaller and therefore end-diastolic volume is smaller. However, the higher heart rate did not quite compensate for the lower stroke volume, resulting in a slightly lower cardiac output.

On the other hand, it is also important to understand the comparative responses of children during a given *absolute* (e.g., running at 8 $km \cdot hr^{-1}$) versus *relative* (e.g., 60% of $\dot{V}O_2max$) exercise intensity. As can be seen in Figure 17.1a, as exercise intensity increases, heart rate increases in both children and adults. Importantly, at any given absolute exercise intensity, children's heart rate is higher compared with adults. For example, at 10 $km \cdot hr^{-1}$, a young man's heart may beat at 180 $beats \cdot min^{-1}$, whereas a 9 year-old boy's heart may beat at close to 200 $beats \cdot min^{-1}$. Likewise, children's maximal heart rate is also higher compared with adults. For example, it is not uncommon for children to reach a heart rate >200 $beats \cdot min^{-1}$ during very intense exercise. In adults, on the other hand, an observation of such a high heart rate is quite rare. Figure 17.1b demonstrates that if children and adults are running at the same relative intensity, the difference in heart rate is very small. For example, at an exercise intensity of 80% $\dot{V}O_2max$ (vigorous intensity), children's heart rate is just slightly greater than adults' (e.g., 180 vs. 174 $beats \cdot min^{-1}$). The implication of this age-related difference is that if heart rate is to be used as an indicator of exercise intensity, as is often recommended for adults, one must keep in mind that for children, the targeted heart rate, as well as the heart rate at a given relative exercise intensity would be higher.

With the increase in exercise intensity, there is also an increase in stroke volume. However, unlike the linear increase in heart rate, stroke volume increases from rest to moderate intensity exercise (about 50% of maximum workload) and plateaus thereafter. This appears to be the case in both children and adults, although, of course, in view of children's smaller body size, and, thus, their smaller left ventricular mass (LVM), stroke volume is much lower in children. Indeed, any increases in body size with growth

are accompanied by increases in the size of the heart, particularly, LVM. These increases are associated with the enhanced stroke volume observed with growth and (Daniels et al., 1995; de Simone et al., 1998; Dekkers et al., 2002).

Cardiac output, which is the product of heart rate and stroke volume, increases linearly with exercise intensity, in both children and adults (Figure 17.1c). At any given exercise intensity, a child's cardiac output will be much lower than an adult's. For example, in the case of Anna and Rachel, while running at 8 $km \cdot hr^{-1}$, Anna's cardiac output was 11.5 $L \cdot min^{-1}$, while Rachel's cardiac output was 18 $L \cdot min^{1}$. Even when running at the same relative intensity, children's cardiac output is lower than that of adults. For example, in a study comparing 7 year-old boys with young men, while running at about 55% of $\dot{V}O_2max$, the boys' cardiac output was about 8.5 $L \cdot min^{-1}$, while that of the men's was about 19.3 $L \cdot min^{-1}$ (Figure 17.1c) (Turley and Wilmore, 1997). However, as is the case for stroke volume, cardiac output at rest and during exercise is also size-dependent. Therefore, child-adult comparisons require size adjustments. Traditionally, the cardiac response is adjusted to body surface area, resulting in stroke index ($ml \cdot beat^{-1} \cdot m^{-2}$) or cardiac index ($ml \cdot min^{-1} \cdot m^{-2}$). Indeed, when cardiac index is considered, there are no appreciable differences between children and adults exercising at moderate to vigorous intensity (Drinkwater et al., 1977; Rowland et al., 2008). The reasoning for adjusting the cardiac response to body surface area likely relates to the thermoregulatory perspective. That is, cardiac output and blood supply to the periphery (to the skin) are instrumental to maintain body temperature, especially at rest (see section on thermoregulation). On the other hand, it may be argued that cardiac output and blood supply is also necessary for the proper functioning of all organs, specifically, working muscles during exercise. Hence, some researchers believe that, during exercise, the cardiac response should be adjusted to body mass, or fat-free mass (reflecting muscle mass). When cardiac output is related to the fat-free mass, children's cardiac output is higher than that of adults', at any given relative exercise intensity (Figure 17.1d). For example, in the study by Turley and Wilmore (1997), while running at 55%

$\dot{V}O_2max$, the boys' cardiac output, relative to their fat-free mass was about 340 $ml \cdot min^{-1}$, while that of the men was only about 275 $ml \cdot min^{-1}$.

Figure 17-1 The increase in heart rate (a,b) and in cardiac output (c,d) in children (dotted line) and in adults (solid line), expressed as a function of absolute exercise intensity (a) and relative exercise intensity (percentage of $\dot{V}O2max$) (b,c,d). (Data based on Turley and Wilmore, 1997).

In summary, similar to adults, children's cardiac output increases with increasing intensity of exercise, in proportion with the increase in stroke volume and heart rate. These responses reflect the increase in $\dot{V}O_2$ (Fick equation).At a given exercise intensity, as well as during maximal exercise intensity, children display higher heart rate lower absolute stroke volume and lower absolute cardiac output. The lower cardiac output does not necessarily denote cardiac insufficiency. Rather, when adjusted for body size, no appreciable differences in cardiac output are observed between children and adults (Vinet et al., 2002). Therefore, from the perspective of the physiological cardiac response, despite their smaller size and different activity habits, children are *not* disadvantaged in the performance of aerobic activities.

Peripheral Vascular Response

In accordance with the Fick equation, the peripheral response to exercise is reflected in the arterio-venous oxygen difference. In other words, in the amount of oxygen extracted from the blood by the working muscles ($(a - \bar{v})O_2$ difference). This section discusses age-related differences in $(a - \bar{v})O_2$ difference, which are dependent on blood flow to working muscles (vascular response) and on muscle enzymatic activity. Age-related differences in the vascular response, namely blood pressure and total peripheralresistance, are also discussed in this section. Muscle enzymatic activity is discussed later in the chapter.

During exercise there is an increase in blood flow to exercising muscles, cardiac muscle and skin, while there is a decrease in blood flow to internal organs and non-exercising muscles. Similar to adults, the blood flow redistribution in children facilitates greater oxygen transport to active muscle. The percent cardiac output that is directed to the exercising muscles appears to be higher in children than adults (Koch, 1980; Leclair et al., 2012). Specifically, Koch (Koch, 1980) showed that post-exercise blood flow to the vastus lateralis was greater in children than young adults. When the same children were tested 1 and 4 years later the difference had decreased, indicating maturation towards the adult response to blood flow distribution (Koch, 1980). These findings have been supported by Pichler et al. (Pichler et al., 2004), who demonstrated that forearm blood flow at rest decreased with increasing age (from 7 to 17 years old).

Furthermore, at an exercise intensity requiring a given $\dot{V}O_2$, children also demonstrate slightly greater $(a\text{-}\bar{v})O_2$ difference than adults. This may be attributed to the fact that a greater proportion of their cardiac output goes to the exercising muscles, although disparity in muscle enzymatic activity may also affect $(a\text{-}\bar{v})O_2$ difference. During submaximal exercise, children's higher $(a\text{-}\bar{v})O_2$

difference partially compensates for their lower cardiac output (relative to adults).

At rest, both diastolic and systolic blood pressure is lower in children than in adults (Paradis et al., 2004). During dynamic aerobic exercise there is an increase in the systolic blood pressure but no change in diastolic blood pressure. This response pattern is similar in children and adults (Rowland and Whatley Blum, 2000). The magnitude of increase in systolic blood pressure depends on the intensity of exercise with no apparent differences between children and adults. A possible exception to the latter may occur during high intensity static exercise (e.g., isometric or 1RM lifting), during which the increase in systolic blood pressure is less in children compared with adults (Turley et al., 2002).

Total peripheral resistance (TPR) is directly proportional to mean arterial blood pressure (MAP) and inversely proportional to cardiac output.

$$TPR = MAP \cdot \dot{Q}^{-1}$$ **Equation 17-2**

During exercise, total peripheralresistance decreases, due to vasodilation in working muscles. While this response is similar in children and adults, the absolute TPR is higher in children at any absolute or relative exercise intensity, reflecting their smaller blood vessels. However, it should be remembered that TPR during exercise should be related to the blood supply in the working muscles. Thus, at a given relative exercise intensity, when TPR is scaled to muscle mass, TPR is *lower* in children compared with adults (Rowland and Whatley Blum, 2000; Turley and Wilmore, 1997). The implication of this lower TPR, is that at a given relative work rate, muscle blood flow is higher in children.

In summary, during aerobic exercise, children demonstrate a lower blood pressure response and lower size-adjusted total peripheralresistance. Their $(a\text{-}\bar{v})O_2$ difference is somewhat higher during submaximal exercise. Therefore, in terms of the peripheral vascular response children are certainly not disadvantaged in the performance of aerobic activities, and in fact, may even have a slight advantage.



Photo 17-3 Kids out for a paddle, exercise for children often does not match the traditional view of exercise.

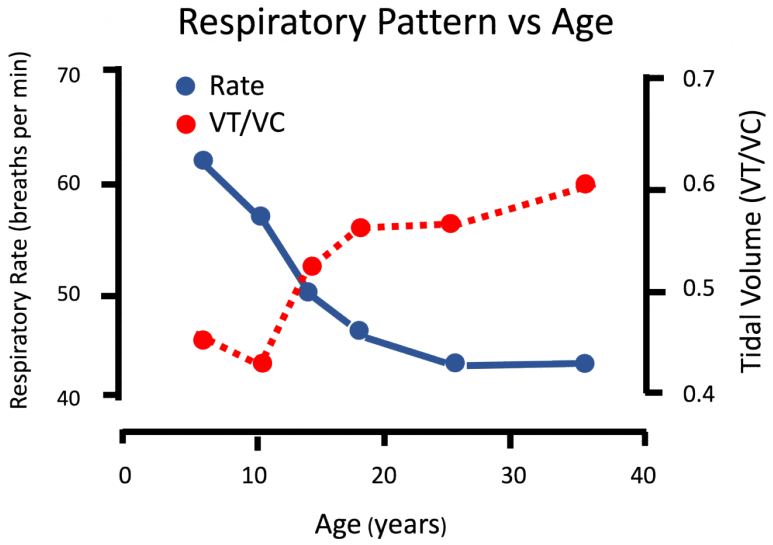
Pulmonary Responses

Pulmonary ventilation ($\dot{V}E$), or the amount of air flowing in and out of the lungs every minute, is lower in children compared with adults at rest and during a given exercise intensity. However, when $\dot{V}_E$ is adjusted to body size (for example, per body mass), girls exhibit a *higher* ventilatory response compared to women during submaximaland maximal exercise (Rowland and Green, 1988). This could also be assumed for boys since pre-pubertal girls are of similar size and pulmonary response as boys. This higher size-adjusted $\dot{V}_E$ is due to age-related differences in the airways. That is, gas exchange takes place in the alveoli. Therefore, all airways leading to the alveoli do not serve in gas exchange and are therefore termed anatomical dead space. In children, the length (or volume) of these airways, where no gas-exchange occurs, is greater relative to the volume of the alveoli, when compared with adults.

Due to their greater relative anatomical dead space, children's fast breathing is considered relatively shallow. In terms of the

measured lung volumes and capacities, this means that the percentage of vital capacity used in each breath (tidal volume) is lower in children, making their breathing pattern inefficient. This breathing inefficiency is reflected in children's lower tidal volume and higher breathing rate at any given submaximal load (Mercier et al., 1991; Rowland and Cunningham, 1997). Importantly, this means that during exercise, the amount of air needed to breathe in and out in order to supply the body with a given volume of oxygen (the ventilatory equivalent, $\dot{V}_E \cdot \dot{V}O_2^{-1}$) has been found to be greater in children than in adults (Macek and Vavra, 1985). Other studies (Rowland and Green, 1988) also found higher $\dot{V}_E/\dot{V}O_2$, and thus, inferior breathing efficiency during submaximal running (at a given speed), in girls compared to women. In other words, there is some evidence that the cost of breathing in children is higher than in adults. During exercise, the cost of breathing adds to the cost of exercise. That is, at any given exercise intensity, this higher cost of breathing contributes to the higher oxygen cost (or$\dot{V}O_2$) observed in children compared with adults. This is especially apparent during locomotion-type of exercise (Bar-Or and Rowland, 2004).

The ventilation determines the gas exchange in the lungs. Despite their lower breathing efficiency, children's ventilation is higher than adults', at any given exercise intensity (Rowland and Cunningham, 1997). This higher ventilation may be due to a lower CO_2threshold drive for respiration. Importantly, children's higher ventilation is beneficial for clearing of CO_2 during exercise.



-1. Breathing rate is about 62/min at age 5 and decreases to about 46/min at age 18. From age 18 to 25, there is a further small decrease to about 42 breaths per min. Tidal volume is about 0.44 of vital capacity in the young boys and increases to 0.57 by age 18, with only a small further increase to 0.6 at age 35. " width="1024" height="743"> **Figure 17-2 Respiratory rate (empty circles) and tidal volume** relative to vital capacity (VT/VC) (filled circles) during walking on a treadmill at 5.6 $km \cdot hr^{-1}$, as a function of age (adapted from Malina et al. 2004 – p.240, figure 12.5, based on data from Robinson 1938).

In summary, compared with adults, children demonstrate an exaggerated ventilatory response to a given metabolic rate, likely due to differences in airway dimensions or proportions, resulting in inefficient breathing (Gratas-Delamarche et al., 1993). Despite their inefficient ventilation, children's ventilation is greater than adults', allowing them to benefit from greater gas exchange during exercise.

Aerobic Capacity

Aerobic capacity is a multifactorial quality. The indicators ofaerobic capacity include: maximal aerobic ($\dot{V}O_2$max), endurance performance, time to exhaustion, and lactate or ventilatorythreshold. Amongst those, maximal aerobic is the most often used indicator of aerobic capacity in both children and adults. There are many factors that determine the

$\dot{V}O_2$max in humans including genetics, fitness and sex, as well as the various cardiovascular variables discussed previously (e.g., maximal cardiac output, $(a\text{-}\bar{v})O_2$ difference). These are similarly relevant to children and adults. However, when age-related differences are of interest, body size and maturity must also be considered.

Absolute $\dot{V}O_2$max (in L of oxygen per minute) increases during growth and (Figure 17.3a). For example, a "typical"$\dot{V}O_2$max for a healthy young man may be 3.5 $L \cdot min^{-1}$. For a 10 year-old healthy boy, a "typical" $\dot{V}O_2$max may be 1.4 $L \cdot min^{-1}$. This age-related

difference reflects the differences in body size and specifically, in the exercising muscle mass.

While there are no available “normal values” for$\dot{V}O_2$max in children, due to differences in measurement protocols used in different studies, numerous studies have demonstrated an increase in $\dot{V}O_2$max with an increase in age. In boys, this increase appears to be linear. However, in girls, $\dot{V}O_2$max appears to increase linearly until the age of 12-14 years, at which time it plateaus until young adulthood (Figure 17.3a). This pattern is evident in the many cross-sectional studies, as well as in the few longitudinal studies conducted on this topic in Europe and North America (Malina et al., 2004). At every age, boys $\dot{V}O_2$max is higher than girls', with the difference increasing as boys and girls get older. The apparent sex-related difference in $\dot{V}O_2$max among young children is a reflection of boys' larger heart size (specifically, LVM), resulting in higher stroke volume and cardiac output. As children mature, specifically during the pubertal period, the disparity in hemoglobin content and muscle mass between boys and girls increases. This is reflected in the increasing sex-related difference in $\dot{V}O_2$max with increased age.

Since $\dot{V}O_2$ is largely dependent on the size of the active muscle, $\dot{V}O_2$max is usually adjusted for body mass. Size-adjusted $\dot{V}O_2$max, expressed in mL of oxygen·kg^{-1}·min^{-1} does not change with increasing age in boys, while in girls, $\dot{V}O_2$max decreases, particularly after the age of 12-14 years (Figure 17.3b). In other words, in males, maximal aerobic capacity, relative to body mass, does not differ between boys and men. Typical $\dot{V}O_2$max values for healthy, normally active boys and men are 45-50 mL·kg^{-1} · min^{-1}. In females, girls exhibit higher $\dot{V}O_2$max compared with women. Part of the explanation for this age-related difference is the fact that women have a higher percentage of body (and a lower percentage of muscle mass), compared with girls. This difference in body composition is not taken into account when adjusting

$\dot{V}O_2$max to general body mass. When $\dot{V}O_2$max is adjusted for fat-free mass, no appreciable differences exist between girls and women (Rowland, 2005).

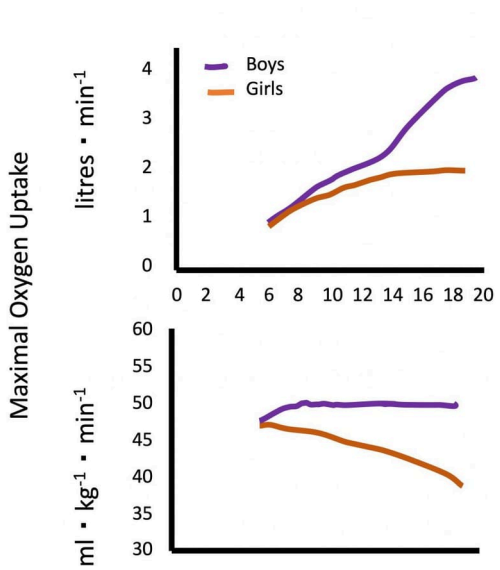


Figure 17-3 Maximal oxygen uptake in boys and girls, with an increase in age; a) absolute $\dot{V}O_2$max; b) $\dot{V}O_2$max relative to body mass.

Metabolic Response –

Fuel utilization during exercise

During exercise, energy is supplied to the working muscles via aerobic and anaerobic metabolic pathways. As exercise intensity increases, there is a shift from aerobic to anaerobic metabolism (see Chapter 6). This shift in metabolism is often reflected by an accumulation of lactate in the blood above a certain exercise intensity, termed the lactatethreshold (see Chapters 10 and 16). At any given relative exercise intensity (e.g., 50% of maximal aerobic power), as well as at maximal exercise intensity, the blood lactate concentration in children is lower than in adults. For example, in adults, the lactatethreshold is said to occur around a blood lactate concentration of 4mM. While this value may vary among individuals, the equivalent threshold concentration in children is suggested to be around 2.5mM (Williams and Armstrong, 1991). More importantly, when expressed as a percentage of $\dot{V}O_2$max, the lactatethreshold in children occurs at a higher percentage of maximal aerobic (%$\dot{V}O_2$max) compared with adults.

For example, Anderson and Mahon (Anderson and Mahon, 2007) reported that among 9-10 year old boys, the lactatethreshold occurred at 64% of$\dot{V}O_2$max whereas in young adult men with similar aerobic fitness (similar $\dot{V}O_2$max), the lactatethreshold occurred at 55% of$\dot{V}O_2$max.

The determination of the lactatethreshold requires invasive measurements. Therefore, the ventilatory threshold is often used to estimate the exercise intensity at which the rate of production of lactate exceeds the rate of removal (see Chapter 10). As is the case with the lactatethreshold, the ventilatory threshold is also reported to occur at a higher percentage of $\dot{V}O_2$max in children compared with young adults. For example, Klentrou et al. (Klentrou et al., 2006) reported that 10-11 years old boys had higher ventilatory threshold than the adults (65% versus 58% of $\dot{V}O_2$max) of similar $\dot{V}O_2$max. Similarly, in the study by Anderson and Mahon (Anderson and Mahon, 2007), boys' ventilatory threshold occurred at 68% of $\dot{V}O_2$max, compared with men's 59% of $\dot{V}O_2$max.

Recall that one of the differences between aerobically trained and untrained individuals is the higher lactatethreshold in the former (see Chapter 10). Along these lines, it may be argued that children's higher lactatethreshold may indicate an ability to rely on aerobic metabolism at higher intensities of submaximal exercise.

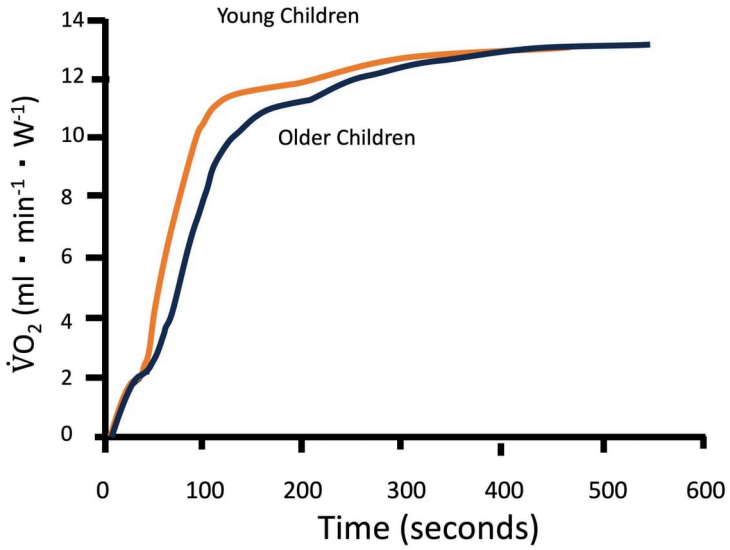


Figure 17-4 Oxygen uptake ($\dot{V}O2$) at the onset of exercise in children showing that younger children reach steady state faster (adopted from Fawkner and Armstrong, 2004).

Metabolic control at the muscle level is often studied non-invasively using $\dot{V}O_2$kinetics at the onset of exercise (see Chapter 10). Indeed, as illustrated in Figure 17-4, children have been shown to have faster $\dot{V}O_2$kinetics at the onset of intense exercise compared with adolescents and young adults (Armstrong and Barker, 2009; Fawkner and Armstrong, 2004). These findings reflect a greater reliance on oxidative energy pathways, resulting in lower accumulation of metabolic by-products, such as lactate. Therefore, the faster$\dot{V}O_2$kinetics observed in children are consistent with the observation that their lactate and ventilatory thresholds occur at a higher percentage of $\dot{V}O_2$max.

Magnetic resonance technology has also been used to investigate muscle metabolism non-invasively. Using this technology, exercise scientists (Ratel et al., 2008) studied the kinetics of phosphocreatine resynthesis after exercise and found that the rate constant of phosphocreatinerecovery and the maximum rate of aerobic ATP production were about 2-fold higher in young boys than in men, indicating that muscle oxidative capacity was higher in children than in adults (see Chapter 10). Collectively, the findings described above of higher lactate and ventilatorythresholds, faster $\dot{V}O_2$ kinetics at the onset of exercise and faster post-exercise phosphocreatinekinetics all point to a greater reliance on aerobic metabolic pathways in children at any given relative exercise intensity. This reliance on aerobic, rather than anaerobic metabolism is instrumental for enhanced exercise endurance. Therefore, from a metabolic perspective, children appear to be more aerobically inclined compared with adults.A case in point is children's fuel utilization during exercise. Recall that, among adults, endurance-trained athletes are typically able to rely more on fat, rather than on carbohydrate utilization during submaximalexercise. This adaptationto training is considered beneficial for endurance performance. Interestingly, during submaximalexercise of the same relative intensity(e.g., 60-70% $\dot{V}O_2$max), children, like endurance athletes, rely more on utilization and less on carbohydrates utilization, compared with adults (Martinez and Haymes, 1992; Timmons et al., 2003). In other words, among exercising children, lipid oxidation contributes relatively more to the

total energy expenditure, compared with adults. For example, Timmons et al. (Timmons et al., 2003) demonstrated that during 60 min of cycling at a moderate-vigorous intensity(70% $\dot{V}O_2$max), oxidation contributed about 40% of the energy requirement for the boys, whereas for the men, only about 20% of the energy came from oxidation (Figure 17.5a). Riddell et al. (Riddell et al., 2008) demonstrated that the oxidation rate during a wide range of exercise intensities is higher in boys compared with men, and that the maximal oxidation rate decreases during puberty. Although the exact mechanisms for this age- or maturation-related change in substrateutilization are not well understood, the higher utilization during exercise has been linked to factors such as higher aerobicenzymatic (SDH) activity in muscle, higher mitochondrialvolume or mitochondria/myofibrillarvolume, greater intramuscular triglyceride deposits, or possibly, greater recruitmentof type I fibres(vs. type II fibres) in children (see highlight box).

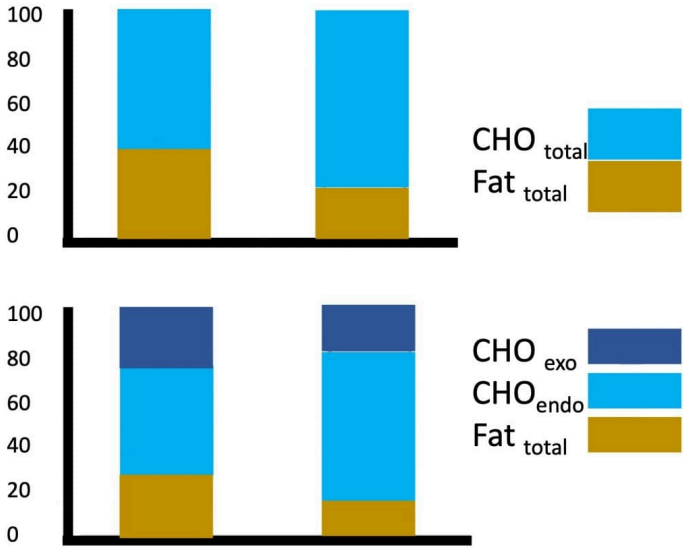


Figure 17-5 Energy contribution from the oxidation of fats vs. carbohydrates during moderate-vigorous intensity cycling (70% V̇O2max) in children (left) vs. adults (right), while consuming water (top) and while consuming a sports drink (bottom). (Data from Timmons et al., 2003).

The greater reliance on oxidation in children was also apparent when a sports drink (containing carbohydrate) was consumed during exercise. Interestingly, the boys utilized more of the exogenous (i.e., ingested) carbohydrates for their energy needs, compared with the men (Figure 17.5b). That is, while consuming a sports drink, reliance on oxidation was still higher in the boys (30%) compared with the men (17%). However, the sports drink provided 22% of the energy for the boys during exercise and only 15% of the energy consumed by the men (Timmons et al., 2003). While the reason for the boys' greater relative utilization of the carbohydrates from the sports drink is unknown, it may be beneficial in preserving the limited endogenous (i.e., stored within the body) carbohydrate stores in the muscle during prolonged exercise, ultimately enhancing endurance capability.

The Differential Motor-Unit Activation HypothesisHighlight Box:

There are numerous performance outcomes in which children's performance is inferior to adults. There are also numerous physiological responses to exercise, such as fatiguability during and after (recovery) intense exercise, glycolytic capacity, substrate utilization during aerobic exercise, the lactate response to incremental exercise, and neuromuscular adaptations to resistance training, which are quantitatively and qualitatively different in children compared with adults. Many of these differences, as outlined in this chapter, are only partially explained by body size differences. This means that there is another factor (or other factors), which must be considered in order to explain children's differential response to exercise.

Canadian researchers have recently proposed that the one factor which is common to this wide array of performance and metabolic child-adult differences in the exercise response is related to age- or maturation-related changes in muscle activation (Dotan et al., 2012). Erling Asmussen, in the mid 1950's observed that the increase in strength with increasing age is more than can be expected from an increase in body size. He postulated that children do not activate, or utilize their muscle to the extent typical of adults (Asmussen and Heeboll-Nielsen, 1955; Asmussen and Heeboll-Nielsen, 1956). Subsequently, numerous authors have provided indirect evidence of this quantitatively lower muscle activation in children (e.g., (Belanger and McComas, 1989; Grosset et al., 2008; O'Brien et al., 2010)). Based on Henneman's size principle (Henneman et al., 1965), which states that with an increase in contraction intensity, there is an increase in recruitment

of type-II muscle fibres, the differential motor unit activation hypothesis states that children's muscle activation is not only quantitatively lower, but also qualitatively different from adults' muscle activation. It is hypothesized that *children are substantially less capable of recruiting or fully employing their higher-threshold, type-II motor units*.

While there is abundant indirect evidence to support this hypothesis (see (Dotan et al., 2012) for detail), it has not been validated. Direct validation would require monitoring of muscle performance while simultaneously recording activation pattern of a large sample of individual motor-units. Presently, there is no appropriate technique to obtain such data.

The indirect evidence supporting the differential motor-unit activation hypothesis includes contractile and power related data, as well as EMG-derived data. Contractile and related data include much slower rate of force in children (Asai and Aoki, 1996; Cohen et al., 2010), along with slower kinetics during maximal contraction (Dotan et al., 2013). EMG-derived data include a slower rate of rise in at the beginning of an explosive contraction (Cohen et al., 2010), and a lower decrease in the mean power frequency during prolonged isometric contractions in children (Armatas et al., 2010; Halin et al., 2003). More recently, two studies demonstrated a higher relative in children compared with adults during progressive cycling to exhaustion (Long et al., 2017; Pitt et al., 2015). The reflects the onset of accelerated recruitment of type-II motor units. Thus, these studies suggest lesser type-II motor unitrecruitment in children. Table 17.1 delineates a wide array of child-adult exercise performance and metabolic difference, highlighting those that can be explained by quantitatively lower muscle activation and those for which such an explanation would not be sufficient. In those cases, the differential motor-unit activation hypothesis may provide the explanation.

Table 17-1 Child-adult exercise performance and metabolic differences, and possible explanatory roles of age-related neuromuscular activation differences.

Children relative to adults (after correcting for differences in body size)	**Neuromuscular Activation-related Mechanisms**	
	Overall lower muscle activation	Lower activation of type-II motor units
Response to exercise or training:		
Lower maximal force	√	√
Lower muscular power	√	√
Slower force Kinetics	——	√
Lower fatiguability/Higher endurance	√	√
Faster recovery	√	√
Slower rate of rise of EMG	——	√
Non-hypertrophic response to resistance training	——	√
Metabolic responses		

Lower peak blood lactate concentration	√	√
Higher (lactatethreshold)	——	√
Faster intra-cellular phosphocreatinerecovery	√	√
Greater utilization Lower carbohydrate utilization	——	√
Faster $\dot{V}O_2$ kinetics at onset and offset of exercise	——	√

Adaptations to Aerobic Training

The question is often asked, how effective is aerobic training in increasing children's $\dot{V}O_2$max and aerobic performance? Any change in $\dot{V}O_2$max is effected through central (cardiac) and/or peripheral (muscle) adaptations. Presumably, an enhanced $\dot{V}O_2$max, results in improved aerobic performance. This section discusses the physiological adaptations (central and peripheral) to aerobic training in children and the observed changes in $\dot{V}O_2$max and aerobic performance.

As previously discussed, $\dot{V}O_2$ is determined by cardiac output (stroke volume and heart rate) and by the arterio-venous oxygen difference. Young athletes have been shown to have higher maximal cardiac output, as well as higher blood volume, compared with untrained peers (Eriksson and Koch, 1973; Nottin et al., 2002b; Rowland et al., 1998). Others have shown increased stroke volume and a decreased heart rate during prolonged, submaximal exercise in endurance trained children (Obert et al., 1998). These are typical responses that would be seen in adults on an aerobic training program. However, it is possible that these cross-sectional studies reflect selection bias (genetic advantage), rather than true adaptations to training. That is, it is possible that the young athletes have genetically greater cardiovascular responses to exercise and that this is one of the reasons they were drawn to, and succeeded in endurance sports. There are very few intervention studies that have examined the cardiac or hemodynamic adaptations to endurance training in children. Some studies have shown that LVM increases as a result of endurance training in children, as it does in adults (Nottin et al., 2002a; Obert et al., 2003), enhancing stroke volume at rest and presumably also during exercise. Exercise training does not seem to have a significant impact on maximum heart rate, on arterio-venous oxygen difference or on total peripheralresistance in children, although there is very limited information on these responses in children.

Changes in left ventricular dimensions and stroke volume will result in increased maximal cardiac output and potentially, greater aerobic capacity. The magnitude of change in maximal aerobic capacity following aerobic training is influenced by genetics, the training program itself, and the interaction between these two factors. Among adults, the training effect on $\dot{V}O_2$max ranges between 0-50% (Bouchard, 1995), although a crude average improvement is about 20% improvement in $\dot{V}O_2$max. In children, numerous studies have investigated the effect of aerobic training on $\dot{V}O_2$max, but only few demonstrated more than 10% improvement. In fact, the crude average improvement in children is about 8% of $\dot{V}O_2$max, with many studies demonstrating no effect at all (Pfeiffer et al., 2008). The reason for the lower trainability in children is not clear. The most likely explanation is that, in most training studies the training program has been designed based on adult guidelines. For example, participants train 3 times per week, 45-60 minutes each session, at an intensity eliciting 75-80% of maximal heart rate. While these guidelines may be effective for adults they may be insufficient to stress the oxygen delivery system in children. That is, in view of the observed higher (lactate or ventilatory threshold) in children, as discussed previously, children may need to train at a higher relative intensity in order to elicit adaptations in the cardiovascular system. Indeed, those studies in which a higher training intensity was used (for example, HR>85% of maximal HR) demonstrated significant increases in

$\dot{V}O_2$max in children (see (Pfeiffer et al., 2008) for details).

