

TEXTBOOK OF CARDIOLOGY



de Jong and van der Waals Eds.
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Textbook of Cardiology

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1: ANATOMY

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1.1: Anatomy of a Heart

Traditionally, the heart is described as having left heart and right heart chambers. Current imaging techniques can show in exquisite detail the heart in its anatomical position inside the living patient's chest and demonstrate the convoluted arrangement of 'right' heart chambers relative to 'left' heart chambers and the fact that right heart chambers are not strictly right-sided nor are left heart chambers left-sided. These important relationships of the chambers can be replicated with an endocast (Figure 1.1.1). In cardiac anatomy, knowledge of the relative disposition of the cardiac chambers is as relevant as the intrinsic chamber morphology. This review considers the cardiac chambers, coronary arteries and the conduction system.

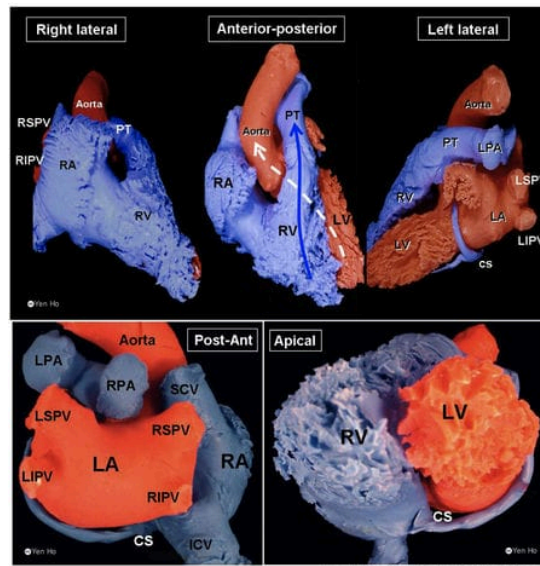


Figure 1.1.1: The endocast is viewed from 5 different perspectives to demonstrate the spatial relationship between right (coloured blue) and left (coloured red) heart chambers and between atria and ventricles. The blue and white arrows represent the right and left ventricular outflow tracts respectively.

1.2: Position of the Heart

The cardiac silhouette is generally taken to be trapezoidal in shape. The rib cage provides good markers for charting the cardiac silhouette. The normal position of the cardiac apex is generally taken to be in the fifth intercostal space in the mid-clavicular line. The lower border is a nearly horizontal line in the area of the left sixth rib to the right sixth costal cartilage (Figure 1.2.1). The upper border is hidden behind the sternum at the level of the second and third cartilages. The right margin of the heart peeps out behind the right border of the sternum between the right third and sixth cartilages. In the infant, the upper part of the cardiac shadow is broad owing to the prominence of the overlying thymus gland.

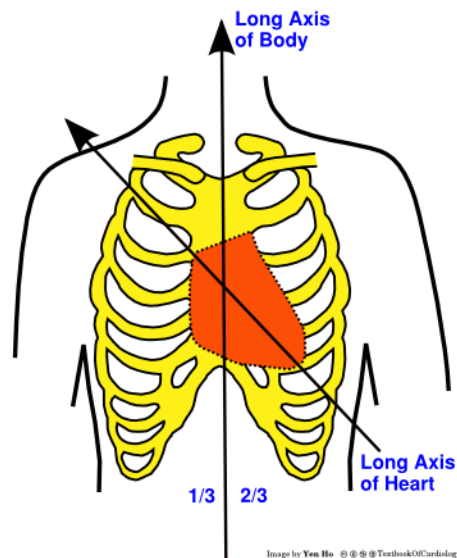


Figure 1.2.1: The long axis of the heart is at an angle to the long axis of the body. Approximately a third of the heart is to the right of the midline of the sternum and the remainder is to the left of the midline.

Inferior to the thymus, a fibrous pericardial sac encloses the mass of the heart. The sac has cuff-like attachments around the adventitia of the great arteries and veins as they enter or emerge from the heart. The pericardial cavity is contained between the double-layered serous pericardium. The parietal pericardium is adherent to the fibrous pericardium while the visceral layer is densely adherent to the cardiac surface forming the epicardium. Due to the contours of the heart and great arteries there exist two recesses within the pericardial cavity. These are the transverse and oblique sinuses. The transverse sinus occupies the inner heart curvature and lies between the posterior surface of the great arteries and the anterior surface of the atrial chambers. The reflection of the serous pericardium around the four pulmonary veins and the inferior caval vein forms the oblique sinus.

When the pericardium is removed, the major part of the heart visible from the front is the ventricular mass. Here, the morphologically right ventricle occupies the greater part (Figure 1.2.2). The left ventricle appears only as a narrow slip along the left cardiac border. The shape of the heart is generally likened to a pyramid. The apex points downwards, forwards and to the left while the base faces posteriorly and to the right. While the cardiac apex is usually represented by the vortex of the left ventricle, the cardiac base is less well defined owing to differences in definition.

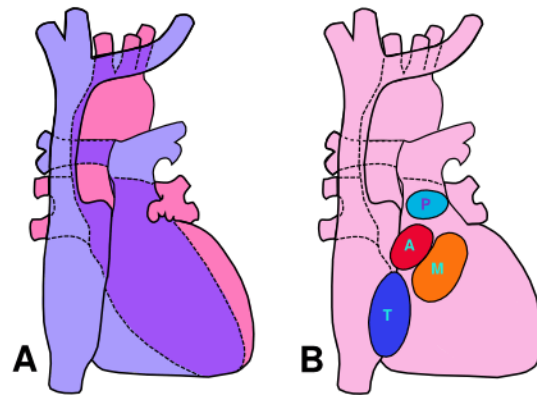


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Figure 1.2.2: **(A)** Viewed from the front, the right atrium and right ventricle overlaps the left atrium and left ventricle. The atrial chambers are to the right of their respective ventricular chambers. **(B)** The four cardiac valves are at different levels and different planes with the pulmonary(P) valve situated the most cephalad. The aortic(A) valve is wedged between the tricuspid(T) and mitral(M) valves.

The anatomical base is formed mainly by the left atrium receiving the pulmonary veins and to a small extent by the posterior part of the right atrium. The base in clinical practice, however, refers to the portion of the heart near the parasternal parts of the second intercostal spaces. The cardiac long axis, therefore, lies in a line drawn from the left hypochondrium towards the right shoulder. This orientation deviates considerably from the long axis of the body. Furthermore, the position of the cardiac septum at about 45° to the median brings the 'right heart' structures anterior to the 'left heart' structures (Figure 1.2.2A). The ventricles are situated inferior and leftward relative to their corresponding atria.

This results in the right atrioventricular junction being in a nearly vertical plane. The left atrium is the most posterior cardiac chamber being directly anterior to the oesophagus at the bifurcation of the trachea. In frontal projection, only its appendage is visible. The aorta has a deep-seated origin and only becomes part of the cardiac silhouette as it arches upwards and backwards, forming a spiral with the pulmonary trunk. The cardiac valves are offset from one another, in keeping with the disposition of the cardiac chambers and great arteries. When viewed in frontal projection, the pulmonary valve, being the most superior valve, is horizontally situated behind the third costal cartilage. The aortic valve lies posterior and to the right, above the nearly vertically orientated tricuspid valve (Figure 1.2.2B). The mitral valve is further posterior, overlapped by the more anterior but inferior tricuspid valve. The aortic valve therefore occupies a central position in the heart, wedged between the two atrioventricular valves.

The cardiac surfaces are described as the sternocostal, diaphragmatic, left and right (Figure 1.2.3). The sternocostal surface is covered anteriorly by the sternum and pleurae. The diaphragmatic surface is horizontally orientated. The sharp angle formed mainly by the right ventricle and occupying the lower heart border is the acute margin of the heart. The rounded obtuse margin of the heart is formed mainly by the left ventricle to the left of the sternocostal surface.

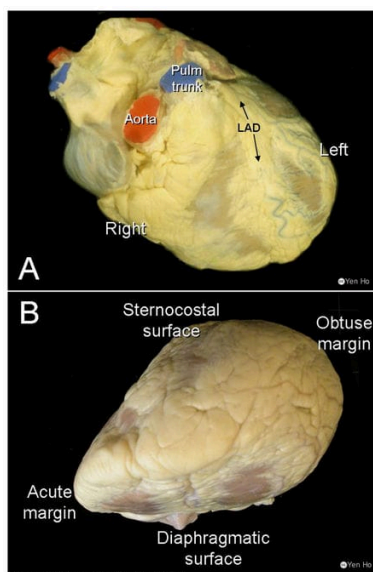


Figure 1.2.3: **(A)** This frontal view shows the right and left surfaces of the heart. The left anterior descending coronary artery buried in epicardial fat marks the plane of the ventricular septum. **(B)** The obtuse and acute margins of the ventricles are demonstrated in this apical view.

1.3: The Atria

The Morphologically Right Atrium

The right atrium is composed of an anterior appendage, a posterior venous sinus, a septal portion and a vestibule. The junction between the appendage and the venous sinus is marked epicardially by an atrial groove the terminal groove, in which lies the sinus node. Inside the chamber, the terminal groove is represented by a muscle bundle, the terminal crest (crista terminalis), from which pectinate muscles radiate into the appendage (Figure 1.3.1). The appendage has a characteristic triangular shape and a wide communication with the venous sinus. The smooth-walled venous sinus receives the superior and inferior caval veins in its cephalic and caudal extremities respectively. The coronary sinus opens close to the septal portion and near the opening of the inferior caval vein. The outlet portion of the atrium, the vestibule leading to the tricuspid valve orifice, is also smooth walled. The obliquely orientated atrial septum extends from right posterior to left anterior position. When viewed from the right atrial aspect, the atrial septum is characterised by a muscular rim – the limbus – which surrounds the flap valve of the oval fossa (Figure 1.3.1). The extent of the true septum, however, is limited to the flap valve and the immediate part of its surrounding muscular rim. On the epicardial side much of the rim is filled by the interatrial groove which separates the right atrium from the right pulmonary veins posteriorly and superiorly. In its anterior part, the infolded rim contains the continuation of the interatrial groove and its musculature extends to the anterior wall of the right atrium, directly related to the transverse pericardial sinus. Only a small portion of the inferior rim is part of the true atrial septum. Its major portion is the continuation of the right atrial wall, the vestibule, overlying the crest of the ventricular septum (Figure 1.3.1). In fetal life, the flap valve of the oval fossa allows venous return mostly from the inferior caval vein to enter the left atrium. After birth the valve is normally large enough to close the interatrial communication as higher left atrial pressure pushes the valve against the muscular rim forming a complete seal. A probe patency (a probe could be passed from right to left atrium through an unsealed antero-superior part of the rim) exists in about a quarter of the normal population and is generally referred to as a PFO.

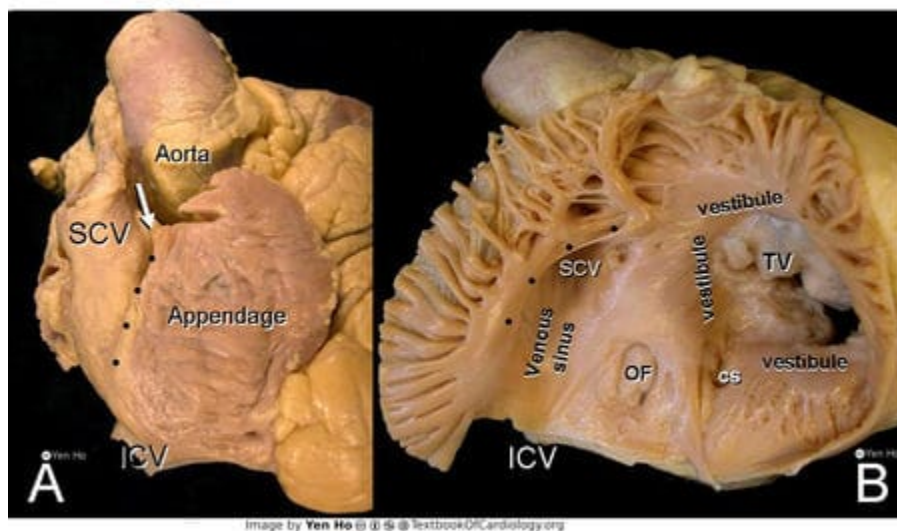


Figure 1.3.1: **(A)** This right lateral view shows the right atrium dominated by its large, triangular shaped appendage. The dots mark the terminal groove. The arrow indicates the crest of the appendage. **(B)** The lateral wall of the appendage incised and flipped backward to show the pectinate muscles and the thin, membrane-like atrial wall between the muscle bundles. The terminal crest (dots) marks the border between the pectinated appendage and the smooth-walled venous sinus. The oval fossa is surrounded by its muscular rim. The smooth-walled vestibule leads to the tricuspid valve orifice.

The Morphologically Left Atrium

The left atrium also has a venous component, a characteristic appendage, a septal component and a vestibule that leads to the mitral orifice. Other than the appendage, the main chamber of the left atrium is relatively smooth-walled. The appendage is hook-shaped with a crenelated external appearance and a narrow junction with the venous component (Figure 1.3.2). The junction is not marked by any structure comparable to the terminal crest although in many hearts there is a prominent infolding of the atrial wall between the orifice of the atrial appendage and the orifices of the left pulmonary veins. The venous portion is anchored by

the pulmonary veins which drain directly into its superior and posterior parts. There are usually four pulmonary venous orifices but variations are not uncommon. The coronary sinus runs inferiorly behind the posterior wall to open into the right atrium. The flap valve of the oval fossa on the septal aspect has a small crescent marking the free edge of the valve at the fossa opening (the site of the PFO) whereas the rest of the valve blends into the atrial wall (Figure 1.3.2).

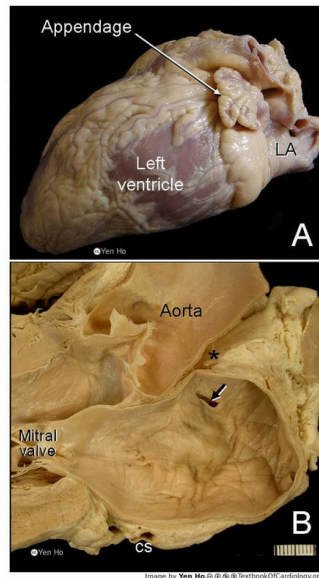


Figure 1.3.2: **(A)** This view from the left-lateral aspect shows the finger-like left atrial appendage with the left atrium situated posteriorly. The left ventricle tapers to a rounded apex. **(B)** This section through the aortic root and mitral valve displays the left atrial aspect of the septum enface. The crescentic edge (arrow) of the fossa valve has not sealed completely resulting in a PFO. The asterisk marks the location of the transverse pericardial sinus.

1.4: The Ventricles

The Morphologically Right Ventricle

Description of the ventricular chambers is facilitated by considering them in terms of three components - inlet, apical trabecular and outlet. The inlet contains the atrioventricular valve and its tension apparatus; the outlet supports the arterial valve. The apical trabecular portion is the most distinctive in each ventricle being characteristically coarse in the right ventricle (Figure 1.4.1A) and fine in the left ventricle. In a similar way, the muscular ventricular septum can be considered in terms of inlet, apical trabecular and outlet portions. A small fibrous area, the membranous septum, is located at this tripartite junction. The attachment of the septal tricuspid valve leaflet divides the membranous septum into atrioventricular and interventricular components (Figure 1.4.1B). It is important to appreciate that the entire ventricular septum is not on one plane. Owing to the 'wrap-around' relationship of the right ventricle to the left ventricle, the various portions are arranged at angles to each other. The inlet septum (between the ventricular inlet portions) is more or less at the sagittal plane of the body. Extending out apically and curving between the inlet and outlet components is the trabecular septum. In lateral projection, the right ventricle is seen to sweep from beneath to above the left ventricle. When viewed in frontal projection the right ventricle passes in front of the left ventricle (Figure 1.1.1). A prominent Y-shaped muscle band, the septomarginal trabeculation, is adherent onto the septal surface. Clasped in between the limbs of the septomarginal trabeculation is the supraventricular crest, a distinctive feature of the right ventricle. The tricuspid valve is separated from the pulmonary valve by this crest (Figure 1.4.1A). Much of the crest is simply the infolded inner heart curvature with fatty tissue containing the right coronary artery on its epicardial aspect. The body of the septomarginal trabeculation gives origin to the moderator band that crosses the ventricular cavity to insert to the anterior wall. The right ventricular inlet component extends from the tricuspid valve orifice to the attachment of the papillary muscle but a discrete demarcation is not seen. The tricuspid valve lacks a well-formed fibrous annulus. Its three leaflets are not always easy to identify owing to clefts within its major leaflets. The commissural chords will identify the divisions between the three leaflets - the antero-superior, the septal and the postero-inferior. The direct attachment of the septal leaflet to the septum is a distinguishing feature of the tricuspid valve.

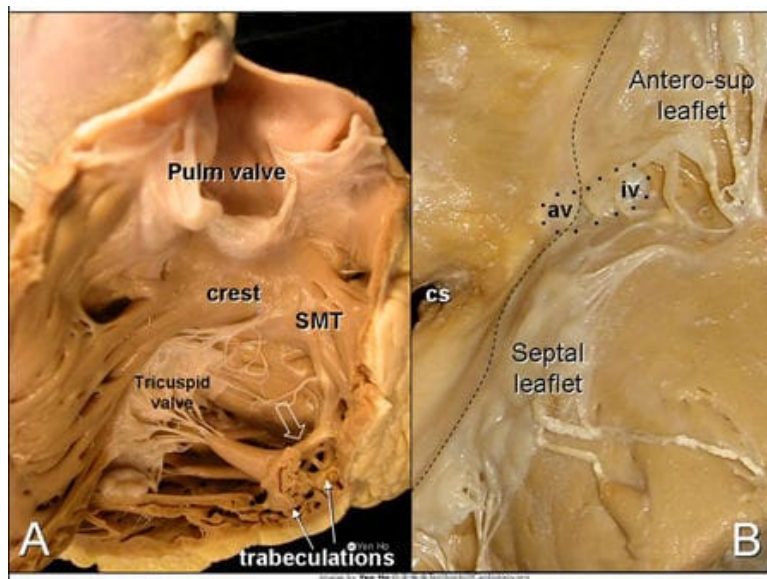


Figure 1.4.1: **(A)** The right ventricle is opened to show the septum and the muscular crest separating tricuspid from pulmonary valves. The moderator band (open arrow) extends from the foot of the septomarginal trabeculation to the free wall of the right ventricle. Coarse trabeculations fill the apical component. **(B)** This close-up view of the tricuspid valve at the commissure between septal and antero-septal leaflets shows the annulus (broken line) crossing the membranous septum (dots) dividing it into atrioventricular(av) and interventricular(iv) components.

The Morphologically Left Ventricle

In contrast to the right ventricle, the left ventricle is a conical structure with thick tubular walls tapering to a rounded apex (Figure 1.3.2A) where the apical wall becomes as thin as 1-2 mm. Very little of the left ventricle is visible from the front of the

heart (Figures 1.1.1 and 1.2.3A) although in the infant a relatively greater portion may be seen. As with the right ventricle, the left ventricle comprises inlet, trabecular and outlet portions. The acute angle between inlet and outlet portions brings the aortic valve in adjacency and in fibrous continuity with the mitral valve. There is no structure comparable to the supraventricular crest in the left ventricle. There is also no structure corresponding to the septomarginal trabeculation on the smooth septal surface (Figure 1.4.2A).

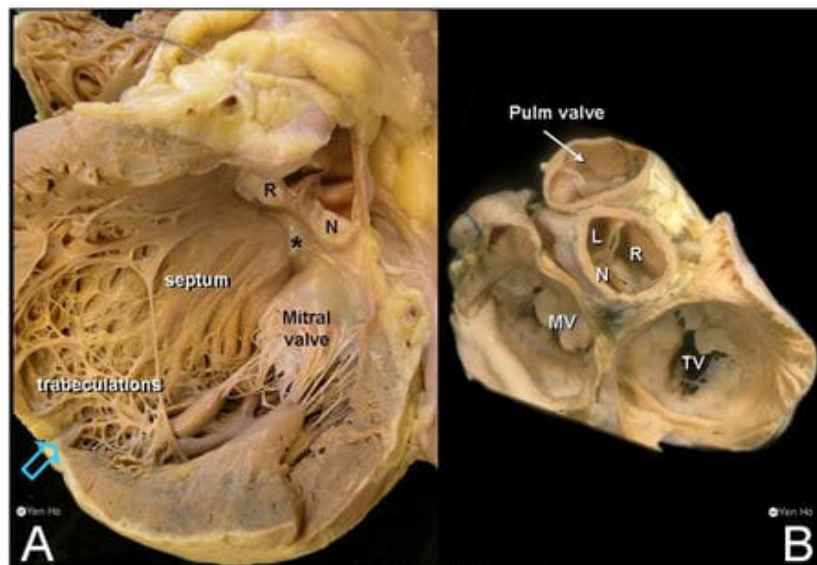


Figure 1.4.2: **(A)** The left ventricle is opened through its outflow tract into the aortic valve. The aortic valve leaflets are in fibrous continuity with the anterior leaflet of the mitral valve. The fibrous continuity is expanded at the right and left fibrous trigones. The right trigone(asterisk) is the landmark for the atrioventricular conduction bundle. Note how the thickness of the left ventricular wall diminishes remarkably at the apex (open arrow). **(B)** This dissection shows the central location of the aortic valve. L, N and R are the left-coronary, non-coronary and right-coronary aortic sinuses respectively.

The inlet component surrounds and contains the mitral valve and its tension apparatus. The outlet component supports the aortic valve but only half its circumference is muscular while the other half is an area of fibrous continuity between aortic and mitral valves. The aortic (antero-superior) leaflet of the mitral valve is suspended like a curtain between the inlet and outlet components. The deeply wedged posterior position of the aortic outflow tract displaces the mitral valve leaflets away from the septum as contrasted with the septal attachment of the tricuspid valve. The trabecular component has characteristically fine trabeculations (Figure 1.4.2A).

The mitral valve annulus is thickened at each commissure to form the left and right fibrous trigones. The annular attachment of the aortic (or anterior) leaflet is related to the membranous septum and right fibrous trigone (together making the central fibrous body). The other leaflet of the mitral valve - the mural (or posterior) leaflet - usually has three scallops. The mitral valve is supported by two groups of papillary muscles in antero-lateral and postero-medial positions. Although textbook pictures tend to portray the papillary muscles as arranged far apart, they are in reality situated close to one another. Each papillary muscle supports the adjacent part of both leaflets and the commissures are marked by fan-shaped commissural chords. The outlet component supports the aortic valve. The semilunar leaflets are attached within the expanded aortic sinuses (of Valsalva). The sinuses are not strictly in right and left position although they are so designated in consideration of the origins of the coronary arteries. The central position of the aorta places it in close relation to each of the cardiac chambers and valves (Figure 1.4.2B).

The commissure between right and left coronary cusps is usually positioned opposite a commissure of the pulmonary valve. The commissure between the left and non-coronary leaflets points towards the left atrium. The commissure between right coronary and non-coronary leaflets lies above the membranous septum and is closely related to the right atrium and right ventricle and the atrioventricular conduction bundle (Figure 1.4.2B).

1.5: Aorta, Pulmonary Arteries, and Coronary Arteries

The Aorta

The ascending aorta arises in right posterior position relative to the pulmonary trunk (Figure 1.1.1, upper panel). It ascends superiorly, obliquely to the right and slightly anterior toward the sternum. On the right is the medial wall of the right atrium. Anteriorly are the right atrial appendage, the right ventricular outflow tract and the pulmonary trunk. The transverse pericardial sinus separates the back of the aorta from the left atrium and right pulmonary artery. The arch of the aorta begins just above the cuff of pericardial reflection, proximal to the origin of the brachiocephalic artery. The arch passes superiorly for a short distance before passing posteriorly to the left and finally terminating on the lateral aspect of the vertebral column. In its course, the arch gives origin to the neck and arm arteries. The arterial duct, a patent channel in fetal life, connects the left pulmonary artery to the aorta just distal to the origin of the left subclavian artery. In the adult, the duct is represented by a fibrous ligament.

The Pulmonary Arteries

The pulmonary trunk is also covered with a cuff of serous pericardium at its origin. It arises from the anterior aspect of the heart, just behind the left lateral edge of the sternum. It swings diagonally to the left side of the ascending aorta (Figure 1.1.1, upper panel). Being a short vessel, it soon bifurcates into the left and right pulmonary arteries. The left pulmonary artery passes in front of the descending aorta and superior to the left main bronchus before branching in the lung hilum. The longer right pulmonary artery traverses the mediastinum under the aortic arch before passing behind the superior caval vein to reach the right lung hilum.

The Coronary Circulation

As mentioned previously, the left and right coronary arteries emerge from the left and right coronary sinuses respectively. Usually the arteries arise from within the sinus just beneath or at the level of the aortic bar (sinutubular junction). In the left sinus there is usually a single orifice but in the right sinus it is usual to find multiple orifices where the early branches of the right coronary artery take direct origin. The main coronary arteries pass within the fatty tissues of the atrioventricular and interventricular grooves. The left coronary has a short main stem that branches into the anterior descending and circumflex arteries (Figure 1.5.1). The circumflex runs in the left atrioventricular groove and the right coronary artery runs in the right atrioventricular groove to variable lengths. From the atrioventricular groove, the encircling arteries give origin to ventricular and atrial branches. An early atrial branch is the sinus node artery which arises slightly more frequently from the right than the left coronary artery. It usually ascends the interatrial musculature to reach the terminal groove but recent evidence has shown a more variable course. In the majority of hearts the posterior descending artery, which runs in the posterior interventricular groove, is a branch from the right coronary artery and this is termed 'right dominance'. In a little under 10% of hearts the posterior descending is a branch of the circumflex giving 'left dominance'. A 'balanced' circulation is seen when both right and left coronary arteries give rise to parallel posterior descending branches. The artery to the atrioventricular node arises from the dominant artery at the cardiac crux.

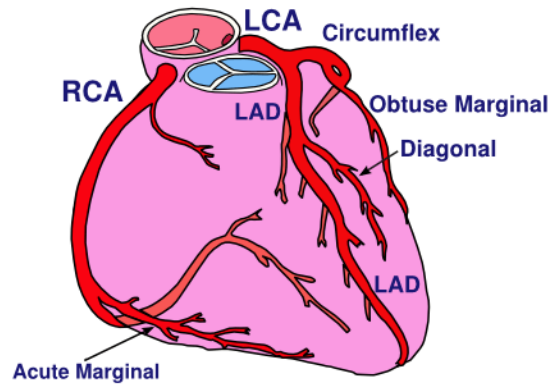


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Figure 1.5.1: Diagram showing the right (RCA) and left (LCA) coronary arteries and their main ventricular branches. The left anterior descending (LAD) and posterior descending (PDA) coronary arteries mark the anterior and posterior margins of the ventricular septum.

After passing through the capillary network, coronary arterial blood is collected by venules which drain to the cardiac veins. The veins drain either to the coronary sinus or directly to the cardiac chambers. The great cardiac vein ascends along the anterior descending coronary and turns into the left atrioventricular groove. In the posterior atrioventricular groove it becomes the coronary sinus. It is joined near its entrance to the right atrium by the middle cardiac vein which ascends in the posterior interventricular groove and the small cardiac vein. The latter ascends along the marginal coronary artery before entering the posterior atrioventricular groove. Atrial veins also empty into the coronary sinus. A further group of veins, the anterior cardiac veins, run across the anterior aspect of the heart to drain directly into the right atrium. In addition to the coronary arteries and veins, the heart also has an extensive lymphatic network. These are divided into the deep, middle and superficial plexuses which drain into collecting channels accompanying the major arterial stems and finally into primary lymph nodes situated in the anterior mediastinum.

1.6: Cardiac and Atrioventricular Conduction

The Cardiac Conduction System

The full complement of the histologically specialised tissues making the conduction system of the heart comprises the sinus node and the atrioventricular system (Figure 1.6.1). The latter is made up of the atrioventricular node, the penetrating atrioventricular bundle and the ventricular bundle branches. The geometry of the right atrium is such that it is made up of bands of muscle which separate the orifices of the great veins and the oval fossa. The spread of excitation from the sinus to the atrioventricular node has been shown to spread preferentially along these broad bands of ordinary atrial myocardium.

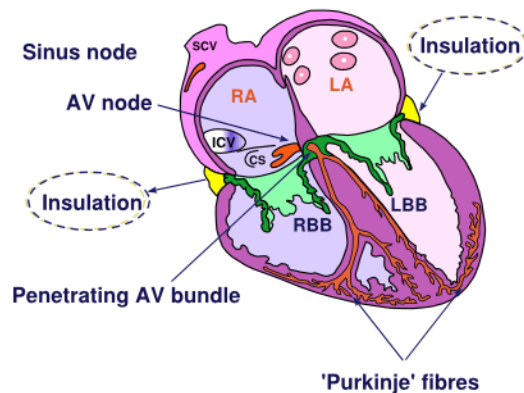


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Figure 1.6.1: The cardiac conduction system. Normally, the insulating fibro-fatty tissue plane at the atrioventricular junction prevents atrial myocardium from contacting ventricular myocardium. The penetrating bundle is the only muscular bridge.

The Sinus Node

The 'ultimum moriens', the last part of the heart to stop beating when the organ is isolated from the body, first prompted Wenckebach to believe that this may also be the seat of the heart beat.[1] The discovery of the sinus node in the heart of a mole culminated in a paper in 1907 in which Keith and Flack described 'a remarkable remnant of primitive fibres persisting at the sinoauricular junction in all mammalian hearts. These fibres are in close connection with the vagus and sympathetic nerves, and have a special arterial blood supply; in them the dominating rhythm of the heart is believed to normally arise'.[2] The subsequent elegant combined anatomico-physiological studies of Lewis and the Oppenheims in 1910 confirmed the pacemaking role of the sinus node.[3] The sinus node predominantly occupies an antero-lateral location of the superior cavo-atrial junction within the terminal groove (Figure 1.6.2A). Only occasionally it is horseshoe-shaped draping over the right atrial summit. In most adult hearts it is shaped like a tadpole measuring about 3mm in diameter at its widest part and 15 to 20mm in length. A tapering 'tail' of the node may be traced from the epicardium to pass intramyocardially toward the inferior part of the terminal crest. The sinus node is easily recognised by the light microscope at low magnification. It is made up of small cells grouped together in interconnecting fascicles set in a fibrous tissue matrix (Figure 1.6.2B). The fibrous matrix becomes more prominent with increasing age. At the margins of the node is a short transitional area where nodal cells merge into atrial myocardium. In places, discrete tongues of transitional cells are found which extend into the terminal crest and toward the myocardial sleeve of the superior caval vein. The blood supply to the node shows considerable variation. A main artery penetrating the length of the node is seen in some hearts. In others, the nodal substance is penetrated by ramifications of an artery approaching the node through one or both ends, there being variations in nodal approaches. Even the origin of the sinus node artery is diverse, arising from the right or left coronary artery at different locations. Collections of ganglion cells are usually observed in the epicardium and also in the environs of the sinus node.

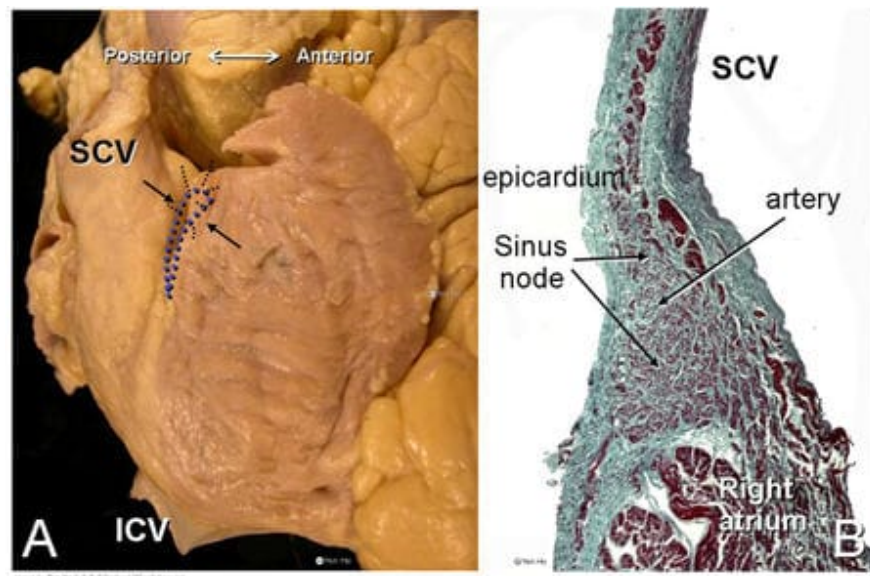


Figure 1.6.2: **(A)** The sinus node (dotted shape) is superimposed onto the terminal groove in this picture of the right atrium viewed from the right side. The arrows indicate the sectioning plane of the histological section shown in B. **(B)** This section from an infant heart is stained in Masson's trichrome stain that colours myocardium red and fibrous tissue blue. The sinus node is readily identifiable by its composition of small myocytes in a fibrous matrix.

The Atrioventricular Conduction System

Occasional reference to this as the system of His-Tawara gives credit to two of the pioneering investigators in this field. The myocardial bridge that connects atrial myocardium to ventricular myocardium across the insulating fibro-fatty tissues of the atrioventricular junction was found by His in 1893 and given the appellation 'penetrating bundle of His'.^[4] Tawara's monograph^[5] accompanied by colour plates in 1906 gave a detailed description of the atrioventricular node and how it was a continuum with the bundle described by His and the ventricular fibres previously described by Purkinje.^[6] This firmly established the presence of an atrioventricular conduction system (Figure 1.6.1) and was subsequently confirmed by Keith and Flack in the same year.^[7] Gross anatomical landmarks to the location of the atrioventricular system are invaluable guides to cardiac surgeons and interventionists who have to perform intracardiac procedures since trauma to any part of the system can produce dire complications.

The atrioventricular node is located at the apex of an angle formed by the tendinous continuation of the Eustachian valve (tendon of Todaro) and the annular insertion of the septal leaflet of the tricuspid valve (Figure 1.6.3). The coronary sinus completes the base of the triangular shape which bears the name 'triangle of Koch' in recognition of Koch's elegant descriptions.^[8] The tendon of Todaro inserts into the central fibrous body. In the adult the atrioventricular node measures about 4 mm in width and 8 mm in length. In histological sections the compact part of the node is easily recognisable being composed of interconnecting fascicles of small cells, closely adherent to the central fibrous body. In cross-section the node appears like a half-oval lying against the fibrous body (Figure 1.6.3D). A transitional zone of attenuated myocardial cells extends into the atrial myocardium. The node becomes the penetrating bundle as the conduction system passes through the central fibrous body (Figure 1.6.3C).

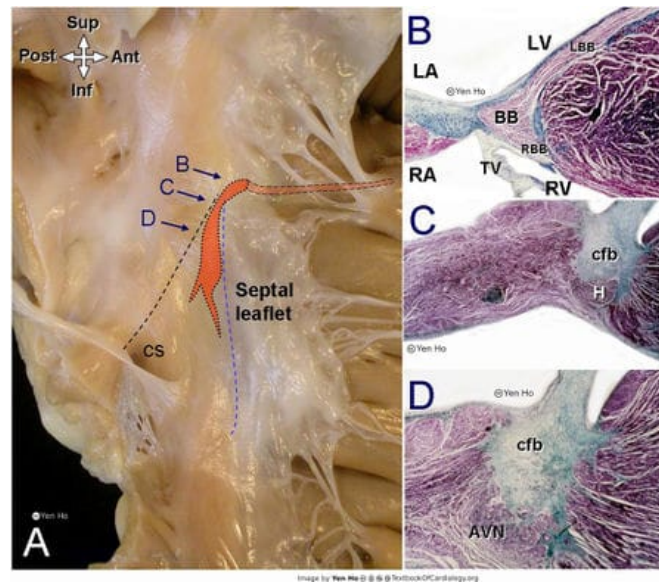


Figure 1.6.3: **(A)** This view of the right atrium and right ventricle shows the anterior and posterior borders of the triangle of Koch (broken lines) that mark location of the atrioventricular node and bundle (orange shapes). The arrows B, C, D indicate the cuts made through the conduction system as shown on the histologic sections. **B, C and D** are step sections stained with Masson's trichrome technique and displayed in similar orientation tracing the atrioventricular conduction system from the AV node (AVN) that adjoins the central fibrous body (cfb), to the penetrating His bundle (H), and the branching bundle (BB) dividing into the left (LBB) and right (RBB) bundle branches.

The penetrating bundle veers to the left as it continues into the branching bundle to emerge in the left ventricle beneath the commissure that separates the right-coronary and non-coronary aortic valve leaflets. The bifurcation into left and right bundle branches marks the beginning of the branching bundle (Figure 1.6.3B). The right bundle branch is cord-like and frequently is the continuation of the nodal-bundle axis. It turns downwards and passes intramyocardially into the substance of the septomarginal trabeculation directly beneath the medial papillary muscle complex. It then passes subendocardially towards the right ventricular apex and crosses the ventricular cavity within the moderator band before ramifying. The left bundle branch is morphologically different from the right bundle branch. It descends from the nodal-bundle axis as a sheet of cells within the subendocardial tissues of the aortic outflow tract. Tawara's original reconstructions show the bundle radiating in fan-like fashion into three major divisions which are interconnected distally by a subendocardial network that ramifies into the ventricular myocardium (Figure 1.6.4).[5] Later investigations using careful serial reconstructive techniques support the trifascicular concept seemingly in conflict with the 'hemiblock' theory which promotes a bifascicular morphology.[9]

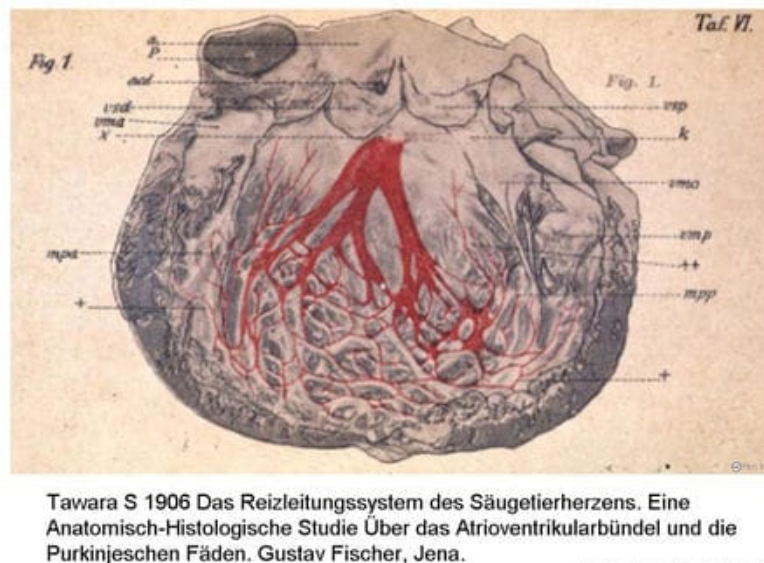


Figure 1.6.4: This picture from Tawara's monograph (1906) shows the tree-fascicular arrangement of the left bundle branch in man. (Tawara S 1906 Das Reizleitungssystem des Säugetierherzens. Eine Anatomisch-Histologische Studie Über das Atrioventrikulärbündel und die Purkinjeschen Fäden. Gustav Fischer, Jena.)

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2: PHYSICAL EXAMINATION

2.1: History

2.2: Common Symptoms

2.3: Physical Findings

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2.1: History

The examination of the patient's history is a critical in the evaluation of (suspected) heart disease. It includes information about the present complaints, development of symptoms over time, medical history and the patient's family. By combining this information, a chronology should be constructed in order to get a profound insight of the patient's disease process. Determining what information is pivotal requires a detailed knowledge of the pathophysiology of cardiac disease. The time invested in carefully examining the patients' history is well invested because this information is often very valuable in the diagnostic process.

The Present Illness

The history taking starts with a careful exploration of the patient's symptoms currently and in the past. The exploration will consist of a thorough questioning of the frequency, intensity, severity, and duration of all patient reported symptoms. Also aggravating and relieving causes should be asked for. In addition to the patient reported symptoms, a strategic questioning of suspected symptoms can be added. Furthermore, current medications, including dosages, the frequency and administration, should be listed.

Antecedent Conditions

There are several systemic disease which may have cardiac involvement. Disease related to cardiac disease include, but are not limited to, are diabetes mellitus, cancer, thyroid disorders, inflammatory disease, and rheumatic fever. Prior treatments should be asked for because they could reveal the nature of the current problems and/or pre-existing disease.

Atherosclerotic Risk Factors

Atherosclerotic cardiovascular disease is the most prevalent type of heart disease in industrialized nations. The most important risk factors for atherosclerotic cardiovascular disease should be asked for are: family history of atherosclerotic disease (including age); diabetes mellitus; lipid disorders; hypertension; and smoking history.

Family History

A family history could provide important information not only in atherosclerotic cardiovascular disease but also for many other cardiac diseases. For example, congenital heart diseases are more common in the offspring of parents, family members or siblings. Genetic diseases, such as neuromuscular disorders, connective tissue disorders (eg, Marfan syndrome), lipid metabolism disorders can [affect](#) the cardiovascular system as well.

2.2: Common Symptoms

Chest Pain

Chest pain has a broad range of causes ranging from non-serious to serious to life threatening (Table 2.2.1). Chest pain is one of the important symptoms of ischemic heart disease. Furthermore, it is also associated with several other forms of heart disease. The most commonly used classification of stable angina is the CSS score (Table 2.2.2), and the Braunwald classification of unstable angina (Table 2.2.3).

Table 2.2.1: Cause of Chest Pain

Cardiovascular	Pulmonary	Gastrointestinal	Musculoskeletal	Psychological	Other
- Acute coronary syndrome - Stable angina pectoris - Aortic dissection (Acute) Pericarditis - Cardiac tamponade - Arrhythmia	- Pulmonary embolism - Pneumonia (Spontaneous) pneumothorax and tension pneumothorax - Tuberculosis - Pleurisy	- Disorders of the esophagus (Acid reflux disease, esophagitis, esophageal spasm) - Hiatus hernia - Achalasia, nutcracker esophagus and other neuromuscular disorders of the esophagus - Functional dyspepsia	- Costochondritis - Radiculopathy - Bornholm disease	- Panic attack - Anxiety - Clinical depression - Somatization disorder - Hypochondria	- Hyperventilation syndrome - Carbon monoxide poisoning - Sarcoidosis - Lead poisoning - Precordial catch syndrome - High abdominal pain - Breast conditions - Herpes zoster commonly known as shingles

Table 2.2.2: Canadian Cardiovascular Society Functional Classification of Angina Pectoris

Class	Definition	Specific Activity Scale
I	Ordinary physical activity (e.g., walking and climbing stairs) does not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.	Ability to ski, play basketball, jog at 5 mph, or shovel snow without angina.
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or under emotional stress, or only during the few hours after awakening, when walking more than two blocks on level ground, or when climbing more than one flight of stairs at a normal pace and in normal conditions.	Ability to garden, rake, roller skate, walk at 4 mph on level ground, have sexual intercourse without stopping.
III	Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on level ground or climbing one flight of stairs at a normal pace in normal conditions.	Ability to shower or dress without stopping, walk 2.5 mph, bowl, make a bed, play golf.

Class	Definition	Specific Activity Scale
IV	Inability to perform any physical activity without discomfort.	Anginal symptoms may be present at rest. Inability to perform activities requiring 2 or fewer metabolic equivalents without angina.

Table 2.2.3: Braunwald Classification of Unstable Angina (UA)

Severity		Clinical Circumstances		
Note: hr = hours; IAM = myocardial infarction; UA = unstable angina.		A	B	C
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	IIA	IIB	IIC
II	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

The five most common characteristics of ischemic chest pain are:

- The pain is classically deep, visceral, and intense. Patient often describe this pain as “pressing”, “tearing”, “constricting”, “burning”. Another common presentation is described as chest heaviness such as “a band across the chest”, or “weight in the centre of the chest”.
- The anginal pain is usually substernal located, but may extend to the left or right chest. Furthermore radiation of the pain is common, typically to the left shoulder and arm. Other locations are possible such as the neck, jaw, epigastrium, and, occasionally, the upper back.
- The duration of the pain is minutes, not seconds.
- The pain tends to be precipitated by exercise. The pain can also be provoked by heavy meals or emotional stress.
- The pain abates promptly by resting (within minutes) or taking sublingual nitroglycerin.

Table 4: Typical features in various types of chest pain

Cause of Pain	Type of Pain	Referred Pain	Response to Posture/ Movement	Response to food/fluid	Tenderness	Response to nitroglycerin
Cardiovascular						
Ischemic cardiac pain	Visceral	Yes	No	No	No	Yes
Aortic dissection	Visceral	Yes	No	No	No	No
Pericarditis	Visceral	Yes	Yes	No	No	No
Arrhythmia	Visceral	No	No	No	No	No

Cause of Pain	Type of Pain	Referred Pain	Response to Posture/ Movement	Response to food/fluid	Tenderness	Response to nitroglycerin
Pulmonary disease	Visceral/ cutaneous	Usually no	No	No	No	No
Pneumothorax	Visceral/ cutaneous	No	Yes	No	Usually no	No
Musculoskeletal	Cutaneous	No	Yes	No	Yes	No
Gastrointestinal	Visceral	Sometimes	No	Yes	No	Sometimes
Psychiatric	Visceral/ cutaneous	No	No	No	No	No

Dyspnoea

Dyspnoea is a frequent complaint of patients with a variety of cardiac diseases. Generally four types of dyspnoea can be distinguished:

- Exertional dyspnoea. Dyspnoea provoked by exercise, usually caused by a mild underlying condition because an increased demand of exertion is needed to precipitate symptoms.
- Dyspnoea at rest. Dyspnoea is suggestive for severe cardiac disease.
- Paroxysmal nocturnal dyspnoea. Dyspnoea characterized by the patient awakening after being asleep or recumbent for an hour or more. This type of dyspnoea is commonly caused by the redistribution of body fluids from the lower extremities into the vascular space and back to the heart, resulting in volume overload. Because of this pathophysiological background it suggests a more severe condition.
- Orthopnoea. Dyspnoea that occurs immediately on assuming the recumbent position. The mild increase in venous return (caused by lying down), before any fluid is mobilized from interstitial spaces in the lower extremities, is responsible for the symptom.

The cause of dyspnoea is certainly not limited to cardiac disease. Exertional dyspnoea, for example, can be due to pulmonary disease or anaemia. Orthopnoea is also a frequent complaint in patients with chronic obstructive pulmonary disease and postnasal drip. Resting dyspnoea is also a common sign of pulmonary disease such as pneumonia or bronchial infection. However, paroxysmal nocturnal dyspnoea is the most specific symptom for an underlying cardiac cause because alternative diagnoses are limited.

Syncope and Pre-syncope

Light-headedness, dizziness, pre-syncope, and syncope are important symptoms, often caused by a reduction in cerebral blood flow. The mentioned symptoms are nonspecific and can be due to a broad range of underlying pathophysiology such as metabolic conditions, dehydration, primary central nervous system disease, or inner-ear problems. Because bradyarrhythmias and tachyarrhythmias are important cardiac causes of these symptoms, they are of importance in the cardiovascular examination. A careful history taking, including preceding symptoms such as palpitations or chest pain, are of great importance. Further information on this topic can be found [here](#).

Transient Central Nervous System Deficits

Transient central nervous system deficits such as transient ischemic attacks (TIAs) suggest the existence of (micro) emboli originating from greater vessels, the carotid arteries or the heart. Rarely a TIA can also be caused by emboli from the venous circulation through an intracardiac shunt. As a result, a TIA should prompt the search for underlying cardiovascular disease. Any sudden loss of blood flow to (parts of) the limbs are also suggestive for an underlying cardioembolic event.

Fluid Retention

Fluid retention is not a very specific symptom for heart disease but may be caused due to reduced cardiac function. Symptoms

associated with fluid retention are peripheral oedema, weight gain, bloating, and/or abdominal pain from an enlarged liver or spleen. Decreased appetite, jaundice, nausea and vomiting can also occur from gut and hepatic dysfunction due to a build up of fluids.

Palpitation

Cardiac activity usually cannot be experienced by individuals in normal resting condition. If a patient is aware of its heart activity it is usually referred to as palpitation. Among cultures and patients there is no standard definition for the type of sensation represented by palpitation. It is often very illustrative to ask the patients to tap with their hand the perceived heartbeat. Most commonly palpitations are caused by an unusually forceful heart beat at a normal rate (60–100 bpm). When a patient senses more forceful contractions as usual without a significant increased heart rate, the palpitations are most commonly the result of endogenous catecholamine excretion. A customary cause of this phenomenon is anxiety. Another common experienced feeling is that of the heart stopping transiently and/or the occurrence of isolated forceful beats. The nature of this sensation is usually premature ventricular contractions. The rapid regular or irregular heart rates most linked to the term “palpitations” are the least common sensation reported by individual patients and is usually supraventricular of origin. More information on palpitations caused by [arrhythmias](#) can be found in chapter 4.

Cough

Although cough is usually associated with disease of pulmonary origin, there are also several cardiac conditions that lead to pulmonary abnormalities which causes subsequent pulmonary disease and subsequent cough. A cough from cardiac origin is usually dry and non-productive. Pleural fluid retention from conditions such as heart failure or pulmonary hypertension from any cause may present as cough. Finally, it should be mentioned that angiotensin-converting enzyme inhibitors, which are frequently used in cardiac conditions, can cause a typical dry cough.

2.3: Physical Findings

Physical Examination - General inspection

The inspection of the patient is an observational task starting from the first contact all the way during the examination. All signs have to be carefully noticed because they can be of importance in the further diagnostic process.

General appearance in severe disease

- Signs of acute life threatening disease which need acute intervention to avert death. First important symptom is the color of the face and skin which could be pallor or cyanotic as a sign of diminished circulation and/or respiration. Furthermore, the respiratory pattern and rate should be assessed for severe signs such as slow and irregular pattern, an audible rasp breathing with foam around the mouth, or in some cases a very fast and superficial breathing pattern. Additionally, the absence or a very weak pulsation could also be a sign of an acute life threatening disease. (For more detailed assessment of the pulse please notice the [paragraph](#) on this topic.) Be aware that these symptoms can be apparent, but their absence does not rule out an acute life threatening disease.
- Signs of severe diseases which are life threatening demands a similar approach with special attention to face color, respiration and pulse. The face color can be pallor, cyanotic or red. Respiration can be fast and superficial, often a sign of severe disease. The pulse is also important in case of severe disease. Furthermore it is important to assess signs of lowered degree of consciousness, emaciation, high body temperature and agitation.

Body position

Observe the patients' position and if there is any preferred position in order to reduce or eliminate pain. For example, the pain of acute pericarditis is often minimized by sitting up, leaning forward, and breathing shallowly. When patients need to sit up right because of increasing dyspnoea when declining, so called orthopnoea, could be a sign of severe heart failure.

Consciousness

The consciousness state of the patient needs to be assessed to be assured of adequate brain functions or any disturbance. Subtle changes in consciousness are not easy to recognize and need special attention. Orientation in time, place and person need to be questioned. Gradual changes in consciousness can be very subtle, such changing conditions due to a delirium, or more apparent, such as somnolence or coma due to severe disease. In respect to heart disease we should be aware of these signs because they can relate to metabolic disease, such as hypoglycaemia in diabetes, and intoxication by medication or carbon monoxide.

Nutrient status

A lowered nutrient status can be a sign of several diseases. Generally there can be less intake, due to starvation, a lack of uptake, due to bowel disease, or a high combustion, due to chronic disease in for example metabolic disease or malign tumor growth. Emaciation, (extreme) low body weight, could be a sign of chronic heart failure or another systemic disorder (e.g., malignancy, infection).

Body composition

The body composition is a combination of skeletal build and soft tissue such as muscles and fat tissue. An abnormal body composition could be one of the signs of syndromes or non-cardiovascular conditions associated with cardiovascular abnormalities, such as for example Marfan syndrome, Down syndrome, Turner syndrome and ankylosing spondylitis (see [Congenital Heart Disease](#)).

Vital signs

The vital signs, including height, weight, temperature, heart rate, blood pressure, respiratory pattern and rate, and peripheral oxygen saturation, can guide diagnosis and management in heart disease.

Height and weight

The height and weight permit the calculation of body mass index (BMI) and body surface area (BSA). Regular weight assessment is an important tool in the follow up of heart failure patients with significant fluid retention. Additionally, weight can be used for the adjustment of medication levels. Central obesity, as assessed by the waist circumference (measured at the iliac crest) and waist-to-hip ratio (using the widest circumference around the buttocks), is an important determinant in the metabolic syndrome and one of the predictors of long-term cardiovascular risk.

Blood Pressure

One of the keystones of the cardiovascular physical examination is the proper measurement of the systemic arterial pressure by cuff sphygmomanometry at both arms. Blood pressure in the arterial system varies during the cardiac cycle, with a peak in the systole and the lowest level in diastole. The difference between the systolic and diastolic pressure is known as the pulse pressure. The arterial pressure is influenced by four important factors:

- Stroke volume of the left ventricle
- Compliance of the aorta and large arteries
- Resistance of the peripheral vasculature, particularly at the arteriolar level
- Blood volume and viscosity in the arterial system

A change in one or more of these factors alters systolic and/or diastolic pressure. The blood pressure fluctuates constantly and is influenced by a variety of factors such as pain, emotional state, physical activity, tobacco, coffee, drug use and consciousness. In order to measure a reproducible blood pressure several aspects have to be taken into account, most important summarized in Table 2.3.1.

Table 2.3.1: Important Aspects of Blood Pressure Measurements

Important Aspects of Blood Pressure Measurements
• Patient seated comfortably, back supported, bared upper arm, legs uncrossed • Arm should be at heart level • Cuff length/width should be 80%/40% of arm circumference • Cuff should be deflated at <3 mm Hg/sec • Column or dial should be read to nearest 2 mm Hg • First audible Korotkoff sound is systolic pressure; last sound, diastolic pressure • No talking between subject and observer

The best way to measure the blood pressure starts with the palpation of the brachial artery, over which the diaphragm of the stethoscope has to be placed over it in the antecubital fossa. The onset and disappearance of the Korotkoff sounds define the systolic and diastolic pressures, respectively. There are some exceptions where the described assessment of the Korotkoff sounds is obsolete. For example, if the diastolic pressure drops near to zero, the point of muffling of the sounds is usually wrongly recorded as the diastolic pressure. The definition of hypertension dictates repeated measures under the same conditions, therefore the operator should record the arm (left/right) and the body position (lying/supine/upright) of the patient to allow reproducible measurements to be made on serial visits. Normal and abnormal blood pressure levels in adult are represented in Table 2.3.2. Please note that the normal levels in children are lower. The risk of cardiovascular disease increases progressively above 115/75 mmHg. Regarding hypotension, in daily practice blood pressure is considered too low only if noticeable symptoms are present.

Clinical trials have demonstrated that humans who maintain arterial pressures at the low end of these pressure ranges have much better long term cardiovascular health. Elevations in all age categories, although more commonly seen in elderly, are generally associated with increased morbidity and mortality.

Table 2.3.2: Classification of blood pressure for adults

Category	Systolic, mmHg	Diastolic, mmHg
Hypotension	<90	<60
Desirable	90-120	60-79
Prehypertension	121-139	or 80-89
Stage 1 Hypertension	140-159	or 90-99
Stage 2 Hypertension	160-179	or 100-119
Hypertensive Crisis	≥ 180	or ≥ 120

Measuring the blood pressure in a different position can be of clinical importance, for example to determine any orthostatic changes in blood pressure. In order to measure orthostatic hypotension the patient has to move from a supine to a standing position with a significant blood pressure drop within 3 minutes. Orthostatic hypotension is defined as a fall in blood pressure of more than 20 mm Hg systolic and/or more than 10 mm Hg diastolic. Orthostatic changes are of special interest in patients complaining of transient central nervous system symptoms, weakness, or unstable gait. Especially elderly have an increased tendency toward orthostatic hypotension due to a decreased compliance of the arteries and/or a decreased compensation mechanism increasing the stroke volume, resulting in a sudden drop of blood pressure which can cause dizziness or syncope. A difference in pressure between the right and left arm of 10 mmHg or more suggests an arterial obstruction in the arterial system of the arm where the lowest pressure is measured. Causes of significant differences between the blood pressure at the right and left arm are subclavian artery disease, aortic coarctation, supraaortic stenosis or dissection. Additionally, in future assessment of the blood pressure the arm with the highest pressure should be measured. Furthermore, note that the pulse pressure is a crude measure of left ventricular stroke volume. A widened pulse pressure suggests that the stroke volume is large; a narrowed pulse pressure, that the stroke volume is small. A widened pulse pressure also can be an indication of atherosclerotic disease, characterised by lengthened, more tortuous, and harder and less resistant arteries.

Pulse

The peripheral pulsations should be assessed by both palpation of the pulse and auscultation for bruits. Pulse abnormalities and bruits increase the likelihood of peripheral arterial disease. Pulsations should be assessed and documented in several arteries in the body in order to get an idea of the state of peripheral vasculature. Easily and fast palpable pulses in healthy individuals include the brachial, radial, and ulnar arteries of the upper extremities and the femoral, popliteal, dorsalis pedis, and posterior tibial arteries of the lower extremities. Minor or absent pulsations suggest a severe stenotic lesion proximal of the palpation site. To assess the cardiac (dys)function through the pulse generally an artery close to the heart should be selected, such as the carotid. Bounding high-amplitude carotid pulses suggest an increase in stroke volume and should be accompanied by a wide pulse pressure on the blood pressure measurement. A weak carotid pulse suggests a reduced stroke volume (Figure 2.3.1).

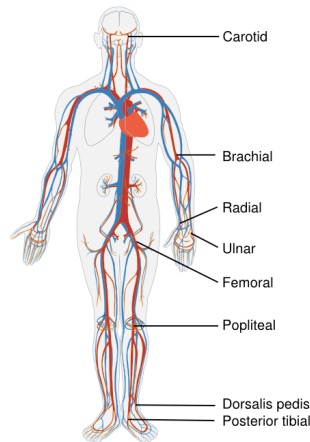


Figure 2.3.1: Body locations for examining the pulse.

When examining the peripheral arterial pulsations by palpitation three important aspects should be noticed:

- The amplitude of the pulse, which correlates with the pulse pressure
- The contour of the pulse wave, depicted by the speed of up- and downstroke and the duration of its summit. In a physiological situation the upstroke is rapid, smooth and almost directly after the first heart sound. The summit is roughly midsystolic and has a smooth and rounded nature. The downstroke is generally less abrupt than the upstroke in a normal situation.
- Variations in the amplitude, either with respiration or from beat to beat.

The contour of the pulses depends on the stroke volume, ejection velocity, vascular capacity and compliance, and systemic resistance. The palpable pulsations reflect both the antegrade pulsatile flow of blood and reflection of the propagated pulse returning from the peripheral artery system. The arterial pulse upstroke increases with distance from the heart. In a physiological state, the percussion wave begins with systolic ejection (just after the first heart sound) and is the mainly monophasic pulse appreciated at the bedside. The dicrotic notch (an exaggerated, early, diastolic wave) demonstrates the aortic valve closure. A bounding pulse may occur in hyperkinetic states such as fever, anaemia, and thyrotoxicosis, or in pathologic states such as severe bradycardia, aortic regurgitation, or arteriovenous fistula. Two distinct pressure peaks in systole relate to a bifid pulse. This phenomenon is consistent with increased vascular compliance and may occur with fever or after exercise in a normal individual. With chronic severe aortic regurgitation, a large stroke volume ejected rapidly into a noncompliant arterial tree produces a reflected wave of sufficient amplitude to be palpated during systole. Hypertrophic obstructive cardiomyopathy can rarely produce a bifid systolic pulse with percussion and tidal (or reflected) waves. Usually the strength of the pulse is graded on a scale of 1 to 4, where 2 is a normal pulse amplitude, 3 or 4 is a hyperdynamic pulse, and 1 is a weak pulse. A low-amplitude, slow-rising pulse, which may be associated with a palpable vibration (thrill), suggests aortic stenosis. In patients over 70 years of age it is particularly important to palpate the abdominal aorta because abdominal aortic aneurysms are more prevalent.

A more than 10 mm Hg fall in systolic pressure with inspiration (pulsus paradoxus) is considered pathologic and a sign of pericardial or pulmonary disease, and can also occur in obesity and pregnancy without clinical disease. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each beat, independent of respiratory phase. Between these two pressures, the sounds are heard only intermittently (during expiration). In order to appreciate this subtle finding, the cuff pressure must be decreased slowly. Tachycardia, AF, and tachypnea make its assessment difficult. Pulsus paradoxus may also be palpable when the pressure difference exceeds 15 to 20 mm Hg. Pulsus paradoxus is not specific for pericardial tamponade and can also accompany massive pulmonary embolus, hemorrhagic shock, severe obstructive lung disease, or tension pneumothorax.

Pulsus alternans is defined by a beat-to-beat variability of the pulse amplitude. When only every other phase 1 Korotkoff sound is audible as the cuff pressure is slowly lowered, in a patient with a regular heart rhythm, independent of the respiratory cycle. Pulsus alternans is generally seen in severe heart failure. Important provoking factors of this phenomenon are severe aortic regurgitation, hypertension, and hypovolemic states. This phenomenon is attributed to cyclic changes in intracellular calcium levels and action potential duration. If it is the pulsus alternans is associated with electrocardiographic T wave the combination appears to increase arrhythmic risk.

Bruits often indicate accelerated blood flow velocity and/or flow disturbance at sites of arterial stenosis. By auscultation the supraclavicular and infraclavicular fossae should be assessed for evidence of subclavian artery stenosis. Additionally, the abdomen, flank, and pelvis should be examined with a stethoscope for evidence of stenosis in the aorta and its branch vessels; and each groin for evidence of femoral artery stenosis.

When patients suffer from aortoiliac disease, muscle atrophy in the legs may be seen. Other signs of chronic low-grade ischemia include thickened and brittle toenails, smooth and shiny skin, and subcutaneous fat atrophy of the digital pads. Patients with limb ischemia with dysfunction of the small arteries have a prolonged capillary refill of 3 seconds or more.

Jugular Venous Pulse

Assessment of the jugular venous pulse (JVP) is a method to assess central venous pressure and right atrium pressure. The examination can provide information about the patient's volume status and cardiac function. Note that the JVP is not useful to assess in children younger than 12 years, because it is hard to assess in this age group.

Ideally the patient is positioned into the semi-upright posture, with an elevation of the head of the bed to 30°, that permits visualization of the top of the right internal jugular venous blood column. A venous arch may be used to measure the JVP more accurately. The JVP is the elevation at which the highest oscillation point of the jugular venous pulsations is usually seen in euvoletic patients. The height of the column of blood seen in the internal jugular vein, vertically from the sternal angle, is added to 5 cm of blood (the presumed distance to the centre of the right atrium from the sternal angle) to obtain an estimate of central venous pressure in centimetres of blood. In patients who are hypovolemic, you may anticipate that the jugular venous pressure will be low. Likewise, in hypervolemic patients, you may anticipate that the JVP will be high. As a result, in hypovolemic patients the head should be in a lowered position (up to 0°), while in a hypervolemic state the head should be subsequently raised of the bed.

Additionally, the characteristics of the right internal jugular pulse should be assessed, because they can reveal clinical signs of right-heart function and rhythm disturbances. The distinctive waves of the jugular vein are summarized in Table 2.3.3 and visualized in Figure 2.3.2.

Table 2.3.3

The jugular venous pulsation has a biphasic waveform.
The a wave corresponds to right A trial contraction and ends synchronously with the carotid artery pulse. The peak of the 'a' wave demarcates the end of atrial systole.
The c wave corresponds to right ventricular C ontraction causing the triCuspid valve to bulge towards the right atrium.
The x descent follows the 'a' wave and corresponds to atrial rela X ation and rapid atrial filling due to low pressure.
The x' (x prime) descent follows the 'c' wave and occurs as a result of the right ventricle pulling the tricuspid valve downward during ventricular systole. The x' (x prime) descent can be used as a measure of right ventricle contractility.
The v wave corresponds to V enous filling when the tricuspid valve is closed and venous pressure increases from venous return - this occurs during and following the carotid pulse.
The "y" descent corresponds to the rapid empt V ying of the atrium into the ventricle following the opening of the tricuspid valve.

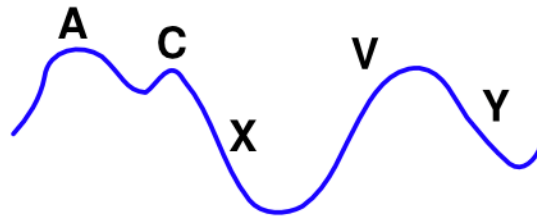


Figure 2.3.2: Jugular venous pulse waveform.

An elevated JVP is the classic sign of venous hypertension, typically in right sided heart failure. JVP elevation can be visualized as jugular venous distension, whereby the JVP is visualized at a level of the neck that is higher than normal. The paradoxical increase of the JVP with inspiration (instead of the expected decrease) is referred to as the Kussmaul sign, and indicates impaired filling of the right ventricle. The differential diagnosis of Kussmaul's sign includes constrictive pericarditis, restrictive cardiomyopathy, pericardial effusion, and severe right-sided heart failure.

Table 2.3.4: There are many JVP abnormalities which can be appreciated after careful assessment. These abnormalities can be linked to a spectrum of disease as highlighted below.

Raised JVP, normal waveform	Raised JVP, absent pulsation	Large a wave (increased atrial contraction pressure)	Cannon 'a' wave (atria contracting against closed tricuspid valve)	Absent a wave (no univocal atrial depolarization)	Large v wave (c-v wave)	Slow y descent
• Bradycardia • Fluid overload • Heart Failure	• Superior vena cava syndrome	• Tricuspid stenosis • Right heart failure • Pulmonary hypertension	• Atrial flutter • Premature atrial rhythm (or tachycardia) • Third degree heart block • Ventricular ectopics • Ventricular tachycardia	• Atrial fibrillation	• Tricuspid regurgitation	• Tricuspid stenosis

Lungs

Evaluation of the lungs and respiration is an important part of the physical examination: Both diseases of the lung can affect the heart, as well as diseases of the heart can affect the lungs.

Auscultation and percussion is also a very important feature of the clinical examination of the lungs and respiratory system. The borders of the lung should be assessed by percussion. Furthermore percussion can reveal dullness, associated with for example abnormal pleural effusion. Several areas of the lungs should be examined by auscultation in an upright position, if possible, both at the back and front of the patients, both base and apical fields covering all lung lobes.

During auscultation the patient's respiratory pattern and rate should be assessed. Tachypnoea is defined as increased breaths 20 or more breaths per minute. Physiological causes of tachypnoea are, for example, heightened oxygen demand due to exercise or labour during pregnancy. Amongst pathophysiological causes, tachypnoea can be a symptom of carbon monoxide poisoning, haemothorax or pneumothorax. Furthermore, pursing of the lips, a breathy quality to the voice, and an increased anteroposterior chest diameter would favour a pulmonary rather than cardiovascular cause of dyspnoea. Special attention is needed in case of so called Cheyne-Stokes respiration or Kussmaul breathing. Cheyne-Stokes is an abnormal pattern of breathing characterized by progressively deeper and sometimes faster breathing, followed by a gradual decrease that results in a temporary stop in breathing called an apnoea. These phenomena can occur during wakefulness or during sleep, where they are called the Central sleep apnoea syndrome. It may be caused by physiological abnormalities in chronic heart failure or damage to respiratory centres. Kussmaul breathing is defined as abnormally slow deep respiration characteristic of air hunger. This typical breathing pattern is caused by respiratory compensation for a metabolic acidosis, most commonly occurring in diabetics in diabetic ketoacidosis. The observation of respiration during sleep may reveal signs of disordered breathing associated with cardiovascular disease (e.g. obstructive sleep apnoea).

