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Heart valve macro- and microstructure

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Each heart valve is composed of different structures of which each one has its own histological profile. Although the aortic and the pulmonary valves as well as the mitral and the tricuspid valves show similarities in their architecture, they are individually designed to ensure optimal function with regard to their role in the cardiac cycle.

In this article, we systematically describe the structural elements of the four heart valves by different anatomical, light- and electron-microscopic techniques that have been presented. Without the demand of completeness, we describe main structural features that are in our opinion of importance in understanding heart valve performance. These features will also have important implications in the treatment of heart valve disease. They will increase the knowledge in the design of valve substitutes or partial substitutes and may participate to improve reconstructive techniques. In addition, understanding heart valve macro- and microstructure may also be of benefit in heart valve engineering techniques.

Keywords: aortic; mitral; pulmonary; tricuspid valve; histology

1. INTRODUCTION

The heart is a three-dimensional organ of particularly complicated configuration. The blood streams in two separate channels of limited space, crossing each other. By doing this, the heart is in a state of increscent torsional motion. The four heart valves play a key role in this sophisticated dynamics as they enable the blood to flow in a unidirectional way. They open and close over three billion times during a normal life. They also have the ability to allow between 1 and over 20 l of blood per minute to run through them during rest, exercise, or other physiological or pathological conditions. The aortic, pulmonary, mitral and tricuspid valves are positioned in a plane, the so-called 'base' of the heart (figure 1). It is this area which was named by early French anatomists the 'fibrous skeleton' of the heart. It consists of densely collagenous fibres and remains almost stationary in contrast to the dynamic movements of the myocardium, leaflets and arteries (figure 2). The fibrous skeleton is anchored to the myocardium in a similar way as tendons are attached to muscles. This design integrates the valves between the heart chambers and the arteries, and secures dynamic valve function throughout life.

The positions of the valve orifices as defined by the fibrous skeleton of the heart also demonstrate the close relationship of the four heart valves to each other (figure 3*a*,*b*). This has important implications with respect to the interaction of individual valve dynamics and has also fundamental importance in the surgical treatment of valve disease (Yacoub & Cohn 2004). However, each heart valve itself has its own anatomical features and histological structures. This allows each valve to function in its individual environment. In example, the aortic and pulmonary valves are challenged by different pressures but positioned in the same direction as flow. On the other hand, the atrioventricular valves are exposed to different flow features as the flow changes its direction when it is ejected by the ventricles. The mitral and tricuspid valve design consider these specific flow characteristics. Both valves also show remarkable differences due to their position in the high- and low-pressure system of the circuit.

The following article will describe the individual macro- and microstructure of the four heart valves. Understanding normal valve structure will be of benefit for the treatment of valve disease and will provide important information for surgical treatment of valve pathology.

2. AORTIC VALVE

The aortic valve (Valva aortae) is part of the aortic root. The latter one connects the heart to the systemic circulation and plays a major role in the function of the heart and cardiovascular system. It also maintains optimal coronary perfusion and plays a role in the maintenance of a laminar flow in the vascular system. Each structure of the aortic root has its individual histological profile and anatomical architecture. The crown shape annulus, the three sinuses of Valsalva and interleaflet triangles, as well as the sinotubular junction, commissures and the aortic valve leaflets interact with each other in a certain way to maintain optimal function. This well-coordinated dynamic behaviour has been shown to be of importance for specific flow characteristics, for coronary perfusion and left ventricular function (Bellhouse & Bellhouse 1968; Bellhouse *et al.* 1968; Brewer *et al.* 1976; Thubrikar *et al.* 1980; Yacoub *et al.* 1999).

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One contribution of 21 to a Theme Issue 'Bioengineering the heart'.

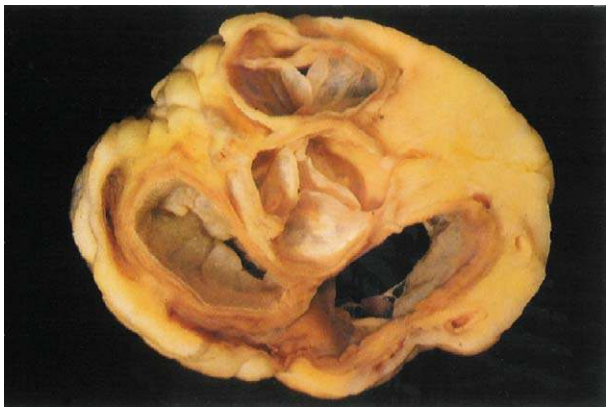

Figure 1. View on the four heart valves from superior (adapted from Anderson & Becker 1982, p. 18).