In spite of the relatively low training effect on $\dot{V}O_2$max in children, training does result in improved endurance performance. For example, following a training program, children will be able to complete a distance run in a shorter duration, even if $\dot{V}O_2$max

does not increase. Possible reasons for this improved performance include better movement economy, improved "tactics" and higher anaerobic ability. Better movement economy is a bioenergetic term associated with the energy cost of locomotory activity. This energy cost is reflected in the O_2 cost at a given submaximal speed, which is shown to be higher in children (Frost et al., 2002) than in adults. It is possible that following training, children's running style becomes less mechanically "wasteful", or more economical, resulting in the ability to perform at a greater speed for a given energy expenditure. Another possible explanation for children's improved performance may be a "learning effect". That is, children, through practice, learn how to pace themselves during prolonged exercise, thus being able to utilize better tactics to improve performance. Finally, every aerobic performance includes an anaerobic component. Long-distance races are characteristically ended by a "sprint to the finish". Rotstein et al (Rotstein et al., 1986) demonstrated that in children, an aerobic training intervention will result in aerobic, as well as in anaerobic adaptations. Therefore, it is possible that the improved performance (shorter time) in prolonged exercise tasks (e.g., 5 km run), reflects, at least in part, improved anaerobic capacity.

Gender Box: Does Intense Training Alter Girls' or Boys' Growth and Maturation?

The increased involvement of young children in intense physical training over the past decades has generated concerns as to its potential effects on children's growth, maturation, and reproductive function (Mansfield and Emans, 1993). These effects are potentially different for females than they are for males, especially around the time of puberty, when boys' and girls' hormonal status differ considerably. The pubertal period is associated with marked physiological and psychological changes, and important neuroendocrine adjustments that result in both physical maturation (i.e., skeletal and growth), and sexual maturation (growth of pubic hair, and in the genitalia). Thus, during the pubertal years, the hormonal milieu of an adolescent athlete undergoes developmental changes, as well as possibly, training-related adaptations (Klentrou, 2006).

Physiologically, puberty is a complicated series of events that are initiated by an increase in the secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus. GnRH acts on the pituitary gland, stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In males, this causes increased release of testosterone from the gonads. Testosterone continues to increase throughout puberty until it reaches adult levels and plays a key role in both physical and sexual maturation (Rilling et al., 1996). In females, sufficient quantities of FSH and LH stimulate ovarian follicular development, the of secondary sex characteristics, and an increased release of female sex steroids (estrogen and progesterone) from the ovaries (Caufriez, 1991). Estrogen and progesterone continue to increase throughout puberty, and play a key role in both physical and sexual maturation (Hamm, 1991).

Early studies on team male athletes in popular sports (i.e., soccer, football and baseball) have demonstrated that elite athletes are more mature than their untrained peers, suggesting that physical training causes early onset of puberty in males (Cacciari et al., 1990; Hale, 1956). However, these results may be affected by sampling bias. In these sports, a greater physical size typically provides an advantage. Therefore, the more mature athletes are the ones that succeed and remain in the sport (Malina et al., 2000). In other words, it is not that elite training *causes* early maturation but rather, early maturing boys are more successful in these elite sports.

It can be argued that boys who participate in individual sports often train from an early age, thus providing a better model to examine the possible effects of physical training on pubertal development. In pubertal male swimmers, 43 weeks of training significantly decreased testosterone levels to below pre-training levels (Carli et al., 1983). Elite male gymnasts, on the other hand, have been found to be generally advanced in pubertal and skeletal development, despite their generally short stature (Buckler and Brodie, 1977; Moore et al., 2010). Others have shown that although the intense training by the young male gymnasts result in reduced body fat, there is no apparent alteration in the timing and extent of their physical and pubertal (Gurd and Klentrou, 2003). Thus, as with team sports, observations of early maturation in male athletes of individual sports are likely attributed to selection bias rather than training *per se*.

In females, numerous studies have suggested that intense gymnastic training may delay and even stunt growth (Georgopoulos et al., 2012; Peltenburg et al., 1984), due to altered hormonal (Theintz et al., 1994; Theintz, 1994). The altered hormonal milieu may result in delayed pubertal onset, delayed age at first menarche, and failure to develop mature skeletal structure (Malina, 1983). Although not supported by current opinion, low body has been cited as the reason for the delayed menstruation or menstrual cycle irregularities among elite female athletes (Frisch and McArthur, 1974). More recent studies have suggested that delayed menarche in elite gymnasts (and other athletes, such as dancers and figure skaters) may be due to genetic factors, and that late-maturing girls often self-select sports which require high relative strength and small bodies, such as gymnastics (Baxter-Jones and Helms, 1996; Loucks, 1995). Indeed, 37% of the variance in the age at menarche has been found to be attributed to genetic factors (Kaprio et al., 1995). On the other hand, a higher prevalence of menstrual dysfunction has been reported for adolescent

athletes in leanness-dependent and weight-dependent sports, as compared with those in other sports (Klentrou, 2006). Despite the arguments for selection bias, there is at least one study which demonstrated stunted growth (shorter stature compared with predicted height) in young elite female gymnasts; however, they did not examine nutritional intake (Theintz et al., 1993). However, the available research supports the role of nutrition-related factors and energy balance, rather than the training intensity per se, in the etiology of exercise-associated menstrual irregularities or delayed growth in young female athletes (Klentrou, 2006). Future research should be longitudinal in nature in order to investigate the long-term effects of sport training, nutrition (fuel availability and utilization) and psychological stress, on the growth and maturation of young females.

Anaerobic Capacity and Recovery from Intense Exercise

As opposed to aerobicfitness, which is widely accepted to be reflected by maximal aerobic uptake ($\dot{V}O_2max$**)**, there is no accepted physiological index of anaerobicfitness. Rather, anaerobic fitness is assessed via anaerobic-type performance. The most widely accepted test of anaerobic performance is the Wingate Anaerobic Test (WAnT) (see chapter 10). Also, unlike aerobic fitness, which is known to be related to health, anaerobic fitness, as reflected by peak or mean mechanical during short duration, high intensity exercise, is not specifically related to any health measure. Perhaps this is the reason for the much lower number of studies that have investigated anaerobic fitness or performance compared to aerobic fitness in children and adolescents.

Anaerobic performance increases with growth and maturation. This increase has been demonstrated in numerous cross-sectional studies (e.g.,(Inbar and Bar-Or, 1986; Van Praagh and Dore, 2002)), as well as in few longitudinal studies (e.g. (Armstrong et al., 2001; Falk and Bar-Or, 1993; Martin et al., 2004)). For example, Van Praagh and Dore (Van Praagh and Dore, 2002), demonstrated such an increase in peak short-term in over 500 boys and girls between 7 and 21 years of age. Importantly, even after correcting for body size, the increase in anaerobic performance with age is readily apparent (Figure 17.6). Regardless of the manner in which body size is taken into account (e.g., body mass, height, muscle cross-sectional area), increases with growth and development. Thus, as opposed to maximal aerobic (but similar to strength, see section on strength), scaling for body size does not eliminate the age-related increase in maximal anaerobic power. Therefore, factors other than body size must explain the age-related increase in anaerobic power.

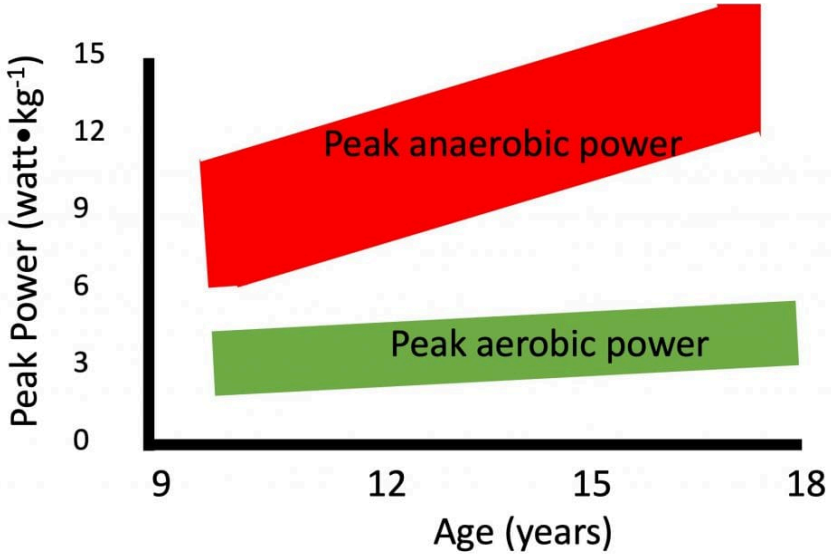


Figure 17-6 Values for peak aerobic power and peak anaerobic power during development. The range does not increase with age, but the actual values do. Peak aerobic power changes little but peak anaerobic power increases substantially. Adapted from Bar-Or and Rowland, 2004 and data from Falk and Bar-Or, 1993.

Factors Affecting the Increase in Anaerobic Power with Growth

There are numerous factors, other than body size, which may explain changes in anaerobic power. Similar to the factors affecting strength (see section on strength), possible increases in type-II fibres distribution, increases in musculotendinous stiffness, and/or possible decreases in co-contraction may result in enhanced anaerobic power. However, the most accepted and widely cited factor explaining the lower anaerobic performance in children compared with adults is the former's "metabolic immaturity". Several studies have demonstrated lower activity in enzymes which are central to anaerobic metabolism, including

phosphofructokinase (PFK, (Eriksson, 1980; Eriksson et al., 1973)) and lactate dehydrogenase (LDH, (Kaczor et al., 2005). Indeed, rate of lactate production in the muscles during exercise has been shown to be lower in children compared with adults. Furthermore, the rate of muscle glycogen utilization during intense exercise has been shown to be much lower in children compared with adults (Eriksson et al,. 1971). Therefore, it is believed that enhanced enzymatic activity, especially during adolescence, is at least partly responsible for the increased anaerobic performance seen during this period. It is still unclear however, what is the reason behind the changes in enzymatic activity. We have recently proposed that these changes may be a reflection of increased utilization of type-II motor units, which is hypothesized to occur with growth and (see highlight box).

It is interesting to note that while maximal aerobic does not change with growth, specifically in boys, maximal does, even when corrected for the increases in body size. This difference in pattern of change is illustrated in Figure 17.6. In a mixed-longitudinal study, Falk and Bar-Or (Falk and Bar-Or, 1993) describe the increase that occurred in peak anaerobic power, as determined in the WanT, among 36 pre- to late-pubertal boys. At the same time, there was no change in the maximal aerobic in these boys. For example, while boys' maximal mechanical on a cycle ergometer at the end of a maximal progressive aerobic test remains about 4 watts·kg^{-1} as they grow, their peak anaerobic power, as determined by the Wingate Test, can increase from 9 watts·kg^{-1} at 10 years, to over 14 watts·kg^{-1} at 18 years. The authors suggested that metabolic specialization occurs during puberty, possibly as a result of increased utilization of type-II motor units (see highlighted box).

Recovery from Intense Exercise

Recovery from intense exercise is notably faster in children compared with adults. That is, following intense exercise, boys are able to repeat their output within a shorter period of time compared with men (Hebestreit et al., 1996; Ratel et al., 2002; Ratel et al., 2004; Zafeiridis et al., 2005). From a methodological perspective, it is difficult to determine whether children's physiological recovery, that is, the return to homeostasis, is also faster than adults'. For example, as discussed earlier in this chapter, maximal heart rate, an indicator of cardiovascular stress, is higher in children than in adults. On the other hand, blood lactate concentration, an indicator of metabolic stress, is lower in children than in adults. Further complicating the comparison is that resting levels (e.g., heart rate) may also differ between children and adults. Therefore, it may be argued that children and adults do not recover from the same level, nor do their physiological responses need to return to the same level. One approach has been to examine net changes in the physiological response to exercise (e.g., heart rate, ventilation, 2 and VO_2, measured at the pulmonary system" href="https://kinesiology.ucalgary.ca/maci...end#-r-or-rer-">RER). Using this approach, Hebestreit et al. (Hebestreit et al., 1996) demonstrated that following the WAnT, children's physiological response recovers faster. Another approach is to match post-exercise values. For example, by using a variable duration WAnT, Dotan et al. (Dotan et al., 2003) matched post-exercise blood lactate levels in men and boys. The authors demonstrated that although the rate of disappearance of blood lactate was similar in the two groups, blood lactate concentration peaked earlier in the boys, thus allowing them to begin their recovery process earlier.

Part of the explanation for children's faster recovery is that their maximal output is lower than adults' (see above). Therefore, for children, there is less disturbance to homeostasis during exercise so they have 'less to recover from' (Falk and Dotan, 2006). Children have a lower proportion of muscle mass. Additionally, their lower output may be a result of a lower utilization of the higher-threshold, more powerful motor units (see highlight box). However, there are other child-adult differences, which may result in faster recovery of performance (Figure 17-7). Some of these differences are simply related to differences in body size, some are metabolic differences and some are qualitative differences related to maturation. For example, children's muscle fibres are smaller in diameter. That means that the diffusion distance of metabolites from the muscle fibre to the blood is shorter. This shorter distance, along with presumed greater capillary density around the muscle fibre, allows metabolites to clear from the muscle faster in children. Likewise, children's shorter circulation distance means that metabolites (e.g., lactate) can be dispersed (e.g., get to inactive muscle, where they can be metabolized) within a shorter time period. From a metabolic perspective, children's faster oxygen kinetics (Armstrong and Barker, 2009; Willcocks et al., 2010), along with their lower concentration of metabolites in the blood (lactate, H^+) also directly results in faster recovery. Thus, children's faster recovery, in terms of performance, as well as the physiological response is due to quantitative and qualitative reasons.

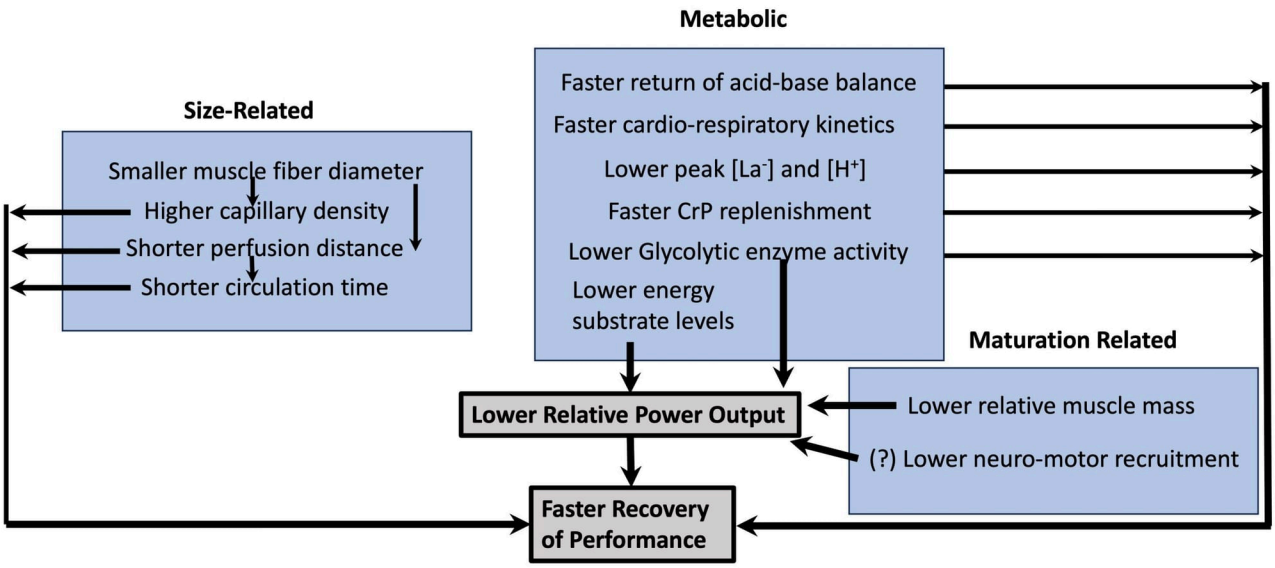


Figure 17-7 Scheme of size-related, metabolism-related and maturation-related factors that may affect children's faster recovery from intense exercise (adapted from Falk and Dotan, 2006).

Muscle Strength and Resistance Training

Ironically, with the general decrease in physical activity, there is an increase in organized sports participation among children and adolescents. With this increase, there is an increase in the physical and training demands of each sport. More importantly, this increase in demands occurs at a younger and younger age. In other words, young athletes today are training more intensely and longer hours than in the past. Their performance level is also higher than in the past. An integral component of the higher demands of sport performance today is the inclusion of resistance training. In fact, many young athletes today, whether they are swimming, playing hockey or various ball-game sports, are involved in resistance training. On the other end of the continuum, resistance training has also become a part of the management of chronic childhood conditions, such as obesity, cerebral palsy and even cancer. Some of the important questions to consider when contemplating resistance training for youth include,

- Is resistance training*effective* in terms of increasing strength during childhood and adolescence?
- Is resistance training *safe* during childhood and adolescence?
- Does resistance training *affect growth* during childhood and adolescence?

The answers to these questions are discussed below. However, before embarking on resistance training and its related issues, one must consider the changes that take place in muscle structure and function during growth and maturation. This background will provide a framework for consideration of the impact of resistance training.

Muscle Structure and Function During Growth and Maturation:

Myogenesis occurs predominantly pre-natally. Muscle fibres develop from embryonic mesodermic cells and the number of muscle fibres in each muscle is believed to be achieved by birth, or soon thereafter. During childhood and adolescence, there is no increase in the number of muscle fibres so post-natal increase in muscle mass is a result of muscle fibre hypertrophy, rather than hyperplasia (Lexell et al., 1992). This means that sarcomeres are added in parallel and in series (Figure 17.8). When sarcomeres are added in parallel, this is achieved first by increased size of myofibrils, then by increased number of myofibrils when these myofibrils split.

Muscle mass increases linearly during childhood with very small differences between boys and girls. During puberty, the increase in muscle mass is greater in boys compared with girls (Tanner et al., 1981). In fact, the increase in muscle mass during puberty can be about twice as large in boys compared with girls (Johnston and Malina, 1966). At the same time, there is a parallel increase in maximal strength (Figure 17-8). There is a lot of literature on the increase in maximal isometricstrength during growth and maturation (see (Blimkie, 1989; Farpour-Lambert and Blimkie, 2008; Sale D.G, 1996)). However, most daily activities, as well as sporting skills, require dynamic, rather than isometricstrength. Performance in many activities (e.g., running, jumping, throwing) requires a quick generation of force in a very short time window. Usually, maximal strength is not attained during this short time

window. That is, these activities require a high rate of force development, or explosive strength. Surprisingly, we know very little about the changes in dynamic, and especially in explosive strength with growth and development, although we assume that these changes are parallel to the changes in isometricstrength.

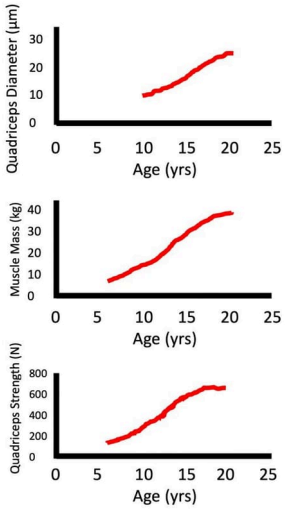


Figure 17-8 Estimated muscle fibre diameter (top), muscle mass (middle), and maximal strength (bottom) with increasing age. [Data from Volger and Bove, 1985 (top); Malina et al., 2004 (middle); Parker et al., 1990 (bottom)].

Factors Explaining Increased Muscle Strength

There are numerous factors that are involved in the increase in strength during growth, above and beyond the increase in body size. Indeed, as seen in Figure 17-8, while muscle diameter and muscle mass can increase about two-fold from age 10 to 15 years, strength increases almost three-fold. When comparing children with adults, their absolute maximal strength is obviously much lower due to their size difference. However, when maximal strength is normalized for body size (for example, using ratio standards with body mass or fat-free mass in the denominator), children are still not as strong as adults (see (Blimkie, 1989; Farpour-Lambert and Blimkie, 2008; Inbar and Bar-Or, 1986; Van Praagh and Dore, 2002) for review). Therefore, factors other than body size must also be considered to explain the strength difference between children and adults. These factors include muscle composition (i.e., fibre type distribution) and neuromuscular activation pattern. Additionally, tendonstiffness may also affect explosive strength. These factors are discussed below.

Type II fibres fibres are known to be larger and able to produce greater force per fibre than type I fibres (see Chapter 5). Therefore, a lower proportion of type II fibres in children may potentially explain the strength difference observed between children and adults. However, the fibre-type distribution is widely considered to be determined by one year of age (Bell et al., 1980; Brooke and Engel, 1969; Dubowitz, 1965; Vogler and Bove, 1985). While few studies suggest that there can be a small increase in the proportion of type II fibres during childhood and adolescence, particularly in males (Jansson, 1996; Lexell et al., 1992), this small increase is insufficient to explain the large age-related differences in static or dynamic strength. Nor are they sufficient to explain the large differences observed in explosive strength between children and adults.

A lower level of neuromuscular activation could also potentially explain children's lower maximal strength. Several studies have suggested that there is lower motor unit activation in children compared with adults (Grosset et al., 2008; O'Brien et al., 2009; O'Brien et al., 2010). For example, using the interpolated twitch technique, O'Brien and colleagues (O'Brien et al., 2010), recently demonstrated that during maximal voluntary knee extension, adults will activate 85% of their total motor neuron pool, while children activate only 70% of the available motor units. In accordance with the Henneman's size principle (Henneman et al., 1965)(see Chapter 3), it was recently proposed that the deficit in motor unit activation in children is made up of proportionately larger amount of type-II motor units (Dotan et al., 2012). This suggests that children utilize less of their higher-threshold, type-II motor units compared with adults (see highlight box). This difference could potentially explain not only children's lower maximal strength, but also their lower explosive strength.

A lower tendonstiffness (higher compliance) is associated with a lower ability to produce force quickly (Wilson et al., 1994). This means that the lower the tendonstiffness, the lower the explosive strength. Therefore, a lower musculo-tendinous stiffness in

children may play a partial role in the lower explosive strength typical of children. Indeed, several studies have demonstrated lower musculo-tendinous stiffness in children compared with adults (Grosset et al., 2007; Lambertz et al., 2003). Lambertz and colleagues (Lambertz et al., 2003) found not only a difference between children and adults, but a progressive increase in musculo-tendinous stiffness in children from 7 to 10 years of age. Thus, children's lower explosive strength, and particularly, the slower of force may be partly explained by the lower musculo-tendinous stiffness, although it cannot account for all the observed age-related differences.



Photo 17-4 Weight training, is an acceptable form of exercise for children if it is supervised. Photo by Brian MacIntosh.

Effects of Resistance Training in Children

One of the myths in resistance training is that it is ineffective in children. In other words, engagement in resistance training among children was not considered to result in enhanced strength. Several early studies supported this view by failing to demonstrate any increase in strength in children who participated in resistance training (Docherty et al., 1987; Vrijens, 1978). However, a closer look at these studies would reveal that either the volume or the intensity of the training program was too low to result in increased strength. Since then, there have been numerous studies which have disputed this myth, demonstrating considerable strength gains in children following resistance training (for reviews see (Behm et al., 2008; Blimkie, 1992; Blimkie, 1993; Falk and Eliakim, 2003; Falk and Tenenbaum, 1996; Malina, 2006)).

One of the most impressive and comprehensive studies on the effects of resistance training in children was reported by Ramsay and colleagues (Ramsay et al., 1990), in which pre-pubertal boys engaged in resistance training over a period of 20 weeks, which is considered a particularly lengthy training duration for a pediatric research study. Significant strength gains were observed in the training group (with minimal strength gains in the non-training group), whether strength was measured using 1RM tests, isometric or isokinetic testing (Figure 17-9). That is, in each of eight different exercises, boys who trained improved by 15-60%, depending on the type of exercise, significantly more than the boys who did not train.

Today, the effectiveness of resistance training in children is accepted among coaches, as well as among health professionals. Indeed, numerous professional organizations, such as the American College of Sports Medicine, the International Federation of Sports Medicine, the National Strength and Conditioning Association, the British Association of Sport and Exercise Sciences, and many more have published position statements in favour of resistance training for children. The Canadian Society for Exercise Physiology came out with a position statement (Behm et al., 2008) advocating the benefits of several types of resistance training for children.

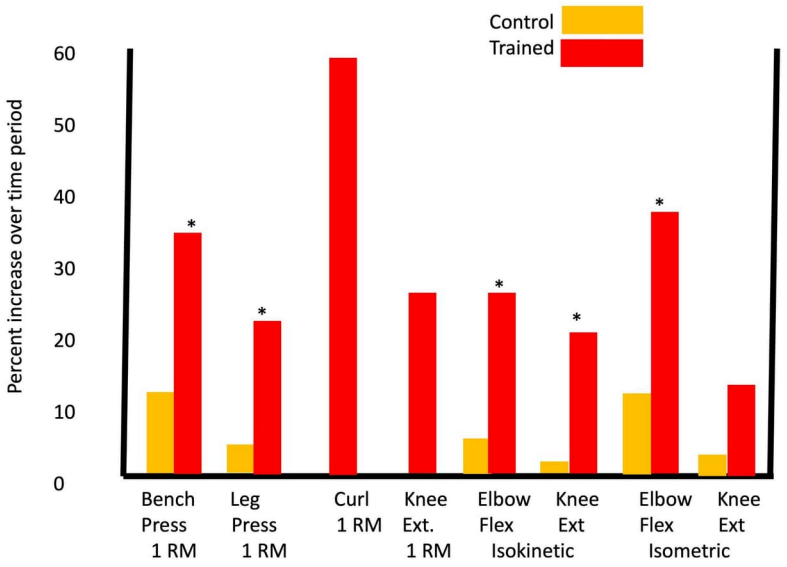


Figure 17-9 Changes in strength in trained vs. untrained pre-pubertal boys following 20 weeks of resistance training (adapted from Sale, 1989, who used data from Ramsay et al., 1990).

Accepting that resistance training is indeed effective in enhancing strength in children, the obvious next question is, how effective is it compared to its effectiveness in adults. In order to answer this question, one would have to design a study in which children and adults, preferably at the same baseline level, participated in an identical training program. Technically and logistically, this would be very difficult to do. Indeed, Lillegard and colleagues (Lillegard et al., 1997) examined the effect of resistance training in early and late-pubertal children but did not observe any clear effect of maturity status. Notably, the number of participants in each group was relatively small, making it difficult to observe real differences.

In an effort to examine the relative effects of resistance training on children compared with adults, Sale (Sale, 1989) merged data from two separate studies in which the effect of resistance training on evoked twitch torque (resulting from electrical stimulation) of the elbow flexors and knee extensors was investigated. Although scientifically combining data from two studies is not recommended, in this case the data were collected by the same research group, using the same equipment and testing techniques, and the training programs were similar, so the approach is justified. In both studies, the training group's strength improved significantly more than the control group, which in view of the above discussion is not surprising. In terms of absolute torque gain at the end of the training period, it is evident that the children improved 50% less than the adults. However, if one compares the relative gain as a percentage of pre-training torque, it is evident that the children improved much more than the adults (about twice as much). Therefore, the answer to whether resistance training is as effective in children as it is in adults is not straight forward. In absolute terms, children improve less. However, relative to their starting level, children may improve more than adults as a result of resistance training.

Mechanisms Explaining the Effects of Resistance Training

Generally, there are two types of mechanisms, which may explain the strength gains observed following resistance training: morphological and neurological adaptations. Both of these mechanisms play a role in children and in adults, but their relative contribution in each age group differs. Morphological adaptations, specifically muscle hypertrophy, are often evident in adults, specifically in men. In children, on the other hand, most studies report no increases in muscle size following resistance training (see (Behm et al., 2008; Falk and Eliakim, 2003; Falk and Tenenbaum, 1996; Sale D.G, 1996; Sale, 1989) for review). Notably, the studies that examined muscle hypertrophy in children have generally used anthropometric techniques (Blimkie, 1989; Granacher et al., 2011; McGovern, 1984; Ozmun et al., 1994; Ramsay et al., 1990; Sailors and Berg, 1987; Siegel et al., 1989). Two studies in which more sensitive methods of measurements were utilized (magnetic resonance imaging and ultrasound) have suggested that muscle hypertrophy, although minimal, may indeed occur among children following resistance training (Mersch and Stoboy, 1989; von Fukunaga et al., 1992). However, even if muscle hypertrophy does occur as a result of resistance training in children, the extent of that hypertrophy is minimal and is likely insufficient to explain the apparent strength gains.

In view of the limited evidence of muscle hypertrophy and its small potential contribution, the main mechanism believed to explain children's strength gain following resistance training, involves neural adaptation. These adaptations are difficult to define, measure and characterize. Therefore, neurological adaptations in children are mainly based on indirect evidence. There are

only three studies that attempted to directly demonstrate neurological changes in children following resistance training. Using the interpolated twitch technique (Chapter 13), Ramsay et al. (Ramsay et al., 1990) demonstrated an increase in motor unit activation of the elbow flexors and knee extensors, following 20 weeks of training. Using the same technique, Waugh et al. (Waugh et al., 2014) could not demonstrate such an increase following 10 weeks of resistance training in young boys, although the number of boys in the study was relatively small. Ozmun et al. (Ozmun et al., 1994) used integrated electromyographic amplitude (IEMG (Chapter 3)) to demonstrate an increase in neuromuscular activation in agonist muscles following eight weeks of training. However, in all cases, the extent of the increased neuromuscular activation of the agonist muscles was much smaller than the increases in strength.

An additional neuromuscular adaptation which may explain some of the strength gains in children may involve improved inter-muscle coordination, which likely plays a more influential role in complex, multi-joint actions. Mitchell and colleagues (Mitchell et al., 2011) observed that young male gymnasts, who presumably engage in extensive resistance training, particularly explosive training, demonstrate much faster rate of muscle activation compared with endurance-trained or untrained boys. Gymnasts were also characterized by a faster rate of force (explosive strength) (Figure 17-10). These findings are supported by a recent study which demonstrated that resistance training (free weights or plyometric training), added to regular soccer training, resulted in enhanced rate of force development, along with increases in the rate of muscle activation (McKinlay et al. 2018).

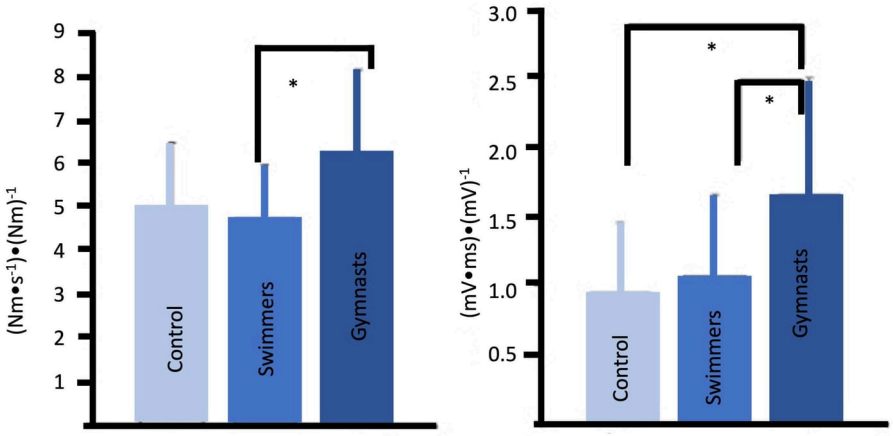


Figure 17-10 Rate of torque (explosive strength) in pre-pubertal gymnasts, swimmers and untrained boys: rate of torque relative to maximal torque (left), rate of increase in electromyographic signal (muscle activity – right) (adapted from Mitchell et al., 2011).

Safety and Resistance Training

Resistance training has been touted to be unsafe for children and adolescents. Admittedly, all types of physical activity are associated with some risk of injury, including resistance training. The question is whether resistance training is associated with greater risk than other activities. Hamill and colleagues (Hamill, 1994) specifically studied the incidence of injuries among adolescent boys engaged in resistance training, weight lifting and other, more pervasive sports such as rugby and soccer. The authors reported that the incidence of injuries in resistance training and weight lifting was several orders of magnitude lower than the more common sports (0.017-0.035 vs. 0.14 to 8 injuries per 1000 participation-hours). Notably, the authors also reported a higher injury incidence in physical education classes compared with resistance training. More recently, Malina (Malina, 2006) reported similarly low incidence among pre-pubertal boys engaged in resistance training. Thus, it appears that, when properly performed and supervised, resistance training is associated with a lower risk of injury compared with many other prevalent activities. On the other hand, it should be noted that the most serious type of injury, which has been reported to result from resistance training (or weight lifting) is an injury to the epiphyseal (growth) plate. Obviously, this type of injury can appear only in children or adolescents, not adults, and, if left untreated, can have potentially serious consequences. Therefore, in addition to the safety rules, which are recommended for adults, there are several safety precautions, which are particularly important for children. These include adherence to the proper technique, the use of properly-sized equipment, the engagement of properly qualified exercise specialists and a higher instructor-trainee ratio. For a detailed list of recommendations and safety precautions, see the Canadian Society of Exercise Physiologists (CSEP) position statement on resistance training in children and adolescents (Behm et al., 2008).