A clinically significant finding in the cardiovascular examination is rales at the pulmonary bases, indicating alveolar fluid collection. This fluid collection can be an important sign of heart failure in patients, however it is not always possible to distinguish rales caused by heart failure from those caused by pulmonary disease. Also the presence of pleural fluid, although useful in the diagnosis of heart failure, can be due to other causes. An additional combination of symptoms, dullness at the left base combined with bronchial breath sounds suggests an increase in heart size from pericardial effusion (Ewart sign) or cardiac enlargement due to another cause. Pathophysiological it is thought to be due to compression by the heart of a left lower lobe bronchus.

If severe right-heart failure develops or when venous return is restricted from entering the heart, venous pressure will increase in the abdomen, leading to hepatosplenomegaly and eventually ascites. These physical findings are not specific for heart disease, nonetheless they do help establish the diagnosis. Heart failure also leads to generalized fluid retention, usually manifested as lower extremity oedema. Oedema in the lower extremities is a sign of fluid retention, the skin can be compressed and will stay in this shape for a limited time. Oedema in lower extremities can also be caused by decreased venous return due to thrombosis or dysfunction of the venous system.

Assessment of the praecordium

Inspection

The praecordium is the front of the chest overlying the heart. First a global inspection should include the assessment shape and symmetry of the chest. A barrel chest could be a sign of chronic breathing problems. Also abnormalities of the shape of spine such as a kyphosis or scoliosis should be noticed, not only because of pathophysiological implications, but also demanding special care with regarding cardiac auscultation.

Scars could be found at different locations as signs of prior thoracic surgery. Most common locations include:

- Midline sternal scar: prior major thoracic surgery such as coronary artery bypass grafting and/or valve replacement
- Left sided thoracic scar (diagonal from under left breast to left axilla): Mitral valve surgery.
- Inferior of clavicle (left and/or right sided): Pacemaker / internal cardiac defibrillator implantation.

Above all, focus should be on visible cardiac pulsations, mostly in the apex region of the heart. In lean people the apex beat may be visible. A visible apex beat could also be a sign of abnormal conditions such as left ventricular aneurysm.

Palpitation

Palpitation of the praecordium should focus on the apex beat (defined as the most inferior point where the cardiac impulse is still palpable). The flat of your hand should be positioned so that the middle finger lies on the left 5th intercostal space of the patient, covering the anterolateral ribcage. The other fingers are positioned on the spaces above and below of the point of maximum pulsation. If no pulsation is felt, move the hand in all directions, feeling for a pulsation. Asking the patient to lean forward may

help locate the apex beat if it is hard to palpate.

Several aspects of the apex beat should be noticed:

- **Presence:** In normal conditions the apex beat is palpable in the majority of patients.
- **Location:** The normal apex beat should be in the 5th intercostal space in the mid clavicular line.
- **Size:** The normal size of the apex beat has a diameter of about 3-4 cm in adults.
- **Amplitude:** The normal character of apex is a short pulsating beat.
- **Duration:** The duration of a normal apex beat is short during systole
- **Thrills:** A thrill is a palpable vibration caused by turbulent blood flow and is always pathological. Feel for a thrill (rather like a cat purring) at the apex, the upper part of the praecordium and in the sternal notch. The commonest cause of a thrill is aortic stenosis.

Presence of the apex beat

Several causes, both physiological and pathological, can be found for the absence of the apex beat. A mnemonic to remember these causes is **DR POPE**:

Physiological causes:

- **Dextrocardia;** the apex will be absent at the on the left side, but it will be present on the right side.
- **Rib;** if the apex beat is behind a rib it can not be found in an intercostal space. Turning the patient to the left lateral position will reveal the apex beat, confirming this cause.

Pathological causes:

- **Pericardial effusion**
- **Obesity and thick chest wall**
- **Pleural effusion (left sided)**
- **Emphysema**

Location of the apex beat

The location of the apex beat has to be assessed with respect to the tracheal position. If trachea is also shifted along with the displacement of apex beat, then it is due to mediastinal shift as a result of conditions such as lung fibrosis, collapse or pneumothorax.

If the trachea is central but the apex is displaced, the causes may be:

- Left ventricular enlargement - the apex will be displaced downwards and laterally.
- Right ventricular enlargement - the apex will be displaced laterally.
- Cardiomegaly due to significant enlargement of other chambers can also cause displacement
- Pectus excavatum - resulting in a different location due to congenital thoracic deformity

Abnormal types (Size, amplitude, duration) of apex beat:

- **Tapping Apex** - This is a close to normal apex beat regarding to size, duration and amplitude with a palpable first heart sound. The palpable first heart sound is mostly caused by mitral stenosis.
- **Hyperdynamic Apex** - The amplitude and duration of the apex beat is forceful but ill-sustained and is palpable over a larger area size than normal (diffuse). A hyperdynamic apex beat is classically seen in ventricular dilatation due to volume overload conditions (aortic regurgitation, hyperdynamic circulation etc).
- **Heaving Apex** - The amplitude of this apex beat is a forceful, the duration sustained and dislocated. Classically seen in ventricular hypertrophy due to pressure overload conditions (aortic stenosis, systemic hypertension etc).
- **Double Impulse Apex** - Two impulses felt during systole rather than the normal single upstroke. This apex beat characteristic can be observed in hypertrophic cardiomyopathy
- **Dyskinetic Apex** - An uncoordinated apex beat can be seen due to dyskinetic movements in the infarcted myocardium.
- **Left parasternal impulse or "heave"** - An apex beat felt at the left side of the sternum due to right ventricular enlargement

Cardiac Auscultation

The acceleration and deceleration of blood and the subsequent vibration of the cardiac structures during the phases of the cardiac cycle are causing heart sounds. In healthy adults, there are two normal heart sounds often described as a lub and a dub (or dup), that occur in sequence with each heart beat. These are the first heart sound (S1) and second heart sound (S2), produced by the closing of the atrioventricular valves and semilunar valves respectively. In addition to these normal sounds, a variety of other sounds may be present including heart murmurs, adventitious sounds, and gallop rhythms S3 and S4. To hear cardiac sounds, use a stethoscope with a bell and a tight diaphragm. The bell is best used to hear low-frequency sounds which are associated with ventricular filling. The diaphragm is best used to appreciate the medium-frequency sounds that are associated with valve opening and closing. Cardiac murmurs are caused due to turbulent blood flow and are usually high-to-medium frequency. In most cases the diaphragm is best used to hear cardiac murmurs. An important exception to this is the low-frequency atrioventricular valve inflow murmurs, such as that produced by mitral stenosis, which are best heard with the bell. Murmurs may be physiological or pathological. Abnormal murmurs can be caused by stenosis restricting the opening of a heart valve, resulting in turbulence as blood flows through it. Abnormal murmurs may also occur with valvular insufficiency (or regurgitation), which allows backflow of blood when the incompetent valve closes with only partial effectiveness.

Auscultation should take place in areas that correspond to the location of the heart and great vessels. Such placement will, of course, need to be modified for patients with unusual body habitus or an unusual cardiac position. When no cardiac sounds can be heard over the precordium, they can often be heard in either the subxiphoid area or the right supraclavicular area. The body positions for the placement of the stethoscope are shown in Figure 2.3.3.

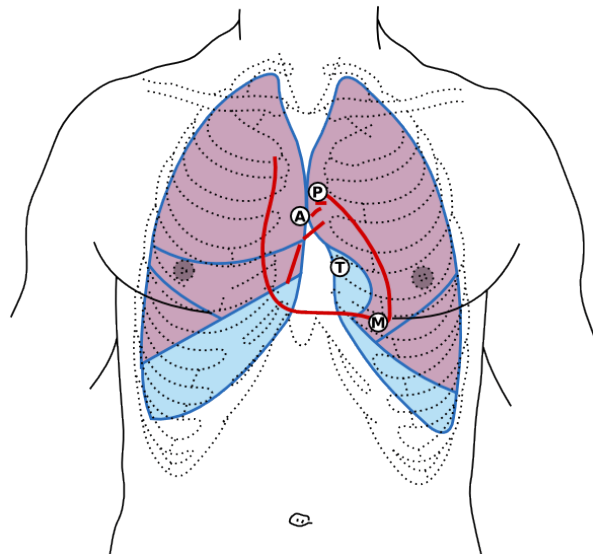


Figure 2.3.3: Locations for cardiac auscultation

Auscultation in various positions is recommended to appreciate sounds and murmurs at maximally. For the first examination the patient should be in a supine position. Furthermore, the patient should be asked to roll partly onto the left side into the left lateral decubitus position. This position brings the left ventricle close to the chest wall. In this position accentuates or brings out a left-side S3 and S4 and mitral murmurs. The other important position is sitting and forward leaning. The patient should be asked to completely exhale and stop breathing in expiration. The stethoscope diaphragm should be pressed along the left sternal border and at the apex. This position accentuates or brings out aortic murmurs maximally.

S1

The first heart tone, or S1, is composed of components mitral (M1) and tricuspid valve closure (T1). Normally the sound of mitral valve closure precedes valve closure slightly. The first heart tone is caused by the sudden block of reverse blood flow due to closure of the atrioventricular valves, i.e. tricuspid and mitral (bicuspid), at the beginning of ventricular contraction, or systole. The papillary muscles in each ventricle start with contraction parallel to the ventricles. The papillary muscles are attached to the tricuspid and mitral valves via chordae tendineae, which hold the cusps or leaflets of the valve to a closed position. During systole the chordae tendineae prevent the valves from blowing into the atria. The closing of the inlet valves prevents regurgitation of

blood from the ventricles back into the atria. The S1 sound results from reverberation within the blood associated with the sudden block of flow reversal by the valves. If T1 occurs slightly after M1, then the patient likely has a dysfunction of conduction of the right side of the heart such as a right bundle branch block.

S2

The second heart tone, or S2, is composed of components the closure of the aortic (A2) and pulmonary valve (P2). Normally A2 precedes P2 especially during inspiration when a split of S2 can be heard in normal conditions. It is caused by the sudden block of reversing blood flow due to closure of the aortic and pulmonary valve at the end of ventricular systole, i.e. beginning of ventricular diastole. As the left ventricle empties, its pressure falls below the pressure in the aorta. Aortic blood flow quickly reverses back toward the left ventricle, catching the pocket-like cusps of the aortic valve, and is stopped by aortic (outlet) valve closure. Similarly, as the pressure in the right ventricle falls below the pressure in the pulmonary artery, the pulmonary (outlet) valve closes. The S2 sound results from reverberation within the blood associated with the sudden block of flow reversal.

Splitting of S2, also known as physiological split, normally occurs during inspiration because the decrease in intrathoracic pressure increases the time needed for pulmonary pressure to exceed that of the right ventricular pressure. A widely split S2 can be associated with several different cardiovascular conditions, including right bundle branch block and pulmonary stenosis.

Extra heart sounds

The rarer extra heart sounds are heard in both normal and abnormal situations. The presence of an extra heart sound is also referred to as a gallop rhythm, because together with the normal heart tones the additional heart sounds resemble this typical sound.

S3

The third heart sound also called a protodiastolic gallop or ventricular gallop. The third heart sound occurs at the beginning of diastole after S2 and is lower in pitch than S1 or S2 as it is not of valvular origin. S3 is thought to be caused by the oscillation of blood back and forth between the walls of the ventricles initiated by intruding blood from the atria. The reason the third heart sound does not occur until the middle third of diastole is probably that during the early part of diastole, the ventricles are not filled sufficiently to create enough tension for reverberation.

The third heart sound is best heard with the bell-side of the stethoscope (used for lower frequency sounds). A left-sided S3 is best heard in the left lateral decubitus position and at the apex of the heart, which is normally located in the 5th left intercostal space at the midclavicular line. A right-sided S3 is best heard at the lower-left sternal border. The way to distinguish between a left and right-sided S3 is to observe whether it increases in intensity with inspiration or expiration. A right-sided S3 will increase on inspiration whereas a left-sided S3 will increase on expiration.

The third heart sound is benign in youth, some trained athletes, and sometimes in pregnancy. If the sound re-emerges later in life it may be caused by pathological disease conditions such as a failing left ventricle as in dilated congestive heart failure. The third heart sound may also be a result of tensing of the chordae tendineae during rapid filling and expansion of the ventricle due to volume overload.

S4

The fourth heart sound when audible in an adult is called a pre-systolic gallop or atrial gallop. This gallop is produced by the sound of blood being forced into a stiff and/or hypertrophic ventricle.

The sound occurs just after atrial contraction at the end of diastole and immediately before S1. It is best heard at the cardiac apex with the patient in the left lateral decubitus position and holding his breath.

The pathological fourth heart sound is a sign of a failing left ventricle or other pathological conditions such as restrictive cardiomyopathy.

The combined presence of S3 and S4 is a quadruple gallop. At rapid heart rates, S3 and S4 may merge to produce a summation gallop.

Murmurs

Heart murmurs are produced as a result of turbulent flow of blood. They are usually heard as a whooshing sound. The term murmur only refers to a sound believed to originate within blood flow through or near the heart associated structures. In order to produce an audible noise rapid blood velocity is necessary. It is important to keep in mind that most heart problems do not produce any murmur and most valve problems also do not produce an audible murmur.

Traditionally, the origin of heart murmurs can be based on six important factors:

- Location – The hearth sounds can be typically best heard in the following areas:
 - Aortic in the parasternal second right intercostal space
 - Pulmonic in the parasternal second left intercostal space
 - Tricuspid area in the parasternal fourth left intercostal space
 - The mitral area in the midclavicular fifth left intercostal space.

Keep in mind that due to many diseases the position of the heart can be altered.

- Intensity – The intensity of murmurs has a wide range. In general the lower intensity is associated with more benign conditions, while higher intensities are associated with pathological conditions. However, keep in mind that a lot of diseases do not produce any heart murmur and valvular diseases do not always produce audible murmurs. The intensity of the murmur can be classified according to Table 2.3.5.

Table 2.3.5: Graduation of Murmurs

Grade	Description
Grade 1	Very faint, heard only after listener has "tuned in"; may not be heard in all positions. Only heard if the patient "bears down" or performs the Valsalva manoeuvre.
Grade 2	Quiet, but heard immediately after placing the stethoscope on the chest.
Grade 3	Moderately loud.
Grade 4	Loud, with palpable thrill (i.e., a tremor or vibration felt on palpation)
Grade 5	Very loud, with thrill. May be heard when stethoscope is partly off the chest.
Grade 6	Very loud, with thrill. May be heard with stethoscope entirely off the chest.

- Timing in the cardiac cycle – Murmurs could be heard early, mid or late in systole, throughout systole (holosystolic), early, mid or late in diastole or continuous. See below for more detail.
- Shape – Several shapes can be distinguished as shown in Figure 2.3.4.
- Radiation – Some of the underlying pathologic disease cause murmurs to radiate. The distinctive pattern follows the blood flow from the point of maximal intensity:
 - Aortic regurgitation – From the aortic valve area into the apex
 - Aortic stenosis – From the aortic valve area into the carotid arteries
 - Hypertrophic cardiomyopathy – From the tricuspid area into to the aortic area
 - Mitral regurgitation – From the mitral area into the left axilla.
- Response to manoeuvres:
 - Normal respiration – The patient should be in a suspine position and breathing normally. In general right-sided cardiac murmurs should increase in intensity with normal inspiration. The increasing intensity during inspiration is caused due to the reductions in intrathoracic pressure that increase venous return from the abdomen and the head, leading to an increased flow through the right heart chambers. The consequent increase in pressure increases the intensity of right-sided murmurs.
 - Sitting and leaning forward - Changes in position are an important part of normal auscultation and can also be of great value in determining the origin of cardiac murmurs. Murmurs dependent on venous return, such as innocent flow

murmurs, are softer or absent in upright positions. Murmurs associated with hypertrophic obstructive cardiomyopathy, are accentuated by reduced left ventricular volume associated with the upright position.

- Rapid squat from the standing position – The rapid change of body position increases venous return and left ventricular volume and therefore accentuates flow murmurs but diminishes the murmur of hypertrophic obstructive cardiomyopathy. The stand-squat manoeuvre is also useful for altering the timing of the midsystolic click caused by mitral valve prolapse during systole. When the ventricle is small during standing, the prolapse occurs earlier in systole, moving the midsystolic click to early systole. During squatting, the ventricle dilates and the prolapse is delayed in systole, resulting in a late midsystolic click.
- Lateral decubitis – In this manoeuvre the patient rolls partly onto the left side and the apex should be auscultated. By bringing the left ventricle closer to the chest, left-sided murmurs are generally louder.
- Valsalva manoeuvre – During this manoeuvre the patient bears down and expires against a closed glottis (hold the breathe and strain hard for 10 seconds). An increasing intrathoracic pressure and markedly reducing venous return to the heart will be caused by this manoeuvre. Almost all cardiac murmurs decrease in intensity, however during strain the murmur of hypertrophic obstructive cardiomyopathy may become louder because and the murmur associated with mitral regurgitation from mitral valve prolapse may become longer and louder because of the earlier occurrence of prolapse during systole. After release of the strain the murmur will decrease and most other murmurs will increase in intensity.
- Isometric hand grip – The patient has to relax his body while squeezing both fists. The manoeuvre increases arterial and left ventricular pressure, thus increasing afterload and flow gradient for mitral regurgitation, ventricular septal defect, and aortic regurgitation; the murmurs should then increase in intensity. The manoeuvre is in particular useful in distinguishing the increasing murmur of mitral regurgitation from a similar or lowering pitch aortic stenosis.

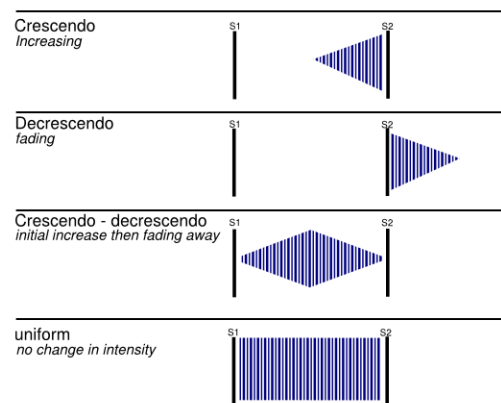


Figure 2.3.4: Murmur sound shapes.

Murmurs categorized by time in cardiac cycle

A schematic scheme of the heart sounds and heart murmurs are shown in Figure 2.3.5.

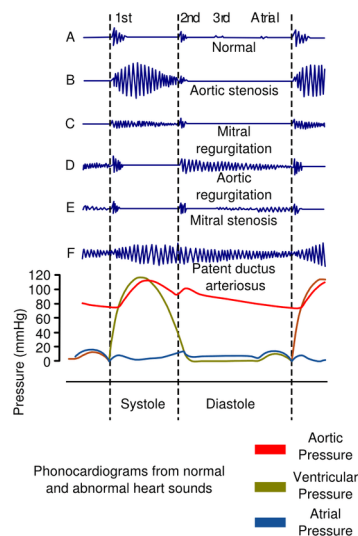


Figure 2.3.5: Representation of the sound waves of murmurs associated with heart disease.

Systolic murmurs are very common and do not always imply cardiac disease. Most murmurs fall in the 1–3 audible intensity range, however murmurs in the 4–6 range are almost always due to pathologic conditions. Again, severe disease can exist with grades 1–3 or no cardiac murmurs. Distinguishing benign from pathologic systolic flow murmurs is one of the major challenges of clinical cardiology. Benign flow murmurs are heard in 80% of children with a declining incidence with increasing age. Other physical conditions known for benign heart systolic murmurs are pregnancy or thin adults or athletic adults. The murmur is usually benign in a patient with a soft flow murmur that diminishes in intensity in the sitting position and neither a history of cardiovascular disease nor other cardiac findings. The physiological flow murmurs are usually heard in grades 1–2 and occur very early in systole. These murmurs have a vibratory quality and are usually less apparent when the patient is in the sitting position (when venous return is less). If an ejection sound is heard, there is usually some abnormality of the aortic or pulmonary valve. The most common systolic murmur is the becoming stronger and fading (crescendo/decrescendo) murmur. This murmur increases in intensity as blood flows early in systole and diminishes in intensity through the second half of systole. This murmur can be caused by a strong flow in a normal heart or to obstructions of flow, as occurs with a stenotic semilunar valve, or hypertrophic cardiomyopathy.

The **holosystolic**, or **pansystolic**, **murmur** is almost always associated with cardiac pathology. The most common cause of this murmur is atrioventricular valve regurgitation. A holosystolic murmur can also be heard in conditions such as ventricular septal defect, in which an abnormal communication exists between two chambers of markedly different systolic pressures. Although it is relatively easy to determine that these murmurs represent an abnormality, it is more of a challenge to determine their origins. Conditions such as mitral regurgitation, which usually produce holosystolic murmurs, may produce crescendo/decrescendo murmurs, adding to the difficulty in differentiating benign from pathologic systolic flow murmurs.

Diastolic murmurs are always abnormal. The most frequently heard diastolic murmur is the high-frequency decrescendo early diastolic murmur of aortic regurgitation. This murmur however needs careful listening because it can be hard to hear due to its high frequency. This murmur is usually heard best at the upper left sternal border or in the aortic area (upper right sternal border) and may radiate to the lower left sternal border and the apex. Although the murmur of pulmonic regurgitation may sound like that of aortic regurgitation when pulmonary artery pressures are high, it is usually best heard in the in a different location. The pulmonic area in the left second intercostal space parasternally is usually the best place to appreciate the murmur. If structural disease of the valve is present with normal pulmonary pressures, the murmur usually has a midrange frequency and begins with a slight delay after the pulmonic second heart sound. Mitral stenosis produces a low-frequency rumbling diastolic murmur that is decrescendo in early diastole, but may become crescendo up to the first heart sound with moderately severe mitral stenosis and sinus rhythm. The murmur is best heard at the apex in the left lateral decubitus position with the bell of the stethoscope. Similar findings are heard in tricuspid stenosis, but the murmur is loudest at a different location, the lower left sternal border.

A **continuous murmur** implies a connection between a high- and a low-pressure chamber throughout the cardiac cycle, such as occurs with a fistula between the aorta and the pulmonary artery. If the connection is a congenital patent ductus arteriosus, the murmur is heard best under the left clavicle; it has a machine-like quality. The most challenging is to distinguish the continuous murmurs from the combination of systolic and diastolic murmurs in patients with combined valve disease (eg, aortic stenosis and regurgitation).

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3: HEART FAILURE

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- 3.2: Definition and diagnosis
- 3.3: Clinical aspects
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3.1: Introduction

History

In 1628, William Harvey first described the circulation. Before this time, there was very little understanding of the nature of heart failure (HF). There are, however, accounts of a disease that now would be called heart failure, and herbal medicines such as the ancient boiled bulb of squill, or, later on, the broom plant (*Cytisus scoparius*) and the foxglove (*Digitalis purpurea*) were used as diuretics to treat heart failure or dropsy (edema). Foxglove was described as a diuretic by William Withering in 1785.[1] The essential glycoside substance digitalis of the leaves of the plant improves contractility of the cardiac muscle and has important parasympathetic effects, particularly on the atrioventricular node. In the 1950s, thiazide diuretics were introduced, and in the 1960s furosemide became available. For a long time, diuretics and digitalis were the main treatment options for HF. Vasodilator therapy for HF was introduced around 1960, and the first randomized trial showing a mortality benefit with nitrates and alphablockers for HF was published in 1986. In 1975, the first ACE inhibitor, captopril, was developed and it was approved for human use in 1981, with data from the first randomized trial being published in 1987. Spironolacton, introduced in 1959, was used (in low dose) for HF only after the introduction of ACE inhibitors. Beta blockers were hardly used in heart failure even though they were shown to be beneficial in the 1970s. It was only in 1994 that data from the first randomized trial demonstrated a mortality benefit with beta blocker therapy.



Figure 3.1.1: oxglove (digitalis), used as a medicine for heart failure.

Framingham heart study

In 1948, the Framingham heart study was launched. At its start, 5209 residents of the town Framingham in the USA, aged between 30 and 62 years, were included in the study in an attempt to determine risk factors for cardiac disease. The study is still in progress today and long term data from the lengthy follow up have been published. This study is considered to be the most important longitudinal source of data on the epidemiology of heart failure[2].

3.2: Definition and diagnosis

Definition of heart failure

The term heart failure (HF) (congestive heart failure or cardiac decompensation or decompensatio cordis) describes an acute or chronic situation in which the amount of blood pumped through the circulation by the heart, is insufficient to meet the body's demands at a normal cardiac filling pressure. According to the guidelines of the European Society of Cardiology, HF is defined as a syndrome in which the patient has the following triad of features: (1) symptoms typical of HF; (2) signs typical of HF; and most importantly (3) objective evidence of a structural or functional abnormality of the heart at rest (Table 3.2.1).

Table 3.2.1: Definition of Heart Failure

Symptoms Typical of Heart Failure	Signs Typical of Heart Failure	Objective evidence of a structural or functional abnormality of the heart at rest
- Breathlessness - Orthopnoea - Paroxysmal nocturnal dyspnoea - Reduced exercise tolerance - Fatigue - Tiredness - Ankle swelling	- Elevated jugular venous pressure - Hepatomegaly - Third heart sound - Pulmonary rales - Pleura effusion - Peripheral oedema - Hepatojugular reflux - Cardiomegaly on X-ray of the thorax	- Abnormal echocardiogram - Abnormal pump function on nuclear imaging or on MRI

Prevalence

The prevalence of HF in the Western world is estimated to be 1-2%, and the incidence is approximately 5-10 per 1000 persons per year (7,9). Coronary heart disease at a young age is more prevalent in men than women, and so the prevalence of HF is also higher in this group compared to age matched women. In older age groups, the prevalence of HF is equal between the sexes.

Acute and chronic heart failure

Heart failure may become a chronic condition, in which HF is persistent either with recurrences or with slow progression. A patient may be described as decompensated when chronic stable HF deteriorates. Acute HF has traditionally been used to describe the nature of the clinical presentation, as severe or of recent onset. Different clinical presentations fall under this definition.

Systolic versus diastolic heart failure

Heart failure patients may be broadly classified into one of two groups, or a combination of both, depending on the left ventricular ejection fraction (LVEF). The LVEF is most often assessed with echocardiography (see Table 3.3.2). When the LVEF is less than 45%, systolic pump function is abnormal and it is named systolic HF.[3] If LVEF is preserved (>50%), symptoms are attributed to impaired relaxation of the heart during diastole and therefore this condition is diagnosed as diastolic HF or HF with a preserved LVEF.[3][4] As a result of impaired relaxation, end diastolic pressure and, subsequently, left atrial- and pulmonary pressure will rise; alveolar pulmonary edema develops as a consequence of these changes. LF diastolic dysfunction may be present in asymptomatic patients, and it is considered an important precursor of heart failure.[5] Frequently, patients have both systolic and diastolic heart failure at the same time, but the term for this ailment is still systolic heart failure. The term heart failure is not limited to a failing left ventricle; the right ventricle may also be involved in the process and there may also be isolated right

ventricular heart failure.

Pathophysiology of heart failure

HF is caused by a loss of cardiac pump function, which can be due to a structural abnormality of the heart muscle (e.g. myocardial infarction) or a change in the heart function (and often structure) in response to an abnormal load (e.g. aortic valve stenosis). The relationship between loading the ventricle (by filling it) and its output was described by Frank and Starling in 1918 and has become the cornerstone in understanding heart failure and how to treat it. The relationship states that as a result of loading the heart (increasing its filling or its pressure), the output increases (Figure 3.2.1).

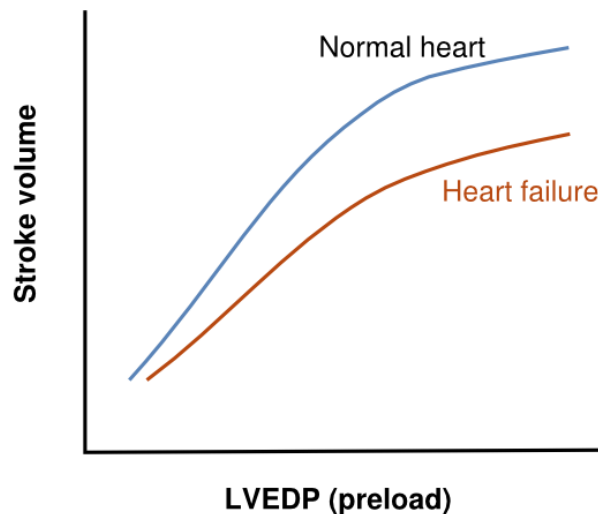


Figure 3.2.1: Frank-Starling curve

A heart that has a lower output can be improved by increasing its volume and its loading pressure. This is what naturally happens (LV dilatation and increased filling pressure) when the heart does not pump out enough volume, and, in the first phase of disease, compensates for the loss of contractility. It takes more energy from the heart to work at an increased loading, but the heart has a reasonable energy reserve. In a chronic situation, remodeling of the heart progresses (by hypertrophy of the myocytes and dilatation by increasing myocyte length and matrix changes), which, in the long term, leads to a further loss in function. The result of this dysfunction is further increased loading pressures in the heart and, by communicating the diastolic loading pressures to the left atrium and pulmonary veins, the pulmonary capillaries may become overloaded and leak water into the lungs. This is the practical restriction of further filling the heart as a tool to improve its function; even poor left ventricles may be filled more to increase their output [6] but the patients' pulmonary capillaries cannot tolerate these hydrostatic pressures and start to leak water.

Hemodynamic explanations (the heart as a pump) use the concept of preload (filling) and afterload (workload of the heart, which is wall tension and arterial pressure or vascular resistance). In this way, the progression of left sided heart failure towards right sided heart failure is explained as follows: prolonged left ventricular failure increases pressures in the left atrium (preload), which in time leads to a subsequent increased resistance in the pulmonary vascular system (which is the afterload of the right ventricle) and eventually may also lead to right ventricular failure. Another relevant issue is afterload of the left ventricle influencing the output of the heart: as the afterload of the aortic pressure also influences the timing of closure of the aortic valve, a high aortic pressure will close the aortic valve early and will, therefore, diminish the output. Decreasing (theoretically diastolic, but more practically systolic) aortic pressure will increase the stroke volume by latter closure of the aortic valves. (Figure 3.2.2)

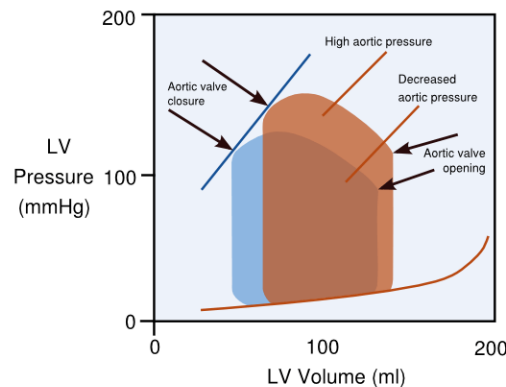


Figure 3.2.2: Effects of decreased afterload. Red arrows indicate aortic valve opening, which occurs later and at higher LV systolic pressure when the diastolic aortic pressure is higher. Blue arrows indicate closing of the aortic valve. Bidirectional arrows represent stroke volume. When aortic pressure is decreased, stroke volume increases as a result of a lower aortic pressure during closure of the aortic valve.

Hormonal/ sympathetic system mechanisms (RAAS/ Sympathetic overstimulation) of heart failure are as important as the hemodynamic mechanisms of heart failure.

A decreased cardiac output leads to diminished renal perfusion and release of hormones in the RAA-system: renin is released into the circulation by the renal juxtaglomerular apparatus, which stimulates the cleavage of angiotensinogen into angiotensin I and II during its passage through the lungs. Angiotensin II stimulates vasoconstriction in the kidneys, and in other vascular systems, increasing blood pressure; the second effect of angiotensin is to stimulate the release of aldosterone from the adrenals into the plasma, which retains sodium from the kidney tubules in the blood and thereby water. The RAA -system, which works as a compensatory mechanism for heart failure to increase blood pressure and blood volume, also stimulates hypertrophy of muscle cells and the formation of fibrosis, which in the long term are detrimental to heart failure.

The other compensatory mechanism for heart failure, stimulation of the sympathetic nervous system, increases heart rate to increase cardiac output, which is a powerful compensatory mechanism. However, chronic stimulation of the sympathetic nerves to the heart, leading to higher heart rates, is toxic to the heart, because of continuous release of norepinephrine to the myocyte. In addition, as a result of their continued stimulation, the betareceptors for norepinephrine are downregulated in heart failure, which further diminishes the function and functional reserve of the heart.

Management

When a patient presents with symptoms of heart failure, it is worthwhile to have a dedicated diagnostic and therapeutic plan, in the order as indicated below (Figure 3.2.3). Clinical aspects are important for diagnosis, but the final diagnosis is only made after objective evidence of heart dysfunction.

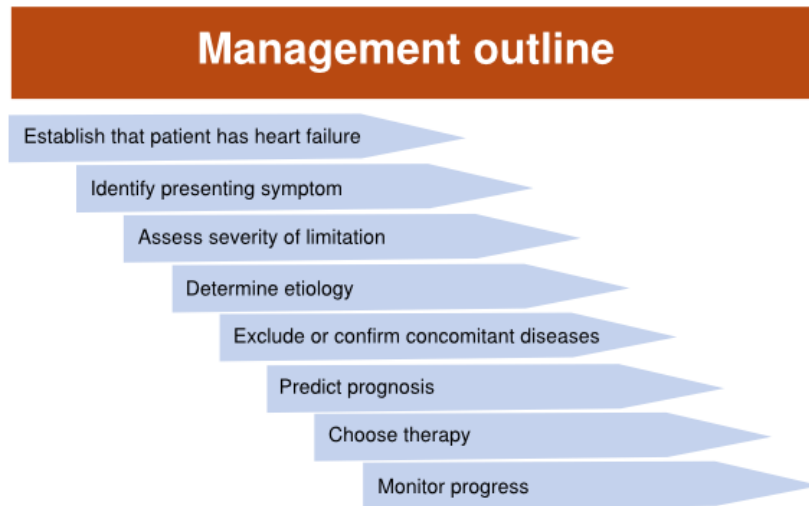


Figure 3.2.3: Management in heart failure.

3.3: Clinical aspects

History

A careful history of the patient is important for the diagnosis and in order to identify the cause of HF. The history (and physical examination) can be used to differentiate between the abovementioned potential causes of HF (refer to Etiology of heart failure). Family history of HF, smoking status, hyperlipidaemia, hypertension and diabetes mellitus are factors that should be taken into account during the assessment of the patient history in order to draw a risk profile of the patient. Finally, the history should include previous events and the response to therapy.

Symptoms and signs

HF can manifest with a multitude of different symptoms and signs, but shortness of breath and tiredness are the most characteristic. The Framingham Heart Study defined major and minor diagnostic criteria for HF.

Major criteria:

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Pulmonary rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H₂O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

Minor criteria:

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia (heart rate >120 beats/min.)

Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

Diagnosis of HF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure in an outpatient population.[7]

Severity of HF

In general, correlation between the severity of symptoms and the severity of HF in terms of loss of maximal oxygen consumption is weak.[3] The New York Heart Association functional classification is used most frequently to classify the severity of HF (Table 3.3.1). Assessing severity is needed for the proper therapy/ medication to be chosen.

Table 3.3.1: NYHA functional classification

Severity Based on Symptoms and Physical Activity	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Physical examination

There are several key features in the clinical examination of a patient presenting with HF. The physical examination should focus on the general appearance of the patient, pulse and blood pressure, signs of fluid overload (increased jugular venous pressure, peripheral edema, ascites and hepatomegaly), the lungs, and the heart (apex, Gallop rhythm, third heart sound, murmurs).

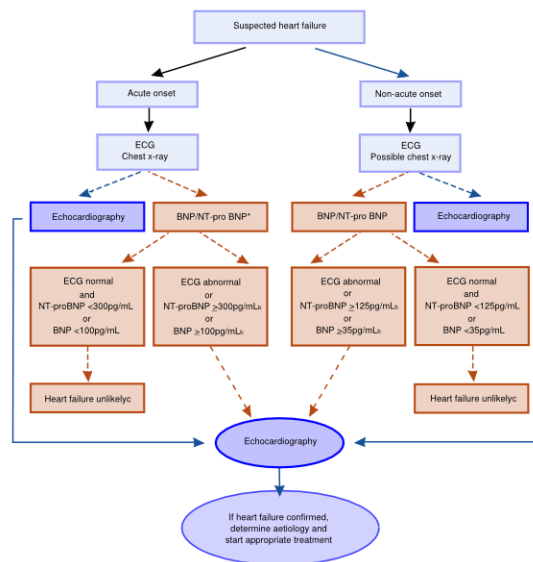


Figure 3.3.1: Flowchart suspected heart failure [3]

Additional diagnostic tests

In order to assist in the diagnosis of HF and to differentiate between possible causes of HF, the following tests are available.

Electrocardiogram

An electrocardiogram (ECG) should be performed on every patient suspected of HF. Several common abnormalities (including possible causes) indicative of HF on the ECG include but are not limited to: sinus tachy- or bradycardia, atrial tachycardia, -flutter, or -fibrillation, ventricular arrhythmias, ischemia (including myocardial infarction), abnormal Q waves, left ventricular hypertrophy, micro voltages, and QRS length >120 ms. Although an abnormal ECG (excluding arrhythmias) has a low positive predictive value for HF, a normal ECG is highly indicative of the absence of HF.

Chest X-ray

A chest X-ray is a part of the standard examination in potential HF patients. Importantly, the X-ray is a tool to detect cardiomegaly (defined as a cardiac: thoracic ratio of > 0,5) or other clues (redistribution, Kerley B-lines and pleural effusion) that indicate HF. It is also important to rule out other causes of dyspnea.

Echocardiography

Echocardiography is the cornerstone in the diagnosis of HF, and should be performed routinely, because ventricular function can be evaluated accurately with this technique. It can provide objective evidence of a structural or functional abnormality of the heart at rest, besides signs and symptoms that are typical of heart failure. Important parameters that can be assessed include, but are not limited to, wall motion, valve function, left ventricular ejection fraction and diastolic function. Diastolic dysfunction might be an important finding in symptomatic patients with a preserved ejection fraction. Refer to Table 3.3.2 for common echocardiographic findings in HF. Transesophageal echocardiography is indicated in patients with an inadequate transthoracic echo window, suspected endocarditis, complicated valvular disease or to exclude a LV thrombus. If echocardiography provides inadequate information or in patients with suspected coronary artery disease, additional imaging includes CT scanning, cardiac magnetic resonance imaging or radionuclide imaging.

Table 3.3.2: Common echocardiographic abnormalities in heart failure

Measurement	Abnormality	Clinical Implications
Left ventricular ejection fraction (LVEF)	Reduced (< 50%)	Left ventricular global systolic dysfunction
Left ventricular wall motion	Akinesis, hypokinesis, dyskinesis	Myocardial infarction/ischaemia, Cardiomyopathy, Myocarditis
Left ventricular end-diastolic diameter	Increased (≥ 60 mm/ >32 mm/m ²)	Volume overload HF likely
Left ventricular end-systolic diameter	Increased (≥ 45 mm/ >25 mm/m ²)	Volume overload, HF likely
Left ventricular fractional shortening	Reduced (<25%)	Left ventricular systolic dysfunction
Left atrial volume index	Increased (volume >34 mL/m ²)	Increased filling pressures, Mitral valve dysfunction
Left ventricular thickness	Hypertrophy (>11 – 12 mm)	Hypertention, Aortic stenosis, Hypertrophic cardiomyopathy
Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral insufficiency)	May be primary cause of HF or complicating factor, Assess haemodynamic consequences, Consider surgery
Mitral diastolic flow profile	Abnormalities of the early and late diastolic filling patterns	Indicates diastolic dysfunction and suggests mechanism

Measurement	Abnormality	Clinical Implications
Tricuspid regurgitation peak velocity	Increased (>3.4 m/s)	Increased right ventricular systolic pressure
Pericardium	Effusion, Haemopericardium, Calcification	Consider tamponade, Malignancy, Systemic disease, Acute or chronic pericarditis, Constrictive pericarditis
Aortic outflow velocity time integral	Reduced (<15 cm)	Reduced low stroke volume
Right ventricular function (e.g. TAPSE)	Reduced (TAPSE < 16 mm)	RV systolic dysfunction
Inferior vena cava	Dilated, with no respiratory collapse	Increased right atrial pressures, Right ventricular dysfunction, Volume overload, Pulmonary hypertension possible

Laboratory tests

A standard blood assessment includes a complete blood count, electrolytes, renal function, glucose and liver function. Furthermore, urinalysis and other tests, depending on the clinical condition of the patient, complete the laboratory assessment. For example, cardiac troponins must be sampled if an ACS is in the differential diagnosis. In patients suspected of HF, values of natriuretic peptides (such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)) can provide important information regarding the diagnosis, management and prognosis of HF. Natriuretic peptides are enzymes, secreted by the atria or ventricles in response to myocardial wall stress. The most commonly used tests are BNP and NT-proBNP measurements, which despite their different half-lives in the plasma, do not differ substantially in terms of diagnostic ability. Cut-off values are different in acute settings with acute dyspnea compared to chronic settings. Normal values are almost 100% specific, and exclude heart failure in patients >18 year old. Abnormal values do not have a 100% predictive value, and objective evidence for heart failure is still needed. The values for BNP and NTproBNP are also used to evaluate the prognosis in patients with known HF, in whom higher values carry a worse prognosis.

Exercise test

An exercise test is not diagnostic for HF, but may be used to identify ischemia as the cause of heart failure, or it can be used to assess the severity of HF, usually in conjunction with maximal oxygen uptake (VO_{2max}) measurement. This test is performed on a treadmill or on a bicycle ergo meter. The patient is asked to give maximal effort while the workload gradually increases. During the test, the ECG is monitored for ischemia. When possible, oxygen consumption should also be measured during the test. Not only is an oxygen consumption test a good tool to discriminate between lung- peripheral- or heart problems, but the obtained value for maximal oxygen uptake (VO_{2max}) has an important prognostic value.

Heart catheterization

Heart catheterization is not always part of the routine diagnosis and work-up of patients with HF. It should be considered however to exclude coronary heart disease (Class of recommendation IIa, level of evidence C, see Table 3.3.3). Coronary angiography is recommended in patients at high risk of coronary artery disease (Class of recommendation I, level of evidence C) and in HF patients with significant valvular disease (Class of recommendation IIa, level of evidence C).

Table 3.3.3: Size of treatment effect.

	Class I Benefit >>> Risk	Class IIa Benefit >> Risk Additional studies with focused objectives needed	Class IIb Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful	Class III Benefit ≥ Risk No additional studies needed
	>> Risk" class="lt-med-42735">Procedure/treatment should be performed/administered	> RiskAdditional studies with focused objectives needed" class="lt-med-42735">It is reasonable to perform/administer treatment	Procedure/treatment may be considered	Procedure/treatment should not be performed/administered since it is not helpful and may be harmful
Level A Multiple (3-5) population risk strata evaluated	>> Risk" class="lt-med-42735"> - Recommendation that procedure or treatment is useful/effective - Sufficient evidence from multiple randomized trials or non-randomized trials	> RiskAdditional studies with focused objectives needed" class="lt-med-42735"> - Recommendation in favor of treatment or procedure being useful/effective - Some conflicting evidence from multiple randomized trials or meta-analyses	- Recommendation's usefulness/efficacy less well established - Greater conflicting evidence from multiple randomized trials or meta-analyses	- Recommendation that procedure or treatment not useful/effective and may be harmful - Sufficient evidence from multiple randomized trials or meta-analyses
Level B Limited (2-3) population risk strata evaluated	>> Risk" class="lt-med-42735"> - Recommendation that procedure or treatment is useful/effective - Limited evidence from single randomized trial or non-randomized studies	> RiskAdditional studies with focused objectives needed" class="lt-med-42735"> - Recommendation in favor of treatment or procedure being useful/effective - Some conflicting evidence from single randomized trial or non-randomized studies	- Recommendation's usefulness/efficacy less well established - Greater conflicting evidence from single randomized trial or non-randomized studies	- Recommendation that procedure or treatment not useful/effective and may be harmful - Limited evidence from single randomized trial or non-randomized studies
Level C Very limited (1-2) population risk strata evaluated	>> Risk" class="lt-med-42735"> - Recommendation that procedure or treatment is useful/effective - Only experts opinion, case studies, or standard-of-care	> RiskAdditional studies with focused objectives needed" class="lt-med-42735"> - Recommendation in favor of treatment or procedure being useful/effective - Only diverging expert opinion case studies, or standard-of-care	- Recommendation's usefulness/efficacy less well established - Only diverging expert opinion case studies, or standard-of-care	- Recommendation that procedure or treatment not useful/effective and may be harmful - Only expert opinion case studies, or standard-of-care

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3.4: Etiology of heart failure

Coronary heart disease

The most important cause (50% of the cases) of HF in the Western world is ischemic heart disease, including myocardial infarction. These patients mainly suffer from systolic HF due to wall motion abnormalities of the affected area and re-modeling of the non-affected parts of the myocardium.

Hypertension

In patients with a high systolic blood pressure (BP), the left ventricle faces an increased afterload (a higher workload pumping the blood against the increased vascular resistance). Over a certain period of time, this will lead to hypertrophy of the cardiac myocardium, and longer term remodeling may lead to pump function disorders (diastolic or systolic). In as many as 60-70% of patients suffering HF, hypertension is the primary or secondary cause of the condition.

Heart rhythm disorders

Atrial fibrillation is a common rhythm disorder in the elderly. With this condition, the atria do not contract in the coordinated fashion as they would in normal sinus rhythm, and therefore the atria never optimally empty. Normally, the 'atrial kick' contributes approximately 15% of the stroke volume. The absence of the atrial kick during atrial fibrillation can contribute to a reduced LVEF. However, atrial fibrillation is seldom the cause of heart failure, but more often a trigger of heart failure in already existing structural heart disease.

Valvular disease

Valvular disease, especially mitral- or aortic, can cause volume and pressure overload of the left ventricle of the heart. This overload causes dilation and / or hypertrophy of the left ventricle, which in the long term decreases the pump function.

Cardiomyopathies

Dilated cardiomyopathy (DCM) is characterized by dilatation of one or both of the ventricles of the heart, with a general decrease in contractility and consequently a decreased pump function. In approximately 30% of the cases, DCM is hereditary.

Hypertrophic cardiomyopathy (see also Hypertension) is characterized by hypertrophy, which may be concentric or asymmetric. The asymmetric form is usually hereditary.

Restrictive cardiomyopathy is characterized by a primary diastolic dysfunction of one or more of the ventricles, leading to increased filling pressures and hypertrophy, and initially a preserved systolic function.

Arrhythmogenic right ventricular cardiomyopathy is characterized by fatty infiltration and fibrosis of the right ventricle or the left ventricle or both and is usually hereditary.

Pericardial disease and Tamponade

Restriction of ventricular filling by a tight (inflamed or constrictive) pericardium or by pericardial effusion and tamponade can be the cause of diastolic HF.

Drugs

- **Drugs that can cause HF are:**

- Cytotoxic agents (chemotherapy, especially doxorubicin)
- The antipsychotic agent clozapine
- **Drugs that can aggravate HF are:**
 - Beta blockers
 - Calcium antagonist
 - Antiarrhythmics
 - Disulfiram

Toxins

- Alcohol
- Cocaine,
- Trace elements (mercury, cobalt, arsenic).

Endocrine disorders

- Diabetes mellitus
- Hypo- or hyperthyroidism
- Cushing syndrome
- Adrenal insufficiency
- Excessive growth hormone in acromegaly
- Pheochromocytoma

Nutritional status

Deficiency of thiamine, selenium, or carnitine, in states of severe cachexia.

Infiltrative and storage disorders

- Sarcoidosis
- Amyloidosis
- Haemochromatosis
- Connective tissue disease

Infectious disease

- Chagas' disease
- HIV infection
- Viral, bacterial or protozoal diseases causing myocarditis.

3.5: Management in investigating etiology of heart failure

1. Assess globally: are there triggers of heart failure. Hypertension, infection, anemia, rhythm disorders. Perform standard laboratory tests: in addition to hemoglobin, leukocytes, thrombocytes, creatinin, sodium and potassium levels, also liver function, thyroid function (TSH), glucose.
2. Assess ischemia: are there indications of ischemic etiology (ECG: Q's or significant and changing ST segments, laboratory: troponins, and echocardiogram: segmental wall motion abnormality in coronary territory areas) ? If yes, then proceed with further coronary artery or myocardial perfusion imaging.
3. Are there no indications for ischemic etiology?
 - Classify phenotype of cardiomyopathy: dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy.
 - Then assess with additional laboratory tests, including creatinin kinase, autoimmune markers, eosinophilia, ferritin and iron saturation. In some suspected cases: calcium and albumin.
 - Look for clues of etiologies: history, family history (including maternal inheritance of diabetes in a family)
 - In case of fever look for infectious etiology, MRI confirmation for possible myocarditis, plasma serology.
 - Look for clues on ECG: microvoltage on the ECG, AV block in combination with later atrial fibrillation. Additional lab may be warranted (monoclonal proteins in case of microvoltage in the presence of sufficient amounts of myocardium and the absence of pericardial fluid or pulmonary emphysema)
 - MRI for further classification of cardiomyopathy and assessment of presence and localization of delayed contrast enhancement
 - Coronary arteriography or coronary CT scan to exclude coronary artery disease
 - Myocardial biopsy in cases where the suspicion of severe underlying disease is high (e.g. fulminant myocarditis, sarcoidosis suspicion on MRI with no other organ involved).
 - Genetic testing after counseling

3.6: Therapy of heart failure

The therapeutic management of HF involves both pharmacological and non-pharmacological treatment. The goal is reduction in mortality and morbidity, prevention of the progression of HF, and the treatment of (non-) cardiovascular co-morbidities.

Non-pharmacological treatment

Non-pharmacological management is of great importance for HF patients. It can have a significant impact on symptoms, functional capacity, wellbeing, morbidity, and prognosis. The most important non-pharmacological options are described below.

Education

Education of both the patient and their family about HF and its symptoms is important. The patient and/or the caregiver should be able to undertake appropriate actions such as adjusting the diuretic dose or contact the physician when necessary. (Class I recommendation, level of evidence C; see Table 3.3.3) Education on the importance and (side) effects of medication should be provided to the patient in order to increase compliance. (Class I recommendation, level of evidence C)

Fluid and sodium restriction

In patients with severe symptoms of HF, restriction of fluid intake (to 1500 ml/day) may be considered. (Class IIa recommendation, level of evidence C). Also, patients should be educated about the salt content of food and advised to minimize their salt intake (< 2 gram/ day) in order to prevent fluid retention. (Class I recommendation, level of evidence C)

Body weight

CHF patients should carefully monitor their body weight. A sudden increase in weight is a potential consequence of fluid retention and deterioration of HF. If patients notice a weight gain of >2kg in 3 days, they should consult their physician. (Class I recommendation, level of evidence C). In obese patients (body mass index >30 kg/m²), weight reduction should be promoted to prevent progression of HF, decrease symptoms and improve the overall wellbeing of the patient. (Class IIa recommendation, level of evidence C). Also, attention should be paid to weight loss due to malnutrition, which is frequently observed in severe HF. An altered metabolism, inflammatory mechanisms or a decreased food intake may be important factors in the pathophysiology of cardiac cachexia in HF. (Class I recommendation, level of evidence C)

Alcohol and tobacco

Alcohol intake should be minimized, as it may increase blood pressure and/or have a negative inotropic effect. (Class IIa recommendation, level of evidence C). Smoking cessation should be encouraged. It is recommended that patients with HF receive support and advice on this topic. (Class I recommendation, level of evidence C). A reduction in alcohol and tobacco intake might also improve co-morbidities, including sleep disorders.

Exercise

Exercise training is recommended to all chronic stable HF patients. Twenty years ago, exercise was strongly discouraged in patients with HF as it was considered to be harmful. Nowadays, numerous studies have demonstrated the opposite. Rehabilitation programs have shown to increase exercise capacity and health related quality of life, and decrease hospitalization rates and symptoms. (Class I recommendation, level of evidence A)

Other

Other non-pharmacological treatment recommendations include immunization of HF patients (pneumococcal- and influenza vaccination should be considered), the consulting of a physician around pregnancy, the screening for depression and sleep disorders that require additional medical attention.

3.7: Pharmacological treatment

A flowchart for the treatment of patients presenting with systolic HF is depicted in Figure 3.7.1. Medications with a class I indication in patients with systolic heart failure are summarized in Table 3.7.1. Indications, mode of action, contraindications of the medication, and possible side effects of drugs included in this algorithm are discussed below.

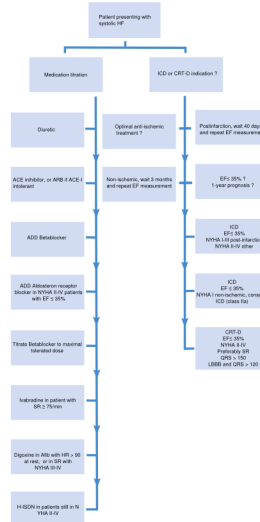


Figure 3.7.1: Treatment options for patients with chronic systolic HF

Table 3.7.1: Medication with a class I indication in patients with systolic heart failure. Note that AT-II antagonists are alternative medicine for ACE inhibitors in case of intolerance (coughing, allergy). Nitrates and Hydralazine are added therapy for patients of Afro-American descent, and alternative therapy for patients that cannot tolerate ACE-inhibitors and AT-II antagonists). Digoxin can also be seen as symptomatic (instead of added preventive) treatment, not always necessary in NYHA III or even IV.

	NYHA I & EF <40%	NYHA II	NYHA III	NYHA IV
Diuretic				
ACE-inhib				
AT-II antagonist		Alternative	Alternative	Alternative
Betablocker	Post infarction			
Aldosterone antagonist		EF < 35%	EF < 35%	EF < 35%
Nitrate / Hydralazine		Afro-American	Afro-American	Afro-American
Ivabradine		SR>75/min & EF<35%	SR>75/min & EF<35%	SR>75/min & EF<35%
Digoxin				

Angiotensin-converting enzyme (ACE) inhibitors

An ACE inhibitor is indicated for every patient with symptomatic systolic HF and an EF ≤ 40 % (NYHA class II-IV). (Class I recommendation, level of evidence A) Contraindications for the use of ACE inhibitors are:

- History of angioedema
- Bilateral renal artery stenosis

- Serum potassium concentration >5.0 mmol/L
- Serum creatinine >220 $\mu\text{mol/L}$
- Severe aortic stenosis

ACE inhibitors relieve the heart by decreasing the preload and afterload. This is achieved through two mechanisms. Firstly, conversion of angiotensin-I to angiotensin- II is inhibited, which reduces vasoconstriction and lowers BP. Secondly, production of aldosterone is decreased, as angiotensin II induces this production. Aldosterone stimulates sodium- and water retention. Possible side effects are symptomatic hypotension (dizziness), hyperkalemia, worsening renal function and cough.

In patients with congestive HF, total mortality and hospitalization are significantly reduced by ACE inhibitors.[8]

Beta Blockers

Beta blockade (in addition to an ACE inhibitor or ARB when ACE inhibitor is not tolerated) is indicated for every patient with symptomatic systolic HF and an EF ≤ 40 % (NYHA class II-IV) and in asymptomatic patients with a LVEF ≤ 40 % after a MI. (Class I recommendation, level of evidence A).[9] Contraindications are:

- Bronchial asthma
- Second - or third degree heart block, sick sinus syndrome, sinus bradycardia

Beta blockers mainly exert their effect by reducing the toxic effects of the sympathetic nervous stimulation on the heart and by deactivating the renin-angiotensin system.

Possible side effects include (symptomatic) hypotension, worsening of HF and bradycardia. The recommendation is 'start low, go slow', i.e. start with a low dose, and titrate every two weeks.

In patients with persistent symptoms after treatment with a combination of beta blocker and ACE inhibitor or ARB, a mineralocorticoid/aldosterone receptor antagonist (MRA) is recommended. (Class I recommendation, level of evidence A)

Diuretics (Loop of Henle diuretics, Thiazides, Aldosterone antagonists)

Diuretics reduce preload by venous vasodilatation and by increasing diuresis. As a result, filling pressures of the heart and the lung vasculature decrease. Although the effects of diuretics on mortality and morbidity have not been studied in patients with HF (irrespective of EF), it is recommended in patients with signs and symptoms of congestion as diuretics relieve dyspnea and edema. Figure 3.7.2 depicts the nephron and the sites where different diuretics work.

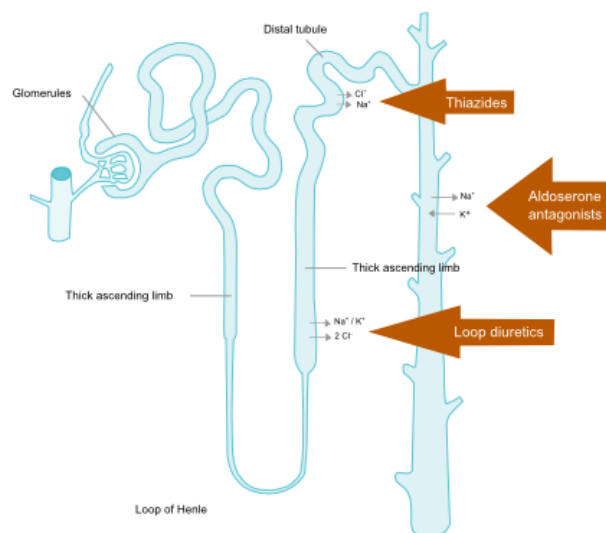


Figure 3.7.2: Diuretics and site of action in the nephron.

Loop of Henle diuretics

Loop of Henle diuretics act on the ascending loop of Henle in the kidney tubules to inhibit sodium and chloride (and indirectly calcium and magnesium) reabsorption. This will ultimately result in increased urine production of sodium and water. Compared to thiazides, loop diuretics produce a more intense and shorter diuresis.

Thiazides

Thiazide increases urine production by decreasing reabsorption of sodium in the distal tubule. This type of diuretic is often used in combination with loop diuretics to enhance their effects, but may be less effective in patients with a severely reduced kidney function.

Aldosterone antagonists

Adding this drug is suggested for patients with moderate to severe symptomatic HF (NYHA class II to IV, refer to Table 3.7.2) and an LVEF < 35%. (Class I recommendation, level of evidence A) Contraindications:

- Serum potassium concentration > 5.0 mmol/L
- Serum creatinine > 220 µmol/L
- Concomitant potassium sparing diuretic or potassium supplements
- Combination of an ACEI and ARB

Aldosterone antagonists reduce sodium retention by the kidney, and inhibit fibrosis formation in the heart.

Possible side effects include hyperkalemia, hyponatremia, worsening renal function, and breast tenderness and/or enlargement. Eplerenon has less mastopathy side effects and is an alternative to spironolactone. In patients with severe heart failure, spironolactone in addition to standard therapy, reduces morbidity and mortality. [10]

Choice and combination of diuretics

Patients with heart failure may be treated with a thiazide diuretic, which should be switched to a loop diuretic if a suboptimal response occurs. In patients with a decreased renal function, a loop diuretic is the mainstay of treatment. Addition of a thiazide diuretic to a loop diuretic can be considered in case of a suboptimal response of loop diuretic alone, when given in sufficient doses (furosemide 250 mg twice daily), suggesting that diuretic resistance is due to distal tubular increased activity of retaining sodium. In all patients with NYHA II or more, except in those with a creatinine clearance < 20 ml/min (creatinine > 220 micromol/L), addition of an aldosterone antagonist should be considered. In special cases in which hypercapnia plays a role, metabolic alkalosis can result from diuretics, and acetazolamide, a reversible carbonic anhydrase inhibitor, is then prescribed as an alternative diuretic.

Angiotensin receptor blockers (ARBs)

ARBs are recommended in patients who do not tolerate an ACE inhibitor. Until recently, the addition of ARBs was the first choice recommendation in patients with HF and EF ≤40% who remained symptomatic despite optimal treatment with ACE inhibitor and beta blocker. As aldosterone antagonists have also proven their effects in NYHA class II patients, aldosterone antagonists have become first choice additional therapy after an ACE inhibitor and beta blocker. Whether ARBs may still be recommended in this patient group as added therapy after the addition of aldosterone antagonist is not known.

Contraindications are:

- Bilateral renal artery stenosis
- Serum potassium concentration > 5.0 mmol/L
- Serum creatine > 220 µmol/L
- Severe aortic stenosis

Possible side effects include symptomatic hypotension (dizziness), hyperkalemia, and a worsening renal function.

Digoxin

In the past, digoxin was the standard treatment in HF. Digoxin inhibits sodium-potassium ATPase in the cell membrane of the myocytes, and, by decreasing the sodium extrusion, also inhibits the exchange of calcium out of the cell for sodium into the cell. More calcium remains in the myocyte and increases the contractility of the heart. In contrast to other inotropics, digoxin does not increase mortality.

In patients with symptomatic HF and atrial fibrillation (AF) with a ventricular rate at rest of >80 beats per minute, use of digoxin may be considered to slow the ventricular rate. (Class I recommendation, level of evidence C)

Digoxin may be considered to reduce HF hospitalization in patients with symptomatic (NYHA class II-IV) systolic HF in sinus rhythm with an EF $\leq 45\%$. These patients should also use an ACE inhibitor (or ARB) and an MRA (or ARB) and preferably a beta blocker. (Class IIb recommendation, level of evidence B) This may also be considered in patients with an EF $\leq 45\%$ and persisting symptoms despite treatment with an ACE inhibitor (or ARB) and an MRA (or ARB). (Class IIb recommendation, level of evidence B)

Contraindications for the use of digoxin are:

- Second- or third degree heart block without a permanent pacemaker, sick sinus syndrome
- Pre-excitation syndromes

Possible side effects include sinoatrial or atrioventricular block, arrhythmias or signs of toxicity (nausea and visual effects as halos).

Ivabradine

Ivabradine lowers the heart rate through inhibition of the If channel in the sinus node. This drug can be used in patients who are still in NYHA class II-IV after treatment with ACE inhibitor (or ARB), beta blocker and an MRA (or ARB), who have a LVEF $\leq 35\%$, are in sinus rhythm and have a heart rate ≥ 75 beats/min. Ivabradine may also be used in patients who do not tolerate, or have contraindications for the use of beta blockers.

Hydralazine and isosorbide dinitrate (H-ISDN)

H-ISDN can be used as an alternative treatment when both ACEI and ARBs are not tolerated by symptomatic HF patients with a LVEF $\leq 45\%$ and dilated LV (or EF $\leq 35\%$). These patients should also receive a beta blocker and MRA. (Class IIb recommendation, level of evidence B). H-ISDN can be used in addition to the standard HF treatments (ACEI, beta blocker and MRA) in patients of Afro-American descent (Class IIb recommendation). H-ISDN may reduce risk of HF hospitalization and risk of premature death in patients with a LVEF $\leq 45\%$ and dilated LV (or EF $\leq 35\%$) with persistent symptoms despite treatment with beta blocker, ACEI (or ARB), and an MRA (or ARB). (Class IIb recommendation, level of evidence B)

Contraindications for the use of H-ISDN are:

- Symptomatic hypotension
- Lupus syndrome
- Severe renal failure

The H-ISDN combination acts by decreasing peripheral vascular resistance.

Possible side effects include symptomatic hypotension or drug-induced lupus-like syndrome.

Other

- Anticoagulants
- Anti platelet agents
- Statins
- Anti arrhythmic medication

- Calcium antagonists

3.8: Therapy of acute heart failure

When severe symptoms of heart failure quickly develop over time, it is termed acute heart failure. In Table 3.8.1, common acute HF medications and their recommended doses are summarized. In Figure 3.8.1, a flowchart for the treatment of acute HF is depicted. The mainstay of acute heart failure therapy includes diuretics, vasodilators, inotropics and vasopressors. Moreover, oxygen and morphine can be added.

Table 3.8.1: Medication in acute heart failure

Medication	Condition	Dose
Diuretics		
Adequate blood pressure and signs of overfilling		
Furosemide i.v.	Renal failure	40 mg 125 mg – max 1000 mg
Bumetanide i.v.	Renal failure	1 mg 3 mg – max 25 mg
Vasodilators		
Adequate blood pressure and signs of severe overfilling		
Nitroglycerine i.v.		20 µg/min – max 200 µg/min (guided by blood pressure)
Nitroprusside i.v.	Hypertensive crisis or in combination with inotropic in case of a cardiogenic shock	0.3 µg/kg/min – max 5 µg/kg/min (guided by blood pressure)
Inotropes		
Dobutamine i.v.	Low blood pressure and/or renal failure with or without overfilling	2-3 µg/kg/min – max 20 µg/kg/min
Dopamine i.v.	Low blood pressure and/or renal failure with or without overfilling	2-3 µg/kg/min – max 20 µg/kg/min
Enoximone i.v.	Signs of peripheral hypoperfusion with or without overfilling, and adequate blood pressure	0.25 – 0.75 mg/kg in 10 minutes; subsequently 1.25 – 7.5 µg/kg/min
Levosimendan i.v.	If beta-blockade is thought to be contributing to hypoperfusion	0.1 µg/kg/min, can be decreased to 0.05 or increased to 0.2 µg/kg/min
Vasopressors		
Adrenalin i.v.	Restore circulation in cardiogenic shock	

Medication	Condition	Dose
Noradrenalin i.v.	Septic shock	

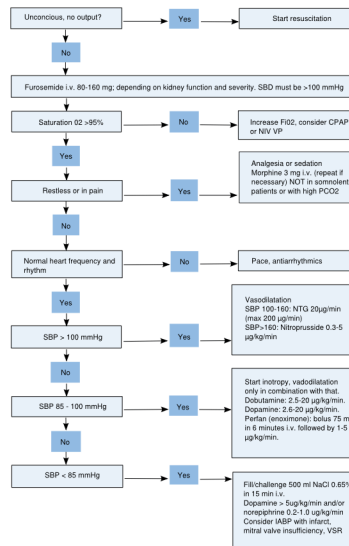


Figure 3.8.1: Flowchart for acute HF.

Patient presents at first aid or emergency room with signs of acute HF.

Table 7.3.2: Medication in chronic heart failure.

Medication	Condition	Dose
Loop Diuretic	Adequate blood pressure and signs of overfilling	
Furosemide	Renal failure	40 mg 80 mg – max 1000 mg
Bumetanide	Renal failure	1 mg 2 mg – max 25 mg
ACE Inhibitors		
Captopril		Start 6.25mg 1 st week 6.25mg three times daily. 3-5 weeks 12.5mg three times daily. >7 weeks 25mg three times daily.

Medication	Condition	Dose
Lisinopril		Start 2.5-5mg 1 st week 2.5-5mg twice daily. 3-5 weeks 5-10mg twice daily. >7 weeks 10-20mg twice daily.
Beta Blockers		
Metoprolol zoc (succinate)	EF >30-45% and NYHA II-III	Start 25mg 1 st week 50mg once daily. 3-5 weeks 100mg once daily. >7 weeks 100-200mg once daily.
	EF <30% and NYHA IV	Start 12.5mg 1 st week 25mg once daily. 3-5 weeks 50mg once daily. >7 weeks 100-200mg once daily.
Bisoprolol	EF >30-45% and NYHA II-III	Start 2.5mg 1 st week 3.75mg once daily. 3-5 weeks 5mg once daily. >7 weeks 7.5-10mg once daily.
	EF <30% and NYHA IV	Start 1.25mg 1 st week 2.5mg once daily. 3-5 weeks 3.75mg once daily. >7 weeks 5-7.5-10mg once daily.
Carvedilol	EF >30-45% and NYHA II-III	Start 6.25mg 1 st week 6.25mg twice daily. 3-5 weeks 12.5mg twice daily. >7 weeks 25mg twice daily.