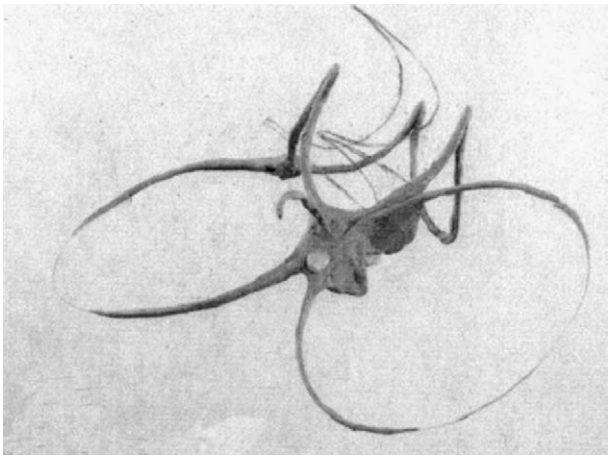

Figure 2. Schematic drawing of the fibrous skeleton of the heart (adapted from Zimmerman & Bailey 1962).

(a) *Nomenclature*

The different structures that compose the aortic root are termed the annulus, commissures, interleaflet triangles, sinuses of Valsalva, sinotubular junction and leaflets. The leaflets were originally named according to their anatomical position as posterior,

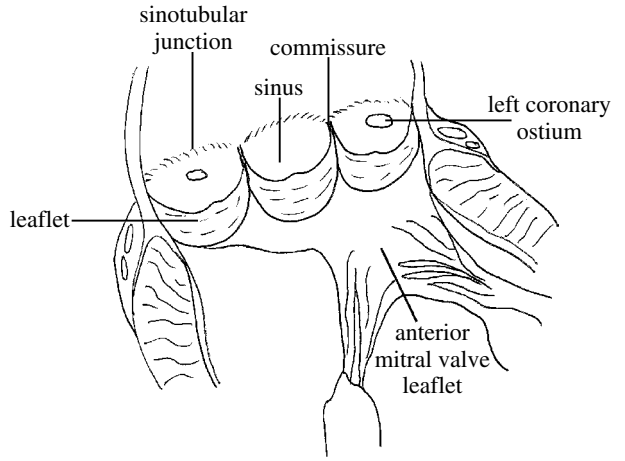

Figure 4. Schematic drawing of aortic root structures after longitudinal opening of the root.

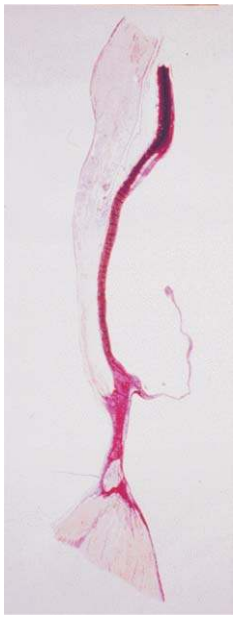

Figure 5. Section through the aortic root (adapted from Yacoub *et al.*1999).

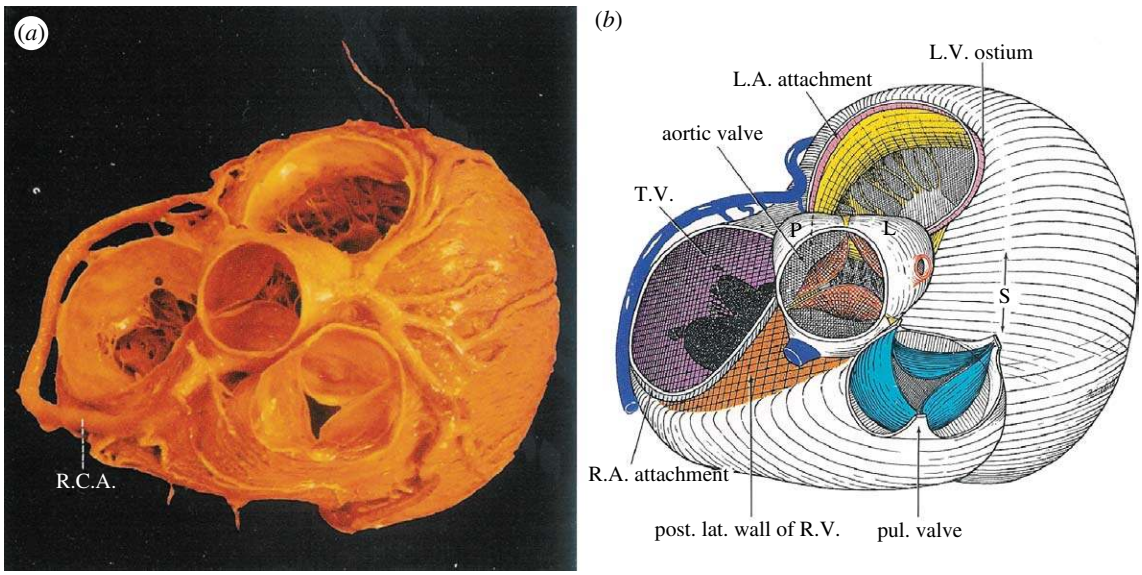

Figure 3. (*a*) View of the four heart valves from superior and (*b*) schematic drawing of the relationship to the right and left ventricle (S, summit of the left ventricle (L.V.), R.C.A., right coronary artery; T.V., tricuspid valve; L.A., left atrium; R.A., right atrium; R.V., right ventricle (adapted from McAlpine 1975, p. 6).