Thermoregulation During Exercise in the Heat

Thermoregulation is the process by which an organism keeps its body temperature within certain boundaries, even when the surrounding temperature is very different (Chapters 9 & 16). Thermoregulation is affected by environmental factors, such as temperature, humidity and wind, as well as by physiological processes such as metabolic rate (exercise), circulation and sweating. In efficientthermoregulation, heat dissipation (via sweating or skin blood flow) must equal heat production (by the muscles). These processes occur in children, as in adults. This section highlights the *differences* between children and adults.

The amount of heat dissipated is dependent on the available surface area. On the other hand, the amount of heat produced is dependent on the exercising muscle mass. The smaller the body, the larger the body surface area-to-mass (BSA/M) ratio. Thus, children's BSA/M ratio can be 30-40% greater than adults'. This geometric difference affects the means of heat dissipation in different environmental conditions (see below).

Physiologically, heat can be dissipated via increasing blood flow to the skin (promoting "dry" heat exchange, also known as conduction and convection), or via sweatevaporation (Chapter 9). By far, the most prominent and consistently observed difference between children and adults in regards to temperature regulation is the former's much lower sweat rate. In any given environmental condition, whether at rest or during exercise, children consistently demonstrate lower sweating rate. For example, during moderate exercise (50% $\dot{V}O_2$max) in dry heat (42C, 20% humidity), sweating rate was lower in pre-pubertal boys compared with men (Figure 17.11a). Sweating rate increases from pre- to late-puberty yet is still lower in late-pubertal boys compared with young men (Falk et al., 1992a; Falk et al., 1992c). Since the number of sweat glands is determined by the age of 2-3 years, the sweating rate per gland is also lower in children (Figure 17.11b). Children's sweating rate remains lower after taking into account differences in body surface area. Thus, absolute and relative sweating rate is considerably lower in children compared with adults. This age-related difference has been demonstrated consistently in various environmental conditions (see (Falk and Dotan, 2008a; Falk and Dotan, 2008b; Falk and Dotan, 2017) for review). The explanation for the difference in sweating rate may be related to age-related differences in gland size, sensitivity or capacity. But it may also reflect the fact that children may not *need* to sweat as much.

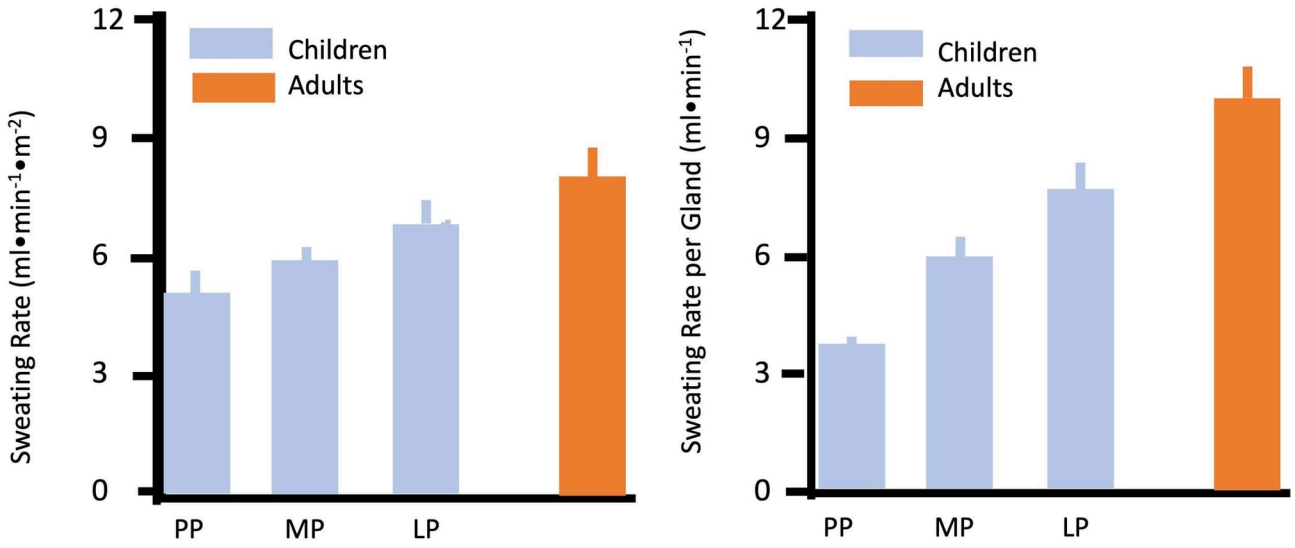


Figure 17-11 sweat rate during exercise in the heat in pre- (PP), mid- (MP) and late-pubertal (LP) boys, as well as young men. A) sweating rate relative to body surface area, b) sweating rate per gland (adapted from Bar-Or and Rowland, 2004. Data from Falk et al., 1992).

As mentioned above, heat dissipation is achieved via increasing skin blood flow and via sweating. Children's blood flow to the skin is greater during exercise in the heat (Drinkwater et al., 1977), and it increases with maturity (Falk et al., 1992b; Falk et al., 1992c). Therefore, it is possible that due to their ability to increase their blood flow to the skin, they do not need to rely on sweatevaporation for effective thermoregulation. In other words, the "strategy" used for thermoregulation is different in children and adults: Children rely more on dry heat loss (via increased skin blood flow), and less on sweatevaporation in order to dissipate the heat produced by the exercising muscles (Falk and Dotan, 2008a; Rowland, 2008).

Does this different thermoregulatory strategy affect the effectiveness of thermoregulation during exercise? In extreme environmental conditions, hot or cold, children may be more vulnerable, but under most conditions, they are at no disadvantage

relative to adults. In fact, there are no epidemiological data demonstrating higher rate of heat injury in children, even during heat waves (see (Falk and Dotan, 2008a; Falk and Dotan, 2017; Rowland, 2008) for review).

In view of children's lower reliance on evaporative heat loss, it may be argued that they may be able to conserve water, relative to adults, during exercise in the heat. However, the issue of proper hydration should not be overlooked. For example, Decher et al. (Decher et al., 2008) demonstrated that among children and adolescents participating in summer sports camps, 50% arrived at their first practice of the day in a hypohydrated state. During exercise, children (as do adults) do not usually consume sufficient fluids and become inadvertently hypohydrated, a phenomenon called "voluntary dehydration". Wilk et al. (Wilk et al., 2001) demonstrated that about 50% of well-trained acclimated adolescent athletes finished a triathlon at 2-3% hypohydration. More importantly, 7% of the athletes were at a more severe (>3%) state of hypohydration at the end of the competition. The same group of authors also demonstrated that even 1% hypohydration is sufficient to negatively affect performance in 10-12 yr old runners (Wilk et al., 2002).

While the rate of dehydration may be similar in children and adults, the implication of this fluid loss is harsher in children. As demonstrated in Figure 17.12, at a similar state of hypohydration (e.g., 1% body mass), children's body temperature increases about 50% more than adults' (e.g., 0.6 vs. 0.4C, respectively). Thus, while children may "conserve" fluids by relying on a lower sweat rate, their need for maintaining proper hydration level is higher. It is unclear whether children's habitual fluid replacement habits are sufficient during competition, specifically in a hot environment. Therefore, it is up to coaches, teachers and parents to ensure that children rehydrate sufficiently.

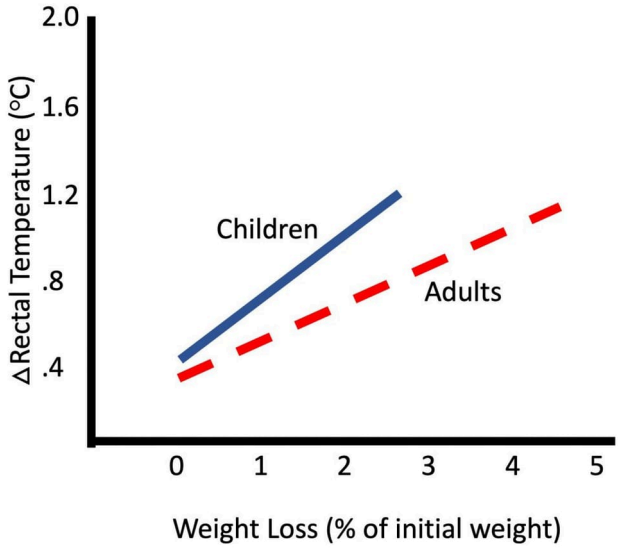


Figure 17-12 The increase in rectal temperature associated with hypohydration, expressed as percentage of body mass (from Bar-Or et al., 1980).

Research Box: Exercise and Bone Development

Osteoporosis is a skeletal disease characterized by low bone mass and deterioration of the micro architecture of bone tissue resulting in bone fragility and susceptibility to fractures. According to the World Health Organization, Osteoporosis is estimated to affect approximately 200 million women worldwide (Kanis, 2007). Although the prevalence of fractures is higher in women, the mortality rate related to fragility fractures is higher in men (Center et al., 1999). A primary risk factor for the of osteoporosis later in life is the inability to attain optimal peak bone mass (PBM) (Heaney et al., 2000). PBM is generally defined as the highest level of bone mass achieved as a result of normal growth and seems to be established for most sites of the skeleton, by early adulthood (Matkovic et al., 1994). In fact, the most rapid bone mineral accumulation occurs approximately one year after the age of peak linear growth (Bailey et al., 1996). It appears, therefore, that there is a critical period, a 'window of opportunity', during which we can greatly influence the amount of bone mass we attain (MacKelvie et al., 2002). That is, the pubertal period is the optimal period to 'put bone in the bank' and increase PBM.

Bone is the product of complex interactions between genetic and environmental factors including diet, hormonal influences, and mechanical stimuli, usually attained through exercise or physical activity (Gordon, 2003; Steelman and Zeitler, 2001). Importantly, many of these environmental factors undergo changes during the pubertal period.

The use of physical activity (PA) in enhancing PBM, maintaining bone health throughout the lifespan and ultimately preventing osteoporosis has been the focus of considerable research, and Canadian researchers have played a noteworthy role in this field. It is generally accepted that engaging in physical activity during growth enhances bone (Boot et al., 1997; Janz et al., 2001; Janz et al., 2006). The Saskatchewan Pediatric Bone Mineral Accrual Study, which has followed over 200 boys and girls from childhood to adulthood (1991 to present)(Bailey, 1997), has provided convincing evidence demonstrating that during the growing years enhances lean mass, as well as bone accrual and that these benefits are retained at least into early adulthood (Baxter-Jones et al., 2008; Baxter-Jones et al., 2003; Jackowski et al., 2011; Scerpella et al., 2011). Furthermore, 'when' activity occurs during the lifespan is important, as at a young age can account for up to 17% of the variance in bone mineral density **(**BMD**)** seen in individuals in their late 20s (Davies et al., 2005).

In addition to the timing of PA, the mechanism by which imparts its benefits on bone is also important. Mechanical loading of sufficient intensity to promote increases in skeletal mass during growth requires strains to be greater than those of normal everyday living. If the bone is properly overloaded, the load will elicit a modeling response making the bone susceptible to new levels of mechanical demand (Bailey et al., 1996). Some of the largest loads placed on the skeleton are physiological in nature, resulting from muscle contractions (Rauch et al., 2004; Schoenau and Frost, 2002). Furthermore, gravitational or ground reaction forces are also capable of generating the loads necessary to elicit a favourable response in bone. These two loading methods have led to the investigation of the bone response to different forms of physical activity or training. Athletes involved in high-impact weight-bearing activities (e.g., gymnastics and running) have higher BMD than athletes of non-weight bearing sports (e.g., cycling and swimming), (Duncan et al., 2002), and non-active youth (Lehtonen-Veromaa et al., 2000). In addition, using quantitative ultrasound, another measure reflecting bone strength, soccer players and hockey players have been shown to have higher values in the tibia and radius, respectively. These differences were already apparent in young, pre-pubertal athletes, supporting sport-specific effects on bone strength, independent of body size, as early as the pre-puberty (Falk et al., 2010). Furthermore, training studies involving resistance training and simple jumping exercises have been shown to have positive effects on the developing skeleton through ground reaction forces and muscle contractions (Fuchs and Snow, 2002; Lehtonen-Veromaa et al., 2000; Ludwa and Klentrou, 2006; McKay et al., 2005; Nichols et al., 2001). Based on a recent systematic review (Ludwa and Klentrou, 2011), structured and controlled interventions are also effective in eliciting bone gains in youth. Future research should focus on increasing our understanding of the nature of the interaction between bone accrual and adaptation, and developing *optimal* interventions to increase PBM, involving and nutrition.

Summary

In summary, this chapter describes the responses and adaptations of children to exercise and training. These responses, for the most part, are similar in pattern to the responses of adults. The magnitude of these responses is, however, different due to the effect of growth and maturation of body structures, and differences in body size. Therefore, physiologically, children are not just small adults. Most of the anatomical and physiological differences observed between children and adults are summarized in Table 17.2.

The chapter first discusses the responses to acute aerobic exercise and to aerobic training. Similar to adults, children's cardiac output increases during exercise, reflecting the increases in stroke volume and heart rate. These responses allow for the increase in $\dot{V}O_2$ in the exercising muscles. At a given exercise intensity, as well as during maximal exercise intensity, children display higher heart rate, lower absolute stroke volume and lower absolute cardiac output. The lower cardiac output does not necessarily denote cardiac insufficiency. Rather, when adjusted for body size, no appreciable differences in cardiac output are observed between children and adults. In addition, children demonstrate lower blood pressure and size-adjusted total peripheralresistance during aerobic exercise. Their **(**a-$\bar{v}$**)**O_2difference is somewhat higher during submaximal exercise. Therefore, despite their smaller size and different activity habits, children are not disadvantaged in the performance of aerobic activities. In fact, due to their slightly favorable peripheral vascular response, as well as their greater reliance on utilization, they may even have a slight advantage in this type of activities.

Children demonstrate an exaggerated ventilatory response to a given metabolic rate, likely due to differences in airway dimensions or proportions, resulting in inefficient breathing. However, despite their inefficient ventilation, children's ventilation is greater than adults', allowing them to benefit from greater gas exchange during exercise.

Boys' maximal aerobic capacity, relative to body mass, is not different than that of men. Girls' mass-adjusted maximal aerobic

capacity is actually higher than women's. In addition, in spite of the relatively low training effect on $\dot{V}O_2$max in children, training does result in improved endurance performance. Possible reasons for this improved performance include higher movement economy, improved "tactics" and higher anaerobic ability. In addition, recovery from intense exercise is notably faster in children compared with adults.

Anaerobic performance and strength increase with growth and maturation. In fact, as opposed to *maximal aerobic power,* scaling for body size does not eliminate the age-related increase in either, maximal or strength. Therefore, factors other than body size must explain the age-related increase in and strength. These factors include possible differences in neuromuscular activation, greater co-contraction of the antagonist muscles in children, as well as lower musculo-tendinous stiffness. While children's performance in high-intensity exercise is lower than adults', their recovery is much faster. The faster recovery may be partly due to their lower amount of work output, but is also due to qualitative age-related differences, mainly due to growth and maturation.

Resistance training has been consistently demonstrated to enhance strength in children. However, while adults' strength enhancement is a result of muscle hypertrophy and neuromuscular adaptations, this is not the case in children. Rather, children's strength appears to increase solely or mostly as a result of neuromuscular adaptations. The nature of these adaptations has not been fully elucidated. In absolute terms, children's strength improves less than adults', but relative to their starting level, children may improve more than adults.

Children are able to tolerate and properly thermoregulate during exercise in the heat. While their sweat rate is much lower than adults', their blood flow to the skin is higher. Children appear to use a different 'strategy' to thermoregulate: they rely more on dissipating heat via dry heat exchange (increasing skin blood flow and losing heat by conduction and convection), and less on sweatevaporation. Therefore, they are able to conserve body water. However, they appear to be more sensitive to a given level of hypohydration, emphasizing the need to encourage fluid consumption during physical activity in a hot environment. This is particularly important for athletes competing in outdoor tournaments.

In conclusion, as demonstrated in Table 17.2, children's performance and responses to exercise and training differ from those of adults. These age-related differences are quantitative, as well as qualitative, demonstrating that in many ways, children are not small adults and should not be regarded as such.

Table 17-2 Anatomical and Physiological comparison between children and adults.

Domain	**Characteristic**	**Children compared with Adults**
Anatomical	Muscle mass *(as % of body mass)*	Boys: lower Girls: similar or higher
	Muscle composition	similar
	Bone mineral density	Lower
Aerobic exercise	Maximal oxygen uptake *Absolute (l* . *min^{-1})*	Lower

	Maximal oxygen uptake *Relative to body mass (ml* . kg^{-1} . min^{-1})	Boys: similar Girls: higher (due to lower body percentage)
	Anaerobicthreshold *(as % of maximal oxygen uptake)*	Higher
	Heart rate – rest	Higher
	Heart rate – maximal	Higher
	Heart rate – given intensity	Higher
	Heart rate – similar relative intensity	Similar or slightly higher
	Cardiac output *absolute*	Lower
	Cardiac output *relative to surface area*	Similar
	(a- $\bar{v}$)O_2 difference exercise	Higher
	Blood pressure – rest	Lower
	Blood pressure – exercise	Lower
	Muscle blood flow – exercise	Higher
	Total peripheral resistance*absolute*	Higher

	Total peripheral resistance*relative to muscle mass*	Lower
	Pulmonary ventilation*absolute*	Lower
	Pulmonary ventilation *relative to oxygen consumption*	Higher
	Cost of breathing	Higher (lower breathing efficiency)
	Alveolar ventilation	Higher
	$\dot{V}O_2$kinetics *(onsetand offset of exercise)*	Faster
	Fuel utilization	Greater relative reliance on fats
	Trainability	Lower
Anaerobic exercise	Anaerobic capacity *Absolute and relative to body mass*	Lower
	Blood lactate levels	Lower
	Anaerobic enzymatic activity	Lower
	Recovery from exercise	Faster
	Trainability	Similar (very little data available)
Muscle strength	Maximal strength *Absolute and relative to body size*	Lower

	Explosive strength *Absolute and relative to body size*	Lower
	Neuromuscular activation	Lower (see Highlight box)
	Musculo-tendinous stiffness	Lower
	Trainability	Similar
Thermoregulation	Thermoregulation effectiveness	Similar
	Sweating rate	Lower
	Skin blood flow	Higher
	Inadvertent dehydration	Similar
	Sensitivity to hypohydration	Higher

Exercises or Topics for Discussion

What are the cardiovascular factors that may change as a result of aerobic training and may explain the typical improvement in $\dot{V}O_2$max seen after training? Are the effects of aerobic training on each of these factors similar in children and in adults? Explain.

You have volunteered to help coach your school's soccer team (grades 4-6 boys and girls). The teacher who has been coaching soccer for the last few years is happy to have you aboard, as she knows you have recently become a kinesiologist. She therefore asks your advise on whether to devote any practice time to develop aerobic ability in the children (they are not particularly well-trained). She asks whether you expect any benefits of aerobic training in these children. What is your advise?

Considering osteoporosis is characteristic of old(er) age, explain why we should be concerned with bone health during childhood. What can we do in order to reduce the risk of osteoporotic fractures in old(er) age?

In your opinion, does athletic training affect (enhance/delay) growth? Justify.

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Bareket has been teaching topics in growth and development, exercise physiology and specifically, pediatric exercise physiology for about 30 years at the undergraduate and graduate level.

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3.7: Chapter 18 - The Role of Physical Activity and Lifestyle in the Elderly

This chapter is in preparation.

Authors are: Jennifer Jakobi and Catherine Amara

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3.8: Chapter 19 - What are the Health Benefits of Regular Physical Activity?



Photo 19-1 Tourists hiking, an example of physical activity.

Learning Objectives

By the end of this chapter, you should be able to:

- Recognize different types of study designs that are used to examine the relationship between physical activity and health.
- Explain the historical developments in research examining the relationship between physical activity and health.
- Describe the benefits of physical activity for reducing the risk of several chronic disease and premature mortality within adult populations.
- Illustrate the dose-response relationship between physical activity and mortality and risk for chronic disease.
- Argue for the health benefits of vigorous activities.
- Explain how different physical activity patterns can influence health.
- Describe the benefits of physical activity for health within children and youth.
- Summarize the Canadian physical activity guidelines.

Key Terms

accelerometer, bone mineral density, cancer, cardiorespiratoryfitness, cardiovascular disease, chronic disease, coronary heart disease, cross-sectional study, dementia, dose-response relationship, experimental study, fracture, ground reaction forces, joint reaction forces, physical activity, meta-analysis, moderate intensityphysical activity, musculoskeletalfitness, obesity, observational studies, physical activity, osteoporosis, prospective cohort study, randomized controlled trial, risk factor, stroke, type 2 diabetes, vigorous intensity physical activity.

Case Study: Research Approach to Study Health Benefits

In this chapter, a case study is not presented. As seen in the other chapters of this book, case presentations are very useful when

examining how engagement in physical activity triggers a given physiological response and how these physiological responses vary from one person to the next. The relationship between physical activity and a given health outcome is not as clear cut as there is no guaranteed health response for a specific person. Rather than looking at individual responses when describing the relationship between physical activity and health, risks of specific health outcomes are compared in large groups of people who have varying physical activity levels. For instance, a researcher may examine whether a greater proportion of a group of inactive people die over a 10-year prior by comparison to similar group of physically active people. Therefore, the health benefits of physical activity in this chapter are illustrated by comparing health outcomes in groups of people with varying physical activity and fitness levels. Several examples have been drawn from the literature.

The Need to Study the Influence of Physical Activity on Health

Participation in moderate intensity and vigorousphysical activity has been a major factor in the evolution of the human species. Humans emerged in conditions that required a high level of habitual physical activity, and an individuals' fitness played a significant role in their ability to survive. Hunting, gathering of food and other necessities, and escaping animal predators were necessary parts of daily life for our ancient ancestors. The most physically fit had an advantage in these activities and were more likely to have survived and passed on their genes to the next generation. Thus, survival of humankind over tens of thousands of years required high levels of physical activity and performance.

Humans began to live in larger settlements around 10,000 BC with the advent of agricultural farming. At this time, the necessity for the majority of the population to engage in moderate intensityphysical activity on a habitual basis continued. This remained the case until the industrial revolution in the latter half of the 18th century. The industrial revolution reflected a gradual transition from an agricultural–based economy towards a machine and manufacturing-based economy. After the start of the industrial revolution, technological progress continued to gain momentum with the development of steam-powered ships, the internal combustion engine, and electrical power. Over time, people enjoyed and became extremely reliant on these power sources. By the end of the industrial revolution survival of mankind was no longer contingent upon the majority of the population performing demanding physical work.

In the past century, technology continued to develop at an accelerated rate. Personal computers, fibre optics, communication satellites, the World Wide Web and a host of other inventions have changed the way we work and travel. Currently, jobs in the workplace and at home and transportation from one place to another rely even less on muscle power than they did only a generation ago (Church et al., 2011). Unless people make an intentional effort to engage in physical activity in their leisure time, it is unlikely that they will accumulate even modest amounts of moderate and physical activity. In fact, as much as 85-90% of the Canadian adult population do not accumulate 150 minutes per week of MVPA – this is less than 30 minutes of MVPA on a typical day (Colley et al., 2011). The focus of this chapter will be to discuss how the low physical activity levels within the population are having a negative influence on their health. Specifically, this chapter explains how a lack of MVPA is a risk factor for premature mortality and several chronic disease.

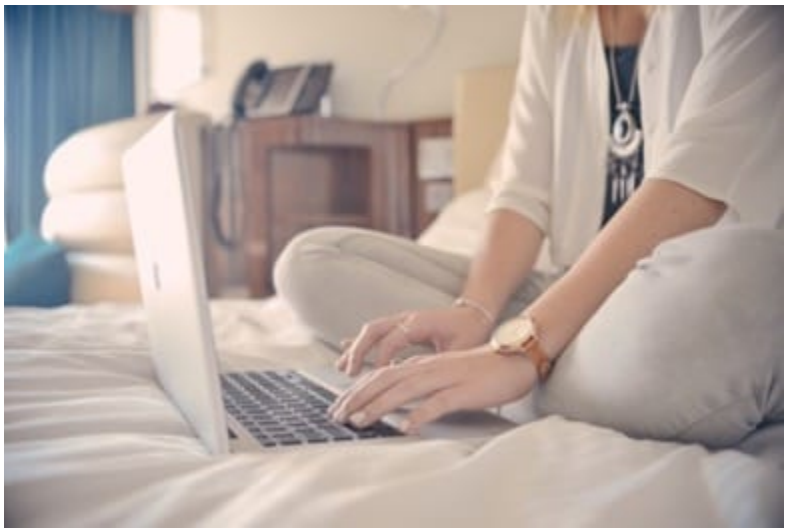


Photo 19-2 Computer use at work and at home occupies many hours of our daily lives. When you get home at the end of a long day, consider putting on your running shoes for some exercise rather than using the computer to stream your favourite show. Photo on Foter.com

Chronic disease refer to diseases that are long-lasting or recurrent. The three leading causes of death in Canada (cancer, diseases of the heart, and cerebrovascular diseases), which combined account for 6 in 10 deaths, are all chronic diseases (Statistics Canada, 2018). A lack of physical activity, particularly MVPA, hereafter referred to as physical inactivity, contributes to all three of these leading causes of death. Approximately 15% of breast cancers, 24% of colon cancers, 25% of strokes, and 27% of heart attacks in Canadian adults could be avoided if 100% of the population engaged in an appropriate amount of MVPA (Janssen, 2012). In addition to being a risk factor for the leading causes of death, physical inactivity is associated with a host of other chronic diseases and conditions, including but not limited to, obesity, diabetes, osteoporosis, physical disability, anxiety, depression, and dementia (Warburton et al., 2010; 2018 Physical Activity Guidelines Advisory Committee, 2018).

Research Design: How the Relationship between Physical Activity and Health is Evaluated

This section provides an explanation of the research study designs that are used by researchers to assess the relationship between physical activity, chronic disease risk, and mortality risk. These relationships can be assessed using observational studies andexperimental study designs. In observational studies researchers collect, record, and analyze data on study participants, but they do not intervene on the participants. That is, the physical activityof the participants is not controlled in any way by the researchers. For example, the participants may complete a questionnaire about their physical activity habits and the researchers will examine whether their reported level of MVPA is related to their future development of a chronic disease. Experimental studies involve some intervention or control of the participants' physical activity levels by the researchers. For example, the participants may be invited into a laboratory 3 times per week over 4 months where they engage in an exercise program that is prescribed and monitored by the researchers. The researchers then determine whether this exercise program impacts the participants' health or measurable risk factor for chronic disease.

Observational Studies

Two types of observational studies are commonly used in physical activity and healthresearch: cross-sectional studies and prospective cohort studies. In cross-sectional studies the physical activity and health variables are measured at the same point in time and the researchers examine whether the variables are related. To demonstrate how a cross-sectional study would be conducted and interpreted, consider the following case, which is illustrated in Figure 21-1. Within a sample of 100 men, physical activity and blood pressure were measured. The 50 participants with the lowest MVPA levels were placed within the Inactive Group while the 50 participants with the highest MVPA levels were placed into the Active Group. Based on the blood pressure measures, participants were considered to have hypertension (blood pressure >140/90 mm Hg) or a normal blood pressure (blood pressure <140/90 mm Hg). Ten of the 50 participants in the Inactive Group, or 20%, had hypertension. Five of the 50 participants in the Active Group, or 10%, had hypertension. Therefore, the likelihood of having hypertension was 100% higher in the Inactive Group by comparison to the Active Group ((20% – 10%) / 10%) 100).

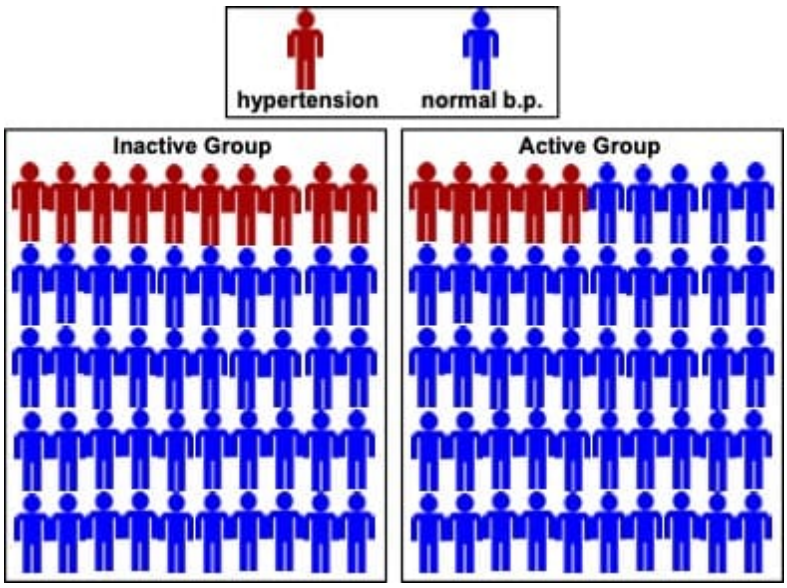


Figure 19-1 Hypothetical example of a cross-sectional study examining the relation between physical activity and hypertension.

As the likelihood of having hypertension was increased in the Inactive group in this cross-sectional study, we can say that physical activity was related or associated to hypertension. However, because this is a cross-sectional study design, we do not know if physical inactivity preceded the development of hypertension or whether hypertension proceeding the development of inactivity. We can only tell that the two variables are related to each other at a specific point in time. Thus, based on this cross-sectional study we could not imply that a lack of MVPA*caused* hypertension. In order for physical activity to be considered a cause of the health outcome, there must be evidence from the other study designs that are described below.

The second type of observational study, prospective cohort study, begins by measuring the physical activity level in a group of participants. This is often referred to the baseline period. At the baseline period the participants must not have the health outcome that is being studied. Participants are then tracked into the future, in what is often called the follow-up period, to see who develops the health outcome or chronic disease. A finding that a greater proportion of the inactive participants develop the chronic disease during the follow-up period implies that physical inactivity precedes the chronic disease, thereby providing some evidence of a causal relationship.
To demonstrate how a prospective cohort study would be conducted and interpreted, consider the following case, which is illustrated in Figure 19-2. Within a sample of 100 men without hypertension, MVPA was measured at baseline and participants were placed into the Inactive Group (least active 50 participants) and the Active Group (most active 50 participants). The participants were then tracked over 10 years, and after the 10-year follow-up was completed, their blood pressure was measured to determine whether or not they had developed hypertension in the follow-up period. Twenty percent (10 out of 50) of the Inactive Group developed hypertension compared to 10% (5 out of 50) of the Active group, indicating that the risk of developing hypertension was 100% higher in the Inactive Group.

Experimental Studies

While prospective cohort studies provide some evidence of a causal relationship, experimental studies provide an even stronger form of causal evidence. The experimental study design that is used most commonly in the physical activity and health research field is referred to as a randomized controlled trial. In this type of study, the participants are randomly allocated (e.g. name drawn out of hat) into a control group and one or more experimental group. The health outcome of interest is measured at baseline in all participants, who are then randomized into the different groups. After randomization, the experimental group(s) undergoes the physical activity intervention, while the control group is not provided with an intervention and is asked to maintain their normal physical activity level. After the intervention is completed, the health outcome is measured again in a follow-up exam to see if greater improvements occurred in the experimental group(s) relative to the control group.

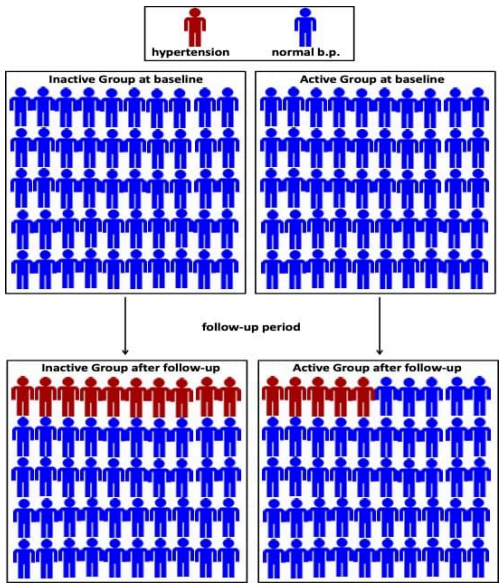


Figure 19-2 Hypothetical example of a prospective cohort study examining the relation between physical activity and hypertension.

To illustrate the randomized controlled trial design, consider a study that examines whether aerobic exercise and/or resistance improves systolic blood pressure. A total of 99 inactive women with hypertension are recruited into the study. Blood pressure is measured in all participants who were then randomly assigned into a Control Group (N = 33), an aerobic Exercise Group (N = 33), or a Resistance Exercise Group (N = 33). Over the next 3 months, the Control Group engaged in no exercise, the Aerobic Exercise Group engages in 150 minutes per week of aerobic exercise, and the Resistance Group engages in 150 minutes per

week of resistance exercise. The exercise interventions were prescribed and monitored by the research team. After the 3-month intervention was completed, the blood pressure of all 99 participants was measured again and the change in blood pressure from the baseline to follow-up exam was determined for each participant. The average change in blood pressure can be compared statistically across the three groups to compare the effects of the physical activity interventions.