Medication	Condition	Dose
	EF <30% and NYHA IV	Start 3.125mg 1 st week 3.125mg twice daily. 3-5 weeks 6.25mg twice daily. >7 weeks 12.5-25mg twice daily.
Nebivolol	EF >30-45% and NYHA II-III	Start 1.25mg 1 st week 2.5mg once daily. 3-5 weeks 5mg once daily. >7 weeks 10mg once daily.
	EF <30% and NYHA IV	Start 1.25mg 1 st week 2.5mg once daily. 3-5 weeks 5mg once daily. >7 weeks 10mg once daily.
Aldosterone antagonist		
Spironolactone/ eplerenone		Start 25mg s.i.d. 1 st week potassium <5.0: 25mg once daily. potassium 5.0-5.5: 12.5mg once daily. potassium >5.5: stop 3rd week potassium <5.0: 25mg once daily. potassium 5.0-5.5: 12.5mg once daily. potassium >5.5: stop
Digoxin		Start 0.5mg, 0.25mg and 0.25 mg, each with 6 hours in between Continue with 0.25mg once daily. Half dose with age above 70 or creatinin above 110 or with amiodarone use
AT II blockers		
Candesartan		Start 4mg 3-5 weeks 8mg once daily. >7 weeks 16mg once daily.

Medication	Condition	Dose
Valsartan		Start 40mg twice daily 3-5 weeks 80mg twice daily. >7 weeks 160mg twice daily.
Hydralazine and isosorbide dinitrate (H-ISDN)		
Hydralazine		Start 25mg three times daily. 3-5 weeks 50mg three times daily. >7 weeks 75-100mg three times daily.
ISDN		Start 20mg twice daily 3-5 weeks 40mg twice daily >7 weeks 80mg twice daily

3.9: Management of HF beyond medication

Device treatment

Prevention of sudden death is an important goal in HF because approximately half of the deaths occur suddenly, and many of these are related to ventricular arrhythmias. Implantable cardioverter-defibrillator (ICD) therapy is recommended in survivors of cardiac arrest, irrespective of EF, when life expectancy is >1 year. (Class I recommendation, level of evidence A).

In symptomatic HF patients (NYHA class II-III) with an EF ≤35% after more than 3 months of pharmacological treatment and a life expectancy >1 year, prophylactic ICD implantation is recommended in patients with ischemic etiology (Class I recommendation, level of evidence A) and non-ischemic etiology (Class I recommendation, level of evidence B).

Cardiac resynchronization therapy (CRT) is indicated in patients with symptomatic heart failure with one type and severity of ventricular conduction delay (LBBB, QRS ≥120 msec), and preferably in patients with sinus rhythm. The responder rate (improvement of at least 5% EF) is about 70%. Recommendation for use of this therapy differs according to heart rhythm, NYHA class, QRS duration and morphology, and LVEF. This is depicted in the Figure 3.9.1.

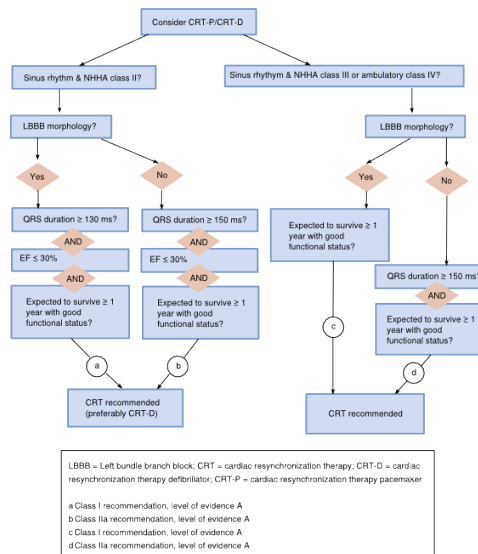


Figure 3.9.1: Flowchart for CRT

Timing of ICD implantation

Figure 3.7.2 offers recommendations to which patients should receive ICD treatment. In this flowchart, the timing of the placement has not been defined completely. In most patients, it should be safe to wait for their ICD whilst receiving (pharmacological) treatment as events typically occur after 6-12 months.[11] An exception to this rule is the group of high risk patients (i.e. patients with major myocardial infarction (MI), who have extensive fibrosis on the MRI or NSVT despite optimal pharmacological treatment); an ICD implantation should not be postponed too long in these patients. Early (within 40 days after event) ICD placement after an acute myocardial infarction has not been shown to reduce mortality, because the patients most at risk of sudden death are also the patients most at risk of death due to heart failure.[12][13][14] For this reason, prophylactic ICD treatment is recommended only after 40 days in post-infarct patients who have an EF < 35%. For non-ischemic heart failure patients, three months is considered a safe waiting time for an ICD. There are, however, also higher risk patients among this group, and a decision should be made for each patient on an individual basis.[15]

Heart transplantation and Left Ventricular Assist Devices

When a patient has severe and progressive HF, his or her prognosis is grim. Considering the paucity of donor hearts, the waiting list for heart transplantation may be long and early consideration of heart transplantation is part of the treatment strategy in HF. Average 2-year survival rates after cardiac transplantation are approximately 80%. A patient in NYHA class III should be evaluated with an exercise test for maximal oxygen uptake, in order to consider further steps. Indication for heart transplantation includes a $VO_{2max} < 14$ ml/min/kg.[16]

Exclusion criteria are pulmonary hypertension (risk of immediate RV donor failure), severe comorbidity, and diabetes mellitus with organ damage. Left Ventricular Assist Devices are more commonly used as a bridge to transplantation, when the patient is on a waiting list. They have evolved from pulsatile to continuous flow pumps, with less complications and a longer durability. Often Left Ventricular Assist Devices become destination therapy.

Management of HF patients with preserved LVEF (HFPEF)

To date, no evidence exists of any treatment reducing morbidity or mortality in this patient group. With the aim of controlling water and sodium retention and to decrease breathlessness and edema, diuretics are prescribed to HFPEF patients. Furthermore, ACE-I, Angiotensin II blockers and/or beta blockers may be considered. The CHARM trial including 3023 HF patients with preserved EF, showed angiotensin II blockade (candesartan) to have a moderate effect on hospital admission but showed no effect on the risk of cardiovascular death.[17]

Prognosis

The life expectancy of a patient with heart failure is determined by age, NYHA class, LVEF, normal level of sodium, systolic blood pressure, use of medication and use of ICD or CRT-D ([Seattle Heart failure score](#)). The mean yearly annual mortality is approximately 10%, varying from <6% per year when a normal LVEF is identified, to > 14% per year with an EF of <15%. Trials with medication illustrate that the (short term) benefit of medication is highest when the NYHA class is higher (Figure 3.9.2).[18]

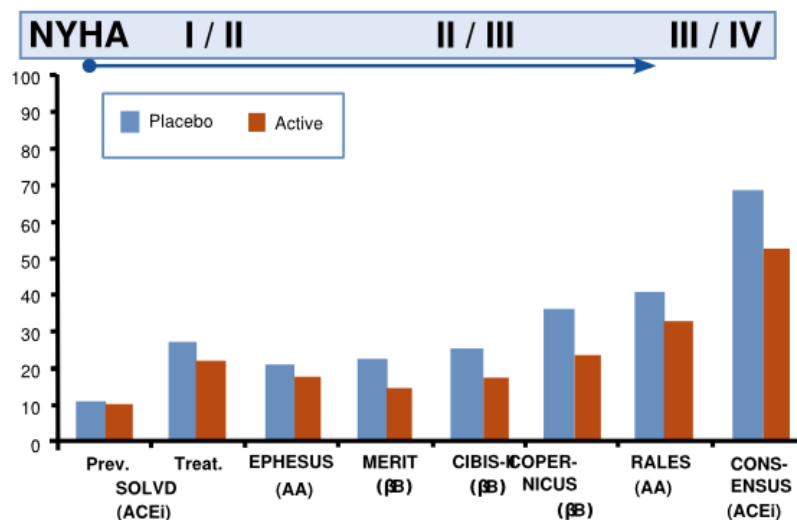


Figure 3.9.2: Two-year mortality in landmark contemporary clinical heart failure trials (from Cleland et al)

3.10: References

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4: CARDIAC ARRHYTHMIAS

A basic knowledge of the cardiac action potential and cardiac conduction system facilitates understanding of cardiac arrhythmias. The effects and side-effects of anti-arrhythmic drugs are depended on the influence on ion channels involved in the generation and/or perpetuation of the cardiac action potential.

[4.1: Introduction to Cardiac Arrhythmias](#)

[4.2: Mechanisms of Arrhythmia](#)

[4.3: References](#)

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4.1: Introduction to Cardiac Arrhythmias

A basic knowledge of the cardiac action potential and cardiac conduction system facilitates understanding of cardiac arrhythmias. The effects and side-effects of anti-arrhythmic drugs are depended on the influence on ion channels involved in the generation and/or perpetuation of the cardiac action potential.

Cardiac Action Potential

The cardiac action potential is a result of ions flowing through different ion channels. Ion channels are passages for ions (mainly Na^+ , K^+ , Ca^{2+} and Cl^-) that facilitate movement through the cell membrane. Changes in the structure of these channels can open, inactivate or close these channels and thereby control the flow of ions into and out of the myocytes. Due to differences in the type and structure of ion channels, the various parts of the heart have slightly different action potential characteristics. Ion channels are mostly a passive passageway, where movement of ions is caused by the electrochemical gradient. In addition to these passive ion channels a few active trigger-dependent channels exist that open or close in response to certain stimuli (for instance acetylcholine or ATP). The changes in the membrane potential due to the movement of ions produce an action potential which lasts only a few hundreds of milliseconds. Disorders in single channels can lead to arrhythmias, as seen in the section [primary arrhythmias](#). The action potential is propagated throughout the myocardium by the depolarization of the immediate environment of the cells and through intracellular coupling with gap-junctions.[1]

In summary during the depolarization, sodium ions (Na^+) stream into the cytoplasm of the cell followed by a influx of calcium (Ca^{2+}) ions (both from the inside (sarcoplasmic reticulum) and outside of the cell). These Ca^{2+} ions cause the actual muscular contraction by coupling with the muscle fibers. During repolarization the cell returns to the resting membrane potential, due to the passive efflux of K^+ (Figure 4.1.1). In detail the (ventricular) action potential can be divided in five phases: [2, 3]

Phase 0: Rapid Depolarization

Rapid depolarization is started once the membrane potential reaches a certain threshold (about -70 to -60 mV). This produces activation of sodium channels and a rapid influx of Na^+ and a corresponding rapid upstroke of the action potential. At higher potentials (-40 to -30) Ca^{2+} influx participates in the upstroke. In the sinus node and AV node a slower upstroke can be observed (Figure 4.1.2). This is because the rapid depolarization in these cells is mainly mediated by the slower acting Ca^{2+} ion channels. The slower activation produces a slower upstroke.

Phase 1: Early Rapid Repolarization

Immediately following rapid depolarization, the inactivation of the Na^+ channel (I_{Na}) and subsequent activation of the outward K^+ channel (I_{to}) and the $\text{Na}^+/\text{Ca}^{2+}$ exchanger ($I_{\text{Na,Ca}}$), which exchanges 3 Na^+ for 1 Ca^{2+} , produces a early rapid repolarization. Due to the limited role of the Na^+ channel in the upstroke of sinus node and AV node cells and the subsequent slower depolarization, this rapid repolarization is not visible in their action potentials (Figure 4.1.2).

Phase 2: Plateau

The plateau phase represents an equal influx and efflux of ions in or out of the cell producing a stable membrane potential. This plateau phase is predominantly observed in the ventricular action potential. The inward movement of Ca^{2+} through the open L-type Ca^{2+} channels ($I_{\text{Ca-L}}$) and the exchange of Na^+ for internal Ca^{2+} by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger ($I_{\text{Na,Ca}}$) are responsible for the influx of ions during the plateau phase. The efflux of ions is the result of outward current carried by K^+ (I_{Kur} and I_{Ks}).

Phase 3: Final Rapid Repolarization

Final repolarization is mainly caused by inactivation of Ca^{2+} channels, reducing the influx of positive ions. Furthermore

repolarizing K^+ currents (delayed rectifier current I_{Ks} and I_{Kr} and inwardly rectifying current I_{K1} and $I_{K,Ach}$) are activated which increase efflux of positive K^+ ions. This results in an repolarization to the resting membrane potential.

Phase 4: Resting membrane potential

During phase 4 of the action potential intracellular and extracellular concentrations of ions are restored. Depending on cell type the resting membrane potential is between -50 to -95 mV. Sinus node and AV nodal cells have a higher resting membrane potential (-50 to -60 mV and -60 to -70 respectively) in comparison with atrial and ventricular cardiomyocytes (-80 to -90 mV). Sinus node cells and AV nodal cells (and to a lesser degree Purkinje fibers cells) have a special voltage dependent channel I_f , the funny current. Furthermore they lack I_{K1} , a K^+ ion channel that maintains the resting membrane potential in atrial and ventricular tissue. The I_f channel causes a slow depolarization in diastole, called the phase 4 diastolic depolarization, which results in normal automaticity. The frequency of the sinus node discharges are regulated by the autonomous nerve system and due to the relative high firing frequency (60-80 beats per minute) the sinus node dominates other potential pacemaker sites.

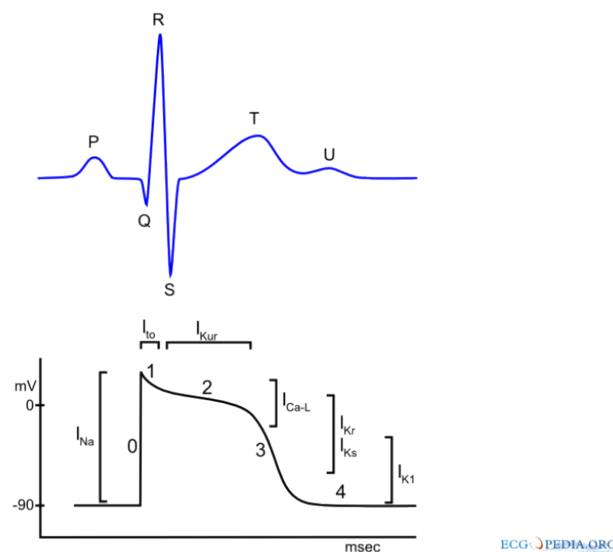


Figure 4.1.1: The cardiac ventricular action potential and relevant ion channels.

Cardiac conduction

The cardiac conduction system (Figure 4.1.2) consist of specialized fast conducting tissue through which the electric activity of the heart spreads from the atria to the ventricles. The characteristics of the different parts of the conduction system are a result of the different characteristics of the individual myocytes. On a larger level, function is controlled predominantly by the autonomic nervous system (both vagal and sympathetic nerve system). Especially the sinus node and atrioventricular node are responsive to the autonomic nerve system. The ganglionic plexus, a conglomeration of both vagal and sympathetic nerves, form the intrinsic cardiac nerve system and innervate through a network of nerve fibers the atria and ventricles. The vagal and sympathetic nerve system are both continually active in the heart, but vagal activity dominates the tonic background stimulation of the autonomic nerve system. Moreover the heart is more susceptible to vagal stimulation. Vagal stimulation provokes a rapid response and the effect dissipates swiftly in contrast to sympathetic stimulation which has a slow onset and offset. Vagal stimulation results in a reduction in sinus node activation frequency and prolongs AV nodal conduction. These effects can occur simultaneously or independent of each other. Sympathetic stimulation exerts reverse effects, accelerating the sinus node firing frequency and improving AV nodal conduction. The autonomic nerve system has a small effect on cardiomyocytes. Vagal stimulation tends to prolong the refractory period and decrease the myocardial contractility. Sympathetic stimulation has the opposite effect on the cardiac tissue. The physiological modulation of cardiac conduction is vital to adaptation of the heart to rest and exercise. However the autonomic nervous system can contribute as a modifier is certain to facilitate the occurrence of certain arrhythmias.[3]

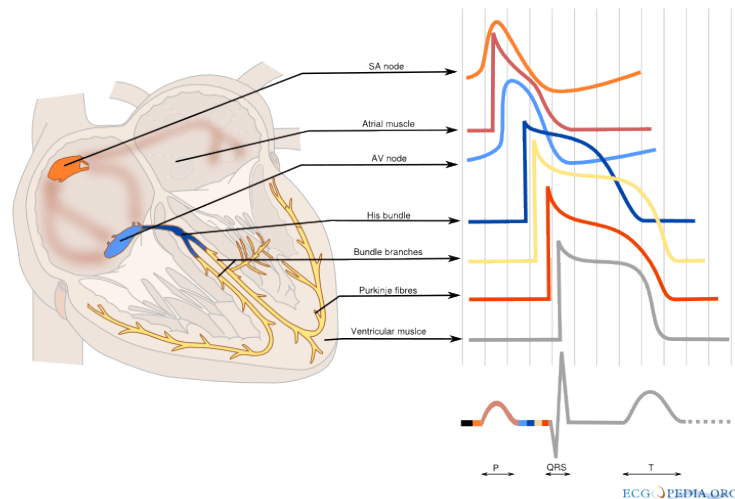


Figure 4.1.2: The different shapes of the cardiac action potential in the heart.

Sinus node

The sinus node is a densely innervated area located in the right atrium which is supplied by the right (55%-60%) or circumflex (40%-45%) coronary artery. It is a small structure of 10-20mm long and 2-3mm wide and contains a diversity of cells. These include pacemaker cells which are discharged synchronously due to mutual entrainment. This results in an activation wave front activating the rest of the atrium.

Atrium

The impulse formed in the sinus node is conducted through the atrium to the AV-node. Evidence indicates three preferential conduction pathways. The pathways show preferential conduction due to their anatomical structure and rather than specialized conduction properties. The three pathways are: the anterior internodal pathway, the middle internodal tract the posterior internodal pathway. The anterior internodal pathway connect to the anterior interatrial band, also known as the Bachmann bundle. This bundle of muscular tissue conducts the sinus wave front from the right to the left atrium.

AV node

The connection between atria and ventricles is facilitated through the AV node, lying in the right atrial myocardium and a penetrating part, the bundle of His. The AV node acts as a gatekeeper, regulating impulse conduction from the atrium to the ventricle. Additionally, due to the phase 4 diastolic depolarization it can exhibit impulse formation. The AV node is supplied in most cases (85%-90%) by the right coronary artery or in the remaining cases the circumflex artery.

Bundle of His

Connecting the distal AV node and the proximal bundle branches, the bundle of His is supplied by both the posterior and anterior descending coronary arteries. It is enclosed by the central fibrous body and membranous septum between the atria and the ventricles. The location and blood supply protect the bundle of His from external influences.

Bundle Branches

From the bundle of His the right bundle branch continues to the right ventricular apex. The left bundle branch splits of and divides in two fascicular branches. Commonly the left bundle branch consist of an anterior fascicle, which activates the anterosuperior portion of the left ventricle. and the thicker and more protected posterior fascicle which activates the inferoposterior part of the left ventricle.

Ventricle

The ventricle is activated through the dense network of Purkinje fibers originating from the bundle branches. They penetrate the myocardium and are the starting point of the ventricular activation. The left ventricular areas first excited are the anterior and posterior paraseptal wall and the central left surface of the interventricular septum. The last part of the left ventricle to be activated is the posterobasal area. Septal activation starts in the middle third of the left side of the interventricular septum, and at the lower third at the junction of the septum and posterior wall. Activation of the right ventricle starts near the anterior papillary muscle 5 to 10 milliseconds after onset of the left ventricle.[4]

4.2: Mechanisms of Arrhythmia

Structural abnormalities or electric changes in the cardiomyocytes can impede impulse formation or change cardiac propagation, therefore facilitating arrhythmias. Arrhythmogenic mechanisms can arise in single cells (automaticity, triggered activity), but other mechanisms require multiple cells for arrhythmia induction (re-entry). We briefly discuss the pathophysiological mechanisms of the main causes of arrhythmia. [5]

Abnormal Impulse Formation

Abnormal Automaticity

The mechanism of abnormal automaticity is similar to the normal automaticity of sinus node cells. Abnormal automaticity can be caused by changes in the cell ion channel characteristics due to drugs (digoxine) or changes in the electrotonic environment (myocardial infarction). Abnormal automaticity can result from an increase of normal automaticity in non-sinus node cells or a truly abnormal automaticity in cells that don't exhibit a phase 4 diastolic depolarization. An important phenomenon in (both normal and abnormal) automaticity is overdrive suppression. In overdrive suppression the automaticity of cells is reduced after a period of high frequency excitation. The cellular mechanism responsible for this effect is an increased activity of the Na^+ , K^+ pump ($\text{I}_{\text{Na, K}}$) which results in an increased efflux of Na^+ , thereby inducing a hyperpolarization.[2]

Triggered Activity

Triggered activity is depolarization of a cell triggered by a preceding activation. Due to early or delayed afterdepolarizations the membrane potential depolarizes and, when reaching a threshold potential, activates the cell. These afterdepolarizations are depolarizations of the membrane potential initiated by the preceding action potential. Depending on the phase of the action potential in which they arise, they are defined as early or late afterdepolarizations (Figure 4.2.1).

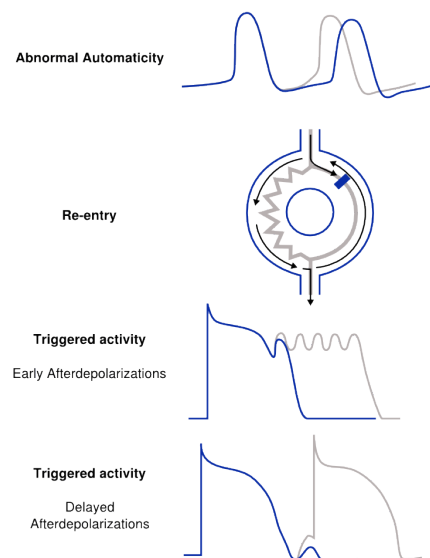


Figure 4.2.1: The different mechanisms of arrhythmia.

- A disturbance of the balance in influx and efflux of ions during the plateau phase (phase 2 or 3) of the action potential is responsible for the early afterdepolarizations. Multiple ion currents can be involved in the formation of early afterdepolarizations depending on the triggering mechanism. Early afterdepolarizations can develop in cells with an increased duration of the repolarization phase of the action potential, as the plateau phase is prolonged. The prolonged repolarization might reactivate the Ca^{2+} channels that have recovered from activation at the beginning of the repolarization. Otherwise disparity in action potential duration of surrounding myocytes can destabilize the plateau phase through adjacent

depolarizing currents.

- Delayed afterdepolarizations occur after the cell has recovered after completion of repolarization. In delayed afterdepolarization an abnormal Ca^{2+} handling of the cell is responsible for the afterdepolarizations due to release of Ca^{2+} from the storage of Ca^{2+} in the sarcoplasmic reticulum. The accumulation of Ca^{2+} increases membrane potential and depolarizes the cell until it reaches a certain threshold, thereby creating an action potential. A high heart rate can result in the accumulation of intracellular Ca^{2+} and induce delayed afterdepolarizations.

Disorders of Impulse Conduction

Conduction block

Conduction block or conduction delay is a frequent cause of bradyarrhythmias, especially if the conduction block is located in the cardiac conduction system. However tachyarrhythmias can also result from conduction block when this block produces a re-entrant circuit (see below). Conduction block can develop in different (pathophysiological) conditions or can be iatrogenic (medication, surgery).

Re-entry

Re-entry or circus movement is a multicellular mechanism of arrhythmia. Important criteria for the development of re-entry are a circular pathway with an area in this circle of unidirectional block and a trigger to induce the re-entry movement. Re-entry can arise when an impulse enters the circuit, follows the circular pathway and is conducted through an unidirectional (slow conducting) pathway. Whilst the signal is in this pathway the surrounding myocardium repolarizes. If the surrounding myocardium has recovered from the refractory state, the impulse that exits the area of unidirectional block can reactivate this recovered myocardium. This process can repeat itself and thus form the basis of a re-entry tachycardia. Slow conduction and/or a short refractory period facilitate re-entry. The reason of unidirectional block can be anatomical ([atrial flutter](#), [AVNRT](#), [AVRT](#)) or functional (myocardial ischemia) or a combination of both.[\[6, 7\]](#)

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5: CORONARY DISEASE

5.1: Chest Pain/Angina Pectoris

5.2: Myocardial Infarction

5.3: Chronic Coronary Disease

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5.1: Chest Pain/Angina Pectoris

Stable angina (pectoris) is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. It can be attributed to myocardial ischemia which is most commonly caused by atherosclerotic coronary artery disease or aortic valve stenosis.

Three major coronary arteries supply the heart with oxygenated blood, the right coronary artery (RCA), the left anterior descending coronary artery (LAD) and the left circumflex artery (LCx). When the coronary arteries are affected by atherosclerosis and the lumen of the coronary arteries progressively narrow, a dysbalance between myocardial oxygen supply and myocardial oxygen consumption may occur, causing myocardial ischemia. In stable angina this imbalance mainly occurs when oxygen demand increases due to exercise, increased heart rate, contractility or wall stress.

A complete history and physical examination are essential to support the diagnosis (stable) angina pectoris and to exclude other (acute) causes of chest pain such as an acute coronary syndrome, aortic dissection, arrhythmias, pulmonary embolism, (tension) pneumothorax or pneumonia, gastroesophageal reflux or spasms, hyperventilation or musculoskeletal pain. [1] In addition, laboratory tests and specific cardiac investigations are often necessary.

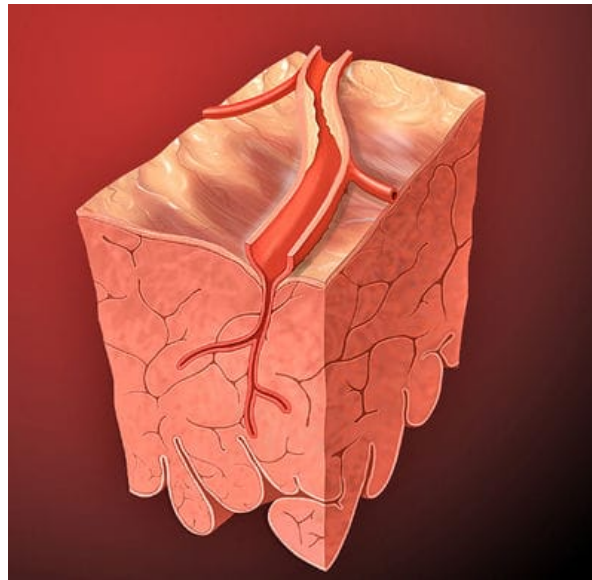


Figure 5.1.1: An epicardial coronary artery with a atherosclerotic narrowing

History

Patients often describe angina pectoris as pressure, tightness, or heaviness located centrally in the chest, and sometimes as strangling, constricting, or burning. The pain often radiates elsewhere in the upper body, mainly arms, jaw and/or back. [2] Some patients only complain about abdominal pain so the presentation can be aspecific. [3], [4]

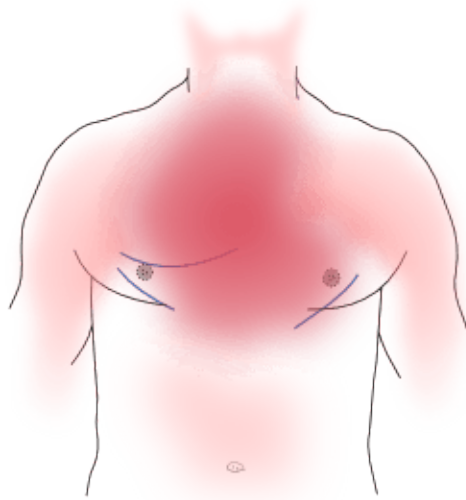


Figure 5.1.2: Typical chest pain is retrosternal. Pain may radiate to the arms, jaw, and / or back.

Angina pectoris however has some characteristics that can help to differentiate between other causes of (chest) pain. Angina pectoris is usually is brief and gradual in onset and offset, with the intensity increasing and decreasing over several minutes. The pain does not change with respiration or position. If patients had angina pectoris previously they are often able to recognize the pain immediately. [5] Angina pectoris is a manifestation of arterial insufficiency and usually occurs with increasing oxygen demand such as during exercise. As soon as the demand is decreased (by stopping the exercise for example) complaints usually disappears within a few minutes. Another way to relieve pain is by administration of nitro-glycerine. Nitro-glycerine spray is a vasodilator which reduces venous return to the heart and therefore decreases the workload and therefore oxygen demand. It also dilates the coronary arteries and increases coronary blood flow. [6] The response to nitro-glycerine is however not specific for angina pectoris, a similar response may be seen with oesophageal spasm or other gastrointestinal problems because nitro-glycerine relaxes smooth muscle tissue. [7]

Depending on the characteristics, chest pain can be identified as typical angina, atypical angina or non-cardiac chest pain, see Table 5.1.1.

Table 5.1.1: Clinical Classification of Chest Pain

Clinical Classification of Chest Pain	
Typical angina (definite)	Meets three of the following characteristics: • Substernal chest discomfort of characteristic quality and duration • Provoked by exertion or emotional stress • Relieved by rest and/or nitroglycerine
Atypical angina (probable)	Meets two of these characteristics
Non-cardiac chest pain	Meets one or none of the characteristics

The classification of chest pain in combination with age and sex is helpful in estimating the pretest likelihood of angiographically significant coronary artery disease, see Table 5.1.2.

Table 5.1.2: Clinical pre-test probabilities in patients with stable chest pain symptoms. Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years. [9]

Typical Angina			Atypical Angina		Non-anginal Pain	
Age	Men	Women	Men	Women	Men	Women
30-39	59	28	29	10	18	5
40-49	69	37	38	14	25	8
50-59	77	47	49	20	34	12
60-69	84	58	59	28	44	17
70-79	89	68	69	37	54	24
<80	93	76	78	47	65	32

- Groups in *white boxes* have a PTP <15% and hence can be managed without further testing.
- Groups in *blue boxes* have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
- Groups in *light pink boxes* have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
- In groups in *dark pink boxes* the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.

The severity of complaints can be classified according to the Canadian Cardiovascular Society as shown in Table 5.1.3.

Table 5.1.3: Classification of angina severity according to the Canadian Cardiovascular Society

Class	Level of Symptoms
Class I	'Ordinary activity does not cause angina' Angina with strenuous or rapid or prolonged exertion only
Class II	'Slight limitation of ordinary activity' Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening
Class III	'Marked limitation of ordinary physical activity' Angina on walking one or two blocks on the level or one flight of stairs at a normal pace under normal conditions
Class IV	'Inability to carry out physical activity without discomfort' or 'angina at rest'

During angina pectoris 'vegetative' symptoms can occur, including sweating, nausea, paleface, anxiety and agitation. This is probably caused by the autonomic nerve system in reaction to stress. [10]

Finally, it is important to differentiate unstable angina (indicating an acute coronary syndrome or even myocardial infarction requiring urgent treatment) from stable angina. Unstable angina typically is severe, occurs without typical provocation and does

not disappear with rest, and has a longer duration than stable angina. It is important to initiate prompt treatment in these patients, as described in the acute coronary syndromes chapter.

Physical Examination

There are no specific signs in angina pectoris. Physical examination of a patient with (suspected) angina pectoris is important to assess the presence of hypertension, valvular heart disease (in particular aortic valve stenosis) or hypertrophic obstructive cardiomyopathy. It should include the body-mass index, evidence of non-coronary vascular disease which may be asymptomatic and other signs of co-morbid conditions. E.g.: absence of palpable pulsations in the dorsal foot artery is associated with an 8 fold increase in the likelihood of coronary artery disease.

Electrocardiogram (ECG)

The electrocardiogram (ECG) is an important tool to differentiate between unstable angina (acute coronary syndrome) and stable angina in addition to the patient's history. Patients with unstable angina pectoris are likely to show abnormalities on the ECG at rest, in particular ST-segment deviations. Although a resting ECG may show signs of coronary artery disease such as pathological Q-waves indicating a previous MI or other abnormalities, many patients with stable angina pectoris have a normal ECG at rest. Therefore exercise ECG testing may be necessary to show signs of myocardial ischemia. [11]

Exercise ECG testing is performed with gradually increasing intensity on a treadmill or a bicycle ergo-meter. Exercise increases the oxygen demand of the heart, potentially revealing myocardial ischemia by the occurrence of ST-segment depression on the ECG. [12]

Laboratory Testing

Laboratory testing in the setting of angina pectoris can be useful to differentiate between different causes of the pain, including an acute coronary syndrome in which there will be elevation of the marker of myocardial necrosis. Anaemia should be ruled out as a cause of ischemia. Renal function is important for pharmacological therapy. Moreover, it might assist in establishing a cardiovascular risk profile.

Stress Testing in Combination with Imaging

Some patients are unable to perform physical exercise. Furthermore, in patients with resting ECG abnormalities the exercise ECG is associated with low sensitivity and specificity.

Table 5.1.4: Characteristics of tests commonly used to diagnose the presence of coronary artery disease. [9]

Diagnosis of CAD		
	Sensitivity (%)	Specificity (%)
Exercise ECG ^{a, 91, 94, 95}	45-50	85-90
Exercise stress echocardiography ⁹⁶	80-85	80-88
Exercise stress SPECT ⁹⁶⁻⁹⁹	73-92	63-87
Dobutamine stress echocardiography ⁹⁶	79-83	82-86
Dobutamine stress MRI ^{b,100}	79-88	81-91
Vasodilator stress echocardiography ⁹⁶	72-79	92-95
Vasodilator stress SPECT ^{96, 99}	90-91	75-84
Vasodilator stress MRI ^{b,98, 100-102}	67-94	61-85

Diagnosis of CAD		
Coronary CTA ^{c,103-105}	95-99	64-83
Vasodilator stress PET ^{97, 99, 106}	81-97	74-91

CAD = coronary artery disease; **CTA** = computed tomography angiography; **ECG** = electrocardiogram; **MRI** = magnetic resonance imaging; **PET** = positron emission tomography; **SPECT** = single photon emission computed tomography.

^a Results without/with minimal referral bias.

^b Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.

^c Results obtained in populations with low-to-medium prevalence of disease.

If the ECG made during exercise testing does not show any abnormalities myocardial ischemia becomes unlikely as cause of the complaints. If the diagnosis is still in doubt, the following additional tests may be performed.

1. Exercise echocardiography means that an echocardiography is made before and during different stages up to peak exercise in order to identify wall motion abnormalities. [13] An alternative is pharmacological stress testing using dobutamine.
2. Myocardium Perfusion Scintigraphy (MPS) is able to show the perfusion of the heart during exercise and at rest based on radiopharmaceutical tracer uptake. [14]
3. Magnetic Resonance Imaging can be done with vasodilatory adenosine or stimulating dobutamine to detect wall motion abnormalities induced by ischemia during pharmacological stress. [15]

The findings on stress testing can be used to determine the choice between medical therapy only or medical therapy and invasive assessment of the coronary anatomy in patients with stable angina. Coronary angiography is recommended based upon the severity of symptoms, likelihood of ischemic disease, and risk of the patient for subsequent complications including mortality based on risk scores. [16] For the algorithm for the initial evaluation of patients with clinical symptoms of angina see Figure 5.1.3.

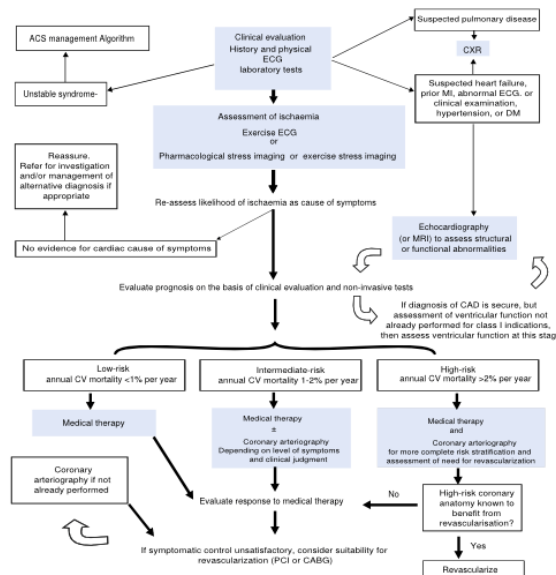


Figure 5.1.3: Algorithm for the initial evaluation of patients with clinical symptoms of angina

Coronoary Angiography

Coronary angiography (CAG) can assist in the diagnosis and the selection of treatment options for stable angina pectoris. During CAG, the coronary anatomy is visualized including the presence of coronary luminal stenoses. A catheter is inserted into the femoral artery or into the radial artery. The tip of the catheter is positioned at the beginning of the coronary arteries and contrast fluid is injected. The contrast is made visible by X ray and the images that are obtained are called angiograms. If stenoses are

visible, the operator will judge whether this stenosis is significant and eligible for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Treatment

Stable angina pectoris is always treated with medical therapy aimed at reducing risk and at alleviating symptoms. Current guidelines recommend revascularization in patients with persistent symptoms despite optimal medical therapy. [17] Furthermore, revascularization is indicated in case of large areas of myocardial ischemia (such as a left main stem stenosis, a proximal LAD stenosis or significant three vessel disease) and in the presence of high-risk features such as ventricular arrhythmia, heart failure, widening of QRS during ischemia, axis deviation during ischemia or hypotension during ischemia. The choice between PCI and CABG depends on the coronary anatomy and clinical characteristics and the choice should be made in a team including (interventional) cardiologists and thoracic surgeons.

Medical Therapy

Initial treatment of stable angina pectoris focuses on medication reducing the oxygen demand of the heart. β blockers lower heart rate and blood pressure. [8] Nitrates dilate the coronary arteries and reduce venous return if used to abort an episode of pain. [18] Antiplatelet therapy (aspirin) reduces the risk of development of a thrombus and thus acute (coronary) ischemic events. [19] Risk factors like smoking, overweight, hypertension, dyslipidemia and diabetes need to be treated in order to prevent disease progression and future events. See chronic coronary diseases.

PCI

The procedure of PCI is similar to a CAG, except this time a catheter with an inflatable balloon will be brought to the site of the stenosis. Inflation of the balloon within the coronary artery will crush the atherosclerosis and eliminate the stenosis. To prevent collapse of the arteric wall and restenosis, a stent is often positioned at the site of the stenosis.

CABG

With CABG, a bypass is placed around the stenosis using the internal thoracic arteries or the saphenous veins from the legs. The bypass originates proximal from the stenosis and terminates distally from the stenosis. The operation usually requires the use of cardiopulmonary bypass and cardiac arrest, however in certain cases the grafts can be placed on the beating heart ("off-pump" surgery)

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5.2: Myocardial Infarction

An acute coronary syndrome (ACS) is most commonly caused by rupture or erosion of an atherosclerotic plaque with superimposed thrombus formation. The underlying process is atherosclerosis, a chronic disease in which artery walls thicken by deposition of fatty materials such as cholesterol and inflammatory cells. The accumulation of this material results in the formation of an atherosclerotic plaque, encapsulated by connective tissue, which can narrow the lumen of the arteries significantly and progressively causing symptoms as angina pectoris or lead to an ACS. Depending on the presence of myocardial damage and typical ECG characteristics, ACS can be divided into ST-segment elevation myocardial infarction (STEMI), and non-ST-segment ACS including non-ST-segment elevation MI (NSTEMI) and unstable angina. In the case of STEMI and NSTEMI, there is biochemical evidence of myocardial damage (infarction). [1]

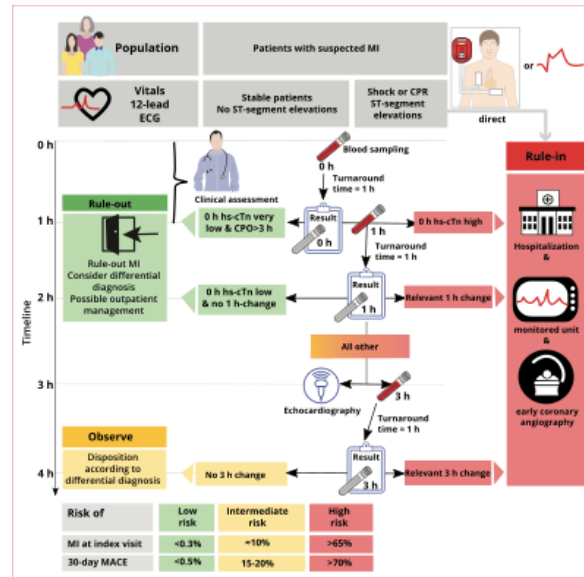


Figure 5.2.1: Myocardial Infarction

History

The most typical characteristic of an ACS is acute prolonged chest pain. [2] The pain does not decrease at rest and is only temporarily relieved with nitroglycerin. Frequent accompanying symptoms include a radiating pain to shoulder, arm, back and/or jaw. [3] Shortness of breath can occur, as well as sweating, fainting, nausea and vomiting, so called vegetative symptoms. Some patients including elderly and diabetics may present with aspecific symptoms. [4], [5]

It is important to complete the medical history (prior history of ischemic events or vascular disease), risk factors for cardiovascular disease (a.o. diabetes mellitus, current smoking, hypertension, hyperlipidemia) and family history (first degree relatives with myocardial infarction before the age 55 of (males) or 65 (females) and/or sudden cardiac death). [6]

Symptoms of heart failure such as orthopnea (dyspnoea when lying flat), progressive dyspnoea and peripheral oedema are indicative of the extent of the problem. [7]

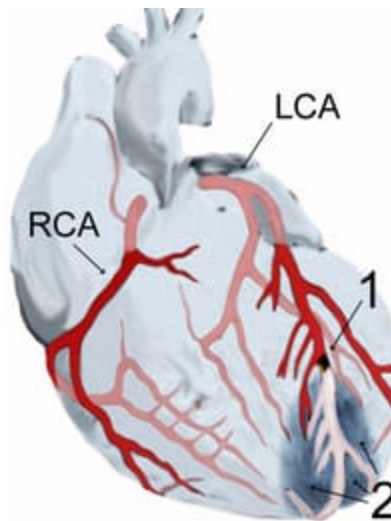


Figure 5.2.2: A myocardial infarction results from a coronary occlusion (1) with necrosis of myocardial tissue (2) distal to the occlusion

Physical Examination

The focus of the physical examination should be to recognize signs of systemic hypoperfusion such as hypotension, tachycardia, impaired cognition, pale and ashen skin.[7] Furthermore, signs of heart failure are important, such as pulmonary crackles during auscultation and pitting oedema of the ankles. In more stable ACS patients, history and physical examination are helpful to exclude other causes of chest pain, such as aortic valve stenosis, aorta dissection, arrhythmias, pulmonary embolism, pneumonia, heartburn, hyperventilation or musculoskeletal problems. [7]

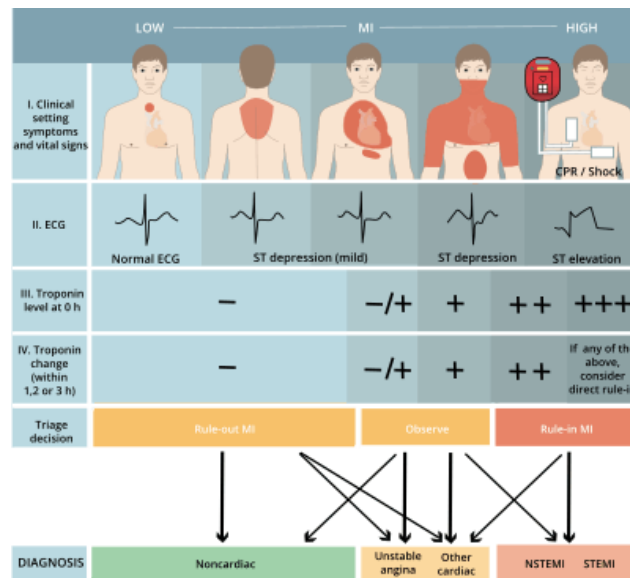


Figure 5.2.3: Different terminology is used during different phases of the chest pain workup. The ECG classifies into ST elevation or not. Troponine definitely classifies into myocardial infarction (damage) or not.

Electrocardiogram (ECG)

An electrocardiogram (ECG) should be made on arrival in every patient with suspected ACS. [7] The ECG is an important and easy modality which can assist in the diagnosis and prognostication of ACS. However, a single ECG may not reflect the dynamic pathophysiology of the ACS. Therefore it is important to make serial ECGs, certainly if a patient has ongoing symptoms. [7]

Furthermore, the ECG is also helpful in localizing the ischemia:

- Anterior wall ischemia - One or more of leads V2-V5
- Anteroseptal ischemia - Leads V1 to V3
- Apical or lateral ischemia - Leads aVL and I, and leads V4 to V6
- Inferior wall ischemia - Leads II, III, and aVF
- Posterior wall - Leads V7-V9
- Right ventricle - Leads V3R, V4R, V1
- Left main coronary artery ischemia - Lead aVR

More information about the [ECG during myocardial infarction](#) can be found on ECGpedia.

Cardiac Markers

Cardiac markers are essential in order to confirm the diagnosis of MI, indicated by elevated Creatine Kinase isoenzyme MB (CK MB) and/or (high-sensitive) troponins. Troponins are more specific and sensitive than CK MB. The cardiac troponin concentration begins to rise around 4 hours after the onset of myocardial cell damage.[8]

With high-sensitive troponins, myocardial cell damage can be detected even earlier. It can take 4-6 hours before the CK MB concentration is elevated. Serial measurements are useful in order to estimate infarct size and increase the sensitivity of the (older) assays. [9]

A pitfall concerning mildly elevated cardiac markers can be patients with renal failure or pulmonary embolism. [10]

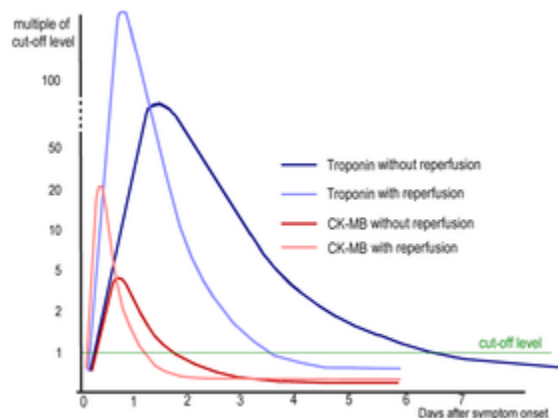


Figure 5.2.4: Rise and fall of several cardiac markers based on whether the myocardium was reperfused or not

Treatment

As the formation of an intracoronary thrombus is a central mechanism in ACS and (recurrent) subsequent outcomes, the cornerstone in the treatment of ACS is antithrombotic treatment. All patients diagnosed with ACS should start with aspirin and a P2Y12 receptor blocker (clopidogrel, prasugrel or ticagrelor). [11] Aspirin and the P2Y12 receptor blocker are both platelet aggregation inhibitors. The treatment of ACS also focuses on medication to reduce the workload of the heart. β blockers lower heart rate and blood pressure, to decrease the oxygen demand of the heart. [12] Nitrates dilate the coronary arteries. [13]

Depending on the (working) diagnosis STEMI or NSTEMI-ACS, the revascularisation strategy varies.

ST-segment elevation Myocardial Infarction

Initial treatment of STEMI is relief of ischemic pain, stabilisation of hemodynamic status and restoration of coronary flow and myocardial tissue perfusion. Reperfusion therapy should be initiated as quickly as possible by preferably primary percutaneous coronary intervention (PCI) or fibrinolysis. Reperfusion is beneficial up to 12 hours after the onset of symptoms. In case of severe hemodynamic compromise, reperfusion therapy may be attempted up to 24 hours after symptom onset. Meanwhile other measures as continuous ECG monitoring, oxygen supply and intravenous access are indicated. [7]

Primary PCI is the preferred revascularisation method for patients with STEMI. It is an effective method of securing and

maintaining coronary patency and avoids the higher bleeding risk associated with fibrinolysis. If a patient is referred to a non-PCI-capable hospital, and transfer to a PCI-capable hospital in order to perform PCI within 2 hours after the onset of symptoms is not possible, fibrinolytic therapy is recommended.

There are circumstances in which transfer to a PCI qualified hospital is recommended:

- Patients with contraindications for fibrinolysis, such as: active bleedings, recent surgery, past history of intracranial bleeding. [14]
- Patients with cardiogenic shock, severe heart failure and/or pulmonary oedema complicating the myocardial infarction. [15], [16]

Available data support the pre-hospital initiation of fibrinolytics if this reperfusion strategy is indicated. Fibrinolytics like streptokinase and rtPA stimulate the conversion of plasminogen to plasmin. Plasmin degrades fibrin which is an important constituent of the thrombus. Fibrinolytics are most effective the first hours after the onset of symptoms, and a benefit is observed in terms of reducing mortality within the first twelve hours. [17] The hazards of thrombolysis are increased bleeding risk, including hemorrhagic strokes. Because re occlusion after fibrinolysis is possible patients should be transferred if possible to a PCI qualified hospital once fibrinolysis is done. [18]

In rare cases, CABG is indicated, such as failed fibrinolysis with coronary anatomy unsuited for PCI and/or failed PCI, when the patient develops cardiogenic shock, life threatening ventricular arrhythmias, has three vessel disease, or mechanical complications of the MI. [19]

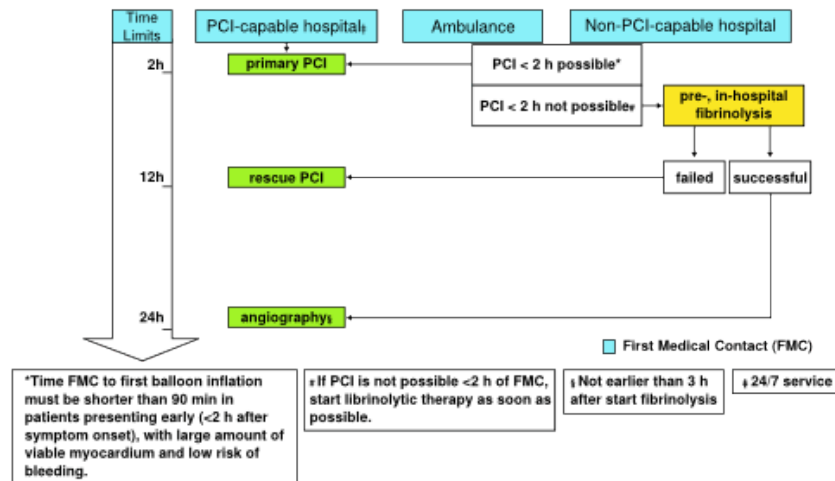


Figure 2 Reperfusion strategies. The thick arrow indicates the preferred strategy.

Figure 5.2.5: Reperfusion strategies. The thick arrow indicates the preferred strategy.

Non-ST-segment elevation Acute Coronary Syndrome

Comparable to STEMI, revascularization in NSTEMI-ACS relieves symptoms, shortens hospital stay, and improves prognosis. However, NSTEMI-ACS patients represent a heterogeneous population, and indication and timing of revascularization depend on many factors, including the baseline risk of the patient. According to current guidelines, depending on early risk stratification a choice has to be made between a routine invasive or a selective invasive (or “conservative strategy”) [20]

Early risk stratification is helpful to identify patients at high risk who might benefit the most from a more aggressive therapeutic approach in order to prevent further ischemic events. [21]

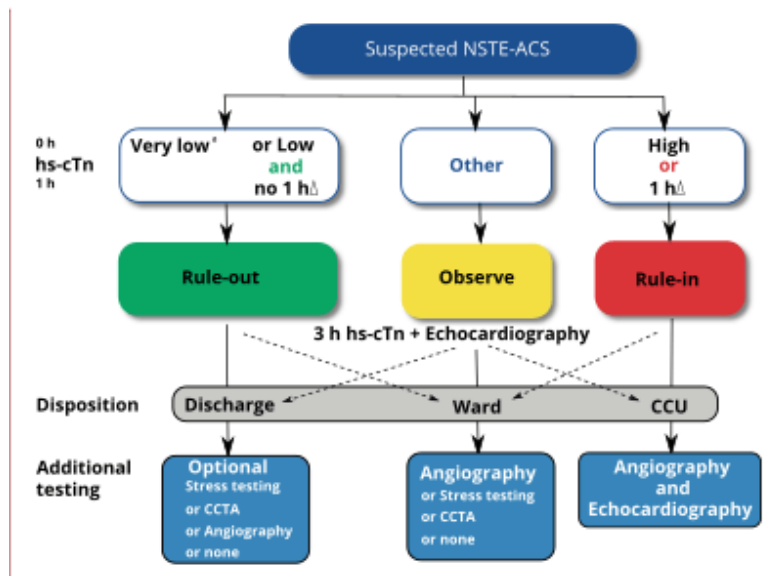


Figure 5.2.6

Early risk stratification can be performed using one of the validated risk scores, such as the GRACE risk score. GRACE calculates the probability of death while in hospital. The following characteristics are taken into account:

- Age
- Heart rate and systolic BP
- Creatinine
- Killip class
- Cardiac arrest at admission
- Elevated cardiac markers
- ST segment deviation

Regarding treatment strategies in NSTEMI-ACS, many randomized controlled trials (RCTs) and meta-analyses have assessed the effects of a routine invasive vs. conservative or selective invasive approach in the short and long term. Recent meta-analysis suggest a benefit of the routine invasive management that is mainly visible in intermediate- to high-risk patients.

Table 1: GRACE Risk Score Model

Risk Category	Low	Intermediate	High
NSTEMI Probability of Death In-hospital (%)	<1	1-3	>3
NSTEMI 6 Month Post-discharge Mortality	<3	3-8	>8
STEMI In-hospital Mortality (%)	<2	2-5	>5
STEMI 6 Month Post-discharge Mortality	<4.4	4.5-11	>11

Selective invasive (“or conservative”) management

Patients undergoing a selective invasive (“or conservative”) management are initially stabilized by medication only, including aspirin and clopidogrel orally and nitro-glycerin, heparin and a beta blocker intravenously. If the patients is unstable or has refractory angina, he/she is referred for coronary angiography. Patients stabilized on medical therapy should undergo a stress test before discharge. Potential advantages of this treatment strategy are a reduction of the number of catheterization procedures. A potential disadvantage is a prolonged stay in the hospital. Although meta-analyses suggest the superiority of a routine invasive management, trials in which the selective invasive strategy was characterized by high rates of revascularization show equivalence of the two strategies.

Routine invasive management

The routine invasive strategy consists of routine, early coronary angiography within 24 hours after admission and subsequent revascularization if appropriate by PCI or CABG based on the angiographic findings. The optimal timing of coronary angiography with an intended routine invasive management is debated. In patients with high risk features, including hypotension, ventricular arrhythmias or a large myocardial area at risk, should undergo urgent angiography (<2 hours).

Cardiac rehabilitation

Cardiac rehabilitation reduces mortality, helps the patient to regain confidence and to resocialise, and helps to reduce risk factors for atherosclerosis. Post-ACS patient should be referred for cardiac rehabilitation.

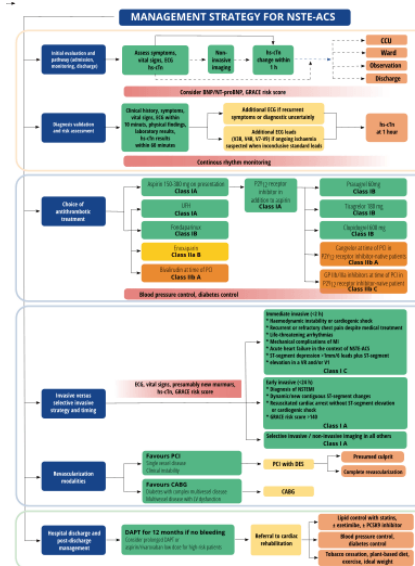


Figure 5.2.7

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5.3: Chronic Coronary Disease

Even though coronary disease mortality rates have declined since 1970, it is still the leading cause of death in many western countries and in an increasing number of non western countries. [1]

The reduction in mortality rates is the result of improved acute care and improved primary and secondary prevention. [2], [3]

The following risk factors for chronic coronary disease are modifiable and should be dealt with. [4]

Cigarette smoking

Damages the endothelium of the blood vessels potentially facilitating cholesterol adherence. Smoking is a reversible and therefore a leading preventable cause of coronary disease. All patients who smoke should be counselled to give up smoking. Nicotine replacement therapy and behavioural therapy can assist. [OR 2.87 for current vs never, PAR 35.7% for current and former vs never.] [4]

Hypertension

Is defined as a systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg. Patients with hypertension should be first treated with non pharmacologic therapies, including salt restriction, weight reduction in overweight/obese patients, and avoidance of excess alcohol intake. Antihypertensive drugs are indicated in patients with persistent hypertension despite non pharmacologic therapy. Most patients will require multiple antihypertensive drug therapies. [OR 1.91, PAR 17.9%] [4]

Cholesterol

Is the felon in the atherosclerosis tale and therefore cholesterol levels in the blood should be optimal, meaning low LDL levels and high HDL levels. Secondary causes of dyslipidemia should be excluded. The target level of LDL is 2,5 mmol/L in stable patients and 1.8 mmol/L in high risk patients, including post ACS patient. This can be achieved by the use of lipid lowering therapy particularly statins. [OR 3.25 for top vs lowest quintile, PAR 49.2% for top four quintiles vs lowest quintile] [4]

Exercise

Lowers morbidity and mortality from coronary disease. [OR 0.86, PAR 12.2%] [4] Patients should be encouraged to exercise 5 times a week during 30 minutes. Referral to fitness program may be useful.

Obesity

Is associated with several risk factors for coronary heart disease, including hypertension, high cholesterol and insulin resistance as well as diabetes. Data show a relationship of higher body weight with morbidity and mortality from coronary disease. All patients who are willing to lose weight should receive information about behaviour modification, diet, and increased physical activity. [OR 1.12 for top vs lowest tertile and 1.62 for middle vs lowest tertile, PAR 20.1% for top two tertiles vs lowest tertile] [4]

Healthy food choices

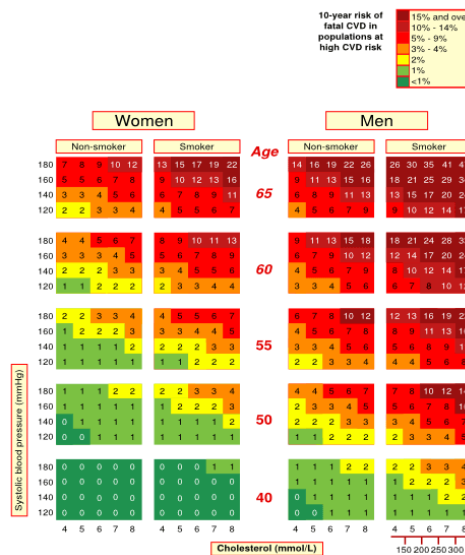
Potentially result in a lower risk of coronary disease. A healthy diet consists of high intake of fruit and vegetables, high fiber intake, a low glycemic index and load, unsaturated fat rather than saturated fat, a limited intake of red or processed meat and intake of omega 3 fatty acids. [OR 0.70, PAR 13.7% for lack of daily consumption of fruits and vegetables] [4]

Several studies have shown that people who have a high intake of fruit and vegetables have reduced risk coronary disease. It is possible that this is due to specific compounds in vegetables and fruits, or because people who eat more vegetables and fruits tend to eat less meat and saturated fat.

- In **diabetes mellitus** tight glycemic control is important to protect against many vascular complications, including coronary disease. [OR 2.37, PAR 9.9%] [4]
- A small amount of **alcohol** results in a lower risk of morbidity and mortality from coronary disease. Max. 3 units/day for men and 2 units/day for women. [OR 0.91, PAR 6.7%] [4]

Screening

Because extensive coronary disease can exist with minimal or no symptoms, screening for coronary disease has been suggested. Although screening results in identifying patients at increased risk there is no evidence that screening actually improves outcome. [5]



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6: VALVULAR DISEASE

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6.1: Epidemiology

Valvular heart diseases are a major burden to society and it is expected that the prevalence will increase.

Rheumatic valve disease used to be the most prevalent etiology of valvular cardiac diseases worldwide. Still, in developing countries, rheumatic heart disease remains the most common cause of valvular heart disease. Over the past 60 years, the etiology of most valvular heart diseases in industrialized countries shifted towards degenerative etiologies, mainly because of a decrease in acute rheumatic fever. However cardiac valve diseases remain common in industrialized countries, mainly because the decrease in rheumatic valve disease is compensated by an increase in degenerative valve disease, with an important contributing fact being the aging population of industrialized countries. The shift in pathologic etiology accounts for differences in patient characteristics and distribution of type of valvular lesions. [1]

In the US population, the national prevalence of moderate and severe valve disease determined by echocardiography was estimated at 2.5%. In another cohort, prevalence based on clinical signs and symptoms, confirmed by echocardiographic imaging, the estimated prevalence of at least moderate valvular disease was estimated at 1.8%. This difference indicates the under diagnosing of valvular heart disease, and illustrates the fact that diagnosis on the basis of clinical information alone is not reliable.[2] Prevalence did not change according to gender, but increased substantially with advancing age, with 13.2 % after the age of 75 years, versus <2% prior to 65 years old. The predominance of degenerative etiologies accounts for the higher prevalence in the elderly. The prevalence of degenerative valve disease is expected to rise with the aging population of Western countries.

Mitral regurgitation was found to be the most frequent valvular disease, with a prevalence of 1.7 %, followed by aortic regurgitation (0.5%), aortic stenosis (0.4%) and mitral stenosis (0.1%).

Mean age of patients presenting to the hospital in the Euro heart survey was 65 years.[3] In this survey, 63% of all cases of native valve disease were of degenerative etiology. Aortic stenosis was found to be the most frequent valvular disease of patients referred for treatment. In 22% of all patients etiology was rheumatic heart disease.

In developing countries, approximately 30 million cases of rheumatic fever occur annually, in general before the age of 20.[4] Approximately 60% of patients will develop rheumatic heart disease, which becomes clinically evident 1 to 3 decades later.[5] Rheumatic heart disease remains the most common cause of valvular heart disease in third world countries. In western countries, rheumatic heart disease is the second most common cause of valvular heart disease

6.2: Pathophysiology

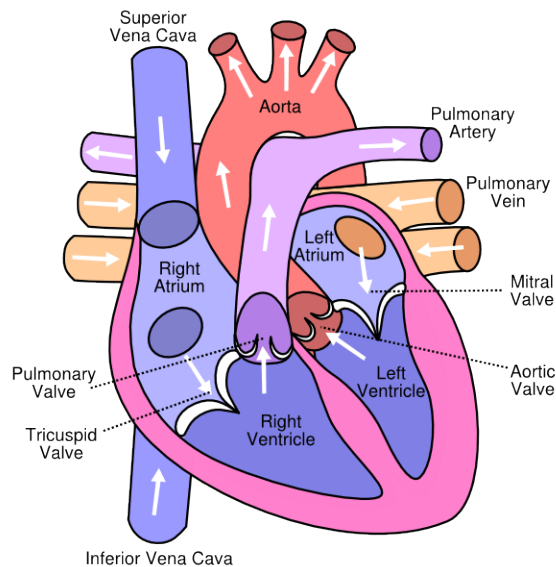


Figure 6.2.1: Diagram of the human heart.

Normal Valves

All cardiac valves have similar well defined interstitial cell layers, covered by endothelium. The three cell layers have specific features, and are named fibrose, spongiosa, and the ventricularis. During the cardiac cycle, the spongiosa rich in glycosaminoglycans, facilitates the relative rearrangements of collagenous and elastic layers. Valvular interstitial cells (VIC) are abundant in all layers of the cardiac valves and comprise a diverse, dynamic population of resident cells. Regulation of collagen and other matrix components is ensured by enzymes, synthesized by VICs. Integrity of valvular tissue is maintained by interaction of valvular endothelial cells (VECs) with VICs. Changes and remodeling of valvular interstitial and endothelium cell leads to changes in properties of the valve and potentially also valve function.

Aortic valve

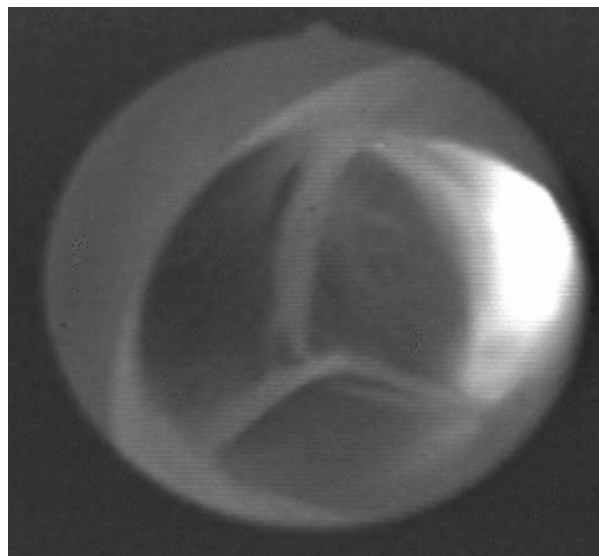


Figure 6.2.2: This animation shows the aortic valve of a pig's heart.

The tricuspid aortic valve separates the left ventricle outflow tract from the aorta. Behind the three semilunar shaped cusps of the aortic valve are dilated pockets of the aortic root, called sinuses of Valsalva. The right coronary sinus gives rise to the right coronary artery, the left coronary sinus gives rise to the left coronary artery. The commissures are the areas where attachments of two adjacent cusps to the aorta meet.

The commissure between the left and non coronary leaflets is positioned along the area of mitro-aortic continuity. The three cusps ascend towards the commissures and descend to the basal attachment with the aorta. Opening and closure of the aortic valve is a passive, pressure driven mechanism in contrast to the mitral valve. Tissue of the aortic cusps is stretched via backpressure in diastolic phase with elongation and stretching of elastin. In the systolic phase, recoil of elastin ensures relaxation and shortening of the cuspal tissue.[6] Optimal functioning of the valve requires perfect alignment of the three cusps.

Mitral Valve

The mitral valve was named after a Mitre, by Andreas Vesalius (*De Humani Corporis Fabrica*, 1543).[7] This active valve is located at the junction of the left atrium and left ventricle. The mitral valve apparatus contains five functional components; leaflets, annulus, chordae tendineae, papillary muscles and subadjacent myocardium. The annulus is a junctional zone of discontinuous fibrous and muscular tissue that joins the left atrium and ventricle. The anterior leaflet spans about one third of the primary fibrous, anterior part of the annulus. Part of the mitral valve anterior leaflet is in direct fibrous continuity with the aortic valve annulus, the mitro-aortic continuity. The posterior, ventricular leaflet is attached to the posterior predominantly muscular half to two third of the annulus. Due to the asymmetric leaflets, the mitral valve orifice has a funnel shape.

Chordae tendinae from both the anterior and posterior papillary muscles are attached to each leaflet. The papillary muscles contract and pull the chordae tendinae during systole, which closes the two mitral valve leaflets.

The mitral valvular complex comprises the mitral valve apparatus and left atrial and ventricular myocardium, endocardium and the mitro-aortic continuity. It contributes to the formation of the left ventricular outflow tract. The timed passage of blood through the valve as well as the tight closure during systole is facilitated by combined actions of the mitral valvular complex.[8]

Pulmonary Valve

The structure of the pulmonary valve is analogous to the aortic valve structure. The leaflets are semilunar shaped, with semilunar attachments. The pulmonary valve has no traditional annulus. Anatomically, three rings can be distinguished, superior at the sinotubular junction, at the musculoarterial junction and a third ring at the base of the sinuses.[9]

Tricuspid valve

The tricuspid valve is located at the junction between the right atrium and right ventricle. The tricuspid valve apparatus consists of 3 leaflets, chordae tendinae, an anterior, posterior and often a third papillary muscle. The peripheral ends of the septal, anterosuperior and inferior or mural leaflets are referred to as commissures. The tricuspid valve has no well defined collagenous annulus. The three leaflets are attached to a fibrous elliptic shaped annulus. The direct attachment of the septal leaflet is a distinctive feature of the tricuspid valve. The prominent papillary muscles support the leaflets at the commissures.

The anterior papillary muscle provides chords to the anterior and mural leaflets, the posterior papillary muscle provides chords to the mural and septal leaflets.

Normal valve function requires structural integrity and coordinated interactions among multiple anatomic components.[10] A variety of pathophysiologic mechanisms can cause cardiac valve disease.

Valvular stenosis, defined as inhibition of forward flow secondary to obstruction caused by failure of a valve to open completely, is almost always caused by a primary cuspal abnormality and a chronic disease process.

Valvular insufficiency, defined as reverse flow caused by failure of a valve to close completely, may result from either intrinsic disease of the valve cusps or from damage to or distortion of supporting structures without primary cuspal pathology.