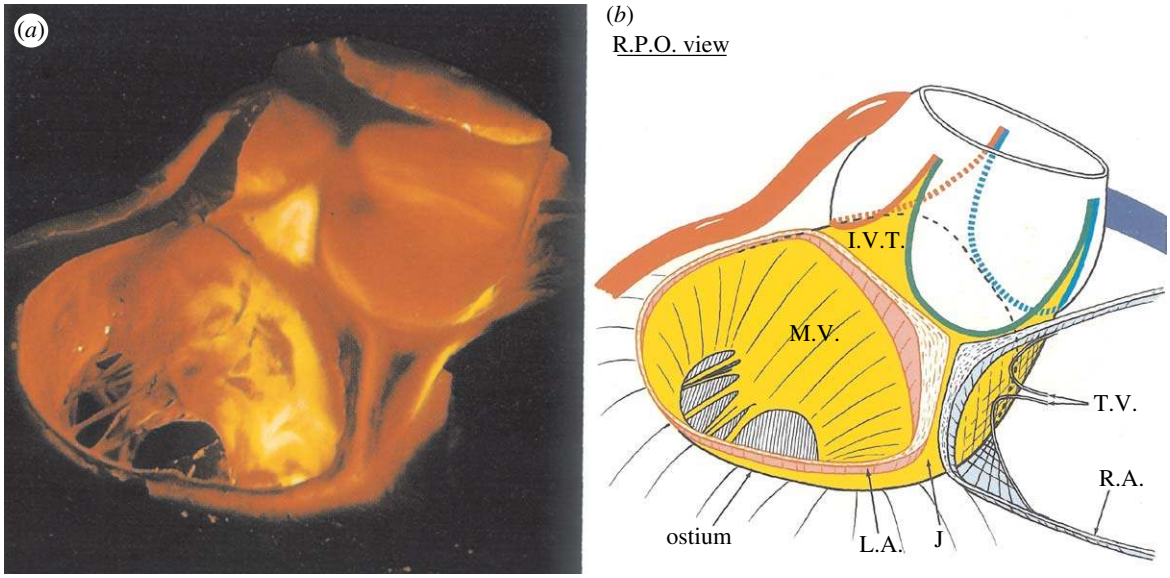

Figure 6. (*a*,*b*) View of the mitral valve (M.V.) and aortic root after removal of the atria. Note the large intervalvular trigone (I.V.T). R.P.O., right posterior oblique; T.V., tricuspid valve; R.A., right atrium; L.A., left atrium; J, junction between the atrioventricular valves. (adapted from McAlpine 1975, p. 13).

right and left (British Terminology Anatomical System) or anterior and right and left posterior (International Terminology Nomenclatura Anatomica). In the 1950s surgeons adopted the simpler termini of non-coronary, right- and left-coronary leaflet according to their relation to the coronary ostia (Choo *et al.* 1999). Although the anatomical nomenclature (1980) describes the atrioventricular valves as having leaflets and the arterial valves as having semilunar valvules, some authors describe the atrioventricular valves as having leaflets and arterial valves as having leaflets as well. However, as most of the publications used the term 'leaflets' for the structure suspended in the lumen between the commissures, leaflets will be the term used in this article.

(**b**) *Macroscopic structure*

The aortic valve has to be seen in context with its structural unit, the aortic root. It is the connecting part between the left ventricle and the ascending aorta and is found in a position wedged between the left and right atrioventricular annuli and the bulging thick left ventricular myocardium (Hokken *et al.* 1997). It comprises the different structures: the annulus, commissures, interleaflet triangles, sinus of Valsalva, sinotubular junction and leaflets (figures 4 and 5). It is important that the aortic root supports the aortic valve and forms the anatomic boundary between the left ventricle and the aorta. However, this boundary is not the same as the haemodynamic junction between the left ventricle and the aorta, which is formed by the leaflets. All structures distal to the haemodynamic junction are subject to arterial pressures, whereas all proximal parts are subjected to ventricular pressures (Anderson 2000).

(i) *Annulus*

Although the word annulus implies that it is a circular structure, the only circular structure of the aortic root is the area where the ventricular structures change to the fibroelastic wall of the arterial trunk. Owing to the semilunar shape where the leaflets are attached to the aortic wall, the annulus forms a crown-like structure which crosses this ventriculo-arterial junction (Anderson *et al.* 1991, 1996). However, the annulus is a well-defined fibrous structure that is firmly attached to the media of the aortic sinuses distally, while proximally it is attached to the muscular and the membranous septa anteriorly (figure 5), the fibrous triangles laterally and the subaortic curtain posteriorly. The three upper parts of the annulus are called commissures.