Historical Perspectives on Physical Activity and Health

The modern history of physical activity and healthresearch began in the 1950's with the work of Dr. Jeremy Morris who studied the development of coronary heart disease in British workers using a prospective cohort design (Morris et al., 1953). Specifically, he found that a group of highly active double-decker bus conductors, who spent the majority of their day on their feet and climbed the stairs on the bus numerous times, had a 30% lower risk of having a heart attack during a two-year follow-up than a group of sedentary bus drivers. Dr. Morris later reported that postmen had a lower risk of developing coronary heart disease than sedentary office clerks and telephone operators (Morris and Crawford, 1958).

Evidence of the health benefits of physical activity continued to build in the latter half of the 20th century. Dr. Ralph Paffenbarger made a number of important contributions. Most notably amongst Dr. Paffenbarger's studies were those based on the alumni of Harvard University. The men who participated in his studies completed a comprehensive physical activity questionnaire and were followed for coronary heart disease, using a prospective cohort study. In his seminal paper published in 1978, Dr. Paffenbarger noted that the amount of stairs climbed, blocks walked, strenuous sports plhttps://kinesiology.ucalgary.ca/ma...ort-study-ayed, and total physical activity energy expenditure all reduced coronary heart disease risk (Paffenbarger et al., 1978). Compared to men with a physical activity energy expenditure above 2000 calories per week, men with a physical activity energy expenditure below 2000 calories per week were 64% more likely to have developed coronary artery disease during the follow-up period. This 1978 publication provided some of the first evidence that participation in physical activity – physical activity performed outside of the occupational setting – has protective effect on chronic disease risk.



Photo 19-3 physical activity has significant health benefits, often these types of activity don't look like traditional forms of exercise. Photo on Foter.com.

In the 1980's, important developments in the discipline were made with the research of Dr. Steven Blair and colleagues from the Cooper Institute in Dallas, Texas. These researchers assembled the Aerobics Center Longitudinal Study, a prospective cohort of over 13,000 adults. Rather than measuring physical activity, this research team h ad their study participants complete a maximal treadmill test to measure their cardiorespiratory (Blair et al., 1989). In addition to genetics, MVPA performed in recent weeks and months is an important determinant of fitness so, to a certain extent, fitness is an objective measure of physical activity.

Prior to Dr. Blair's work, research in the field, such as the studies conducted by Dr. Paffenbarger, relied on subjective measures of physical activity that were obtained by questionnaire. Objective measures of fitness, such as those obtained in the Aerobic Centre Longitudinal Study, provide additional insight into the contribution of physical activity to good health. The initial findings from Dr. Blair and colleagues prospective cohort study were quite striking (Blair et al., 1989). By comparison to the most fit men (top 20th percentile), the least fit men (lowest 20th percentile) had a 244% greater risk of dying during the follow-up period. Similarly,

compared to the most fit women, the least fit women had a 365% greater risk of dying during the follow-up period. Note how strong these risks are for low fitness (measured objectively) in comparison to those for physical inactivity (measured subjectively) observed by Paffenbarger and colleagues (Paffenbarger et al., 1978) in the Harvard Alumni Study. One of the consequences of using imprecise measurement techniques, which is typical of subjective measures of physical activity obtained by questionnaire, is that the relationship between physical activity and health that the researchers report on within their research paper will be weakened by comparison to what the true relationship is. In other words, the true association between physical activity and the health outcome may be underestimated when physical activity is measured using a physical activity questionnaire, which is typical of most of the published studies in this field. Thus, the way in which physical activity is measured should be considered when interpreting the associations between physical activity and health. Recent prospective cohort studies have, for the first time, looked at the association between objective measures of MVPA, as determined with an accelerometer, and health outcomes. As expected, these studies found very strong associations between MVPA and health. For instance, Borgundvaag and Janssen reported that mortality risk was increased by over 400% in the least active group by comparison to the most active group when MVPA was measured with an accelerometer (Borgundvaag and Janssen, 2017). Conversely, a review of studies that used questionnaire measures of MVPA suggested that physical inactivity was only associated with a 35% increased risk of mortality (Warburton et al., 2010).

There has been an infusion of randomized controlled trial in recent years. These randomized controlled trials have typically been fairly small in size (<100 participants), have focused on risk factor (e.g. blood pressure, bone mineral density) and not disease outcomes (e.g. heart disease, osteoporosis), and have not been as rigorously conducted as the randomized controlled trials conducted in clinical and medical research disciplines. Thus, the strength of the experimental studies in the physical activity sciences has traditionally been weak in comparison to those conducted in clinical medicine. However, since the turn of the century, large and well-controlled, randomized lifestyle based interventions have been conducted that meet the most rigorous standards (Tuomilehto et al., 2001; Diabetes Prevention Program Research Group, 2002). Consider, for instance the Finnish Diabetes Prevention Study (Tuomilehto et al., 2001). The 552 study participants were randomly assigned to an intervention group or a control group. The intervention group received individual counselling aimed at reducing weight, increasing physical activity, and improving diet. After four years, 23% of the participants in the control group had developed diabetes, which was more than double the 11% figure noted in the intervention group.

Relationships between Physical Activity and the Risk of Mortality and Chronic Disease

The next section of this chapter summarizes the relationship between physical activity with premature mortality and several important chronic disease. Example studies from the literature have been selected to highlight some of the key findings and issues. There have been entire chapters, and in some cases books, that cover the relationships that are discussed in a few paragraphs in this chapter. Table 21.1 summarizes the extent of the risk for premature mortality and several chronic conditions for the average physically inactive individual compared with the average physically active individual.

Table 21-1 Risks for premature mortality and chronic disease associated with physical inactivity

Condition	Extent of increased risk in physically inactive individuals
Premature mortality	↑↑
Cancer	↑
Cardiovascular disease	↑↑
Type 2 diabetes	↑↑↑

Osteoporosis	↑↑↑
Poormental health	↑↑
Poor health	↑↑↑

↑Risk for condition increased by approximately 1-24%; ↑↑ risk for condition increased by approximately 25-49%; ↑↑↑ risk for condition increased by 50% or more.

Physical Activity and Mortality

More than 100 prospective cohort studies have examined whether physical activity reduces the risk of premature mortality. The finding from these studies indicate that most active individuals experience about a 30% reduction in the risk of dying during follow-up compared to the least active individuals (Warburton et al., 2010; 2018 Physical Activity Guidelines Advisory Committee, 2018). The protective effects of physical activity extend to both sexes, adults of different ages, and to different racial and ethnic groups (Warburton et al., 2010; 2018 Physical Activity Guidelines Advisory Committee, 2018). Findings from one study suggest that about 1 in 6 deaths are attributable to a physically inactive lifestyle and that physically inactive people live an average of 3 years shorter than active people (Paffenbarger et al., 1986).

The pattern of the relationship between the weekly duration of MVPA and mortality risk is shown in Figure 19-3. This figure was generated from the findings of an 8-year prospective cohort study of over 400,000 Taiwanese adults (Wen et al., 2011). This figure shows how there are large differences in mortality risk between individuals who are inactive compared to those with low activity levels, and more modest differences in mortality risk between those with high activity compared to those with very high activity levels. About 70% of the total benefits that MVPA has on mortality risk occur within the first 150 minutes per week (2018 Physical Activity Guidelines Advisory Committee, 2018).

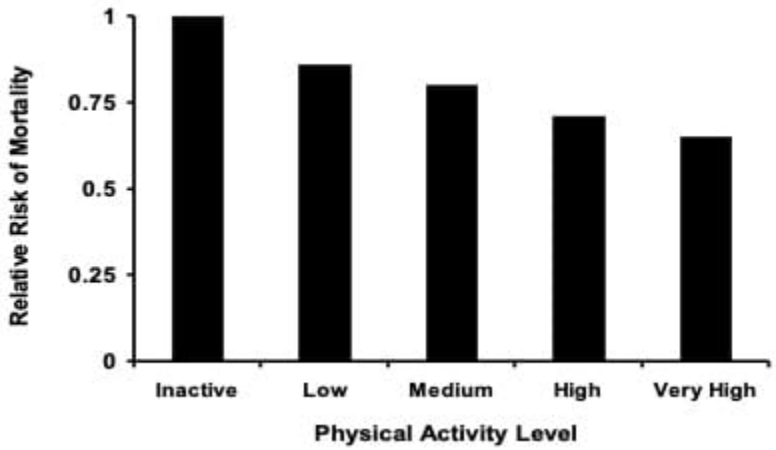


Figure 19-3. Relation between physical activity and all-cause mortality in Taiwanese adults. Risk of mortality decreases as level of physical activity increases. Figure created from data presented in Wen et al., 2011.

Walking is the most common form of physical activity among adults. Several studies have examined the influence of walking on mortality risk (Siegel et al., 1995). Walking for at least 2 hours per week is associated with a reduced risk of premature mortality. Consider findings from the Copenhagen City Heart Study, a prospective cohort of 7308 healthy men and women followed over 12 years (Schnohr et al., 2007). Compared to men who walked <½ hour per day and who walked at a slow pace, men who walked >2 hour per day at a slow pace had a 57% reduction in mortality risk. In addition to the duration of physical activity, additional findings from the Copenhagen City Heart Study indicate that the intensity is also important. Specifically, compared to men who walked > 2 hours per day and who walked at a slow pace, men who walked >2 hour per day at a fast pace had a 35% reduction in

mortality risk.

There is also strong and consistent evidence that cardiorespiratory is inversely related to mortality risk. One study examining the relation between cardiorespiratory fitness and mortality was based on a follow-up of the 1981 Canada Fitness Survey (Villeneuve et al., 1998). Within this sample of 7916 Canadian adults, an undesirable cardiorespiratory fitness level, as determined using the Canadian aerobic fitness step test, was associated with a 52% increased risk of death.

Physical Activity and Cardiovascular Disease

Within Canada about one third of all deaths are caused by cardiovascular disease (Statistics Canada, 2018). Cardiovascular disease is the leading cause of hospitalizations in Canada, with about 14% of all hospitalizations being caused by cardiovascular disease (Statistics Canada, 2008).

A vast scientific literature has examined the role that physical activity and cardiorespiratory play in the risk of cardiovascular disease. From these studies it can be concluded that physical inactivity and low cardiorespiratory fitness are causally linked to an increased risk of several forms of cardiovascular disease including coronary heart disease and stroke (Kohl, 2001). Higher physical activity and physical activity levels both have a protective effect on cardiovascular disease risk (Kohl, 2001).

The pattern of the relationship between physical activity and cardiovascular disease risk indicates that as physical activity levels get increasingly higher, cardiovascular disease risk continues to decrease (Kohl, 2001). A typical example of this pattern is illustrated in the left panel of Figure19-4. This figure shows an inverse, curvilinear association between total weekly physical activity energy expenditure – whether it be strenuous sports or other non-vigorous activities – and the risk of having a heart attack (Paffenbarger et al., 1978). This figure is based on findings from the Harvard Alumni Study that was discussed in Section 3 of this chapter.



Photo 19-4 Fire Fighting, a job requiring a high level of occupational fitness to ensure the safety of those involved. The required fitness has protective effects against cardiovascular disease.

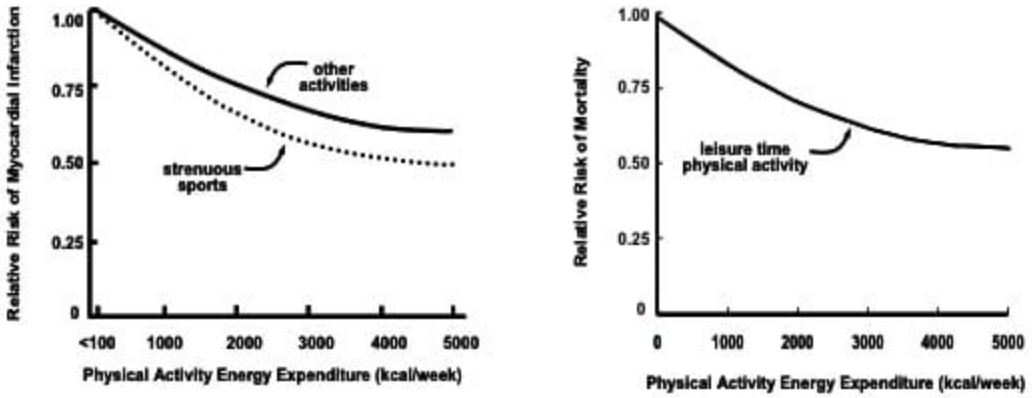


Figure 19-4 Left Panel. Relation between physical activity and coronary heart disease risk in men without cardiovascular disease. Adapted from reference (Paffenbarger et al., 1978). Right Panel. Relation between physical activity and mortality risk in older adults with cardiovascular disease. Adapted from reference (Janssen and Jolliffe, 2006).

As with coronary heart disease, a high physical activity and fitness level are causally linked to a decreased risk of stroke. A meta-analysis, which summarized the evidence from all of the published studies, indicated that relative to inactive individuals, moderately active individuals have a 17% reduction in stroke risk and highly active individuals have a 25% reduction in stroke risk (Lee et al., 2003).

In addition to providing protection against the development of cardiovascular disease, engagement in physical activity is important in the management of poor health and the prevention of mortality in individuals with existing cardiovascular disease (Jolliffe et al., 2001; Thompson et al., 2003). A prospective cohort study of 1,045 elderly men and women with coronary heart disease indicated that baseline physical activity was related to all-cause mortality risk over a 9 year follow-up period (Janssen and Jolliffe, 2006), as illustrated in the right panel of Figure 19-4. Note how the curvilinear pattern of the relation between physical activity and cardiovascular disease risk in healthy adults (left panel in Figure 19-4) is similar to the pattern of the relation between physical activity and mortality risk in adults with cardiovascular disease (right panel in Figure 19-4). Hopefully you have started to see an emerging theme about the relationship between physical activity and health – there are very large health benefits when comparing inactive individuals with even moderately active individuals, but further increases in activity level have progressively less impacts on chronic disease and mortality risk.

Physical Activity and Cancer

Cancer has overtaken cardiovascular disease as the leading cause of death in Canada (Canadian Cancer Statistics Advisory Committee, 2018; Statistics Canada, 2018). Over 200,000 new cases of cancer and 80,000 deaths from cancer occur in Canada each year (Canadian Cancer Statistics Advisory Committee, 2018). The 5 most common cancer sites are skin, prostate gland, lung, colon/rectum, and breast (Canadian Cancer Statistics Advisory Committee, 2018).

Risk factors for cancer can be non-modifiable (e.g. age, sex, race) or modifiable and can vary by the site of the cancer. There are several modifiable risk factors for cancer such as tobacco, exposure to too much ionizing radiation and too much sunlight, a poor diet (e.g. lack of fruits and vegetables), obesity, and physical inactivity and low fitness. Some risk factors, such as physical inactivity and low fitness, are associated with more than one form of cancer and thereby impact overall cancer rates and deaths. For instance, results from the Aerobics Center Longitudinal Study indicate that, within adults who were cancer free at the start of the study, the risks for dying from any form of cancer during the follow-up period decreased with increasing levels of cardiorespiratory (Farrell et al., 2007). Specifically, compared to unfit men, the risk of dying from cancer was reduced by 33% in moderately fit men and by 51% in highly fit men.

Studies of physical activity including occupational physical activity have demonstrated that physical activity is associated with reduced risk for colon cancer (Lee, 2007). Individuals engaging in aerobic physical activity for 3 to 4 hours per week at a moderate intensity orvigorous intensity have a 30% reduction in the risk of developing colon cancer. A dose-response relationship also is apparent, with risk decreasing at higher levels of physical activity.

There is consistent evidence that routine participation in physical activity provides protection against breast cancer, particularly within postmenopausal women. Consider the findings from the American Association of Retired Persons Diet and Health Study (Peters et al., 2009). This prospective cohort study followed 182,862 postmenopausal women over 7 years, during which time

6,609 women developed breast cancer. Compared to women who never engaged in activity, the risk of developing breast cancer was reduced by 8% in women who were active 3-4 times per week and by 15% in women who were active 5 or more times per week.

While the earliest studies of physical activity and cancer risk primarily focused on colon and breast cancer, more recent work has examined other cancer sites. In addition to colon and breast cancer, there is now strong and consistent evidence demonstrating that increased participation in MVPA is associated with an approximately 10% to 25% reduction in the risk of developing bladder cancer, endometrial cancer, esophageal cancer, gastric cancer, renal cancer, and lung cancer (2018 Physical Activity Guidelines Advisory Committee, 2018). Limited evidence indicates that MVPA is associated with small reductions in the risk of head and neck cancer, hematologic cancers, ovarian cancer, pancreatic cancer, and prostate cancer (2018 Physical Activity Guidelines Advisory Committee, 2018). Researchers have also considered whether physical activity provides health benefits for individuals who have been diagnosed with cancer (Newton and Galvao, 2008). The results from both observational and experimental studies indicate that participation in physical activity following cancer diagnosis can reduce cancer symptoms, help manage the side effects and outcomes of cancer treatment (surgery, radiation and chemotherapy), improve health, maintain physical function, and reduce fat gain and muscle and bone loss (Newton and Galvao, 2008). Furthermore, regular physical activity post-diagnosis increases survivorship by about 50% (Newton and Galvao, 2008).

Physical Activity and Type 2 Diabetes

More than 3 million Canadians live with diabetes, with about 90% of these being cases of diabetes (Canadian Diabetes Association, 2012). Type 2 diabetes increases the risk of cardiovascular disease, renal disease, cancer, blindness, and physical andmental disability. Life expectancy is reduced by 5 to 10 years in people with *type 2 diabetes.*

Physical activity and low cardiorespiratory are strong risk factor for the development of diabetes in both men and women. Results from the Nurses Health prospective cohort study will be used to highlight these associations (Hu et al., 1999). In an 8-year follow-up of 70,102 women from the Nurses Health Study who had no history of diabetes, the risk of developing type 2 diabetes was reduced by 25% in moderately active women and by 46% in highly active women. Interestingly, among Nurses Health Study participants who did not perform physical activity, the risk of developing type 2 diabetes w as reduced by 27% in women who walked a modest amount and by 42% in women who walked a lot. The dose-response relationship is further illustrated in Figure 19-5 (left panel).

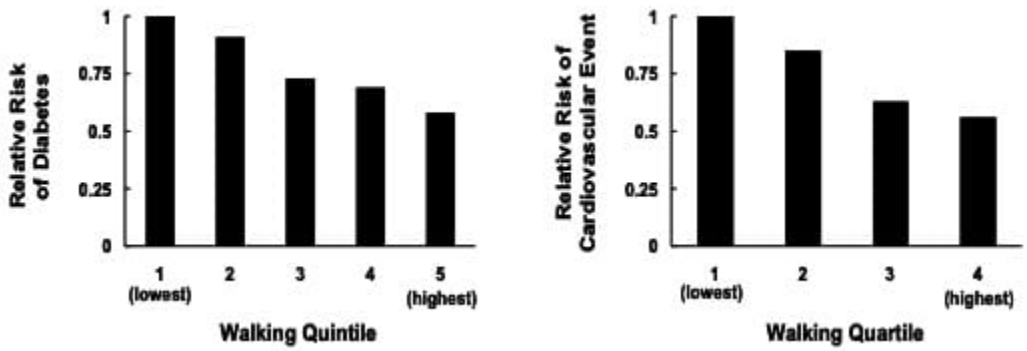


Figure 19-5 Left Panel. Relation between walking and the risk of developing diabetes in women who did not perform vigorous exercise. (Figure created from data presented in Hu et al., 1999). Right Panel. Relation between walking and the risk of developing cardiovascular disease in women with diabetes who did not perform vigorous exercise. (Figure created from data presented in Hu et al., 2001).

Additional results from the Nurses Health Study suggest that physical activity provides protection against the development of chronic disease within adults with diabetes (Hu et al., 2001). Hu and colleagues examined a subset of 5125 women from the Nurses Health Study who had diabetes at baseline. Over a 14-year follow-up period, the risk of developing cardiovascular disease was about 50% lower in the most active (top 25th percentile) diabetic women compared to the least active (lowest 25th percentile) diabetic women. Similarly, the diabetic women who walked the most (top 25th percentile) reduced their risk of developing cardiovascular disease by about 50% compared to the diabetic women who walked the least (lowest 25th percentile). The relationship between walking and the risk of cardiovascular disease in diabetic participants who did not perform physical activity is illustrated in Figure 19-5 (right panel).

Physical Activity and Obesity



Photo 19-5 Increased waist circumference has significant negative health effects.

About 1 in 4 Canadian adults have obesity and about 1 in 10 Canadian children and youth have obesity (Statistics Canada, 2018). Obesity results from a chronic energy imbalance whereby intake exceeds expenditure; physical inactivity therefore plays an important role in the obesity problem. Results from cross-sectional and prospective cohort studies have shown, in general, that physical activity is related to obesity such that physically active individuals are less likely to have and develop obesity in comparison to inactive individuals (Ross and Janssen, 2001; Ross and Janssen, 2007; 2018 Physical Activity Guidelines Advisory Committee, 2018).

There has been considerable debate about the amount of physical activity required to prevent weight gain throughout adulthood. In 2002, the Institute of Medicine recommended that adults should accumulate 60 to 90 minutes of physical activity on a daily basis to prevent unwanted weight gain (Food and Nutrition Board (Institute of Medicine), 2003). In 2003, the International Association for the Study of Obesity suggested that for most adults 45-60 minutes of moderate intensity per day would be sufficient to prevent unwanted weight gain (Saris et al., 2003). The 2018 Physical Activity Guidelines for Americans scientific report concluded that attenuation of weight gain is most pronounced when MVPA exceeds 150 minutes per week (2018 Physical Activity Guidelines Advisory Committee, 2018). Thus, the volume of physical activity needed for the prevention of weight gain is higher than the volume of physical activity needed to prevent chronic disease and premature mortality.

The role of physical activity as a treatment strategy for obese individuals has received considerable attention. Early reviews of the literature suggested that increasing physical activity in the absence of caloric restriction through diet was only associated with a 1-2 kg weight loss (National Institutes of Health National Heart Lung and Blood Institute, 1998). However, few of the earlier weight loss studies prescribed a volume of physical activity that would have resulted in a meaningful energy expenditure (Ross and Janssen, 2001). For example, Mourier and colleagues conducted an 8-week randomized controlled trial in a group of 21 overweight patients with diabetes (Mourier et al., 1997). Participants in the intervention group completed 3 aerobic exercise sessions per week, each session lasting 45 minutes at 75% of $\dot{V}O_2$max. This 8-week exercise program would have resulted in a total energy expenditure of ~6700 calorie. Given that 1 kg of fat contains 7700 *calories* of energy, the expected weight loss from this physical activity intervention would have been slightly less than 1 kg over the 8-week intervention (assuming diet remained calorie-neutral). Thus, the fact that participants in the intervention group only lost an average of 1.5 kg in this study is not surprising given the modest amount of physical activity prescribed. In other words, while 135 minutes per week of moderate intensity has a significant impact on many of the other health outcomes discussed in this chapter, based on the laws of thermodynamics, this volume of physical activity would only have a minimal effect on body fat and weight.

The results from some randomized controlled trial have indicated that physical activity in the absence of acalorie restricted diet can be associated with significant weight loss if the duration of physical activity is sufficient. For instance, Ross and colleagues demonstrated that moderately obese men and women lost about 7% of their body weight over a 3 to 4 month period by engaging in approximately 60 minutes of moderateaerobic physical activity on a daily basis, primarily in the form of brisk walking, in the absence of changes in caloric intake (Ross et al., 2000; Ross et al., 2004).

Physical Activity and Osteoporosis

Osteoporosis related fracture are common amongst older adults. In fact, at least 1 in 3 women and 1 in 5 men will suffer from an osteoporosis related fracture during their lifetime (Osteoporosis Canada, 2017). Two million Canadians are affected by osteoporosis and over 80% of fractures in people aged 50 or older are attributable to osteoporosis (Osteoporosis Canada, 2017).

Early understanding about the benefits of physical activity on the risk of developing osteoporosis was generated from cross-sectional studies (Borer, 2005). The results from these studies suggested that athletes in sports that include running, jumping, and other weight bearing activities (e.g. soccer, running, basketball, weight lifting) have higher bone mineral density (BMD) values than non-athletes. Conversely, athletes in sports that do not involve running and jumping (e.g. swimming, speed skating, cross-country skiing) have comparable BMD values as non-athletes.

Mineral and bone mass increase throughout growth and maturation and peak at around age 20. From about age 20 to age 50, bone loss tends to occur very slowly, at a rate of less than 0.5% per year. Evidence from several randomized controlled trial has demonstrated that prolonged exercise interventions that involve either ground reaction force (e.g. running, jumping) or joint reaction force (e.g. weight training) increase BMD in young adults (Borer, 2005). For example, one randomized controlled trial prescribed 8 months of weight training or running to female college students (Snow-Harter et al., 1992). The weight training consisted of 3 sessions per week of 3 sets of 10 exercises. Participants in the running group ran 7-17 km per week at 75% of their maximal heart rate. Bone mineral density in the lumbar spine region improved by about 1.3% in both the weight trainers and runners in response to the 8-month exercise interventions. These may seem like trivial changes in bone mineral density but recall that bone loss during the early adult years is very slow at <0.5% per year. Thus, these 8-month exercise programs would have reversed approximately 3 years of bone mineral loss in the young women who participated in the study. Over the long term, this may have delayed or prevented the development of osteoporosis in these women as they aged.

After age 50, bone mineral loss is accelerated, particularly in women. Postmenopausal women tend to lose between 1-2% of their bone mass each year. Exercise involving ground reaction force or joint reaction force is an effective strategy for reducing and even reversing age-related loss in bone mineral content in older adults (Borer, 2005). In one 11 month long experimental study of 39 women aged 65 years, a ground reaction force exercise program (jogging, walking, stairs) increased total body mineral by 2% (Kohrt et al., 1997). Similarly, a joint reaction force exercise program (weight training, rowing) increased in bone mineral density by 1.6% (Kohrt et al., 1997).

Limited research has considered whether engagement in physical activity helps prevent the transition into a diseased state of osteoporosis, and most of the existing studies have focused on the occurrence of osteoporotic fractures. Consider the following two examples. First, a 20 year prospective cohort study of men aged 50 years and older (Kujala et al., 2000). In this study, men who participated in physical activity were only one third as likely to have a hip fracture during the follow-up period in comparison to men who did not participate in vigorousphysical activity. Second, a 4 year prospective cohort study of elderly women (Cummings et al., 1995). In this study, women who walked for exercise in the baseline exam had a 30% lower risk of having a hip fracture during the follow-up than women who did not walk for exercise. The results from these studies confirm that physical activity, particularly when vigorous in nature, provides some protection against the risk of osteoporosis and related fractures.

Physical Activity and Mental Health

Physical activity is associated with several measures of health including mood, anxiety, depression, and cognitive function. The benefits of physical activity on mental health include acute or post-recovery effects from a single session of exercise, chronic effects from engaging in regular physical activity over many weeks and months, the prevention of mental health disorders (e.g. development of depression or dementia), and improving mental health within persons suffering from a mental health disorder.

Strong evidence demonstrates that bouts of physical activity, when performed at an intensity that exceeds the lactate or ventilatorythreshold, can result in immediate improvements in mood (Oliveira et al., 2015). Similarly, a meta-analysis of 36 RCTs concluded that participating in a 20-30 minute long bout of MVPA improves symptoms of anxiety such as feelings of apprehension, fear, worry, and nervousness (Ensari et al., 2015). Literature reviews that have compared the effects of exercise to other treatments have reported that exercise is just as effective, or perhaps even more effect, as standard care treatment for anxiety (Wegner et al., 2014; Ensari et al., 2015).

Observational studies provide evidence that physical activity protects against the onset of depression and its symptoms. In the published prospective cohort studies the risk of developing depression symptoms was reduced by approximately 50% among active adults compared to inactive adults (Physical Activity Guidelines Advisory Committee, 2018). Although the minimal, optimal, and type of physical activity needed to protect against the development of depression and its symptoms is not known, it is clear

that the volume of physical activity is related to depression in a dose-response manner such that increasing benefits occur with more activity. In one prospective cohort study of 1,947 community-dwelling adults aged 50 and older, the risk for developing depression was 131% lower in the moderately active group and 395% lower in the highly active group in comparison to the group with the lowest activity levels (Strawbridge et al., 2002). Interestingly, within that study the effect of inactivity on the risk of developing depression was greater than the effect of any of the other risk factor considered including age, gender, financial status, neighbourhood problems, education, and disability status.

Participation in physical activity is associated with improved scores on neurophysiological tests that assess processing speed, memory, and executive function (2018 Physical Activity Guidelines Advisory Committee, 2018). Physical activity also delays the onset of cognitive decline and the incidence of dementia by about 40% (2018 Physical Activity Guidelines Advisory Committee, 2018). It is encouraging that moderate intensity that most older adults are capable of performing, such as walking, have a protective effect. In one prospective cohort study of 2,257 physically capable men aged 71 to 93 years, men who walked the least (<0.25 miles per day) had an 80% higher risk of developing dementia than men who walked the most (>2 miles per day) (Abbott et al., 2004).



Photo 19-6 Physical activity has a positive effect on one's health.

In addition to being an effective preventive measure, physical activity is a useful treatment strategy for individuals with health problems. A meta-analysis of 14 randomized controlled trial that were conducted on people diagnosed with depression reported that the mean reduction in depression symptoms was equivalent to 1 standard deviation of the mean score for those measures (Lawlor and Hopker, 2001). It is also encouraging that the effects of routine physical activity on symptoms within depressed individuals are equivalent to those of drug therapy (Blumenthal et al., 2007). As with depression, a meta-analysis of 10 randomized controlled trails of older adults with cognitive impairments concluded that physical activity interventions provided meaningful benefits to cognitive function (Heyn et al., 2004).

Physical Activity and Functional Health

This section reviews evidence related to the effects of physical activity on simple functional activities within middle-aged and older adults. Examples of functional activities considered in this section include the ability to walk at a normal speed on a flat surface, climb a flight of stairs, perform basic activities of daily living (e.g. bathing, dressing, grooming), and perform activities that enable one to live independently (e.g. shopping, travel in community, light housework).

Prospective cohort studies have consistently shown that middle-aged and older adults who participate in regular physical activity, particularly aerobic activity, have a reduced risk of developing functional limitations in the order of 30% (2018 Physical Activity Guidelines Advisory Committee, 2018). Furthermore, greater amounts of physical activity are associated with lower risks than modest amounts of activity. There is also evidence that changes in physical activity influence subsequent disability risk. Specifically, a prospective cohort of 549 older adults were studied annually from 1984 to 2000 (Berk et al., 2006). Four groups were formed depending on their physical activity level during the baseline and annual follow-up visits: Sedentary (low activity at baseline and during follow-up), Exercise Increasers (low activity at baseline and high activity during follow-up), Exercise

Decreasers (high activity at baseline and low activity during follow-up), and Exercisers (high activity at baseline and during follow-up). Over the 16-year follow-up, the increase in the disability index score was far greater in the Sedentary (+0.37) and Exercise Decreasers (+0.27) than in the Exercise Increasers (+0.17) and Exercisers (+0.11). These are encouraging findings which indicate that physical activity, even when begun later in life, can help postpone the onset of physical disability.

Regular physical activity in older adults with existing functional limitations improves their functional ability. The majority of the published experimental study have included both aerobic and strengthening activities in the interventions (Physical Activity Guidelines Advisory Committee, 2018). For this reason, physical activity programs aimed at improving health in older adults with pre-existing functional limitations reflects a pattern of physical activity that involves 30-90 minutes of MVPA performed on 3-5 days per week, in which most of this time is devoted to aerobic and strengthening activity, with a shorter amount of time spent on other forms of activity such as flexibility and balance (Physical Activity Guidelines Advisory Committee, 2018).

Gender Feature

Physical Activity Improves Health in Both Genders

MVPA levels are different in men and women such that the average man accumulates more MVPA over a week than the average women. Data in a nationally representative sample of Canadian adults, in which physical activity was measured objectively over one week using accelerometers, indicates that the average Canadian man accumulates 27 minutes per week of MVPA and that the average Canadian women accumulates 21 minutes per week of MVPA (Colley et al., 2011). While 23% of Canadian men achieve the guideline for MVPA (e.g. at least 150 minutes of MVPA accumulated in bouts of at least 10 minutes), only 17% of Canadian women do (Colley et al., 2011). Chronic disease and premature mortality risks are also different in men and women. At any given age men have a higher risk of dying and developing coronary heart disease and stroke than women. Conversely, at any given age women have a higher risk of developing osteoporosis, health problems, and health problems.

Although MVPA levels, premature mortality risk, and the risk of many chronic diseases is different in men and women, participation in regular MVPA reduces the risk of premature mortality and chronic disease risk irrespective of gender. Furthermore, the strength of the relationships between MVPA, premature mortality, and chronic disease risk are remarkably comparable in men and women. Put another way, the health benefits of physical activity are similar in men and women.