Rheumatic valve disease

Chronic rheumatic valve disease is characterized by chronic, progressive deforming valvular disease. Anatomic lesions combine to varying degrees fibrous, or fibrocalcific distortion of leaflets or cusps, valve commissures and chordae tendineae, with or without annular or papillary muscle deformities.

Stenosis results from fibrous leaflet and chordal thickening and commissural and chordal fusion with or without secondary calcification. Fusion of a commissure in an open position can cause regurgitation, as well as scarring induced retraction of chordae and leaflets.

6.3: Aortic valve Stenosis

Obstruction of the left ventricle outflow can occur at subvalvular level (eg hypertrophic cardiomyopathy), supra-ventricular level or valvular level. Aortic valve stenosis is left ventricle outflow obstruction at valvular level.

In industrialized countries, aortic stenosis is the most common lesion among patients referred for treatment of valvular disease.[11] Age-related degenerative calcified aortic stenosis is the most common cause of aortic stenosis in adults in North America and Western Europe. The second most common cause is calcification of a congenitally bicuspid aortic valve. Other rare causes of calcified aortic stenosis include Fabry disease, lupus erythematosus, Paget disease, and ochronosis with alkaptonuria. The most common etiology of aortic stenosis worldwide remains rheumatic heart disease.

Prevalence of aortic valve abnormalities increases due to age-related pathology in the ageing population.

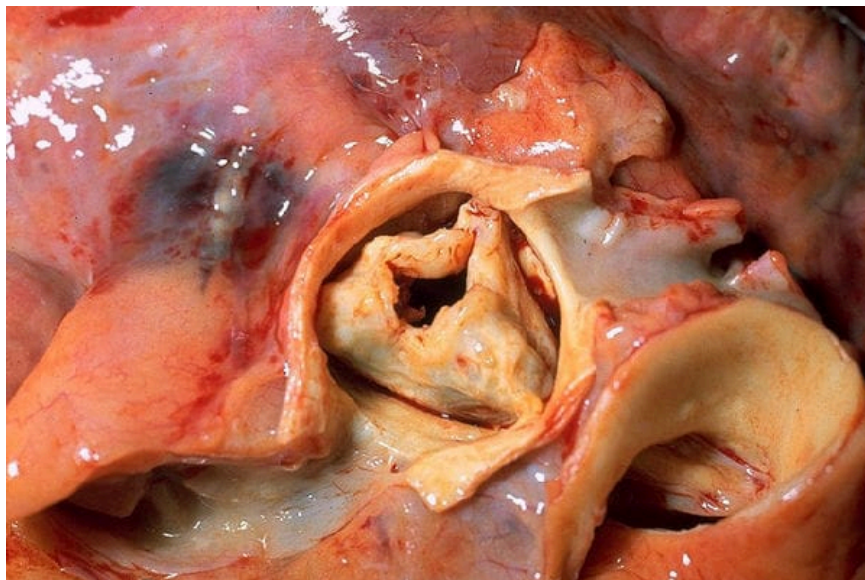


Figure 6.3.1: Gross pathology of rheumatic heart disease: aortic stenosis. Aorta has been removed to show thickened, fused aortic valve leaflets and opened coronary arteries from above. Autopsy, CDC/Dr. Edwin P. Ewing, Jr.

The first detectable macroscopic modifications of the calcification process is named aortic valve sclerosis. [6] Aortic sclerosis, seen as calcification or focal leaflet thickening with normal valve function, was detected in 25% of people at 65 years of age, this increases to 48% in people aged >75% in a population-based echocardiographic study.[12] [13]

The prevalence of calcified aortic stenosis is estimated at 2 % of people 65 years of age, increasing to 3-9% after the age of 80 years.[2][13]

Calcified degenerative aortic valve stenosis was previously considered to be the result of a passive degenerative process due to long-term mechanical stress in combination with calcium accumulation. Recently this concept is revised. Calcified degenerative aortic stenosis is considered an active pathobiological process, including proliferative and inflammatory changes, lipid accumulation, renin-angiotensin system activation, valvular interstitial cell transformation, ultimately resulting in calcification of the aortic valve.[14][15] [16] [17] Risk factors for development of calcific aortic stenosis are similar to those for vascular atherosclerosis such as diabetes, hypertension, and cholesterol levels.[18] [19] Progressive calcification leads to immobilization of the cusps causing stenosis.

Severity of outflow obstruction gradually increases in aortic valve stenosis. Left ventricular output is maintained by adaptation of the increasingly hypertrophic left ventricle. This compensational mechanism serves to normalize the left ventricle wall stress. Left ventricular hypertrophy in combination with the prolonged systolic phase of the cardiac cycle results in increased myocardial oxygen demand. The mismatch between oxygen demand and supply is the main mechanism for angina in aortic stenosis.

As the stenosis progresses, the left ventricle becomes less compliant with subsequent limited preload reserve. Eventually, the left

ventricle will decompensate with a decline in cardiac output and rise in pulmonary artery pressure.

Aortic stenosis is assessed by estimating the mean systolic pressure gradient and aortic valve area (AVA). The normal aortic valve area is 3-4 cm². Mild aortic stenosis is defined as an aortic valve area 1.5 cm², mean gradient less than 25 mm Hg, or jet velocity less than 3.0 m per second, moderate aortic stenosis as an area of 1.0 to 1.5 cm², mean gradient 25 to 40 mmHg, or jet velocity 3.0 to 4.0 m per second. A valve area of <1 cm², a mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second implies severe aortic stenosis. The valve area may decrease by as much as 0.12 ± 0.19 cm² per year.^[20] In late stages of severe aortic stenosis, cardiac output declines due to systolic dysfunction of the left ventricle, with a decline in the transvalvular gradient.

Table 6.3.1: Standard values associated with aortic stenosis at varying levels of severity.

Aortic stenosis severity	Valve area	Mean pressure gradient	Jet velocity
Mild	1.5 cm ²	less than 25 mmHg	less than 3.0 m per second
Moderate	1.0 to 1.5 cm ²	25 to 40 mmHg	3.0 to 4.0 m per second
Severe	less than 1.0 cm ²	greater than 40 mmHg	greater than 4.0 m per second

Clinical Presentation

Symptoms of degenerative aortic stenosis manifest with progression of the disease. The first symptoms usually commence in the seventh or eight decade. Symptoms are typically noted on exertion. Dyspnoea on exertion is the most common encountered first symptom. Other symptoms are angina, precipitated by exertion and relieved by rest, syncope and heart failure. The findings on physical examination vary with the severity of the disease. On auscultation, a systolic ejection crescendo-decrescendo murmur, radiating to the neck is audible, often accompanied by a thrill. An elevated left ventricular pressure in patients with aortic stenosis, in conjunction with mitral annulus calcifications predisposes to rupture of mitral chordae tendineae, which may produce a regurgitant systolic murmur.^{[21] [22]}

The first heart sound is usually normal or soft in patients with aortic stenosis. The second heart sound may be delayed due to prolongation of systolic ejection time. The S₂ also may be single because of superimposed aortic and pulmonic valve components, or the aortic valve component is absent or soft because the aortic valve is too calcified and has become immobile. If the aortic component is audible, this may give rise to a paradoxical splitting of S₂. A pronounced atrial contraction can give rise to a palpable and audible S₄.

When stroke volume and systolic pulse pressures fall in severe aortic stenosis, a pulsus parvus (small pulse) may be present. A wide pulse pressure is also characteristic of aortic stenosis. A pulsus parvus et tardus (the arterial pulse is slow to increase and has a reduced peak) can be appreciated by palpating the carotid pulse of patients with severe aortic stenosis. The stenotic valve decreases the amplitude and delays the timing of the carotid upstroke. Rigidity of the vasculature may hamper this sign in the elderly.

Diagnostic options

Chest Radiography

In aortic stenosis, cardiac silhouette and pulmonary vascular distribution are normal unless cardiac decompensation is present. Post-stenotic dilatation of the ascending aorta is frequent. Calcification of the valve is found in almost all adults with severe aortic stenosis; however, fluoroscopy may be necessary to detect it. A late feature in patients with aortic valve stenosis is cardiomegaly. In patients with heart failure, the heart is enlarged, with congestion of pulmonary vasculature.

Electrocardiography

In approximately 85% of patients with aortic stenosis, left ventricle hypertrophy, with or without repolarization abnormalities is seen on electrocardiography (ECG). Left atrial enlargement, left axis deviation and conduction disorders are also common. Atrial

fibrillation can be seen at late state and in older patients or those with hypertension.

Echocardiography

The best non-invasive diagnostic tool to confirm the diagnosis of aortic stenosis, assess the number of cusps and the annular size, is ultrasonic examination of the heart. Quantification of valvular calcification is possible. In 1998, the American college of cardiology/American Heart Association (ACC/AHA) task force [23] recommended the diagnostic use of echocardiography.

Echocardiographic imaging evaluates the severity and etiology of the primary valvular lesion, secondary lesions, and coexisting abnormalities. The size and function of the atria and ventricles can be evaluated as well as hemodynamic characteristics. Echocardiography is also performed for postprocedural evaluation of patients. Transthoracic echocardiography is recommended for re-evaluation of asymptomatic patients: every year for severe AS; every 1 to 2 years for moderate AS; and every 3 to 5 years for mild AS.[24]

To assess the severity of aortic stenosis, transvalvular gradients and maximum jet velocity is measured using Doppler echocardiography, and aortic valve area is calculated. The systolic gradient across the stenotic aortic valve depends on stroke volume, systolic ejection period, and systolic pressure in the ascending aorta. The stenotic valve area is inversely related to the square root of the mean systolic gradient. Due to their flow-dependency these measurements are most valuable in normotensive patients.

Valve thickening and calcification, as well as reduced leaflet motion can also be assessed using Doppler.

Computed tomography

Although the role of computed tomography (CT) in clinical management is currently not well defined, this imaging modality could improve assessment of the ascending aorta. CT has an established role in evaluating the presence and severity of aortic root and ascending aortic dilatation in patients with associated aortic aneurysms. The high sensitivity and specificity of CT in detecting high-grade coronary artery stenosis could be useful to preoperatively rule out coronary artery disease.

Both electron beam and multislice cardiac CT can be useful in quantifying valve calcification, which have been shown to correlate with echocardiographic assessment and clinical outcome. Prior to transcatheter aortic valve implantations, CT provides information concerning the aortic valve area, annulus size, and the distance between the aortic cusps and the coronary ostia.

Cardiac Magnetic Resonance Imaging

Cardiac MRI (CMR) has an established role in evaluating aortic root and ascending aorta anatomy. It can be used to measure the aortic valve area, but the role of CMR in the management of aortic stenosis is currently not well defined.

Cardiac Catheterization

Cardiac catheterization remains the gold standard to detect coronary artery disease. Currently, in patients with aortic stenosis, cardiac catheterization is most often performed to identify the presence of concomitant coronary artery disease (CAD). In patients with inconclusive noninvasive tests, hemodynamic abnormalities can be assessed by cardiac catheterization. Coronary angiography is recommended prior to aortic valve replacement.

Exercise Testing

Since aortic stenosis is a progressive disease, most common in the elderly population, many patients with aortic stenosis do not recognize gradually developing symptoms and cannot differentiate fatigue and dyspnea from aging and physical deconditioning. Lifestyle modification may mask symptoms. Although contraindicated in patients with severe aortic stenosis, Exercise testing is useful for risk stratification and eliciting symptoms. Under supervision, it is reasonable to propose exercise testing in patients >70 years who are still highly active.

Treatment

Medical Treatment

For many years the standard of care for patients with significant aortic valve stenosis has been to provide antibiotic prophylaxis against infective endocarditis. However, current AHA guidelines for prevention of infective endocarditis no longer recommend antibiotic prophylaxis for this group of patients. Exceptions are patients with a prior episode of endocarditis, patients with prosthetic valves or with additional complex cardiac lesions with a high risk for the development of endocarditis. Patients who have had rheumatic fever should still receive antibiotic prophylaxis against recurrences of rheumatic fever

No medical treatment has proven to delay the progression of aortic stenosis. Surgery is inevitable for symptomatic patients. Patients at prohibitive risk for intervention may benefit from medical treatment including digitalis, diuretics, ACE inhibitors, or angiotensin receptor blockers, if experiencing heart failure. Beta-blockers should be avoided in these circumstances.

Table 6.3.2: Current Guidelines for indications for aortic valve replacement

Class I	Class IIa	Class IIb	Class III
1. AVR is indicated for symptomatic patients with severe AS. (Level of Evidence: B) 2. AVR is indicated for patients with severe AS undergoing coronary artery bypass graft surgery (CABG). (Level of Evidence: C) 3. AVR is indicated for patients with severe AS undergoing surgery on the aorta or other heart valves. (Level of Evidence: C) 4. AVR is recommended for patients with severe AS and LV systolic dysfunction (ejection fraction less than 0.50). (Level of Evidence: C)	AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves (Level of Evidence: B)	1. AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension). (Level of Evidence: C) 2. AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset. (Level of Evidence: C) 3. AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate to severe valve calcification, that progression may be rapid. (Level of Evidence: C) 4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area less than 0.6 cm², mean gradient greater than 60mmHg, and jet velocity greater than 5.0 m per second) when the patient's expected operative mortality is 1.0% or less. (Level of Evidence: C)	AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the Class IIa/IIb recommendations. (Level of Evidence: B)

Surgery

The definitive treatment for aortic valve stenosis is aortic valve replacement.

The first cardiac valve surgery under direct vision was an aortic valve replacement, performed in 1960 by dr. Dwight Harken.^[25]

The aortic valve was replaced by a caged ball valve, which became the standard for aortic valve replacement.[26] [27]

A total of more than 70 different mechanical aortic valve models have been introduced in aortic valve replacement and implanted in humans in the past 5 decades. The mechanical prostheses can be divided into 3 large groups: the first generation of ball valves, second generation of tilting-disc valves, and the last generation of bileaflet valves.[28] Mechanical prostheses are extremely durable but require continuous use of anticoagulants.

Biological valves include homografts and autografts, as well as stented bioprostheses. Stented bioprostheses are constructed of porcine valves or bovine pericardium sewn onto an artificial stent. All heterograft valves are preserved with glutaraldehyde, to reduce the antigenicity of the tissue and prevent calcification. The fixation process can be performed at various pressures. Higher fixation pressures may lead to earlier calcification. First-generation bioprostheses were porcine valves, preserved with high-pressure fixation (60 to 80 mmHg) and placed in the annular position

Second-generation prostheses are of porcine or pericardial origin, and are treated with low- pressure (0.1 to 2 mmHg) or zero-pressure fixation. Several second-generation bioprostheses may be placed in the supra-annular position, which allows implantation of a slightly larger prosthesis. Third-generation prostheses are treated with zero- or low-pressure fixation and additional processes to reduce calcification.

In 1962 Donald Ross implanted the first aortic valve allograft. In 1967 he replaced a patient's malfunctioning aortic valve with the patient's own pulmonary valve. An aortic or pulmonary valve homograft was then used to replace the patient's pulmonary valve. This procedure is known as the Ross Procedure. Currently, the Ross procedure may be considered for bicuspid aortic valve stenosis, in particular for young women of reproductive age.

Transcatheter Intervention

In 2002, the first transcatheter aortic valve implantation was performed by Dr. Alain Cribier [29]. A transcatheter aortic valve implantation is a less invasive treatment option for patients at prohibitive risk for conventional aortic valve replacement. In this technique, the native valve is not excised. After balloon valvuloplasty, the prosthetic valve is implanted in the aortic position, with the frame of the prosthesis covering the native valve. The bioprosthesis can be implanted retrograde or antegrade. Currently 4 different approaches may be used in this technique: transfemoral, retrograde; transapical, antegrade; transaortic, retrograde; and transsubclavian, retrograde. Transcatheter aortic valve implantation is assessed in randomized clinical trials and registries.

Prognosis

Aortic valve stenosis has a severe prognosis when any symptoms are present, with survival rates of only 15–50% at 5 years. Strongest predictors of poor outcome in the elderly population are high New York Heart Association (NYHA) class (III/IV), associated mitral regurgitation and left ventricular dysfunction. Survival is only 30% at 3 years with the combination of these three factors.

6.4: Bicuspid Aortic valve

Bicuspid Aortic valve disease affects as many as 1-2% of the population, and is the most frequent congenital cardiovascular malformation in humans.[30] A bicuspid aortic valve may be part of a phenotypic continuum of congenital aortic valve disorders, associated with unicuspid valves, bicuspid valves, the normal tricuspid valves and the rare quadricuspid forms. Understanding of the pathogenesis of aortic valve malformation remains incomplete.

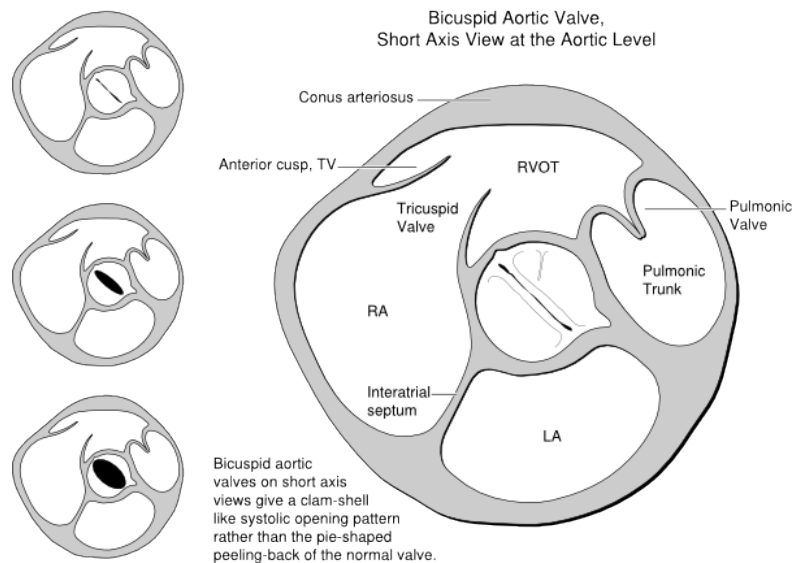


Figure 6.4.1: Heart bicuspid aortic valve anatomy by Patrick J. Lynch, medical illustrator, 2006

Bicuspid aortic valves are three to four times more common in men than in women. Bicuspid aortic valve disease results from abnormal cusp formation during valvulogenesis, but coexisting genetic abnormalities of the aorta and proximal coronary vasculature are often present. Moreover, nonvalvular findings occur in up to 50% of patients with bicuspid aortic valves. Associated findings are aortic dilation, aneurysms and dissection.

During valvulogenesis, adjacent cusps of the bicuspid valve fuse to form a single aberrant cusp. This fusion results in large leaflet, yet smaller than 2 normal cusps, with most often a central raphe or ridge. Fusion of the right coronary and noncoronary cusps is associated with cuspal pathology. Fusion of the right and left coronary cusps is associated with coarctation of the aorta.

Although endocarditis can be a devastating complication of bicuspid aortic valve disease, straightforward bicuspid aortic valve disease is no longer an indication for bacterial endocarditis prophylaxis according to the ACC/AHA practice guidelines. The risk of endocarditis is felt to be low in patients with straightforward bicuspid aortic valve disease. An exception to this recommendation is a patient with a prior history of endocarditis.[31]

Clinical Presentation

In infancy, bicuspid aortic valve disease is often asymptomatic. By adolescence an estimate 1 of 50 children born with these abnormalities will have clinically significant obstruction or regurgitation.[24]

Complications of bicuspid aortic valve disease are common in adulthood.[32] The abnormal shear stress leads to valve calcification and further aortic root dilation has been reported. [33] The most common complication is aortic stenosis, caused by premature fibrosis, stiffening, and calcium deposition. The majority of patients under 65 years of age with significant aortic valve stenosis have bicuspid aortic valve disease. A more rare complication of bicuspid aortic valve disease is aortic regurgitation. 15% of all cases of aortic regurgitation in the Euro Heart survey had bicuspid aortic valve disease. On auscultation, an ejection sound can be audible, best heard at the apex. There may be associated murmurs of aortic stenosis, incompetence, or coarctation of the aorta when these lesions are present.

Diagnostic Options

Echocardiography

Echocardiography is used to confirm the diagnosis of bicuspid aortic valve disease. Reported sensitivities and specificities of echocardiography for detecting BAV anatomy are 92% and 96% respectively. To establish the diagnosis, visualization of the aortic valve in systole in the short-axis view is essential. During diastole, the raphe can make the valve appear trileaflet. In the long-axis view, the valve often has an eccentric closure line and there is doming of the leaflets. Transesophageal echocardiography may improve visualization of the leaflets in case of inconclusive transthoracic echocardiography.

In all patients, serial transthoracic echocardiography should be performed to evaluate the valve and disease progression. Annual cardiac imaging is recommended for patients with significant valve lesions or with aortic root diameters >40 mm. Complete imaging of the thoracic aorta should be performed periodically for surveillance.^[34]

Cardiac Magnetic Resonance Imaging and Computed Tomography

The thoracic aorta is visualized by alternative imaging modalities such as cardiac magnetic resonance imaging (MRI) or computer tomography (CT). Both cardiac MRI and CT images can help to confirm the bicuspid anatomy of the aortic valve.

Treatment

Medical treatment

In patients with bicuspid aortic valve disease, high blood pressure should be treated aggressively. The ACC/AHA guidelines for the management of adult congenital heart disease and guidelines for the management of patients with valvular heart disease suggest that it is reasonable to use beta-blockers in this population (Class IIa recommendation).^[35] This is in accordance with the standard of care at many centers to slow the progression in Marfan-associated aortopathy.

Surgery

Indications for surgery are similar to indications for patients with “degenerative aortic valve disease”; intervention is indicated for severe valvular dysfunction, symptomatic patients, and patients with evidence of abnormal left ventricular dimensions and function.

In children and young adults, the bicuspid valve is not calcified and balloon valvuloplasty is recommended. A prosthetic valve implantation would be suboptimal due to the continuing growth of the child.

Indications for valvuloplasty in children include peak-to-peak gradients >50 mm Hg with ST- or T-wave changes at rest or with exercise. Valvuloplasty is also indicated for symptomatic children with peak-to-peak gradients >60 mm Hg. ^[35]

Surgical options for adult bicuspid aortic valve disease include valve replacement (bioprosthetic or mechanical valves), Ross procedure or valve repair (for those with aortic incompetence) Surgical aortic valve replacement is the most common procedure in adults with bicuspid aortic valve disease, for either aortic valve stenosis or regurgitation. Indications of interventions are similar to those described for tricuspid aortic valve disease in the ACC/AHA guidelines for the management of patients with valvular heart disease.^[33]

Approximately 30% of adults with bicuspid aortic valve disease undergoing aortic valve replacement will need aortic root surgery. Surgical attention for dimensions of the aortic root is essential because of the risk for further root dilation. The ascending aorta in patients with bicuspid aortic valve disease increases 0.2 to 1.2 mm/year.^[36]

Guidelines suggest that changes in root size more than 0.5 cm/year are an indication for root replacement. Aortic root dimensions of 5.0 cm require intervention and aortic root dimensions of 4.5 cm require intervention if surgery is performed for valvular indications according to current guidelines.

Prognosis

Life expectancy in adult patients with bicuspid aortic valve disease is not shortened when compared to the general population. 10-year survival in asymptomatic adults with bicuspid aortic valve disease with a spectrum of valve function, was 96%.[32] In asymptomatic adults with bicuspid aortic valve disease without significant valve dysfunction the 20-year survival was 90%.[37]

6.5: Aortic Regurgitation

A variety of etiologies can cause aortic regurgitation by preventing proper coaptation of the aortic valve leaflets with a subsequent diastolic reflux of blood from the aorta into the left ventricle. Etiology of aortic regurgitation can be primary valvular, or it can be primarily caused by aortic root or disease.

The origin of primary valve disease may be calcific aortic disease, idiopathic degenerative disease, endocarditis, rheumatic disease, a bicuspid aortic valve, or myxomatous proliferation of valvular tissue. In the majority of patients the disease is caused by rheumatic disease. However, in Western countries the disease is most often of degenerative origin. In the Euro Heart Survey degenerative aortic regurgitation accounted for approximately half of the cases of aortic regurgitation, 15% of cases had a bicuspid aortic valve.^[11] Accelerated degeneration of valve leaflets, resulting in regurgitation similar to carcinoid syndrome related regurgitation, can be caused by certain anorectic medications, such as fenfluramine and phentermine.^[22]

Aortic annulus dilation, without primary involvement of the leaflets may result in aortic regurgitation due to leaflet separation. Aortic regurgitation of primary aortic root or annulus aetiology includes idiopathic aortic root dilatation, aortic dissection, trauma, and chronic severe systemic hypertension. Aortitis represents less than 5% of the aetiologies of aortic regurgitation and may be due to inflammatory disease, such as giant cell, Takayasu and Behcet syndrome. Syphilis and ankylosing spondylitis may affect the aortic valve, but may also be associated with aortic dilatation. Other systemic arteritides and connective tissue disorders such as Marfan syndrome, Reiter disease, Ehlers-Danlos syndrome, osteogenesis imperfecta, and rheumatoid arthritis can lead to annular dilatation and valvular insufficiency. In patients without generalized tissue disease the same pattern of ascending aortic enlargement is known as annuloaortic ectasia. Chronic aortic regurgitation itself may lead to progressive aortic root dilatation.

Aortic valve regurgitation is often accompanied by other valvular abnormalities. Aortic valvular insufficiency is most commonly seen in combination with aortic stenosis. Aortic insufficiency due to rheumatic aetiology is often associated with mitral valve disease. The valve leaflets are retracted by fused commissures and by fibrotic scarring of the leaflets itself.

Aortic cusp prolapse can be isolated, or due to myxomatous degeneration, sometimes with associated mitral or tricuspid valve involvement. In 15% of patients with ventricular septum defect, prolapse of an aortic cusp leads to aortic insufficiency.

Isolated aortic regurgitation is often caused by a primary aortic annular etiology. Rheumatic origin is much less common in patients with pure aortic regurgitation. In approximately 10% of cases, aortic regurgitation results from infective endocarditis, with perforation or erosion of leaflets.

It is of considerable clinical importance to distinguish between acute aortic regurgitation and chronic regurgitation since acute aortic regurgitation can be life-threatening if not treated immediately, in contrast to chronic regurgitation which can be tolerated for years.

Pathophysiology

In patients with aortic insufficiency the regurgitating volume increases the total stroke volume. This volume might equal the effective forward stroke volume in patients with severe aortic regurgitation. In chronic aortic regurgitation, several compensatory mechanisms ensure cardiac output.

Acute aortic regurgitation

Acute aortic regurgitation is a sudden hemodynamically significant aortic incompetence, which can often be catastrophic. An increase in left ventricular end diastolic volume with absence of ventricular remodeling may lead to elevated left atrial and pulmonary artery wedge pressure and decreased effective cardiac output, with compensatory tachycardia to maintain sufficient output.

Acute severe aortic regurgitation typically occurs with infective endocarditis, trauma, and aortic dissection. The left ventricle cannot dilate sufficiently. The patient may present with chest pain due to increased myocardial oxygen consumption combined with decreased coronary blood flow from changes in diastolic perfusion. Coronary blood flow in acute aortic insufficiency occurs during systolic cardiac phase. Other symptoms of acute aortic regurgitation are tachypnea, tachycardia and rapidly progressive pulmonary edema and/or cardiogenic shock.

Chronic Aortic regurgitation

Aortic root dilatation, annular dilation and congenital bicuspid valve are, in developed countries, the most common causes of severe chronic aortic valve regurgitation.

The slow process of chronic aortic regurgitation allows adaptation of the ventricle to the increased preload and afterload. The left ventricular compensates to the regurgitant flow, the increased volume and pressure by enlargement. The left ventricle end diastolic pressure remains relatively low and does not approach the aortic diastolic pressure. The additional stroke volume is responsible for increased systolic pressure and eventually the wide pulse pressure. The systolic hypertension further increases left ventricle afterload.

In contrast to the compensatory mechanism in mitral valve regurgitation, a modest concentric left ventricular hypertrophy accompanies the eccentric hypertrophy, with a normal mass-to-volume ratio.[38] In a chronic state, progressive left ventricle dilatation leads to pre- and afterload mismatch. With gradually decompensation and deterioration of systolic function, the ventricle is not able to sustain perfusion.

Table 6.5.1: Causes of aortic regurgitation

Causes of Aortic Regurgitation
Aortic root/annular dilation
Congenital bicuspid valve
Previous infective endocarditis
Rheumatic
In association with other diseases

Clinical Presentation

Patients with aortic regurgitation typically present with symptoms of left sided heart failure including dyspnea on exertion, orthopnea, fatigue, and occasionally paroxysmal nocturnal dyspnea. Angina is less common in patients with aortic regurgitation compared to aortic stenosis. The reduced aortic diastolic blood pressure reduces the coronary blood flow, resulting in angina. The same mechanism is presumed to cause syncope.

Diagnostics

Chest Radiography

Chest Radiography in acute aortic regurgitation reveals minimal cardiac enlargement, with normal aortic root and arch. In acute aortic regurgitation, signs of left heart failure are frequent. Cardiomegaly with left ventricular enlargement is the main feature on chest radiography in chronic aorta regurgitation. The ascending aorta may be enlarged in case of an aortic aneurysm or aortic dissection but Chest X-ray is not a sensitive examination to detect ascending aortic aneurysm.

Pulmonary congestion is noted at advanced stages of chronic AR, when heart failure has developed.

Electrocardiography

Electrocardiography in patients with aortic regurgitation may be normal early in the disease. Left ventricular hypertrophy is the main feature of aortic regurgitation, with or without associated repolarization abnormalities. Left axis deviation may be present.

Echocardiography

Echocardiography is used to evaluate the anatomy of the aortic valve and other valves, as well as aortic leaflets and the aortic root.

The regurgitation mechanism and etiology can be assessed. Three types of mechanisms can be identified; enlargement of aortic root with normal cusps, cusp prolapse or fenestration and poor cusp tissue quality or quantity. Doppler is used for quantifying the aortic regurgitation by the width of regurgitant jet and its extension into the LV, the rate of decline of aortic regurgitant flow and diastolic flow reversal in the descending aorta.

Severe aortic regurgitation is defined as effective regurgitant orifice (ERO) area of $>0.30\text{cm}^2$, regurgitant volume $>60\text{mL}$, or a regurgitant fraction of $>50\%$

Preoperatively transoesophageal echocardiography is performed to more accurately evaluate the anatomy and mechanism of the aortic valve regurgitation.

Treatment

The only direct method to reduce aortic regurgitation is surgical treatment. However, some patients may benefit from medical treatment.

Medical treatment

The relative reduction of myocardial blood supply due to increased demand and/or associated obstructive coronary artery disease may cause angina. Angina may be treated by reducing aortic regurgitation, reduction of myocardial demand or revascularization of the myocardium. Clinical heart failure is treated with traditional therapy, including digitalis, diuretics, and ACEI. In severe heart failure, parenteral inotropic and vasodilator therapy may be needed.

Table 6.5.2: Current guidelines for medical treatment of aortic regurgitation.

Class I	Class IIa	Class IIb	Class III
Vasodilator therapy is indicated for chronic therapy in patients with severe AR who have symptoms or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors. (Level of Evidence: B)	Vasodilator therapy is reasonable for short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction before proceeding with AVR. (Level of Evidence: C)	Vasodilator therapy may be considered for long-term therapy in asymptomatic patients with severe AR who have LV dilatation but normal systolic function. (Level of Evidence: B)	1. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with mild to moderate AR and normal LV systolic function. (Level of Evidence: B) 2. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for AVR. (Level of Evidence: C) 3. Vasodilator therapy is not indicated for long-term therapy in symptomatic patients with either normal LV function or mild to moderate LV systolic dysfunction who are otherwise candidates for AVR. (Level of Evidence: C)

Surgical treatment

Surgical treatment in case of isolated Aortic valve regurgitation is aortic valve replacement. Aortic valve replacement is indicated

in all symptomatic patients with severe Aortic regurgitation and in all asymptomatic patients with severe Aortic regurgitation with left ventricular ejection fraction (LVEF) <50% or left ventricular dilatation (end-diastolic diameter >75 mm or end-systolic diameter >55 mm).

When an aneurysm of the aortic root is associated with severe aortic regurgitation a Bentall procedure can be indicated. The ascending aorta is replaced by a composite graft comprising an aortic prosthesis, with re-implantation of the coronary arteries. When aortic enlargement is localized in the supra-coronary part of ascending aorta, replacing the supra-coronary section of the ascending aorta may be sufficient which is considered technically easier.

Although the prosthetic valve replacement remains the standard for aortic valve regurgitation, aortic valve repair procedures are performed with a combination of different surgical techniques. The quality of the cusps is essential for repair. The annulus and sinotubular junction can be surgically readapted to the cusps, eliminating the regurgitation.

Table 6.5.3: Current guidelines for surgical treatment of aortic regurgitation.

Class I	Class IIb
1. An adolescent or young adult with chronic severe AR* with onset of symptoms of angina, syncope, or dyspnea on exertion should receive aortic valve repair or replacement. (Level of Evidence: C) 2. Asymptomatic adolescent or young adult patients with chronic severe AR* with LV systolic dysfunction (ejection fraction less than 0.50) on serial studies 1 to 3 months apart should receive aortic valve repair or replacement. (Level of Evidence: C) 3. Asymptomatic adolescent or young adult patients with chronic severe AR* with progressive LV enlargement (end-diastolic dimension greater than 4 standard deviations above normal) should receive aortic valve repair or replacement. (Level of Evidence: C) 4. Coronary angiography is recommended before AVR in adolescent or young adult patients with AR in whom a pulmonary autograft (Ross operation) is contemplated when the origin of the coronary arteries has not been identified by noninvasive techniques. (Level of Evidence: C)	1. An asymptomatic adolescent with chronic severe AR* with moderate AS (peak LV-to-peak aortic gradient greater than 40 mm Hg at cardiac catheterization) may be considered for aortic valve repair or replacement. (Level of Evidence: C) 2. An asymptomatic adolescent with chronic severe AR* with onset of ST depression or T-wave inversion over the left precordium on ECG at rest may be considered for aortic valve repair or replacement. (Level of Evidence: C)

6.6: Mitral Stenosis

Etiology and Pathology

The leading cause of mitral stenosis is rheumatic fever, causing post-rheumatic deformities. Other rare etiologies of left atrial outflow obstruction include congenital and degenerative mitral valve stenosis, severe mitral annular and/or leaflet calcification, carcinoid disease, neoplasm, left atrial thrombus, infective endocarditis with large vegetations, certain inherited metabolic disorders such as Fabry's disease, mucopolysaccharidosis, Whipple's disease, gout, rheumatic arthritis, lupus erythematosus, methysergide therapy, and cases related to previous implanted prosthesis or commisurotomy.

Rheumatic valvular disease causes diffuse thickening of the valve leaflets by fibrous, or fibrocalcific distortion, with fusion of one or more commissures, valve commissures, and fusion and shortening of the subvalvular apparatus. This combined with increasingly rigid cusps results in narrowing of the valve.

The area of the normal mitral valve orifice is 4-6 cm². In patients with mitral stenosis, when the valve area approaches 2 cm² or less, an early, mid and late diastolic transvalvular gradient is present between the left atrium and ventricle. With progressive mitral stenosis, transvalvular pressure gradient increases. Mitral transvalvular flow depends on cardiac output and heart rate. Shortening of diastolic phase in increased heart rate causes symptoms by reducing forward cardiac output. Mitral stenosis develops gradually, and may be asymptomatic for years.

Clinical Presentation

Patients with mitral stenosis may be asymptomatic for years. Mean age of presentation of symptoms is fifty to sixty years old. The presenting symptom in patients with mild mitral stenosis is typically dyspnea precipitated by stress or atrial fibrillation. Progression of disease with increasing left atrial and pulmonary venous pressures will cause progressive dyspnea. At advanced stage, patients are often thin and frail and complain of weakness and fatigue due to low cardiac output. When pulmonary hypertension and right ventricular failure develop, signs of tricuspid regurgitation, abdominal discomfort due to hepatomegaly and ascites can be present.

On physical examination, heart size is usually normal. An apical diastolic thrill can be palpated. A holodiastolic murmur can be auscultated at the apex with a presystolic accentuation in sinus rhythm. The intensity of this murmur is determined by the transmitral gradient. In patients with severe stenosis, calcified leaflets, or low cardiac output no diastolic murmur may be audible. An opening snap may be present due to sudden tensing of the pliable leaflets during opening. S₁ may be loud when the mitral leaflets are pliable. Thickening and calcification will diminish S₁ in more advanced stages. With pulmonary hypertension, S₂ becomes prominent and a murmur of tricuspid regurgitation located at the xyphoid can be present. In severe mitral valve stenosis with pulmonary hypertension, pulmonary rales are audible. Intermittent malar flushes, jugular distension, and peripheral cyanosis may be present.

Diagnostics

Chest Radiography

Signs of left atrial enlargement are often the earliest changes on chest radiography.

Straightening of the left heart border by prominent pulmonary arteries coupled with left atrial enlargement can be observed as well as a double contour of the left atrium and elevation of the left main stem bronchus. Distension of the pulmonary arteries and veins in the upper lung fields and pleural effusions indicate elevated pulmonary pressures. Kerley B lines may be observed in severe mitral stenosis.

Electrocardiography

Electrocardiography is in many cases normal and cannot assess the severity of mitral stenosis accurately. Atrial arrhythmias are

more common in patients with advanced mitral stenosis. In sinus rhythm signs of left atrial enlargement may be present with a prolonged P wave and a negative deflection in lead V1 and left axial deviation of P wave. Signs of right ventricular hypertrophy with right-axis deviation, a tall R wave in V1, and secondary ST-T-wave changes may be present in cases of severe pulmonary hypertension

Echocardiography

The primary diagnostic method for assessing mitral valve pathology and pathophysiology is echocardiography. The severity and consequences of the mitral stenosis can be evaluated. The valvular anatomy and morphology including valve thickening, mobility, calcification, subvalvular deformity and anatomic lesions can be assessed

Rheumatic mitral stenosis can cause reduced diastolic excursion of the leaflets and thickening or calcification of the valvular and subvalvular apparatus. Doppler is used to determine the peak and mean transvalvular pressure gradients. The valve area can be measured accurately by three-dimensional echocardiogram. Transesophageal echocardiography is able to provide more detailed information of the mitral valvular pathology than transthoracic echocardiography.

Cardiac Catheterization

Cardiac catheterization can provide information regarding coronary artery status. This diagnostic tool is not necessary to establish the diagnosis of mitral stenosis.

Prognosis

The progression of mitral stenosis ranges from 0.1–0.3cm²/year.[39] Survival rates of 80% at 10 years have been reported with asymptomatic mitral valve stenosis. Once symptoms develop related to pulmonary hypertension 10-year survival is 0–15%. Progressive heart failure is the most common cause death in the untreated patients with mitral stenosis.

Treatment

Medical treatment

No medical treatments will relieve mitral stenosis. Dyspnea may be transiently relieved by diuretics or long acting nitrates. In order to slow the heart rate, Beta-blockers or calcium-channel blockers can be prescribed. Patients with atrial fibrillation should be on anticoagulants with a target INR of 2-3. In patients with severe mitral stenosis, cardioversion should not be performed prior to intervention since it does not durably restore sinus rhythm. After successful intervention cardioversion is indicated if atrial fibrillation is of recent onset and the left atrium only moderately enlarged.

Percutaneous mitral commissurotomy

Mitral stenosis can be relieved by percutaneous mitral commissurotomy. This procedure was introduced in 1980 and used worldwide ever since [40][41]. The results of balloon valvotomy are comparable to open commissurotomy.[42]

The commissural splitting of percutaneous mitral commissurotomy substantially increases the valvular area. Pulmonary pressures decrease immediately. Procedural mortality has been reported 0–3%. In 2-10% leaflet tearing results in severe mitral regurgitation. Preprocedural condition of the patients and the experience of the operator and operating team are of major influence on the complication rate of percutaneous mitral commissurotomy. Long-term results of a successful procedure have been reported with event-free survival ranges from 35–70% after 10–15 years.

Surgical intervention

Open commissurotomy or valve replacement is indicated if balloon valvotomy is unfeasible.

The concept of surgical repair of the mitral valve was first introduced in 1902 by Sir Thomas Lauder Brunton, a Scottish physician.(Brunton L, Edin MD: Preliminary note on the possibility of treating mitral stenosis by surgical methods. Lancet 1902; 1:352

[43]). The first successful mitral valve operation was a transventricular commissurotomy by Elliot Cutler in 1923. The following transventricular valvulotomies performed with the cardiovalvulotome resulted in regurgitation and Cutler abandoned the procedure.

In 1948, Dwight Harken reported his series of patients with mitral stenosis successfully treated with a valvuloplasty procedure.[44]

After development of cardiopulmonary bypass, the closed commissurotomy has been replaced by an open mitral commissurotomy. This allows not only correction of commissural fusion, but also chordal and papillary fusion.

Surgical intervention can improve the functional capacity and long-term survival of patients with mitral stenosis substantially. Survival rates of 96% and freedom from valve-related complications of 92% at 15 years have been reported.[45] Surgery should be performed before New York Heart Association (NYHA) class III symptoms are present.

6.7: Mitral regurgitation

Mitral valve regurgitation results from inadequate mitral leaflet coaptation during systole. This allows the systolic regurgitation of blood from the high-pressure LV to the normally low-pressure LA. The regurgitating volume depends on both the size of the regurgitant orifice and the pressure gradient between the left ventricle and the left atrium. In primary mitral regurgitation, inadequate mitral leaflet coaptation results from an abnormality in any of the functional components of the mitral apparatus. Secondary or functional mitral regurgitation results from left ventricle disease and remodeling.

During systole, combined papillary muscle contraction and contraction of the dynamic annulus promote leaflet coaptation. Calcification of the annulus may hinder the sphincter-like contraction of the annulus allowing regurgitation. Secondary mitral regurgitation due to annulus dilation may be caused by ischemic or dilated cardiomyopathy. The regurgitant volume causes left ventricular enlargement and contractile dysfunction. Left ventricle dilation may cause enlargement of the mitral annulus and the regurgitant orifice, increasing the mitral regurgitation. Positive inotropes, diuretics and vasodilators reduce the size of the left ventricle and the regurgitant orifice, and decrease the regurgitant flow.

Etiology

Three different types of primary mitral regurgitation can be defined; leaflet retraction from fibrosis and calcification, annular dilatation and chordal abnormalities (including rupture, elongation, or shortening). Functional mitral regurgitation results from LV dysfunction with or without annular dilation. Mitral regurgitation was classified by Carpentier into three types based on leaflet and chordal motion: normal leaflet motion (type I), leaflet prolapse or excessive motion (type II), and restricted leaflet motion (type III).[46]

Chronic Mitral Valve Regurgitation

Degenerative mitral valve disease is the most common cause of mitral regurgitation in Europe.

Myxomatous mitral valve degeneration is also known as floppy mitral valve or mitral valve prolapse. Prolapse is defined as excursion of one or both leaflets above the plane of the annulus during systole.[47] Prolapse of the middle portion of the posterior leaflet is the most common finding in degenerative MR.[48]

Mitral regurgitation in Barlow syndrome or parachute mitral valve is due to annular dilatation and extensive hooding of leaflets with large amounts of excessive leaflet tissue. In mitral regurgitation, the mass-to-volume ratio of the enlarged, thin walled left ventricle is less than one.[38]

Clinical Presentation

Patients with mild to moderate compensated chronic mitral regurgitation may remain asymptomatic for many years. The adapted left ventricle maintains normal forward cardiac output. The left ventricle ejection fraction in chronic mitral regurgitation may be greater than normal due to the compensatory cardiac adaptations. Progression of severity depends on etiology of regurgitation; in patients with connective tissue disease regurgitation tends to progress more rapidly than patients with mitral valve prolapse or rheumatic mitral regurgitation. Progression in acute rheumatic fever is often rapid. Acute progression may be caused by endocarditis or chordae rupture.

Gradual progression and eventually decompensation results in decreased cardiac output with physical activity and pulmonary congestion. Patients present with weakness, fatigue, palpitations, dyspnea on exertion. Hepatomegaly, peripheral edema and ascites due to right sided heart failure can be associated with rapid clinical deterioration.

Acute mitral regurgitation is associated with sudden pulmonary congestion and edema.

On physical examination the apical impulse is displaced laterally, indicating left ventricular enlargement. S1 is normal or diminished. S2 may be single, closely split, normally split, or even widely split as a consequence of the reduced resistance to LV ejection. A widely split S2 is often audible, due to shortening of LV systole and early closure of the aortic valve. The P2 component of the second heart sound may be increased if pulmonary hypertension has developed. The apical systolic murmur is typically

holosystolic and radiates to the axilla, depending on the direction of the regurgitant jet. It can be blowing, moderately harsh, or even soft. An S3 gallop often is present, reflecting the transmitral diastolic flow during the rapid filling phase.

Early in the disease process of patients with Barlow syndrome, a characteristic midsystolic click can be appreciated, followed by a late systolic murmur; with disease progression the murmur becomes holosystolic, and the midsystolic click may become inaudible.[46]

Acute Mitral Valve Regurgitation

Immediate intervention is often necessary in acute mitral regurgitation. Etiology can be organic or functional. Organic causes include rupture of a major chorda tendinea (in myxomatous mitral valve disease) or papillary muscle (due to myocardial infarction), leaflet perforation (of endocarditic origin), and dysfunction of a prosthetic valve due to endocarditis or paravalvular regurgitation. Regurgitation of functional etiology results from left ventricular abnormalities such as dyskinetic wall due to ischemia or dilated ventricle due to cardiomyopathy.

Acute mitral regurgitation is associated with dyspnea and orthopnea, caused by sudden pulmonary congestion and edema. Acute papillary muscle rupture may mimic the presentation of a patient with a postinfarction ventricular septal defect.[49]

On physical examination no signs of cardiac compensatory mechanisms are present. The increase in left atrial pressure diminishes the pressure gradient between the left ventricle and left atrium by midsystole. The murmur of mitral regurgitation is shortened and of decreased intensity, it may be soft, short of even inaudible. An S3 gallop usually is present. The volume overload is increasing the severity of MR over time, and leads to a greater percentage of the LV stroke volume being ejected in a retrograde fashion.

Diagnostic Options

Chest Radiography

In chronic mitral regurgitation chest radiography demonstrates enlargement of the left ventricle and atrium. The mitral annulus may be calcified. In acute mitral regurgitation, no adaptive left atrium or ventricle enlargement has developed. Signs of interstitial or alveolar pulmonary edema may be present.

Electrocardiography

Signs of left ventricular hypertrophy and left atrial enlargement due to chronic volume overload may be seen on the electrocardiogram. Atrial fibrillation is a common finding late in the natural history of the disease. Q-waves may be seen in ischemic mitral regurgitation. In patients with acute mitral regurgitation, left atrial and ventricular enlargement may not be evident and the electrocardiogram may be normal or show only nonspecific findings. The resting electrocardiogram of patients with asymptomatic mitral valve prolapse is normal. A variety of ST-T-wave changes, including T-wave inversion and sometimes ST-segment depression, particularly in the inferior leads, can be found in patients with symptomatic mitral valve prolapse.

Echocardiography

Mitral valve pathology and pathophysiology is primary assessed by echocardiography. Left atrial and ventricular dimensions can be quantified. The etiology and mechanism of mitral regurgitation can be identified by echocardiography. Leaflet abnormalities and chordal morphology and function is assessed by echocardiography. Fused subvalvular apparatus due to rheumatic valvulitis and leaflet destruction due to endocarditis can be visualized by echocardiography. Myxoid degeneration of the mitral valve is characterized by an excess of tissue and by leaflets of more than 5mm thickness. Annular dilatation is characterized by a ratio of >1.3 anterior-posterior diameter of the annulus to the length of the anterior leaflet in diastole. The regurgitation caused by annular dilatation and incomplete leaflet coaptation is directed straight back into the left atrium.

In ischemic MR, the apical displacement of the leaflets can be quantified by measuring the tenting area and the leaflet opening angles.

Color doppler analysis can be used to grade the severity of the regurgitation and permits visualization of the origin, extent,

direction, duration, and velocity of disturbed backward flow of the regurgitant leak or leaks into the left atrium.[46] MR is considered severe when the jet area is $>10\text{cm}^2$ or $>40\%$ of the left atrial area.

Cardiac Catheterization

Coronary ischemic causes of mitral regurgitation can be identified by cardiac catheterization.

Treatment

Surgical

The hemodynamic overload on the heart caused by mitral regurgitation can ultimately only be corrected by surgically restoring valve competence. For all valve surgery timing of surgery is essential. Irreversible left ventricular dysfunction will result in suboptimal results indelayed surgery. Due to the operative risk and risk of valve prosthesis surgery should however be delayed as long as possible

Mitral valve regurgitation is surgically corrected by mitral valve replacement or repair. Mitral valve repair is generally found to be superior to replacement, with preservation of left ventricular function and part of the mitral valve apparatus [50] [51] [52] [53] and without the use of a prosthesis. In mitral valve regurgitation indication for valve surgery is influenced by symptomatic status, ventricular functional status, and the procedure to be performed. Repair might be considered in asymptomatic patients with normal left ventricular function or patients with severe impairment of left ventricular function who might not be candidates for mitral valve replacement.

For most patients, mitral valve surgery is performed for the relief of symptoms or to prevent worsening of asymptomatic left ventricular dysfunction.

6.8: Tricuspid Stenosis

Tricuspid stenosis (TS) is most commonly of rheumatic origin and combined with tricuspid regurgitation. The anatomical characteristics are similar to those of mitral stenosis, including fibrous leaflet thickening and fusion and shortening of the subvalvular apparatus. The preponderance of cases is in young women. Other etiologies of right atrial obstruction are rare and include congenital tricuspid atresia, right atrial tumors and carcinoid syndrome

The normal valve area of the tricuspid valve is 7–8cm². Reduction of valve area to <2 cm² causes a pressure gradient. A small diastolic pressure gradient (<5 mmHg), gradient between the right atrium and ventricle can be present due to tricuspid stenosis. The gradient is increasing on inspiration. A mean pressure gradient >5mmHg is considered indicative of significant TS and is usually associated with symptoms.

Clinical presentation

A tricuspid opening snap and a characteristic mid-diastolic murmur may be audible along the left sternal border on auscultation. Carvallo's sign, an increase of murmur intensity on inspiration, may be present. Distention of jugular veins, ascites, pleural effusion and peripheral edema may be present due to increased right atrial pressures.

Reduced cardiac output causes symptoms of fatigue and malaise. The pulmonary congestion of mitral stenosis may be masked in severe tricuspid stenosis.

Diagnostic Options

Chest radiography

Cardiomegaly with an increase in right atria and pulmonary artery size is demonstrated on chest radiography.

Electrocardiography

An increased P-wave amplitude is seen on the electrocardiogram if the patient is in normal sinus rhythm.

Echocardiography

The tricuspid valve structure and function is commonly assessed by echocardiography. The annular size can be measured and the right pressures can be evaluated.

Tricuspid stenosis due to rheumatic disease is characterized by leaflet thickening with reduced motion and frequent commissural fusion. The chordae are shortened and thickened, and diastolic doming is present. Carcinoid syndrome is characterized by retraction of leaflets towards the apex during systole. A prolonged slope of antegrade flow across the tricuspid valve can be seen on Doppler. Tricuspid stenosis is considered severe when the mean transvalvular gradient is >5 mmHg.

Treatment

The therapeutic approach for tricuspid regurgitation is dictated by the etiology of the regurgitation and overall condition of the patient. In a limited number of patients percutaneous balloon tricuspid dilatation has been performed. This is a treatment option in cases of isolated and pure tricuspid stenosis, but it frequently induces regurgitation.[54] Tricuspid balloon valvotomy, combining commissurotomy leaflet augmentation and annuloplasty, can be used to treat tricuspid stenosis; however, with this treatment the potential for inducing severe tricuspid regurgitation still exists. A biological prosthesis is preferred in case of tricuspid valve replacement, since it has satisfactory long-term durability and mechanical prosthesis carries a higher risk of thrombosis.

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6.9: Tricuspid Regurgitation

Functional tricuspid regurgitation results from distortion of the architecture and coordinated actions of the tricuspid leaflets, annulus, chords, papillary muscles, and right ventricular (RV) wall. This distortion is most commonly caused by right ventricular dilation and dysfunction from left sided heart disease with pressure/volume overload conditions.

Pressure volume overload conditions cause enlargement of the tricuspid annulus and the saddle shape becomes more circular. The normal annular excursion can be reduced by 50% in severe tricuspid regurgitation.[55] Functional tricuspid regurgitation is a marker of poor prognosis in patients with left ventricular cardiomyopathy. Pure tricuspid regurgitation may result from rheumatic fever, infective endocarditis, carcinoid causes, rheumatoid arthritis, radiation therapy, anorectic drugs, trauma, Marfan's syndrome, tricuspid valve prolapse, papillary muscle dysfunction, or congenital disorders.

Right ventricular infarction with severe regional wall motion abnormality or disruption of the papillary muscle may cause regurgitation. Right ventricular dilatation with annular enlargement and valvular incompetence can be seen in Eisenmenger syndrome and pulmonary hypertension.

Clinical Presentation

A reduction in cardiac output related to tricuspid regurgitation, may cause symptoms of fatigue and weakness. Right-sided heart failure may cause ascites, congestive hepatosplenomegaly, pulsatile liver, pleural effusions, and peripheral edema.

With progression of the disease, patients become cachexic, cyanotic and jaundice may be present. A parasternal pansystolic murmur increasing on inspiration may be appreciated on auscultation (Carvallo's sign). An S₃, increasing with inspiration and decreasing with a Valsalva maneuver may be audible, as well as an increased P₂ if pulmonary hypertension has developed.

Diagnostic Options

Chest Radiography

Cardiomegaly, increased right atrial and ventricular size and a prominent azygous vein can be demonstrated on chest x-ray. Chest Radiography may reveal pleural effusion, and ascites by upward diaphragmatic displacement.

Echocardiography

The tricuspid valve structure and function can be assessed echocardiographically and specific abnormalities can be identified. Distinction between primary and functional forms of tricuspid regurgitation can be made with echocardiography. The annular size can be measured. This imaging modality is used to evaluate the degree of regurgitation, pressures and ventricular function. Severe regurgitation is characterized by systolic flow reversal in the hepatic veins and a vena contracta diameter of more than 7 mm.

Cardiac catheterization

Cardiac catheterization is not necessary to diagnose tricuspid regurgitation. Increased right atrial and right ventricular end-diastolic pressures and the degree of pulmonary artery hypertension can be evaluated by catheterization. Pulmonary artery pressures of over 60 mmHg are usually due to left-sided lesions leading to secondary tricuspid regurgitation.

Treatment

Treatment strategy for tricuspid regurgitation is dictated by the etiology and the underlying cause of the disease and the overall condition of the patient. Primary tricuspid regurgitation has a poor prognosis without treatment. Functional tricuspid regurgitation may improve following treatment of its cause. Correction of concomitant mitral regurgitation may worsen tricuspid regurgitation.

Risk factors for persistence or worsening of tricuspid regurgitation are reduced right ventricular function and the diameter of tricuspid annulus.

Medical

When pulmonary hypertension is the underlying cause of tricuspid annular dilation, medical management alone may minimize the need for surgical intervention

Surgical

Surgical treatment can be recommended for primary tricuspid regurgitation, when there is pulmonary hypertension, important dilatation of the annulus (diameter $>40\text{mm}$ or $>21\text{mm/m}^2$).

Surgical options for tricuspid regurgitation include annuloplasty or valve replacement with a mechanical valve or bioprosthesis. Functional tricuspid regurgitation may be repaired by suture annuloplasty (De Vega procedure) or by ring annuloplasty. Long-term outcomes of ring annuloplasty are superior to those of suture annuloplasty. Annuloplasty can be optimized by the use of intraoperative transesophageal echocardiography. Bioprostheses are generally preferred above mechanical prostheses for the tricuspid position, as mentioned in the section about tricuspid stenosis.

6.10: Pulmonary Valve Stenosis

Etiology and Pathology

Pulmonary valve stenosis can be caused congenital, carcinoid and rheumatic disorders or extrinsic compression. The typical dome-shaped pulmonary valve stenosis is the most common form of right ventricular outflow tract obstruction. Stenosis is caused by fusion of the pulmonary valve leaflets and a narrowed central orifice. The valve is usually mobile and associated with medial abnormalities and dilation of the pulmonary trunk. Pulmonary valve stenosis may be associated with Noonan, Williams, Alagille, Keutel or rubella syndromes.[56]

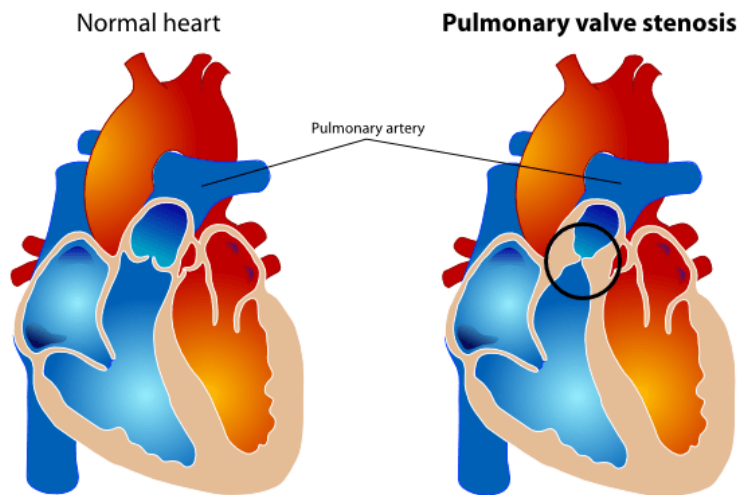


Figure 6.10.1: The diagram shows a healthy heart and one suffering from Pulmonary valve stenosis.

Clinical Presentation

Most patients with mild to moderate pulmonary valve stenosis are asymptomatic. Severe pulmonary valve stenosis may cause exertional dyspnea and fatigue, chest pain, palpitations and syncope. On physical examination, thrill along the left sternal edge, and a long systolic ejection murmur with late peak may be appreciated. S2 may be widely split with reduced or absent P2.

Diagnostic Options

Chest Radiography

Chest radiography may show dilated pulmonary arteries, occasionally with calcification of the pulmonic valve. In case of severe pulmonary valve stenosis, oligemic lung fields can be seen.

Electrocardiography

Right ventricular hypertrophy can be seen on electrocardiography as an axis deviation to the right. Right bundle branch block may also be present. Patients with Noonan syndrome invariably have a left bundle branch block.

Echocardiography

Transthoracic echocardiography confirms the diagnosis. The level of obstruction, valvular, supravalvular or right ventricular outflow tract, can be identified. Valvular stenosis is characterized by mildly thickened leaflets with restricted systolic excursion. The pressure gradient can be measured. Associated cardiac conditions can be demonstrated with echocardiography.

Cardiac catheterization

Cardiac catheterization is not necessary to diagnose pulmonic valve stenosis. Hemodynamic consequences and severity of pulmonary valve stenosis can be assessed with cardiac catheterization.

Treatment

Invasive intervention is recommended in case of symptomatic disease, or when the gradient across the valve is >40 mmHg.

Medical

Supportive and symptomatic treatment of right ventricular failure is recommended.

Surgical

The treatment of choice for stenosis at the valvular level is balloon valvuloplasty. Long-term results are satisfactory and the procedure relatively safe. Surgical valvotomy is very effective with minimal recurrence, however significant pulmonary regurgitation may occur. Pulmonary valve replacement is indicated if the patient is not suitable for balloon valvuloplasty or surgical valvotomy.

6.11: Pulmonary Valve Regurgitation

Etiology and Pathology

Physiologic pulmonic regurgitation, qualified as trace to mild, is present in nearly all individuals. Pulmonary valve regurgitation can be caused by valvular disease such as infective endocarditis (rarely involves pulmonic valve) or connective tissue disease, carcinoid, congenital heart disease, or it can be secondary to pulmonary hypertension, which causes dilation of the valve ring. Pulmonic regurgitation can result in impairment of right ventricular function and eventual clinical manifestations of right-sided volume overload and heart failure.

Clinical Presentation

Patients are often asymptomatic. Symptoms of right-sided heart failure develop when the severity and duration of the regurgitation results in right ventricular enlargement and decompensation. Symptoms include dyspnea on exertion, light-headedness, lethargy, peripheral edema, chest pain, palpitations, and abdominal pain. Often these symptoms are accepted by the patient and attributed to poor physical fitness, causing a delay in presentation. The jugular venous pressure is usually increased in pulmonary valve regurgitation. A palpable impulse may be present at the left lower sternal border due to right ventricular enlargement. On auscultation P2 may be delayed due to increased right ventricular end-diastolic volume and increased ejection time with large stroke volume. P2 can be accentuated in case of pulmonary hypertension. The murmur of pulmonary regurgitation is heard best at the third to fourth intercostal space along the left sternal border and increases with inspiration.

Diagnostic Options

Chest Radiography

Chest radiography of patients with pulmonic regurgitation with tricuspid regurgitation may demonstrate cardiomegaly and enlargement of the right-sided heart contour. Pure pulmonic regurgitation may have specific signs on chest radiography. Prominent central pulmonary arteries with enlarged hilar vessels and loss of vascularity in the peripheral lung fields suggest severe pulmonary hypertension.

Electrocardiography

Signs of right ventricular hypertrophy can be seen on the Electrocardiogram if pulmonary hypertension is present including a tall R wave in V₁ or qR in V₁, R wave greater than S wave in V₁, R wave progression reversal in the precordial leads and Right axis deviation. A right bundle branch block can be present.

Echocardiography

Echodoppler is the main diagnostic tool for recognizing pulmonic regurgitation. Regurgitant jet and velocity is visualized by Doppler. The width of the regurgitating jet can be used to quantify the severity. Diastolic regurgitation as well as early peak flow velocity in systole suggests the presence of pulmonary hypertension. Echocardiography can reveal right ventricular hypertrophy and dilatation. Right ventricular volume overload is characterized by abnormal septal wall motion. Structural abnormalities of the pulmonic valve or congenital absence of the valve can be demonstrated by echocardiography.

Treatment

The right ventricle normally adapts to low-pressure volume, high-pressure volume overload in contrast, ultimately leads to heart failure. Determining the underlying cause of pulmonic regurgitation and possible coexisting pulmonary hypertension is essential for appropriate therapy. Treating the cause of pulmonary hypertension can relieve symptoms and decrease the severity of PR. If medical management is insufficient, surgical treatment options should be evaluated. The presence of severe right heart failure

due to pulmonic regurgitation surgical pulmonic valve reconstruction or replacement can be considered.

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7: MYOCARDIAL DISEASE

Overall, myocardial diseases can be subdivided into two types: **primary and secondary myocardial diseases**. Whereas the primary type most commonly has a genetic cause, secondary myocardial diseases are mostly acquired but may be precipitated by a genetic background. Overall, the dilated type is the most prevalent manifestation of cardiomyopathy, and may be induced by a multitude of precipitating factors, such as chronic ischemia or alcohol abuse. The most common primary myocardial disease is hypertrophic cardiomyopathy, which is associated with a wide variety of genetic abnormalities. In the light of their substantially larger prevalence, we will first describe the secondary myocardial diseases, after which the less frequently occurring primary myocardial diseases will be discussed.

7.1: Myocardial Disease - Secondary

7.2: Myocardial Disease - Primary

7.1: Myocardial Disease - Secondary

Myocardial disease subsequent to a known origin is termed secondary myocardial disease. Timely correction of the originating disease may result in reversal of the cardiomyopathy. Nine different etiologies can be distinguished:

- Hypertension
- Ischaemia
- Valvular disease
- Alcohol
- Metabolic cardiomyopathy
- Takotsubo cardiomyopathy
- Peripartum cardiomyopathy
- Tachycardia

Hypertension or valvular disease

Inadequately treated hypertension or aortic stenosis results in adaptation of the left ventricle by means of hypertrophy. Although primarily considered an adaptive process to systolic overload, hypertrophy of the left ventricle is associated with ventricular dysfunction, arrhythmias, and sudden cardiac death. The process of hypertrophy involves enlargement and proliferation of myocytes, and interstitial fibrosis characterized by deposition of collagen type I and III. With increasing fibrosis, the compliance of the ventricle decreases resulting in loss of diastolic function before systolic function becomes impaired. Within this process of increasing myocardial mass, the coronary vasculature fails to adapt accordingly. In an attempt to accommodate to the increase in myocardial oxygen demand, coronary autoregulatory vasodilation results in an increase in coronary flow by during resting conditions. This partial exhaustion the coronary vasodilator reserve renders the myocardium at relative high risk for ischemia, and hence, patients may suffer from anginal complaints even in the absence of significant coronary artery disease. In patients with LVH, atrial fibrillation and ventricular arrhythmias, including multifocal ventricular extrasystoles, and short runs of ventricular tachycardia, are frequently found. The combination of myocardial fibrosis, maladaptation of the vasculature causing ischemia, autonomic imbalance and a prolongation of the action potential may serve as arrhythmogenic substrate in patients with LVH, resulting in an increased risk of sudden cardiac death.

Adequate antihypertensive treatment can regress left ventricular mass. In patients with aortic stenosis, ultimate treatment is valvular replacement to relief the systolic overload of the ventricle. With regression of the ventricle, improved diastolic, and preserved systolic function result, as well as a relief of vascular maladaptation-induced ischemia; the combination of which results in a decrease in cardiovascular events.

Ischemic cardiomyopathy

Chronic myocardial ischemia due to diffuse coronary atherosclerosis can cause cardiomyopathy of the dilated type (DCM). This ischemic cardiomyopathy may occur following one or multiple (silent) myocardial infarction(s), but may also occur from chronic (silent) ischemic myocardial damage. As such, it may be a progressive course of ventricular dilatation and ventricular dysfunction, but may also be the first manifestation of ischemic heart disease.

The extent of viable, or hibernating, myocardium determines the clinical relevance of revascularization of the ischemic myocardium. In patients with viable myocardial tissue, reperfusion improves symptoms, and supposedly prognosis. Several non-invasive tests may be used for this purpose, such as nuclear techniques, dobutamine echocardiography or contrast-enhanced cardiac MRI. However, the prognosis of ischemic cardiomyopathy is worse than non-ischemic forms of DCM, mainly due to a high risk of major ventricular arrhythmias. Moreover, subsequent ischemic episodes have a high impact on ventricular function in ischemia-related DCM.

As stated previously, revascularization may improve long-term prognosis in patients with objectively viable myocardium. In the absence of viability, routine heart failure therapy is the cornerstone of treatment including beta-blockade and ACE-inhibition (or angiotensine antagonists), and ICD implantation in a selection of patients.

Alcohol

Long-term alcohol abuse, >80g of alcohol per day (equivalent to 1 liter of wine) for more than 5 years, may lead to a dilated form of cardiomyopathy. Alcohol-induced dilated cardiomyopathy is the leading cause of non-ischemic dilated cardiomyopathy, some claim that it accounts for even up to 50% of cases. Most probably a genetic predisposition for DCM also plays an important role, as excess alcohol consumption itself prevails far more often than alcoholic cardiomyopathy (ACM). Both direct toxic effects of ethanol and its metabolites, as well as frequently occurring concomitant deficiencies of vitamins, minerals or electrolytes may adversely affect myocardial function.

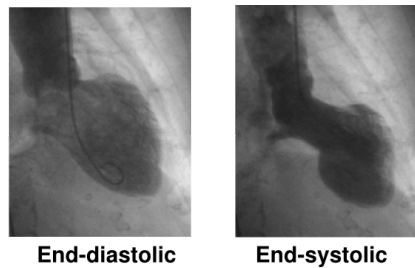
Two stages of ACM are recognized when the disease is left untreated. The first stage comprises asymptomatic ventricular dilatation in which diastolic dysfunction may be present, at least partly due to interstitial fibrosis of the myocardium. Fifty percent of asymptomatic patients have echocardiographic signs of LVH with preserved systolic function. The second stage is characterized by impairment of systolic function, and clinically overt heart failure. The prognosis of untreated ACM is comparable to DCM, but is far more favourable in patients that abstain from alcohol use, or dramatically reduce alcohol intake (to less than 60g of ethanol per day). Most of the improvement follows abstinence within 6 months, but ventricular function may improve for up to 2 years. Heart failure therapy may improve ventricular function, but has only been shown to benefit survival in patients that practise abstinence.