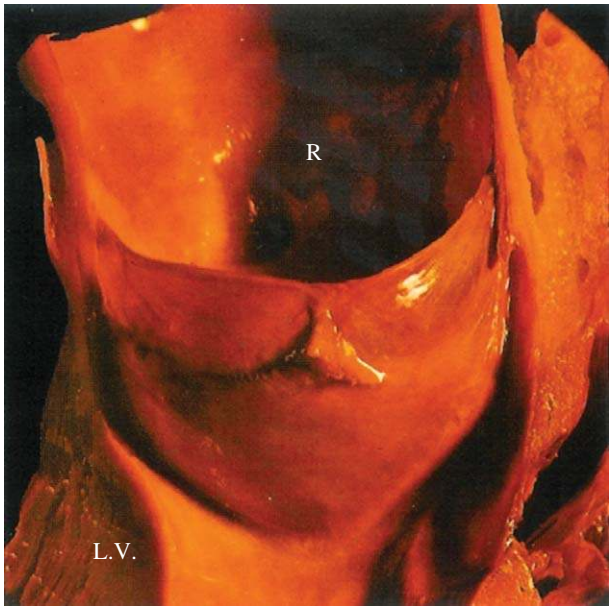

Figure 7. View of the right coronary leaflet. The lannula is approximately one-third of the leaflet height. The nodulus of Arantii forms a triangle (adapted from McAlpine 1975, p. 22).

(ii) *Commissures*

The apex of the crown-like annulus in the area where the lannula of two leaflets are attached to the aortic wall at the height of the sinotubular junction is called a

commissure. In this area, two leaflets are hinged to the aortic wall parallel for a short distance. Therefore, there are three commissures. The commissure between the right- and left-coronary leaflets is positioned anteriorly and is more or less opposite to the corresponding commissure of the pulmonary valve. The commissure between the right and non-coronary leaflets is on the right anterior and the one between the left- and non-coronary leaflets is usually on the right posterior aspect of the aortic root. The commissures are of fibrous structure and suspend the valve leaflets. They are located above three triangular areas called interleaflet triangles.

(iii) *Interleaflet triangles*

The three areas between the anatomic boundary and the apex of the crown-like annulus are called interleaflet triangles. They are extensions of the ventricular outflow tract and reach the level of the sinotubular junction in the area of the commissures (Anderson 2000). The triangle between the right- and the left-coronary sinuses faces the pulmonary valve and has its base on the septal component of the right ventricular outflow tract. Fixation to the pulmonary artery is achieved in 50% of cases by the ligament of the infundibulum. The triangle between the right- and non-coronary sinuses faces the right atrium and is in direct continuity with the membranous septum proximally. It is in this area where the conduction system is in close relationship with the aortic root. The bundle of His, coming from the anterior extension of the AV node, penetrates through the central fibrous body just below the inferior margin of the membranous ventricular septum at the crest of the muscular ventricular septum under this triangle, which is also closely related to the septal leaflet of the tricuspid valve. Finally, the triangle between the left- and non-coronary sinuses is in direct continuity inferiorly with the aortic or anterior leaflet of the mitral valve (figure 6*a*,*b*). It is these triangles that separate and mark the three sinuses in the normal valve.

(iv) *Sinus of Valsalva*

On the aortic side of the annulus the aortic root is composed of three almost symmetrical bulges, the sinuses, named after the Italian anatomist, Antonio Valsalva. They are confined proximally by the attachments of the valve leaflets and distally by the sinotubular junction. At the base, ventricular musculature is partly incorporated. The sinus wall itself is predominantly made up of aortic wall, although it is thinner than the native aorta. At the level of a well-defined ridge, which is the sinotubular junction ends the dilatation of the sinuses.

Two of the sinuses give rise to the coronary arteries at specific points and have an important influence on coronary flow. In general, the sinuses are called with regard to the coronary ostia: right-, left-, and non-coronary sinus, of which the non-coronary sinus is the largest in most cases (Underwood *et al.* 2000). Muriago and co-workers analysed the location of the coronary ostia in normal hearts. They found that the left coronary ostium arises within the sinus in 69%, above the sinotubular junction in 22% and at the level of the junction in 9% of all cases. The right coronary ostium arises in 78% within the sinus, in 13% above the junction and in 9% at the level of the junction. They also showed that the right coronary ostium has an accessory coronary ostium in 74% of all cases (Muriago *et al.* 1997).

(v) *Sinotubular junction*

The well-defined ridge at the top of the sinus is called the sinotubular junction. It marks the point of transition from the aortic root to the ascending aorta. The sinotubular junction runs through the upper part of each commissure and, therefore, marks also the upper end of the attachment of each valve leaflet. This is of immense importance, because dilatation of the aortic root at this level has been shown to cause aortic incompetence (Furukawa *et al.* 1999).

(vi) *Leaflets*

The central structures of the aortic valve are the three aortic leaflets. They consist of four components: the hinge, the belly, the coapting surface and the lannula with the noduli of Arantii (figure 7). The noduli of Arantii are located at the midpoint of the free edge of the coapting surface. On either side of this nodule is a thin crescent-shaped portion called the 'lannula'. This lannula consists of a thin margin at its free end and continues in the coaptation region where the three leaflets meet each other and ensure complete valve closure. The lannulae are attached to the wall of the aortic root in the area of the commissures. The main part of each leaflet is called the belly. In this area, the leaflets appear to be almost transparent. Macroscopically, the specific arrangement of collagen structures of each leaflet can be identified. This impression is in accordance with the findings of Clark and co-workers, who performed measurements of leaflet thickness in relaxed and stressed states (Clark & Finke 1974*a*,*b*). They showed that human leaflets thickness varied from 177 to 1.76 μm in relaxed state and from 150 to 1.75 μm in stressed state.