Resistance Training, Muscular Fitness, and Health

The relations between physical activity and fitness with health that have been covered so far in this chapter are, for the most part, based on aerobic and cardiorespiratory-based measures of physical activity and fitness. The protective effects of strength– or resistance-based physical activities and fitness have not been as well studied. Nonetheless, the available information suggests that these types of activity and fitness measures protect against many chronic disease and mortality risk. For instance, in the Health Professional's Follow-up Study of over 40,000 men, those who reported participating in 30 minutes or more of weight training per week had a 23% reduction in coronary heart disease risk compared to those who performed no weight training (Tanasescu et al., 2002). A 19 year follow-up of 8,677 men from the Aerobics Center Longitudinal Study indicated that men within the lowest muscular strength group (lowest third) had a 64% higher risk of cancer mortality than men in the highest muscular strength group (top third) (Ruiz et al., 2009). A 13-year follow-up of 8,116 adults from the 1981 Canada Fitness Survey suggests that direct measures of musculoskeletal fitness provide some protection against mortality risk (Katzmarzyk and Craig, 2002). Take for example the sit-ups test (maximal number of sit-ups performed in 60 seconds). In comparison to the best performers, Canadian men and women in the lowest sit-ups quartiles were about 150% more likely to die during the follow-up period (Katzmarzyk and Craig, 2002).

Physical Activity and Heath in Children and Youth

Although not as plentiful as in adults, there is considerable knowledge about the health benefits of physical activity in school-aged children and youth. These studies have focused on risk factor (e.g. high blood pressure, obesity, symptoms of anxiety) that may already be present in the growing years, rather than on the disease outcomes (e.g. coronary heart disease) that do not occur until older ages. Many chronic disease take decades to develop and have their origins in childhood. Thus, it is important to study the relationship between physical activity and health within the pediatric population.

A systematic evaluation and meta-analysis of the existing studies linking physical activity to several risk factor in school-aged children and youth was published in 2010 (Janssen and Leblanc, 2010). This evaluation reached the following conclusions

regarding the amount, intensity, and type of physical activity needed for health in this age group:

Amount of Physical Activity: There is strong and consistent evidence based on several risk factor (e.g. obesity, blood pressure, blood lipids, insulin resistance, BMD, measures of health) that participating in as little as 2 or 3 hours of MVPA per week is associated with health benefits. There is a dose-response relationship between physical activity and health in children and youth. Thus, there are differences in health measures between the least active and somewhat active young people, and also between somewhat active and highly active young people.

Intensity ofPhysical Activity:Moderate intensity andvigorous (MacIntosh et al., 2021) are associated with many health benefits. The available information suggests that vigorous intensity activities provide additional health benefits beyond moderate intensity activities. At present, there is a lack of evidence on the health benefits of low intensity activities.

Type of Activity: Many health outcomes responded almost exclusively to aerobic -type physical activities. However, BMD is more favourably affected by resistance and high-impact activities such as jumping exercises.

Research Feature

Physical Activity in Preschool Aged Children

A new area of research interest within the physical activity and health field is to discern the health benefits of physical activity for children younger than 5 years of age. Society has traditionally thought of the early years as being a time of life when children are habitually “active enough.” However, studies that have assessed the physical activity levels of preschool children using objective measures have reported MVPA levels that are much lower than what most people would expect.

Take for instance, a 2011 study of 30 preschool (3 to 5 years old) children from Ontario (Obeid et al., 2011). Children in this study wore accelerometers on their right hip for one week. These accelerometers detected and recorded the participants’ movement every 3 seconds. The results of this study indicated that, in a typical day, participants accumulated 219 minutes of physical activity. However, 66% of this activity was of a low intensity; only 21% was of a moderate intensity and only 14% was of a vigorous. Additional findings indicated that the 45 minutes per day of MVPA that the participants accumulated was extremely intermittent and sporadic in nature. In fact, 95% of the MVPA was accumulated in brief bursts of activity that were less than 15 seconds in length. Interestingly, there were no differences in light, moderate, or vigorous intensity physical activity levels in the boys and girls that were examined in this study. This suggests that gender differences in physical activity do not start at a young age.

A key strength to this study is the objective assessment of physical activity using accelerometers. In particular, the measurement of each 3 second time period over a full week allowed the researchers to measure the sporadic physical activity patterns of preschool aged children. A key limitation of this study is its small sample size. Larger and more diverse studies of preschool aged children are needed to gain a better understanding of the physical activity levels in this age group. Future research also needs to address the relationship between physical activity and health in preschoolers.

The period of life for which we know the least about the health benefits of physical activity is the early years. As part of a rigorous process to develop physical activity recommendations for the early years, a group of experts recently conducted a systematic review of the available studies to evaluate the relationship between physical activity and health indicators during the early years (Carson et al., 2017). This committee found evidence from observational studies that higher amounts of physical activity are consistently associated with favourable indicators of motor development, fitness, and bone and skeletal health. Furthermore, favourable associations were found for a variety of types of physical activity, including active play, aerobic activities, dance, and both organized and unstructured activities. For infants, more time spent in the prone position (i.e. tummy time) was associated with good health. More research in this age group is needed to determine the specific amount, intensity, frequency, or type of physical activity needed to promote good health.

Dose-Response Issues in Physical Activity and Health

Components of Physical Activity Dose

The primary components used to determine physical activity dose, or the total energy expended from physical activity, are duration and intensity. Physical activity is usually defined as being of a light, moderate intensity, orvigorous. As explained below, physical activity intensity can be defined in both relative and absolute terms.

Most exercise physiologists define physical activityintensityin relative terms.Relative intensity refers to the level of effort required by a person to do an activity relative to their ownmaximum.For instance, when using heart rate, moderate intensity,is defined as 50 to 69% of maximal heart rate whilevigorousis defined as 70% or more of maximal heart rate.

Another way to express physical activity intensity is in absolute terms, which is the approach taken by most researchers who look at the relationship between physical activity and health. Absolute intensity refers to the absolute amount of energy used by the body per minute of activity, where 1.0 metabolic equivalent(MET) refers to resting energy expenditure.When using an absolute scale,moderate intensity activities refer activities from 3.0 to 5.9 MET s andvigorousrefers to activities where the MET value is 6.0 or higher.This method of describing moderate to vigorous physical activity ignores the capabilities or fitness of the client (MacIntosh et al., 2021).

One way to sum up how much physical activity a person has accumulated over a week, or their dose of physical activity, is to calculate the energy expenditure based on theMETvaluesand the duration of all activities performed.For instance, if a person performs 100 minutes ofmoderate intensityactivity at 4 METs and 30 minutes ofvigorousat 8.0 METs over a week, their weekly dose of physical activity is 640 MET minutes (100 4 + 30 8) or 10.7 MET hours (640 MET minutes/ 60minutes per hour).

Higher intensity activities appear to have a beneficial effect on some health outcomes independent of the physical activity dose (Paffenbarger et al., 1978; Hu et al., 1999; Manson et al., 2002). Consider the example illustrated in Figure 19-6. This example is explained in greater detail in the Highlight Box. This figure comes from a cross-sectional study of American adults (Janssen and Ross, 2012). Within that study, a given amount of energy expended fromvigorous was associated with a greater reduction in the prevalence of the metabolic syndrome than a corresponding amount of energy expended from moderate intensity activity.

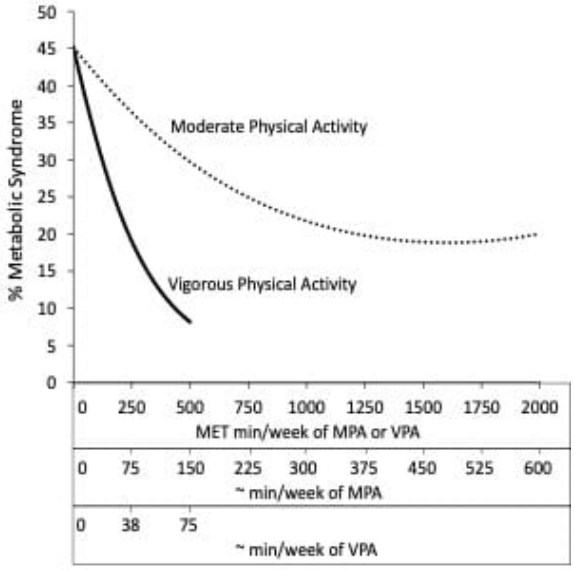


Figure 19-6 Estimated prevalence of the metabolic syndrome according to energy expenditure (minutes per week) of physical activity (MPA) and physical activity (VPA). In addition to the energy expenditure, the approximate times needed to accumulate the energy expenditure for moderate and vigorous activity are also shown on the x-axis. Figure taken from reference (Janssen and Ross, 2012).

Estimated prevalence of the metabolic syndrome according to energy expenditure (minutes per week) of physical activity (MPA) and physical activity (VPA). In addition to the energy expenditure, the approximate times needed to accumulate the energy expenditure for moderate and vigorous activity are also shown on the x-axis. Figure taken from reference (Janssen and Ross, 2012).

Highlight Feature: Physical Activity Intensity Impacts Health

In this cross-sectional study of 1,841 adults, the authors used accelerometers to measure physical activity over 7 consecutive days (Janssen and Ross, 2012). The data recorded from the accelerometers was used to estimate the energy expenditure from physical activity (3.0 – 5.9 MET s) and from physical activity (≥ 6.0 METs). In addition to wearing the accelerometers for one week, participants had their waist circumference measured, their blood pressure taken, and a fasting blood sample drawn. Triglyceride, high density lipoprotein (HDL)-cholesterol, and glucose levels were measured in the fasted blood

samples. Participants who had 3 or more of the following risk factor were considered to have metabolic syndrome: high waist circumference (men ≥ 94 cm, women ≥ 80 cm), high triglycerides (≥ 1.7 $mmolL^{-1}$), low HDL-cholesterol (men < 1.0 $mmolL^{-1}$, women < 1.3 $mmolL^{-1}$), elevated blood pressure (systolic pressure ≥ 130 mm Hg or diastolic pressure ≥ 85 mm Hg or use of hypertension medication), and elevated glucose (≥ 5.6 $mmolL^{-1}$ or diagnosed diabetes) (Alberti et al., 2009). The metabolic syndrome is a clustering of cardiometabolic risk factors that increases cardiovascular disease, diabetes, and all-cause mortality risks (Ardern and Janssen, 2007).

The results from this study, which are further illustrated in Figure 21.6, show that energy expenditure from physical activity had a smaller impact on the metabolic syndrome than the same energy expended from physical activity. For instance, between 0 and 500 MET minutes per week of moderate intensity physical activity, the prevalence of the metabolic syndrome risk decreased by 15%. While between 0 and 500 MET minutes per week of vigorousphysical activity, the prevalence of the metabolic syndrome decreased by 37%. To accumulate 500 MET minutes, one would have to engage in about 150 minutes of moderate physical activity and only 75 minutes of vigorous physical activity. Thus, within this study half the duration of vigorous physical activity produced double the health benefit. Furthermore, the benefit obtained from moderate intensity physical activity elicits no further benefit after about 1200 MET minute.

The second main component of physical activity dose, duration, is a function of the session duration and frequency of participation in activity. Results of experimental studies that evaluated the effect of a single longer bout of activity (e.g. a single 30 minute session) to the effect of three or four shorter bouts of activity performed across the day (e.g. three 10 minute sessions), performed on several days per week, indicate that performing multiple shorter bouts produced changes in fitness and risk factor for cardiovascular disease and diabetes that are quite similar to those produced by the single longer bout (Hardman, 2001). For example, in a randomized controlled trial of 50 overweight women, 30 minutes of brisk walking performed *in a single session* on 5 $days{\cdot}wk^{-1}$ resulted in a 14% increase in $\dot{V}O_2max$ and a 7% loss in weight; while 30 minutes of brisk walking *accumulated in 3 sessions* on 5 $days{\cdot}wk^{-1}$ resulted in a 16% increase in $\dot{V}O_2max$ and a 9% loss in weight (Jakicic et al., 1995).

Observational study that have used accelerometers to assess physical activity on a minute-by-minute basis over 7 full days have considered whether MVPA accumulated in intervals as short as one minute can benefit health, as long as enough of this sporadic or intermittent physical activity is accumulated over the course of the day. These studies have found that when the total duration of physical activity is matched, sporadic or intermittent physical activity is associated with the same health benefits as longer bouts of physical activity (2018 Physical Activity Guidelines Advisory Committee, 2018). For instance, in a cross-sectional sample of Canadian adults, each additional MET -hour per week of MVPA was associated with a 10% decrease in the likelihood of having the metabolic syndrome irrespective of whether that MVPA was accumulated in one or two bouts of physical activity lasting at least 10 minutes or through many short spurts of sporadic physical activity (Clarke and Janssen, 2014).

Another question to ask is whether a person should accumulate their suggested weekly dose of physical activity over several days of the week, or whether a couple of longer sessions performed on 1 or 2 days would be acceptable. Consider, for instance, the “weekend warrior” who is quite active, but who compresses all of their weekly activity into the weekend. Is this a healthy pattern of physical activity? A recent study addressed this question by comparing the benefits of the weekend warrior pattern of physical activity to the benefits of a regularly active pattern of physical activity where participants were active on at least 3 days of the week (O’Donovan et al., 2017). In this study both physical activity patterns were associated with a reduced risk of cancer, cardiovascular disease, and mortality. Furthermore, the risk reductions were very comparable in the weekend warrior and regularly active groups. This suggests that the total amount of physical activity accumulated over the week is important while the pattern of accumulation is not.

Minimal and Optimal Amounts of Physical Activity

A large proportion of the population would like to know the minimal amount of physical activity needed to produce meaningful health benefits. This likely depends on a person’s current physical activity level. A person who has been at complete bed rest may benefit just from getting out of bed for a few minutes each day. Some of the research presented in this chapter suggests that a small amount of walking, even at a light pace, can reduce mortality risk in very inactive individuals with a chronic disease such as diabetes. Unfortunately, few studies have carefully considered the minimal amount of physical activity needed for good health in the general public. Nonetheless, the associations between physical activity and various health outcomes, as illustrated in Figures 19-3 through 19=6, indicate that only a modest amount of moderate intensity is required to bring about meaningful benefits for many health outcomes. This is perhaps best reflected from the findings of a study of over 400,000 Taiwanese adults. This study

found that individuals who accumulated 90 minutes per week of MVPA, which averages out to only 15 min per day, had a 14% reduced risk of mortality and had a 3 year longer life expectancy compared to individuals who accumulated no MVPA (Wen et al., 2011).

Similar to the issues around defining the minimal amount of physical activity needed for health, it is unclear as to what point an increase in physical activity provides no further health benefits. The plateau may also vary by health outcome – it may be quite low for some health outcomes and quite high for others. For instance, there is a linear relation between miles run and HDL-cholesterol levels that does not plateau even at 80 miles run per week (Williams, 1997). This suggests that continued health benefits, at least for some variables, can be achieved even after running 10 hours per week at a vigorous pace. Although health benefits may not completely level off at high activity levels, there are certainly diminishing returns once a moderate level of physical activity is reached (2018 Physical Activity Guidelines Advisory Committee, 2018).

Translation of Research Findings into Public Health Recommendations

Recommendations for Fitness and Health

Scientific understanding of the health benefits of physical activity is of little relevance if this information cannot be translated to the general public so they can apply this to their lives to improve their health. In recent decades there has been increasingly growing efforts to develop public health messages, through physical activity guidelines, about the appropriate amount, intensity, frequency, and type of physical activity needed for good health. These guidelines have been developed by experts in the field who were tasked with synthesizing the findings from the scientific literature and applying the information to create messages that can be clearly communicated to the public.

The first endorsed recommendations for physical activity were those of the ACSM**.** In their 1975 exercise guidelines book (American College of Sports Medicine) and 1978 position statement (American College of Sports Medicine), the ACSM recommended that people engage in exercise on 3-5 days of the week for 15-60 minutes at an intensity of 50-85% $\dot{V}O_2$max. These recommendations were geared towards the appropriate exercise for developing and maintaining fitness in healthy adults. They were not geared towards health outcomes. For two decades after the ACSM guidelines were developed, physical activity guidelines continued to focus on the appropriate exercise for fitness. This changed in 1995 with the publication of the U.S. Centers for Disease Control (CDC) and the ACSM recommendation on physical activity and public health (Pate et al., 1995). This recommendation was intended to communicate to the general public how much and what types of physical activity are needed to maintain good health. The following recommendation was issued by the panel: “Every U.S. adult should accumulate 30 minutes or more of moderate intensity on most, preferably all, days of the week”. Since these initial public health recommendations for physical activity and health, several other organizations and countries have developed their own recommendations. Canada’s most recent guidelines and recommendations for physical activity are discussed in the following few paragraphs (Tremblay et al., 2011; Tremblay et al., 2016; Tremblay et al., 2017). Note that the recommendations for children of the early years (0-4 years) and school-aged children and youth (5-17 years) are no longer contained within a stand along physical activity guideline. Rather, the physical activity recommendations for these age group are now included within 24-hour movement behaviour guidelines. These 24-hour guidelines also include recommendations for sedentary behaviour and sleep, which are not discussed here. Copies of Canada’s physical activity and 24-hour movement guidelines and their accompanying recommendations and promotional materials can be downloaded for free at http://www.csep.ca/guidelines.

The Early Years (0-4 years)

- Infants (< 1 year): Be physically active several times a day in a variety of ways, particularly through interactive floor-based play—more is better. For those not yet mobile, this includes at least 30 minutes of tummy time spread throughout the day while awake.

- Toddlers (1-2 years): At least 180 minutesd^{-1} of a variety of physical activities at any intensity, including energetic play, spread throughout the day—more is better.

- Preschoolers (3-4 years): At least 180 minutesd^{-1} spent in a variety of physical activities spread throughout the day, of which at least 60 minutes is energetic play—more is better.



Photo 19-7

Play is the most common form of exercise for young children.

School-Aged Children and Youth (5-17 years)

- Accumulate at least 60 minutes per day of physical activity involving a variety of aerobic activities.Vigorousphysical activities, and muscle and bone strengthening activities should each be incorporated at least 3 days per week;
- Several hours per day of a variety of structured and unstructured light physical activities.

Adults (18-64 years)

- Accumulate at least 150 minutes of vigorous aerobic physical activity per week, in bouts of 10 minutes or more.
- It is also beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 days per week.
- More physical activity provides greater health benefits.

Older Adults (65 years and older)

- Accumulate at least 150 minutes of vigorous aerobic physical activity per week, in bouts of 10 minutes or more.
- It is also beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 days per week.
- Those with poor mobility should perform physical activities to enhance balance and prevent falls.
- More physical activity provides greater health benefits

Summary

In the current technologically driven society, the majority of the population is extremely inactive (Colley et al., 2011; Colley et al., 2017). Unfortunately, there is now clear and strong scientific evidence that, irrespective of age and gender, an inactive lifestyle

is strongly and causally related with several measures of poor health. Because physical inactivity is a highly prevalent condition and because it has such a strong impact on chronic disease risk, a significant proportion of chronic disease in Canada is directly attributable to physical inactivity. In fact, about 1 in 4 cases of coronary artery disease, stroke, and colon cancer in Canada are caused by inactivity and about 1 in 3 cases of diabetes and osteoporosis are caused by inactivity (Janssen, 2012).

Systematic reviews of the literature and consensus meetings help by Canadian and international experts in the area of physical activity and health, have led to improved physical activity recommendations for Canadians of all ages (Tremblay et al., 2011; Tremblay et al., 2016; Tremblay et al., 2017). These guidelines indicate that to achieve substantial health benefits, adults and older adults should accumulate at least 150 minutes of MVPA on a weekly basis, school-aged children and youth should accumulate at least 60 minutes of MVPA on the average day, and children of the early years should accumulate at least 180 minutes of activity of any intensity on the average day. Activity levels above these cut- points will be associated with even greater health benefits.

Exercises or Topics for Discussion

Add Topics of Discussion

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3.9: Chapter 20 - High Altitude Physiology- Climbing Earth's Highest Peak

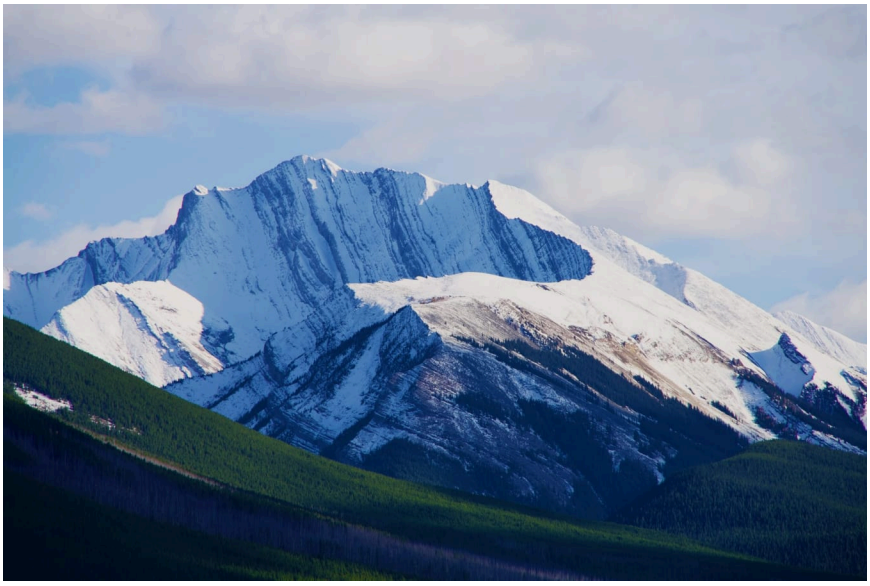


Photo 20-1 Mountain in Kananaskis (photo by Brian R. MacIntosh)

Learning Objectives

After reading this Chapter, you will:

- Describe the effect of high altitude on the oxygen cascade
- Describe the initial and prolonged effect of high altitude on respiratory, cardiovascular, and metabolic function
- Describe the limiting factors during exercise at high altitude
- Discuss pathophysiological effects of high altitude with respect to the central nervous and pulmonary systems
- Discuss the rationale behind training in the high-altitude environment

Key terms

barometric pressure, hypoxic ventilatory response, hypercapnic ventilatory response, hypoxic pulmonary vasoconstriction, Alveolar gas equation, alveolar ventilation, oxygen dissociation curve, peripheral chemoreceptors, central chemoreceptors, acid-base balance, Fick equation, ventilation perfusion mismatch, diffusion limitation, Fick principle, erythropoiesis, periodic breathing, acute mountain sickness, high altitude cerebral edema, high altitude pulmonary edema, acclimatization, adaptation.

Case Presentation: Rachel Takes a Sojurn

Through her success with cycling and her Kinesiology studies, it was always clear that Rachel had lofty ambitions. Consistent with this, after completing her second year of University, Rachel decided to try her hand at climbing with the ultimate goal of reaching the top of Mt Everest.

Although very fit from her athletics, she had not spent any time at high altitude and so decided to take a trip to the Nepal Himalaya, to undertake a 15-day trek to Everest Base Camp at around 5300m above sea level. In her summer break, she set aside one month for this trip. At around day 4 (3800m), Rachel – who normally can run very fast before getting puffed, found herself breathless, slowly trekking up a steady incline to the Tengboche monastery. As she continued to trek towards the base of Mt Everest, she noticed many further changes to her body: her resting heart rate was increased; her ability to run was decreased; and her sleep was less restful.

Three days after huffing and puffing her way up to the monastery, Rachel is delighted to reach the mighty Khumbu glacier and Everest base camp. She is interested to find a group of physiologists performing research up at basecamp and quickly volunteers for their studies. She performed various exercise, respiratory, vascular, and blood tests for these researchers.

The next morning, she woke up feeling like she hadn't even been to sleep and began to feel a little bit nauseous. Over the course of the day, her nausea worsened, and she started to develop a headache. By lunch time, Rachel was in a bad state; she didn't even feel like eating her beloved Nepali momo's! Her headache was pounding, she had lost her appetite, and felt like she had no energy.

At this stage, a knowledgeable Sherpa recognized these features as being consistent with Acute Mountain Sickness (AMS). An expedition doctor, resident at Everest base camp, examined Rachel and found a heart rate of 100 b·min^{-1}, BP 120/80 mmHg and a peripheral 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-dea#capillary">capillary O_2 saturation (2 in the peripheral circulatory system"" href="https://kinesiology.ucalgary.ca/maci.../pha-tend#spo2">SpO_2) of 80%. Her lungs were clear to auscultation and despite feeling sick, Rachel was still fully alert. The doctor confirmed the clinical diagnosis of AMS and knowing that the most effective treatment for AMS is to descend to a lower altitude, he advised trekking down with her Sherpa to a village 1000m lower.

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Introduction

Over 400 years ago (1650 AD), Blaise Pascal persuaded his brother-in-law to carry the newly invented mercury barometer to the top of a mountain in central France. In doing so, the pair discovered that barometric pressure (derived from the Greek words *Baros* meaning 'weight', and *metron* meaning 'measure') decreased with increasing altitude. 300 years ago, the composition of the air and the critical importance of oxygen were discovered (Lavoisier 1777). Therefore, it may seem surprising that it was not until 200 years ago that the early balloonists fatally unearthed the disturbing, yet seemingly obvious, truth; ascent to high altitudes can place an enormous stress on the human body – even to the point of causing death (see Table 20-1).

Table 20- 1 Ten important discoveries in high altitude physiology

Date	Discoverer	Discovery	
1644	Torricelli	Invented the mercury barometer	
1648	Pascal	Pressure decreases with increasing altitude	
1777	Lavoisier	Discovery of oxygen	
1875	Tissandier	Zenith balloon mission	

1878	Paul Bert	The publication ‘barometric pressure‘ describing, for the first time, the oxygen and carbon dioxide dissociation curves for haemoglobin	
1911	Douglas and Haldane	Pikes peak expedition showed the increase in ventilation with 2 in the arterial blood or a part of the body is less than adequate” href=”https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia”>hypoxia	
1913	T. H Ravenhill	Publishes ‘Some Experiences of Mountain Sickness in the Andes’ in which he describes mountain sickness including pulmonary and cerebral subclassifications	
1944	Houston and Riley	Operation Everest 1: showed that it is possible to survive at the barometric pressure of the summit of Everest	
1953	Tenzing and Hillary	First ascent of Mt Everest	
1978	Messner and Habeler	First ascent of Mt Everest without supplemental oxygen	

Subsequent work identified factors other than altitude that can influence barometric pressure including latitude (with higher pressures near the equator), season, temperature, and humidity. Altitude, however, has by far the greatest influence on barometric pressure and the relationships between altitude, barometric pressure, and inspired oxygen pressure are shown in Figure 20-1.

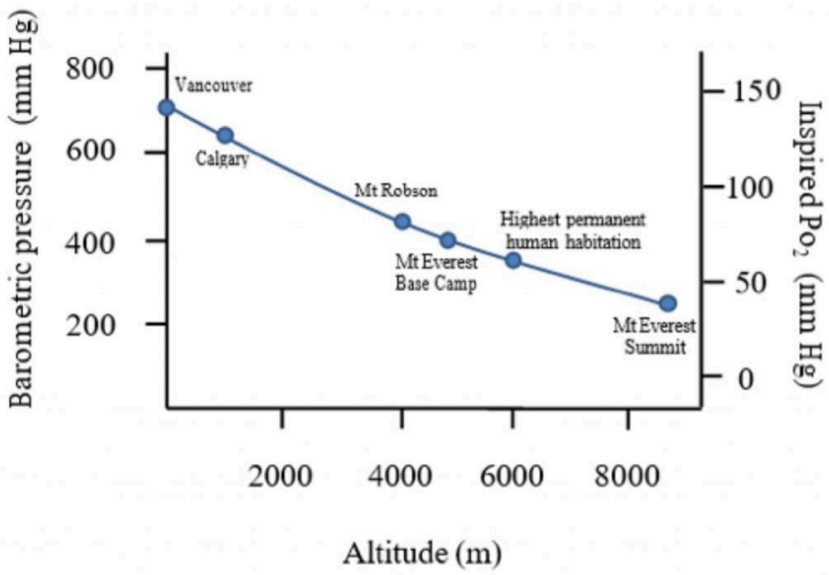


Fig 20-1 Relationship between barometric pressure and altitude and partial pressure of O_2 and altitude. Barometric pressure on the left axis (ranging from 0 to 700 mmHg) is plotted against altitude (from sea level to 9000 m). On the right, partial pressure of oxygen is shown, plotted against altitude. Example cities are plotted with their altitude, barometric pressure and partial pressure for O2: Vancouver at sea level is 640 mmHg 100 kPa, and 148 mmHg; Calgary at 1045 m is 82.7 kPa and 132 mmHg, Mount Robson at 3954 m is 62 kPa and 85 mmHg, Mt Everest Base Camp is 5000 m, 53 kPa and 73 mm Hg, Highest permanent human habitation is 6000 m, 44.4 kPa and 52 mmHg and mt Everest Summit is at 8849 m, 33.7 kPa and 40 mm Hg." width="1024" height="696"> **Fig 20-1 Relationship between barometric pressure and altitude and partial pressure of O_2 and altitude.** As altitude increases there is a decline in barometric pressure and inspired partial pressure of oxygen.

This causal chain (increased altitude decreased barometric pressure decreased inspired oxygen pressure) forms the basis for understanding the effects of altitude on the human body. In this chapter we will explore the respiratory, cardiovascular, muscular, haematologic, and neurologic responses to altitude.

Respiratory Response

At sea level, barometric pressure (PB) of the air is approximately 760 mm Hg (Figure 20-1). When this air is inspired into the human airways, it is warmed and moistened with water such that the inspired pressure is 47 mm Hg lower than barometric pressure. The fraction of this inspired air that is oxygen is about 0.2094. Therefore, the pressure of oxygen inspired is given by the product of the fraction of oxygen and the dry inspired air pressure.

This is shown in equation 20-1:

$PI\ O_2 = (PB - P\ H_2O) \cdot FIO_2$ **Equation 20-1**

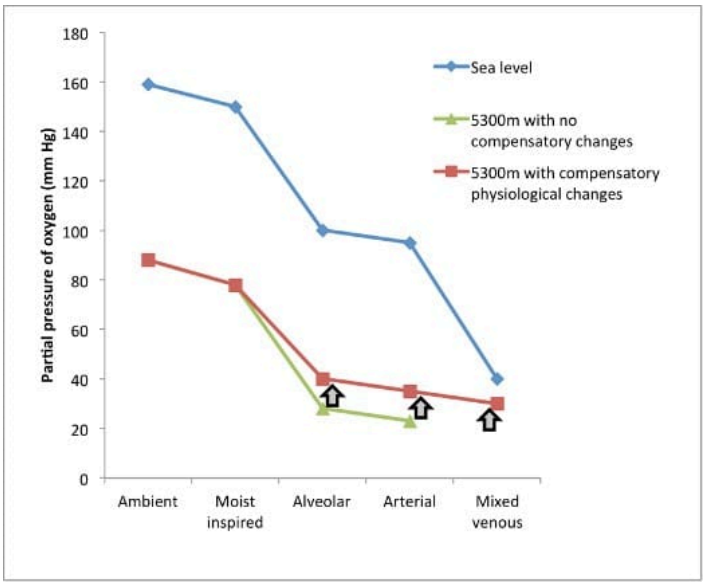
Where, PIO_2 = 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure of inspired oxygen; PB = barometric pressure;- PH_2O = water vapour pressure; FIO_2 = fraction of inspired oxygen.

When we ascend to altitude, our inspired oxygen pressures (PIO_2) decrease on account of the decreased barometric pressure. The water vapour pressure and the fraction of oxygen in the air are, however, constant across altitudes for a given relative humidity. The journey of oxygen molecules from the ambient air to where they are finally used is long and arduous. This path that oxygen must follow is known as the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade and can be used as a framework to help understand the effects of high altitude on the respiratory, cardiovascular, and haematologicsystems and how they respond during exercise.

Oxygen cascade

Let us consider our friend, Rachel. Before embarking on her trek, at UBC Vancouver (sea level) her PIO_2 is approximately

150 mm Hg (Figure 20-2). Her alveolar PO_2 is considerably lower than this and is determined by the balance of oxygen removal by pulmonary 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-dea#capillary">capillaries and oxygen replenishment by ventilation. At sea level and with resting ventilation, her alveolar PO_2 is approximately 100 mm Hg; giving a drop from the pharynx to the alveoli of 50 mm Hg. Between her alveolae and the pulmonary blood there is a further decrease of approximately 5-10 mm Hg owing to $\dot{V}:\dot{Q}$ mismatch, imperfect diffusion, and some shunt. Across the tissues the PO_2 drops further according to the oxygen uptake of the specific tissues.



2 is plotted for these locations: for sea level, and 5300 m altitude with and without compensation. Values for sea level are: 160 mmHg for ambient, 150 mm Hg for moist inspired, 100 mm Hg for alveolar, 95 mm Hg for arterial, and 40 mm Hg for mixed venous. Values for 5300 m altitude without compensation are: 87 mm Hg for ambient, 79 for moist inspired, 27 for alveolar and 22 for arterial. With physiological compensation (increased ventilation and increased cardiac output), values for ambient and moist inspired are not changed, but arterial moves up to 40 mm Hg and arterial is 35. Mixed venous is 30. " width="522" height="430"> **Figure 20-2 PO_2 values from inspired air to mixed venous blood at sea level and at 5300m, with (red line) and without (green line) compensatory changes.** Note the dangerously lowPO_2 in the alveoli and arterial blood when these compensatory changes are not made. Note that it is impossible to remove as much O2 from the arterial blood at 5300m as was removed at sea level unless physiological compensation occurs.