Metabolic cardiomyopathy

The group of metabolic cardiomyopathies comprises a heterogenous group of myocardial disease secondary to a disruption in metabolism. Metabolic cardiomyopathy associated with diabetes mellitus is most common. Independent of its influence on hypertension or coronary artery disease, high levels of plasma glucose are increasingly associated with a direct deteriorative effect on ventricular function. Other examples of metabolic disease able to induce cardiomyopathy are nutritional deficits such as thiamine deficiency, or storage diseases, and mutations in AMP kinase.

Tako-tsubo cardiomyopathy

The prevalence of tako-tsubo cardiomyopathy is largely unknown, but the syndrome predominantly affects women between 60 and 65 years of age. Patients with Tako-tsubo cardiomyopathy present with electrocardiographic features mimicking an acute coronary syndrome in association with elevated cardiac biomarkers, but in the absence of significant coronary artery disease. The disease has inherited its name from the distinct angiographic feature of apical ballooning, resembling an octopus-pot or "*Tako-tsubo*". Left ventricular function is typically impaired in the apical and mid ventricular regions, with preserved basal function, although reverse patterns may be seen. High levels of catecholamines have been suggested to play an important role in the etiology of the syndrome, which can be associated with emotional or physical stress, or in extremes in case of subarachnoid hemorrhage. This catecholamine storm may induce severe peripheral coronary spasm, leading to its clinical presentation. Treatment usually consists of aspirin, ACE-inhibitors or angiotensin receptor antagonists in case of preserved blood pressure, beta-blockers to reduce heart rate, and nitrates to counteract coronary spasms. LV function may restore rapidly within a few hours or days, even when admission ejection fraction was severely impaired, and clinical outcome is good although the disease may recur in approximately 5% of patients.



Neurogenic
Stress

- myocardial stunning
- heart failure
- angina
- coronary spasm
- arrhythmias
- stress cardiomyopathy,....

A Takotsubo is a jar used in Japan to catch octopus

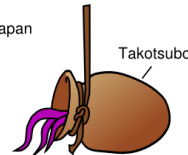


Figure 7.2.1: Tako-tsubo cardiomyopathy

Peripartum cardiomyopathy

Left ventricular systolic function impairment within 1 month of delivery, or during the first 5 months post partum, in the absence of pre-existing cardiac disease, and in the absence of another recognized cause for the cardiac dysfunction is termed peripartum cardiomyopathy.

Presentation is typically with features of left ventricular failure, although many features are undistinguishable from normal changes in pregnancy, due to which mild forms may not even be recognized. An inflammatory component has been suggested, in addition to malnutrition, viral infection, an abnormal immune response, and familial predisposition. Recurrence of the disease in subsequent pregnancies is noted, and makes the previously mentioned etiologies hard to explain. Most probably, peripartum cardiomyopathy results from predisposition to DCM, triggered to uncover by the high cardiovascular burden of the pregnancy.

Standard heart failure therapy can be instituted in peripartum cardiomyopathy, but the use of ACE-inhibitors and angiotensin receptor antagonists is contraindicated during pregnancy after the first trimester due to their possible adverse effects on the fetus. In extreme cases, the potential risks for the fetus should however be balanced against the critical need for preservation of ventricular function in order to provide both the mother and the fetus the best chance for a favourable clinical outcome. Pregnancy is also associated with a high risk of thrombo-embolism, as it is a hypercoagulable state per definition, which is enhanced by the presence of an impaired ventricular function in case of peripartum cardiomyopathy, and prophylaxis is therefore recommended.

Despite optimal treatment, LV function may normalize in as less as 50% of patients, and may deteriorate to end-stage heart failure in 15%. Potential recurrence in future pregnancies requires counselling of patients to prevent subsequent episodes of symptomatic heart failure and progression of ventricular dysfunction.

Tachycardia-induced cardiomyopathy

Persistently high heart rates (above 110 beats per minute), such as in sustained ventricular tachycardia, or associated with atrial fibrillation, results in heart failure when left untreated. Normalization of the heart rate by means of beta-blockade subsequently leads to normalization of ventricular function, and is therefore the cornerstone in treatment of tachycardia-induced cardiomyopathy.

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7.2: Myocardial Disease - Primary

Five different groups of primary myocardial disease exist; which are defined as diseases of the myocardium with impaired cardiac function, also referred to as cardiomyopathies.

- Hypertrophic cardiomyopathy (HCM)
- Dilated cardiomyopathy (DCM)
- Restrictive cardiomyopathy (RCM)
- Arrhythmic cardiomyopathy (ACM)
- Unclassified cardiomyopathy (UCM)

Hypertrophic cardiomyopathy

The essential characteristics of hypertrophic cardiomyopathy (HCM) are unexplained hypertrophy of the left ventricle in the absence of causal cardiac or systemic disorders. Distinctive features further comprise myocyte disarray, familial occurrence, and an association with sudden cardiac death (SCD).

Genetics

The identification of the genetic background of HCM resulted in the hypothesis that HCM is a disease of the sarcomere; the contractile unit of the cell. First, mutations were found in the cardiac B-myosin heavy chain gene, while later on other sarcomeric proteins were found to play a role in HCM (Table 7.3.1).

Table 7.3.1

Sarcomeric Genes Associated with HCM
α -Tropomyosin
Cardiac Troponin T
Troponin I
Myosin-binding Protein C
Regulatory Myosin Light Chain
Essential Myosin Light Chain
Cardiac Actin
Titin
Troponin C
α -Myosin Heavy Chain

It was shown that macroscopic hypertrophy of the myocardium is not essential for neither diagnosis nor prognosis, as mutations for example in troponin T may lead to only minor or no hypertrophy, whereas it is associated with a high incidence of SCD. Nowadays HCM is considered a genetic disorder, inherited mainly autosomal dominant with an incomplete and age-related penetrance. Pathological findings may include myocardial hypertrophy, small-vessel disease and myocyte disarray with or without fibrosis. The prevalence of HCM in the adult population is approximately 1 in 500. But as in only 60% of HCM patients mutations in the abovementioned known sarcomeric genes are present, non-sarcomeric variants of HCM or mutations in regulatory genes, have gained interest. Left ventricular hypertrophy in young children is known most often not to be caused by sarcomeric HCM, but rather by inherited metabolic disorders and syndromes with extracardiac features. These diseases may cause to non-sarcomeric HCM as they include Fabry disease and Danon disease. Recognition and diagnosis of HCM may involve familial counselling, which also helps to find the presence of extracardiac features, and may influence treatment.

Epidemiology

The prevalence of the HCM phenotype was found to be approximately 0.2%, or 1 in 500, in several epidemiological studies. This frequency is notably higher than its occurrence in daily clinical practice. Hence, a large amount of patients remains undiagnosed, most probably without symptoms or inferences for their prognosis.

Pathophysiology

Left ventricular outflow tract obstruction (LVOTO)

The subdivision of HCM into obstructive and non-obstructive forms is clinically important, and is based on the presence or absence of a LV outflow tract gradient during rest and/or after provocation. The presence of such a gradient typically results in a loud apical systolic ejection murmur. The obstruction leads to an increase in intraventricular pressures, impairing LV function by increasing myocardial wall stress and oxygen demand. The obstruction is located either sub-aortic or mid-cavity, where the sub-aortic location is most common and is caused by systolic anterior motion (SAM) of the mitral valve and mid-systolic contact with the ventricular septum. SAM is thought to be facilitated by either an abnormal valvular apparatus loose enough to allow movement, or a hemodynamic force with an anterior component during systole. A drag-effect probably attributes to SAM, which refers to the force exerted by a fluid in the direction of the flow. Apart from its role in sub-aortic obstruction, SAM also results in concomitant mitral regurgitation. The sub-aortic gradient and associated LV pressure increase are pathophysiologically significant and may worsen outcome. LVOTO is an independent predictor for HCM-related death, progression of the disease in terms of New York Heart Association (NYHA) class III or IV, and death due to heart failure or stroke. A gradient threshold of 30 mmHg is prognostically important, but a further increase is not associated with further increased risk. Chronic outflow tract obstruction results in an increase in LV wall stress, myocardial ischemia and fibrosis, and justifies intervention in severely symptomatic patients when optimal medical management is insufficient.

HCM patients can be divided into hemodynamic subgroups based on the representative obstructive gradient:

1. Obstructive - gradient under resting conditions equal to or greater than 30 mm Hg (2.7 m/s by Doppler)
2. Provocable obstructive (latent) - gradient less than 30 mm Hg under resting conditions and equal to or greater than 30 mm Hg with provocation
3. Nonobstructive - less than 30 mm Hg under both resting and provoked conditions.

LV outflow gradients are routinely measured noninvasively with continuous wave Doppler echocardiography. To define provocable gradients, treadmill or bicycle exercise testing is the preferred stress test, given that HCM-related symptoms are typically elicited with exertion. Pharmacological induction of stress by intravenous infusion of dobutamine is considered contra-indicated.

Diastolic Dysfunction

HCM is, in contrast to other cardiomyopathies, characterized by early occurrence of diastolic dysfunction (both active and passive phases), while systolic function is typically preserved, even before signs of hypertrophy. The passive relaxation during filling of the ventricle is hampered by increased chamber stiffness, increasing filling pressures and decreasing myocardial blood flow. Isovolumetric relaxation in early diastole is prolonged in HCM. Diastolic dysfunction may well lie at the basis of heart failure in non-obstructive HCM with preserved systolic function.

Ischemia

Myocardial hypertrophy disrupts the subtle equilibrium of blood flow throughout the myocardial layers. Patients with HCM show an increase in coronary blood flow velocity compared to healthy individuals reflecting an autoregulatory decrease in microvascular resistance to adapt to an increase in oxygen demand during resting conditions. The coronary reserve is therefore partly exhausted. Apart from the changes in the coronary microcirculation, systolic extravascular compression might play a role. Most importantly, HCM results in a progressive mismatch between muscle tissue and vascular growth, resulting in a high risk of myocardial ischemia especially for the subendocardial layers. The presence of myocardial ischemia is an important determinant of progression of the disease as it promotes scarring and remodelling of the ventricle.

Arrhythmia

Myocardial fibrosis associated with HCM is an important arrhythmogenic substrate. Functional consequences of HCM may therefore provide a trigger for ventricular arrhythmias, i.e. ischemia and LVOTO, resulting in non-sustained ventricular tachycardia in approximately 20% of patients. Other functional consequences as diastolic dysfunction, mitral regurgitation, as well as LVOTO are associated with atrial fibrillation (AF) which is observed in 20-25% of HCM patients.

Wall thinning and Cavity Dilation

Over time, thinning of the hypertrophic LV wall may occur in patients with severe LVH which may account for the lack of marked echocardiographic LVH in the elderly. While mechanisms of LV remodelling in HCM are still to be defined, cavity dilation and hampered systolic function occur in less than 5% of patients.

Clinical diagnosis

The cornerstone of HCM diagnosis is represented by echocardiography and electrocardiography. In the overall population, the diagnostic criterion of HCM is a maximal wall thickness greater or equal to 15 mm. However, virtually any wall thickness may be associated with the presence of an HCM mutant gene, including wall thickness well within the normal range. Therefore, for both echocardiography and electrocardiography, criteria have been established for the diagnosis of HCM in patients with high risk for HCM. Specificity of these criteria relies significantly on the a-priori chance of HCM, and is therefore only pertinent in first-degree relatives of index cases with confirmed HCM, whom therefore all have a 50% a-priori chance of carrying an HCM mutation. HCM is confirmed in a first-degree relative when either 1 major or 2 minor echocardiographic criteria (Table 7.3.2), or 1 minor echocardiographic and 2 minor electrocardiographic criteria (Table 7.3.3) are present.

Echocardiography

Two-dimensional echocardiography is the easiest diagnostic modality for detection of HCM, (Table 7.3.2) but cardiac magnetic resonance imaging (CMR) may be used when echocardiography is inconclusive, acoustic windows are insufficient, or when more detailed anatomic information is needed for clinical decision making. Echocardiographic characteristics include thickening of the left ventricular wall without cavity dilatation, and a normal or hyperdynamic left ventricle. Left ventricular outflow tract obstruction is not mandatory for the diagnosis of HCM. Moreover, as mentioned previously, although the diagnosis of HCM is based on a cut-off value for maximal wall thickness of 15 mm in the overall population, multiple HCM-linked mutations are associated with only minor LVH, but represent a high risk of sudden cardiac death.

Table 7.3.2: Echocardiographic diagnostic criteria for HCM in first-degree relatives of index cases with HCM.

Major	Minor
• LV wall thickness $\geq$13 mm in the anterior septum or $\geq$15 mm in the posterior septum or free wall • Severe SAM (septum-leaflet contact)	• LV wall thickness of 12mm in the anterior septum or posterior wall or of 14mm in the posterior septum or free wall • Moderate SAM (no septum-leaflet contact) • Redundant mitral valve leaflets

Electrocardiography

Electrocardiographic signs of HCM are typical as the increase in myocardial tissue increases the size of the QRS complexes. Therefore, a typical ECG characteristic of HCM is that it meets voltage criteria for LVH, and shows changes in repolarization (Table 7.3.3).

Table 7.3.3: Electrocardiographic diagnostic criteria for HCM in first-degree relatives of index cases with HCM.

Major	Minor
- Left ventricular hypertrophy and repolarization changes - T-wave inversion in leads I and aVL (=3mm) (with QRS-T wave axis difference =30°, V3-V6 (=3mm) or II and III and aVF (=5mm) - Abnormal Q (>40 ms or >25% R wave) in at least two leads from II, III, aVF (in absence of left anterior hemiblock), V1-V4; or I, aVL, V5-V6	- Complete bundle branch block or (minor) interventricular conduction defect (in LV leads) - Minor repolarization changes in LV leads - Deep S V2 (>25mm)

Medical treatment

Asymptomatic HCM patients should only receive drugs when symptoms of diastolic dysfunction are present. Verapamil is the treatment of choice, improving diastolic filling and relaxation of the ventricle, decreasing diastolic filling pressures.

In symptomatic patients, first line medical treatment consists of a calcium-channel blocker or a betablocker. Verapamil is the first choice, but diltiazem may be used as an alternative. Second, beta-blockers may be used when symptoms prevail, and can be used solitarily or in combination with a calcium-channel blocker. In severely symptomatic patients, diuretics may be used, but with high caution as a small drop in ventricular filling pressure may reduce stroke volume and cardiac output dramatically in HCM patients. A combination can be made with either calcium-channel blockers or beta-blockers.

Patients presenting with ventricular tachyarrhythmia or supraventricular atrial fibrillation, amiodarone may be used, and may even improve symptoms and prognosis. Disopyramide has negative inotropic action and results in peripheral vasoconstriction and may improve symptoms when diastolic dysfunction is most prominent (i.e. with preserved ejection fraction).

Invasive treatment of obstructive HCM

In patients where maximal medical treatment does not control the symptoms, invasive debulking of the myocardial septum may be considered when a marked outflow gradient is present. Treatment options comprise percutaneous alcohol septal ablation, or surgical septal myectomy.

Surgical myectomy has shown excellent long-term result, but 15-20% of patients may suffer from ventricular remodelling and dilatation of the left ventricle. Since the introduction of alcohol ablation, surgical myectomy is reserved for patients with HCM with concomitant disease that independently warrants surgical correction, such as coronary artery bypass grafting of valve repairs, in whom surgical myectomy can be performed as part of the operation.

Septal ablation may be considered in patients with outflow tract gradients of more than 30 – 50 mmHg at rest or 60-100 mmHg after provocation. By injection of 1-3 mL of pure alcohol over 5 minutes into the first or second septal branch, a small myocardial infarction is created. Furthermore, the alcohol induces septal hypokinesis, adding to a reduction of the outflow tract gradient. The gradient may resolve immediately, but this process may take weeks to months. When the outflow tract obstruction persists, patients can be treated a second time.

Dual Chamber Pacing

In patients with medically refractory symptoms, whom are suboptimal candidates for invasive treatment, permanent dual chamber pacing may be considered. Pacing may alleviate symptoms by decreasing the outflow tract pressure gradient. However, maintaining a reduction in gradient requires pre-excitation of the right ventricular apex and distal septum, and complete ventricular capture. For optimal results, this should therefore be performed in highly experienced centers only.

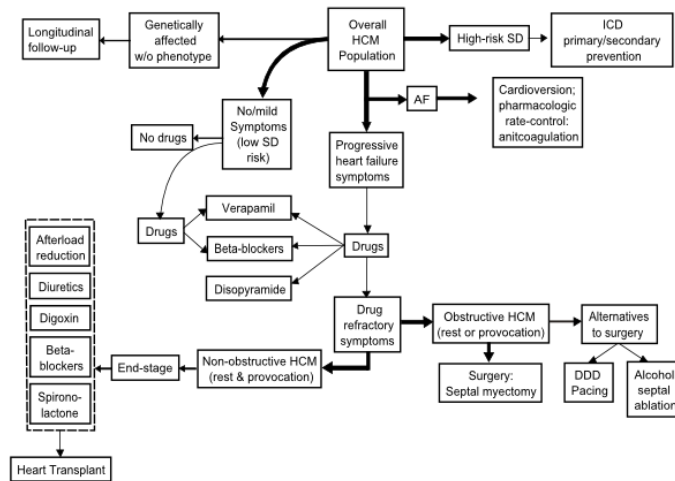


Figure 7.3.1: Treatment strategy in HCM.

Prognosis and outcome

In general, symptoms of HCM increase with age. Mortality rates have been reported to account between 2 and 3% per year. Most importantly, patients with HCM may be at high risk of sudden cardiac death, which may even be its initial presentation, in particular in asymptomatic or mildly symptomatic young patients. HCM is the most common cause of SCD in young people, including athletes. The pathophysiological basis for this predilection is unclarified, and although SCD is most frequent in young people less than 30 to 35 years old, an increased risk for SCD extends thereafter. Although HCM presentation and clinical manifestation is heterogeneous, and it has a relatively low prevalence, clinical markers as shown in Table 7.3.4 may identify patients at high risk for SCD. Patients at high risk of SCD are eligible candidates for ICD implantation.

Table 7.3.4: Risk Factors for SCD

Major	Minor
- Cardiac arrest (ventricular fibrillation) - Spontaneous sustained ventricular tachycardia - Family history of premature sudden cardiac death - Unexplained syncope - LV thickness = 30mm - Abnormal exercise blood pressure (increase in systolic blood pressure =20 mmHg) - Nonsustained ventricular tachycardia (Holter)	- Atrial fibrillation - Myocardial ischemia - LV outflow tract obstruction - High-risk mutation - Intense (competitive) physical exertion - Fibrosis on CMR

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by ventricular dilatation (one or both ventricles) and impaired myocardial contractility. The impairment of myocardial function cannot be explained by abnormal loading conditions alone, such as valve disease or systemic hypertension. The prevalence of DCM is approximately 36 per 100,000; in at least 50% of patients with DCM, its cause cannot be determined which is referred to as idiopathic DCM. DCM is a condition of which causes and presentations are highly heterogeneous. The diagnosis of idiopathic DCM should only be made after exclusion of the specific cardiomyopathies with a dilated phenotype.

Genetics

The genetic background of DCM is not as clear as in HCM. Although previously thought to be sporadic, genetic transmission is now thought to account for 30-40% of cases. Multiple genes have been identified that are linked with the occurrence of DCM. Genetic disease may account in part for the primary forms of DCM, but importantly, genetic predisposition may well lead to DCM in case of exposure to precipitating factors such as (emotional) stress, excessive alcohol use or stress upon the cardiovascular system; secondary DCM.

The expression of DCM in the familial form is frequently incomplete, and hence its prevalence is supposedly underestimated to a large extent. Even minor abnormalities may progress into overt DCM, and accurate clinical screening of (asymptomatic) relatives is therefore mandatory for early identification of familial DCM cases.

Pathophysiology

In general, a wide variety of factors can induce or contribute to the development of DCM including arterial hypertension, myocarditis, alcohol abuse or tachyarrhythmias. A subsequent increase in wall stress combined with activation of neurohumoral pathways induces complex cellular and molecular maladaptation, and programmed cell death finally leads to a decrease in the number of functioning cardiomyocytes. This process of cardiac remodelling itself results in systolic and/or diastolic dysfunction, leading to increased wall stress, and thereby creating a vicious circle of progressive systolic dysfunction (Figure 7.3.2).

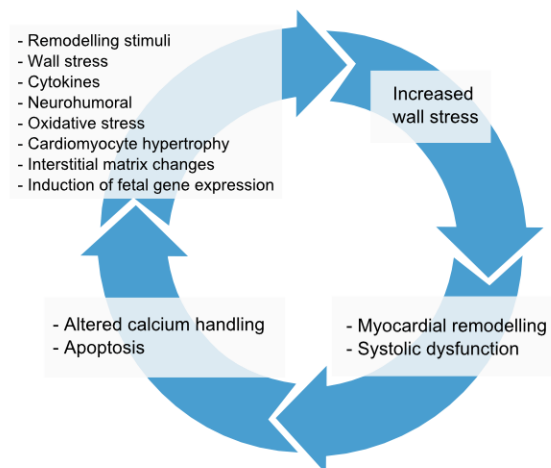


Figure 7.3.2: Process of cardiac remodelling

The failing myocardium has several distinct factors promoting apoptosis of cardiomyocytes in vitro; catecholamines, wall stress, angiotensin II, nitric oxide and inflammatory cytokines. Hence, medical management of DCM aims at antagonizing these pathways, reducing stress signalling in, and remodelling of the failing heart.

Clinical diagnosis

The most common initial manifestation of DCM is heart failure, in which clinical symptoms do not differ from heart failure of other causes. An important feature of the physical examination is a gallop rhythm of S3 and S4. S3 and S4 may fuse in tachycardic patients with new onset of heart failure. Special attention should focus upon excluding valvular heart disease as a cause, and excluding right-sided involvement.

Diagnostic testing in DCM focuses on identification of reversible causes, which focuses on the history (alcohol use) but also includes plasma biomarker evaluation, non-invasive imaging, electrocardiography, and exercise testing.

Echocardiography is an important diagnostic modality in DCM, as it can be used to assess both the size and shape of the LV, but also to determine LV function by assessing the LV ejection fraction (LVEF). Furthermore, valvular heart disease

or pericardial abnormalities can be excluded. CMR evaluation may contribute to identification of specific cardiomyopathic conditions, especially when acoustic windows are suboptimal. The cardiac response to exertion is an established risk factor in DCM patients, which may be evaluated by cardiopulmonary exercise testing. Dilatation of the ventricular cavity results in myocyte stretch. In response, B-type natriuretic peptide is released, which is a well-known neurohormone that can be used to evaluate progression of DCM and to guide medical treatment. High plasma concentrations (twice the ULN) are strongly associated with increased long-term mortality.

Electrocardiography does not provide an accurate diagnostic mean in DCM, but can identify several characteristics associated with unfavourable prognosis, or identify factors contributing to DCM, and therefore is an important modality in the evaluation of DCM patients. Sinus tachycardia is frequently present, and non-specific ST-segment or T-wave changes as well as changes in P-wave morphology may well be present. AF is an important feature associated with high mortality; its control may contribute to improve cardiac performance. Furthermore, the presence of AF may indicate tachycardia-induced DCM. 24-hour Holter monitoring can reveal decreased heart rate variability or complex ventricular arrhythmias which are associated with a high risk for mortality. Finally, prolonged QTc intervals are associated with high mortality.

Management of DCM

Management of symptoms and progression of DCM accord to those described in the management of heart failure. Hence, also in DCM, diuretics and neurohumoral antagonists provide the basis for management of symptoms, and preventive ICD or pacemaker implantation is indicated in selected patients. Most importantly, surgical or percutaneous correction of underlying conditions facilitating progression of DCM, such as coronary artery disease, valvular heart disease or congenital abnormalities is warranted.

Specific dilated cardiomyopathies

It is important to note that there are several causes of secondary DCM. A foursome of these is of utmost importance to recognize early on, as accurate diagnosis influences the patients treatment strategy and chance for complete recovery: **Takotsubo**, **Peripartum cardiomyopathy**, **Tachycardia-induced cardiomyopathy**, **Alcoholic cardiomyopathy** (all described under '[Myocardial Disease - Secondary](#)').

Cardiomyopathy in muscular dystrophy

Defined as primary disorders of skeletal and/or cardiac muscles of genetic etiology, muscular dystrophies were primarily described based upon the distribution and extent of skeletal muscle involvement. The involvement of the heart was commonly attributed to processes extrinsic to the heart, resulting in restrictive lung disease, subsequent pulmonary hypertension, and secondary myocardial dysfunction. Intrinsic dysfunction is increasingly recognized as an important etiology for myocardial function impairment in the presence of muscular dystrophy. Typical forms of dystrophy are based on deficiency of dystrophin, of which mutations have been described in X-linked DCM. Furthermore, histological changes were found in the myocardium similar to those in skeletal muscles, which suggest a common etiology, and moreover cardiac manifestations may be present even in the absence of myopathic symptoms.

Treatment of cardiac dysfunction is treated according to the nature of cardiac involvement. Conduction disorders may present which require pacing, and standard heart failure therapy may be instituted in case of ventricular dilatation and functional impairment. Ventricular tachyarrhythmias may be found in particular in myotonic dystrophia, and require the implantation of an internal cardiac defibrillator to prevent its associated sudden cardiac death.

Prognosis and outcome

DCM has a highly variable clinical course. Approximately half of DCM patients respond well to routine heart failure medication, and a minority of patients even shows an improving clinical course. Conversely, a subgroup can be identified with a highly unfavourable clinical course, not responsive to heart failure medication and rapidly progressing to inotropy- or LVAD-dependency. Overall, 5-year survival rates approximate 30%.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is characterized by an increase in ventricular wall stiffness, impairing its diastolic function. Systolic

function is usually preserved in early stages of the disease, but may deteriorate with progression of the disease. RCM is less frequent in the developed world than the previously described HCM and DCM, but is an important cause of death in Africa, India, South and Central America, and Asia due to the high endemic incidence of *endomyocardial fibrosis*. The spectrum of restrictive cardiomyopathies can be classified as shown in Table 7.3.5, according to its cause.

The most important specific causes of RCM will be discussed in detail below.

An important differentiation is that between RCM and constrictive pericarditis. Constrictive pericarditis is similarly characterized by impaired ventricular filling with preserved systolic function, but may be adequately treated by pericardiectomy, which makes this distinction of major clinical importance.

Table 7.3.5: Classification of Restrictive Cardiomyopathy

Noninfiltrative	Infiltrative	Storage Disease	Endomyocardial
- Idiopathic cardiomyopathy - Familial cardiomyopathy - Hypertrophic cardiomyopathy - Scleroderma - Pseudoxanthoma elasticum - Diabetic cardiomyopathy	- Amyloidosis - Sarcoidosis - Hurler disease - Fatty infiltration	- Hemochromatosis - Fabry disease - Gaucher disease - Glycogen storage disease	- Endomyocardial fibrosis - Hypereosinophilic syndrome - Carcinoid heart disease - Metastatic cancers - Radiation * - Toxic effects of anthracycline * - Drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

Infiltrative cardiomyopathy

Amyloidosis

Amyloidosis is a disease that results from tissue deposition of fibrils that have a distinct secondary structure of a beta-pleated sheet configuration, leading to characteristic histological changes. Amyloid depositions can occur in almost any organ, but usually remains clinically undetected unless extensive depositions are present.

Types of amyloidosis

The most frequent types of amyloidosis are the AL (primary) and AA (secondary) types. AL amyloidosis is a plasma cell dyscrasia, which can occur solitarily or in association with multiple myeloma. AA amyloidosis can be considered a complication of chronic inflammatory disease states such as rheumatoid arthritis, in which the depositions consist of fragments of serum amyloid A, which is an acute phase reactant.

Hereditary amyloidosis has been increasingly recognized in the last decade, and results from mutations in the gene for transthyretin. Some mutations are clinically limited to the myocardium. Its incidence increases with increasing age, with a predilection for men, but its prognosis is better than that of the AL type. Senile systemic amyloidosis results from deposition of normal wild-type transthyretin. This form of amyloidosis is clinically predominated by an infiltrative cardiomyopathy, but progression is slow and prognosis is better than of other acquired forms.

Cardiac amyloidosis

Cardiac amyloidosis is a progressive infiltrative cardiomyopathy. The primary form carries the highest cardiac involvement of approximately one third to half of patients, where deposits may be present even in the absence of clinical symptoms. Secondary amyloidosis is less frequently accompanied by cardiac infiltration, approximately 5% of cases, and is less likely associated with

ventricular dysfunction due to a smaller size and more favourable location of the depositions. Familial amyloidosis is associated with clinical signs of cardiac involvement in a quarter of patients, typically presenting after the age of 35 with a distinct involvement of the cardiac conduction system. In senile amyloidosis, the extent of deposits may vary widely from solitary atrial involvement up to extensive ventricular infiltration.

Clinical manifestations

Apart from the occurrence of cardiac disease in the presence of known AL amyloidosis or connective tissue disease or other chronic inflammatory disorders, cardiac amyloidosis should be considered in case of:

- Restrictive cardiomyopathy of unknown origin
- Left ventricular hypertrophy with a converse low-voltage ECG
- Congestive heart failure of unknown origin, not responding to contemporary medical management.

Clinical diagnosis

Diagnostic testing should include a 12-lead ECG, possibly with Holter monitoring, and routine echocardiography. Specific characteristics are a low-voltage 12-lead ECG with increase septal and posterior wall ventricular thickness.

Physical Examination

A physical examination may reveal an elevated jugular venous pressure, and signs of systemic edema. Auscultation frequently reveals an apical murmur due to mitral regurgitation, and a third heart sound, but the presence of a fourth heart sound may exclude amyloidosis, as atrial infiltration causes impaired atrial contraction.

Electrocardiography

Routine 12-lead ECG shows low voltage in the limb leads, and a pseudoinfarct pattern in approximately 50% of patients. Furthermore, conduction abnormalities occur frequently, as does atrial fibrillation.

Echocardiography

Thickening of the left ventricular wall with diastolic dysfunction are early echocardiographic features of the disease. In advancing disease, wall thickening increases, resulting in a restrictive cardiomyopathy. "Sparkling" myocardium is a distinct characteristic of cardiac amyloidosis, referring to an increased echogenicity of the myocardium. However, only a minority of patients has this pattern. Doppler evaluation shows a restrictive pattern with E dominance and a short deceleration time. Furthermore, intracardiac thrombus is common, which is associated with atrial fibrillation and left ventricular diastolic dysfunction.

The thickening of the ventricular wall caused by amyloidosis may be misinterpreted as hypertrophy on echocardiography. An important distinctive characteristic of amyloidosis is the voltage-to-mass ratio. Unlike normal hypertrophic myocardium, the increased ventricular mass in amyloidosis is associated with a decrease in electrocardiographic voltage.

Management

Few treatments for cardiac amyloidosis exist, and those available are dependent on the type of amyloidosis present. Hence, typing of the disease is pertinent. AL amyloidosis may be treated with chemotherapy using alkylating agents alone or in combination with bone marrow transplantation. Heart transplantation in combination with bone marrow transplantation after high-dose chemotherapy was shown to result in approximately a third of treated patients surviving over 5 years, but as the great majority of patients with AL amyloidosis has severe non-cardiac amyloidosis, most patients are not suitable transplant candidates. Patients with other types of amyloidosis frequently have less affected hearts, and progression of the disease is slow. AA amyloidosis may respond to anti-inflammatory and immunosuppressive drugs that reduce production of the acute-phase reactant protein. If heart failure is present, it is usually more prone to routine medical treatment to reduce symptoms. If needed, heart transplantation can be performed successfully. In patients where transthyretine is the amyloidogenic protein, liver transplantation may be curative as transthyretine is produced in the liver, but the cardiac disease may progress regardless in some patients.

Overall, caution should be taken in prescribing digitalis, nifedipine, verapamil and ACE-inhibitors to cardiac amyloidosis patients. There is a high susceptibility to digitalis intoxication, nifedipine-induced hemodynamic deterioration, verapamil-induced left ventricular dysfunction, and ACE-inhibitor induced profound hypotension. If atrial fibrillation is present, or systolic ventricular function is severely impaired anticoagulation is indicated to prevent intracardiac thrombi. In selected patients with conduction disorders, pacemaker implantation may be considered. If ventricular function is severely impaired, ICD implantation may be considered. Nonetheless, prognosis of especially AL amyloidosis is poor.

Sarcoidosis

Sarcoidosis is a multi-system inflammatory condition characterized by the formation of non-caseating granulomas, most frequently affecting the lungs and lymphatic system. Myocardial involvement is seen in one quarter of cases only. Genetic factors are suggested as there was found to be an aggregation of cases within families.

Pathophysiology

Non-caseating granulomas may infiltrate the myocardium, leading to fibrotic scarring of the myocardium. Involvement of the myocardium is usually patchy, resulting in a relatively high likelihood of false-negative results from biopsy. Cardiac sarcoidosis must be differentiated from chronic active myocarditis and giant cell myocarditis.

Clinical Diagnosis

Patients may present with syncope, heart block or congestive heart failure. Sudden cardiac death may well be the initial manifestation of the disease due to malignant ventricular arrhythmias, but both atrial and ventricular arrhythmia is common at initial presentation. Symptoms of heart failure may result from direct myocardial involvement, but can also be due to extensive pulmonary fibrosis; cor pulmonale.

Physical examination may include signs of extracardiac sarcoidosis, a right sided third heart sound, and both S3 and S4, as well as murmurs of tricuspid regurgitation or mitral regurgitation.

Initial consideration of the diagnosis is often based on chest radiographs showing bilateral hilar lymphadenopathy. CMR is emerging as a highly sensitive and specific test for sarcoidosis, and nuclear imaging techniques may show regional perfusion defect due to the granulomatous inflammation on SPECT, or focal uptake on PET CT. electrocardiography is useful to assess the extent of conduction system involvement. Echocardiography shows left ventricular dilatation with hypokinesis, right ventricular enlargement and hypertrophy and possibly left ventricular aneurysm formation.

Minimal evaluation of a patient suspected of cardiac sarcoidosis consists of a 12-lead ECG, Holter monitoring and echocardiography.

Management

Early detection of the disease is critical for its clinical course. Immunosuppression using corticosteroids to halt the progression of inflammation is the treatment of choice in sarcoidosis, to which myocardial dysfunction, conduction disturbances, and arrhythmias may all respond. Most important is the differentiation of sarcoidosis from giant cell myocarditis, which is a more aggressive disorder requiring intensive medical and mechanical support and frequently necessitating heart transplantation. Pacemaker or ICD implantation is indicated in patients with conduction disorders or malignant arrhythmias, as medical treatment is usually ineffective in these cases.

Storage diseases

Hemochromatosis

Hemochromatosis is defined as a disorder of the iron metabolism, resulting in accumulation of iron in parenchymal tissues. In particular cardiac, liver, gonadal and pancreatic involvements are typical for hemochromatosis, in which the toxicity of redox-active iron results in organ dysfunction. Typically, hemochromatosis leads to a combination of heart failure, cirrhosis,

impotence, diabetes and arthritis. Although several organ systems are usually involved, cardiac complications predominate the initial presentation, which are dependent on the site and amount of cardiac depositions. DCM is the typical phenotype of cardiac involvement, but a restrictive pattern may be present.

The most frequent, adult-onset, form of hemochromatosis was found arise from mutations in the HFE-gene, coding for a transmembrane protein involved in iron uptake in the liver and the intestine. Less frequently, mutations in the transferrine 2-encoding gene may result in hemochromatosis. The juvenile form of hemochromatosis results from mutations in the genes encoding hepcidin and hemojuvelin. The disease may also be acquired and result from ineffective erythropoiesis secondary to a defect in hemoglobin synthesis, chronic liver disease, chronic excessive oral or parenteral intake of iron, or from multiple blood transfusions.

Three stages of the natural history of adult-onset hemochromatosis can be differentiated. The first stage, the biochemical stage, is characterized by an iron overload which remains confined to the plasma compartment. Transferrin saturation is increased. The second phase, the deposition phase, is characterized by iron accumulation in parenchymal tissues, accommodated by an increase in serum ferritin levels. The third and final stage is that of organ dysfunction. Juvenile hemochromatosis is a more rapidly progressing disease, which leads to early organ dysfunction, around the age of 30, and is frequently characterized by premature death due to severe cardiac complications.

The invariably present symptoms of heart failure may frequently be accompanied by arrhythmias, especially ventricular extrasystoles, supraventricular tachycardia, and atrial fibrillation or flutter; either due to atrial iron depositions, or ventricular dysfunction resulting in increased ventricular pressure. Furthermore, conduction system involvement may lead to AV block or sick sinus syndrome.

Diagnostic features

Symptoms at initial presentation may vary. Echocardiography may show increased left ventricular wall thickness, ventricular dilatation, and ventricular dysfunction. CMR imaging represents a sensitive mean and may aid in early detection of the disease. Electrocardiographic characteristics include ST-segment and T-wave abnormalities as well as supraventricular arrhythmias, but occur as the disease advances. Biochemical testing reveals increased elevated transferrine saturation, increase plasma iron levels with low or normal iron binding capacity.

Management

Repeated phlebotomy is the cornerstone of hemochromatosis treatment, although chelating agents such as deferoxamine may be considered. Early detection of the disease is critical, as depletion of iron overload may result in complete reversal of symptoms at this stage. Evidence was found that a threshold exists beyond which iron depletion does not result in recovery of function. At end-stage disease, heart transplantation is a viable option with good survival rates. Importantly, screening of first degree relatives is important to ensure early detection of hereditary forms of hemochromatosis.

Fabry disease (angiokeratoma corporis diffusum universale)

Fabry disease is an X-linked inheritable deficiency of the lysosomal alpha-galactosidase A, resulting in an accumulation of glycosphingolipids in the lysosomes. There is a wide variety of know mutations, which all result in a different level of alpha-galactosidase inactivity, and hence, clinical manifestation may range from isolated myocardial disease to systemic involvement.

Patients may suffer from angina pectoris and myocardial infarction due to the accumulation of the aforementioned lipids in the endothelium of the coronary arteries, but the epicardial vessels show no abnormalities on angiography. Ventricular function is hampered due to thickening of the ventricular walls, which results in impaired diastolic compliance with a preserved systolic function, and may even precede myocardial hypertrophy. Other common features of the disorder include systemic hypertension, congestive heart failure, and mitral valve prolapse. The surface electrocardiogram may reveal a short P-R interval, atrioventricular block, and ST-segment and T wave abnormalities. Echocardiography may be inconclusive, but CMR imaging may differentiate Fabry disease from other infiltrative processes. Definite diagnosis is made on endomyocardial biopsy. Treatment of Fabry is safe and effective, and consists of enzyme-replacement therapy.

Gaucher Disease

Gaucher disease is an inheritable deficiency of beta-glucosidase, resulting in accumulation of cerebroside. Cardiac involvement results in impaired cardiac function due to reduced ventricular compliance. Treatment of Gaucher disease consists of enzyme replacement therapy, or liver transplantation as a last resort. Response to treatment with respect to recovery of symptoms is heterogeneous.

Glycogen storage disease

Glycogen storage disease may result in cardiac involvement in case of type II, III, IV and V, but survival until adulthood is rare except for type III disease. Cardiac involvement is characterized by left ventricular hypertrophy, electrographically and echocardiographically, but cardiac symptoms are frequently absent.

Endomyocardial fibrosis

Endomyocardial fibrosis is an important cause of congestive heart failure in equatorial Africa. Prevalence up to 20% has been reported, mostly familial in children or young adults, although symptoms occurred only in a minority of detected cases. The disease predominantly occurs in black individuals, but may rarely present in white subjects.

The fibrous lesions hamper cardiac function by impairing the inflow of the ventricles, affecting the left or both ventricles most commonly. Solitaire right-sided involvement is less frequent, occurring in approximately 10% of cases. Symptoms are concordant with the ventricles involved, an atrial fibrillation and ascites are known factors associated with a poor prognosis. Clinical diagnosis is based upon clinical presentation, lab testing, and angiography. Left-sided myocardial biopsy is relatively contraindicated, as it may result in systemic emboli.

Endomyocardial fibrosis is a relentless disease, half of patients not making it beyond 2 years after detection, depending on the extent of symptoms at presentation. Medical management is only effective in the early stages of the disease, and is aimed at relief of symptoms. Surgical correction of the clinical consequences of the disease, i.e. valve replacement, improves hemodynamic characteristics, but mortality is high, and fibrosis may reoccur.

Hypereosinophilic syndrome: Löffler Endocarditis

The hypereosinophilic syndrome is a systemic disease, involving several organ systems. Cardiac involvement, Löffler endocarditis, is usually present when eosinophil counts are high for a longer period of time. The eosinophilia itself may occur from several different causes.

Histopathology shows eosinophilic myocarditis extending into the subendocardium, endocardial thickening, and inflammation of the small intramural coronary vessels.

Clinical features of the disease are weight loss, cough, fever, and a rash. Cardiac involvement may not induce clinical symptoms in the early stages of the disease, but as the disease progresses as much as 50% of patients develop cardiomegaly or congestive heart failure.

Cardiomegaly may be suspected on chest radiography, and the electrocardiogram shows non-specific abnormalities of the ST-segment and T-waves. Conduction defects may also occur. Echocardiography often shows a normal systolic function, and may show apical obliteration by thrombus. Obliteration of the apex with a preserved systolic function is a key characteristic of the disease on angiography. Endomyocardial biopsy can provide the diagnosis, but may be false-negative.

Routine care applies to these patients. Diuretics and neurohumoral blockade are appropriate, as is anticoagulation. Corticosteroids and cytotoxic drugs increase survival in patients with Löffler endocarditis, and interferon may be used as a last option in refractory patients. Surgical therapy may be considered as palliative treatment in the fibrotic phase of the disease.

Arrhythmic cardiomyopathy: Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic Right Ventricular Cardiomyopathy, (ARVC, or ARVD: Arrhythmogenic Right Ventricular Disease, also AC Arrhythmogenic Cardiomyopathy) is characterized by fatty replacement and fibrosis of the heart. Most commonly, the right ventricle apex and outflow tract are involved. However, the left ventricle can be affected too. As a result of the fatty replacement and fibrosis, ventricular arrhythmias are common in this disease and can lead to palpitations, syncope and sudden death. At more advanced ages, right ventricular failure can occur.

ARVC is a progressive disease, and its incidence is estimated to be 1:3.000-1:10.000. The disease usually manifests at adolescence. Although the diagnosis is more often confirmed in athletes, physical activity is not thought to have a causal relationship with the disease. ARVC can occur in families; more than 9 different chromosomal defects have been described, most often with autosomal dominant inheritance. One unique form of ARVC, called Naxos disease (after the Greek island where it was first diagnosed), has an autosomal recessive pattern of inheritance.

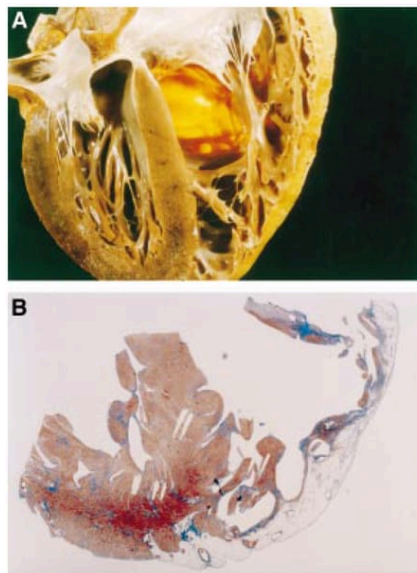


Figure 7.3.3: A section throughout the heart of an ARVC patient. (A) Transmurular fatty replacement of the right ventricular free wall. (B) Myocardial atrophy is confined to the right ventricle and substantially spares the interventricular septum as well as the left ventricular free wall. Reproduced with permission from BMJ Publishing Group Ltd.

Diagnosis

ARVC is a difficult diagnosis to make. Therefore, the European Society of Cardiology has created a list of diagnostic criteria for the diagnosis of ARVC, which were updated in 2009 (Tables 7.3.6 - 7.3.11). An online calculator can help in assessing the risk in an individual patient.

Tables 6-11: The Revised Task Force Criteria for ARVD / ARVC Revised Task Force Criteria.

I. Global or regional dysfunction and structural alterations*				
Major			Minor	
By 2D Echo:	By MRI:	By RV Angiography:	By 2D Echo:	By MRI:

I. Global or regional dysfunction and structural alterations*

- Regional RV akinesia, dyskinesia, or aneurysm - and 1 of the following (end diastole): - PLAX RVOT =32 mm (corrected for body size [PLAX/BSA] =19 mm/m²) - PSAX RVOT =36 mm (corrected for body size [PSAX/BSA] =21 mm/m²) - or fractional area change =33%	- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction - and 1 of the following: - Ratio of RV end-diastolic volume to BSA =110 mL/m² (male) or =100 mL/m² (female) - or RV ejection fraction =40%	Regional RV akinesia, dyskinesia, or aneurysm	- Regional RV akinesia or dyskinesia - and 1 of the following (end diastole): - PLAX RVOT =29 to <32 mm (corrected for body size [PLAX/BSA] =16 to <19 mm/m²) - PSAX RVOT =32 to <36 mm (corrected for body size [PSAX/BSA] =18 to <21 mm/m²) - or fractional area change >33% to =40%	- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction - and 1 of the following: - Ratio of RV end-diastolic volume to BSA =100 to <110 mL/m² (male) or =90 to <100 mL/m² (female) - or RV ejection fraction >40% to =45%
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*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

II. Tissue Characterization of Wall

Major	Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in =1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in =1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

III. Repolarization Abnormalities

Major	Minor
Inverted T waves in right precordial leads (V ₁ , V ₂ , and V ₃) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS =120 ms)	Inverted T waves in leads V₁ and V₂ in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V₄, V₅, or V₆ Inverted T waves in leads V₁, V₂, V₃, and V₄ in individuals >14 years of age in the presence of complete right bundle-branch block

IV. Depolarization/Conduction Abnormalities

Major	Minor
-------	-------

IV. Depolarization/Conduction Abnormalities

- | | |
|--|---|
| <ul style="list-style-type: none"> Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V₁ to V₃) | <ul style="list-style-type: none"> Late potentials by SAECD in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG Filtered QRS duration (fQRS) ≥114 ms Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms Root-mean-square voltage of terminal 40 ms =20 μV Terminal activation duration of QRS =55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V₁, V₂, or V₃, in the absence of complete right bundle-branch block |
|--|---|

V. Arrhythmias

- | Major | Minor |
|--|---|
| <ul style="list-style-type: none"> Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL) | <ul style="list-style-type: none"> Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis >500 ventricular extrasystoles per 24 hours (Holter) |

VI. Family History

- | Major | Minor |
|--|---|
| <ul style="list-style-type: none"> ARVC/D confirmed in a first-degree relative who meets current Task Force criteria ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation | <ul style="list-style-type: none"> History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead. Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories. |

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. E.g.: in TMEM43, DSP, PKP2, DSG2, DSC2, JUP.

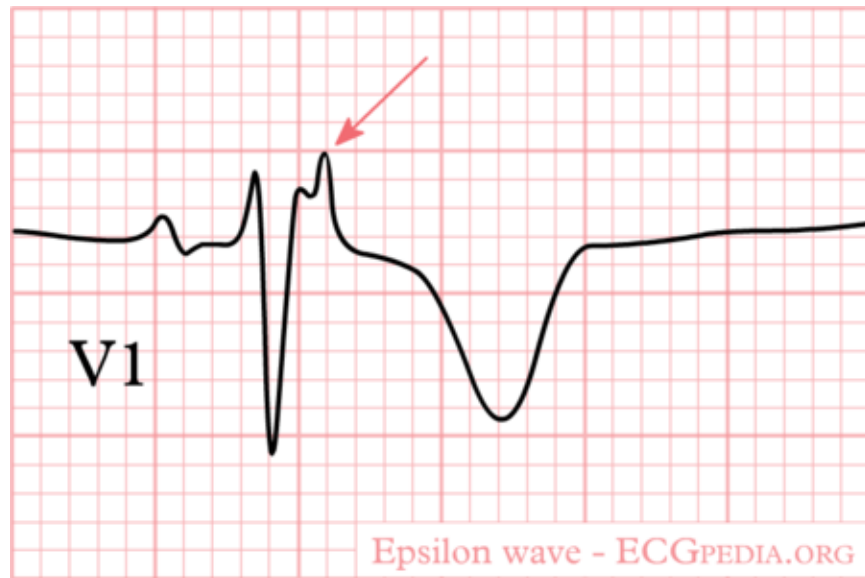


Figure 7.3.4: ECG with an epsilon wave in V1, a major depolarization/conduction abnormality

Treatment

Treatment focuses on avoiding complications.

- Medication:
 - Anti-arrhythmics: Sotalol better than Amiodarone.
 - ACE-inhibitors to prevent cardiac remodelling
- ICD implantation is recommended for the prevention of sudden cardiac death in patients with ARVC with documented sustained VT or VF who are receiving chronic optimal medical therapy.
- ICD implantation can be considered for the prevention of sudden cardiac death in patients with ARVC with extensive disease, including those with left ventricular involvement, 1 or more affected family member with SCD, or undiagnosed syncope when ventricular tachycardia or ventricular Fibrillation has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year.
- Radiofrequency ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent ventricular tachycardia, despite optimal anti-arrhythmic drug therapy.

Unclassified Cardiomyopathy: Left ventricular non-compaction

Left ventricular non-compaction (LVNC) is characterized by distinct structural abnormalities:

A two-layered structure of the myocardium, with a thin compacted epicardial band and a thick non-compacted endomyocardial part, overall resulting in a thickened myocardium. LVNC is diagnosed by the ratio between the maximal non-compacted and compacted myocardial layer thickness measured during end-systole. In adults, a non-compacted/compacted thickness ratio of ≥ 2 confirms the diagnosis, whereas a ratio of ≥ 1.4 is considered diagnostic in children. The non-compacted layer is further characterized by prominent trabeculations, with intertrabecular spaces in direct connection with the left ventricular cavity. The non-compacted regions are predominantly found in the lateral, apical or inferior wall of the left ventricle. Where normal myocardium, originally consisting of a sponge-like structure of myocardial fibres, shows a pattern of basal to apical, and epicardial to endocardial compaction of the myocardial fibres during the 5th to 8th week of embryonal development, non-compaction supposedly originates from halting of this process due to a genetic defect.

Clinical Presentation and Diagnosis

Age of onset may be highly variable, with cyanosis, failure to thrive or dysmorphic features described in the neonatal period, to adult patients presenting with LV failure or ventricular arrhythmia. Possibly, sudden cardiac death entails one of the manifestations of LVNC, although evidence is only limited at this moment. Owing to technical advances in the field of echocardiography, predominantly an increase in image resolution, LVNC has only recently been recognized as an independent

entity in the spectrum of cardiomyopathies, which supposedly has frequently been misdiagnosed as HCM in the past.

Two-dimensional echocardiography entails the cornerstone of LVNC diagnostics, enhanced by intravenous contrast agents if necessary. Magnetic resonance imaging may pose an option in case acoustic windows are insufficient. ECG abnormalities in patients with LVNC are mostly non-specific.

Considering the genetic background of LVNC, inheriting most commonly autosomal dominant, echocardiographic evaluation of family members of LVNC patients is pertinent.

Treatment and Prognosis

Treatment strategies are mainly extrapolated from other cardiomyopathies: standard heart failure therapy in case of LV dysfunction, beta-blockade and/or amiodarone in non-sustained VT in the absence of LV dysfunction, and ICD placement indicated in patients with LVEF <35%, sustained VT or recurrent unexplained syncope. Routine anticoagulation is not indicated, but anticoagulation may be instituted in case of ventricular dilatation or systolic LV function impairment.

The prognosis of LVNC has currently not yet been defined. One small report indicates a high mortality risk, owing to a high prevalence of sudden death, but community-based populations may well show a different prognosis as many patients with LVNC are non-symptomatic at the initial diagnosis.

8: PERICARDIAL DISEASE

The pericardium comprises two layers; the visceral layer that adheres to epicardial surface of the heart, and the parietal layer that surrounds most of the heart. Pericardial disease is common, and diagnosis is usually straightforward as the pericardium reacts to disruption by a wide variety of agents and processes in a relatively uniform manner. Typical presentation is with chest pain and fever, production of pericardial fluid with possible cardiac tamponade, or a constrictive pattern by thickening, retraction and calcification.

[8.1: Pericardial Disease - Acute](#)

[8.2: Pericardial Disease - Chronic](#)

[8.3: Pericardial Disease - Specific Types](#)

8.1: Pericardial Disease - Acute

Cardiac Tamponade

An increase in intrapericardial pressure, resulting in compression of the heart, and thereby a restriction of cardiac inflow, is termed cardiac tamponade. Tamponade may result from pericardial effusion of any cause. The intrapericardial pressure importantly determines to what extent cardiac inflow is decreased, but two factors need to be taken into consideration. First, intrapericardial pressure is determined not only on the amount of fluid that accumulates, but also on the rate with which this accumulation proceeds, and the available distensibility of the pericardium. Chronic effusions may therefore lead to small increases in intrapericardial pressures in the presence of large fluid accumulations, and small accumulations may directly lead to severe cardiac tamponade for example after free wall rupture. Second, the intravascular volume and intra-atrial, and -ventricular pressures determine at what pressure inflow becomes impaired. When intrapericardial pressure exceeds right atrial pressure (approximately 8 mmHg), tamponade typically follows. However, in patients in whom intra-atrial pressure is decreased, for example due to volume depletion, tamponade may already occur at lower intrapericardial pressures; low-pressure cardiac tamponade.

With increasing intrapericardial pressure, clinical features increase with severe hemodynamic compromise as its end stage. First, small changes in intrapericardial pressure induce subtle changes in arterial pressure, cardiac output, and variations in arterial pressure with inspiration (pulsus paradoxus). When intrapericardial pressure reaches levels similar to right atrial and diastolic right ventricular pressure echocardiographic evidence of tamponade may be found in diastolic collapsing of the right atrium, and increased variations of blood flow velocity over the cardiac valves with respiration. Fulminant clinical tamponade presents with symptoms that depend on its etiology. Acute cardiac tamponade based upon aortic or free wall rupture presents with syncope and sudden collapse, whereas tamponade in the setting of an acute inflammatory pericarditis may present with pericardial chest pain, and dyspnoea. Therefore, in patients presenting with chest discomfort, dyspnoea, tachycardia or tachypnoea, cardiac tamponade should be suspected when jugular distension, hypotension or pulsus paradoxus is present. Auscultation may reveal pericardial friction rub, and heart sounds may be faint. Echocardiography shows pericardial effusion, the previously mentioned diastolic collapsing of the cardiac cavities, increased flow velocity over tricuspid and pulmonary valves, and decreased flow velocity over the aortic and mitral valves.

When secondary to inflammatory pericarditis, tamponade up to moderate severity may be treated by anti-inflammatory drugs. In severe tamponade, pericardiocentesis should be performed to immediately alleviate intrapericardial pressure. Surgical drainage should be considered when pericardiocentesis is unsuccessful, or when tamponade recurs.

Acute pericarditis

Acute inflammation of the pericardium may result from a wide variety of etiologies (Table 8.2.1), and typically presents with chest pain, a pericardial friction rub on auscultation, and repolarization changes on the electrocardiogram.

Table 8.2.1

Causes of Acute Pericarditis
• Acute idiopathic pericarditis • Infectious pericarditis: ◦ Viral ◦ Tuberculosis ◦ Bacterial ◦ Others • Postpericardiotomy syndrome • Postmyocardial infarction pericarditis • Renal insufficiency • Neoplastic disease • Chest trauma • Irradiation • Collagen diseases

Patients present with a rapid-onset chest pain syndrome located precordial and retrosternal, and radiating to the subclavian region, the back and the trapezoid region. Chest pain is of moderate severity, lasting for several days, and increases with inspiration or chest movement. Patients typically alleviate the pain by sitting and leaning forward.

A pericardial friction rub is pathognomonic of pericarditis, and ECG changes are frequently present, which comprise diffuse concave ST-segment elevation, with positive T-waves in several leads. Atrial injury is accompanied by PR-segment depression. After several hours to a few days, ST-segments return iso-electric, and negative T-waves may occur subsequently, which may persist for several weeks although they frequently normalize within days. Pericardial effusion may be present, and can be diagnosed by chest X-ray when fluid accumulation exceeds 250mL, or by echocardiography.

Although initial presentation may mimic ST-segment elevation myocardial infarction (STEMI). Onset of chest pain is less abrupt in acute pericarditis, and varies with respiration. Furthermore, diffuse ST-segment changes are present in pericarditis, whereas STEMI presents with ST-segment elevation, and reciprocal depression, in leads corresponding to the ischemic myocardium. Biomarkers can be positive in both syndromes.

Treatment consists of aspirin while pain and fever are present, which usually adequately alleviates symptoms. Another option is NSAIDs, which are recommended when aspirin is insufficient or contraindicated. Corticosteroids should, however, be avoided as they are associated with relapsing pericarditis. Hospital admission may be necessary in patients with high fever, large effusions or cardiac tamponade.

Recurrent pericarditis

In 8 to 80% of patients, pericarditis recurs after a first episode of acute pericarditis. A continuous type, in which symptoms recur shortly after cessation of anti-inflammatory therapy, and an intermittent type, in which symptom-free periods of more than 6 weeks separate recurrences, can be distinguished. Frequently resulting from inadequate therapy or corticosteroid-use during the initial episode, subsequent recurrences are usually less severe. A recurrence should be treated according to the same procedures as for the first event. Pericardiectomy may be considered the last resort in severely refractory recurrent pericarditis, but its results are unpredictable. Prognosis of the disease is excellent, as severe complications are rare.

Pericardial effusion

Fluid accumulation in the pericardium, pericardial effusion, is a common finding on routine echocardiography, and is asymptomatic in the absence of inflammation or cardiac tamponade. It may result from any disease of the pericardium, or be iatrogenic. Most frequently it results from idiopathic pericarditis, malignancy, or iatrogenic defects (Table 8.2.2).

Table 8.2.2

Causes of Pericardial Effusion
• Any type of acute pericarditis • Cardiac surgery • Acute myocardial infarction • Heart failure • Chronic renal failure • Iatrogenic • Metabolic diseases • Autoimmune diseases • Trauma • Chylopericardium • Pregnancy • Idiopathic

Where the use of electrocardiography and chest radiography is limited in pericardial effusion, echocardiography may reveal an echo-free space in the anterior or posterior sacs, present throughout the cardiac cycle. The absence of cavity collapse indicates the absence of tamponade.

Treatment of pericardial effusion depends on the extent of symptoms, and the etiology underlying the effusion. Asymptomatic mild pericardial effusion (<10mm sum of echo-free spaces in anterior and posterior sacs) may be left untreated. Control echocardiography is indicated at 3-6 months. In moderate (10-20mm sum of echo-free space) to large effusions, a complete history, routine physical examination, ECG, chest radiography and routine blood analysis is indicated. Treatment is then based upon its expected etiology, standard treatment with aspirin or NSAIDs to relieve pain, with invasive procedures indicated in case of tamponade with hemodynamic compromise or recurrent pericarditis as discussed previously. Specific etiologies of pericardial effusion must be managed accordingly.

Chronic pericardial effusion

Pericardial effusion is considered chronic when moderate to large effusions persist for at least 3 months. Resulting most frequently from idiopathic cause, intrapericardial pressure is frequently elevated in these patients, which may lead to unexpected tamponade in up to 30% of patients. Hence, pericardiocentesis is indicated to alleviate the fluid accumulation, and pericardiectomy should be considered when large effusions recur. Long term outcome is excellent with this approach.

8.2: Pericardial Disease - Chronic

The pericardial layers may become rigid, thickened, and may fuse, resulting in restriction of cardiac filling; constrictive pericarditis. In contrast to cardiac tamponade, where cardiac is hampered throughout diastole, cardiac filling is prohibited in the last two-thirds of diastole in constrictive pericarditis, with preserved abrupt filling in early diastole.

Chronic constrictive pericarditis

Any form of pericarditis may end in constrictive pericarditis, presenting with chronic fatigue, dyspnoea, jugular distension, proto-diastolic pericardial knock, hepatomegaly, ascites, peripheral oedema, and pleural effusion. Atrial fibrillation is a common finding, and diffuse flattened or negative T-waves are usually present. These suggestive clinical findings, in addition to a physiology of restriction or constriction on echocardiography, and the presence of a thickened pericardium provide the diagnosis. However, a thickened pericardium may be absent, which does not rule out constrictive pericarditis. Pericardiectomy is the only effective treatment, which should be instituted shortly after diagnosis, as surgical mortality increases with increasing age and functional impairment.

Table 8.3.1: Differential diagnosis between chronic constrictive pericarditis and restrictive cardiomyopathy.

Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical Examination	
Early diastolic precordial impulse	Apical impulse may be prominent
Pericardial Knock	
No murmur	Third sound may be present Regurgitant murmur common
Electrocardiography	
Low voltage	Low voltage in amyloidosis
Frequent atrial fibrillation	Frequent atrial fibrillation
Normal QRS complex	Bundle branch block
Chest Radiography	
Pericardial calcification possible	Non-specific cardiomegaly
Echocardiography	
Normal wall thickness	Pericardial thickening
Diastolic notch of interventricular septum	
Increased wall thickness (amyloidosis)	Enlarged left and right atria
Doppler studies e' septal =8 cm/sec and normal S' mitral annular velocity	

Constrictive Pericarditis	Restrictive Cardiomyopathy
Mitral inflow increase during expiration Mitral flow propagation velocity M-mode colour =45cm/s Increased diastolic flow reversal in the hepatic vein with expiration e' septal <8cm/s and decreased mitral annular velocity	Mitral inflow velocity without respiratory variation Mitral flow propagation velocity M-mode colour <45cm/s Increased diastolic flow reversal in the hepatic vein with inspiration
Cardiac catheterization	
RVEDP and LVEDP usually equal RV systolic pressure <50mmHg	RVEDP >one-third of RV systolic pressure LVEDP often >5mm greater than RVEDP
Endomyocardial biopsy	
Normal or non-specific changes	May reveal specific causes
CT/MR imaging	
Pericardium thickened or calcified	Normal pericardium
CT, computer tomography; e', e wave velocity by tissue velocity imaging;	
LVEDP, left ventricular end-diastolic pressure; MR, magnetic resonance;	RV, right ventricular; RVEDP, right ventricular end-diastolic pressure.

Subacute elastic constriction

Elastic cardiac constriction, in contrast to the rigid chronic constriction, results from an elastic thickened pericardium, which still allows distension during the respiratory cycle. It may be seen in the first period after acute inflammatory or infectious pericarditis, and may progress to chronic pericardial constriction, or prove to be a transient process.

Effusive-constrictive pericarditis

Presenting with cardiac tamponade on admission, effusive-constrictive pericarditis is characterized by a persistent increase in right atrial and end-diastolic ventricular pressures after intrapericardial pressure has been alleviated by pericardiocentesis. Apart from idiopathic cases, it may accompany chest radiation, cardiac surgery, neoplasia, and tuberculosis. Most frequently, the disease will progress to persistent constriction for which epicardiectomy is indicated, but it may rarely be a transient phenomenon.

Transient cardiac constriction

Clinical and hemodynamic features of constrictive pericarditis may dissipate spontaneously, which is seen commonly (20%) in idiopathic acute pericarditis with effusion, but may also be seen in tuberculous and purulent pericarditis. Hence, a primarily conservative approach may alleviate the need for epicardiectomy.

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8.3: Pericardial Disease - Specific Types

Infectious pericarditis

Idiopathic/Viral pericarditis

This is the most frequent form of pericarditis, accounting for more than 80% of cases, of which most probably are of viral etiology, but virus identification is cumbersome and no treatment consequences exist. The disease is frequently accompanied by pericardial effusion, cardiac tamponade, and left pleural effusion, but prognosis is notably good.

Tuberculous pericarditis

Predominantly found in developing countries, and in patients with human immunodeficiency virus (HIV) infection, tuberculous pericarditis is rare in the Western world and presents typically with symptoms of acute pericarditis. Identification of *Mycobacterium tuberculosis* yields the diagnosis, which may be found in pericardial or other bodily fluids, or may be assumed when caseating granulomas are found. Routine tuberculosis treatment, comprising three antituberculous agents, yields a good prognosis although a subacute constrictive pericarditis is common, requiring pericardiectomy but with excellent outcome.

Purulent pericarditis

Purulent pericarditis has a high mortality, owing to the intangible diagnosis and the related severity of the underlying disease. Cardiac tamponade is frequent, and acute constrictive pericarditis may occur. The disease should be considered in all patients presenting with high fever, dyspnoea, and tachycardia with intrathoracic or subphrenic infections, or sepsis with symptoms that suggest pericardial involvement. Pericardiocentesis is indicated even in the absence of tamponade when the disease is confirmed, and appropriate antibiotic treatment should be instituted. Long-term prognosis is however excellent in patients that survive until discharge.

Post myocardial infarction pericarditis

Pericardial effusion frequently occurs in the early stage after myocardial infarction, which remains asymptomatic and can be left untreated. Within the first week after myocardial infarction, acute pericarditis may occur, which is related to the extent of the infarction. The presence of a pericardial rub may distinguish chest pain and ECG changes resulting from acute pericarditis from recurrent ischemia.

Weeks to months after myocardial infarction, pleuropericarditis of autoimmune nature may prevail, termed Dressler's syndrome. However, this syndrome is rare, and treatment with corticosteroids yields a good prognosis.

Neoplastic pericarditis

Lung cancer is the most frequent cause of neoplastic pericarditis. Cardiac tamponade in patients with a history of malignancy, in the absence of inflammatory signs indicates a possible malignant etiology, as is lack of response to NSAIDs in this patient group. When the effusion is indeed of malignant origin (approximately 40% of cases), treatment aims at alleviation of symptoms and the prevention of recurrences. A balance should be sought between pericardiocentesis in which recurrence is frequent, and pericardiectomy, which may be overly aggressive in this critically ill subset of patients.

Hypothyroidism

With increasing severity of primary hypothyroidism, the prevalence of pericardial effusion increases. Thyroid hormone replacement therapy results in remission of the effusion.

Post-pericardiotomy pericarditis

Pericarditis is common after cardiac surgery (18%), of which the etiology is unclear although an autoimmune origin has been proposed. In contrast to other forms of pericarditis, post-pericardiotomy pericarditis may be effectively treated with corticosteroids and NSAIDs.

9: ATHEROSCLEROSIS

- 9.1: Introduction to Atherosclerosis
- 9.2: Arterial Vessel in Homeostasis
- 9.3: Arterial Vessel in Atherosclerosis
- 9.4: Complications of Atherosclerosis
- 9.5: Risk Factors of Atherosclerosis (incomplete)
- 9.6: References

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9.1: Introduction to Atherosclerosis

A 53 years old man, without medical history or medication visits the family physician and makes an anxious impression. His friend has recently suffered from a myocardial infarction (MI) and he is worried that he might also soon face the same situation. As for family medical history, he has a father with hypertension and an uncle with diabetes mellitus. He does not seem to have any symptoms or complaints at this moment, but he has been smoking for 25 years and is overweight. Because of these characteristics he is worried that he will suffer from a MI. Upon physical examination, his BMI was 29 kg/m^2 , RR was 152/90 mmHg and heart rate was 75 bpm. The family physician orders a blood test for lipid profile and glucose. Both turn out to be in the normal range.

The family physician gives the patient advice concerning primary prevention for atherosclerosis; quit smoking, try to achieve weight reduction, do regular physical activity, restrict alcohol consumption to less than 3 drinks a day and follow a varied and balanced diet. Regarding hypertension, the advice is to keep his RR under 140/90 mmHg. Antihypertensive medication is not indicated at this moment, because his 10-years risk of death due to cardiovascular disease (Systematic Coronary Risk Evaluation) is lower than 20%. He is advised to undergo regular checkups of cardiovascular risk profile or report to the doctor's office in case of chest pain.