The component where the leaflets are attached to the annulus in a crescent or semilunar fashion is called the hinge area. In this area, leaflet attachment crosses the ring-like junction of the aortic wall and the ventricular mass. The thick collagenous bundles of the leaflets are hinged to the annulus in such a way that they transmit the stress on the leaflets to the aortic wall. With regard to leaflet sizes, the non-coronary leaflet tends to be the largest, followed by the left coronary leaflet and the right coronary leaflet, although most of the differences are statistically not significant (Vollebergh & Becker 1977; Silver & Roberts 1985; Kunzelman *et al.* 1994*b*).

(c) *Microscopic structure*

The histological structures of the aortic valve have been well described (Benninghoff *et al.* 1930). However, with advanced light-, electron-microscopic and immuno-histochemical techniques the ultrastructure of different aortic root structures is now accessible. So far, most investigations have focused on the aortic valve leaflets. Until now, there has been no systematic

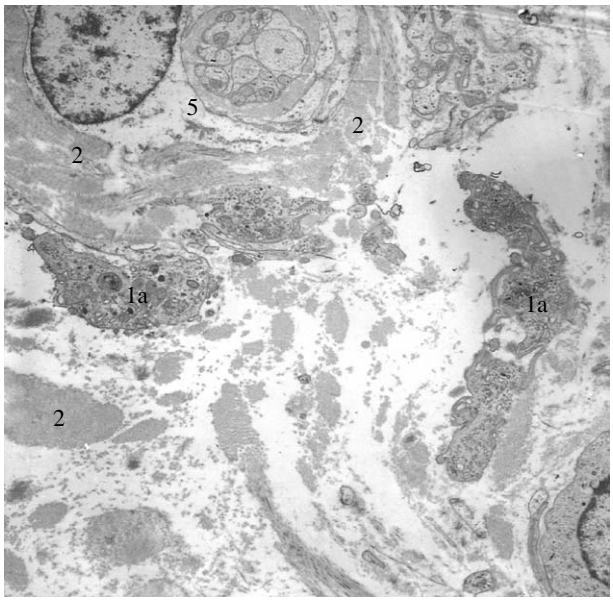

Figure 8. Electron micrograph of annulus tissue. Inside a network of collagenous fibrils and fibroblasts, a non-myelinated nerve can be identified. 1a, fibroblast; 2, collagenous fibrils; 5, non-myelinated nerve (magnification × 6900).

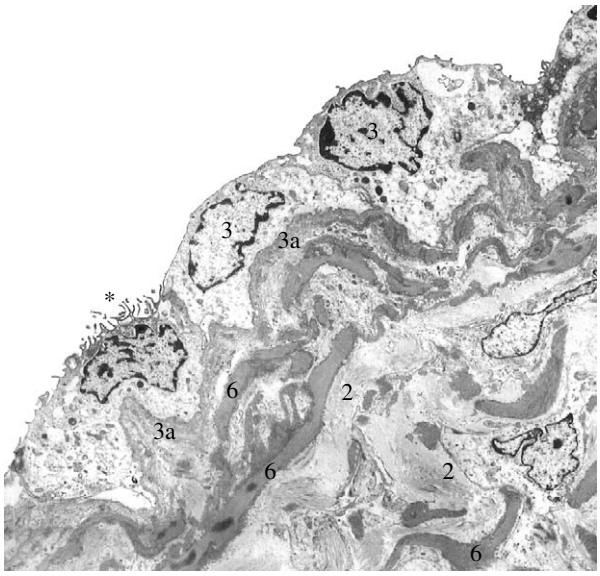

Figure 9. Electron micrograph of commissure tissue in the area of the endothelial cell layer. The endothelial cells are separated by the basal layer from the elastic fibres and collagenous fibrils. The endothelial cells show microvilli at their surface, which increase the overall surface area for an increased exchange of substances. 2, collagenous fibrils; 3, endothelial cell; 3a, basal layer; ∗, microvilli (magnification × 6900).

analysis of the different aortic root structures with regard to contractile and neuronal structures.

(i) *Annulus*

The aortic valve leaflets are attached to the sinus wall via a very dense collagenous meshwork known as the annulus (Missirlis & Armeniades 1977). Cutting through this structure in the non-coronary sinus, where no myocardial muscle supports the sinus, gives the impression of a cartilaginous structure. It is in this zone where the layers of the leaflets show a specific arrangement. The ventricular and arterial layer divide apart, and the intermediate collagenous layer shows a cuneiform structure. The ventricular layer continues as the endocardial layer, whereas the arterial layer continues into the sinus wall. Small vessels are located in the connective tissue layer. Within the annulus, elastic and collagenous fibrils are present. In addition, neuronal structures can also be identified (figure 8).

(ii) *Commissures*

The force on the closed valve is transmitted to the annulus primarily by a system of collagen fibres. Most of these fibres seem to originate at the commissure level. The collagen fibres of the intermediate layer are orientated in a radial fashion in the area of the commissures. Here, they do not only infiltrate the intima layer of the aortic root; they also radiate into the media layer where they are anchored (figure 9). This special arrangement offers optimal transfer of pressure load of the valve leaflets to the aortic wall (Peskin & McQueen 1994).