The situation at altitude is, however, different. For example, when Rachel is up at Everest base camp (~5300m); the barometric pressure is 420mm Hg, which yields a PIO_2 of 78 mm Hg. Let us now consider the hypothetical situation that would occur if Rachel had no respiratory, cardiovascular, or haematologic changes. In this hypothetical situation, the difference between inspired and alveolar PO_2 (determined by the balance between ventilation and pulmonary O_2 uptake) would not change from sea level (50 mm Hg), giving an alveolar PO_2 of 28 mm Hg and hence an arterial PO_2 of ~ 23 mm Hg, a remarkably low value that is probably incompatible with life. Luckily for Rachel, her body does respond to this reduced oxygen environment with significant respiratory, cardiovascular, and haematologic changes that make life at this altitude possible. We will now consider each step along the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade in a little more detail.

Inspired to Alveolar Partial Pressure of Oxygen

As one might have guessed, the respiratory system responds to the decrease in oxygen levels at high altitude with an increase in ventilation. This increase in ventilation acts to increase the pressure of oxygen in the alveoli. When we increase ventilation, however, it is not only the oxygen levels in the alveoli that change; an increase in ventilation causes a decrease in alveolar CO_2 pressure ($PACO_2$).

Because nearly all the CO_2 at the end of expiration is due to the body's production of CO_2 (i.e, the contribution of inspired ambient CO_2 can be ignored), the amount of CO_2 that is removed (or produced) by the body will be equal to the ventilation multiplied by the fraction of CO_2 in the exhaled breath. This fraction of CO_2 can be converted to a pressure by way of a conversion factor K:

2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...-%CC%87o2-peak">$\dot{V}CO_2 = \dot{V}A \cdot (\cdot K^{-1})$ **Equation 20-2a**

Rearranged, this gives the ventilation equation.

$PACO_2 = \dot{V}CO_2 \cdot \dot{V}A^{-1} \cdot K$ **Equation 20-2b**

Where $PACO_2$, is the alveolarPCO_2, 2 is usually measured as pulmonary release of carbon dioxide but can also be measured with sampling of arterial and venous blood and measurement of blood flow (Fick equation). "" href="https://kinesiology.ucalgary.ca/maci...a#v-%CC%87co2-">$\dot{V}CO_2$ is the body production of CO_2 in $L \cdot min^{-1}$ (normally ~ 200 ml/min at rest), $\dot{V}A$ is alveolar ventilation in $L \cdot min^{-1}$ (equal to the total ventilation minus the dead space ventilation; see chapter 7 and K is a constant (0.863) necessary to equate dissimilar units for $\dot{V}CO_2$ ($ml \cdot min^{-1}$) and $\dot{V}_A$ ($L \cdot min^{-1}$) to P_ACO_2 pressure units (mm Hg). The ventilation equation is useful to us, because it highlights the inverse relation between P_ACO_2 and $\dot{V}A$; a doubling of ventilation will halve the alveolar PCO_2 or halving the $\dot{V}_A$ will double the P_ACO_2.

How does an increase in ventilation affect alveolar O_2 pressure? Intuitively, the alveolar PO_2 will depend upon the pressure of inspired O_2. Alveolar will also depend on the ventilation; the higher the ventilation, the more oxygen there will be in the alveoli. Because we have already seen that ventilation is inversely proportional to $PACO_2$, we can appreciate that the lower the $PaCO_2$, the higher the alveolar PO_2 will be. Thus, alveolar PO_2 is directly proportional to the PIO_2 and inversely proportional to the PCO_2.

Because the relationship between and CO_2 production is not 1 (i.e for each mole of oxygen consumed, approximately 0.8 moles of CO_2 is produced – the 2 and VO_2, measured at the pulmonary system" href="https://kinesiology.ucalgary.ca/maci...end#-r-or-rer-">respiratory exchange ratio, R), we cannot simply assume that the decrease in $PaCO_2$, with an increase in ventilation will equal the increase in PaO_2. The rise in PO_2 in the alveolar gas with an increase in ventilation will be greater (in accordance with the respiratory exchange ratio) than the decrease in PCO_2 in the alveolar gas. These relations can be summarized in the 2 = PIO_2 – $PACO_2$?R-1 +F the alveolar gas equation is used to estimate the partial pressure of alveolar air which is difficult to do" href="https://rb.gy/kce19i">alveolar gas equation:

$PAO_2 = PIO_2 - PACO_2 \cdot R^{-1} + F$ **Equation 20-3a**

Where F is a correction factor usually equal to about 2 mm Hg and can therefore be ignored.

We observed before that if no physiological adaptation took place with high altitude, on exposure to 5300m, Rachel's alveolar PO_2 would drop to ~28 mm Hg; an extremely low and dangerous value. However, Rachel's ventilation at 5300m would be expected to increase by ~75% (i.e. from 10 $L \cdot min^{-1}$ to 17.5 $L \cdot min^{-1}$), which according to the ventilation equation would result in alveolar PCO_2 of approximately ~25 mm Hg (assuming no change in CO_2 production).

$P_AO_2 = P_IO_2 - PaCO_2 \cdot R^{-1}$ **Equation 20-3b**

P_AO_2= 78-25/0.8 = 46.75 mm Hg

Using this example of Rachel, with and without hyperventilation, we can see that hyperventilation increases alveolar PO_2 by approximately 12 mm Hg (28-40 mm Hg), making it possible for humans to live at high altitude. The increase in ventilation with high altitude exposure is obviously a very important means for increasing the oxygen pressure in the blood and indeed represents probably the most important adaptation to the high-altitude environment in the acute setting. The increase in oxygen pressure by this hyperventilation increases the binding of oxygen to haemoglobin in accordance with the 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve. This is discussed further below. The mechanisms controlling this increase in ventilation will be also discussed later in this chapter.

Alveolar to Arterial PO_2

We saw above that Rachel's alveolar PO_2 at 5300m is ~42 mm Hg, and this drops to about 35 mm Hg in the arterial blood.

Before considering the reason for the drop in PO_2 between the alveoli and the arterial blood, we will review the anatomy of this junction.

Between the alveolar spaces and the pulmonary capillaries is an exceedingly thin space over which oxygen is transferred to the blood and carbon dioxide is transferred to the alveolar space. Diffusion across this barrier was described in chapter 7 and is affected by many different variables as dictated by Fick's law of diffusion. Diffusion of gas across a membrane is directly proportional to the tissue area of exposure (A), the pressure gradient across the membrane (P1-P2), and the diffusion constant for the particular gas (D) and is inversely proportional to the thickness of the membrane (T). The diffusion constant is in turn directly proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight of the gas.

These relations can be summarized in the following 2 equations:

Vgas = (A/T)·D·(P1-P2) **Equation 20-4a**

D = sol · MW **Equation 20-5**

The diffusion constant for CO_2 is considerably higher than for O_2, meaning that diffusion limitation of CO_2 is not a problem in humans. The diffusion constant for CO_2 is much greater than O_2 owing to its far greater solubility in tissues.

Because it is usually not possible to measure the surface area and thickness of the alveolar 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-dea#capillary">capillary membrane in humans, the equation is often rewritten as

Vgas= DL (P1-P2) **Equation 20-4b**

Where DL combines the factors of surface area, thickness, and diffusion constant.

Therefore, it can be appreciated that: thickening of the alveolar 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-czz#capillary">capillary membrane, decreased surface area for diffusion, or a decrease in pressure gradient across the membrane could contribute to a decrease in pulmonary gas exchange.

In addition to properties of the alveolar-capillary interface, it has been shown that diffusion will depend upon how easily molecules through the pulmonary capillary blood and how avidly the red blood cells and haemoglobin molecules will take up oxygen. In situations where a haemoglobin molecule has a very high affinity for O_2 (i.e at high altitude on the steep portion of the 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve), diffusion of oxygen across the alveolar-capillary membrane becomes rate limiting in a process known as 'diffusion limitation.' This diffusion limitation is especially apparent during exercise at high altitude (see below).

This diffusion limitation can be shown by modelling the uptake of oxygen in the red blood cells transiting the alveolar-2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-dea#capillary">capillary interface (Figure 20-3). It can be appreciated that at sea level, by the time the red blood cells reach approximately 1/3 of the way across the capillary, the PO_2 is about equal to the alveolar value (~100 mm Hg). At high altitude, there are three factors that contribute to a lack of equilibration between alveolar and pulmonary capillaary PO2. These are: the decreased driving force (P1-P2), reduced transit time due to increased cardiac output and the high affinity of haemoglobin for oxygen (steep part of 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve). The PO_2 in the capillary blood never reaches that of the alveolus, even at the end of transit.

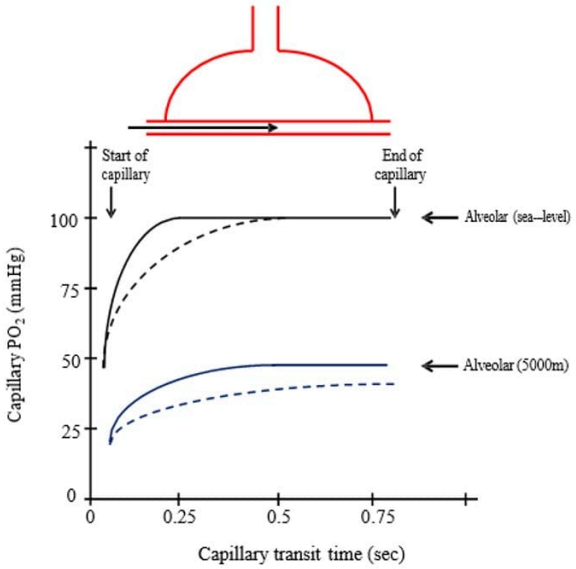


Figure 20-3 Changes in capillary PO_2 and transient time at rest (solid lines) and during exercise (dashed lines) at sea level (black line) and 5000m (blue line). At sea level (rest and exercise) and during rest at 5000m, blood is in the capillary long enough to achieve approximate equilibrium with alveolar PO_2. However, during exercise at 5000m, the transit time of blood through the capillaries is too rapid to allow equilibrium, leading to a suppressed PaO_2. Therefore, pulmonary diffusion is a major factor limiting oxygen transport during aerobic exercise at high altitude.

Other factors thought to contribute to widening of the Alveolar arterial gradient at high altitude are ventilation perfusion mismatch (caused by sub clinical pulmonary edema; see below) and opening of intra pulmonary shunts.

Arterial to Mixed Venous PO_2 Difference

The difference between the arterial and venous PO_2 is the final step in the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade and is due to the extraction of oxygen from the systemic capillaries. This extraction of oxygen is dependent upon cardiac output, the metabolic rate, and the oxygen carrying capacity of the blood. The mixed venous PO_2 is strictly defined as the PO_2 in the blood draining all systemic tissues including the myocardium and is therefore measured in the pulmonary artery. It can be viewed as the average tissue oxygenation throughout the whole body and as such all the compensatory adaptations at altitude act to increase $P\bar{v}O_2$ towards sea level values.

The uptake of oxygen by a given tissue (2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ in $ml \cdot min^{-1}$) can be defined as the product of two variables:

- the difference in oxygen content between the arterial blood supplying the tissue and the venous blood draining the tissue
- the blood flow through the tissue. When the body is considered as a whole, blood flow through the tissue is the cardiac output.
- $P\bar{v}O_2$

This relation is known as the Fick principle and can be defined as:

$\dot{V}O_2 = C(a\text{-}\bar{v})O_2 \cdot \dot{Q}$ **Equation 20-6a**

Where $\dot{V}O_2$ is in $mL \cdot min^{-1}$; $C(a\text{-}\bar{v})O_2$ is the difference in oxygen content between arterial and mixed venous blood, and $\dot{Q}$ is the cardiac output.

This can be rearranged to:

$C(a\text{-}\bar{v})O_2 = \dot{V}O_2 \cdot \dot{Q}^{-1}$ **Equation 20-6b**

And because CaO_2 is related to [Hb] and (via the 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve; denoted by a factor – k) to PO_2 this can be further rearranged to:

$(a\text{-}\bar{v})PO_2 \cdot [Hb] \cdot k = \dot{V}O_2 \cdot \dot{Q}^{-1}$ **Equation 20-6c**

And

$(a\text{-}\bar{v})PO_2 = \dot{V}O_2 \cdot \dot{Q}^{-1} \cdot (k\ [Hb])^{-1}$ **Equation 20-6d**

Therefore it can be appreciated that the difference between the arterial and venous PO_2 at high altitude is directly proportional to the metabolic rate of the tissues, and inversely proportional to the cardiac output and [Hb].

At high altitude, Rachel's resting 2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ is approximately 250 $ml \cdot min^{-1}$, approximately equal to that at sea level. Her resting cardiac output and [Hb] are both increased. The net effect is that Rachel's $A\text{-}\bar{v}PO_2$ at high altitude is decreased. During exercise the $\dot{V}O_2$ of the muscles and the whole body are increased leading to an increase in $A\text{-}\bar{v}PO_2$. The cardiovascular response to exercise will be discussed after the control of ventilation is considered.

Control of Ventilation at High Altitude

Central Chemoreceptors

As reviewed in chapter 7, the control of breathing at rest involves detection of oxygen and carbon dioxide levels in the body by sensors, a relaying of this signal to the central controller in the brainstem, and efferent output from this central controller to the muscles of respiration.

At sea level, the main chemical controller of breathing is the 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure of CO_2. This CO_2 acts indirectly via H^+ ion at mainly the central chemoreceptor in the medulla but also at the peripheral chemoreceptor at the 2 content is low."" href="https://kinesiology.ucalgary.ca/maci...a#carotid-body">carotid body.

The central chemoreceptors are a group of neurons that lie in the medulla and respond to changes in hydrogen ion concentration in the surrounding extracellular fluid (ECF) to bring about a change in ventilation. An increase in H^+ concentration stimulates breathing whilst a decrease inhibits breathing. Because the blood brain barrier is relatively impermeable to hydrogen ions, the major contributor to brain ECF hydrogen ion concentration in the arterial blood is PCO_2 (not H^+) that diffuses into the brain ECF is hydrated to carbonic acid and then to H^+ ions that stimulate the central chemoreceptors to increase ventilation.

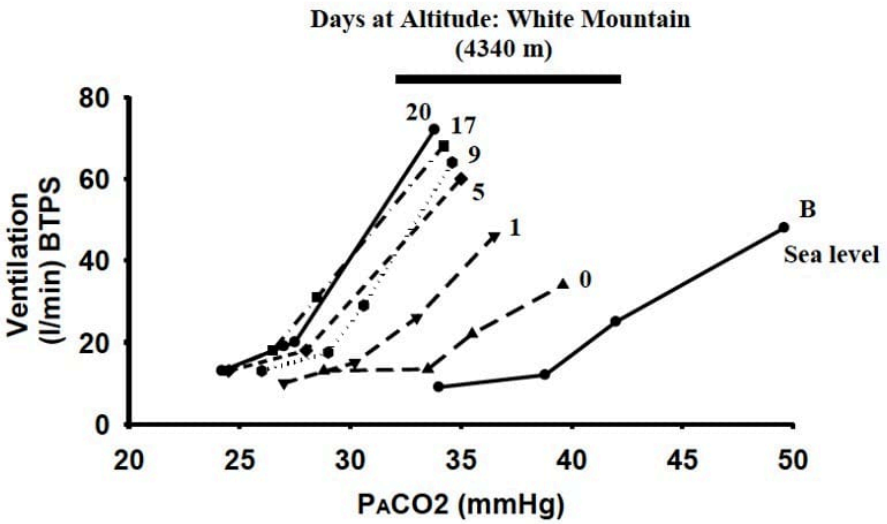
The sensitivity of the body to changes in CO_2 can be determined experimentally by increasing the pressure of CO_2 in the arterial blood (i.e. by breathing a 5% CO_2 gas mixture) and measuring the resultant increase in ventilation using a spirometer.

Ventilatory CO_2 sensitivity $= \Delta\dot{V}E \cdot \Delta PaCO_2^{-1}$ **Equation 20-7**

Where

$\dot{V}E$ is the ventilation ($L \cdot min^{-1}$); and $PaCO_2$, is the 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure of CO_2 in the arterial blood.

When the ventilation is measured at multiple levels of arterial $PaCO_2$, a 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">hypercapnic ventilatory response curve (HCVR) can be constructed as shown on Figure 20-4.



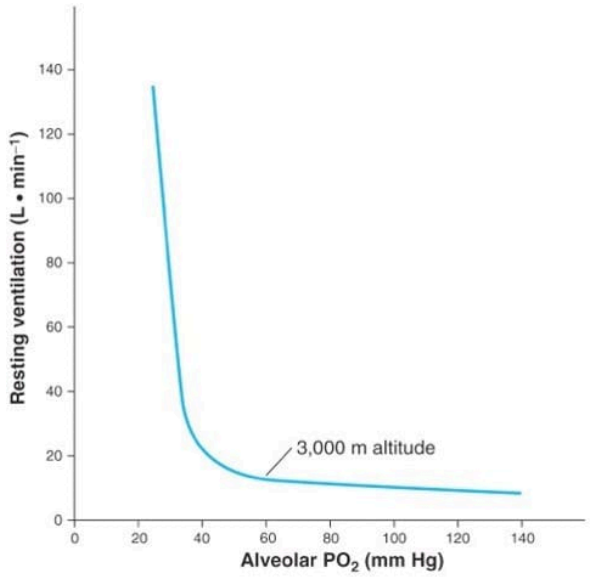
2increasing from 34 mm Hg to 50 mm Hg ventilation increases from 5 l/min to 45 l/min. Increasing carbon dioxide results in increased ventilation. A little to the left of this is the response to CO2 on first moving to altitude (4340 m). Here, ventilation increases from 8 l/min at 27 mm HG to 42 l/min at 36 mm Hg. One day later, ventilation rises with more sensitivity to CO_2; ventilation increases from 8 l/min to 42 l/min. After 5 days, ventilation increases from 11 l/min to 58 l/min when CO_2 is increased from 26 mm Hg to 35 mm Hg. This progression occurs after 9, and 17 days at altitude until after 20 days, ventilation increases from 12 l/min at PCO_2 = 24 mm Hg to 70 l/min with a PCO_2 of 34 mm Hg." width="854" height="500"> **Figure 20-4 Hypercapnic ventilatory response at sea level and over time at high altitude (4340 m on White Mountain, Colorado, USA).** Numbers represent days spent at high altitude. Note that the ventilation vs $PaCO_2$, curves are shifted leftwards and become steeper with time spent at this elevation – forming an example of elevations in the ventilatory response to hypercapnia.

At high altitude, the ventilatory CO_2 sensitivity is increased leading to a steepening of the HCVR. In addition, the $PaCO_2$, at which ventilation will be stimulated is decreased resulting in a leftward shift in the 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">HCVR (Fan and Burgess et al., 2010). Because the ventilatory response to CO_2 is predominantly at the central chemoreceptors (rather than the peripheral chemoreceptors; see chapter 10 on control of breathing), we can conclude that at high altitude the central chemoreceptors are more sensitive to changes in PCO_2 and will increase ventilation at lower levels of CO_2. Potential mechanisms explaining this 'resetting' of the HCVR are still under debate.

Peripheral Chemoreceptors

The peripheral chemoreceptors lie in the carotid sinus and aortic body. These receptors are highly vascular and respond rapidly to changes in oxygen 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure but also to a lesser degree, to changes H^+ and CO_2.

When exposed to low levels of ambient oxygen 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure, ventilation increases by a process known as the 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">hypoxic ventilatory response (see Figure 20-5). From Figure 20-5 it can be seen that the ventilatory response to 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia is not linear; between alveolar partial pressures of oxygen of 500 and 50 mm Hg, the ventilatory response is relatively stable with only a minor increase in ventilation., whereas, below an alveolar PO_2 of 50 mm Hg ventilation increases steeply, especially if alveolar PCO_2 is held constant. Interestingly, 50 mm Hg lies at the point on the 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve where saturation begins to fall steeply, and therefore the steepening of the 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">hypoxic ventilatory response can be seen as a mechanism that attempts to keep the PO_2 on to the flat portion of the oxygen dissociation curve.



2 and resting ventilation. As you go up a mountain and altitude increases, resting ventilation will increase. When alveolar PO_2 decreases from 140 to 60 mm Hg, the increase in resting ventilation is small, increasing from 6 l/min to 12 l/min. Further decreases in PAO2 result in progressively more increase in ventilation, reaching 30 l/min at a PAO_2 of 32 mm Hg. Further changes in PAO_2 will result in severe changes in resting ventilation, such that when PAO_2 reaches 25 mm Hg, resting ventilation will be in excess of 120 l/min. " width="480" height="474">
Figure 20-5 Relationship between resting ventilation and progressive reductions in alveolar PO_2. This relationship is called the hypoxic ventilatory response. Note that it is not until alveolar PO_2 is reduced to below 50mmHg that ventilation starts to increase.

Integrated Ventilatory Response to High Altitude

Acute exposure to high altitude results in a decrease in alveolar PO_2 and therefore arterial 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure of oxygen as described above. This decrease in partial pressure of oxygen results in stimulation of the peripheral chemoreceptors (predominantly at the carotid sinus) with a resultant increase in ventilation. This initial increase in ventilation (the 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response-">hypoxic ventilatory response) decreases PCO_2 and increases PO_2 in the alveolar gas according to the ventilation and gas equations.

The decrease in arterial PCO_2 (and consequent increase in arterial – 2. Ventilation removes CO_2 from the body and when more CO_2 is removed than is produced by metabolism, this removal results in decreased [H+] (alkalosis) because of the following reaction is driven to t" href="https://kinesiology.ucalgary.ca/maci...tory-alkalosis-">respiratory alkalosis) acts to inhibit the peripheral chemoreceptor. In addition, because CO_2 is freely diffusible across the blood brain barrier, a decrease in cerebral spinal fluid (CSF) CO_2 occurs, thus raising CSF and brain ECF. causing inhibition at the central chemoreceptors. Both of these effects act to return ventilation back towards sea level values.

However, over a period of hours to days at high altitude the body compensates for the respiratory alkalosis by increasing bicarbonate excretion in the kidney and increasing bicarbonate removal from the ECF by the choroid plexus. Thus the inhibition at the central and peripheral chemoreceptors is removed and the ventilation once again increases.

Cardiovascular response

Along with the respiratory changes described above, the cardiovascular system reacts and adapts to the high-altitude environment. The cardiovascular response is important as it acts to transport the oxygen from the pulmonary 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-czz#capillary">capillaries to the systemic capillaries of the target tissues and from the discussion of the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade above, cardiovascular variables determine the drop in PO_2 from the arterial to the venous blood. Three major cardiovascular variables will be considered below: cardiac output and its constituents (heart rate and stroke volume), pulmonary pressures, and mean arterial pressures.

Cardiac Output

One of the things that Rachel noticed when she was at high altitude was that her resting heart rate, which was usually around 45 beats per minute, had increased to about 70 beats per minute. This increase in heart rate results in an increased cardiac output (because stroke volume is unaffected by acute 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...-max#hypoxemia">hypoxia). Increased cardiac output is useful because it maintains oxygen delivery in the face of a decreased arterial PO_2. The increase in heart rate is mediated through an increase in sympathetic outflow resulting from hypoxic stimulation of the peripheral chemoreceptors.

With chronic exposure to high altitude, cardiac beta adrenoceptors down-regulate resulting in a decrease in resting HR back towards, but never reaching, sea level values.

Stroke volume is consistently decreased with chronic exposure to high altitude. A decrease in stroke volume can be caused by either a decrease in contractile ability (increased end systolic volume), or a decrease in ventricular filling (decreased end diastolic volume). Evidence from echocardiographic studies have confirmed that at high altitude, there are no changes in end- systolic volume (contractile ability) and a consistent decrease in end-diastolic volume (ventricular filling).

A decrease in end diastolic volume at altitude can be accounted for by a decrease in plasma volume (as discussed below) and subsequent decrease in ventricular filling. Another factor contributing to the decrease in left ventricular end diastolic volume at high altitude could be right ventricular dilation and subsequent impaired filling of the left ventricle.

The net result of these changes is that cardiac output decreases back towards sea level values with time at altitude.

Systemic Blood Pressure

Mean arterial pressure is the product of cardiac output and total peripheralresistance. We have already seen that at rest, cardiac output is increased during both acute and chronic 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia, in a process. To understand the effect of hypoxia on MAP we will also need to consider the effect of hypoxia on the contractile state of the blood vessels – the total peripheral resistance.

Hypoxia stimulates peripheral chemoreceptors , which in turn increases sympathetic neural activity. This increase in sympathetic nervous activity would normally lead to norepinephrine release in the walls of systemic arterioles and constrictive effect. However, reduced oxygen content in the blood causes arteriolar dilation. The balance between these dilator and constrictor forces determines the total peripheralresistance. For example, if local reduced oxygen content and dilation outweighs sympathetically mediated constriction, then a decreased total peripheral resistance will result. If on the other hand, the sympathetically mediated constriction outweighs the local reduced oxygen content mediated dilation, then an increase in total peripheral resistance will occur.

Acute exposure to high altitude causes a decrease in total peripheralresistance and increase in cardiac output leading to a slightly decreased mean arterial pressure. Chronic exposure to high altitude leads to an increase in total peripheralresistance and an increase in cardiac output (compared to sea level), leading to an increase in mean arterial pressure.

These effects are summarized in Table 20-2.

Table 20-2 Cardiovascular variables at high altitude

	Sea level	Acute Exposure to 5000m	Chronic Exposure to 5000m
HR (bpm)	70	80	75
SV (mL)	70	70	60

Cardiac output ($L \cdot min^{-1}$)	5	5.6	5.2
MAP (mm Hg)	100	95	110
RAP (mm Hg)	5	5	5
TPR (mm $Hg \cdot L^{-1} \cdot min^{-1}$)	20	16	20
Pulmonary pressure mean (mm Hg)	10	20	25
PVR (mm $Hg \cdot L^{-1} \cdot min^{-1}$)	2	3	3.5

Pulmonary Pressure

The most striking change in the cardiovascular system is probably the increase in pulmonary artery pressure. This increase in pressure is caused by alveolar 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia in a process called vasoconstriction (2 in the alveolar spaces results in vasoconstriction of the pulmonary arterioles" href="https://kinesiology.ucalgary.ca/maci...soconstriction–">HPV).

Analogous to in the systemic arteries, mean arterial pressure is determined by the product of the right ventricular cardiac output and the peripheral resistance of the pulmonary system. Therefore, to understand the changes in pulmonary arterial pressure, we need to consider the changes to the pulmonary vascularresistance, and the cardiac output. As discussed above, cardiac output increases with acute high-altitude exposure, and then decreases to a level still above sea level values. Interestingly, in response to alveolar 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia the pulmonary vessels constrict causing an increase in pulmonary vascular resistance. As a result of both the increase in cardiac output and pulmonary vascular resistance, high altitude causes an increase in mean pulmonary arterial pressure.

This 2 in the alveolar spaces results in vasoconstriction of the pulmonary arterioles" href="https://kinesiology.ucalgary.ca/maci...soconstriction–">HPV in many situations can be seen as a beneficial physiological response because it can act to increase ventilation-perfusion matching. Alveoli that are poorly ventilated will be relatively hypoxic and therefore the adjacent pulmonary vasculature will constrict, meaning that less blood flow is through poorly ventilated alveoli and more blood flow will be redirected towards the better ventilated alveoli (those units with no alveolar hypoxia).

Another example where hypoxic pulmonary vasoconstriction response is imperative is in the transition of the fetal circulation to life outside the uterus. In utero, the function of gas exchange is provided by the placenta and as such the lungs are non-functional. Oxygenated blood is diverted from going through the lungs via the combined action of hypoxic pulmonary vasoconstriction and a patent ductus arteriosus (a conduit between the pulmonary artery and the aortic arch). When the baby takes its first breath, the alveoli are filled with oxygen rich air, hypoxic pulmonary vasoconstriction is released allowing for essential pulmonary blood flow and thus gas exchange.

Unlike the situations of local 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia and transition of the fetal to neonatal circulation, during the situation of high altitude the response is largely deleterious. With hypoxia in all alveolar- 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-czz#capillary">capillary units, widespread vasoconstriction occurs resulting in an increase in pulmonary artery pressure. If the increase in pulmonary artery pressure is too great, stress induced damage to the pulmonary vessels may occur leading to the condition high

altitude pulmonary edema. If this increased pulmonary artery pressure is sustained, it can cause right ventricular failure with significant morbidity and mortality.

Highlight box- How long until Everest is 'unclimbable' without supplemental oxygen?

The Italian climber, the Duke of Abruzzi, at the turn of the last century completed an "oxygenless" ascent to 7500 m in the Karakoram despite ominous predictions by the British Alpine Club, " . . .*21 500 ft (6553 m) is near the limit at which man ceases to be capable of slightest further exertion*" (West, 1998). Naturally, it was not long before attention turned towards Mt Everest, which in 1892 had been declared the highest mountain in the world. Mountaineers were irrevocably drawn to the ultimate challenge, and, in 1924, Edward Norton (1884–1954) ascended to within 300 m of its summit without supplementary O_2, a remarkable feat eclipsed by the untimely deaths of George Mallory and Andrew Irvine some two days later. These courageous attempts motivated a series of pioneering studies by Rodolfo Margaria (1901– 1983) and Joseph Barcroft (1872–1947), who subsequently concluded that an oxygenless ascent of Mt Everest would not be possible (Barcroft and Douglas et al., 1931). However, the legendary ascent by Reinhold Messner and Peter Habeler in 1978 overcame these previous negative predictions; the last 3% of Mt Everest had finally been conquered 54 years after Norton's initial bid, having claimed no fewer than 39 lives in the process. Messner's quote on reaching the top clearly establishes that the summit of Mt Everest was tantalizingly close to the limits of human tolerance, ". . .*Now, after the hours of torment . . . I have nothing more to do than breathe . . .I am nothing more than a single, narrow, gasping lung, floating over the mists and the summits*." (Messner, 1979). By 1986, Messner had confirmed his place in mountaineering history having climbed all 14 of the 8000 m peaks without supplementary O_2.

Seasonal variations in barometric pressure at these extreme altitudes have a major impact on systemic O_2 transport and are thus of considerable physiological significance. Previous theoretical calculations have identified that a mere 4 mm Hg decrease in summit barometric pressure would reduce a climber's predicted $\dot{V}O_2max$ by about 10%. These small but critical reductions in PO_2 likely reflect why Everest was only summited without oxygen some 25 years after its first 'summer' ascent, a remarkable feat that was achieved on 22 December 1987 by Sherpa, Ang Rita.

The physiological significance of these achievements came to light in the early 1980's when two landmark studies (West and Boyer et al., 1983; Sutton and Reeves et al., 1988) measured the

$\dot{V}O_2max$ of healthy volunteers on the summit at a mere 1.07–1.17 $L \cdot min^{-1}$ or 15 $ml \cdot kg^{-1} \cdot min^{-1}$. These maximal energy expenditures are comparable to those typically observed in exercising patients with congestive heart failure or in patients following heart transplantation, albeit 5.5 miles lower at sea level! Furthermore, the geographical location of Mt Everest at a latitude of 28°N results in a barometric pressure that is considerably higher than if it were located near one of the poles. Without this "equatorial bulge" a climber would not be able to summit without supplementary O_2 (West and Wagner, 1980). It is, however, known that the physical challenge of climbing Mt Everest without supplementary O_2 is becoming more difficult as the summit appears to be increasing in height at a rate of 3 $cm \cdot year^{-1}$ and steadily moving northeastward at 6 $cm \cdot year^{-1}$. This is a consequence of it being located on the great fault system, which continues to push India under Nepal and China thus creating the Himalayas. These facts raise the question of how much longer an "oxygenless" ascent will remain physiological possible?

Messner's total body mass including equipment was reported to be 74 kg, which at an ascent rate of 2 $m \cdot min^{-1}$ during the last 100 m of the climb would have resulted in a output close to 150 $kg \cdot m^{-1} \cdot min^{-1}$. Estimations suggest that a submaximal effort would have required a $\dot{V}O_2max$ of approximately 3.5 METs (1 MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) (West and Wagner, 1980). Assuming a constant growth rate of 3 $cm \cdot year^{-1}$ and (2011) height of 8868.92 m, a climber with a $\dot{V}O_2max$ of 3.5 METs would therefore have to make their assault on the summit during the summer months before about 39 460 AD. A winter ascent would need to be launched before 29 107 AD. By about 104 167 AD, a climber's $\dot{V}O_2max$ on the summit would equate to their basal metabolic rate measured at sea level, emphasizing the futility of any summit bid!

High Altitude Illness: Acute Mountain Sickness, and High-Altitude Cerebral Edema

Acute Mountain Sickness

In the case presentation, Rachel became progressively more ill about 12 hours after arriving at Everest base camp. Her predominant symptoms were headache, malaise, decreased appetite, and nausea. These constitute the classic symptoms of acute mountain sickness. Even despite being in excellent physical condition ($\dot{V}O_2max$ = 62 ml·kg^{-1}·min^{-1}), and taking a slow and careful ascent profile, she developed these distressing symptoms. Her experienced Sherpa guide quickly recognized what was going on and the mountain doctor prescribed the most effective and simple treatment, immediate descent.