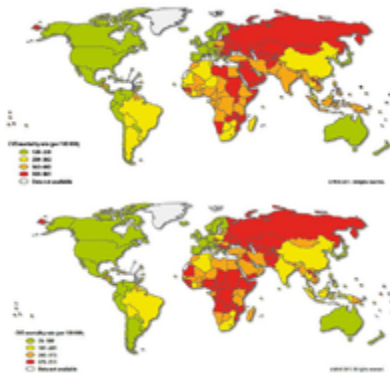


Figure 9.1.1: World map CVD mortality rates in males (left) and females (right)

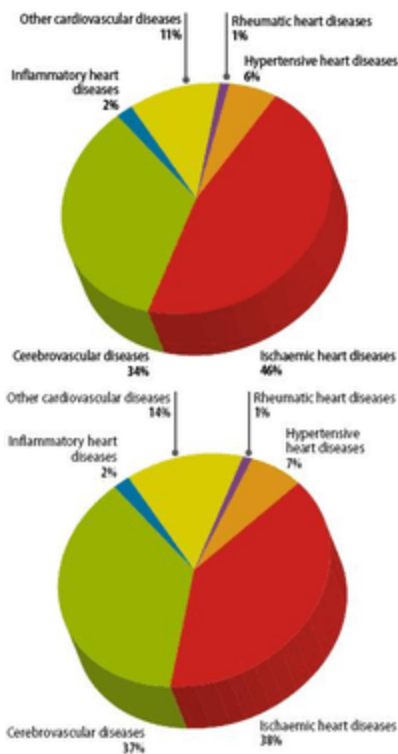


Figure 9.1.2: Distribution of CVD death among males (left) and females (right) in 2008

Since the 20th century, cardiovascular disease (CVD's) has grown to be the leading cause of death and disability in the world, illustrated by 17.3 million deaths per year in 2008. Amongst cardiovascular disease, coronary heart disease (46% among males, 38% among females) and cerebrovascular disease (34% among males, 37% among females) account for the largest proportion of CVD. In 2008, heart attack and stroke were responsible for 7.3 million deaths and 6.2 million deaths, respectively. Obstructive coronary and cerebrovascular diseases are caused, in the vast majority of cases, by atherosclerosis. Atherosclerotic vascular disease begins early in life and over time can eventually lead to obstructive arterial disease. Once atherosclerotic lesions become clinically significant, serious acute complications such as ischemic heart disease, MI and stroke may occur. This chapter deals with the complex pathological process of atherosclerosis, possible consequences of atherosclerosis and the most recent treatment for atherosclerosis in order to prevent CVD's.

9.2: Arterial Vessel in Homeostasis

The core of the pathogenesis of atherosclerosis is a disease state of the arterial wall. In order to understand the pathogenesis of atherosclerosis, it is thus necessary to know about the function and normal morphology of non-pathological arteries.

Three layers of arterial vessel

The normal arterial vessel consists of 3 layers, namely intima, media and outer adventitia.

The intima is located closest to the arterial lumen and is therefore most 'intimate' with the blood. This layer is composed of a single layer of endothelial cells (endothelium), connective tissue, and several smooth muscle cells. The endothelium functions as an active metabolic barrier as well as a carrier between blood and the arterial wall. It plays a crucial role in atherosclerosis. Connective tissue consists of a matrix of collagen, proteoglycans and elastin. Lymphocytes, macrophages and other types of inflammatory cells may occasionally reside in the intima.

The media is the middle layer and its inner and outer boundaries are formed by the internal and external elastic laminae. The media consists of layers of smooth muscle cells with contractile and synthetic function. As for the contractile function, smooth muscle cells enable vasoconstriction and vasodilatation. As for the synthetic function, they are responsible for the growth of the vascular extracellular matrix.

The most external vessel wall layer is called the adventitia and contains fibroblasts, connective tissue, nerves, lymphatics and vasa vasorum. Inflammatory cells may also occasionally reside in the adventitia.

There is a constant dynamic interchange between the arterial wall and its cellular components and the surrounding extracellular matrix. By understanding the physiology of this dynamic interchange and the function of each cellular component, the dysfunction of these cellular components leading to atherogenesis can be better understood.

Cellular components involved in atherosclerosis

Endothelial cells

The normal artery wall contains endothelial cells that manage the homeostasis of the wall by structural, metabolic, and signaling functions. The endothelium plays a role as a barrier to elements contained in the blood, but is also an active biologic interface between the blood and other tissues, regulating cellular and nutrient trafficking. It has several important functions such as keeping certain elements in blood separated from the vessel and maintaining a balance between pro-coagulant and anticoagulant activity, pro- and anti-inflammatory response, and contracted and relaxed vasomotor tone.

The endothelium produces antithrombotic molecules in order to prevent blood from clotting. Certain molecules such as heparin sulfate, thrombomodulin, and plasminogen rest on the endothelial surface whereas molecules such as prostacyclin and nitric oxide (NO) enter the blood. Endothelium can produce prothrombotic molecules when it encounters stressors; however, it normally maintains a balanced anticoagulant state, maintaining blood fluidity.

Endothelial cells also have an important function as a regulator of the immune response. In a normal situation without pathologic stimuli, endothelial cells are not capable to attract and bind patrolling leukocytes, thus maintaining an anti-inflammatory state. When local injury or infection initiates pathologic stimulation, endothelial cells respond by secreting chemokines that attract white blood cells to the injured area. Additionally, endothelium produces cell surface adhesion molecules, which recruit mononuclear cells to the endothelium and therefore promote their migration to the injury site. This response is important for the development of atherosclerosis.

Another function of endothelium is to modulate contraction of smooth muscle cells in the media by releasing substances such as vasodilators and vasoconstrictors. Vasodilators (e.g. NO, prostacyclin) and vasoconstrictors (e.g. endothelin) fine-tune the resistance of the vessel and subsequently alter the arterial blood flow. Endothelium normally maintains a state of net relaxed vasomotor tone with a predominance of vasodilators. Endothelium can also respond to various physical stimuli such as shear stress and can additionally dilate the blood vessel. The endothelium principally regulates such response through release of NO.

This endothelial-dependent response is called flow-mediated vasodilation (FMD), which can be measured for clinical evaluation of endothelial function. For example, impairment of FMD is observed in the early stages of atherosclerosis. However, endothelial function tests are currently not recommended to be used for surrogate markers in clinical practice since the tests are technically challenging and the validation of clinical benefits in the evaluation of cardiovascular risk requires more evidence.

As mentioned earlier, endothelial cells can respond to or in other words get 'activated' due to changes in the local extracellular milieu. Examples of such changes are common stresses (e.g. shear stress and mild changes in temperature), transient infections and minor trauma. The term 'endothelial cell activation' (EC activation) refers to a change from the normal state, illustrated by loss of barrier function, pro-adhesive (leukocyte adhesion), vasoconstriction, and procoagulant properties. EC activation is not necessarily linked to disease and can be temporary and mild or permanent and severe.

In conclusion, the normal arterial endothelium consists of a dynamic interface with net anticoagulant properties, net relaxation of smooth muscle cells and anti-inflammatory characteristics. Endothelial cells may react to various changes in homeostasis and become 'activated endothelial cells'.

Vascular smooth muscle cells

As mentioned earlier, smooth muscle cells have two functions, namely contractile and synthetic. Vasoconstriction and vasodilatation are regulated by various vasoactive substances such as angiotensin II, acetylcholine, NO and endothelin, which are released by endothelium. Another element of contractile function is the elasticity of the vessel, which is regulated by the lamina elastica. They are situated between the smooth muscle cells and are responsible for the stretching of the vessel during systole and diastole. This function is crucial in the pathogenesis of atherosclerosis, because it prevents the weakening of the vessel wall that can prevail as a complication of atherosclerosis. For example, aneurysm due to weakening of the vessel wall is a serious complication of atherosclerosis.

It is important to understand the synthetic function of smooth muscle cells since the dysfunction of it is thought to contribute to the pathogenesis of atherosclerosis. Normally the smooth muscle cells synthesize collagen, elastin and proteoglycans that form the connective tissue matrix of the vessel wall. Smooth muscle cells can also synthesize vasoactive and inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). These mediators stimulate leukocyte migration and induce the endothelial cells to express leukocyte adhesion molecules as mentioned earlier. This synthetic function is found to be more dominant in case of an atherosclerotic plaque, which is illustrated in the next section (1.2). Although smooth muscle cells rarely divide in normal circumstances, it can proliferate in response to injury, which is an important sign of atherosclerotic plaque formation.

Extracellular matrix

Vascular extracellular matrix in the media consists of elastin, proteoglycans and fibrillar collagen, which are principally synthesized by smooth muscle cells as mentioned earlier. With the provision of flexibility by elastin and biomechanical strength by fibrillar collagen, the arterial vessel is able to maintain the structural integrity despite high pressure within the lumen.

9.3: Arterial Vessel in Atherosclerosis

Three pathologic stages of atherogenesis

Atherogenesis can be divided into five key steps, which are 1) endothelial dysfunction, 2) formation of lipid layer or fatty streak within the intima, 3) migration of leukocytes and smooth muscle cells into the vessel wall, 4) foam cell formation and 5) degradation of extracellular matrix. Via these consecutive steps, an atherosclerotic plaque is formed. The formation of the plaque can also be divided into three major stages namely 1) the fatty streak, which represents the initiation 2) plaque progression, which represents adaption and 3) plaque disruption, which represents the clinical complication of atherosclerosis.

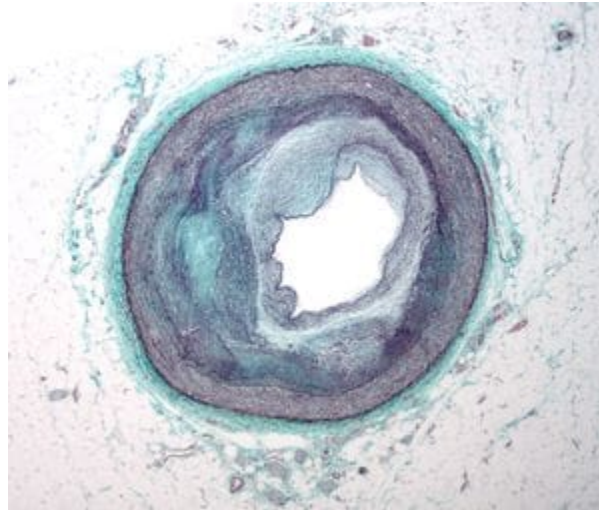


Figure 9.3.1: Atherosclerotic plaque in a coronary artery

Initiation and formation of atherosclerotic plaque

The earliest visible signs of atherogenesis are the fatty streak and pre-existing lesions of adaptive intimal thickening. Fatty streak is a yellow discoloration on the surface of the artery lumen, which is flat or slightly elevated in the intima and contains accumulations of intracellular and extracellular lipid. At this stage of initiation, the fatty streak doesn't protrude substantially into the artery wall nor impedes blood flow. This process is already visible in most people by the age of 20. At this stage, there are no symptoms and this lesion may even diminish over time. Initiation of fatty streak development is most likely caused by endothelial dysfunction, since it involves entry and modification of lipids within the subintima. This modified layer of lipids creates a proinflammatory environment and initiates the migration of leukocytes and formation of foam cells (Figure 9.3.2). Intimal thickening mainly contains smooth muscle cells and proteoglycan-collagen matrix with a few or no infiltrating inflammatory cells.

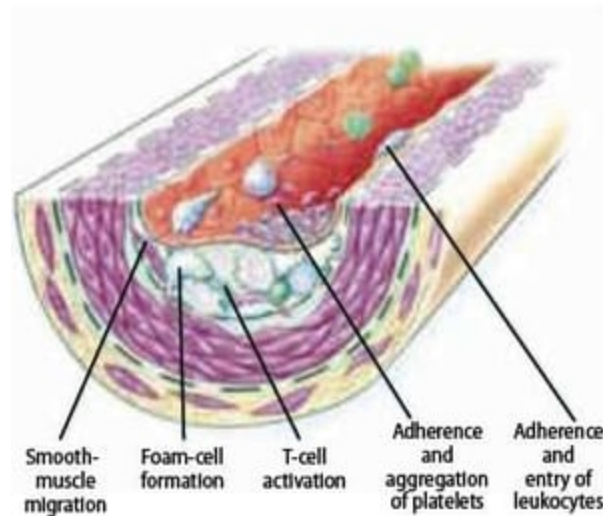


Figure 9.3.2: Fatty streak formation

Endothelial dysfunction

Endothelial dysfunction is a primary event in atherogenesis, which can be caused by various agents, such as physical stress and chemical irritants. Endothelial dysfunction is also observed in other pathological conditions, which are often related to atherosclerosis such as hypercholesterolemia, diabetes, hypertension, heart failure, cigarette smoking and aging.

Factors Correlated with Endothelial Dysfunction

- Increased age
- Male sex
- Family history of coronary heart disease
- Tobacco smoking
- Elevated cholesterol
- Low HDL-cholesterol
- Diabetes mellitus
- Hypertension
- Obesity
- High fat consumption

Endothelial cells can display different reactions according to various levels of physical stress. There are two atheroprotective endothelial functions from physical stress. When endothelial cells are exposed to laminar flow, which display minimal physical stress, they secrete NO. NO functions as an anti-atherosclerotic substance through vasodilation, inhibition of platelet aggregation and anti-inflammatory effects. The second function is executed, when exposed to laminar flow by an expression of the antioxidant enzyme superoxide dismutase. This enzyme performs anti-atherosclerotic role by acting against reactive oxygen species, which are produced by chemical irritants or transient ischemia in the vessel.

Interventions that enhance endothelial function

- L-arginine
- Estrogen
- Antioxidants
- Quit smoking
- Reducing cholesterol
- Exercise

Unfortunately, these two atheroprotective endothelial functions can be impaired by several factors. The first factor is disturbed flow (low shear stress with rapid fluctuations), which is typically located at arterial branch points and bifurcations and can impair the protective functions. This is well illustrated by the difference in prevalence of atherosclerosis between branched arteries and bifurcated vessels. Bifurcation areas such as the common carotid and left coronary arteries are common deposition sites for

atherosclerosis than arteries with few branches such as the internal mammary artery. Thus, many observations show that the distribution of atherosclerotic lesions is common in large vessels and they vary in location and frequency among different vascular beds. These findings encourage a belief that hemodynamic factors play an important role in atherogenesis. Furthermore, the fact that hypertension intensifies the severity of atherosclerotic lesions additionally supports this hypothesis.

Another major factor that can impair the atheroprotective endothelial function is chemical irritants such as cigarette smoking, abnormally high circulating lipid levels and high glucose level (diabetes mellitus). They can contribute to endothelial dysfunction and are all well-known risk factors for atherosclerosis. Exposure to chemical irritants promotes endothelial dysfunction by increasing endothelial production of reactive oxygen species, which alter the metabolic and synthetic functions of endothelial cells. As a result, the endothelium becomes inclined to exhibit proinflammatory processes, such as secreting inflammatory cytokines.

In conclusion, hemodynamic and chemical stressors contribute to disturbance of endothelial homeostasis and promote endothelial dysfunction. This results in impairment of permeability barrier function, secretion of inflammatory cytokines, stimulation of adhesion molecules on the cell surface that promote leukocyte recruitment, and altered antithrombotic properties and release of vasoactive molecules (Figure 9.3.3). Consequently, these effects establish the groundwork for further advancement of atherosclerosis.

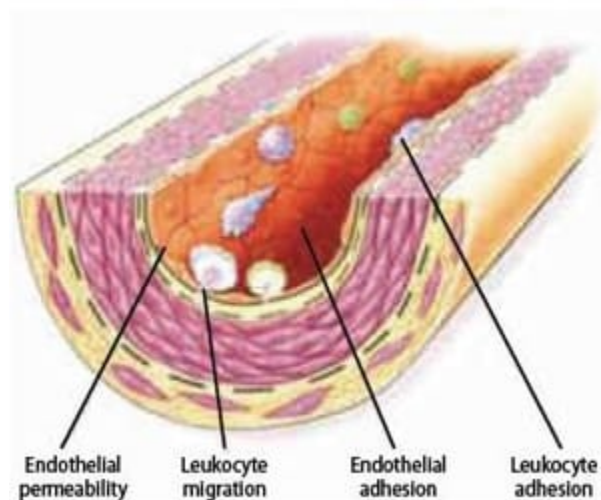


Figure 9.3.3: Endothelial dysfunction: Leukocyte adhesion and migration into the deep layer of the intima.

Lipoprotein entry and modification

Disruption of the integrity of endothelial barrier due to endothelial dysfunction allows the passage of circulating lipoproteins (low-density lipoprotein, LDL) into the intima. By binding to proteoglycans, LDL particles start to accumulate. This accumulation is a critical process in atherogenesis since LDL may undergo chemical modifications while residing longer in the intima. It is needless to say that an elevated circulating LDL concentration strongly contributes to this accumulating process. Another major risk factor for this process is hypertension since it causes augmented vessel wall stress. Elevated vessel wall stress influences smooth muscle cells to synthesize proteoglycans in the intima, promoting LDL-binding with proteoglycans and therefore contributing to “trapping” of lipoproteins and lipid accumulation within the intima. At this point, macrophages adhere to dysfunctional endothelial cells and transmigrate into the intima. These macrophages are called ‘foam cells’ after they have taken up lipids.

As mentioned earlier, chemical modification occurs with LDL when chronic accumulation takes place inside the intima. There are several types of chemical modification that may occur. One is called oxidation and it results from the chemical reaction of reactive oxygen species and pro-oxidant enzymes produced by endothelial or smooth muscle cells, or macrophages penetrating the intima. This type of oxidative stress leads to cellular dysfunction and damage in endothelial cells and macrophages. Furthermore, chronic hyperglycemia can stimulate glycation of LDL that may ultimately alter LDL into an antigenic and proinflammatory molecule. This explains why diabetes mellitus is a major risk factor for atherosclerosis. The biochemical modification of LDL into a proinflammatory molecule contributes to the inflammation process established by endothelial dysfunction. Furthermore, the oxidized LDL molecule induces tissue damage, which can initiate angiogenesis, forming new vasa vasorum in the plaque. It also induces leukocyte recruitment and foam cell formation in the fatty streak throughout the plaque development.

Leukocyte recruitment

Leukocyte recruitment to the arterial wall is another key step in atherogenesis, which is dependent on two important factors; expression of leukocyte adhesion molecules (LAM) on the endothelial wall and chemoattractant signals that direct diapedesis (intruding of molecules through the intact vessel wall). These two factors mainly direct monocytes to the atherosclerotic lesion. T lymphocytes that play a central role in the immune system reside within plaques at all stages of atherogenesis, mainly producing cytokines.

As mentioned earlier, modified LDL can maintain leukocyte recruitment by inducing LAM and chemokine expression. It can also stimulate endothelial and smooth muscle cells to produce proinflammatory cytokines. These proinflammatory cytokines can also induce LAM and chemoattractant cytokine expression, equivalent to the working of modified LDL. In conclusion, modified LDL can directly or indirectly promote leukocyte recruitment and atherogenesis.

Foam cell formation

When monocytes enter the intima, they differentiate into phagocytic macrophages. These phagocytic macrophages may become foam cells when they absorb lipoproteins. They don't phagocytose LDL with a classic cell surface LDL-receptor, since it does not recognize modified LDL, but with a family of 'scavenger' receptors that do bind and internalize modified LDL. Uptake by scavenger receptors avoids negative feedback inhibition from the high cholesterol content unlike the classic LDL-receptors, and allows the macrophages to imbibe cholesterol-rich lipid that results into the formation of foam cells. This uptake seems to be beneficial at first sight, since it absorbs the inflammatory modified-LDL, however since these foam cells have impaired trafficking, they will be locally accumulated in the plaque and encourage the plaque progression by serving as a source of proinflammatory cytokines.

Plaque progression

The atherosclerotic plaque at this stage is called fibrous cap atheroma featuring two characteristics, which are lipid-rich necrotic core and encapsulation by a fibrous cap (Figure 9.3.4). The fibrous cap is an area between the vessel lumen and the core of the plaque, which contains dead foam cells, macrophages, smooth muscle cells, lymphocytes and extracellular matrix. A distinctive hallmark of this phase is necrosis with macrophage infiltration around a lipid pool and loss of proteoglycans or collagen. At this point, the deposition of free cholesterol is not easily visible and the plaque does not always cause luminal restriction of blood flow due to a compensatory outward remodeling of the plaque wall. This remodeling preserves the diameter of the vessel lumen and thus may evade detection by angiography. Continuous plaque growth at a later stage contains cellular debris, higher free cholesterol and results into complete depletion of extracellular matrix. From this stage, the fibrous cap atheroma may go through episodes of hemorrhage with or without calcification and even fibrous cap disruption. Progressive vessel narrowing may result in ischemia and can cause ischemic symptoms such as angina pectoris or intermittent claudication.

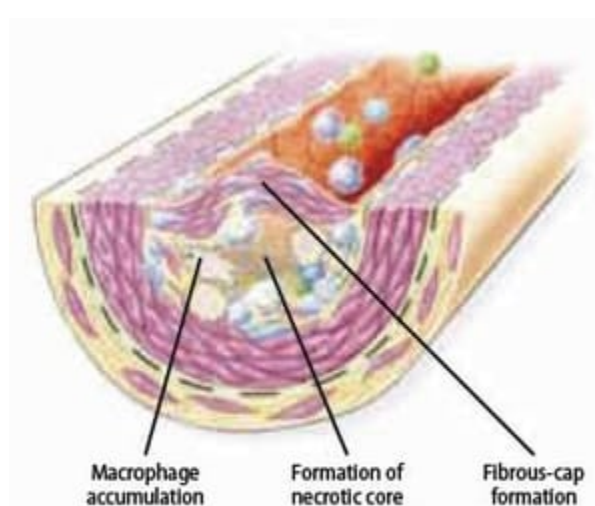


Figure 9.3.4: Fibrous cap formation and the necrotic core.

Smooth muscle cell migration

Smooth muscle cells play a central role at the phase of transition from fatty streak to plaque formation. During this phase, smooth muscle cells migrate from the media to the intima. After migration, smooth muscle cells proliferate within the intima and secrete extracellular matrix macromolecules. Additionally, foam cells, activated platelets and endothelium stimulate substances that induce the migration and accumulation of smooth muscle cells. For example, foam cells release platelet derived growth factor (PDGF), cytokines and growth factors that directly contribute to the migration and proliferation process, and they also activate smooth muscle cells and leukocytes to reinforce inflammation in the atherosclerotic lesion. Although plaque progression is traditionally known as a gradual and continuous process, recent evidence claims that this process can be strongly accentuated by bursts of smooth muscle replication. The observation of small ruptures within the plaque occurring without any clinical symptoms or signs supports this suggestion. These small ruptures expose tissue factor secreted by foam cells that stimulates coagulation and microthrombus formation in the lesion. Such microthrombi contain activated platelets that release additional factors such as PDGF and heparinase that can further stimulate local smooth muscle cell migration and proliferation. Heparinase stimulates smooth muscle cell migration and proliferation by degrading heparan sulfate, which normally counteracts this process.

Extracellular matrix metabolism

Metabolic processes in extracellular matrix play a central role in bridging the plaque progression to plaque rupture. Ultimately, this process weakens the fibrous cap, predisposing it to rupture. This process is influenced by the balance of matrix deposition synthesis by smooth muscle cells and degradation by matrix metalloproteinases (MMP), a class of proteolytic enzymes. For example, PDGF and TGF- β stimulate interstitial collagen production, while inflammatory cytokines such as IFN- γ inhibits collagen synthesis. TGF- β also induces formation of fibronectin and proteoglycans. It is an important regulator since it enhances the expression of protease inhibitors, leading to the inhibition of proteolytic enzymes that promote matrix degradation. On the other hand, inflammatory cytokines weaken the fibrous cap by stimulating local foam cells to secrete MMP that degrades collagen and elastin of the fibrous cap. Furthermore, the deeper parts of the thickened intima undergo necrosis due to poor nourishment.

Plaque rupture

Integrity of plaque

Chronic shifting of the balance towards extracellular matrix metabolism leads to serious consequences for the plaque integrity. As mentioned earlier, it accelerates inflammatory stimulation or activation of apoptosis pathways and therefore leads to death of smooth muscle and foam cells. Cell death leads to release of cellular contents, whereby more lipids and cellular debris is absorbed to the dynamic lipid core. Due to this process, the size of the lipid core grows and as a result alters biomechanical environment and hence the stability of the plaque. One example of this is a plaque border adjacent to the normal tissue, called shoulder region, which is the main location where the hemodynamic stress is focused. As the size and the protrusion of the plaque in the vessel increase, the hemodynamic stress will also increase around the shoulder region. Furthermore, local accumulation of foam cells and lymphocytes at this site makes the plaque more susceptible to rupture by accelerating degradation of extracellular matrix. However, although shoulder area is considered as the weakest point where the fibrous cap would mostly likely rupture, there have been autopsy studies that showed an equal number of ruptures occurring at the midportion of the fibrous cap. When the fibrous cap is very thick and contains small lipid core, the plaque is called stable and it may reinforce the narrowing of the artery, but on the other hand diminishes the susceptibility to rupture. Plaques with thinner fibrous caps are called vulnerable plaques. They are identified by a large necrotic core, rich with lipid, taking about 25% of the plaque area, and a thin fibrous cap of less than 65 μ M thickness, which separates the necrotic core from the vessel lumen. Vulnerable plaque is infiltrated by a large amount of macrophages and a smaller amount of T-lymphocytes. It typically lacks smooth muscle cells due to apoptosis. This type of lesion causes less obstruction in the artery, but is more fragile and has higher susceptibility to rupture and trigger thrombosis than a thick fibrous cap. At this stage, plaque hemorrhage can occur due to rupture of vasa vasorum within a plaque. Vasa vasorum is a newly formed vascularization in the plaque due to tissue damage. Due to its fragility it may rupture easily, increasing the risk to form intraplaque hemorrhage. Intraplaque hemorrhage may lead to subsequent rupture of the fibrous cap (Figure 9.3.5) or occlusion of the vessel through intramural hematoma. Plaque calcification is another factor that contributes to plaque rupture. It usually occurs in areas of necrosis and elsewhere in the plaque and can eventually lead to higher rigidity of the vessel wall. Calcification is dependent on mineral deposition and resorption by osteoblast-like and osteoclast-like cells in the vessel wall. In conclusion, there are seven important factors associated with plaque ruptures; range of inflammation area, considerable size of lipid core, fibrous cap thinner than 65 μ M, apoptosis leading to fewer smooth muscle cells, disrupted balance of proteolytic enzymes and their inhibitors, plaque calcification, and hemorrhage in the plaque. Although it remains difficult to foresee the clinical consequences, progression to a complicated plaque can lead to major cardiovascular disease, mostly affecting individuals

in their 60s and 70s, although it may also occur among people at an earlier age.

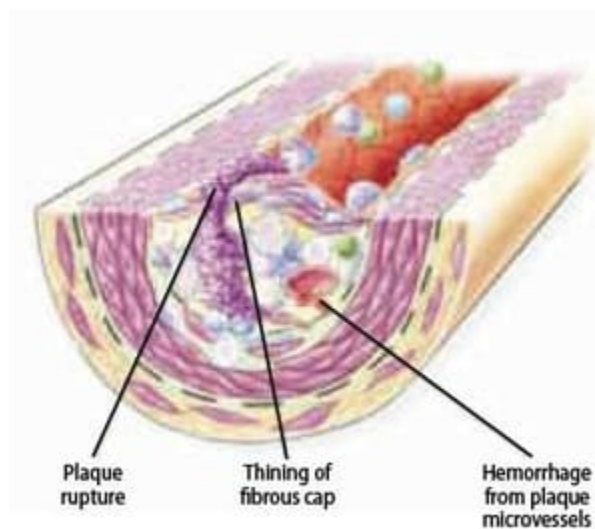


Figure 9.3.5: The ruptured plaque.

Thrombogenic potential after rupture

When the fibrous cap is ruptured, the highly thrombogenic components of the necrotic core, including tissue factor, gets in direct contact with the circulating monocytes in the blood. It is believed that these circulating monocytes in the blood play a stronger role as a source of tissue factor than the necrotic core. Tissue factor stimulates platelet activation and thus can initiate and propagate thrombus. The thrombus formed at the rupture site is called white thrombus due to its grossly white appearance of rich platelet. At the proximal and distal ends near the site of white thrombosis there is another type of thrombus composed of layers of red blood cells and fibrin and is therefore called red thrombus. Thrombosis can be healed through several processes such as penetration of smooth muscle cells, neovascularization via vasa vasorum, proliferation of extracellular matrix, inflammation and re-endothelialization on the luminal surface. Thus clinically, ruptures can be silent and heal, without major clinical complications such as MI and stroke. For example, small non-occlusive thrombi may be reabsorbed into the plaque, continuing the process of smooth cell growth and fibrous deposition. The extent of how occlusive and transient the thrombus will be is largely dependent on the thrombogenic potential of the plaque.

The counter-balancing of coagulation and fibrinolysis also determines the probability of a major clinical event due to occlusive thrombosis. Inflammatory stimuli in the plaque environment incite smooth muscle cells, endothelial cells, and foam cells to release tissue factor that initiates the extrinsic coagulation pathway. Inflammatory stimuli also stimulate expression of antifibrinolytics such as plasminogen activator inhibitor-1 and consequently enhance thrombosis. As mentioned earlier, the activated endothelial cells also contribute to thrombosis and coagulation by depositing fibrin at the vascular wall. Thus, the inflammatory and dysfunctional condition of the plaque environment decreases the counterbalancing of coagulation and fibrinolysis, increasing the probability of major clinical complications of atherosclerosis.

The concept of 'vulnerable plaque' has developed into a new concept of 'vulnerable patient' as the concept of pathogenesis of atherosclerosis was linked to a person's susceptibility to coagulation and thus vascular events, which can be influenced by many personal factors such as genetics (e.g. procoagulant prothombin gene mutation), coexisting condition (e.g. diabetes), and lifestyle factors (e.g. smoking, obesity).

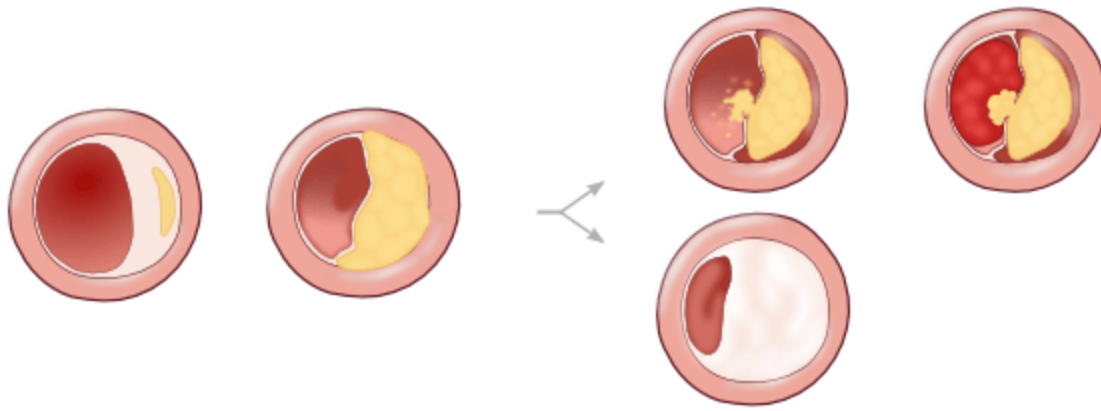


Figure 9.3.6: Progression of coronary atherosclerosis can be gradual (bottom) or can lead to plaque rupture with acute occlusion of a coronary vessel due to clot formation

9.4: Complications of Atherosclerosis

The clinical complications of atherosclerosis are highly dependent on the location and size of affected vessels, the duration of the chronic process, and the type of plaque, since the severity of impairment of atherosclerosis differs throughout the vasculature. For example, 'stable plaque' can easily result into angina pectoris due to its thick fibrous cap that directly affects the diameter of the relatively small coronary vessels. On the other hand, 'vulnerable plaque' is non-stenotic, but can easily cause acute thrombosis and therefore myocardial infarction due to its fragility towards rupture when located at physically stressed areas such as bifurcations. Often with 'vulnerable plaques' there are relatively few symptoms, however they are more numerous and dispersed throughout the arteries compared to 'stable plaque'. Thus, you can either have an occlusion due to the growing plaque or due to the embolization of the ruptured fragments of the original plaque.

Most Common Locations of Atherosclerosis

- Dorsal section of the abdominal aorta
- Proximal coronary arteries
- Popliteal arteries
- Descending thoracic aorta
- Internal carotid arteries
- Renal arteries

Due to the difficult detection of 'vulnerable plaques' while they are widely dispersed, it is highly important to tackle the risk factors prior to plaque rupture. Thus in the following paragraph, we will highlight the clinical risk factors associated with atherosclerosis. The four major clinical consequences of atherosclerosis are listed and explained below.

1. **Acute narrowing of the vessel lumen:** When the plaque ruptures, it will release its pro-coagulants in the bloodstream and that will lead to the formation of thrombus at the rupture site. The rupture often occurs at sites of erosion and fissuring on the fibrous cap surface. This thrombus may cause a complete occlusion of a particular vessel and result in ischemic necrosis (infarction) of the tissue that this particular vessel is supplying to. Clinically this is manifested as stroke, MI, gangrene of several possible organs such as intestine, spleen or lower extremities. These occlusions may also dissolve spontaneously due to pro-fibrinolytic enzymes such as streptokinase and tissue plasminogen activator (TPA).
2. **Chronic occlusion:** When the occlusion is gradual and incomplete, it may chronically disturb the blood supply to tissues in the distribution of the affected vessel. This can result in chronic ischemia of those tissues that can additionally lead to complaints of angina pectoris or intermittent claudication or to organ atrophy (e.g. atrophy of kidney, intestines and skin due to impairment of blood flow in renal artery, mesenteric artery, peripheral vasculature among diabetics.).
3. **Embolism:** Embolization is the transfer of the fragments of disrupted atheroma to distal vascular sites, which results into occlusion of those sites. For example, fragments of thrombi in abdominal aorta may transfer to the popliteal artery subsequently resulting in gangrene of the leg. Ulceration of atheroma may also produce 'cholesterol crystal emboli'. This type of emboli is visualized as needle-shaped areas in affected tissues, mostly detected in the kidney.
4. **Aneurysm:** After a chronic period, atherosclerotic lesion may extend into the medial layer, resulting into atrophy and loss of elastic tissue. This can subsequently cause dilatation and weakness of the artery, forming aneurysm. Over time, aneurysms may suddenly rupture and result in a life-threatening situation for the patients.

9.5: Risk Factors of Atherosclerosis (incomplete)

Recent studies have shown that atherosclerosis is not just the inevitable process of aging, but also a process with many modifiable components. A worldwide INTERHEART study has established the importance of nine potentially modifiable risk factors for atherosclerosis, which account for over 90% of the population-attributable risk of a first MI (Figure 9.5.1). A variety of non-modifiable risk factors such as advanced age, gender and hereditary coronary heart disease are important to recognize in patients with atherosclerosis. Recently the role of several biological markers associated with the development of cardiovascular events is accentuated since one out of five cardiovascular events occurs in patients lacking the earlier mentioned risk factors.

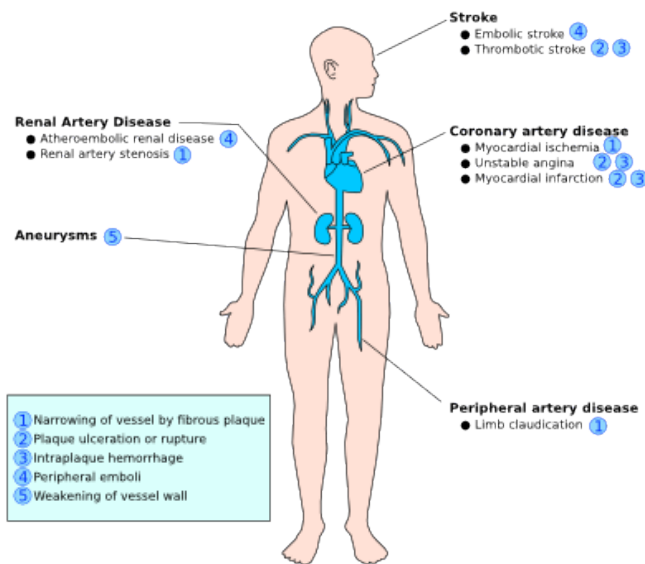


Figure 9.5.1: Complications of atherosclerosis

Common risk factors

Dyslipidemia

One of the major modifiable risk factors for atherosclerosis is hypercholesterolemia. Studies show that dyslipidemia (defined as an elevated apo B to apo A-1 ratio) was responsible for 49% of the population-attributable risk of a first MI. In countries with high consumption of saturated fat and high cholesterol levels (e.g. the United States), observational studies have shown that the mortality rates from coronary disease are higher compared with countries with traditionally low consumption of saturated fat and cholesterol levels (e.g. Japan). Several trials have shown that the risk of ischemic heart disease positively correlates with higher total serum cholesterol levels. For example, the impact of hypercholesterolemia can be illustrated by an observational result from the Framingham Heart Study, which shows that a person with a total cholesterol level of 240 mg/dl has twice the coronary risk a person would have with a cholesterol level of 200 mg/dl. However, it is a mistake to think that all lipoproteins consisting of cholesterol are harmful since cholesterol can provide critical functions to all cells that need to form membranes and to synthesize products such as steroid hormones and bile salts.

Incidence of atherosclerosis and coronary artery disease increases with higher levels of LDL particles. As mentioned earlier, LDL can accumulate in the intima of the artery in excess and undergo chemical modifications that activate endothelial cells to proceed to atherosclerosis. When people generally refer to 'bad cholesterol', they are referring to LDL particles. On the other hand, high levels of high-density lipoprotein (HDL) constitute 'good cholesterol' since it protects against atherosclerosis by reversing the cholesterol transport from peripheral tissues to the liver for disposal and functions as an antioxidant. In order to give additional explanation to what is 'bad cholesterol,' all lipid and lipoprotein abnormalities that are associated with higher coronary risk will be named subsequently: increased total cholesterol, increased LDL-cholesterol, low HDL-cholesterol, elevated total-to-HDL-cholesterol ratio, hypertriglyceridemia, increased non-HDL-cholesterol, elevated lipoprotein A, elevated apolipoprotein B (apo B is primarily found in LDL), decreased apolipoprotein A-I (apo A-1 is found in HDL), small and dense LDL particles.

There are several causes for persistent elevated levels of LDL, such as high fat consumption or genetic abnormalities (e.g. familial hypercholesterolemia). Familial hypercholesterolemia is a condition with deficient LDL receptors that cannot efficiently dispose LDL from the circulation. There are two types of this disease with different manifestations. Patients with the heterozygote type have only one defective gene for the receptor and suffer from high serum level of LDL, easily developing atherosclerosis. Homozygotes have a complete lack of normal LDL receptors and thus may experience cardiovascular events already in the first decade of life. In the absence of genetic abnormalities, the quantity of cholesterol in serum is strongly related to saturated fat consumption.

Table 9.5.1: Nine modifiable risk factors for atherosclerosis according to INTERHEART study

Modifiable Risk Factors for Atherosclerosis
• Dyslipidemia • Tobacco smoking • Lack of physical activity • Abdominal obesity • Psychosocial factors • Daily consumption of fruits and vegetables • Regular alcohol consumption • Hypertension • Diabetes Mellitus

Table 9.5.2: Recommendations regarding dyslipidemia

General Recommendations	Specific Diet Recommendations
• A varied and balanced diet • Regular fish intake (n – 3 fatty acids) • Fruits and vegetables, 3-5 portions per day, cereals and grain products, skimmed dairy products, and low-fat meat • Restriction of fatty products and products with a high caloric density. • The total fat intake should not be higher than 30% of calorie intake. The saturated fat intake should not be higher than 30% of total lipids • The cholesterol intake should be under 300 mg per day	• Avoid hard margarines and products of animal origin (meat, dairy products) • Increase intake of omega-3 fatty acids from fish oils and certain vegetal oils • Increase intake of polyunsaturated fatty acids, soluble fibers, and phytosterols • Exercise and body weight reduction within obese group • Normalization of glycemia in diabetic patients • Reduce the intake of refined sugars and replace them with complex sugars from fruits, vegetables, and grain products

Lipid-Altering therapy

Controlling serum lipids is a key step to limit the consequences of atherosclerosis. Major clinical trials have shown that coronary events and mortality significantly decreased when total and LDL-cholesterol levels were reduced for the primary and secondary prevention of CAD events.

One of the most important strategies to reduce the complications of atherosclerosis is diet and exercise. In order to decrease cholesterol, Mediterranean diet is often recommended. Mediterranean diet consists of low animal fat, high olive oil, moderate energy consumption, nuts, vegetables, regular and moderate wine, lots of whole grains and beans. A meta-analysis of six randomized trials showed that Mediterranean diet led to greater reduction in total cholesterol than low fat diets among overweight/obese population. Mediterranean-styled diet in this context means replacement of saturated fats with polyunsaturated fats such as omega-3 fatty acid and α -linolenic acid. Polyunsaturated fats are potential anti-atherogenic due to their inhibiting action on cytokine-induced expression of leukocyte adhesion molecules at endothelial cells. Exercise and loss of excessive weight

also contributes to improve abnormal lipid levels by reducing triglycerides and increasing HDL.

In primary prevention, pharmacologic agents are the second option when lifestyle modifications fail to achieve targeted lipid profile. There are several groups of lipid-altering medicines such as HMG-CoA reductase inhibitors (statins), niacin, fibric acid derivatives, cholesterol intestinal absorption inhibitors, and bile acid-binding agents. In the clinical setting, statins are widely used, being the most cost-effective LDL-lowering drugs. They reduce intracellular cholesterol concentration by inhibiting HMG-CoA reductase, which is an enzyme that synthesizes cholesterol. This results into increased LDL-receptor expression and therefore leads to higher clearance of LDL molecules from blood. They also affect the liver and thereby lower the rate of VLDL synthesis, which results into lower levels of serum triglyceride. Statins also raise HDL, but this mechanism is not fully understood yet.

Large studies, which have evaluated the effects of statin therapy, showed that ischemic cardiac events, the occurrence of MI and mortality rates were significantly reduced by implementing statin therapy. This significant improvement did not only apply to people with known preexisting atherosclerotic disease, but also to people within lower ranges of LDL and without preexisting atherosclerotic disease. For example, West of Scotland Coronary Prevention Study (WOSCOPS trial) evaluated the effect of pravastatin on rates of nonfatal MI or CHD death, nonfatal MI, all cardiovascular deaths and total mortality among patients with hypercholesterolemia without preexisting CVD for five years. Use of pravastatin resulted in 31% risk reduction ($p < 0.001$) in nonfatal MI or CHD death, and a 32% risk reduction ($p = 0.033$) in all cardiovascular deaths as compared to the control group.

Inhibiting HMG-CoA reductase results in several mechanisms that explain the beneficial effect of using statins. One beneficial mechanism is via lowering LDL and raising HDL. This results into less lipid content in atherosclerotic plaques and improve their biologic activity. Furthermore, the anti-thrombotic and anti-inflammatory profile is enhanced by other mechanisms such as increased NO synthesis and fibrinolytic activity, inhibition of smooth muscle proliferation and monocyte recruitment, and reduced production of matrix-degrading enzymes by macrophages. Several studies suggest that other mechanisms also contribute to the anti-inflammatory profile. For example, statins reduce endothelial expression of leukocyte adhesion molecules and macrophage tissue factor production by inhibiting the macrophage cytokines or by activating PPAR- α . Another anti-inflammatory action of statins, supported by clinical trials is reducing the serum level of C-reactive protein, which is a marker of inflammation.

Although statin therapy can reduce the risk of atherosclerotic cardiovascular disease by about one third, there is still a need for additional risk-reducing therapies. Thus, a new idea was developed to raise HDL cholesterol as a treatment for atherosclerosis. With the finding of the high-HDL phenotype of a human genetic deficiency of cholesteryl ester transfer protein (CETP), a new class of drugs was developed, which inhibits CETP. CETP functions as a mediator for transfer of cholesteryl ester from HDL to VLDL/LDL, which is then cleared by LDL receptors in liver. Thus when CETP is inhibited, this transfer process is inhibited and the direct hepatic HDL clearance pathway takes over. This leads to less fractional clearance of HDL from plasma, which is beneficial for atherosclerosis. Although the absolute clearance rate of HDL remains the same, the key step for atherosclerosis, which is the removal of cholesterol from macrophage foam cells in artery wall by HDL, is reduced.

The most recently investigated CETP inhibitors are torcetrapib, anacetrapib, and dalcetrapib. In the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, involving 15,000 patients at high risk for coronary heart disease, torcetrapib was clinically investigated. Unfortunately this trial was prematurely stopped due to the finding of an increase in cardiovascular events associated with an undiscovered off-target effect. Anacetrapib and dalcetrapib are still under active clinical investigation, since they lack the off-target effects of torcetrapib.

Tobacco smoking

Tobacco use, including environmental smoking exposure, is known to increase the risk of atherosclerosis and ischemic heart disease based on numerous studies. For example, INTERHEART study shows that smoking is responsible for 36% of the population-attributable risk of a first MI. Other studies showed that smoking is an independent major risk factor for coronary heart disease, cerebrovascular disease and total atherosclerotic cardiovascular disease. The Atherosclerosis Risk in Communities Study measured the direct effect of smoking on the development of atherosclerosis. They measured intima-medial thickness of the carotid artery of 10,914 patients for three years with ultrasound. Their result showed that current smokers had a 50% increased progression of atherosclerosis in comparison to nonsmokers during the study period. Also patients with environmental tobacco smoke exposure (passive smokers) had 20% higher rate of atherosclerotic progress versus patients without environmental smoke exposure.

Tobacco smoking can lead to many mechanisms that contribute to atherosclerosis. Smoking also leads to increased LDL levels, decreased HDL levels in blood and elevated insulin resistance. In addition it enhances oxidative modification of LDL by releasing free radicals and reduces generation of nitric oxide. This can promote endothelial dysfunction and thus lead to

impairment of vasodilatation of coronary arteries and reduction of coronary flow reserve even in passive smokers. Tobacco smoking inappropriately stimulates sympathetic nervous system, increasing heart rate, blood pressure and perhaps coronary vasoconstriction. Smoking promotes a prothrombotic environment through inhibition of endothelial release of tissue plasminogen activator, elevation of fibrinogen concentration in blood, enhancement of platelet activity (possibility related to sympathetic activation) and enhanced expression of tissue factor. Smoking can even damage the vessel wall and ultimately cause a decrease in the elasticity of the artery, enhancing the stiffness of vessel wall. Smoking has been associated with increased C-reactive protein and fibrinogen, suggesting a correlation with inflammatory response, which is an important part of atherogenesis. There have also been findings that show higher expression of leukocyte adhesion molecules among smokers than nonsmokers. Smoking may additionally induce tissue hypoxia through displacement of oxygen with carbon monoxide in hemoglobin.

To stop smoking is known as one of the most effective preventive measures of CVD and their complications. Soon after cessation, cardiac risks due to smoking decreases in a short period, and continues to diminish when cessation is permanently preserved. The risk for cardiovascular disease among patients with coronary heart disease decreases 7-47%. Not only does cessation of smoking reduce risk of CVD, but also substantially reduce the risk of all-cause mortality.

Lack of physical activity

INTERHEART study showed that lack of exercise accounted for 12% of the population-attributable risk of a first MI. Recent evidence shows that physical activity of even a moderate degree can protect against coronary heart disease and all-cause mortality. The beneficial effects of physical exercise are a decrease of triglyceride levels and blood pressure, elevation of HDL, enhancement of insulin sensitivity and production of NO by the endothelial cells, and of course weight loss. Although large scale randomized primary prevention trials are lacking, physical activity should be promoted to anyone with risk of developing atherosclerosis.

Table 9.5.3: Physical Activities with similar benefits to health

Activity	Duration
Washing and waxing a car	45-60 minutes
Washing windows or floors	45-60 minutes
Playing volleyball	45 minutes
Wheeling self in wheelchair	30-40 minutes
Bicycling - 8 km	30 minutes
Pushing a pushchair - 2.5 km	30 minutes
Walking - 3 km	30 minutes
Swimming laps	20 minutes
Playing basketball	15-20 minutes

Obesity

The American Heart Association has published an article, identifying obesity as an independent risk factor for coronary heart disease. Obesity is correlated with several risk factors for atherosclerosis such as hypertension, insulin resistance, glucose intolerance, decreased HDL serum level and hypertriglyceridemia. Weight loss is an important treatment to prevent many obesity-related risk factors for atherosclerosis that has just been mentioned.

Diet

A healthy diet reduces CVD risk. In general, when following the rules for a healthy diet, no dietary supplements are needed. N-3 polyunsaturated fatty acid (PUFA) consumption mainly from oily fish, is potentially associated with beneficial effects on cardiac risk factors, notably reduction in triglycerides but not all randomized, controlled trials have shown reductions in CV events. Thus current recommendations are to increase PUFA intake through fish consumption, rather than from supplements. Recently, the

largest study ever conducted with a so-called 'Mediterranean' diet, supplemented with extra-virgin olive oil or nuts, reduced the incidence of major cardiovascular events in patients at high risk of CV events but without prior CV disease.[1]

Alcohol consumption

Alcohol is harmful when used chronic or excessive and can lead to various complications such as liver and heart failure, increased cancer risk, neurological complications and injuries. However despite these adverse effects, moderate drinking (US parameters; women: <2 drinks per day, men: <3 drinks per day) may have protective benefits with regards to coronary heart disease according to several prospective cohort studies. These studies showed that moderate drinking resulted in a reduction of risk in coronary heart disease by 40-70% compared to no or heavy drinkers. This beneficial effect was seen in various groups without or with known risk for coronary heart disease and adults older than 65 years old. In a meta-analysis study, alcohol drinkers had lower relative risk for CVD mortality (0.75, 95% CI 0.70-0.80), coronary heart disease mortality (0.75, 0.68-0.81) and incidence of coronary heart disease (0.71, 0.66-0.77) than nondrinkers.

Psychosocial factors

Mentioned by INTERHEART study, psychosocial factors may directly contribute to the early development of atherosclerosis. Psychological stress may directly damage endothelium and indirectly aggravate other common risk factors such as smoking, dyslipidemia and hypertension. Due to the difficulty in quantifying the extent of atherosclerosis, studies showing the relationship between stress and atherosclerosis have been limited. Epidemiologic studies have shown stronger link between psychosocial factors (loss of job, depression and bereavement) and MI and sudden death.

Estrogen Status

Women and men have different risk for cardiovascular diseases throughout life. For example, at young age, men have an estimated four- to fivefold higher risk than women. However this difference diminishes and the age point of no difference is strongly related to the moment of menopause. From this observation, it has been suggested that estrogen may play athero-protective roles, since the levels of estrogen declines after menopause. In premenopausal women, estrogen raises HDL levels and reduces LDL levels in blood. Estrogen can even exhibit antioxidant and antithrombotic properties and can improve endothelium-dependent vasodilatation.

In the past, hormone replacement therapy has been suggested by several studies due to the findings of potential athero-protective roles of estrogen. However, these findings were not confirmed in the randomized primary prevention study of the Women's Health Initiative not in the HERS trial of secondary prevention. These studies showed that hormone replacement therapy (estrogen-progestin replacement) may increase cardiovascular risk in women and have no cardioprotective effect. Thus hormone replacement therapy is currently not recommended for reducing cardiovascular risk, due to its possible harmfulness consequences according to current clinical trials.

Biomarkers

Biomarkers can serve to identify patients with subclinical atherosclerotic disease that are at risk of developing cardiovascular events.

Homocysteine

Homocysteine is an intermediary amino acid produced during the conversion of methionine to cysteine. A significant positive correlation was found between the serum levels of homocysteine and the incidence of cardiovascular diseases. Although the clear mechanism of this correlation is undetermined, the overall result of the most current evidence suggests that homocysteine can modestly contribute to cardiovascular risk by inducing vascular injury. Homocysteine promotes oxidative stress, intimal thickening, disruption of elastic lamina, hypertrophy of smooth muscle cells, vascular inflammation platelet accumulation and production of occlusive thrombi when elevated in blood. Several conditions can cause hyperhomocystinemia, such as genetic defects in methionine metabolism or insufficient consumption of folic acid, which is involved in the methionine pathway. Such disorders cause premature and severe atherosclerosis. Despite this observational relationship, there is no data yet that proves reducing high serum level of homocysteine will lead to a decrease in atherosclerosis or its complications.

Lipoprotein A

Some studies have concluded that lipoprotein (a) is an independent risk factor for coronary artery disease. As lipoprotein (a) contains apo (a), which structurally resembles plasminogen, lipoprotein (a) interferes with fibrinolysis by competing with plasminogen binding with molecules. This leads to impairment of plasminogen activation, plasmin generation and lysis of fibrin clots. In addition, lipoprotein (a) binds with macrophages through a high-affinity receptor, promoting foam cell production and deposition of cholesterol in atherosclerotic plaques. As with homocysteine, not all studies support this theory of correlation, although increased risk of cardiovascular events appear to correlate with people with highest lipoprotein (a) serum level.

C-Reactive Protein and other markers of inflammation

Since the participation of inflammatory cells and mediators in atherosclerosis is well established, markers of inflammation have received a lot of attention. Several markers of inflammation such as C-reactive protein (CRP), fibrinogen and amyloid A are produced by hepatocytes in an acute phase under the influence of cytokines such as IL-6 when they mobilize from intima to the liver during the fatty streak stage. From these markers, CRP has shown the greatest association with atherosclerosis as a marker of low-grade systemic inflammation. A significant association between elevated CRP level in blood and prevalence of atherosclerosis has been shown in more than 30 epidemiologic studies. Different studies showed that higher basal CRP levels (four-fold higher) were found in patients with MI as compared to controls. Several studies have proposed that elevated plasma CRP can be an independent predictor for many cardiovascular diseases based on the result that CRP plasma value was able to predict the long-term risk of first MI, ischemic stroke or peripheral vascular disease among the male group. In addition, recent studies have shown that CRP also has a role as a mediator in atherogenesis. By inducing adhesion molecule expression and release of IL-6 and monocyte chemoattractant protein-1 via endothelial cells, CRP sustains the inflammatory state of atherosclerosis by recruiting monocytes and lymphocytes.

Infection

A variety of infectious agents such as Chlamydia pneumonia, cytomegalovirus and Helicobacter pylori were identified in the lesions of atherosclerosis and this observation raised the suggestion that these infectious agents may contribute to atherogenesis. However, to date, the definite proof of this theory is lacking and also there haven't been any clinical studies that showed significant relationship between the antibiotic treatment against these infectious agents and the risk of cardiac events of the survivors of acute coronary syndromes. Chlamydia is a strong candidate among other infectious agents, since they produce heat shock protein 60 (HSP-60) that activates macrophages and stimulates the production of matrix metalloproteinases. Furthermore, HSP-60 can also stimulate foam cell formation, lipoprotein oxidation, and increased pro-coagulant activity, which are the major attributing components of atherosclerosis. Although there is no evidence to date, some researchers believe that exogenous pathogens can cause endothelial injury and inflammation that can lead to initiation or exacerbation of atherosclerosis.

Co-morbidity groups

Hypertension

Hypertension is defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg. Elevated blood pressure is a well established risk factor for atherosclerosis, including mortality from coronary heart disease and stroke. For example, cardiovascular disease doubles with every 20 mmHg increase in SBP or every 10 mmHg increase in DBP.

One of the mechanisms of hypertension contributing to atherosclerosis is injury of vascular endothelium by elevated hemodynamic stress. Injury of endothelium may increase the permeability of the vessel wall to lipoproteins. Increased blood pressure may also increase the number of scavenger receptors on macrophages, which enhances the development of foam cells. Furthermore, increased cyclic circumferential strain in hypertensive arteries can result into promoting LDL accumulation in the intima and facilitation of their oxidative modification. Finally, hypertension can contribute to atherogenesis due to the presence of Angiotensin II, which not only works as a vasoconstrictor, but also as a pro-inflammatory cytokine.

Table 9.5.4

Lifestyle Recommendations for Hypertension

- Weight reduction in overweight individuals
- Reduction of salt consumption to < 6g daily
- Restriction of alcohol intake to < 10-30g/day (men) and < 10-20g/day (women)
- Regular physical activity
- Smoking cessation

Antihypertensive therapy

Antihypertensive therapy can either consist of lifestyle interventions or pharmacotherapy. Lifestyle modifications consist of diet, body weight reduction, increased activity, and cessation of smoking. As for diet, high consumption of fruits, vegetables, dairy products low in fat, fish oils, potassium and reduced consumption of sodium and alcohol are recommended. The indication for pharmacotherapy depends on the severity of hypertension and on the assessment of total CVD risk. Several large trials have shown that pharmacotherapy for hypertension can substantially reduce major cardiovascular events such as MI and stroke. Drug therapy is indicated when chronic SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg, or if target organ damage is present.

Diabetes Mellitus

With estimated global incidence of 170 million people, diabetes mellitus is a large problem worldwide. Diabetes mellitus increases the risk of acute coronary events by three- to five folds and 80% of diabetic patients will face atherosclerosis-related cardiovascular diseases. Risk for atherosclerosis among diabetics is considered to be as high as in patients with previous MI. Based on this observation, the National Cholesterol Education Program report from the United States and guidelines from Europe considers type 2 diabetes to be a CHD equivalent, categorizing it to the highest risk for MI.

There are several possible mechanisms that make this group particularly vulnerable to atherosclerosis. An example of mechanism is non-enzymatic glycation of lipoproteins, which promotes uptake of cholesterol by scavenger macrophages. Furthermore, pro-thrombotic and anti-fibrinolytic properties of diabetes can also contribute to this vulnerability. The high prevalence of endothelial dysfunction among diabetes group leads to reduced bioavailability of NO and enhanced leukocyte adhesion. The most effective prevention of atherosclerosis among diabetes group is tight regulation of serum glucose levels. This intervention significantly reduces the risk of microvascular complications such as retinopathy and nephropathy. Furthermore, intense anti-diabetic regime also reduced macrovascular outcomes such as MI and stroke among a group of diabetes type 1. Additionally managing hypertension and dyslipidemia among diabetic groups also significantly reduces the risk of cardiovascular diseases.

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10: PULMONARY EMBOLISM

Pulmonary embolism (PE) is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream (embolism). Usually this is due to embolism of a thrombus (blood clot) from the deep veins in the legs, a process termed venous thromboembolism.

10.1: Introduction to Pulmonary Embolism

10.2: Signs and Symptoms

10.3: Risk Factors

10.4: Diagnosis

10.5: Treatment

10.6: Prognosis

10.7: References

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10.1: Introduction to Pulmonary Embolism

Pulmonary embolism (PE) is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream (embolism). Usually this is due to embolism of a thrombus (blood clot) from the deep veins in the legs, a process termed venous thromboembolism. A small proportion is due to the embolization of air, fat, talc in drugs of intravenous drug abusers or amniotic fluid. The obstruction of the blood flow through the lungs and the resultant pressure on the right ventricle of the heart leads to the symptoms and signs of PE. The risk of PE is increased in various situations, such as cancer or prolonged bed rest.[1]

Symptoms of pulmonary embolism include difficulty breathing, chest pain on inspiration, and palpitations. Clinical signs include low blood oxygen saturation and cyanosis, rapid breathing, and a rapid heart rate. Severe cases of PE can lead to collapse, abnormally low blood pressure, and sudden death.[1]

Diagnosis is based on these clinical findings in combination with laboratory tests (such as the D-dimer test) and imaging studies, usually CT pulmonary angiography. Treatment is typically with anticoagulant medication, including heparin and warfarin. Severe cases may require thrombolysis with drugs such as tissue plasminogen activator (tPA) or may require surgical intervention via pulmonary thrombectomy.[1]

10.2: Signs and Symptoms

Symptoms of PE are sudden-onset dyspnea (shortness of breath), tachypnea (rapid breathing), chest pain of a "pleuritic" nature (worsened by breathing), cough and hemoptysis (coughing up blood). More severe cases can include signs such as cyanosis (blue discoloration, usually of the lips and fingers), collapse, and circulatory instability due to decreased blood flow through the lungs and into the left side of the heart. About 15% of all cases of sudden death are attributable to PE.[1]

On physical examination, the lungs are usually normal. Occasionally, a pleural friction rub may be audible over the affected area of the lung (mostly in PE with infarct) . A pleural effusion is sometimes present that is transudative, detectable by decreased percussion note, audible breath sounds and vocal resonance. Strain on the right ventricle may be detected as a left parasternal heave, a loud pulmonary component of the second heart sound, and raised jugular venous pressure.[1] A low-grade fever may be present, particularly if there is associated pulmonary hemorrhage or infarction.[2]

More rarely, inability of the right ventricle to remove fluid from the tissues leads to fluid accumulation in the legs (peripheral edema), congestion of the liver with mild jaundice and tenderness, and ascites (fluid in the abdominal cavity).

10.3: Risk Factors

The most common sources of embolism are proximal leg deep venous thrombosis (DVTs) or pelvic vein thromboses. Any risk factor for DVT also increases the risk that the venous clot will dislodge and migrate to the lung circulation, which happens in up to 15% of all DVTs. The conditions are generally regarded as a continuum termed venous thromboembolism (VTE).

The development of thrombosis is classically due to a group of causes named Virchow's triad (alterations in blood flow, factors in the vessel wall and factors affecting the properties of the blood). Often, more than one risk factor is present.

- *Alterations in blood flow:* immobilization (after surgery, injury or long-distance air travel), pregnancy (also procoagulant), obesity (also procoagulant), cancer (also procoagulant)
- *Factors in the vessel wall:* of limited direct relevance in VTE
- *Factors affecting the properties of the blood* (procoagulant state):
 - Estrogen-containing hormonal contraception
 - Genetic thrombophilia (factor V Leiden, prothrombin mutation G20210A, protein C deficiency, protein S deficiency, antithrombin deficiency, hyperhomocysteinemia and plasminogen/fibrinolysis disorders)
 - Acquired thrombophilia (antiphospholipid syndrome, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria)
 - Cancer (due to secretion of pro-coagulants)

10.4: Diagnosis

The diagnosis of PE is based primarily on validated clinical criteria combined with selective testing because the typical clinical presentation (shortness of breath, chest pain) cannot be definitively differentiated from other causes of chest pain and shortness of breath. The decision to do medical imaging is usually based on clinical grounds, i.e. the medical history, symptoms and findings on physical examination, followed by an assessment of clinical probability.[1]

The most commonly used method to predict clinical probability, the Wells score, is a clinical prediction rule, whose use is complicated by multiple versions being available. In 1995, Wells *et al.* initially developed a prediction rule (based on a literature search) to predict the likelihood of PE, based on clinical criteria.[3] The prediction rule was revised in 1998 [4] This prediction rule was further revised when simplified during a validation by Wells *et al.* in 2000. [5] In the 2000 publication, Wells proposed two different scoring systems using cutoffs of 2 or 4 with the same prediction rule. [5] In 2001, Wells published results using the more conservative cutoff of 2 to create three categories.[6] An additional version, the "modified extended version", using the more recent cutoff of 2 but including findings from Wells's initial studies[7] [8] were proposed. [9] Most recently, a further study reverted to Wells's earlier use of a cutoff of 4 points [5] to create only two categories. [10]

There are additional prediction rules for PE, such as the Geneva rule. More importantly, the use of *any* rule is associated with reduction in recurrent thromboembolism. [11]

The Wells score: [12]

- clinically suspected DVT - 3.0 points
- alternative diagnosis is less likely than PE - 3.0 points
- tachycardia - 1.5 points
- immobilization/surgery in previous four weeks - 1.5 points
- history of DVT or PE - 1.5 points
- hemoptysis - 1.0 points
- malignancy (treatment for within 6 months, palliative) - 1.0 points

Traditional interpretation [5][6] [13]

- Score >6.0 - High (probability 59% based on pooled data [14])
- Score 2.0 to 6.0 - Moderate (probability 29% based on pooled data [14])
- Score <2.0 - Low (probability 15% based on pooled data [14])

Alternative interpretation [5][10]

- Score > 4 - PE likely. Consider diagnostic imaging.
- Score 4 or less - PE unlikely. Consider D-dimer to rule out PE.

Blood tests

Early primary research has shown that in low/moderate suspicion of PE, a normal D-dimer level (shown in a blood test) is enough to exclude the possibility of thrombotic PE. [15] This has been corroborated by a recent systematic review of studies of patients with low pre-test probability (PTP) of PE and negative D-dimer results that found the three month risk of thromboembolic events in patients excluded in this manner was 0.14%, with 95% confidence intervals from 0.05 to 0.41%, though this review was limited by its use of only one randomized-controlled clinical trial, the remainder of studies being prospective cohorts. [16] D-dimer is highly sensitive but not very specific (specificity around 50%). In other words, a positive D-dimer is not synonymous with PE, but a negative D-dimer is, with a good degree of certainty, an indication of absence of a PE. [17]

When a PE is being suspected, a number of blood tests are done, in order to exclude important secondary causes of PE. This includes a full blood count, clotting status (PT, aPTT, TT), and some screening tests (erythrocyte sedimentation rate, renal function, liver enzymes, electrolytes). If one of these is abnormal, further investigations might be warranted.

Imaging

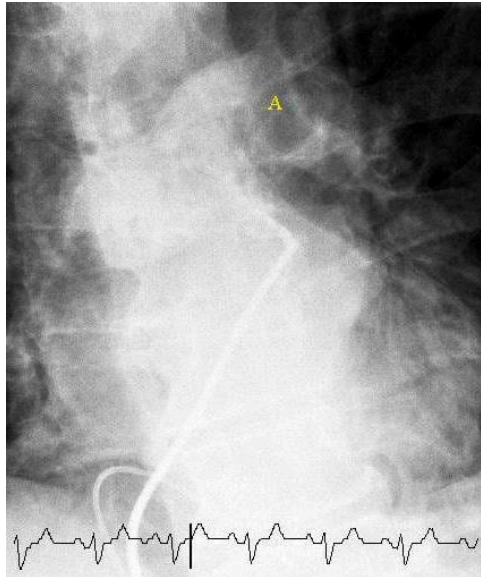


Figure 10.4.1: Selective pulmonary angiogram revealing significant thrombus (labeled A) causing a central obstruction in the left main pulmonary artery. ECG tracing shown at bottom.

The gold standard for diagnosing pulmonary embolism (PE) is *pulmonary angiography*. Pulmonary angiography is used less often due to wider acceptance of CT scans, which are non-invasive. CT pulmonary angiography is the recommended first line diagnostic imaging test in most people.

Non-invasive imaging

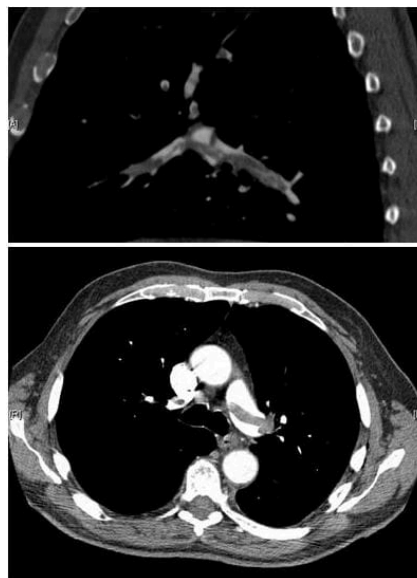


Figure 10.4.2: CT pulmonary angiography (CTPA) showing a saddle embolus and substantial thrombus burden in the lobar branches of both main pulmonary arteries.