(iii) *Interleaflet triangles*

The three triangles are not bounded by ventricular musculature, but by a thinned fibrous wall of the aorta between the expanded sinuses. The triangle between the left-coronary and non-coronary sinus forms part of

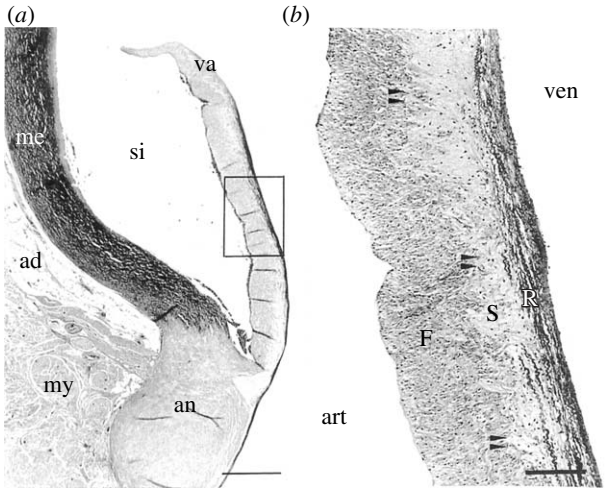

Figure 10. (*a*) Section through the aortic root showing the attachment of the leaflet to the annulus. (*b*) Magnification of the leaflet demonstrating the three layers. art, arterial side; ven, ventricular side; si, sinus; va, valvula; me, tunica media aortae; ad, adventitia; my, myocardium; an, annulus; F, lamina fibrosa; S, lamina spongiosa; R, lamina radialis; arrows indicate the transmission zone between the lamina spongiosa and fibrosa. Scale bars, 144 μm (adapted from Fastenrath 1995, p. 35).

the aortic–mitral valvular curtain. It is histologically fibrous and equivalent to the mitral valve leaflet structure. The triangle between the non-coronary and the right-coronary aortic sinus is incorporated within the membranous part of the septum and is also made of fibrous tissue. In contrast, the triangle between the right-coronary and left-coronary sinus in the area of the subpulmonary infundibulum is supported by muscular tissue and only fibrous at its apex (Yacoub *et al.* 1999; Anderson 2000). Recent studies demonstrate that the interleaflet triangles may express a range of cytoskeletal

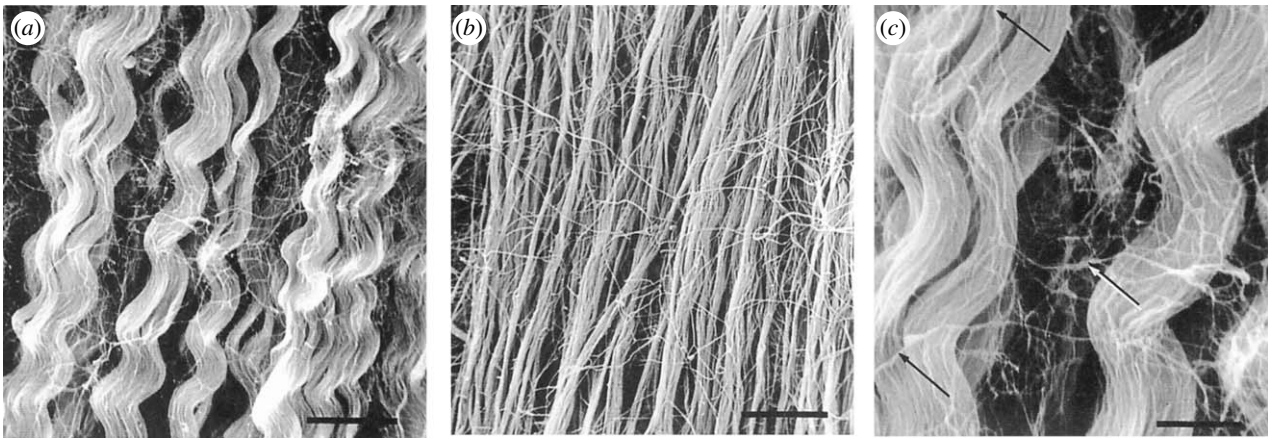

Figure 11. Electron micrograph of the arrangement of collagenous fibrils of the lamina radialis of an aortic valve leaflet at different magnifications. Arrows indicate non-directional fibrils surrounding helical arranged collagenous fibrils. (*a*,*b*) Scale bars, 8 μm and (*c*) 3 μm (adapted from Fastenrath 1995, p. 43).