Acute mountain sickness (AMS) is a self-limiting condition affecting a large proportion of previously healthy men and women who ascend to high altitude. The incidence depends upon both the absolute altitude and the rate of ascent such that below an altitude of 2000m, AMS is rare, and above 5000m, AMS is almost universal. Because the rate of ascent is an important factor, AMS is particularly an issue in places where rapid ascent to high altitude by aircraft, cable car, or railway is possible such as at ski resorts and some villages in South America and the Himalaya.

Early reports of the altitude related illness date back centuries, but a clear report of the illness was not documented until the British Doctor, TH Ravenhill in the early 20th century, published his observations of illness in a high-altitude population. As a medical officer serving in a Chilean high-altitude mining company, he observed an illness of headache and tiredness, which he correctly attributed to altitude.

CLINICAL FEATURES :

The predominant symptom of AMS is a headache and indeed the current diagnostic criteria requires a headache to be present for the diagnosis to be made. Other symptoms include anorexia, malaise, nausea, vomiting, and sleep disturbance. The onset of symptoms normally occurs at approximately half a day after ascent to a high altitude and persists for no more than 5 days. Physical examination may be unremarkable, however, fever, inspiratory crackles, and low 2 in the peripheral circulatory system"" href="https://kinesiology.ucalgary.ca/maci.../pha-tend#spo2">SpO_2 may be present.

PREDISPOSING FACTORS:

Although AMS is nearly universal if ascent is sufficiently rapid, and altitude is sufficiently high, there are a number of other factors that make AMS more likely. Factors making AMS more likely are: previous AMS, low oxygen saturations, blunted 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">hypoxic ventilatory response, and exercise (Richalet and Larmignat et al.,(2012). Factors with no apparent effect on AMS include aging, $\dot{V}O_2max$ and hypoxic pulmonary vasoconstriction response.

MECHANISMS OF AMS :

The mechanisms underlying AMS are related to 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ra-max#hypoxia">hypoxia but the fact that symptoms do not occur immediately (in contrast to the hypoxia, which occurs immediately) indicates that hypoxia initiates a series of events that ultimately result in AMS. Proposed mechanisms include fluid retention, increased microvascular permeability, and raised intracranial pressures (Figure 20-6).

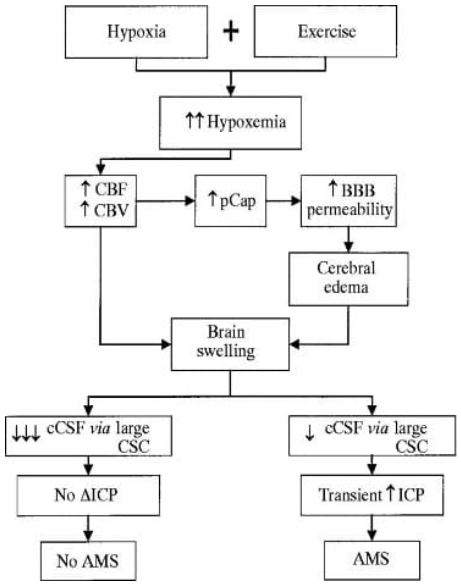


Figure 20-6. Pathophysiology of AMS. In this model, the initial stress is hypoxemia. Hypoxemia is translated through a series of cellular, molecular and physiological signals ultimately to cause brain swelling due to cerebral edema and elevated cerebral blood volume (CBV). Hypoxemia stimulates cellular and molecular responses that may alter endothelial permeability. Hypoxemia is also implicated in upregulation of inducible nitric oxide synthase, and nitric oxide (NO) has been implicated in the pathophysiology of headache and blood brain barrier (BBB) permeability. Through peripheral chemoreceptor activation, hypoxemia can elevate circulating arginine vasopressin levels which, in turn, causes anti-diuresis and increased extracellular water levels. The sum of these peripheral responses to hypoxia arrives at the brain (and in this model they are exaggerated by exercise) and influences BBB permeability, cerebral edema and CBV. These changes cause elevated intracranial pressure in those with a cerebrospinal capacitance that cannot buffer the swelling brain. Intracranial pressure causes the symptoms of AMS via compression of the brain. Although definitive research is lacking, the interplay between brain water content, brain blood volume and intracranial dynamics ultimately determines who develops AMS. Modified from (Roach and Hackett, 2001).

PREVENTION AND TREATMENT :

Prevention of AMS typically involves a slow, graded ascent to high altitude. General advice includes that when above 3000m, each night should be spent no more than 300m above the previous nights and a rest day should be taken every 2-3 days of climbing.

In addition, prophylactic 2 combines with water to form bicarbonate" href="https://kinesiology.ucalgary.ca/maci...#acetazolamide">Acetazolamide can be taken. Acetazolamide is a carbonic anhydrase inhibitor which acts to promote the renal excretion of bicarbonate, thus producing a metabolic acidosis. The lowered then acts on the peripheral chemoreceptors to increase ventilation, increase PO_2 and decrease PCO_2. These are the changes associated with acclimatization, therefore acetazolamide can be seen to hasten the acclimatization process and minimize the occurrence of AMS. These changes are outlined in Figure 20-7.

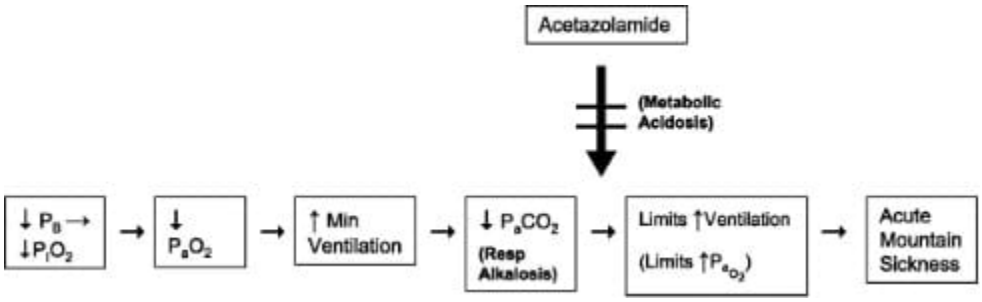


Figure 20-7 Simplified explanation for acetazolamide's efficacy in the reduction of acute mountain sickness (AMS). At high altitude, reduced barometric pressure (PB) and reduced partial pressure of inspired oxygen (PiO_2) result in hypoxemia, which drives ventilation. Increases minute ventilation leads to decreased arterial PCO2, which without acetazolamide will limit the increase in ventilation and result in acute mountain sickness. Acetezolamide will cause acidosis with an increase in PaCO2 and allow further increases in minute ventilation, preventing acute mountain sickness.

Hyperventilation causes a respiratory (Resp) 2 or H+"" href="https://kinesiology.ucalgary.ca/macintosh/otep">alkalosis that limits the rise in ventilation and leads to symptoms of AMS. By generating metabolic acidosis, 2 combines with water to form bicarbonate" href="https://kinesiology.ucalgary.ca/maci...#acetazolamide">acetazolamide is able to attenuate the effects of 2. Ventilation removes CO_2 from the body and when more CO_2 is removed than is produced by metabolism, this removal results in decreased [H+] (alkalosis) because of the following reaction is driven to t" href="https://kinesiology.ucalgary.ca/maci...tory-alkalosis-">respiratory alkalosis and improve AMS.

Because the underlying cause of AMS is the 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia, treatment in the most basic form is centred around improving oxygenation. Improving oxygenation can be achieved by

- not ascending to higher altitude
- if symptoms are not improving, then descending to lower altitude
- treatment in a hyperbaricGamow bag.

Often AMS is self-limiting and improves with rest.

Acetazolamide has also been shown to be effective in the treatment (in addition to in prophylaxis) of AMS.

High Altitude Cerebral Edema

Another form of serious altitude illness, high altitude cerebral edema (HACE) normally occurs 1- 2 days after the onset of the typical AMS symptoms. The clinical features include the same symptoms of AMS; headache, nausea, and fatigue, however also include an impaired level of consciousness, hallucinations, papilloedema and if not treated- coma and death. HACE often is coexistent with HAPE as both indicate a failure of adequate adaptation to the high-altitude environment.

HACE is thought to represent an extreme form of AMS (Figure 20-6) with a similar underlying pathophysiology. It is proposed that hypoxia leads to an extracellular fluid accumulation (edema) within the cranial cavity. Because the cranial cavity is a rigid structure, an increase in extracellular fluid volume can quickly cause an increase in intracranial pressures with associated neurological disturbance (confusion, altered level of consciousness, and papilloedema). The edema appears to be related to vessel leakiness (vasogenic) rather than neuronal cell dysfunction (cytotoxic), because the degree hypoxia in HACE cases is not normally sufficient to cause failure of cerebral cellular ion pumps and subsequent cytotoxic edema.

Like AMS, some subjects are more prone to developing HACE. One hypothesis for inherent susceptibility is that some subjects have a 'tighter fit' of their brain within their rigid boney cavity. Therefore, for a given increase in brain ECF volume, these subjects will have a greater increase in intracranial pressure i.e. their cranial cavity is less compliant. This is known as the 'tight fit hypothesis' (Hackett, 1999).

The treatment of HACE is similar to that of AMS in that the most important treatment involves optimizing oxygenation. Options again include descent to lower altitude, hyperbaric treatment in a Gamow bag, and oxygen administration. Strategies to decrease intracranial pressures involve dexamethasone treatment.

Research Box: High Altitude Pulmonary Edema

High altitude pulmonary edema (HAPE) is a condition affecting normally healthy individuals upon rapid ascent to high altitude. initially presents with breathlessness. However, the breathlessness in HAPE continues to deteriorate and is then accompanied by productive cough. Chest pain, weakness and headache are also common symptoms. Clinical signs include central cyanosis tachypnea, tachycardia, and lung crackles on auscultation. These lung crackles indicate fluid in the alveoli – pulmonary edema. A chest x-ray (not normally performed because of low availability in mountainous regions) demonstrates bilateral patchy opacities with a normal cardiac silhouette (Milledge, 2006).

Pathophysiology

A Non-Cardiogenic Pulmonary Edema:

The first reports of HAPE again can be traced back to TH Ravenhill at the beginning of the 20th century, when he described the various forms of mountain sickness in the highlands of South America. He divided mountain sickness into 2 forms: Soroche (meaning cerebral) and Puna (meaning cardiac). Despite this initial description, it was not until about 50 years later that investigations into the pathophysiology of HAPE were performed.

The most common reason for fluid in the lungs is left-sided heart failure, leading to elevated pulmonary 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-czz#capillary">capillary pressures and fluid shifts into the alveoli. Therefore, early investigation focused on the heart. Patient's ECG's showed a right axis deviation, potentially indicating right ventricular hypertrophy. This right ventricular hypertrophy could have been caused by either left-sided heart failure, or primary elevated pulmonary pressures. Research has revealed that pulmonary artery pressures were markedly raised and importantly, left sided heart pressures were not elevated (Penaloza and Sime, 1969). This lay to rest ideas that HAPE was caused by heart failure and indicated that pulmonary arterial hypertension may be an important factor. In the latter half of the 20th century, focus turned to describing the nature of the fluid with the hope of gaining further insight into the pathophysiology of HAPE.

WHAT'S IN THE FLUID? Edema in any tissue can be caused by an increased hydrostatic pressure, decreased plasma oncotic pressure, damage to the vascular membrane, or impaired lymphatic and vascular reuptake of the fluid. Bold studies performed in the late 1980's helped clarify the pathophysiology of HAPE by analyzing the cytological, biochemical, and immunologic make-up of the pulmonary edema fluid. Schoene and his co-workers in 1986 performed bronchoalveolar lavage (an invasive medical technique for obtaining alveolar fluid samples) on 3 mountaineers on Mt Denali with established HAPE and compared this with healthy controls on the same mountain (Schoene and Hackett et al., 1986). The bronchoalveolar lavage fluid showed increased levels of high molecular weight proteins, red blood cells, macrophages, and inflammatory markers indicating that the alveolaredema involved an increased permeability of pulmonary capillaries and that inflammation may contribute to this.

Subsequent studies in the Italian alps showed that in the early stages of HAPE, the alveolar fluid was rich in high molecular weight proteins but contained no evidence of inflammation (Swenson and Maggiorini et al., 2002). This demonstrated that the inflammatory response, although potentially important in the maintenance of HAPE, is not responsible for the initiation of HAPE.

High Altitude Pulmonary Edema Susceptible Mountaineers:

In the late 20th century, it became apparent that there were groups of climbers who were especially prone to developing HAPE, whereas other climbers were relatively resistant. This fact spawned a series of studies comparing HAPE susceptible and non-HAPE susceptible after rapid ascent to altitude. These daring studies, mostly performed in the Capanna Margherita laboratory in the Italian Alps, have yielded significant insight into the pathophysiology of HAPE.

In one such study, Duplain and colleagues took a group of susceptible and non-HAPE susceptible mountaineers rapidly up to 4600 m and 'successfully' induced HAPE (Duplain and Sartori et al., 2000). The pulmonary artery pressures and exhaled nitric oxide were measured in these subjects and it was found that those who developed HAPE had significantly higher pulmonary pressures and significantly lower exhaled nitric oxide. Inhalation of nitric oxide in these subjects has also been shown to be an effective treatment for HAPE (Scherrer and Vollenweider et al., 1996). These studies have led to the hypothesis that a genetic propensity to decreased pulmonary production is an important factor in the of HAPE. In accordance with this, there have been further studies finding a defect in the endothelial nitric oxide synthase gene in those susceptible to HAPE (Droma and Hanaoka et al., 2002).

Other factors that have been shown to predispose to the of HAPE include a blunted 2 in the arterial blood" href="https://kinesiology.ucalgary.ca/maci...atory-response–">hypoxic ventilatory response, an exaggerated pulmonary vascular response to exercise and 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia, increased sympathetic tone, and small lung volumes (Figure 20-8).

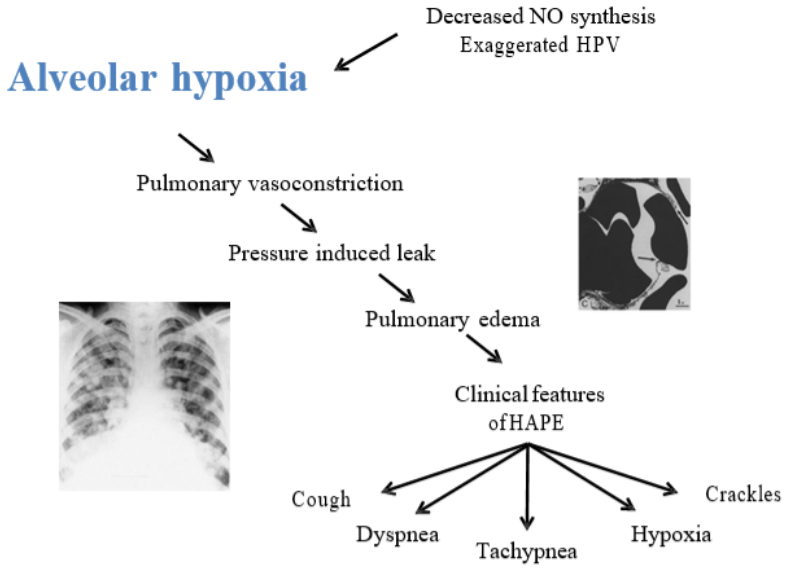


Figure 20-8 Pathophysiology of HAPE. Alveolar hypoxia causes hypoxic pulmonary vasoconstriction. This vasoconstriction is patchy and therefore results in an increased pressure in some capillaries and a subsequent pressure induced leak (see insert to the left from (West and Mathieucostello, 1995). This fluid leaks into the alveolar spaces to cause pulmonary edema (see chest X ray insert to the left; patchy opacities throughout both lung fields. Pulmonary edema gives rise to the clinical symptoms and signs of HAPE: cough, dyspnea, tachypnea, hypoxia, and crackles. Factors that may predispose to developing HAPE include decreased endogenous nitric oxide levels and an exaggerated hypoxic pulmonary vasoconstriction response.

A STRESS-INDUCED LEAK: The increased pulmonary pressures cause an increased pulmonary 2 and CO_2) as well a small molecules and water occurs across capillary walls" href="https://kinesiology.ucalgary.ca/maci...-czz#capillary">capillaryhydrostatic pressure, so much so that the capillary endothelium begins to strain and even ruptures; leading to the extravasation of red blood cells, large protein, and macrophages into the alveolarspace. This alveolar edema leads to ventilation perfusion mismatch and impaired pulmonary gas exchange. This gives rise to breathlessness, cough, cyanosis, tachycardia, and the lowered 2 in the peripheral circulatory system"" href="https://kinesiology.ucalgary.ca/maci.../pha-tend#spo2">SpO_2.

TREATMENT: Treatment of HAPE involves reducing the stimulus for the vasoconstriction; alveolar 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia, and secondly by directly dilating the pulmonary arteries, thereby reducing the hydrostatic pressure and fluid movement to the alveolarspace.

Methods of reducing the alveolar hypoxia include: descent to lower altitudes, hyperbaric treatment in a Gamow bag if descent is impossible, and oxygen administration by facemask or nasal cannula. Methods to directly dilate pulmonary vessels and decrease pulmonary pressures include pharmacological treatment with the calcium blocker Nifedipine, the phosphodiesterase inhibitor Sildenafil, or the glucocorticoid Dexamethasone.

Sleep at High Altitude

Decreased quality of sleep is an almost universal subjective complaint amongst visitors to high altitude and this is supported by objective evidence of an increased frequency of arousals, decreased time spent in 'deep' sleep (stage 3 and 4 slow wave sleep), a decreased time spent in REM sleep, and the of periodic breathing. The reason for these changes in sleep is, like the rest of the illnesses we have discussed, the underlying 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia; however, in contrast to acute mountain sickness, periodic breathing at high altitude gets worse and not better during acclimatization. This implies that the etiology of periodic breathing at altitude is distinct from that of AMS.

The mechanism of periodic breathing at high altitude is thought to involve an increase in sensitivity of the peripheral and central chemoreceptors such that any disturbance in breathing (i.e., a sigh or a breath hold) will trigger overcompensation in ventilation, resulting in alternating periods of apnea and hyperventilation. For example, if during sleep at sea level, someone has a transient breath hold (a decrease in ventilation), the PCO_2 at the central chemoreceptors will increase. This will result in an increase in ventilation to bring the PCO_2 back to baseline and stabilize the breathing pattern. At high altitude, the

increase in ventilation for a given increase in $PaCO_2$, is increased (central chemo sensitivity is increased). Therefore, after a breath hold, the ventilation will increase to a level greater than is required and $PaCO_2$ is decreased below baseline and below the threshold to breathe – resulting in an apnea. An unstable system is created where the breathing pattern oscillates between hyperventilation and apnea. A ventilation trace of periodic breathing is shown in Figure 20-9. Acetazolamide can also be used to help reduce the degree of periodic breathing during sleep and improve sleep quality; this is another pathway in which Acetazolamide can improve symptoms of AMS.

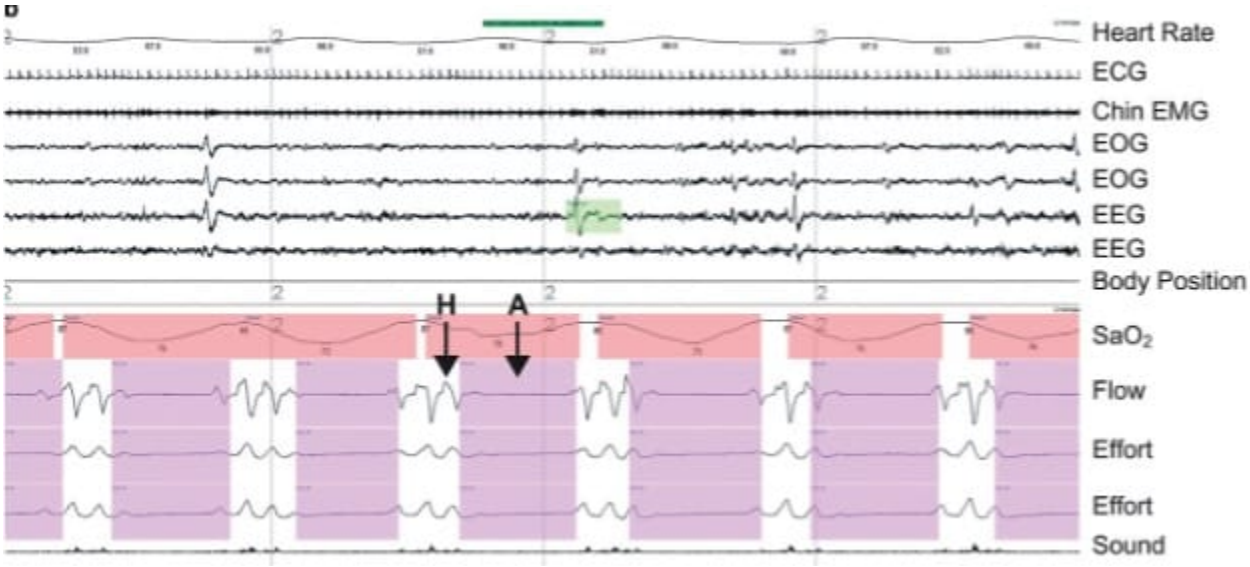


Figure 20-9 A 2-min epoch from a polysomnogram from one subject during sleep at 5050 m showing central sleep apnea (CSA). Arrow H indicates the period of hyperpnea, and arrow A the period of apnea. Arterial oxygen saturation (SaO_2) reading showing periods of desaturation. Nasal airflow reading measured by pressure transduced nasal cannula. Respiratory effort, measured by piezoelectric bands, highlight the period of hyperpnea (H) and longer period of apnea (A). ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram.

Blood Response

Haemoglobin

One of the most well-known physiological responses to high altitude is the increase in haemoglobin concentration. This increase in haemoglobin concentration is useful because it results in an increase in oxygen carrying capacity of the blood and therefore increases the body's ability to supply oxygen to the tissues. Interestingly, there is no apparent correlation between haemoglobin concentration at high altitude and exercise performance. This physiological response has however been exploited in the sporting world with blood doping and EPO injections.

Oxygen Transport

To understand how an increased haemoglobin concentration helps us at high altitude we need to review how oxygen is transported in the blood. The total amount of oxygen carried in the blood is the amount of oxygen carried by haemoglobin, and the amount of oxygen dissolved in the blood. Of these two, oxygen carried by haemoglobin is by far the most important. The amount of oxygen carried by haemoglobin can be calculated as the product of the total haemoglobin concentration in $g{\cdot}dL^{-1}$, the amount of oxygen each gram of haemoglobin can carry ($ml{\cdot}g^{-1}$), and the percentage of this total haemoglobin that is saturated with oxygen. This is summarized in the formula below.

Oxygen content = [Hb]·oxygen saturation·oxygen carrying capacity of haemoglobin + oxygen dissolved in the blood **Equation 20-8**

Because oxygen is poorly soluble in blood, this contribution towards total oxygen content is extremely small ($0.003{\cdot}PaO_2$). If we again take the case of Rachel at 5000m, her oxygen saturation was ~80%, PaO_2= 50, haemoglobin concentration 17.0 $g{\cdot}dL^{-1}$, and oxygen carrying capacity (1.34 $ml{\cdot}g^{-1}$).

This results in:

Oxygen content = 17.0·0.80·1.34 + 50·0.003

Oxygen content = 18.34 $mL \cdot dL^{-1}$

Interestingly, if we look at the situation of sea level, Rachel's haemoglobin concentration is likely to have been ~14 $g \cdot dL^{-1}$, her oxygen saturation 98% and her oxygen carrying capacity unchanged at 1.34 $ml \cdot g^{-1}$ and her PaO_2 of 100 mm Hg. This gives a sea level total oxygen content of:

Oxygen content = 14.0·0.98·1.34 +100·0.003

Oxygen content = 18.68 $mL \cdot dL^{-1}$, a value very similar to that at 5000m altitude.

If there was no increase in Hb concentration with altitude, the total oxygen content would be about 20% lower than at sea level:

Oxygen content = 14.0·0.80·1.34+50·0.003

Oxygen content = 15.16 $mL \cdot dL^{-1}$

Figure 20-10. Dissolved oxygen and haemoglobin bound oxygen contribution to total oxygen content. This maintenance of oxygen content, although important at rest, is especially important during exercise when the amount of oxygen taken up by the muscles is greatly increased. Next we will review the potential mechanisms for the increase in haemoglobin with altitude.

Why does Haemoglobin Concentration Increase at High Altitude?

The increase in haemoglobin concentration at high altitude is caused initially by a decrease in plasma volume and then later by an increase in red blood cell production (fig 20-11). The initial plasma volume contraction is caused by 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia mediated diuresis, and the increase in red blood cell production (erythropoiesis) is caused by a hypoxia mediated increase in erythropoietin secretion.

The link between 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia and erythropoietin secretion involves hypoxia inducible factor 1 alpha (HIF 1 alpha). HIF 1alpha is a protein that is rapidly degraded by normoxia but accumulates during hypoxia. It has many different effects, but importantly, it binds to the promoter region of the erythropoetin gene and upregulates transcription.

Acute exposure to 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia results in a rise in blood erythropoietin concentration that is detectable within hours. The erythropoetin concentration reaches a maximum after ~ 48 hours (Milledge and Cotes 1985), and then declines to reach sea level values after about 3 weeks. If we plot the changes in EPO concentration, and packed cell volume (an index of erythropoeisis and Hb concentration), against the time spent at altitude, we can see that packed cell volume is very slow to increase (over a period of 3 weeks) whilst the EPO peaks early with altitude exposure and then declines to reach sea level values after ~ 3 weeks.

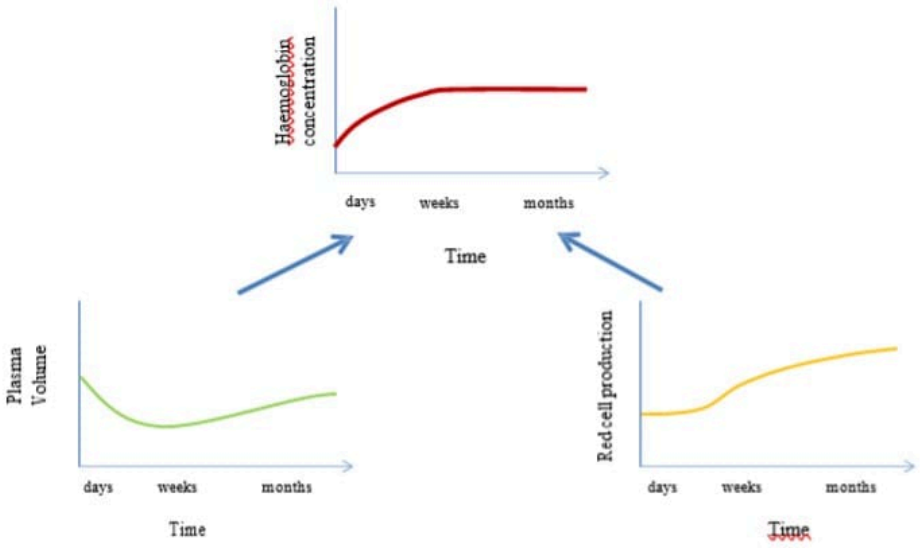


Figure 20-11. Time course of haemoglobin, plasma volume, and red cell production changes at high altitude of PV and RBC volume. Over a period of days, plasma volume contracts (bottom left), red cell production remains constant (bottom right) and therefore haemoglobin concentration increases (top). Over a period of weeks, plasma volume reaches a low point, red blood cell production begins to increase resulting in a further increase in haemoglobin concentration. Over a period of months, plasma volume increases towards baseline levels, and red cell production remains reasonably constant. This results in a steady haemoglobin concentration.

However this increase in haemoglobin concentration is not without its disadvantages. The price paid for the increase in oxygen carrying capacity of the blood is an increase in blood viscosity with an associated increase in vascularresistance. This disadvantageous response is most apparent in chronic mountain sickness patients, where haemoglobin concentration can reach levels of above 22 $g \cdot dL^{-1}$ with attendant symptoms and signs of headache, malaise, pulmonary hypertension, and cyanosis. This condition is best treated with descent to a lower altitude or the removal of blood from the body.

Acid-Base Balance

With ascent to high altitude, changes in respiratory and renal function lead to changes in CO_2 and HCO_{3-} in the blood. These changes can have a marked effect on and protein function. How these changes in respiratory and renal function affect pH is considered below.

When CO_2 is dissolved in blood it reacts with water to form carbonic acid (H_2CO_3) at a one-to-one ratio. This carbonic acid then dissociates into H^+ and bicarbonate at concentrations determined by the dissociation constant for carbonic acid (KA).

$CO2 + H_3O\ H_3CO_3\ HCO_{3-} + H^+$ **Equation 20-9**

$KA = [HCO_{3-}][H^+] \cdot [H_2CO_3]^{-1}$ **Equation 20-10a**

And because H_2CO_3 is produced at a 1 to 1 ratio from CO_2 then CO_2 can replace H_2CO_3.

Therefore, taking logs:

$\log KA = \log [H^+] + \log [HCO_{3-}] \cdot [CO_2]^{-1}$ **Equation 20-10b**

$-\log [H^+] = -\log KA + \log HCO_{3-}] \cdot [CO_2]^{-1}$ **Equation 20-10c**

If we let '–log = p,' then we have:

$pH = pKA + \log [HCO_{3-}] \cdot [CO_2]^{-1}$ **Equation 20-10d**

where pKA is 6.1.

This is known as the Henderson-Hasselbalch equation.

How does this mathematics relate to physiology at high altitude? Because of the hypoxic induced hyperventilation described above, the arterial PCO_2 levels are decreased at high altitude. This decrease in $PaCO_2$, causes an increase in according to the Henderson-Hasselbalch equation:

$pH = 6.1 + \log ([HCO_{3-}]\cdot[CO_2]^{-1})$

at sea level:

$pH = 6.1 + \log (24/40\cdot0.03)$

where 0.03 is the conversion factor (Henry's constant) from mM to 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide" href="https://kinesiology.ucalgary.ca/maci...tial-pressure-">partial pressure in mm Hg according to Henrys law (see chapter 7)

$pH = 7.4$

At high altitude, the hyperventilation associated hypocapnia, causes a decrease in bicarbonate and therefore an increase in . For example at an altitude of 5000m arterial PCO_2 typically decreases to 25 mm Hg and HCO_{3-} is typically ~20 $mmol\cdot L^{-1}$ and therefore:

$pH = 6.1 + \log (20/0.03\cdot25)$ $pH= 6.1 + \log 26.7$

$pH = 6.1 + 1.43$

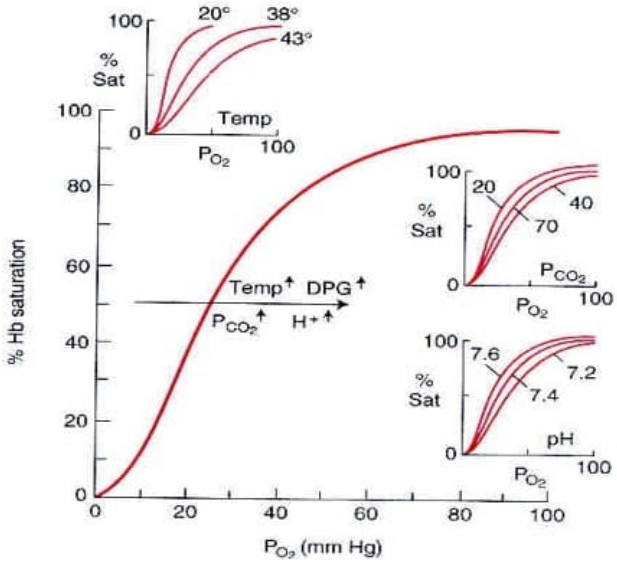
$pH = 7.53$

This 2. Ventilation removes CO_2 from the body and when more CO_2 is removed than is produced by metabolism, this removal results in decreased [H+] (alkalosis) because of the following reaction is driven to t" href="https://kinesiology.ucalgary.ca/maci...tory-alkalosis-">respiratory alkalosis typically causes a metabolic compensation, involving bicarbonate excretion through the kidneys. This decrease in bicarbonate reduces the base to acid ratio and hence brings the back down towards neutral (7.4).

Acid Base Balance and the Oxygen Dissociation Curve

Changes in of the body can have far reaching effects, mainly due to alteration in protein function. In the case of high altitude, the change in pH has marked effects on the 2 from Hb, but often used to describe the relative occupation of Hb with oxygen" href="https://kinesiology.ucalgary.ca/maci...ociation-curve">oxygen dissociation curve.

As reviewed in chapter 7, many factors can affect the position of the oxygen dissociation curve: an increase in temperature, CO_2, H+, and 2,3 bisphosphoglycerate (2,3 BPG) shift the curve to the right, whilst a decrease in temperature, CO_2, H+, and 2,3 BPG all cause a leftward shift in the curve.



80% saturated by 60 mm Hg, then a slow increase to 98% saturated at 80 mm Hg. Shifts of the curve to the right occur with increased temperature, increased PCO2 and decreased pH. Diphosphoglycerate also shifts the curve to the right. Leftward shifts of the curve relate to the opposite changes of these variables." width="444" height="400"> **Figure 20-12 Example of how the oxygen dissociation curve may initially be shifted to the left at high altitude due to the influence of hypocapnia (low $PaCO_2$,) and alkalosis (high pH)**. Following partial acclimatization, acid-base correlation of the alkalosis will then further alter the curve (West, 2010).