CT pulmonary angiography (CTPA) is a pulmonary angiogram obtained using computed tomography (CT) with radiocontrast rather than right heart catheterization. Its advantages are clinical equivalence, its non-invasive nature, its greater availability to patients, and the possibility of identifying other lung disorders from the differential diagnosis in case there is no pulmonary embolism. Assessing the accuracy of CT pulmonary angiography is hindered by the rapid changes in the number of rows of detectors available in multidetector CT (MDCT) machines. [18] According to a cohort study, single-slice spiral CT may help diagnose detection among patients with suspected pulmonary embolism. [19] In this study, the sensitivity was 69% and specificity was 84%. In this study which had a prevalence of detection was 32%, the positive predictive value of 67.0% and negative predictive

value of 85.2% (click here to adjust these results for patients at higher or lower risk of detection). However, this study's results may be biased due to possible incorporation bias, since the CT scan was the final diagnostic tool in patients with pulmonary embolism. The authors noted that a negative single slice CT scan is insufficient to rule out pulmonary embolism on its own. A separate study with a mixture of 4 slice and 16 slice scanners reported a sensitivity of 83% and a specificity of 96%. This study noted that additional testing is necessary when the clinical probability is inconsistent with the imaging results. [20] CTPA is non-inferior to VQ scanning, and identifies more emboli (without necessarily improving the outcome) compared to VQ scanning. [21]

Ventilation/perfusion scan (or *V/Q scan* or *lung scintigraphy*), which shows that some areas of the lung are being ventilated but not perfused with blood (due to obstruction by a clot). This type of examination is used less often because of the more widespread availability of CT technology, however, it may be useful in patients who have an allergy to iodinated contrast or in pregnancy due to lower radiation exposure than CT. [22]

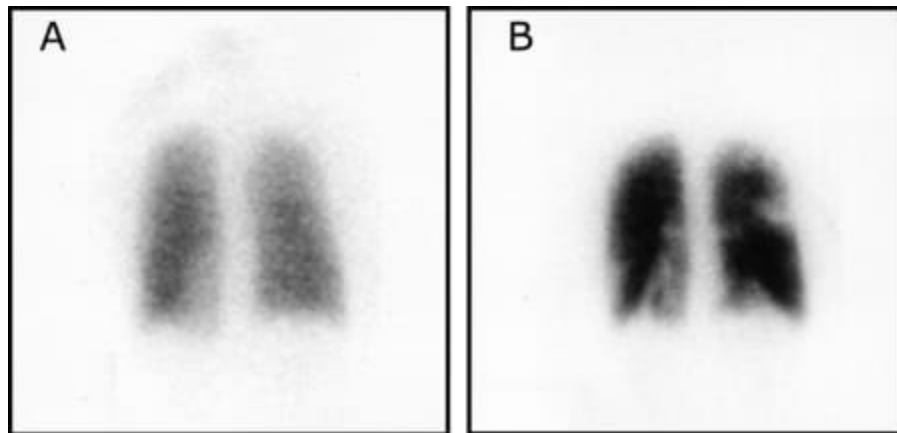


Figure 10.4.3: Ventilation-perfusion scintigraphy in a woman taking hormonal contraceptives and valdecoxib. (A) After inhalation of 20.1 mCi of Xenon-133 gas, scintigraphic images were obtained in the posterior projection, showing uniform ventilation to lungs. (B) After intravenous injection of 4.1 mCi of Technetium-99m-labeled macroaggregated albumin, scintigraphic images were obtained, shown here in the posterior projection. This and other views showed decreased activity in multiple regions.

Low probability diagnostic tests/non-diagnostic tests

Tests that are frequently done that are not sensitive for PE, but can be diagnostic.

- *Chest X-rays* are often done on patients with shortness of breath to help rule-out other causes, such as congestive heart failure and rib fracture. Chest X-rays in PE are rarely normal, [23] but usually lack signs that suggest the diagnosis of PE (e.g. Westermark sign, Hampton's hump).
- *Ultrasonography of the legs*, also known as *leg doppler*, in search of deep venous thrombosis (DVT). The presence of DVT, as shown on ultrasonography of the legs, is in itself enough to warrant anticoagulation, without requiring the V/Q or spiral CT scans (because of the strong association between DVT and PE). This may be valid approach in pregnancy, in which the other modalities would increase the risk of birth defects in the unborn child. However, a negative scan does not rule out PE, and low-radiation dose scanning may be required if the mother is deemed at high risk of having pulmonary embolism.

Electrocardiogram

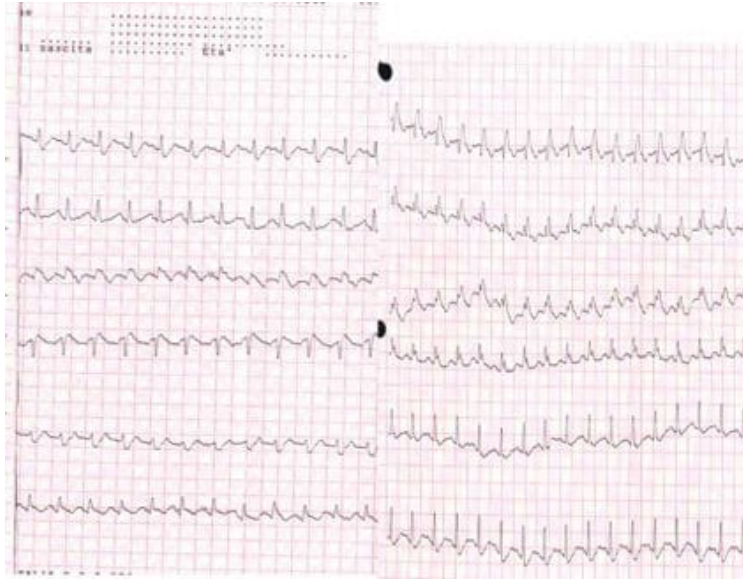


Figure 10.4.4: Electrocardiogram of a patient with pulmonary embolism showing sinus tachycardia of approximately 150 beats per minute and right bundle branch block.

An electrocardiogram (ECG) is routinely done on patients with chest pain to quickly diagnose myocardial infarctions (heart attacks). An ECG may show signs of right heart strain or acute *cor pulmonale* in cases of large PEs - the classic signs are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III ("S1Q3T3"). [24] This is occasionally (up to 20%) present, but may also occur in other acute lung conditions and has therefore limited diagnostic value. The most commonly seen signs in the ECG is sinus tachycardia, right axis deviation and right bundle branch block. [25] Sinus tachycardia was however still only found in 8 - 69% of people with PE. [26]

Echocardiography

In massive and submassive PE, dysfunction of the right side of the heart can be seen on echocardiography, an indication that the pulmonary artery is severely obstructed and the heart is unable to match the pressure. Some studies (see below) suggest that this finding may be an indication for thrombolysis. Not every patient with a (suspected) pulmonary embolism requires an echocardiogram, but elevations in cardiac troponins or brain natriuretic peptide may indicate heart strain and warrant an echocardiogram. [27]

The specific appearance of the right ventricle on echocardiography is referred to as the *McConnell's sign*. This is the finding of akinesia of the mid-free wall but normal motion of the apex. This phenomenon has a 77% sensitivity and a 94% specificity for the diagnosis of acute pulmonary embolism in the setting of right ventricular dysfunction. [28]

Algorithms

Recent recommendations for a diagnostic algorithm have been published by the PIOPED investigators; however, these recommendations do not reflect research using 64 slice MDCT. [29] These investigators recommended:

- Low clinical probability. If negative D-dimer, PE is excluded. If positive D-dimer, obtain MDCT and based treatment on results.
- Moderate clinical probability. If negative D-dimer, PE is excluded. *However*, the authors were not concerned that a negative MDCT with negative D-dimer in this setting has an 5% probability of being false. Presumably, the 5% error rate will fall as 64 slice MDCT is more commonly used. If positive D-dimer, obtain MDCT and based treatment on results.
- High clinical probability. Proceed to MDCT. If positive, treat, if negative, additional tests are needed to exclude PE.

Pulmonary Embolism Rule-out Criteria

The Pulmonary Embolism Rule-out Criteria, or PERC rule, helps assess people in whom pulmonary embolism is suspected, but unlikely. Unlike the Wells Score and Geneva score, which are clinical prediction rules intended to risk stratify patients with suspected PE, the PERC rule is designed to rule out risk of PE in patients when the physician has already stratified them into a low-risk category.

Patients in this low risk category without any of these criteria may undergo no further diagnostic testing for PE: Hypoxia - $\text{SaO}_2 < 95\%$, unilateral leg swelling, hemoptysis, prior DVT or PE, recent surgery or trauma, age > 50 , hormone use, tachycardia. The rationale behind this decision is that further testing (specifically CT angiogram of the chest) may cause more harm (from radiation exposure and contrast dye) than the risk of PE. [30] The PERC rule has a sensitivity of 97.4% and specificity of 21.9% with a false negative rate of 1.0% (16/1666). [31]

10.5: Treatment

In most cases, anticoagulant therapy is the mainstay of treatment. Acutely, supportive treatments, such as oxygen or analgesia, are often required.

Anticoagulation

In most cases, anticoagulant therapy is the mainstay of treatment. Heparin, low molecular weight heparins (such as enoxaparin and dalteparin), or fondaparinux is administered initially, while warfarin, acenocoumarol, or phenprocoumon therapy is commenced (this may take several days, usually while the patient is in the hospital). Low molecular weight heparin may reduce bleeding among patients with pulmonary embolism as compared to heparin according to a systematic review of randomized controlled trials by the Cochrane Collaboration. [32] The relative risk reduction was 40.0%. For patients at similar risk to those in this study (2.0% had bleeding when not treated with low molecular weight heparin), this leads to an absolute risk reduction of 0.8%. 125.0 patients must be treated for one to benefit.

It is possible to treat low risk patients (risk class I or class II) as outpatients. [33] A randomized trial of 344 patients (171 outpatients and 168 inpatients) found that outcomes were equivalent whether patients were treated in hospital or at home (there was one death at 90 days in each group). [33] [34] This confirms the findings of an earlier systematic review of observational studies. [35]

Warfarin therapy often requires frequent dose adjustment and monitoring of the INR. In PE, INRs between 2.0 and 3.0 are generally considered ideal. If another episode of PE occurs under warfarin treatment, the INR window may be increased to e.g. 2.5-3.5 (unless there are contraindications) or anticoagulation may be changed to a different anticoagulant e.g. low molecular weight heparin. In patients with an underlying malignancy, therapy with a course of low molecular weight heparin may be favored over warfarin based on the results of the CLOT trial. [36]

Similarly, pregnant women are often maintained on low molecular weight heparin to avoid the known teratogenic effects of warfarin, especially in the early stages of pregnancy.

People are usually admitted to hospital in the early stages of treatment, and tend to remain under inpatient care until INR has reached therapeutic levels. Increasingly, low-risk cases are managed on an outpatient basis in a fashion already common in the treatment of DVT. [37]

Warfarin therapy is usually continued for 3–6 months, or "lifelong" if there have been previous DVTs or PEs, or none of the usual risk factors is present. An abnormal D-dimer level at the end of treatment might signal the need for continued treatment among patients with a first unprovoked pulmonary embolus. [38]

Thrombolysis

Massive PE causing hemodynamic instability (shock and/or hypotension, defined as a systolic blood pressure <90 mmHg or a pressure drop of 40 mmHg for >15 min if not caused by new-onset arrhythmia, hypovolemia or sepsis) is an indication for thrombolysis, the enzymatic destruction of the clot with medication. It is the best available medical treatment in this situation and is supported by clinical guidelines. [39] [40] [41]

The use of thrombolysis in non-massive PEs is still debated. The aim of the therapy is to dissolve the clot, but there is an attendant risk of bleeding or stroke. [42] The main indication for thrombolysis is in submassive PE where right ventricular dysfunction can be demonstrated on echocardiography, and the presence of visible thrombus in the atrium. [43]

Surgery

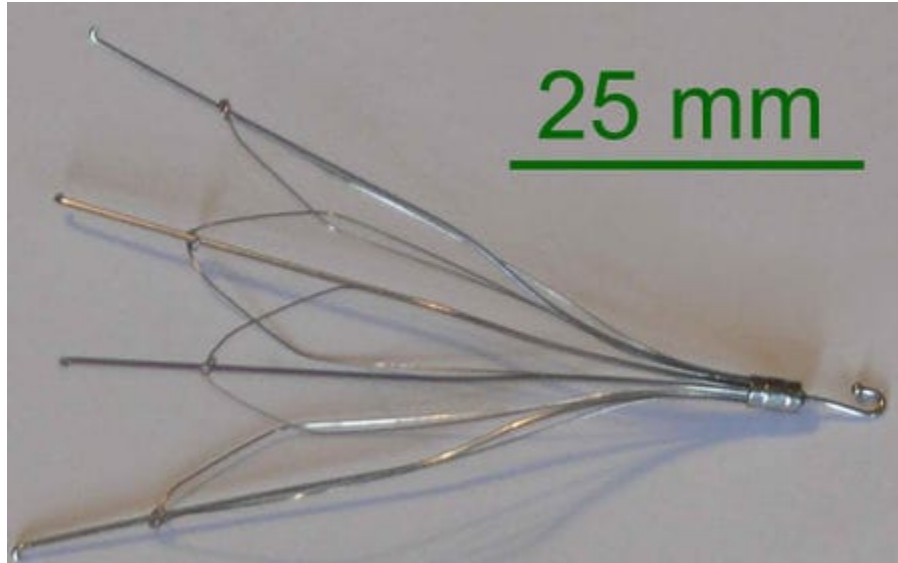


Figure 10.5.1: Used inferior vena cava filter.

Surgical management of acute pulmonary embolism (pulmonary thrombectomy) is uncommon and has largely been abandoned because of poor long-term outcomes. However, recently, it has gone through a resurgence with the revision of the surgical technique and is thought to benefit selected patients. [44]

Chronic pulmonary embolism leading to pulmonary hypertension (known as *chronic thromboembolic hypertension*) is treated with a surgical procedure known as a pulmonary thromboendarterectomy.

Inferior vena cava filter

If anticoagulant therapy is contraindicated and/or ineffective, or to prevent new emboli from entering the pulmonary artery and combining with an existing blockage, an inferior vena cava filter may be implanted. [45]

10.6: Prognosis

Mortality from untreated PE is said to be 26%. This figure comes from a trial published in 1960 by Barritt and Jordan [46], which compared anticoagulation against placebo for the management of PE. Barritt and Jordan performed their study in the Bristol Royal Infirmary in 1957. This study is the only placebo controlled trial ever to examine the place of anticoagulants in the treatment of PE, the results of which were so convincing that the trial has never been repeated as to do so would be considered unethical. That said, the reported mortality rate of 26% in the placebo group is probably an overstatement, given that the technology of the day may have detected only severe PEs.

Prognosis depends on the amount of lung that is affected and on the co-existence of other medical conditions; chronic embolization to the lung can lead to pulmonary hypertension. After a massive PE, the embolus must be resolved somehow if the patient is to survive. In thrombotic PE, the blood clot may be broken down by fibrinolysis, or it may be organized and recanalized so that a new channel forms through the clot. Blood flow is restored most rapidly in the first day or two after a PE. [47] Improvement slows thereafter and some deficits may be permanent. There is controversy over whether or not small subsegmental PEs need to be treated at all [48] and some evidence exists that patients with subsegmental PEs may do well without treatment. [49] [50]

Once anticoagulation is stopped, the risk of a fatal pulmonary embolism is 0.5% per year. [51]

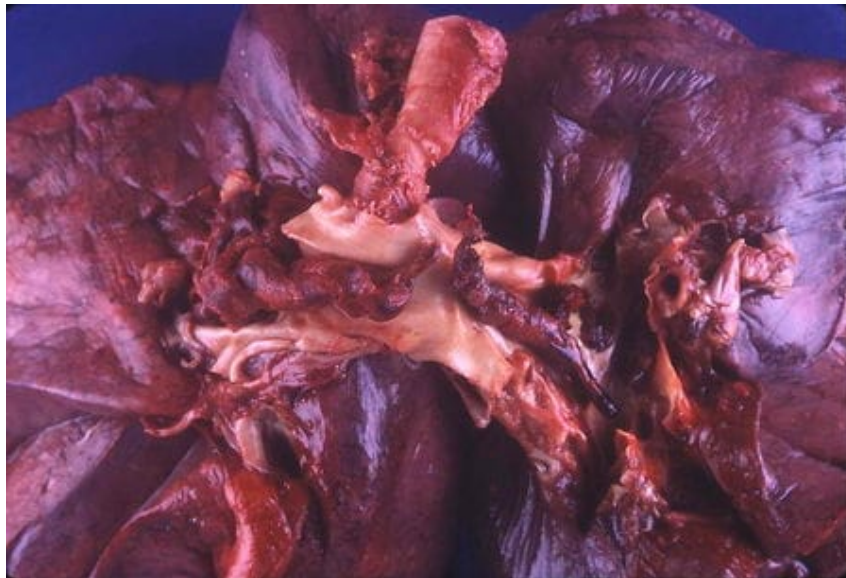


Figure 10.6.1: Large saddle embolus seen at PA.

Predicting mortality

The PESI and Geneva prediction rules can estimate mortality and so may guide selection of patients who can be considered for outpatient therapy. [52]

Underlying causes

After a first PE, the search for secondary causes is usually brief. Only when a second PE occurs, and especially when this happens while still under anticoagulant therapy, a further search for underlying conditions is undertaken. This will include testing ("thrombophilia screen") for Factor V Leiden mutation, antiphospholipid antibodies, protein C and S and antithrombin levels, and later prothrombin mutation, MTHFR mutation, Factor VIII concentration and rarer inherited coagulation abnormalities.

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11: CONGENITAL

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11.1: Septal Defects

Atrial septal defect

Case Report

Introduction

Atrial septal defect (ASD) is common, accounting for approximately 7 percent of congenital heart disease. The ASD's can occur in several different anatomic portions of the atrial septum, and the location of the defect generally reflects the abnormality of embryogenesis that led to the anomaly. The functional consequences of an ASD are determined by its diameter, the anatomic location and the presence or absence of other cardiac anomalies.



Figure 11.1.1: Heart from the right side view, showing different locations of atrial septal defects.

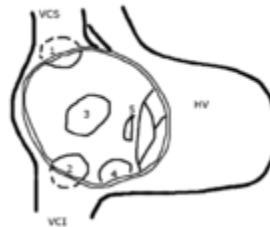


Figure 11.1.2: Schematic drawing showing the location of different types of ASD, the view is into an opened right atrium. VCS, superior caval vein. VCI, inferior caval vein. HV, right ventricle. 1, upper sinus venosus defect. 2, lower sinus venosus defect. 3, secundum defect. 4, defect involving coronary sinus. 5, primum defect.

Classification

The various forms of ASD's are differentiated from each other by the structures of the heart involved and the formation during embryological development.

The ostium secundum defect is the most frequent form of ASD (70%), localized at the fossa ovalis with a diameter of about 1 – 2 cm. It commonly arises from an enlarged foramen ovale, inadequate growth of the septum secundum or excessive absorption of the septum primum.

The sinus venosus defect (15% of all ASD's) is localized high in the atrial septum, at the inflow of the superior caval vein. Note that in 80-90% of patients this defect is accompanied by an anomalous pulmonary venous drainage of the right pulmonary vein into the right atrium. Inferior sinus venosus defects do exist, but are very exceptional.

The ostium primum defect is localized low in the atrial septum at the atrioventricular junction. It forms the atrial component of the category of congenital heart disease referred to as atrioventricular defects, with a common atrioventricular junction and an abnormal atrioventricular valve.

The coronary sinus defect, localized at the atrial ostium of the coronary sinus, is rare and usually accompanied by other cardiac defects like anomalous drainage of the superior vena cava.

Pathophysiology

The presence of an ASD will in all cases gradually lead to a left to right shunt across the defect. At birth the volume of blood shunting from systemic to pulmonary circulation is small, because the right ventricle is still relatively thick-walled and noncompliant. In response to a decrease in pulmonary vascular resistance after birth, the right ventricle remodels and its compliance increases. This leads to a decrease in right atrial pressure and an increase in shunt volume across the defect during the first years of life.

The blood shunts during the late systole and early diastole, leading to a diastolic volume overload of the right atrium and right ventricle, but also the pulmonary veins and arteries. This volume overload of the pulmonary circulation will consequently lead to right-sided dilatation. The end diastolic increase in pressure of pulmonary circulation can result in systemic venous stuwung. This stuwung is augmented by another mechanism caused by the right ventricular volume overload; deviation of the ventricular septum to the left and the decrease in left ventricle preload because of the left to right shunt, lead to a decrease in stroke volume of the left ventricle. The renine-angiotensin system is activated, leading to an increase in intravascular volume and signs of venous stuwung. The right-sided volume overload is usually well tolerated for years, but in adulthood hemodynamic factors can influence the shunt size in both directions. If the right ventricle will start failing due to chronic volume overlad, the left to right shunt can decrease. If the left ventricle function will decline due to hypertension or coronary artery disease, the lef to right shunt can increase. In 10-20% of adult patients with an isolated ASD pulmonary hypertension will develop, leading to a decrease in left to right shunt and eventually right to left shunt with cyanosis (Eisenmenger syndrome).

Evaluation and therapy

Most ASDs less than 8mm in diameter close spontaneously in infants, however above the age of 4 years spontaneous closure is unusual. During childhood and early adulthood most patients with moderate to large uncorrected ASDs are asymptomatic. Most of them will become symptomatic during adulthood (usually from the age of 40) and require closure of the defect. Indications for closure of an ASD in adulthood are development of symptoms and a high rate of shunt flow. Decreased exercise tolerance, fatigue, dyspnoe, syncope and paradoxal embolization are manifestations of such symptomatic ASDs that warrant closure of the defect. Atrial arrhythmias are usually one of the first presenting symptoms, however these symptoms alone are not an indication for closure, since the incidence after the procedure is not likely to be reduced.



Figure 11.1.3: Chest radiograph, left lateral view, of a 34-year old female who recently underwent percutaneous closure of her ASD with an Amplatzer device.

When closure of the ASD is indicated, this can be performed with surgery or percutaneous intervention. Surgical closure is usually performed using a patch of pericardium or Dacron. Prior to surgery, a comprehensive noninvasive evaluation is essential to exclude pulmonary hypertension and associated anatomic defects such as anomalous pulmonary and systemic

venous connections. In nearly all cases, echocardiography can resolve these questions, obviating the need for cardiac catheterization. Transcatheter closure avoids cardiopulmonary bypass, thoracotomy, and atriotomy, and is associated with excellent outcomes. As a result, this approach has largely replaced surgery in many centers for patients with a defect that is less than 20 mm in diameter.

Outcome

The short- and long-term outcomes are generally excellent after either surgical or transcatheter closure of an isolated ASD in children. Several investigations showed that there is almost no increase in long-term mortality or serious morbidity compared to controls, following surgical repair of an ASD under 25 years of age. The perioperative mortality is low (< 1%) and there are few perioperative complications (about 10%). However late in adulthood about 50% of all patients develop sinus node dysfunction and symptomatic supraventricular tachyarrhythmias.

When the ASD is closed percutaneously the short-term outcomes (less than one year) are excellent, with reported procedure success rates of 88 to 98%.

Ventricular septal defect

Case report

Introduction

The ventricular septal defect is the most common congenital heart defect in childhood (30%). Most patients have an isolated VSD, however a VSD also occurs in combination with other defects like Tetralogy of Fallot, which will be discussed elsewhere. About five percent of all patients with a VSD have a chromosomal abnormality, including trisomy 13, 18 and 21. Due to a high rate of spontaneous closure (50%) VSD is less seen in adulthood.

There are three main anatomic components of the interventricular septum (Figure 11.1.4); the septum of the atrioventricular canal (1), the muscular septum (2), the parietal band or distal conal septum (3). VSDs may occur at various locations in any of the three components. The location of the defect is not of particular interest when taking the characteristics of the intracardiac shunt in account. However it is important in terms of the frequency of involvement of the atrioventricular valves and the rate of spontaneous closure and additionally the relation to the AV pathway when considering surgical correction.

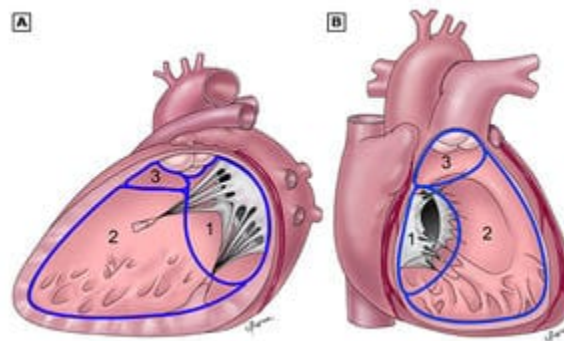


Figure 11.1.4: Schematic drawing showing three main anatomic components of the interventricular septum: the septum of the atrioventricular canal (1), the muscular septum (2), the parietal band or distal conal septum (3).

Classification

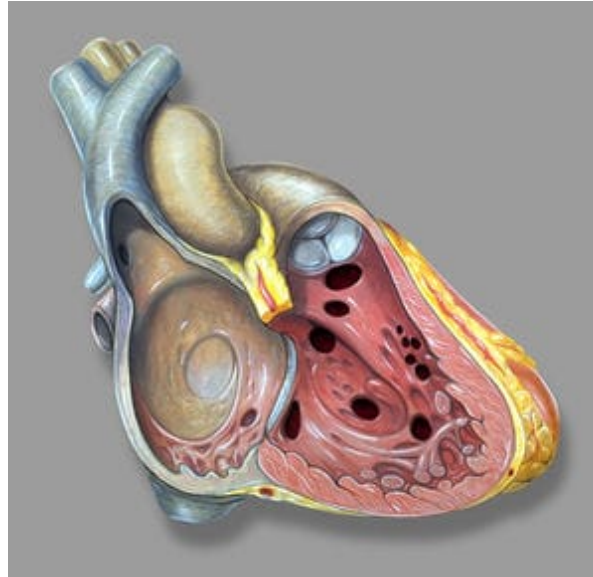


Figure 11.1.5: Heart from the right side view, showing different locations of ventricular septal defects.

The VSD can be classified into four types, related to the anatomic components involved;

- Type 1 is the infundibular VSD, which results from a defect in the septum below the aortic and pulmonary valves. The loss of support to the adjacent septal leaflets of these valves causes cusp prolapse into the VSD leading to progressive aortic regurgitation, which is the hallmark of this defect.
- Type 2, the membranous VSD, is the most common type of VSD (around 80%) and results from a deficiency of the membranous septum. This defect borders the septal leaflet of the tricuspid valve and might also extend into the muscular septum when it is referred to as a perimembranous VSD.
- Type 3 are inlet VSDs, located beneath both mitral and tricuspid valves. Despite proximity to those valves, this type of defect is not associated with mitral or tricuspid regurgitation unless associated with atrioventricular canal defect. This typically large defect is often associated with Down syndrome.
- Muscular defects (type 4) are located within the trabecular septum and accounts for 5 – 20% of all VSDs. It is bordered only by muscle, away from the cardiac valves. Muscular defects can be small or large in size and consist of a single or multiple defects.

Pathophysiology

The severity of the shunt across the VSD is determined by its size and the ratio of pulmonary to systemic vascular resistance. In small or restrictive VSDs the diameter of the defect is $\leq 25\%$ of the aortic annulus diameter. These small defects cause small left to right shunts with no left ventricular overload or pulmonary hypertension.

Moderate sized VSDs, measuring 25 – 75% of the aortic annulus diameter, result into mild volume overload of the pulmonary arteries, left atrium and left ventricle with no or only mild pulmonary hypertension.

In large defects, defined as those with diameters equal or greater than 75% of the aortic annulus, there is no restriction of blood flow across the septum, leading to equal pressures in both right and left ventricle. The large left to right shunt initially only leads to excessive volume overload in the pulmonary arteries, left atrium and left ventricle. The chronic pressure and volume overload combined with the increase flow leads to irreversible changes of the pulmonary vasculature, which results in an increase in pulmonary vascular resistance. This increase in resistance leads to a reversal of the shunt through the VSD causing right to left shunt with cyanosis (Eisenmenger syndrome).

Evaluation

Small defects are usually asymptomatic, however are fairly easy to detect during physical examination. There can be a palpable thrill accompanied by a holosystolic murmur grade 4-6. In some muscular defects the murmur is non holosystolic, due to the

contraction and thereby closure of the defect during systole. In moderate sized defects, with a large systemic to pulmonary flow of at least 1:2, a middiastolic rumble is audible due to the increased flow across the mitral valve. The pulmonary component of the second heart tone is loud. Only in a large VSD accompanied by the Eisenmenger syndrome and central cyanosis there is barely any shunt murmur audible. However there are murmurs audible caused by the pulmonary hypertension; an early diastolic murmur due to the pulmonary valve regurgitation and a holosystolic murmur due to the tricuspid valve regurgitation. Defects with large shunts that cause symptoms like decreased exercise tolerance and dyspnoea are usually detected and closed early in childhood.

The ECG and chest X-ray of a patient with a small VSD are usually normal, but can show signs of left atrial and left ventricle overload in moderate sized defects.

With echocardiography the localisation, size and hemodynamic influence of the VSD can be investigated. Dilatation of the left atrium and left ventricle might be present and the pressures in the pulmonary artery can be estimated by means of the tricuspid regurgitation. Invasive measurement by means of catheterization is only indicated when there is doubt about the shunt size and the pulmonary vascular resistance.

Treatment

Treatment and prognosis of a VSD depends on the size and localisation of the defect, the pulmonary vascular resistance and possible concomitant defects. Spontaneous closure occurs mainly in small defects, of which 75 percent closes before age 10. In patients with a small defect no pulmonary hypertension develops, however there is an increased risk of endocarditis.

In patients with significant shunts studies have shown that surgical closure reduces pulmonary artery pressure and improves long-term survival. Therefore, repair of VSD should be considered in all adult patients who are symptomatic or have signs of left ventricular volume overload.

Medical treatment is reserved for (1) asymptomatic patients without evidence of left ventricular volume overload and (2) patients with symptoms and/or left ventricular volume overload who are not candidates for repair such as those with large defects and Eisenmenger syndrome.

Repair of VSD has been historically performed surgically. However, percutaneous VSD repair has been growing given the desire of young adults to avoid surgery. Surgical and percutaneous VSD closure should be performed by surgeons and cardiologists with appropriate training and expertise.

Indications for closure of a VSD in an adult are included in the 2008 American College of Cardiology/American Heart Association (ACC/AHA) adult congenital heart disease guidelines as follows. Similar recommendations are included in the European Society of Cardiology and the Canadian Society of Cardiology guidelines.

- Closure of a VSD is indicated when there is a $Q_p/Q_s \geq 2$ and clinical evidence of LV volume overload.
- Closure of a VSD is indicated when the patient has a history of infective endocarditis.
- Closure of a VSD is reasonable when there is net left to right shunting with a $Q_p/Q_s \geq 1.5$ with pulmonary artery pressure less than two thirds of systemic pressure and PVR is less than two thirds of systemic vascular resistance.
- Closure of a VSD is reasonable when there is net left to right shunting with a $Q_p/Q_s \geq 1.5$ in the presence of LV systolic or diastolic dysfunction or failure.

Indications for surgical closure of VSD in infants and young children may include:

- Infants <6 months (<3 months for those with trisomy 21) who have uncontrolled heart failure despite maximal medical and dietary interventions or who have pulmonary hypertension.
- Children with a persistent significant shunt ($Q_p/Q_s > 2:1$), should undergo surgical repair even in the absence of elevated PA pressures.
- Subpulmonic and membranous defects, regardless of size, with aortic regurgitation should be surgically corrected before the aortic valve is permanently damaged. The decision to close small defects with aortic valve prolapse without aortic regurgitation is controversial.

Closure of a VSD is not recommended in patients with severe irreversible pulmonary artery hypertension.

Transcatheter device VSD closure is a treatment option for isolated uncomplicated muscular VSDs, and for certain membranous VSDs, in selected patients with suitable anatomy. Appropriate anatomy for transcatheter closure includes a VSD location remote from the tricuspid and aortic valves with an adequate rim. Successful transcatheter closure has been accomplished in the

presence of multiple muscular or membranous fenestrations.

The technical success rate of transcatheter closure of selected muscular and membranous VSDs is high (93-100%) and the mortality rate is low (0 – 2.7%).

Outcome

The long-term outcome for children who undergo surgical closure of VSD in childhood is generally excellent. Early surgical repair results in near normal long-term growth in the vast majority of patients. Most survivors are asymptomatic and lead normal lives.

Adults with repaired VSD without residua have excellent outcomes and normal survival, with a 25year survival of 83%. However, long-term survival is less favorable when repair is done at older age or in presence of pulmonary hypertension. Although the prognosis after surgical repair of uncomplicated VSD is excellent in the majority of patients, long-term residua and sequelae are not uncommon including conduction disease, cardiac arrhythmias, residual VSD, endocarditis, tricuspid regurgitation, ventricular dysfunction, pulmonary hypertension, and aortic regurgitation.

Development of complete atrioventricular block is the most significant of the transcatheter procedural complications. Approximately 6% of patients who underwent transcatheter closure of membranous defects, developed complete heart block necessitating pacemaker implantation. Real-time three-dimensional transesophageal echocardiography has been increasingly used to guide such procedures. Given the lack of data on long-term outcomes following catheter closure of VSD in adults, patients should be followed every one to two years at an adult congenital heart disease center.

Atrioventricular septal defect

Case report

Introduction

The atrioventricular septal defect (AVSD) consist of several different lesions with a common atrioventricular (AV) junction and abnormal AV valves, consisting of five leaflets (Figure 11.1.6). The AVSD makes 3 percent of all congenital heart defects in children.

When the AVSD is complete it consists of a defect on the atrial and on the ventricular side of the common AV-valve ring. (Figure 11.1.6, middle). The complete AVSD is usually associated with Down Syndrome, but also with other cardiac defects like ASD type 2, persisting left inferior caval vein and tetralogy of Fallot.



Figure 11.1.6: Left: schematic drawing of a normal heart with a normal mitral (M) and tricuspid (T) valve. Middle: a complete AVSD where the mitral and tricuspid valve is replaced by a common valve with a right anterosuperior leaflet (1), a right inferior leaflet (2), a superior bridging leaflet (3), an inferior bridging leaflet (4), and a left mural leaflet (5). Right: showing the anatomic arrangement in an incomplete AVSD. a=aorta, p= pulmonary artery.

In an incomplete AVSD the superior and inferior bridging leaflets are connected with each other and with the interventricular septum in the centre. (Figure 11.1.6, right) Due to this connection there are two divided AV inlets, leaving no open communication between the ventricles, thus no VSD exists. However there is a rather large defect in the interatrial septum. The incomplete AVSD

is often referred to as ostium primum defect or ASD type 1. The left AV-valve consist of three leaflets (there is a cleft in the mitral valve) and is usually incompetent. Due to one common AV junction in both types of AVSD, the aortic valve is not in the usual wedged position between the two separate AV inlets, but located more anterior. Therefore the outflow tract of the left ventricle is elongated and slightly constricted. In angiography this abnormally shaped outflow tract is known as a gooseneck.

Pathophysiology

The exact pathophysiology depends on the location and severity of the defect. In a complete AVSD there is combined right and left ventricular overload due to the left-to-right shunt at atrial and ventricular level combined with the regurgitation of the right and left AV valve. As a result the elevated pulmonary pressures due to the extremely high flow will rapidly convert to pulmonary hypertension. This will lead to bidirectional shunting across the defect with a preferably right-to-left shunt and cyanosis (Eisenmenger syndrome).

In an incomplete AVSD the hemodynamic consequences are comparable to an ASD type 2. However the serious left AV-valve regurgitation can cause an increase in the atrial left-to right shunt.

Evaluation

The complete AVSD leads to symptoms of heart failure early in childhood and most patients will have been surgically corrected in adulthood. During physical examination signs of a residual shunt or regurgitation of the AV-valves might be present. This defect is rarely diagnosed in adulthood and usually there is Eisenmenger syndrome present, with clinical signs previously described in isolated ASD or VSD. The clinical symptoms of an incomplete AVSD are comparable with those of an ASD type 2. During physical examination a murmur of the regurgitant AV-valve might be audible.

The ECG shows a deviation of the heart axis to the left, in contrast to the right axis deviation in atrial septal defects. This is due to the abnormal position of the His bundle which causes a delay in conduction through the left anterior fascicular branch.

Treatment and outcome

The survival for patients with a complete AVSD without corrective surgery is very limited, most patients will not reach adulthood. Therefore surgical correction at an early age (usually in the first year of life) is advised. Patients with a corrected complete AVSD need lifelong cardiologic follow up, due to frequent residual defects like residual VSD, progressive regurgitation of the left AV-valve, pulmonary hypertension and often rhythm- or conduction disorders. Patients with Down Syndrome and complete AVSD are more likely to develop progressive pulmonary hypertension, even after corrective surgery.

The aberrant anatomy of the AV-valves, even after corrective surgery, is important when reviewing echocardiographic images. They can, for example, be easily mistaken for vegetations in endocarditis.

The survival for patients with an incomplete AVSD is higher compared to the complete AVSD, but generally worse compared to other ASD types. This is due to the concomitant disorders of the left AV-valve and the conduction system. Left AV-valve regurgitation will lead to an increase in left-to-right shunt and earlier development of pulmonary hypertension compared to ASD type 2. In childhood there is usually already an indication for correction of the defect in which the anatomically abnormal AV-valve can be repaired. However a slight amount of regurgitation will remain present. In some cases the progressive failure of the AV-valve will require a second repair or replacement, but in most patients the insufficiency will remain mild.

Besides the AV-valve problems there are frequent rhythm and conduction disorders; atrial fibrillation, supraventricular tachycardia, complete heartblock or sinus dysfunction. Depending on the kind of disorder patients can require medical treatment or a pacemaker.

11.2: Patent Ductus Arteriosus

Case report

Introduction

The ductus arteriosus (DA) is a fetal vascular connection between the main pulmonary artery and the descending aorta that diverts blood away from the pulmonary bed (Figure 11.2.1). After birth, the DA undergoes active constriction and eventual obliteration. A patent ductus arteriosus (PDA) occurs when the ductus fails to completely close postnatally.

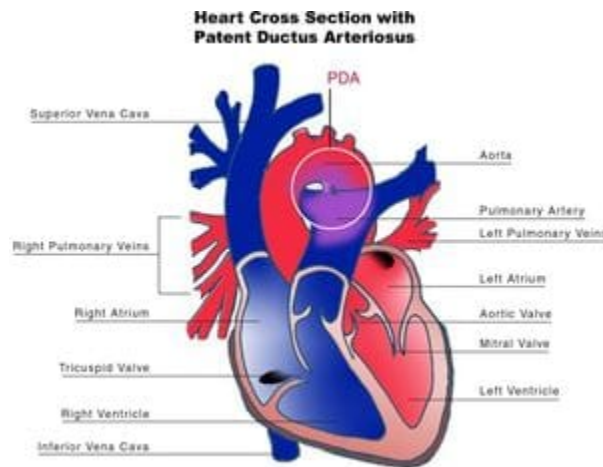


Figure 11.2.1: Schematic cross-section of the heart showing a patent ductus arteriosus.

The incidence of PDA has increased dramatically over the last two decades. This is due to the improved survival rate of premature infants, because the incidence of PDA significantly increases in infants born before 30 weeks gestation.

The reported incidence of an isolated PDA among term infants ranges from 0.03 to 0.08 percent.

There is a female predominance for PDA with a 2:1 female to male ratio in most case series of term infants. The incidence of PDA is also greater in infants born at high altitude compared to those born at sea level, and in infants with congenital rubella.

PDA may present with other congenital heart lesions, especially those associated with hypoxemia. PDA should be considered when the clinical features of left-to-right shunt seem out of proportion to the particular lesion being considered.

Evaluation

The clinical manifestations of a PDA are determined by the degree of left-to-right shunting, which is dependent upon the size and length of the PDA, and the difference between pulmonary and systemic vascular resistances.

The hemodynamic consequences of the PDAs can be categorized by the degree of left-to-right shunting based upon the pulmonary to systemic flow ratio ($Q_p:Q_s$) [21].

- Small — $Q_p:Q_s < 1.5$ to 1
- Moderate — $Q_p:Q_s$ between 1.5 and 2.2 to 1
- Large — $Q_p:Q_s > 2.2$ to 1

Typical findings during physical examination are a continuous murmur and a low diastolic blood pressure. In small shunts the ECG and chest x-ray are normal. In larger left-to-right shunts signs of left atrial and left ventricular overload might be present.

Echocardiography is a very sensitive and specific method to identify the left-to-right shunt.

Treatment and outcome

Patients with an open PDA have an increased risk of infectious endarteritis, heart failure, pulmonary hypertension and most of these patients become symptomatic in adulthood. Patients with a non-restrictive PDA rarely reach adulthood, unless the pulmonary vascular resistance increases leading to a decrease in left ventricular overload. This hemodynamic state is known as Eisenmenger syndrome in which the shunt is reversed and there is cyanosis present. Patients in who the ductus is closed in childhood have a normal life expectancy.

In patients with a PDA, the primary management decision is whether to actively close the PDA, or to conservatively observe and monitor the patient's cardiac status on a regular basis.

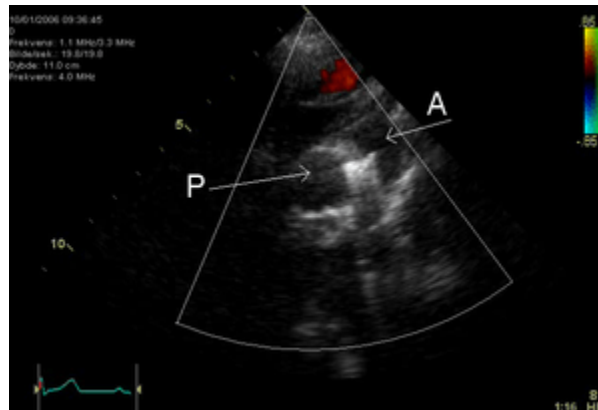


Figure 11.2.2: Echocardiographic image showing a coil in the ductus arteriosus. P=pulmonary artery, A= aorta.

PDA closure is recommended for patients with a significant left-to-right shunt who are symptomatic, have evidence of left-sided volume overload or have reversible pulmonary arterial hypertension. Closure results in resolution of symptoms and a decrease in the likelihood or severity of PAH, and the development of irreversible pulmonary vascular disease (Eisenmenger syndrome).

PDA closure is not recommended in patients with severe and irreversible PAH because of the procedural risk, the fact that closure does not improve survival, and right to left ductal shunting may be necessary to maintain cardiac output during episodes of increasing pulmonary vascular resistance.

Interventions for PDA closure include: pharmacological treatment which is used exclusively in premature infants, surgical ligation or percutaneous catheter occlusion. Surgical closure has a low mortality (<1%) in children and young adults. In adult patients the perioperative risk is increased (around 3%) due to a higher rate of complications like bleeding, heart failure in a compromised left ventricular function and damage to the recurrent laryngeal nerve or phrenic nerve.

Percutaneous PDA occlusion was first introduced in 1967 and provides an alternative to surgical ligation. Many different techniques have been developed, however the two techniques most commonly used are coils or occlusion devices. Both techniques lead to a full occlusion of the PDA and normalization of left ventricular hemodynamics.

11.3: Coarctation of the Aorta

Case report

Introduction

Coarctation of the aorta is a narrowing of the thoracic aorta, typically located in the region of the obliterated ductus arteriosum. (Figure 11.3.1) The relation to the position of the left subclavian artery differs, in most patients the left subclavian artery is located anterior of the coarctation. Aortic coarctation is frequently associated with diffuse hypoplasia of the aortic arch and isthmus.

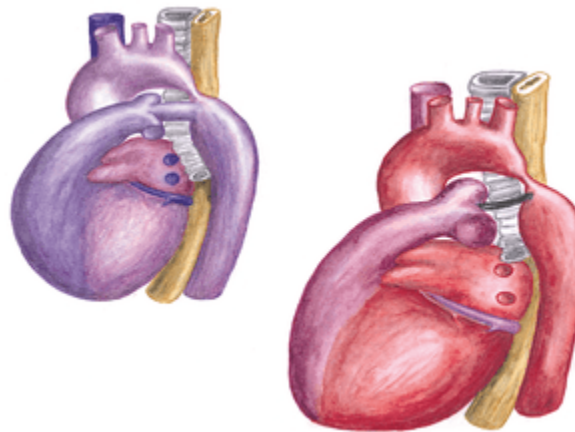


Figure 11.3.1: Schematic drawing of the anatomy prenatal (left) and postnatal (right) in coarctation of the aorta. In the normal situation (without coarctation) only 10 percent of the fetal cardiac output flows through the descending aorta. Therefore there are no hemodynamic consequences prenatal of coarctation of the aorta. In the postnatal situation, after closure of the ductus arteriosus, around 75% of cardiac output needs to pass the coarctation, leading to obstruction.

The incidence of coarctation of the aorta is 4 in 10,000 live births, accounting for 5–9% of the children with congenital heart defects, occurring two to five times more frequently in males than females.

Coarctation of the aorta can be an isolated congenital heart defect, however usually it coincides with other congenital defects. Associated heart defects are patent ductus arteriosus, ventricular septal defect, mitral valve stenosis and valvular and subvalvular aortic stenosis. Furthermore around 75% of all patients with a coarctation of the aorta have a bicuspid aortic valve.

The development of coarctation aorta depends on genetic as well on non-genetic factors. Parents with coarctation aorta have a 2% (male) or 4% (female) chance of passing this defect to their child.

Pathophysiology

Coarctation aorta has no hemodynamic consequences in utero, because only 10% of the total cardiac output crosses from the ascending to the descending aorta. However after birth the ductus arteriosus and foramen ovale close, leading the whole cardiac output through the narrowed aortic segment. This leads to an increase in resistance in the left ventricular outflow tract, resulting in an elevated systolic pressure in the left ventricle and upper extremities. When coping with the elevated pressures, the left ventricle will become hypertrophic.

If the coarctation is severe or in the acute phase (after birth when the ductus is closed), systolic dysfunction of the left ventricle and heart failure can occur.

Most adult patients are asymptomatic unless severe hypertension is present leading to headache, epistaxis, heart failure, or aortic dissection. In addition, claudication may occur due to reduced flow to the lower extremities.

Evaluation

Coarctation of the aorta is easily diagnosed without invasive methods, by means of physical examination, echocardiography or MRI. The combination of weak or absent femoral arterial pulses and upper body hypertension in physical examination points into the direction of coarctation of the aorta. Nevertheless, studies have shown that the diagnosis in hypertensive patients is often missed by the referring doctor. As a consequence, a significant number of asymptomatic subjects with aortic coarctation are probably not detected until adult life, so their incidence at birth is likely to be underestimated. Late detection of subjects with aortic coarctation can have detrimental effects on survival. For, without correction, the mean life expectancy of patients with aortic coarctation is 35 years and 90% of those patients die before reaching the age of 50 years.

Chest radiograph varies with age and severity of the coarctation. In infants with heart failure, the chest radiograph shows generalized cardiomegaly with increased pulmonary vascular markings due to pulmonary venous congestion. In older children and adults, the heart size may be normal but notching of the posterior one-third of the third to eighth ribs due to erosion by the large collateral arteries might be present.

Transthoracic echocardiography, including suprasternal notch views, is useful for initial imaging and hemodynamic evaluation in suspected aortic coarctation. Echocardiographic evaluation should also include measurement of the dimensions of the aortic annulus, aortic sinuses, sinotubular ridge, and ascending aorta; identification of aortic valve anatomy; determination of left ventricular size and function; and identification of any potential associated lesions such as ventricular septal defect, subvalvular aortic stenosis and mitral valve deformity.

Treatment and outcome

Since surgical repair of aortic coarctation became available in 1944, survival of patients with aortic coarctation has dramatically improved and the number of patients who were operated on and reach adulthood is steadily increasing. However, life expectancy is still not as normal as in unaffected peers. Survival of patients operated at a median age of 16 years was 91% at 10 years, 84% at 20 years and 72% at 30 years after operation. Survival of post-coarctectomy patients is significantly affected by age at operation and nowadays early repair is advocated. Even after early repair—before the age of 5 years—the estimated survival is still reduced, with 91% of the operated patients alive at 20 years and 80% at 40 to 50 years after surgery. However, repair of aortic coarctation is still recommended in patients at older age when diagnosis is delayed, because it improves blood pressure regulation and is probably associated with a lower risk of cardiovascular events in later years and improved survival.

There are several surgical techniques used for correction of the aortic coarctation. (Figures 11.3.2 & 11.3.3) Resection of the narrowed aortic segment with end-to-end anastomosis is the most commonly used technique. The subclavian flap aortoplasty and dilatation with a patch are not in use anymore due to a decreased blood flow in the left arm and a high rate of aneurysmatic deformation of the vessel respectively. When end-to-end anastomosis is not feasible, an interposition graft might be used instead. Sometimes a complete resection of the stenosis is not possible, for example when the carotid arteries are part of the coarctation, then an extended aortic arch repair or extra-anatomic bypass might be an appropriate choice.

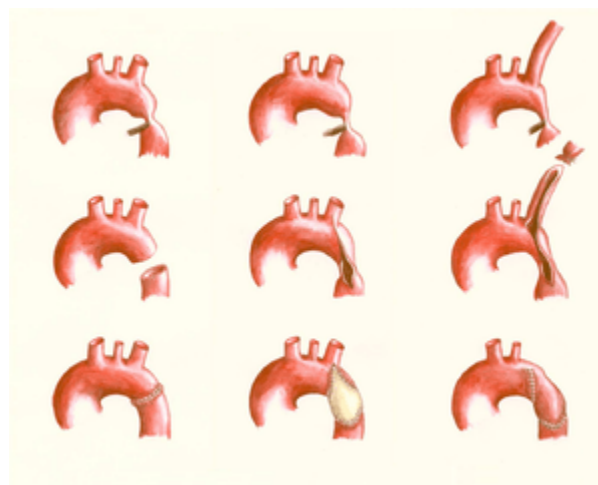


Figure 11.3.2: Schematic drawing showing surgical procedures for repair of coarctation of the aorta. Left: resection with end-to-end anastomosis. Middle: dilating technique using a patch; this technique is used in coarctations involving a long segment of the aorta. Right: the subclavian flap aortoplasty, using the left subclavian artery.

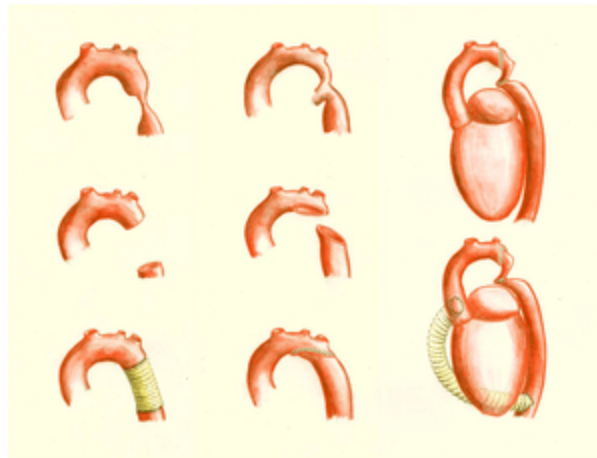


Figure 11.3.3: Schematic drawing showing surgical procedures for repair of a coarctation of the aorta. Left: an interposition graft. Middle: the extended aortic arch repair. Right: the extra-anatomical bypass.

Transcatheter interventions for native aortic coarctation have been used for over 20 years. Transcatheter treatment for native aortic coarctation has been shown to be feasible, relatively safe and effective at short term and intermediate follow-up and is rapidly becoming the treatment of choice. Older age, however, seems to be a risk factor for suboptimal outcome after balloon angioplasty possibly due to a more fibrotic and rigid aorta. Especially in the full grown patient, stent placement seems a particularly attractive option, resulting in an almost complete relief of the gradient in 95% of the patients. Another benefit of stent placement is the ability to address longer segment coarctations, which typically have a poorer outcome after balloon angioplasty alone. Long-term results, however, are to be awaited. Concern after surgery or catheter intervention falls chiefly in seven categories: recoarctation, aortic aneurysm formation or aortic dissection, coexisting bicuspid aortic valve, endocarditis, premature coronary atherosclerosis, cerebrovascular accidents and systemic hypertension.

11.4: Transposition of the Great Arteries

Case report

Introduction

Transposition of the great arteries (TGA) accounts for 5-8% of all congenital heart defects and occurs 2-3 times more frequently in males. TGA is best defined as a normal atrioventricular connection with an abnormal ventricular-arterial connection; the morphological left atrium is connected through the left ventricle with the pulmonary artery and the morphological right atrium through the right ventricle with the aorta. (Figure 11.4.1) The aorta is often located on the right side and in front of the pulmonary artery (D-TGA). In 70 percent there is an isolated form of TGA, in 30 percent the TGA is accompanied by other heart defects, like VSD or obstruction of the left ventricle outflow tract.

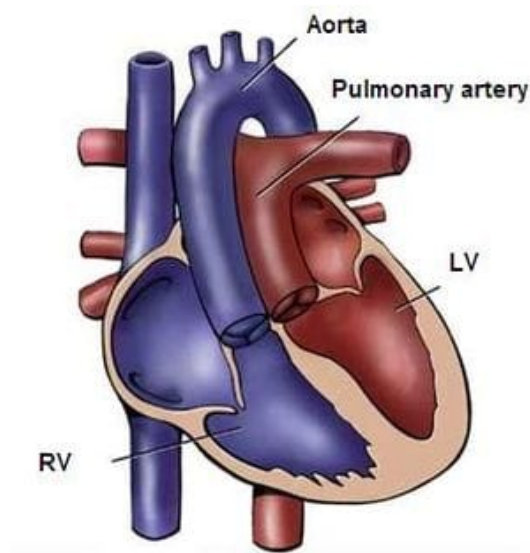


Figure 11.4.1: Schematic drawing showing transposition of the great arteries. The pulmonary artery is located above the left ventricle (LV) and the aorta is located above the right ventricle (RV).

Pathophysiology

The circulation in TGA patients is not serial but parallel (Figure 11.4.2); the venous blood is returned to the systemic circulation through the right atrium and ventricle, while the arterial oxygenated blood is directed back into the pulmonary artery through the left atrium and ventricle. Due to this abnormal circulation there is severe cyanosis directly after birth, therefore it is critical for the ductus arteriosus and foramen ovale to remain open. Without treatment there is a mortality of 30% within one week, 50% within one month and 90% within one year. When an associated VSD is present the chances of survival are higher due to more shunting thus more oxygenated blood in the systemic circulation. These patients are able to reach early adulthood without corrective surgery or intervention. However the pulmonary hypertension that develops in this situation will eventually lead to severe problems.

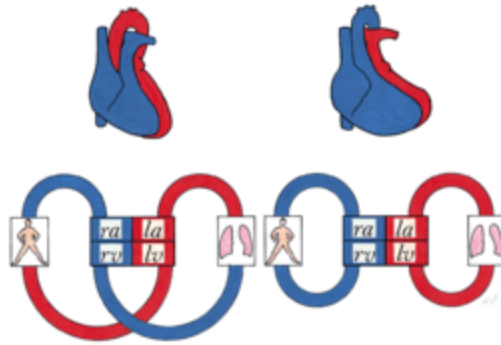


Figure 11.4.2: Schematic drawing of the circulation in transposition of the great arteries. Left: normal position of the great arteries with the pulmonary and systemic circulation serially connected. Right: transposition of the great arteries with a parallel circulation.

Treatment

Mortality of TGA has dramatically improved from 90 percent for unoperated patients to rates of less than 5 percent following corrective surgery using the arterial switch operation. Most patients are referred for surgical repair during the first three to five days of life. The choice of surgical procedure is dependent on the presence and nature of other cardiac anomalies. In patients without any other cardiac defect (simple D-TGA), arterial switch operation is the recommended procedure. In general, the arterial switch operation has replaced the earlier atrial switch procedures developed by Mustard and Senning. In patients with D-TGA and a ventricular septal defect (VSD), the preferred procedure is arterial switch operation and VSD closure. In patients with D-TGA, large VSD, and significant pulmonary stenosis, the Rastelli procedure, an alternative surgical approach, should be considered. In some cases, arterial switch operation with or without repair of the left ventricular outflow obstruction is used. Both the arterial switch operation and Rastelli procedures are surgical anatomic corrections resulting in a morphologic left ventricle as the systemic ventricle. In comparison to atrial switch procedures, which involved the rerouting of venous return in the atria and are now only rarely performed, the arterial switch operation appears to have similar long-term survival rates with reduced long-term morbidity primarily due to a lower risk of atrial arrhythmias and heart failure. As a result, it is the recommended procedure in most patients with D-TGA.

Outcome

The long-term survival rates for patients with D-TGA following surgical correction are excellent for both arterial switch operation and atrial switch procedures. The long-term survival 20 years after discharge is about 95 and 80 percent for arterial switch and atrial switch respectively. Progressive congestive heart failure and sudden death are the principal causes of death. Perioperative mortality is greater in patients with complex (additional cardiac anomaly) D-TGA compared to those with simple D-TGA. There are no clinical trials comparing outcomes of arterial switch and atrial switch procedures. Reintervention is common following both approaches.

Patients who undergo surgical repair for D-TGA have a reduced exercise capacity primarily due to pulmonary disease. Patients after arterial switch operation appear to have better exercise capacity than those who underwent atrial switch procedures. The decrease in exercise capacity, however, does not limit ordinary activity as most patients meet the criteria for New York Heart Association functional class I.

It appears that patients with D-TGA may have mild long-term neurodevelopmental impairment, most likely due to perioperative factors including hypoxemia, acidosis, cardiopulmonary bypass, and hemodynamic instability.

11.5: Congenitally Corrected Transposition of the Great Arteries

Congenitally corrected transposition of the great arteries

Introduction

The congenitally corrected transposition of the great arteries (ccTGA) is characterized by a normal anatomical position of both atria, with an abnormal connection between the atria and the ventricles. The right atrium is connected with the left ventricle and the left atrium is connected with the right ventricle. (Figure 11.5.1) Furthermore the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. There are, in conclusion, abnormal atrioventricular connections and abnormal ventricular-arterial connections present in ccTGA. CcTGA is a very rare defect, accounting for about 1% of all congenital heart disease.

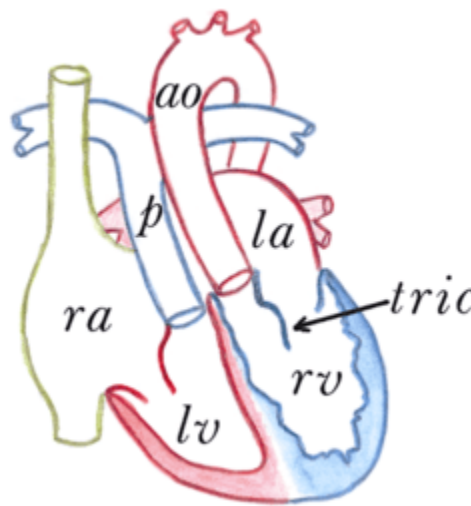


Figure 11.5.1: Congenitally corrected transposition of the great arteries. RA = right atrium. LA = left atrium. RV = right ventricle. LV = left ventricle. p = pulmonary artery. ao = aorta. tric = tricuspid valve.

Pathophysiology

The blood flow in ccTGA is 'corrected' because oxygenated blood flows through the systemic circulation and deoxygenated blood is transported to the lungs. In this particular heart defect the right ventricle functions as a systemic ventricle. With the atrioventricular valves following the position of the ventricles, the tricuspid valve is now the systemic AV-valve.

Additionally the coronary arteries are a mirror image of the normal anatomic situation. The coronary artery on the right side of the heart runs like a morphological left coronary artery; starting with a main stem which divides into a left anterior descending and circumflex branch. The coronary artery on the left is the morphological right coronary artery, which now runs around the tricuspid valve on the left.

Even the conduction system is abnormal in this congenital heart defect. Normally the AV node is positioned at the base of the interatrial septum, from where the His bundle arises into the interventricular septum. Due to misalignment in ccTGA there is no bundle directly from the normal AV node into the interventricular septum. Usually there is an additional AV node located more anterior and laterally from where a long bundle arises which runs beneath the pulmonary valve leaflets into the interventricular septum. Due to the long route this bundle is rather vulnerable. Where in normal hearts the electrical activation of the ventricles in the septum runs from left to right, in ccTGA it is the exact opposite; the septum is activated from right to left, which is visible on the ECG as an abnormal initial activation.

There is a VSD present in 60% of all ccTGA patients, who will often become symptomatic at younger age. Pulmonary valve stenosis is seen in 30 – 50% of patients, usually in those who already have a VSD as well. Abnormal anatomy of the tricuspid valve (M. Ebstein like) is seen in 25-30% of patients, sometimes accompanied by VSD or pulmonary valve stenosis. More than 80 percent of patients have an abnormal function of the tricuspid valve, which often becomes insufficient.

Evaluation

When only ccTGA is present, without other cardiac defects, the diagnosis is often not recognized until adulthood. However, when there is a VSD and/or pulmonary valve stenosis present, it presents short after birth with cyanosis and heart failure or even a total AV-block.

Adult patients are usually recognized due to an abnormal ECG, abnormal chest radiograph, systolic murmur due to the regurgitation of the systemic AV-valve, occurrence of atrial tachycardia or an AV-block. Reduced exercise capacity might be present.

The ECG is the most typical for ccTGA; left heart axis deviation, septum activation in mirror image (no Q-wave in I, aVL and V6, no R-top in V1) and a rather deep Q-wave in III and aVF. Echocardiography is a good diagnostic tool to review the exact anatomy. The right ventricle positioned on the left side is identified by the typical morphology of the trabeculae. Furthermore the tricuspid valve has a lower insertion compared to the mitral valve.

Treatment and outcome

Patients with ccTGA require lifelong follow up due to the risk of arrhythmias and associated sudden death, increase of pulmonary valve stenosis, increase of tricuspid valve regurgitation, supraventricular tachycardia, heart failure or endocarditis. Due to the complex anatomy and the low incidence of this pathology, this is best acquired at a specialised centre of congenital heart disease.

Arrhythmias need treatment, preferably not with negative inotropic agents, but digoxin and possibly amiodaron are preferred. When presenting with atrial arrhythmias conversion to sinus rhythm is highly important in these patients, who are in need of their 'atrial kick'.

Many patients with ccTGA require pacemaker placement, often already in childhood or early adulthood. Frequent followup in these patients is required due to the high complication rate; dislocation of the lead which is located in the smooth-walled left ventricle and risk of infection or endocarditis.

Determining the right time to replace the tricuspid valve is difficult in these patients. Preferably this is done just before the right systemic ventricle starts dilating and fails, but it remains an estimation which should be made for each individual patient.

To restore normal blood flow through the ventricles, with the left ventricle functioning as the systemic ventricle, there is an option to perform a double switch operation. During this procedure both atria and both great arteries are switched, meaning a combination of the arterial switch and the atrial switch procedure. From a physiologic point of view this operation is worth considering while the left ventricle will function as systemic ventricle, however it is associated with a high perioperative mortality due to the extent of surgery. Furthermore the left ventricle requires training prior to surgery, to be able to cope with the high arterial pressure after years of low pulmonary pressure. In conclusion the chance of success of this double switch operation is very low in patients above 16 years of age.

11.6: Univentricular Heart

Case report

Introduction

Around 10 percent of all congenital heart defect patients have just one functioning ventricle. The other ventricle is present, however it is rudimentary or underdeveloped so it can not function normally. In utero this causes rarely any problems, due to the parallel circulation the other ventricle takes over both functions. It is after birth, if the ductus arteriosus closes, when problems arise.

Pathophysiology

The hypoplastic left heart syndrome (HLHS) is the most common type of univentricular heart. (Figure 11.6.1) Not only the left ventricle, but often the aortic valve, ascending aorta and aortic arch are hypoplastic as well. This will redirect blood from the left atrium into the right atrium, where it will be mixed with venous blood and pumped into the right ventricle and pulmonary artery. The whole systemic circulation depends on the shunt from pulmonary artery through the ductus arteriosus into the aorta. When the ductus starts closing the consequences are dramatic, with severe cyanosis and acidosis.

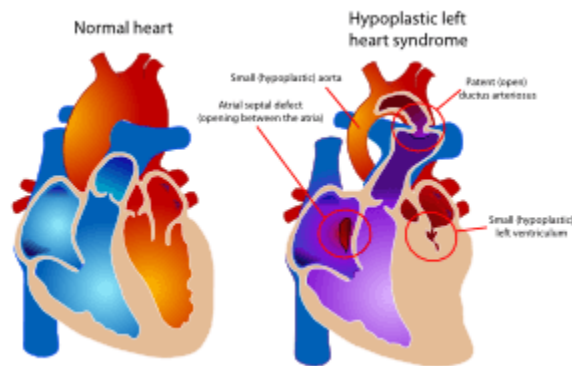


Figure 11.6.1: Schematic drawing representing the hypoplastic left heart syndrome.

When a hypoplastic right ventricle is present with associated atresia of the pulmonary artery, the pulmonary circulation after birth will solely depend on the left-to-right shunt through the ductus arteriosus. When the ductus starts closing, progressive cyanosis is the main presenting symptom.

Other cardiac defects associated with only one functional ventricle are: tricuspid valve atresia, mitral valve atresia, severe form of Ebstein anomaly, double inlet left ventricle and unbalanced AVSD.

All patients with one functioning ventricle have complete mixing of saturated and desaturated blood leading to chronic hypoxemia (Figure 11.6.2). Furthermore there is a chronic volume overload to the ventricle, serving as both pulmonary and systemic ventricle, leading to an early development of heart failure.

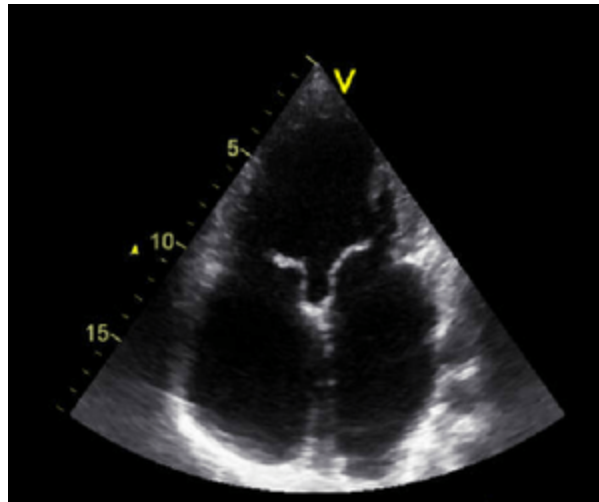


Figure 11.6.2: Echocardiographic image of a male patient with a univentricular heart.

Due to the obligatory intracardiac shunting the pulmonary 'filter' is bypassed, which will increase the chance of cardiovascular accidents and brain abscesses.

Treatment

In case of a ductus-dependent defect initial treatment immediately after birth consists of prevention of ductus closure. At first this can be achieved pharmacologically with prostaglandin, however due to the many side effects this is no long-term solution. When there is a dependent pulmonary circulation an aortopulmonary shunt will be constructed during the first weeks of life to ensure accurate blood flow to the lungs after discontinuation of the prostaglandin.

If there is a dependent systemic circulation the surgical treatment usually consists of three different steps. Since the anatomy is by no means normalized, one can not speak of a surgical correction, it is referred to as a definitive palliation. At first a Norwood or Sano procedure is performed in neonates where a neo-aorta is constructed by dividing the pulmonary artery. Second stage is the construction of a cavopulmonary shunt, also known as bidirectional Glenn shunt, which is performed at 4 -6 months of age. The third and final stage is known as Fontan procedure and performed at 18 - 30 months of age, where a total cavopulmonary connection is created. (Figure 11.6.3) All surgical procedures are described in more detail separately.

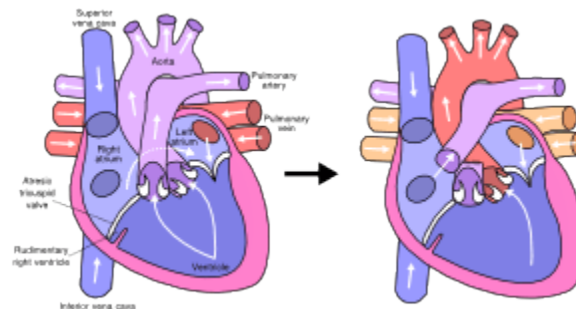


Figure 11.6.3: Schematic drawing showing the Fontan procedure.