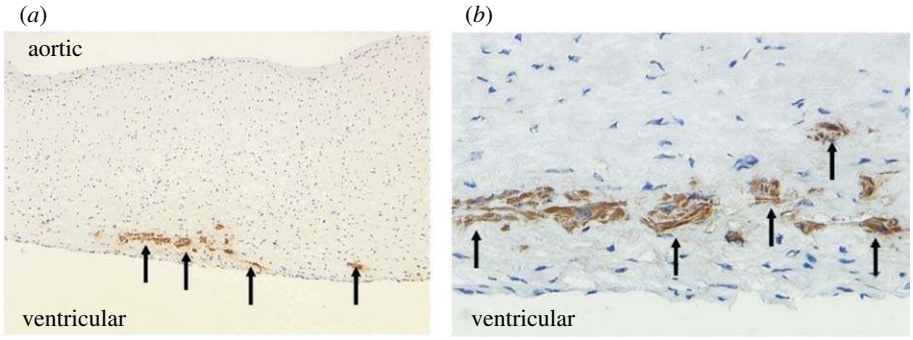

Figure 12. Photomicrographs showing immuno-histochemical staining of an aortic valve leaflet with antibodies against smooth muscle cell alpha-actin. Arrows indicate muscle fibres (*a*, magnification × 25; *b*, magnification × 40).

and contractile proteins as vimentin, desmin and smooth muscle α-actin, indicating that these structures may be involved in the regulation of aortic root function (Dreger *et al.* 2003).

(iv) *Sinus of Valsalva*

Arteries are connected to the heart with so-called arterial fibre-rings. They show histological and structural similarities to tendons. These tendon-like structures do not have well-defined boundaries in the area of anatomical, structural and embryonic connection of the heart and the aorta. Therefore, the sinuses are arranged with very different components. However, the largest part of all of three sinuses is composed in a similar manner to the three layers of the aortic wall: tunica intima, tunica media and tunica externa (adventitia). The inner layer of the intima is composed of endothelial cells arranged in the direction of the vessel. The subendothelial connective tissue is arranged in the same manner as the endothelial cells. This layer is divided from the intima by the membrana elastica interna. The media is composed of circular arranged structures: smooth muscle cells, elastic fibres, collagen fibres type II and III and proteoglycans. The adventitia is the external layer. It is separated from the intima by the membrana elastica externa. Similar to the intima, the elements of the externa are arranged in a longitudinal fashion and composed of collagen fibres of type I. Although the wall of the sinuses is

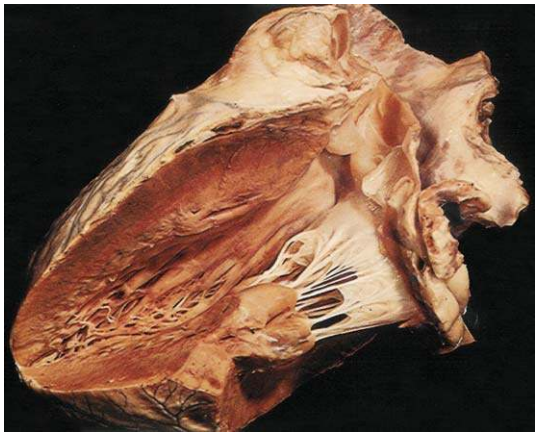

Figure 13. Section through the left ventricle demonstrating the mitral valve apparatus and its relation to the aortic valve (adapted from Anderson & Becker 1982, p. 72).

principally arranged in this manner, the thickness of its wall is significantly thinner compared with the ascending aorta (Sauren *et al.* 1980).

(v) *Sinotubular junction*

The sinotubular junction shows the same principal arrangement of tissue elements compared with the sinuses and the ascending aorta. However, the diameter of the wall is thicker than the diameter of the sinus wall. This fact defines the ridge as the upper part of the aortic root.

(vi) *Leaflets*

The aortic valve leaflets are covered by a continuous layer of endothelial cells with a smooth surface on the ventricular side and numerous ridges on the arterial side. The cells are joined to one another by junctions similar to those present on endothelial cells elsewhere in the vascular system. In contrast to the arrangement of endothelial cells elsewhere, the arrangement of the endothelial cells is across, not in line with the direction of flow (Deck 1986). It has been suggested that biaxial force, rather than shear stresses which occur in all blood vessels, might be responsible for this arrangement. Between the ventricular and aortic surfaces, there are up to five layers of connective tissue: lamina ventricularis, lamina radialis, lamina spongiosa, lamina fibrosa and lamina arterialis. There is some confusion about the nomenclature of the layers. We describe the layers in the adoption of the nomenclature of Gross and Kugel (Gross & Kugel 1931), although we define the lamina ventricularis as an additional layer that can be found between the lamina radialis and the ventricular endothelium. Over all, three distinct layers, the lamina radialis, lamina spongiosa and the lamina fibrosa can easily be identified (figure 10). Within the connective tissue, the elastic and collagen fibres show a preferential arrangement and orientation (figure 11). They are mechanically coupled to each other in a well-defined honeycomb or sponge-like structure. It has been suggested that this special arrangement maintains the collagen fibre orientation and maintain collagen geometry after external forces have been released (Scott & Vesely 1995, 1996; Vesely 1998; Adamczyk *et al.* 2000). The arterial layer contains coarse bundles of circumferential collagen fibres, which form the macroscopical folds parallel to the free edge of the leaflets. It is this arrangement of fibres that transfers the load of the leaflets to the wall of the aortic root (Clark & Finke 1974*a*,*b*; Missirlis & Armeniades 1977; Broom 1978; Peskin & McQueen 1994; Connolly *et al.* 1997). Between the extracellular components reside interstitial cells. Initially described as smooth muscle cells (Bairati *et al.* 1978; Bairati & DeBiasi 1981), these cells show characteristics of fibroblasts and smooth muscle cells (Filip *et al.* 1986), and have been therefore designated as myofibroblasts (Messier *et al.* 1994). However, having the same contractile properties as fibroblasts (Brown *et al.* 1996) or smooth muscle cells, these cells may play an active role in the normal function of the aortic valve and undergo geometric alterations during the cardiac cycle (figure 12*a*,*b*). These findings are supported by the fact that aortic valve leaflets are supplied by oxygen via vessels as well as diffusion from the valve surface (Weind *et al.* 2000, 2002). Vessel density is thereby dependent on leaflet thickness and being increased in the hinge area. The metabolic activity of aortic valve leaflets might be greater than can be supported by diffusion alone. This may have important implications for the function of valve leaflets during the cardiac cycle.