This leftward shift can be considered beneficial at extreme altitudes as it optimizes in the pulmonary capillaries; for a given PO_2 in the pulmonary blood, oxygen saturation will be increased. Normalization with metabolic compensation and in increase in 2,3BPG tends to shift the curve back towards its resting position at after time at altitude.

Acid Base Research at Extreme High Altitude

In 2008, a group of scientists from the UK set off to Mt Everest with the goal to obtain arterial blood gas samples at the summit of Mt Everest (Grocott and Martin et al. 2009). Until then arterial samples had been taken in 2 hypobaric chamber studies in which barometric pressure was gradually decreased to that of the summit of Mt Everest. Blood gas samples were taken in four subjects just below the summit at a height of 8400m. These represent the highest blood gas samples to be obtained to date and yield significant insight not only into high altitude physiology, and as the authors point out, but also into the physiology of critically ill patients in the intensive care unit.

At 8400m the average blood gas parameters for the four subjects were as follows: 7.53, PO_2 24.6 mm Hg, PCO_2 24.6 mm Hg, base excess -6.9, lactate of 2.2 $mol{\cdot}L^{-1}$, haemoglobin of 19.3 $g{\cdot}dl^{-1}$, oxygen saturation of 54% and an average alveolar to arterial gradient of 5.4 mm Hg (Grocott and Martin et al. 2009). These values represent the highest altitude that such recordings have ever been recorded and also possibly the lowest arterial oxygen pressures and saturations ever recorded in healthy humans.

Throughout the ascent of Everest, calculated oxygen content remained stable despite the reduced SaO_2 (owing to the increase in haemoglobin concentration) until approximately 7100m. This remarkable maintenance of oxygen content indicates that a decreased oxygen content is not responsible for the marked decrease in exercise performance at these altitudes.

Brain Response

The brain is the arguably the most sensitive organ in the body. It perhaps is not surprising that brain blood flow is usually well maintained at high altitude (Severinghaus and Bainton et al., 1966; Ainslie and Ogoh, 2010). Indeed, in order to compensate for marked reductions in the CaO_2 during the initial arrival to high altitude, brain blood flow may increase by 20-30% in order to maintain effective cerebral oxygen delivery. Even at extremes of altitudes (>8000m) it has been reported that cerebral vasodilation occurs, again compensating for reductions in CaO_2 (Wilson and Edsell et al., 2011). Despite this maintenance of cerebral oxygen delivery, ascent to altitude results in a subtle decline in some of our more sophisticated cognitive skills.

The mountain environment is potentially dangerous and the complex decisions needed for safe travel require a normal functioning brain. Some of the tragedies that have occurred at high altitude, such as the events on high on Everest in 1996, may have resulted from a critical loss of judgment (Krakauer, 1997). The mortality on descent from the summit of Everest is three times greater for those climbers not using oxygen than in those who did (Huey and Eguskitza, 2000). More recently a study into all the deaths on Mount Everest between 1921–2006 found that of the 212 deaths, 94 occurred above 8000 m (Firth and Zheng et al. 2008). Most of these deaths occurred on descent. Cognitive impairment, ataxia, profound fatigue, late summit times, and the tendency to fall behind companions were all features seen in non-survivors. Respiratory distress, nausea, vomiting, and headache, common indicators of altitude illness at 2500-5000m, were rarely noted in the non-survivors above 8000m.

Acclimatization to High Altitude: Truths and Misconceptions

The biggest misconception about acclimatization is that it returns the body to the sea level condition and the effects of high altitude are nullified by acclimatization. An example – at 4200m: Alveolar PO_2 following acute exposure is about 45 mmHg. Alveolar PO_2 following full acclimatization is about 54 mmHg! Patients with COPD with an arterial PO_2 less than 55 mmHg are normally placed on a form of continuous oxygen therapy. Thus, the most important feature of acclimatization is hyperventilation. Polycythemia and the associated increased haemoglobin concentration is slow to develop and of minor value. Other features include increases in cellular oxidative enzymes and the concentration of capillaries in some tissues. Hypoxic pulmonary vasoconstriction is not beneficial as discussed.

Exercise at Altitude

When we exercise at altitude, there are two different and independent stressors to which the body must respond and adapt to: 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia and exercise. The simultaneous presence of both stressors has an additive effect that will influence maximal exercise capacity, endurance time until and overall exercise performance. When considering the physiological responses to exercise at altitude, we need to consider a number of factors:

- the degree of hypoxia incurred;
- the intensity (absolute vs relative workload) and duration of exposure to hypoxic conditions
- the inter-individual variability in adapting to hypoxic environments (responders vs non- responders)

These factors are outlined briefly below, followed by consideration of how exercise at altitude impacts each step of the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade (Figure 20-13).

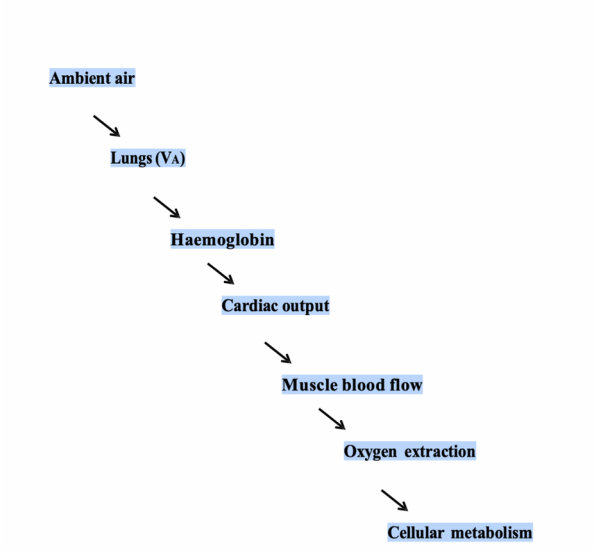


Figure 20-13 The flow of ambient oxygen, and eventual delivery to the cell is dependent upon a number of links composing the oxygen cascade pathway. During exercise at altitude, adjustments are made to various components of this pathway to optimize oxygen delivery to the working muscle in order to compensate for a reduction in inspired oxygen levels. After acclimatization to altitude, some of the links in the pathway are unregulated (e.g., RCV, HB) forming the basis of the 'life high-train low' concept of training.

- **The degree or extent of** 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">**hypoxia incurred**
- As mentioned, at low altitude, resting SaO_2 is well maintained and thus only results in marginal disruption to homeostasis; however as we ascend to more moderate altitude (>3000m) a slight decrease in resting SaO_2 (e.g., 98 to 92%) is observed as the ambient PIO_2 can decreases to 110 mm Hg compared with 159 at sea level. At high altitude (approx. 5000m), ambient PO_2 will decrease to around 85 mm Hg with resting SaO_2 approaching 80% and lower. These decreases in PIO_2 and SaO_2 present a significant disruption to our resting haemostasis.

- **The intensity and duration of exposure to hypoxic conditions**
- As observed at sea level, the relative stress/intensity of exercise out plays a major role in the subsequent physiological and metabolic adjustments (e.g., cardiovascular, respiratory, hormonal). Furthermore, it should be noted that when performing the same absolute workload at altitude as at sea level, a greater relative exercise intensity is elicited that results in a greater physiological challenge and disruption to homeostasis. The main reason for this is that although the $\dot{V}O_2$for a given output at high altitude is similar at sea level and altitude, the relative exercise intensity is greater as a result of the decline in $\dot{V}O_2$max (i.e. a constant power output represents a higher percentage of $\dot{V}O_2$max at high altitude). For example, cycling at a power output of 100W at sea level may elicit a $\dot{V}O_2$of 1.5 $L \cdot min^{-1}$, a value around 50% of sea level $\dot{V}O_2$max (Figure 20-15). When cycling at an identical workload of 100W at 4300m, a $\dot{V}O_2$ of 1.5 $L \cdot min^{-1}$may also be found. However, due to a reduction in $\dot{V}O_2$max at this altitude (approximately 25%), this represents a significantly greater relative exercise intensity of 65% of $\dot{V}O_2$max. As a result of this higher relative intensity, more dramatic physiological and metabolic adjustments are required to maintain homeostasis for a given absolute workload when performed at altitude compared to sea level.

Figure 20-14 The effects of altitude on maximal and sub-maximal oxygen consumption. Although the oxygen cost of cycling at 100 W does not change, the decrease in maximal oxygen uptake results in this being a greater % of maximal oxygen uptake.

- Inter-individual variability in adapting to hypoxic environments (responders vs non- responders)
- A final factor determining the physiological response to altitude is whether the individual is acclimatized to altitude. Thus, a sea level resident who is exposed, acutely, to a high-altitude environment will respond differently when compared to an individual who has been acclimatization to high altitude.

Exercise and the Oxygen Cascade

For reasons discussed, there are a number of physiological and metabolic adjustments made both at rest and during exercise at high altitude when compared with sea level. A primary goal of our body, regardless of the barometric pressure,

is to ensure that an adequate amount of oxygen is delivered to the exercising muscles. We accomplish this through adaptations in the various links that make up the “2 from atmosphere to tissue; alveolar > arterial > capillary > venous” href=”https://kinesiology.ucalgary.ca/maci...oxygen-cascade”>oxygen cascade” (Figure 20-13). One well-reported observation as that maximal oxygen consumption is progressively reduced upon ascent to high altitude (Fig 20-15). Factors that influence this reduction in exercise capacity are outlined below.

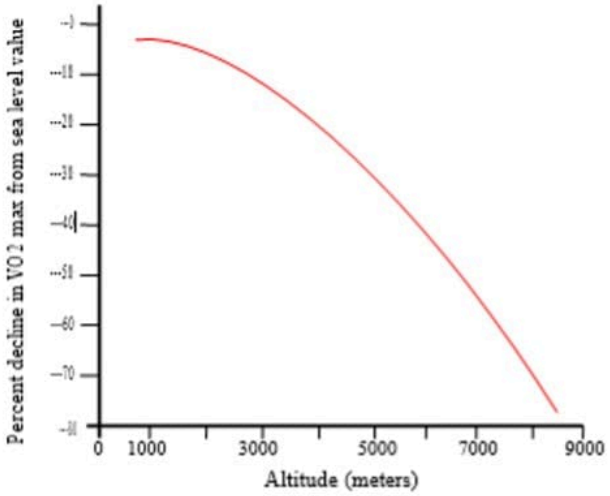


Figure 20-15; Effect of altitude on maximal oxygen uptake. As altitude increases, maximal oxygen uptake decreases.

Step 1- the Lungs

Total and ventilation, like at rest, are greater during submaximal exercise at high altitude when compared to at sea level (see Figure 20-16). Elevations in submaximal ventilation are a beneficial response as it helps to preserve alveolar and arterial oxygen pressures and thus maximize oxygen content. The mechanism underling this greater increase in submaximal ventilation is likely due to the greater reductions in PaO_2 and thus more marked peripheral chemoreflex activation. Although maximal ventilation during exercise is unaltered when compared to sea level, heavy exercise stresses lung capacity to the limit. For example, unlike at sea level, PaO_2 decreases during exercise at high altitude. This decrease in PaO_2 is caused mainly by an incomplete diffusion but also by ventilation perfusion mismatch and shunting.

Figure 20-16 Effect of increasing altitude on ventilation during graded-intensity exercise. V̇E, ventilation.

Diffusion limitation at altitude during exercise: Diffusion (i.e. movement of O_2 from the alveoli to the pulmonary capillaries) across the pulmonary and tissue capillaries can become limiting at altitude, especially during exercise. As discussed in Chapter 7, the 2, partial pressure of oxygen; PCO_2, partial pressure of carbond dioxide” href=”https://kinesiology.ucalgary.ca/maci...tial-pressure-“>partial pressure of oxygen determines the driving force from one place to another. This diffusion driving force is equal to the alveolar to venous PO_2 difference. Although the transit time remains at 0.25 sec, the driving force for diffusion is much less than at sea level. For example, the diffusion driving force is approx. 60 mmHg at sea level (calculated from subtracting PAO_2 [e.g., 100mmHg] from PvO_2 [40 mmHg]). In contrast, at 5000m, this diffusion driving force is approx. 20 mmHg (PAO_2 [e.g., 50mmHg] from PvO_2 [25 mmHg]). These changes results in marked reductions in SaO_2 and related arterial 2 in the arterial blood” href=”https://kinesiology.ucalgary.ca/maci...-max#hypoxemia”>hypoxemia during exercise that contributes to the decline in maximal oxygen consumption.

Step 2 – Haemoglobin

As reviewed in the section on blood response, upon exposure to altitude >2500m, significant increases in haemoglobin concentrations occur. Although an increased production of red blood cells is often viewed as the best-known feature of adaption to high altitude, this response has little role in acclimatization to high altitude that occurs over 2-3 days. Plasma volume contraction, and later, polycythaemia underlie this increase in haemoglobin concentration. The somewhat controversial topic of exposure to high altitude to improve sea level performance is highlighted in the research box below.

Step3 to 5 – Cardiac Output and Oxygen Extraction:

The next critical step in the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade is oxygen transport via cardiac output. Consideration of the importance of $\dot{Q}$ and the influence of 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia on oxygen delivery and utilization during exercise can be appreciated with the 2 = Q(dot)a?O_2-Q(dot)v?O_2 or Q(dot)?(aO_2-vO_2) is based on the principle that the amount of substance taken up by an organ (or organism) is equal to the amount delivered minus the amount coming out" href="https://rb.gy/tgb0j7">Fick equation:

2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ = $\dot{Q}(a\text{-}\bar{v})$ O_2 difference **Equation 20-11**

The components of the Fick equation provide an accurate assessment of how critical elements associated with oxygen delivery and utilization are affected by both short- and long-term exposure to high altitude. These are discussed below:

Cardiac output: Cardiac output ($\dot{Q}$) is a function ofHR and SV. Upon initial exposure to altitude, HR and thus $\dot{Q}$ increase in an attempt to compensate for the reduction oxygen content of the blood. This response helps ensure that adequate amounts of oxygen are transported to tissues, including during exercise. During submaximal workloads, the alterations in $\dot{Q}$ and local muscle blood flow allow for sufficient oxygen delivery to working muscles. Consequently, for a given submaximal workload, 2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ remains unchanged from sea level vales. Thus, a higher $\dot{Q}$ at altitude compared with sea level maintains a similar level of oxygen being transported to and utilized by working muscles. Because of reductions in maximal heart rate and SV (due to declines in plasma volume and increased hematocrit), with prolonged exposure (>1-2 weeks) to high altitude, maximal exercise cardiac output is reduced by 20-30%. Below 6000m, oxygen consumption at a particular output stays the same because of greater tissue extraction (i.e., increased a-$\bar{v}$ O_2 oxygen differences).

Heart rate: The initial increase in $\dot{Q}$ is achieved by an increase in HR, Stimulation of the beta – receptors by cardiac sympathetic nerves and circulating epinephrine, are major contributors to the increase in HR at rest and during submaximal exercise. The alpha-adrenergic arm of the SNA may also regulate HR during acclimatization to altitude (Calbet et al., 2003). There is overwhelming evidence that the sympathetic nervous activity is increased during both short and longer-term exposure to high altitude (e.g., arterial noradrenaline and adrenaline levels, MSNA, noradrenaline spillover) (Mazzeo and Bender et al., 1991; Wolfel and Groves et al., 1991) (Hopkins and Bogaard et al., 2003) (Hansen and Sander, 2003) (Mazzeo and Child et al., 2000). It is also possible that partial parasympathetic withdrawal may mediate elevations in resting and exercising heart rates (Hopkins and Bogaard et al., 2003). In contrast, maximal HR during exercise is reduced with increasing severity of 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia. Estimates reveal an approximately 1 $bmin^{-1}$ reduction in peak HR for every 7-mmHg decrease in barometric pressure below 530 mmHg (approximately 130 m of altitude gained above 3100 m).

Stroke volume: Upon initial exposure to altitude, SV appears to be only marginally affected during submaximal exercise. However, with a prolonged exposure to altitude, SV clearly declines over time, stabilizing after 1-2 weeks. Loss of plasma volume is likely to be an important mechanism explaining this reduction in SV. Reductions in plasma volume will lead to reductions in LV filling thereby yielding a lower stroke volume (via the Frank-Starling effect). It is also possible that the increase in the after-load placed upon the heart can contribute to the reduction in SV over time at altitude. Elevations in SNA at altitude results in a progressive increase in systemic vascularresistance and thus MAP. At higher exercise intensities, O_2 delivery cannot keep up with muscle demand. This limitation is reflected by the well-known progressive decline in $\dot{V}O_2$max with increasing altitude (Figure 20-16) (Calbet and Boushel et al., 2003). This reduction during initial exposure is directly associated to the decline in the exercising CaO_2 as maximal $\dot{Q}$ is unaltered in the short-term. With partial acclimatization (1-3 weeks), for a given output, $\dot{Q}$ is reduced from initial exposure due to:

- a decrease in SV due to a reduced venous filling
- a decrease in maximalHR due to a reduction in cardiac responsiveness to -adrenergic stimulation (Wagner, 2000) and/or an increase in vagal tone (Hopkins and Bogaard et al., 2003)

As a result of these declines in $\dot{Q}$and muscle blood flow with acclimatization, $\dot{V}O_2$max is still reduced despite significant increases in CaO_2 coupled with enhanced O_2 extraction by the muscle. The reduction in $\dot{V}O_2$max is predominantly explained by the reduction in $\dot{Q}$max as well as re-distribution of blood flow to non-exercising tissues (Calbet and Boushel et al., 2003). At higher altitudes, a fall in maximalHR can also contribute to the decline in $\dot{Q}$max.

$(a-\bar{v})O_2$ DIFFERENCE

Muscle blood flow: Studies at 4300 m and 5260 m have revealed that while SaO_2 and red blood cell numbers increase with acclimatization, net oxygen delivery to exercising muscles did not increase accordingly (reviewed in: (Mazzeo, 2008). This reduction was the result of a decrease (20-30%) in muscle blood flow during exercise, thereby offsetting the improvements in O_2 content. Thus, O_2 delivery to the muscle remains unchanged after acclimatization when compared with short-term altitude exposure. Thus, it seems that O_2 delivery to exercising muscle during submaximal exercise is tightly regulated so that delivery = demand. The mechanisms underpinning these reductions in muscle blood flow are likely caused by:

- increases in nor-adrenaline concentrations
- reductions in $\dot{Q}$

Oxygen extraction: A number of studies have reported that oxygen diffusing capacity is not a limiting factor during exercise at high altitude (reviewed in: (Mazzeo 2008)). Additionally, fractional extraction by exercising muscle appears to be the same before and after acclimatization, suggesting that diffusion and utilization by is not compromised. Studies collectively show that – as with sea-level exercise – as 2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ increases, working muscles are capable of extracting oxygen as needed under hypoxic conditions during submaximal exercise. Thus, working muscle can match delivery and extraction to match metabolic demand during submaximal exercise at altitude. At these intensities, reductions in $\dot{Q}$ and O_2 delivery are compensated for by increased O_2 extraction (as indicated by an increase in the $(a-\bar{v})O_2$ differences compared with short-term altitude exposure yielding values similar to that found during absolute workload at sea level.

Step 6: Cellular metabolism:

The final step in the 2 from atmosphere to tissue; alveolar > arterial > capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade is cellular metabolism. To date, assuming adequate energy intake, there are few significant measurable changes in muscle or cellular metabolism at high altitude or with acclimatization. Levels of adenosine triphosphate, creatine phosphate, muscle and heart glycogen, oxidative and glycolyticenzymes remain unchanged with acclimatization. Recent research using sophisticated measurement techniques have also revealed that 9-11 days of exposure to high altitude (4560m) does not markedly modify integrated measures of mitochondrial functional capacity in skeletal muscle despite significant decrements to enzyme concentrations involved in the tricarboxylic acid cycle and phosphorylation (Jacobs and Boushel et al. 2012). Thus, the mechanisms behind improved exercise capacity at high altitude following partial acclimatization are likely independent of changes in cellular metabolism.

EXERCISE CAPACITY: Altitude *perse* causes marked improvements in events of short duration and high intensityexercise (e.g., sprints and throwing events) and marked impairments in events of long duration and lower intensity (e.g. endurance sports). Gravity decreases by 0.3 $cm{\cdot}sec^{-2}$ for every 1000m of altitude, and wind resistance decreases with decreased air density. Both of these factors are beneficial at altitude for athletes involved in short-term maximal events. At altitude, there is a decline in running events greater than 800 m (or over >2 min). In the Mexico City Olympic in 1968, many athletes who had world-class times at sea level were defeated by high altitude natives (eg, Kenyans and Ethiopian runners). Figures 20-17 and 20-19 show the typical physical performance decrements as a function of exercise duration and elevation.

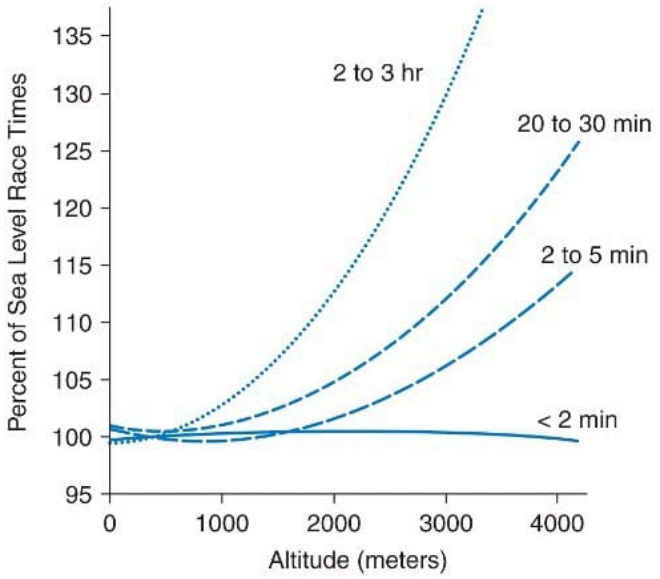


Figure 20-17 Physical performance decrements as a function of event duration and elevations up to 4300 m. Each regression line illustrates how performance changes at altitude for sea level events that lasted less than 2 minutes, 2 to 5 minutes, 20 to 30 minutes, and 2 to 3 hours. (Modified from:(Fulco and Rock et al., 1998)).

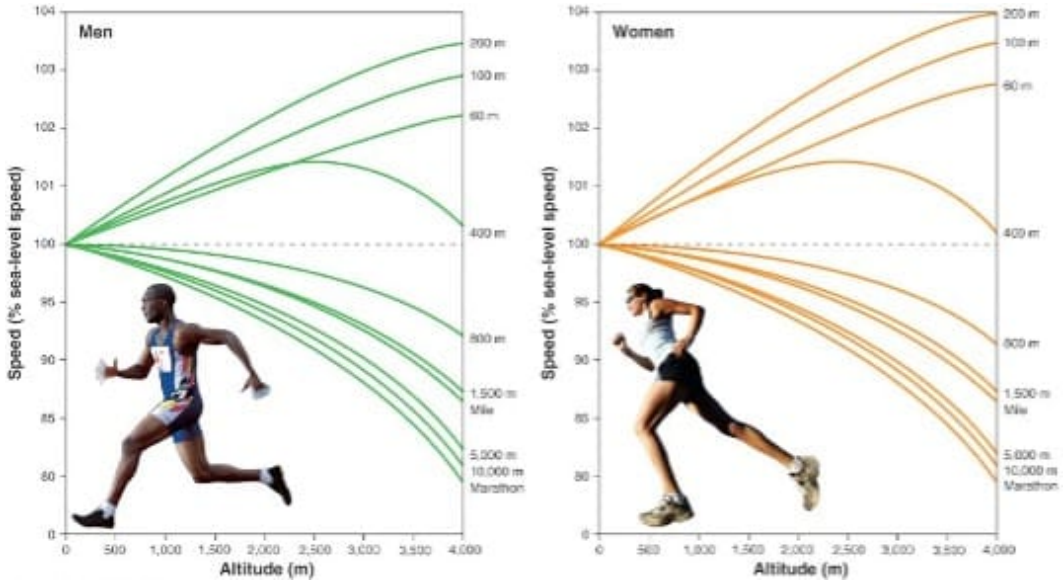


Figure 20-18 Running performance predicted at different altitudes. In running events, as the distance of the race gets longer the negative effects of altitude on speed are observed in both males and females. Modified from (Peronnet and Thibault et al., 1991).

EXERCISE PERFORMANCE: High altitude training has become a mainstay in endurance sports, with live high-train low being the current protocol of choice. Athletes either live or sleep in artificial or natural hypoxic conditions with the aim to increase serum erythropoietin concentrations, which are thought to improve maximum and thus exercise performance. Changes, however, are not very striking and only apparent in so-called responders, who are not a well-defined group and may be as little as 50% of the trained study population. Whereas some studies show minor improvement (Stray-Gundersen and Levine 2008), others report no change (Lundby and Millet et al., 2012; Robach and Lundby, 2012) or even worsening. Furthermore, the mechanisms behind the proposed beneficial changes remain obscure and are far from being proven.

There is an evident lack of sufficiently powered randomized, double-blinded studies, with training protocols that are identical and comparable for all groups. Several studies discriminate between responders and non-responders, without clearly assessing the characteristics of the so- called responders. Until this has been done, it remains unclear if such a group really exists and how these subjects are characterized. This, however, would be of immense value, so protocols could be tailored to athletes' needs. Taken together, the current literature on natural or artificial 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia somewhat documents improved performance at high but not low altitude. Nevertheless, many elite athletes and their coaches strongly believe in altitude

training for competition at sea level. In addition, athletes from Kenya (located at 2000-3000m ASL) are well known for their superior endurance performance at sea level. Thus, some benefits of high-altitude training cannot be excluded.

ALTITUDE EXPOSURE TRAINING TECHNIQUES :

Taking some of the information about altitude training into consideration, various techniques have been devised in order to expose the athlete to the beneficial effects of high altitude whilst not reducing their ability to train effectively. These have been labelled 'Live High – Train High, 'Live Low – Train High' and 'Live High – Train Low'. The typical altitudes used are around 2000-2500m, which, in itself, reduces the risk of some of the unhelpful effects of altitude exposure. The 'low' altitudes may not actually be at sea level, but could be 1250m, for example. However, the difference between the two altitudes is significant enough to have an effect on training.

Live High – Train High: Maximum exposure to altitude. Evidence of a positive effect at sea level is controversial, and there is less support for this method amongst experts.

Live Low – Train High: The idea behind this regime is that the athlete is exercising in a low oxygen environment, whilst resting in a normal oxygen environment. There have been some interesting findings suggesting that this technique might work, but there are no good studies showing that the technique makes any difference to the ultimate competitive performance of the athlete at sea-level. Additionally, training intensity is reduced so some athletes may find that they actually lose fitness using this regime.

Live High – Train Low (LHTL**):** The theory behind this regime is that the body will acclimatize to altitude by living there, whilst training intensity can be maintained by training at (or near) sea level. Hence, the beneficial effects of altitude exposure are harnessed whilst some of the negative ones are avoided. However, residence at altitude must be for more than 12 hours per day and for at least 3 weeks. With this technique, some improvements in sea-level performance have been shown in events lasting between 8 and 20 minutes (Bailey and Davies, 1997; Bailey and Davies et al., 1998). However, as mentioned there are a lack of sufficiently powered randomized, double-blinded studies, with training protocols that are identical for all groups. Support for the lack of 'true' influence of LHTL comes from the first placebo-controlled and double-blinded design (Nordsborg and Siebenmann et al., 2012). In this study, 16 endurance cyclists trained for 8 wk at low altitude (<1,200 m). After a 2-wk lead-in period, athletes spent 16 $h day^{-1}$ for the following 4 wk in rooms flushed with either normal air (placebo group, n = 6) or normobaric2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia, corresponding to an altitude of 3,000 m (LHTL group, n = 10). Physiological investigations were performed twice during the lead-in period, after 3 and 4 wk during the LHTL intervention, and again, 1 and 2 wk after the LHTL intervention. Weekly training effort was similar between groups. Hb mass, in normoxia, and at a simulated altitude of 2,500 m and mean output in a simulated, 26-km time trial remained unchanged in both groups throughout the study. Exercise oxygen cost (i.e.,2 inhaled and O_2 exhaled"" href="https://kinesiology.ucalgary.ca/maci...-ph#v-%CC%87o2–">$\dot{V}O_2$ measured at 200 W) did not change during the LHTL intervention and was never significantly different between groups. The authors concluded that, 4 weeks of LHTL, using 16 $h{\cdot}day^{-1}$ of normobaric hypoxia, did not improve endurance performance or any of the measured, associated physiological variables.

Body Composition and Nutrition

Weight loss and muscle atrophy are common at altitude. Studies have reported weight losses of 100-200$g{\cdot}day^{-1}$. The weight loss is due to a combination of factors including: dehydration (via hyperventilation induced respiratory fluid loss and reductions of fluid intake), energy imbalance, increased activity levels and elevations in basal metabolic rate. Although in the past, lack of available food would likely have played an important role in the of a negative energy balance, it is not the case today due to better energy dense food and availability even at extreme altitudes. In addition, although the sensation of exertion during climbing at high altitude is high, the actual energy expenditure is not high (Westerterp and Kayser et al., 1992). Thus, it is energy intake that is reduced at altitude and it is this that induces an energy deficit resulting in the loss of body mass. The mechanisms responsible for the reduction in energy intake are unclear but may involve the influence of 2 in the arterial blood or a part of the body is less than adequate" href="https://kinesiology.ucalgary.ca/maci...ossary/gra-max">hypoxia on the central pathways of appetite control (Bailey and Ainslie et al., 2004).

Summary

Ascent to – and exercise at – altitude has an impact on each step of the 2 from atmosphere to tissue; alveolar > arterial

> capillary > venous" href="https://kinesiology.ucalgary.ca/maci...oxygen-cascade">oxygen cascade. The most beneficial response to the initial exposure to high altitude is the increase in ventilation which helps offset the reductions in arterial P_{O_2} and hence blood oxygen content. Thereafter, increases in hemoglobin concentration further facilitate elevations in oxygen content. There is a well-established decline in $\dot{V}O_2$max with increasing altitude (Figure 20-15). This reduction during initial exposure is directly associated with the decline in the exercising CaO_2 as maximal $\dot{Q}$ is unaltered in the short-term. With acclimatization, there are declines in $\dot{Q}$ and muscle blood flow and hence $\dot{V}O_2$max is still reduced despite significant increases in CaO_2 coupled with enhanced O_2 extraction by the muscles. The reduction in $\dot{V}O_2$max is predominantly explained by the reduction in $\dot{Q}$max as well as re-distribution of blood flow to non-exercising tissues. At higher altitudes, a fall in maximal HR can also contribute to the decline in $\dot{Q}$max.

There are many pathophysiological effects of the high-altitude environment. The most common is AMS – a self-limiting condition affecting a >50% of those who ascend >3500m. The incidence depends upon both the absolute altitude and the rate of ascent such that at below an altitude of 2000m, AMS is rare, and above 5000m it is almost universal. More serious forms of altitude illness include pulmonary and cerebral edema. Although medications for the treatment of altitude illness are available, descent still remains the most effective approach (if possible).

High altitude training has become a mainstay in many endurance sports, with a variety of approaches to do this. Athletes either live or sleep in artificial or natural hypoxic conditions with the aim to increase serum erythropoietin concentrations, which are thought to improve maximum and thus exercise performance. Changes, however, are not very striking and only apparent in so-called responders, who are not a well-defined group and may be as little as 50% of the trained study population.

Topics for Discussion

- Describe the mechanisms that drive the two most important responses of acclimatization; hyperventilation and elevations in hemoglobin
- Provide an overview of why maximal exercise capacity is reduced at high altitude
- You have been ask to volunteer and help organize a trek to Everest basecamp. What precautions would you take during ascent and what would be the main medications that would be prudent to have for the treatment of altitude illness?
- Describe the advice and considerations you would give to an athlete at sea-level who is wanted to incorporate some form of 'altitude' training into their schedule.

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Phil studied human physiology in the UK before post-doctoral studies at the University of Calgary. He started his first appointment as a Lecturer in Physiology at the University of Otago (New Zealand) in 2015 before moving to his job at UBC, Okanagan Campus in 2009. He is a full Professor and holds a Canada Research Chair in Cerebrovascular Physiology. In addition to lab-based work, Phil has led over 12 high-altitude research expeditions. He has published over 300 peer-reviewed publications in the area of environmental physiology. In his spare time, Phil stays active with his family and attempts to climb, ski and kite-surf as much as possible.

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Joseph studied medicine and physiology at the University of Otago, New Zealand. During his medical studies he developed an interest in high altitude physiology and performed research as part of multiple high-altitude research expeditions in the Nepal Himalaya and the Peruvian Andes. Joseph then completed his PhD in brain physics at the University of Cambridge, (United Kingdom) focussing on invasive monitoring of severe traumatic brain injured patients. Joseph is currently completing internal medicine training in Auckland, New Zealand, and is an honorary senior lecturer in Anaesthesiology. In his spare time, Joseph enjoys playing the bassoon and running slowly.

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