Outcome

With an expanding cohort of survivors of surgical palliation through Fontan completion, increasing information is being accumulated on the long-term morbidity of these patients. Active areas of interest include exercise tolerance, neurodevelopmental outcome, and quality of life.

When assessed prospectively by formal exercise testing, children with HLHS after surgical repair showed considerable age-related decline in exercise performance. Among patients participating in treadmill or bicycle ergometry, those aged 8 to 12 performed at 70 percent of predicted peak oxygen consumption, whereas older children reached only 60 percent of predicted

performance.

Several reports have demonstrated significant neurodevelopmental impairment in survivors of HLHS following staged repairs or cardiac transplantation. There is a paucity of data on the quality of life for patients with HLHS. In one report of survivors and their families, parents reported poorer functional health status than patients assessed at 18 years of age.

Risk factors that lower survival include noncardiac congenital anomalies and/or genetic disorder, particularly chromosomal defects, prematurity, low birth weight for gestational age, and living in a high poverty neighborhood.

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11.7: Tetralogy of Fallot

Case report

Introduction

In 1888 Etienne Louis Arthur Fallot described the 'maladie bleue' as a combination of:

- Stenosis of the pulmonary artery (PS)
- Ventricular septal defect (VSD)
- Deviation of the origin of the aorta to the right
- Hypertrophic right ventricle

This constellation of findings has since become known as tetralogy of Fallot (TOF). (Figure 11.7.1)

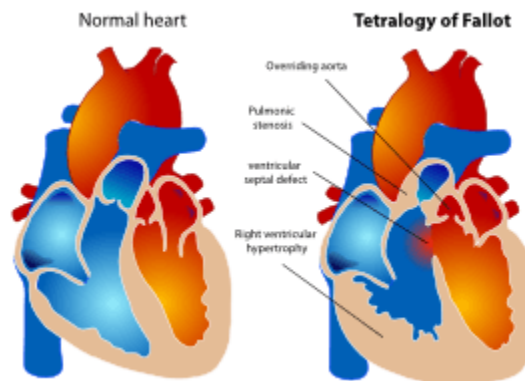


Figure 11.7.1: Schematic drawing representing the four features of tetralogy of Fallot.

The prevalence of TOF is about 3.9 per 10,000 live births. This defect accounts for about 7 to 10 percent of cases of congenital heart disease and is one of the most common congenital heart lesions requiring intervention in the first year of life.

Anatomy

In fact there is only one anatomic abnormality in TOF; a misalignment of the interventricular septum. As a consequence the muscular part of the interventricular septum is not able to fuse with the cranial part of the septum (leaving a ventricular septal defect) and overriding of the aorta, which causes stenosis of the right ventricular outflow tract. The hypertrophy of the right ventricle is a direct consequence of the elevated pressure in the right ventricle due to the large unrestrictive VSD.

Pathophysiology

The combination of infundibular PS and a VSD causes the blood flow in utero to flow directly into the aorta, leading to a high chance of underdevelopment of the pulmonary valve and arteries. Therefore pulmonary valve stenosis and hypoplasia of the pulmonary arteries are often found in TOF patients. Stenosis at the origin or more distally of the right or left pulmonary artery are frequently found, so is total absence of (usually the left) pulmonary artery. Furthermore about 33% percent of all TOF patients has a descending aorta on the right side.

The physiologic consequences of TOF are largely dependent upon the degree of right ventricular outflow obstruction. Since the VSD is typically large and unrestrictive, the pressure in the right ventricle reflects that of the left ventricle. As a result, the direction of blood flow across the VSD will be determined by the path of least resistance for blood flow, not by the size of the VSD. If the

resistance to blood flow across the obstructed right ventricular outflow tract is less than the resistance to flow out of the aorta into the systemic circulation, blood will naturally shunt from the left ventricle to the right ventricle and into the pulmonary bed. In this situation, there is predominately a left-to-right shunt and the patient will be acyanotic.

As the degree of right ventricular outflow obstruction increases, the resistance to blood flow into the pulmonary bed also increases. If the right ventricular obstruction is significant enough to increase resistance, it will be easier for blood to cross the VSD from the right ventricle into the left ventricle and go out the aorta, which now becomes the path of least resistance. This right-to-left shunt across the VSD will result in a large volume of desaturated blood entering the systemic circulation and cyanosis and polycythemia will ensue.

One of the physiologic characteristics of TOF is that the right ventricular outflow obstruction can fluctuate. An individual with minimal cyanosis can develop a dynamic increase in right ventricular outflow tract obstruction with a subsequent increase in right-to-left shunt and the development of cyanosis. In the most dramatic situation, there can be near occlusion of the right ventricular outflow tract (RVOT) with profound cyanosis. These episodes are often referred to as "hypercyanotic spells". The exact etiology of these episodes is unclear, although there have been a number of proposed mechanisms, including increased infundibular contractility, peripheral vasodilatation, hyperventilation, and stimulation of right ventricular mechanoreceptors.

Treatment

Patients with TOF can undergo either palliative (shunts) or corrective (intracardiac repair) surgery. Although most children with TOF undergo intracardiac repair as their initial intervention, the principle of shunts remains an important palliative procedure for infants who may not be acceptable candidates for intracardiac repair due to prematurity, hypoplastic pulmonary arteries, or coronary artery anatomy.

Shunts are constructed to increase the blood flow to the lungs, to improve the development of the pulmonary arteries. Many patients who underwent intracardiac repair initially had a palliative shunt. Blalock and Taussig first reported successful surgical palliation of TOF in 1945. The procedure, which has since come to bear their names, used a subclavian artery to create an aorta-to-pulmonary artery connection. The technique has been modified and is now usually performed using a Gortex tube to create the connection.

A different type of shunt is the aortopulmonary anastomosis, where a direct connection between the descending aorta and left pulmonary artery (Potts) or between the ascending aorta and the right pulmonary artery (Waterston) is constructed.

Intracardiac repair of TOF was reported by Lillehei in 1954. It consists of patch closure of the ventricular septal defect and enlargement of the RVOT. The latter is accomplished by relieving pulmonary stenosis, resecting infundibular and subinfundibular muscle bundles and if necessary by a transannular patch, creating unobstructed flow from the RV into the pulmonary arteries.

Outcome

A few decades ago the perioperative mortality in TOF patients was rather high (until 25 percent) but gradually declined to the current risk of around 3%. The survival in TOF patients after surgery is, although slightly less than the average population, considerably good. The longest follow-up cohort shows a survival rate of 85% after 35 years. However the rate of morbidity is very high in TOF patients due to a wide range of residual defects, that can increase over time. Therefore all patients with TOF require a lifelong, regular cardiologic follow up.

The main complications of TOF include pulmonary regurgitation, residual right ventricular outflow tract obstruction, pulmonary hypertension and residual shunt.

Intracardiac repair with a transannular RVOT patch can result in chronic severe pulmonary regurgitation. This leads to RV enlargement and patients may develop decreased exercise tolerance, right heart failure, and arrhythmias. A surgical prosthetic pulmonary valve may be necessary to restore the valve competence and improve RV function and functional status in TOF patients. Residual RVOT obstruction can persist after the original intracardiac operation due to hypertrophied subvalvar muscle, annular hypoplasia, pulmonary valve stenosis, supralvar pulmonary stenosis, or branch pulmonary artery stenosis. Mild obstruction is usually well tolerated, but significant obstruction may require reoperation or catheter-based intervention. Relief of pulmonary artery stenosis by balloon dilation or stenting may be necessary prior to pulmonary valve replacement.

Pulmonary hypertension can be present in TOF patients due to: hypoplastic pulmonary arteries with associated high vascular

resistance, excessive shunting across the surgically constructed shunts (mainly Potts or Waterston shunts) or presence of multiple pulmonary artery stenosis.

A residual VSD shunt is present in about 20 percent of all operated TOF patients, requiring a reoperation in 5 – 10 percent of them. Residual shunt might be due to detachment of the patch or an additional septal defect which was not recognized during surgery.

11.8: Marfan Syndrome

Case report

Introduction

Marfan syndrome (MFS) is an autosomal dominant condition with a reported incidence of 1 in 3000 to 5000 individuals and is one of the most common inherited disorders of connective tissue. While most MFS patients have an affected parent, around 15 – 30 percent have a de novo mutation. MFS is associated with a broad range of clinical symptoms and associated disorders, ranging from classic ocular, cardiovascular, and musculoskeletal abnormalities to manifestations including involvement of the lung, skin, and central nervous system.

Progressive dilatation of the ascending aorta is one of the key features, which causes a high risk of sudden death due to aortic dissection or rupture in young Marfan patients. (Figures 11.8.1 & 11.8.2)



Figure 11.8.1: Echocardiographic image of aortic root dilatation in Marfan syndrome.

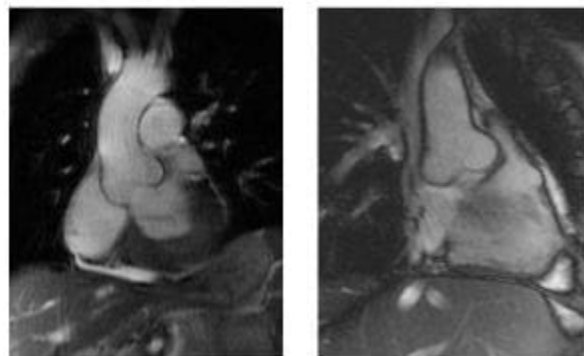


Figure 11.8.2: Magnetic resonance imaging of the aorta, showing aortic root dilatation in Marfan syndrome.

The underlying genetic defect is localised in the fibrillin gene on chromosome 15 (FBN1) in which recently around 600 different mutations are found. However in about 10% of MFS patients there is no mutation identified in the FBN1 gene, furthermore FBN1 mutations also occur across a wide range of milder phenotypes that overlap the classic Marfan phenotype. Therefore it is not possible to diagnose MFS solely with genetic information.

Criteria for diagnosis of Marfan syndrome

The 2010 revised Ghent criteria puts greater weight on aortic root aneurysm/dissection and ectopia lentis as the cardinal clinical features of MFS and on testing for mutations in FBN1 and other relevant genes.

In the absence of family history of MFS, the presence of one of any of the following criteria is diagnostic for MFS:

- Aortic criterion (aortic diameter $Z \geq 2$ or aortic root dissection) and ectopia lentis*
- Aortic criterion (aortic diameter $Z \geq 2$ or aortic root dissection) and a causal FBN1 mutation
- Aortic criterion (aortic diameter $Z \geq 2$ or aortic root dissection) and a systemic score ≥ 7
- Ectopia lentis and a causal FBN1 mutation as defined above that has been identified in an individual with aortic aneurysm

In the presence of family history of MFS (as defined by the above criteria), the presence of one of any of the following criteria is diagnostic for MFS:

- Ectopia lentis
- Systemic score ≥ 7 points*
- Aortic criterion (aortic diameter $Z \geq 2$ above 20 years old, $Z \geq 3$ below 20 years, or aortic root dissection)*

For criteria with an asterisk (*), the diagnosis of MFS can be made only in the absence of discriminating features of Shprintzen-Goldberg syndrome (SGS), Loays-Dietz syndrome (LDS), or vascular Ehlers-Danlos syndrome (vEDS) and after TGFBR1/2, collagen biochemistry, or COL3A1 testing if indicated.

The revised Ghent nosology includes the following scoring system for systemic features:

- Wrist AND thumb sign: 3 points (wrist OR thumb sign: 1 point)
- Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1 point)
- Hindfoot deformity: 2 points (plain pes planus: 1 point)
- Pneumothorax: 2 points
- Dural ectasia: 2 points
- Protrusio acetabuli: 2 points
- Reduced upper segment/lower segment ratio (US/LS) AND increased arm span/height AND no severe scoliosis: 1 point
- Scoliosis or thoracolumbar kyphosis: 1 point
- Reduced elbow extension (≤ 170 degrees with full extension): 1 point
- Facial features (at least 3 of the following 5 features: dolichocephaly [reduced cephalic index or head width/length ratio], enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia): 1 point
- Skin striae: 1 point
- Myopia >3 diopters: 1 point
- Mitral valve prolapse (all types): 1 point

A systemic score ≥ 7 indicates systemic involvement.

Pathophysiology

Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation, and dissection, is the main cause of morbidity and mortality in the MFS. Dilatation of the aorta is found in approximately 50 percent of children with MFS and progresses with time. Approximately 60 to 80 percent of adult patients with MFS have dilatation of the aortic root (with normal range adjusted for patient body surface area and age) by echocardiography, often accompanied by aortic regurgitation. Dilatation may also involve other segments of the thoracic aorta, the abdominal aorta, the root of the pulmonary artery or even the carotid and intracranial arteries. Untreated MFS is frequently associated with aortic dissection, which begins just above the coronary ostia and extends the entire length of the aorta; it is a type I dissection in the DeBakey classification or a type A in the Dailey scheme. Approximately 10 percent of dissections begin distal to the left subclavian (type III or type B) but dissection is rarely limited to just the abdominal aorta. Many patients with MFS and aortic dissection have a family history of dissection.

Mitral valve prolapse (MVP) is frequently identified in patients with MFS. However, only one point in the systemic score is assigned for MVP since it is a nonspecific feature and most patients with mitral valve prolapse do not have MFS. The frequency of MVP in MFS increases with age and is greater in women. Tricuspid valve prolapse may also occur.

Treatment

Beta blockers decrease myocardial contractility and may also improve the elastic properties of the aorta, particularly in patients with an aortic root diameter <40 mm thereby decreasing the risk of aortic dissection and delaying the aortic dilatation. Prophylactic treatment with beta blockers is considered the standard of care in adults with MFS. Furthermore patients with MFS are advised to avoid any contact sports, exercise at maximal capacity, and isometric activities.

The exact aortic root diameter at which elective surgery should be performed is uncertain. The current guidelines recommend elective operation for patients with MFS at an external diameter of ≥ 50 mm to avoid acute dissection or rupture. Indications for repair at an external diameter less than 50 mm include rapid growth (>2 mm/y), family history of aortic dissection at a diameter less than 50 mm, desire of pregnancy or presence of progressive aortic or mitral valve regurgitation. However one must take into account that a predicted aortic root diameter varies with body size and age and may be smaller in women. Smaller patients have dissection at a smaller aortic root size and 15 percent of patients with MFS have dissection at a diameter less than 50 mm.

The classic aortic root surgery is the Bentall procedure in which the ascending aorta is replaced, together with the aortic valve, by a graft with prosthetic valve. In this procedure the coronary arteries need to be reimplanted in the aortic graft. In patients with anatomically normal valves, in whom the insufficiency is due to the dilated annulus or dissection, valve-sparing operations with root replacement by a Dacron prosthesis and with reimplantation of the coronary arteries into the prosthesis (David's procedure) or remodelling of the aortic root (Yacoub's procedure) have now become the preferred surgical procedures. Aortic regurgitation is, however, a common complication, requiring reoperation in 20% of patients after 10 years.

Outcome

The reported operative mortality of the Bentall procedure is 1.5% for elective and 11.7% for emergency operations. Five- and 10-year survival rates of 84 and 75%, respectively, have been reported. This relatively limited prognosis is due to late sequelae associated with MFS; 75% require reoperations, 10% mitral valve surgery, 1% develop endocarditis and 1% a CVA. Marfan syndrome has also been associated with a considerably higher risk of re-dissection and recurrent aneurysm than other aetiologies of aortic disease. Long-term results of valvesparing aortic root replacement in Marfan syndrome are still unknown.

11.9: Ebsteins Anomaly

Case report

Introduction

Ebsteins anomaly, named after Wilhelm Ebstein (1836 – 1912) (Figure 11.9.1) is a congenital heart defect of the morphological tricuspid valve. The prevalence of Ebstein's anomaly is about 1 in 50.000 – 200.000 with a similar incidence in both males and females.



Figure 11.9.1: Wilhelm Ebstein (1836 – 1912).

As its name clearly indicates, the tricuspid valve consists of three leaflets; anterosuperior, septal and inferior. The Ebstein's anomaly consists of a variety of anatomical and functional abnormalities of the tricuspid valve. Typical features are:

- displacement of the septal and inferior leaflet downwards from the atrioventricular junction and toward the body of the right ventricle or the apex
- the anterior leaflet is not displaced, enlarged (sail-like) and can show fenestrations
- the tricuspid valve inlet is displaced towards the right ventricular outflow tract and often stenotic
- atrialisation of the right ventricle because of a downward extension of the tricuspid valve, leaving a small right ventricle or only a right ventricular outflow tract

Pathophysiology



Figure 11.9.2: Schematic drawing showing Ebstein's anomaly of the tricuspid valve. Left: normal heart with open right ventricle. Right: Ebstein's anomaly with displacement of the septal and posterior tricuspid leaflet, leading to atrialisation of a significant part of the right ventricle.

The Ebstein's anomaly can be isolated or associated with other cardiac defects like ASD or patent foramen ovale, pulmonary outflow tract obstruction, VSD, coarctation of the aorta, ccTGA, one or more accessory conduction pathways or patent ductus arteriosus.

The primary hemodynamic consequence of Ebstein's anomaly is tricuspid regurgitation (TR), which varies in severity. Severe TR causes a volume overload and right-sided cardiac chamber dilation and dysfunction, leading to a decrease in cardiac output. In some cases even hepatic congestion and failure can arise.

Ebstein's anomaly can be classified as mild, moderate, or severe based upon the extent of apical displacement of the valve leaflets with resultant tricuspid regurgitation, and the degree of right ventricular dysfunction.

Symptoms such as cyanosis and heart failure from severe TR may appear soon after birth, because of high pulmonary vascular resistance. However, symptoms often improve as pulmonary vascular resistance decreases. At a later age, symptoms such as exertional dyspnea, fatigue, cyanosis, and palpitations may recur; these symptoms may be insidious in onset. Palpitations due to atrial tachyarrhythmia are present in 20 to 30 percent of cases. Some of these arrhythmias may be due to Wolff-Parkinson-White syndrome, since up to 20 percent of patients have one or more accessory pathways; the majority of these pathways are located around the orifice of the malformed tricuspid valve. Patients with Ebstein's anomaly who have an interatrial communication are at risk for paradoxical embolization, brain abscesses, and sudden death.

Treatment

Indications for surgical tricuspid valve repair or replacement are:

- decrease in exercise capacity
- progressive cyanosis
- progressive right ventricular dilatation or dysfunction
- occurrence of paradoxal embolism
- supraventricular arrhythmias despite pharmacological or ablation therapy
- progressive cardiomegaly on chest radiograph

There are two main surgical techniques used in tricuspid valve repair. The Danielson repair consists of horizontally plicating the atrialized portion of the RV while multiple commissuroplasty stitches are placed. The Carpentier technique consists of detaching the large sail-like anterior leaflet from the valve annulus and translocating it in a clockwise division in order to create what essentially becomes a single leaflet valve. The atrialized portion of the RV is plicated but in a vertical not a horizontal fashion. If repair is not possible and the patient has reached adult size, tricuspid valve replacement becomes necessary. A biologic prosthesis, such as a porcine valve, is usually chosen because of the high incidence of thromboembolism with a mechanical prosthesis placed in the right heart.

Outcome

The prognosis varies with the severity of the disease. The 1 and 10 year survival rates for all liveborn patients have been estimated 67 percent and 59 percent respectively. The major causes of death are heart failure, perioperative, and sudden death.

However, survival is probably increasing as advances in diagnostic and surgical techniques and postoperative care have led to improvements in surgical outcome.

11.10: Pulmonary Hypertension

Case report

Introduction

Pulmonary hypertension (PH) is a progressive life-threatening condition and associated with a high rate of mortality, despite medical intervention. PH is characterized by elevated pulmonary arterial pressure and secondary right ventricular failure.

The definition of pulmonary hypertension (PH) is based upon right heart catheterization where PH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest.

Classification

PH is classified into five groups:

1. Pulmonary arterial hypertension (PAH). This group consists of idiopathic PAH and PAH due to connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease, drug- and toxin-induced PH and pulmonary capillary hemangiomatosis.
2. Pulmonary hypertension owing to left heart disease. PH due to systolic dysfunction, diastolic dysfunction, or valvular heart disease is included in this group.
3. Pulmonary hypertension owing to lung diseases or hypoxemia. This group includes PH due to chronic obstructive pulmonary disease, interstitial lung disease, other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, and other causes of hypoxemia [4].
4. Chronic thromboembolic pulmonary hypertension. This group includes patients with PH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature.
5. Pulmonary hypertension with unclear multifactorial mechanisms. These patients have PH caused by hematologic disorders (eg, myeloproliferative disorders), systemic disorders (eg, sarcoidosis), metabolic disorders (eg, glycogen storage disease), or miscellaneous causes

Pulmonary arterial hypertension in congenital heart disease

In approximately 6% of adults with congenital heart disease PAH develops. In fact congenital heart disease has emerged to be one of the commonest associated causes of PAH.

The occurrence of PAH in congenital heart disease is usually the result of systemic-to-pulmonary shunting, leading to a blood volume overload of the pulmonary vasculature. Left to right shunts are most common; VSD, ASD, patent ductus arteriosus or AVSD.

Pathophysiology

The pathogenesis of PH is complex and just beginning to be elucidated. In patients with congenital heart disease, left-to-right intracardiac shunting increases flow through the pulmonary vasculature, this causes shear forces that disrupt the vascular endothelium and activate cellular mechanisms critical to the pathogenesis and progression of PAH.

The mechanism of damage to the pulmonary vasculature differs in patients with ASD compared to VSD. Vascular injury is related to the degree and duration of volume overload alone with an ASD, whereas high pressure shear forces also contribute with a VSD.

In patients with an ASD, shunting is delayed until maturation of the pulmonary vasculature occurs. The normal pulmonary vasculature is able to accommodate the increased volume of flow by vasodilating and recruiting previously unperfused vessels; thus, pulmonary artery pressures do not rise significantly in most patients with an ASD until adult life. In contrast to patients with an ASD, clinical sequelae always develop in patients with a large (nonrestrictive) VSD. Severe PAH is present from birth because of

the unique hemodynamics. The combined effect of volume overload and shear forces elevates the pulmonary vascular resistance, which becomes fixed during childhood. As a result, shunt reversal (right-to-left flow) is common, with hypoxemia resulting. This is often referred to as the Eisenmenger syndrome.

Eisenmenger syndrome forms a small percentage (1%) of CHD patients and is defined as CHD with an initial large systemic-to-pulmonary shunt that induces progressive pulmonary vascular disease and PAH, with resultant reversal of the shunt and central cyanosis. Eisenmenger syndrome represents the most advanced form of PAH associated with CHD. An important subgroup in this Eisenmenger population is patients with Down syndrome.



Figure 11.10.1: Photo showing typical features of chronic hypoxemia in Eisenmenger syndrome, with typical digital clubbing with cyanotic nail beds.

Classification

Pulmonary arterial hypertension in congenital heart disease can be divided into four quite distinct phenotypes, which may be feasible to use in clinical practice.

A. *Eisenmenger syndrome*. This includes all systemic-to-pulmonary shunts resulting from large defects and leading to a severe increase in pulmonary vascular resistance (PVR) and a reversed (pulmonary-to-systemic) or bidirectional shunt; cyanosis, erythrocytosis, and multiple organ involvement are present.

B. *PAH associated with systemic-to-pulmonary shunts*. This includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still prevalent, and no cyanosis is present at rest.

C. *PAH associated with small defects*. This includes small defects (usually VSD <1 cm and ASD <2 cm of effective diameter assessed by echocardiography).

D. *PAH after corrective cardiac surgery*. In this group of patients the congenital heart disease has been corrected, but PAH is still present immediately after surgery or recurs several months or years after surgery in the absence of significant postoperative residual lesions.

Treatment

Early treatment of PH is generally suggested because advanced disease may be less responsive to therapy. PAH is characterized by symptoms of dyspnea, fatigue, chest pain, and syncope. Primary therapeutic strategy should be considered in all patients with PAH and consists of diuretic, oxygen, anticoagulant, and digoxin therapy, as well as exercise and lifestyle advices.

Injured endothelial cells release factors that are known to contribute to PAH. Inhibition of these factors forms the basis of some of the advanced therapies for PAH. Patients with CHD-PAH who progress to NYHA functional class II, III, or IV, qualify for advanced therapy. This is irrespective of any primary therapy given.

Advanced therapy is directed at the PAH itself, rather than the underlying cause of the PAH. For PAH treatments with advanced therapy three main pathways have been detected: prostacyclin, nitric oxide and endothelin-1. This resulted in therapies with

prostanoids such as epoprostenol, phosphodiesterase-5 inhibitors such as sildenafil and endothelin-1 receptor antagonists such as bosentan.

Outcome

The prognosis is generally poor but varies according to the severity of the underlying cause, the functional abnormalities, and the hemodynamic abnormalities. Factors that may indicate a poor prognosis include age at presentation greater than 45 years, NYHA functional class III or IV, failure to improve to a lower NYHA functional class during treatment, pericardial effusion, large right atrial size, elevated right atrial pressure, septal shift during diastole, decreased pulmonary arterial capacitance (ie, the stroke volume divided by the pulmonary arterial pulse pressure) and increased N-terminal brain natriuretic peptide level.

Therapy improves exercise capacity and functional class, however the impact on mortality has been less well established.

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12: WOMEN'S HEART HEALTH

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12.1: Facts and Figures

Epidemiology

Cardiovascular disease (CVD) is the leading cause of death in women worldwide. According to the Global Burden of disease CVD caused almost 32% of deaths in women worldwide vs. 27% in men.[1] In Europe 54% of all female deaths are from CVD vs. 43% men.[2] After at least two decades of growing awareness regarding sex differences in coronary artery disease, the evolving knowledge of the clinical consequences is emerging. Although recent reports document decreases in CHD mortality for women, reductions lag behind those realized for men.[3] Another worrying fact is that we see a mortality increase among younger women.[4]

In general cardiovascular events among women appear approximately 7-10 years later in women than in men. The lower incidence of CVD in premenopausal women compared with men of similar age and the menopause associated increase in CVD have long suggested that estrogens underlie a protective effect on the cardiovascular system for women.

It is known that estrogens improve the arterial wall response to injury and inhibit the development of atherosclerosis by promoting re-endothelialization, inhibiting smooth muscle cell proliferation, and matrix deposition following vascular injury.[5]

Estrogens also decrease systemic vascular resistance, improve coronary and peripheral endothelial function and prevent coronary artery spasm in women with and without atherosclerosis. Pre-menopausal women with hormonal imbalances and estrogen deficiencies have a higher risk of developing premature atherosclerosis.[6]

12.2: Gender Differences in the Pathophysiology of Atherosclerosis

Atheroma burden and vascular function

There is emerging evidence that there are gender- differences in the atherosclerotic process and the mechanisms underlying ischemic heart disease. Recent data support a sex-specific role for microvascular dysfunction in ischemic heart diseases. Most important findings are listed below:

1. Women have more symptoms and physical limitations but less obstructive coronary artery disease than men along the entire spectrum of acute coronary syndromes.
2. The syndrome of chest pain without obstructive coronary artery disease is distinctly more common in women than in men.
3. In women chest pain symptoms and disability do not correlate with severity of coronary stenoses.
4. Young and middle-aged females show higher rates of adverse outcomes after acute MI than men of similar age, despite less severe coronary narrowing, smaller infarcts, and more preserved systolic function.

Given the lower burden of obstructive coronary artery disease (CAD) and preserved systolic function in women, which contrasts with greater rates of myocardial ischemia and near-term mortality compared with men, we propose the term “ischemic heart disease” as more appropriate specific to women rather than CAD or coronary heart disease (CHD).

Microvascular angina pectoris

This paradoxical difference, where women have lower rates of anatomical CAD but more symptoms, ischemia, and adverse outcomes, appears linked to abnormal coronary reactivity that includes microvascular dysfunction. Symptoms as the result of microvascular dysfunction should be called microvascular angina. Abnormal coronary reactivity is often the result of diffuse (microvascular) atherosclerosis which is often seen in women, in contrast to the obstructive atherosclerosis which is more common in men (Figure 12.2.1).

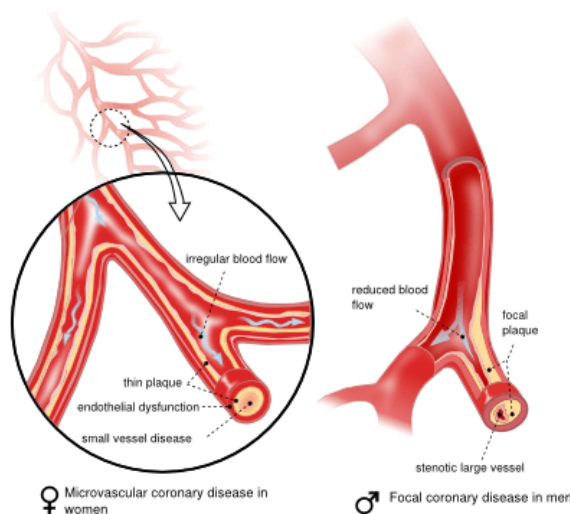


Figure 12.2.1

Studies have shown that the plaque morphology changes after menopause. At younger age (<65 yrs) women with an acute myocardial infarction have more often plaques erosions than the classical pattern of plaque rupture and thrombus formation as seen in men. These erosive plaques can cause distal embolization with micro-emboli, leading to endothelial dysfunction of the microvascular beds with angina-like chest pain. This diffuse pattern of atherosclerosis often translates in atypical chest pain.

When obstructive coronary artery is absent these women do not receive the proper preventive medication as the atherosclerosis in the microvasculature progresses, leading to ischemia and possibly fatal arrhythmias. After menopause it is known that the microvascular atherosclerosis can progress towards more pronounced atherosclerosis with eventually obstructive plaque formation.

It is this combination of non-obstructive cardiovascular disease with loss of endothelial function in the epicardial and microvascular beds which can lead to chest pain which is not well understood.

For women with evidence of ischemia but no obstructive CAD, anti-anginal and anti-ischemic therapies can improve symptoms, endothelial function, and quality of life; however, trials evaluating impact on adverse outcomes are needed. Women experience more adverse outcomes compared with men because obstructive CAD remains the current focus of therapeutic strategies. Continued research is indicated to devise therapeutic regimens to improve symptom burden and reduce risk in women with ischemic heart disease.

Syndrome X

Cardiac syndrome X (CSX; differentiated from the metabolic syndrome X) is currently defined by typical, angina like chest pain without flow-limiting stenoses on coronary angiography and exclusion of non-cardiac chest pain. Microvascular angina is more prevalent in women than in men. There is a whole range of factors that contribute to the dysfunction of the microvascular beds:

1. Distal embolization of erosive plaques
2. Chronic inflammation
3. Spasm which is often a result of dysfunctional smooth muscle cells
4. Smoking, hypertension and dyslipidemia can result in endothelial dysfunction

12.3: Risk Factors

Risk estimates associated with traditional cardiovascular risk factors are overall similar in women and men across various regions of the World. However, the increased risk associated with hypertension and diabetes and the protective effect of exercise and alcohol appear to be larger in women than in men.[7] It is also important to make a difference between pre and post menopausal status.

Smoking

Smoking is the single most important preventable cause of IHD in women. It is a relatively large risk factor for myocardial infarction in women under the age of 55 when compared to men. Smoking enhances the inflammatory process, activates the coagulation system and promotes LDL oxidation. Smoking leads to down-regulation of the estrogen receptor in the endothelial wall leading to endothelial dysfunction and atherosclerosis. The combination of smoking and the use of oral contraceptives has a synergistic effect by inducing endothelial dysfunction and activation of the coagulation system. After cessation the risk declines rapidly.

Hypertension

Hypertension is a highly prevalent risk factor that becomes more common in women than in men and is particularly prevalent among black women.[7] After menopause the renin activity in plasma increases which leads to sodium retention. By the age of 60 almost 50% of all women have clinically manifest hypertension, defined as a systolic blood pressure > 140 mmHg and a diastolic blood pressure of 90 mmHg.[6] Hypertension in women compared to men more often leads to CVA, left ventricular hypertrophy and diastolic dysfunction. The structural changes of the myocardium can become clinically manifest by dyspnea, supraventricular tachycardia such as atrial fibrillation, angina due to endothelial dysfunction. Slightly elevated blood pressure leads in women more than in men to endothelial dysfunction.[6] Hypertension is 2 to 3 times more common in women taking oral contraceptives, especially among obese and older women. Blood pressure lowering strategies have demonstrated to reduce the risk of ischemic heart disease and stroke

Dyslipidemia

In women there is a stronger fluctuation of lipid levels throughout life. Due to hormonal changes total and LDL cholesterol levels increase with an average of 10-14% after menopause.[6] Low HDL and high triglycerides seem to be more important risk factors in women than in men. Data from the Nurses Health Study shows that HDL was the lipid parameter that best discriminated the risk of ischemic heart disease.[7] Hypertriglyceridemia is associated with a 37% increase in CVD risk in women compared to 14% in men.[7] The dynamic changes of the lipid profiles due to age and menopausal status play an important role in the prevention of cardiovascular disease in women.

Obesity

Obesity is an important risk factor for diabetes, hypertension and cardiovascular disease. There is a gradient of coronary risk with increasing overweight, with the heaviest category of women having a four-fold increased risk for CVD compared with lean women. Around menopause there is a shift from gynoid fat distribution to android. This central obesity in women leads more than in men to the metabolic syndrome, with an increased relative risk of insulin resistance, dyslipidemia and hypertension.

Diabetes

Diabetes is associated with a higher risk for ischemic heart disease in women than in men (RR2.0). This is partly due to a higher rate of coexisting risk factors in women with diabetes compared to men. Another important factor is that diabetes is more difficult to treat since less women reach treatment goals when compared to men. In women diabetes is an independent risk factor for developing heart failure. Diabetes during pregnancy has a 7-12 fold risk for developing diabetes later in life.

Women specific risk factors

Estrogens improve the arterial wall response to injury and inhibit the development of atherosclerosis by promoting re-endothelialization, inhibiting smooth muscle cell proliferation and matrix deposition following vascular injury. They also have a vasodilative effect. Premenopausal women with hormonal dysfunction and estrogen deficiency have a higher risk for developing premature atherosclerosis.[6] The polycystic ovarian syndrome, a condition also known as PCOS have a high risk for developing the metabolic syndrome and type 2 diabetes and are therefore an at risk population. Also women with premature ovarian failure (menopause before the age of 40) have a higher risk for developing CVD.

“Novel” risk factors

In an effort to make a more accurate estimation of cardiovascular risk, more than 100 new risk markers have been proposed. There is however a slight resistance to use these markers since the lack of evidence that they really make risk estimation more accurate. A recent summary of systematic reviews conducted for the United States Preventive Services Task force has reviewed the evidence of 9 novel risk factors. Of the risk markers evaluated C-reactive protein was the best candidate for screening, however, evidence is still lacking to recommend routine use. The Reynolds Risk score, which is a risk score specifically designed for women, incorporated CRP which reclassified 15 % of the intermediate risk women to high risk.

Depression & Acute stress

Data from the INTERHEART study shows, that particular in women the combined exposure psychological risk factors such as depression, chronic emotional distress and acute stress such as major life events, are significantly associated with acute myocardial infarction (OR 2.6 in men and 3.5 in women). A stress-induced condition known as “Takotsubo cardiomyopathy” is almost exclusively seen among women. Due to severe emotional stress these women present with symptoms mimicking acute myocardial infarction. Also the ECG and echocardiogram show all the signs of infarction. However the CAG is often normal with no signs of coronary obstruction. The severe impaired left ventricular function usually normalizes completely after a couple of months.

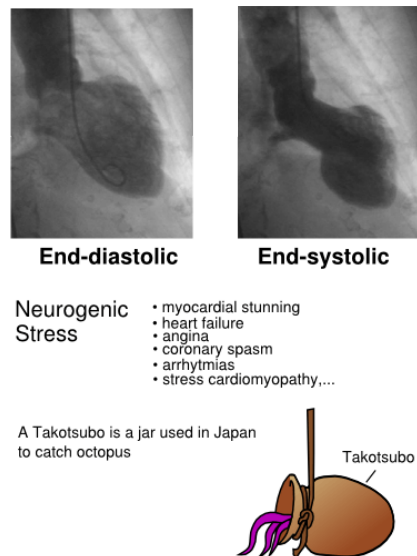


Figure 12.3.1: Takso-tsubo cardiomyopathy

12.4: Risk Factor Assessment

Which risk factors should be assessed?

Global cardiovascular risk should be assessed in **ALL** women in menopause consulting the physician.

Many women appear healthy with no symptoms of CVD nevertheless, they are potentially at increased risk

The following risk factors should be assessed

- Age
- Blood pressure
- Total plasma cholesterol
- Cigarette smoking

Other important information to establish:

- Personal and family history of cardiovascular disease
- Gynecological and obstetric history, including age at menopause
- Body weight
- Waist circumference
- Diet
- Alcohol consumption
- Physical fitness
- Fasting plasma low density (LDL) cholesterol

Additional parameters to consider are:

- Fasting plasma glucose
- 75-g oral glucose tolerance test (advisable in high risk patients or in those with abnormal fasting plasma glucose)
- Fasting plasma high-density lipoprotein (HDL) cholesterol
- Fasting plasma triglycerides

Which patients can be managed for global cardiovascular risk by a menopause physician?

- A woman with a high-risk profile or overt cardiovascular disease requires intensive management including drug therapy
- Collaboration with a cardiovascular specialist is essential if global cardiovascular risk is high, or if cardiovascular disease is present.

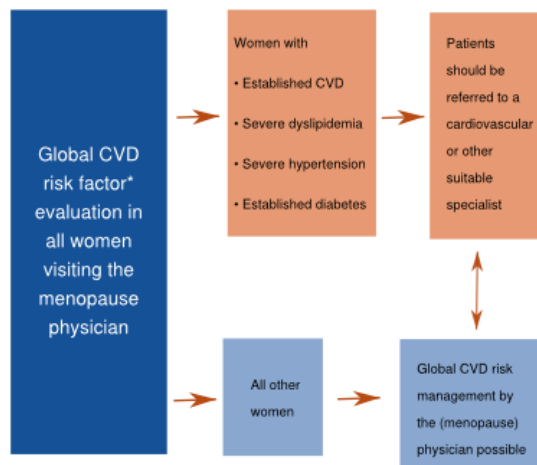


Figure 12.4.1

12.5: Clinical Presentation

The clinical presentation of cardiac complaints differ between men and women. Female patients as well as their treating physicians often do not recognize or interpret their complaints as heart problems. Women present less typical as what we are used when men present with heart problems. Typical symptoms, as we have learned from our male patients, such as heavy pressure on the chest which radiates to the left arm or the jaws are often absent in women. Women more often present with complaints such as “tightness”, “out of breath” en “tiredness”. When women get older (>60 yrs) and the risk of obstructive coronary artery disease rises, the clinical presentation becomes more typical (substernal pain, with radiation to jaw and/or left arm).

As a result women are often not recognized and do not receive the proper preventive medication. This could in part explain the higher mortality of cardiovascular diseases in women.

Women who are diagnosed with non cardiac chest pain have twofold increased risk to develop a coronary event in the next 5-7 years and have a four times higher risk for re-hospitalization. This implicates that diagnostic testing is limited and that women should be more aggressively treated for their risk factors.

Chest pain syndromes are more common in women then in men and are less related to the presence of atherosclerosis in the epicardial coronary arteries.[8]

There are no gender-specific criteria for the interpretation of ECG's. Non specific ECG changes at rest, a lower exercise capacity and a smaller vessel size contribute to the lower sensitivity and specificity of non-invasive testing in women. At younger ages, endogenous estrogen level can induce ECG changes mimicking ischemia.

Chest pain complaints in women should always be related to their risk factor profile. It should also be noted that in women, very often chest pain is related to not well regulated hypertension. Blood pressure changes increase vascular wall pressure of the coronary arteries which translates in chest discomfort often at rest. In addition hypertension more often leads to diastolic dysfunction in women en hypertrophy which can result in chest pain. A small dose of nitrates can be effective.

12.6: Treatment

Symptom management in patients with non-obstructive cardiovascular disease is a challenge. Important to differentiate between vasospastic forms and complaints related to endothelial dysfunction.

Lifestyle behaviors can prevent and reduce the risk of getting heart disease and should therefore be primary focus in the GP-practice. Strategies adapt health lifestyle changes are listed below Adapted from Assessment and Management of cardiovascular risk in women (ESC/ESH/2007):[9]

Smoking: TARGET: permanently stop smoking all forms of tobacco

- Explain detrimental effects
- Assess the degree of addiction and readiness to cease smoking
- Gain commitment
- Establish a smoking cessation strategy (nicotine replacement, counseling and/or pharmacological intervention)
- Arrange a schedule of follow up visits to monitor progression.

Diet: TARGET: Adopt healthy diet

- Explain importance of a varied diet and the need to adjust energy intake to achieve and maintain ideal body weight.
- Encourage the consumption of:
 - Fruits and vegetables (the five-a-day guideline)
 - Whole grain cereal and bread
 - Low-fat dairy products
 - Fish, especially those rich in omega-3
 - Lean meat
- Total fat intake should be no more than 30% of energy intake, with saturated fats comprising in one third of total fat intake.
- Total cholesterol intake < 300mg/day
- Help to identify Foods that are high in saturated fats and cholesterol in order to reduce or remove them.
- Suggest replacement of saturated fats with complex carbohydrates, monounsaturated and polyunsaturated fats from vegetables and fish.
- Stress the importance of avoiding Foods containing high levels of salt. Reduce overall intake of salts.

Physical Fitness: TARGET: Undertake regular physical exercise

- Explain health benefits of increased physical activity (regain and maintain energy levels, improvement of lipid levels, managing bodyweight, relieving stress)
- Encourage to increase physical activity by climbing stairs, walking or cycling
- The standard for physical activity is > 30 minutes of moving activity for 7 days per week
- A health women should exercise at 60-75% of the average maximum heart rate

Obesity: TARGET: Body Mass Index < 25 kg.m2 or waist circumference < 88

- Explain that by consuming 500-1000 calories/day less than required to maintain the current weight, she can lose about 500 grams/week and ultimately achieve weight loss of 5-15%
- Stress that regular exercise assists in weight loss
- Give diet advice (as described earlier)

Lipids

Elevated lipid levels are a significant cardiovascular risk factor. Due to hormonal changes in menopause, total and LD cholesterol levels rise by approximately 10-14%. A low HDL cholesterol as well as high triglycerides is a stronger risk factor for CVD then in men. HDL and triglycerides play an important role in the metabolic syndrome. Women in menopause have an increased risk of

developing the metabolic syndrome. This is partly due to the changes in body weight and the distribution of fat tissue since there is a shift from gynoid to android fat distribution. HDL is hardly influenced by menopause. The dynamic changes in lipid profiles remain an important point in the prevention of cardiovascular disease in women.

Bloodpressure

In women, after the age of 55 the systolic blood pressure rises. After menopause plasma renin levels increase and there is an increase in the sensitivity for salt. By the age of 60 more than half of all women have clinically manifest hypertension (defined as a blood pressure $> 140/90$ mmHg). In women hypertension is more often associated with CVA, left ventricular hypertrophy and diastolic dysfunction. These structural changes can give an array of complaints such as dyspnea, palpitations and chest pain.

Post-menopausal hormone therapy

The initiation or continuation of hormone replacement therapy should be decided according to the individual patient. Given the many potentially beneficial effects of estrogens on cardiovascular physiology, much expectation was placed on hormone therapy for CVD prevention. However several studies did not support beneficial effects of hormone therapy and in the WHI study (women's health initiative) the study was terminated due to a small increase in CVD. In a woman < 60 years, who recently menopausal with menopausal symptoms and without CVD, the initiation of replacement therapy does not cause early harm. If a woman is at increased risk, HRT therapy is safe to use in the younger women with indications. It should be noted however, that HRT should not be initiated solely for the prevention of cardiovascular disease and should not be regarded as a substitute for antihypertensive treatment.

12.7: Conclusions

- Cardiovascular disease in women is the number 1 cause of death in the Western World.
- Cardiovascular risk increases after menopause, regardless of the age it occurs.
- Women share similar cardiovascular risk factors however there are important sex differences in the prevalence of coronary atherosclerosis and coronary vascular physiology.
- There are gender differences in the regulation of vasomotor function of microvessels.
- Women more often have chest pain by less obstructive coronary artery disease.
- In women with persistent chest pain with the absence of obstructive coronary artery disease treatment of symptoms en risk factors is essential.
- The GP or menopause physician plays an important role in the identification of global cardiovascular risk factors (e.g. hypertension, dyslipidemia, diabetes)
- Cardiovascular specialists and menopause physicians must work as a team to assess global risk for the individual woman.
- Atherosclerosis is the underlying cause of cardiovascular disease.
- Prevention and reduction of cardiovascular disease as early as possible must be a priority

12.8: Case 1

Case 1: 60- year old woman with risk factor (mis)management

Patient presented at the emergency room with atypical complaints. She was nauseous had a burning sensation in the chest. She had consulted her GP several times with atypical chest pain. No further action was taken then.

History

Several weeks of extreme tiredness, burning chest pains, not related to exercise.

Risk factors

Her father had his first heart attack at age 50. She had hypertension during both pregnancies. She menopaused at age 46 with a lot of menopausal complaints such as flushes. She had a smoking history of 10 years.

Physical examination

BMI=26, blood pressure: 180/100 mmHg, pulse: 80 r.a., normal heart sounds, grade II/VI systolic murmur.

Lab: glucose

7 mmol/L, Total cholesterol: 7,1 mmol/L, LDL-cholesterol: 4,5 mmol/L, HDL cholesterol: 0,9 mmol/L, Triglycerides: 2,5 mmol/L.

Additional Cardiac Investigation

ECG showed T-wave inversion in the precordial leads. Cardiac enzymes were positive. Cardiac catheterization showed an 80% stenosis of the left main coronary artery. The echocardiogram show wall segment disorders of the anterior wall and a grad II mitral valve insufficiency.

Follow-up

She received PTCA of the left main en her lipid profile and blood pressure was treated. She recovered and is doing well.

Learning points

- Atypical presentation of acute coronary syndrome
- In women cardiac complaints are often atypical
- She was not categorized as a high risk patient
- Risk factors should always be optimized,

12.9: Case 2

Case 2: 52-year old woman with microvascular disease

Patient is referred for a second opinion to the cardiologist with complaints of tiredness and chest pain. She was evaluated 3 months earlier with chest pain. Cardiovascular analysis then showed no cardiac pathology.

History

Patient, who runs every week 10 kilometers, complains that she noticed shortness of breath and tiredness during her weekly run which she describes as abnormal. During running she has no chest pain. She does however experience chest pain, which she describes as "heavy" feeling on the chest, when there is an abrupt change of temperature. Also slight radiation to the left arm.

Risk factors

Menopausal, positive family history, smoking history (she quit 15 years ago), obstetric history normal, Alcohol consumption: 2U/day

Physical examination

BMI=26, blood pressure: 145/90 mmHg, pulse: 70 r.a., normal heart sounds, no murmurs.

Lab: glucose

5 mmol/L, Total cholesterol: 6,9 mmol/L, LDL-cholesterol: 3,5 mmol/L, HDL cholesterol: 1,3 mmol/L, Triglycerides: 4,5 mmol/L.

Additional Cardiac Investigation

ECG and exercise stress test were completely normal. Vascular scanning of the carotid arteries showed moderate plaque formation in the carotid bulb. No chest pain during exercise. Myocardial perfusion scan showed ischemia in the inferior segments of the heart. Cardiac catheterization: vessel wall irregularities in all coronary arteries, no significant obstructions.

Follow-up

Blood pressure and lipid profiles was optimized with ACE inhibition and a statin. She was advised to lose weight and drink less alcohol with regard to her elevated triglycerides. She received a low dose b-blocker and was without complaints within 3 months.

Learning points

- Complaints without obstructive heart disease
- Risk factors should always be optimized, blood pressure in lipid profile was inadequate
- Limitation of diagnostic tests.

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13: HISTORY OF SCIENTIFIC PROGRESS IN CARDIOVASCULAR DISEASE

13.1: Historical timeline - BCE-1852

13.2: Historical timeline - 1852-1967

13.3: Historical timeline - 1969-2004

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13.1: Historical timeline - BCE-1852

Milestones in knowledge of heart and vascular disorders

Palaeolithic era (*Spain*): Oldest anatomical drawing in El Pindal cave of a mammoth with a dark smudge at the shoulder, which is thought to represent the heart.

2698–2598 BCE (*China*): Huang Ti, the Yellow Emperor, was thousands of years ahead of his time in writing in *Nei Ching* (Canon of Medicine): "The blood current flows continuously in a circle without a beginning or end and never stops" and "all the blood is under control of the heart". He also recorded the association between salt intake and a "hardened pulse".

1550 BCE (*Egypt*): Papyrus Ebers stated that after death the heart becomes the witness of the body's behavior during life. To avoid incriminating testimony, the Egyptians buried the heart separately from the body.

600 BCE (*Greece*): Alcmaeon noted empty arteries in animals after death and inferred that arteries normally contained air.

400 BCE (*Greece*): Hippocrates, the Father of Medicine (460–370 BCE), challenged the belief that illness was caused by the gods; he believed illness was caused by an imbalance of the four bodily humors: yellow bile, black bile, blood, and phlegm. He was also the first to recognize stroke.

310–250 BCE (*Egypt*): Erasistratus described the heart, veins, arteries and valves, but claimed that arteries contained "pneuma" (air or spirit or soul), which was replaced each time a person breathed; when an artery was cut, blood rushed in as the pneuma escaped.

131–201 CE Greco-Roman physician Claudius Galen, with knowledge gained from animals killed by Roman gladiators, described the heart and the movement of blood in the arteries, but claimed that the liver was the center of the circulation and that the blood passed from the right to the left side of the heart.

980–1037 (*Persia*): Avicenna (Ibn Sina) stated that the heart is located centrally to all organs of the body, and that the left side of the heart was created as a store of spirit and soul.

1210–1288 (*Syria*): Ibn al-Nafis described the pulmonary and coronary circulation in *The Perfect Man*.

1452–1519 (*Italy*): Leonardo da Vinci incorrectly drew the liver as the center of circulation. But he stated "vessels in the elderly through the thickening of the tunics, restrict the transit of the blood." This is one of the earliest descriptions of arteriosclerosis.

1509–1553 (*Spain*): Michael Servetus described the pulmonary circulation in his book *Christianismi Restitutio*.

1510–1559 (*Padua, Italy*): Matteo Realdo Colombo described the heart valves.

1525–1603 (*Rome, Italy*): Andrea Cesalpino noted that the circulation system is a closed system, and was the first in modern times to coin the term "blood circulation".

1553–1619 (*Padua, Italy*): Hieronymus Fabricius demonstrated valves in veins, which help to "prevent dilatation of veins".

1555 (*Padua, Italy*): Andreas Vesalius (1514–1564) stated that the heart, and not the liver, was the center of the circulation.

1559 (*Italy*): Riva di Trento discovered that there are two coronary arteries, each supplying blood to half of the heart.

1628 (*England*): William Harvey (1578–1657), a physician, published his thesis that the heart pumped blood around the body, in *De Motu Cordis*.

mid-1600s (*Switzerland*): Jacob Wepfer found that patients who died with "apoplexy" had bleeding in the brain. He also discovered that a blockage in one of the brain's blood vessels could cause apoplexy.

1706 (*France*): Anatomy professor Raymond de Vieussens first described the structure of the heart's chambers and vessels.

1712–1780 (England): John Fothergill both forecast the role of psychosocial factors and advised that a restricted diet "might greatly retard the progress" of coronary heart disease.

1677–1761 (England): Stephen Hales, an English clergyman and scientist, first measured blood pressure by inserting a brass tube into the artery of a horse. This was a scientific experiment, published in 1733, demonstrating that the heart exerts pressure in order to pump blood. The horse died.

1745–1827 (Italy): Alessandro Volta discovered that electric energy was produced by heart muscle contractions.

1749–1832 (England): Edward Jenner, better known for smallpox vaccine, made the essential link between angina pectoris and disease of the coronary arteries.

1752–1832 (Italy): Antonio Scarpa described arterial aneurysm.

1772 (England): William Heberden (1710–1801) described angina pectoris: "they who are afflicted with it, are seized while they are walking (especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes". He was also the first to write about hyperlipidemia as a risk factor when he noticed that the serum of an obese patient who suddenly died was "thick like cream".

1775 (Scotland): John Hunter (1728–1793), a surgical pathologist, wrote "in a sudden and violent transport of anger, he fell down and expired immediately", illustrating the importance of emotion, stress and anger in precipitating coronary death. Hunter himself suffered from angina pectoris and died suddenly after a violent argument with a hospital colleague.

1785 (England): William Withering described the use of digitalis in coronary heart disease in his monograph *An Account of the Foxglove*. Foxglove had been used for centuries by American Indians.

1791 (Italy): Luigi Galvani discovered that electrical stimulation of a frog's heart led to contraction of the cardiac muscle.

1799 (England): Caleb Hillier found something hard and gritty in the coronary arteries during an autopsy and "well remembered looking up to the ceiling, which was old and crumbling, conceiving that some plaster had fallen down". He discovered, however, that the vessels had hardened, and stated that "a principle cause of the syncope anginosa is to be looked for in disordered coronary arteries".

1815 (England): London surgeon Joseph Hodgson claimed inflammation was the underlying cause of atherosclerosis and it was not a natural degenerative part of the ageing process.

1815 (France): M.E. Chevreul named the fatty substance extracted from gallstones "cholesterol" from the Greek "khole" (bile) and "stereos" (solid).

1819 (France): Rene Theophile Laennec (1781–1826), invented the stethoscope. He rolled paper into a cylinder while examining a young woman with cardiac symptoms as he was reluctant to apply his ear to the chest.

1838 (France): Louis René Lecanu showed that cholesterol was present in human blood.

1841 (Austria): Carl Von Rokitansky championed the thrombogenic theory, proposing that deposits observed in the inner layer of the arterial wall derived primarily from fibrin and other blood elements rather than being the result of a purulent process. This theory came under attack from Rudolf Virchow.

1843 J. Vogel showed that cholesterol was present in atherosclerotic plaques.

1844 (Denmark): First pathology report of plaque rupture in a coronary artery in Bertel Thorvaldsen, the celebrated neoclassical Danish artist and sculptor, who died of sudden cardiac death in the Royal Theatre in Copenhagen.

1850 Ventricular fibrillation first described.

1850s Ophthalmoscope invented, allowing direct visualization of arteries at the back of the eye.

1852 (England): Fatty material in the coronary arteries described by Sir Richard Quain, which he attributed to nutrition. He linked the fatty heart to "languid and feeble circulation, a sense of uneasiness and oppression in the chest, embarrassment and distress

in breathing, coma, syncope, angina pectoris, sudden death..."

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13.2: Historical timeline - 1852-1967

1856 (*Germany*): Rudolf Virchow, a Pole, believed that disease occurred at cellular level, and also described cerebral emboli causing stroke. Virchow also emphasized the societal causes of disease as "disturbances of human culture".

1867 (*England*): Lauder Brunton, pharmacologist, discovered that amyl nitrite relieved angina.

1872 (*France*): Gabriel Lippmann invented the capillary electrometer, the precursor of the electrocardiograph.

1893 (*Holland*): Willem Einthoven (1860–1927) introduced the term electrocardiogram or ECG/EKG; distinguished five deflections – PQRST (1895); constructed the first electrocardiograph in 1901, which weighed 270 kg, occupied two rooms and required five people to operate it; transmitted the first ECG from hospital to his laboratory 1.5 km away via telephone cable (in 1905); published the first normal and abnormal ECGs (1906) and won the Nobel Prize (1924).

1895 (*Germany*): Physicist Wilhem Konrad Roentgen (1845–1923) discovered X-rays, which are still used to visualize the heart.

1896 (*Italy*): Scipione Riva-Rocci invented the sphygmomanometer to measure blood pressure.

1897 The introduction of modern aspirin. In one of life's little ironies, Bayer's first aspirin advertisements said that the drug did "not affect the heart".

1906 (*Germany*): M. Cremer, first oesophageal ECG by a professional sword swallower. First fetal ECG from the abdominal surface of a pregnant woman.

1907 (*England*): First case report of atrial fibrillation by Arthur Cushny, professor of pharmacology at University College, London.

1912 James B. Herrick described heart disease resulting from hardening of the arteries.

1912 First human cardiac catheterization (no X-ray visualization) by Fritz Bleichroeder, E. Unger and W. Loeb.

1915 (*USA*): Establishment of organization in New York City, which became the American Heart Association.

1920 (*USA*): First ECG of acute myocardial infarction by Harold Pardee.

1923 (*USA*): First operative widening of scarred cardiac valve by E. Cutler and S.A. Levine.

1925 (*United Kingdom*): Widening of narrowed mitral valve by Souter, who stretched the valve ring with his fingers.

1928 (*United Kingdom*): Sir Alexander Fleming discovered penicillin, which is used to treat rheumatic fever.

1928 "Apoplexy" divided into categories based on the cause of the blood vessel problem, and replaced by the term "cerebral vascular accident (CVA)".

1929 (*Germany*): First documented right heart catheterization in human by Werner Forssmann using radiographic techniques.

1931 (*USA*): First description of the use of exercise to provoke attacks of angina pectoris by Charles Wolferth and Francis Wood.

1931 (*USA*): First artificial cardiac pacemaker, which stimulated the heart by transthoracic needle, developed by Dr Albert Hyman.

1937 (*USA*): First prototype heart lung machine built by physician John Heysham Gibbon, and tested on animals. He performed the first human open heart operation in 1953 using the machine.

1938 (*USA*): First human heart surgery, first surgical correction of a congenital heart defect: closure of patent ductus arteriosus performed by surgeon Robert E. Gross.

1944 (*China*): First repair of patent ductus arteriosus in China.

1944 (*USA*): First operation on "blue baby" (Fallot's tetralogy) at Johns Hopkins.

- 1944** (USA/Sweden): First repair of coarctation of aorta by Crafoord and Grosse.
- 1947** (USA): First defibrillation of human heart during cardiac surgery, by Claude Beck in Cleveland.
- 1948** (USA): "Blind finger" closed heart surgery for mitral stenosis reintroduced by Dr Dwight Harken and Dr Charles Bailey.
- 1948** (USA): California physician Lawrence Craven noticed that 400 of his male patients who took aspirin for two years had no heart attacks. By 1956, he had chronicled the health of 8000 patients taking aspirin and found no heart attacks in the group.
- 1948** (USA): Start of the Framingham Heart Study where, for the first time, a large cohort of healthy men and women were studied prospectively.
- 1949** (USA): Portable Holter Monitor invented by Norman Jeff Holter to record ambulatory ECG.
- 1950** The International Society of Cardiology established, later joined with International Cardiology Federation and renamed World Heart Federation.
- 1950** (Canada): First pacemaker invented by John Hopps.
- 1952** (USA): First prosthetic valve implanted in aorta by surgeon Charles Hufnagel.
- 1952** (USA): First successful human open heart surgery under hypothermia by Walton Lillehei and John Lewis, who implanted the first synthetic valve in a five-year-old girl who had been born with an atrioseptal defect (hole in her heart).
- 1952** (USA): External cardiac pacemaker designed by Paul Zoll.
- 1953** (USA): First demonstrated coronary artery disease among young US soldiers killed in action in Korea (later observed in the casualties of the Viet Nam War too) by William F. Enos, Robert H. Holmes and James Beyer.
- 1954** (United Kingdom): First carotid endarterectomy by Eastcott, Pickering and Rob.
- 1954** (India): Called on WHO to address the coming epidemic of cardiovascular disease in developing countries.
- 1955** (United Kingdom): First reported mitral valve replacement by Judson Chesterman.
- 1950s** Minimization of bias for the reliable assessment of cardiovascular treatments by introduction of randomization into clinical trials (at instigation of Sir Austin Bradford Hill).
- 1956** (USA): First report of the successful ending of ventricular fibrillation in humans by externally applied countershock published by Dr Paul Zoll.
- 1957** First battery-powered external pacemaker.
- 1958** (USA): Seymour Furman inserted a pacemaker in a patient who lived for 96 days.
- 1958** (Sweden): Internal long-term cardiac pacing by Åke Senning.
- 1958** Start of development of a selective coronary angiography procedure by Mason Sones.
- 1959** WHO established Cardiovascular Diseases program.
- 1960s** High blood pressure identified as a treatable risk factor for stroke.
- 1960** (USA): First Coronary Care Unit in Bethany, Kansas.
- 1960** (Framingham, USA): Cigarette smoking found to increase the risk of heart disease.
- 1960** (USA): First replacement of heart valve with Starr-Edwards mechanical valve, developed by Albert Starr and Lowell Edwards.
- 1961** (USA): Framingham Heart Study investigators coined the term "risk factors" for the development of coronary heart disease. High cholesterol level, blood pressure, and electrocardiogram abnormalities found to increase the risk of coronary heart disease.

1961 (USA): First use of external cardiac massage to restart a heart by J.R. Jude.

1961 (USA): First direct current defibrillation with external paddles by Bernard Lown and Barough Berkowitz.

1960s First human implant of totally implantable pacemaker.

1964 (USA): First transluminal angioplasty performed on a narrowed artery in the leg by Charles T. Dotter.

1965 (USA): Michael DeBakey and Adrian Kantrowitz implanted mechanical devices to help a diseased heart.

1967 (South Africa): First whole heart transplant from one person to another by Dr Christiaan Barnard.

1967 (USA): Saphenous vein coronary bypass graft by Dr Rene Favaloro.

1967 (Framingham, USA): Physical inactivity and obesity found to increase the risk of heart disease.

13.3: Historical timeline - 1969-2004

1969 (USA): First use of artificial heart in human by Denton Cooley.

1972 (USA): The Stanford Three Community Study started (later becoming The Stanford Five-City Project); this showed a 23% reduction in coronary heart disease risk caused by community-based interventions that change lifestyle-related risk factors such as physical activity, dietary habits and tobacco use.

1972 (Finland): North Karelia Project began, aimed at preventing cardiovascular disease among residents. Cardiovascular mortality rates for men, aged between 35 and 64 years, decreased by 57% from 1970 to 1992.

1974 (Framingham, USA): Diabetes linked to cardiovascular disease. 1970s Aspirin recognized as preventing heart attacks and stroke.

1970s Development of computerized tomography (CT) to aid early diagnosis of stroke.

1977 (Switzerland): First coronary PTCA (percutaneous transluminal coronary angioplasty); Andreas Gruentzig inserted a balloon-tipped catheter into a coronary artery and inflated the balloon, and thus successfully opened a blockage and restored blood flow.

1977 (Italy): The Martignacco Project community prevention trial resulted in reduction of coronary heart disease through community-based interventions that change lifestyle-related risk factors such as physical activity, dietary habits and tobacco use.

1977 (Framingham, USA): Effects described of triglycerides and LDL- and HDL- cholesterol on heart disease.

1978 (Framingham, USA): Psychosocial factors found to affect heart disease.

1978 (Australia): North Coast Healthy Lifestyle Program showed significant reduction in smoking.

1978 (Switzerland): Swiss National Research Program community prevention trial resulted in reduction of smoking, blood pressure and obesity.

1978 Atrial fibrillation (irregular heart beat) found to increase the risk of stroke.

1979 (South Africa): Coronary Risk Factor Study community prevention trial resulted in reduction of smoking, blood pressure and composite coronary heart disease risks.

1979 (Germany): First use by Peter Rentrop of intracoronary streptokinase, a clot-dissolving drug to stop a heart attack in progress.

1981 (Framingham, USA): Filter cigarettes found to carry as much risk for coronary heart disease as unfiltered cigarettes. 1981 USA Report on relationship between diet and heart disease.

1982 (USA): First permanent artificial heart, designed by Robert Jarvik, and implanted by Willem DeVries, in a 61-year-old man.

1983 (USA): List of 246 coronary risk factors published by Hopkins and Williams (list now much longer).

1980s Minimization of random error for the reliable assessment of cardiovascular treatments by introduction of large-scale "megatrials" (at instigation of Sir Richard Peto).

1986 (France): First coronary stent implanted by Jacques Puel and Ulrich Sigwart.

1987 (Japan): M. Okada used a laser to burn channels in the heart muscle to help revascularize the heart in patients with coronary heart disease.

1987 (Framingham, USA): High blood cholesterol levels found to correlate directly with risk of death in young men.

1988 (Framingham, USA): High levels of HDL-cholesterol found to reduce risk of death.

1988 ISIS-2 trial shows emergency treatment for heart attacks with aspirin and fibrinolytic "clot-busting" drugs saves lives.

1988 (*Framingham, USA*): Isolated systolic hypertension found to increase risk of heart disease.

1988 (*Framingham, USA*): Cigarette smoking found to increase risk of stroke.

1990 Randomized trials showed that lowering blood pressure lowers the risk of stroke.

1990 (*United Kingdom*): Meta-analysis of trials by Clinical Trial Service Unit (CTSU) in Oxford showed that lowering blood pressure lowers the risk of coronary disease.

1991 (*China*): Tianjin CVD Intervention Program community prevention trial led to the creation of non-smoking environments and increased sales of low-sodium seasonings.

1992 (*Canada*): The Victoria Declaration on Heart Health affirmed that CVD is largely preventable, that there is the scientific knowledge to eliminate most CVD, and that the public health infrastructure and capacity to address prevention were lacking.

1990s (*USA*): Hostility (including traits such as anger, cynicism, and mistrust), a major component of type A behavior, shown to be associated with an increased risk of heart attack and other cardiac complications in healthy persons and patients with coronary heart disease.

1992 (*China*): First heart-lung transplant in China.

mid-1990s (*Scandinavia, United Kingdom, USA*): Remarkable improvement in survival of coronary heart disease patients treated with statins.

1995 (*Spain*): The Catalonia Declaration: Investing in Heart Health, and its follow-up convention in 1997, emphasized the importance of investments in heart health and provided examples of many successful CVD prevention programs worldwide.

1998 (*USA*): Hypertension gene in men identified.

1998 New advances: gene therapy grows new blood vessels to the heart; strong confirmation that "superaspirin" IIb/IIIa receptor blocker drugs prevent blood clots; the importance of inflammation in cardiovascular disease recognized; study on the deadly effects of smoking fewer than 10 cigarettes per day.

1998 (*Singapore*): The Singapore Declaration: Forging the Will for Heart Health in the Next Millennium.

2000 (*Canada*): The Victoria Declaration on Women, Heart Disease and Stroke addressed the importance of science and policy in action and the need to tackle gender disparities in health. It called upon all stakeholders to join forces and take appropriate action to control the cardiovascular disease epidemic.

2000 First World Heart Day, which has become a global annual event.

2000 The entire human genome is mapped.

2000 WHO 53rd World Health Assembly endorsed Global strategy for noncommunicable disease (NCD) prevention and control, which outlines major objectives for monitoring, preventing and managing NCDs with special emphasis on major NCDs with common risk factors and determinants – cardiovascular disease, cancer, diabetes and chronic respiratory disease.

2001 (*Japan*): The Osaka Declaration: Health, Economics and Political Action: Stemming the Global Tide of Cardiovascular Disease emphasized the global nature of the CVD burden and highlighted the need to address economic and political factors in order to tackle CVD.

2002 (*United Kingdom*): The Heart Protection Study showed that statins could benefit people with diabetes and those with cholesterol levels previously considered low.

2002 (*USA*): NASA's Commercial Invention of the Year Award given for the DeBakey Ventricular Assist Device, based on space shuttle technology, and developed by Michael DeBakey and NASA engineer David Saucier. The pump, used to treat heart failure, was one-tenth the size of previous heart-assist devices, and was first used in a patient in 2000.

2003 (*Switzerland*): WHO Framework Convention on Tobacco Control adopted at the 56th World Health Assembly.

2003 (*Switzerland*): The World Health Report: "Shaping the Future" highlighted CVD as the first of three growing threats that make up the "neglected global epidemics". The report called for action at the national and global levels to prevent and control CVD.

2004 (*Switzerland*): WHO Global Strategy on Diet, Physical Activity and Health endorsed by World Health Assembly.

2004 (*Italy*): Milan Declaration on Heart Health: Positioning Technology to serve Global Heart Health.

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