3. MITRAL VALVE

The mitral valve (Valva atrioventricularis sinistra or Valva bicuspidalis or Valva mitralis) is composed of two leaflets. Owing to its similarity to the mitre of a bishop it is termed 'mitral' valve. Located between the left atrium and left ventricle, the mitral valve participates with its subvalvular apparatus to the geometry of the left ventricle and plays an important role in left ventricular performance (Yacoub & Cohn 2004). During the cardiac cycle, the mitral valve undergoes dynamic changes in its size and shape (Tsakiris *et al.* 1978; Ormiston *et al.* 1981). The structures that compose the mitral valve are called the annulus, leaflets, chordae tendinae and the papillary muscles (figure 13). The latter ones are localized in a posteromedial and anterolateral position in the left ventricular cavity. The morphology of the papillary muscles is very variable in particular the one of the posteromedial muscle. In the following section, we will focus on the mitral annulus, leaflets and chordae tendinae.

(a) *Macroscopic structure*

(i) *Annulus*

The mitral valve annulus defines the opening area of the mitral valve. It is composed anteriorly of a fibrous component, which is localized between the two fibrous trigones, the trigonum fibrosum dextrum, the central part of the skeleton of the heart and the trigonum fibrosum sinistrum. In the anterior part of the annulus, the fibres show a parallel and circular orientation and built the more rigid aspect of the mitral annulus (Puff 1965). However, this part is in mild concave form, because it is directly related to the circular aspect of the aortic orifice. This has important implications in the design of mitral valve reconstruction and replacement substitutes. In contrast to the anterior part, the lateral and posterior part of the annulus form the more 'contractile' part (Yacoub & Cohn 2004). They are linked to the anterior part of the annulus by the left and right fibrous trigone. The annulus enables the orifice to undergo complex changes in its shape during the cardiac cycle not only in a horizontal, but also in a vertical plane (figure 14). It has been suggested that this ability has important implications to stress distribution on the leaflets and valve function (Salgo *et al.* 2002).

(ii) *Leaflets*

The central aspects of the mitral valve are the two leaflets. The anterior leaflet (aortic leaflet, septal leaflet or cuspis anterior) is in continuity to the aortic root. It is the bigger one of the two leaflets and forms at its ventricular side a part of the left ventricular outflow tract. The leaflets can be divided into the zone of attachment to the annulus, the 'translucent' zone, the 'rough' zone, where the chordae tendinae are attached to the ventricular side of the leaflet and into the free margin (Anderson & Becker 1982). The posterior leaflet (mural leaflet or cuspis posterior) is attached to the atrioventricular mitral ring as demonstrated in figure 15. It is in 91% of cases divided into three parts (posteromedial or right, intermediate and anterolateral or left) of which the intermediate part is wider and higher than the other two (Bezerra *et al.* 1992). Although the posterior leaflet is attached to almost two-thirds of the circumference and although its area is significantly larger than the area of the anterior leaflets (Kunzelman *et al.* 1994*a*), it participates to a lesser extent with its plane in the

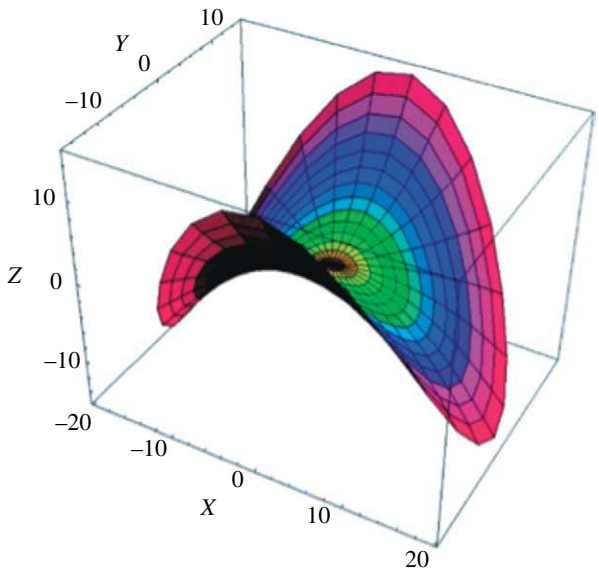

Figure 14. Non-planar model of the mitral valve annulus showing saddle-shaped three-dimensional geometry (adapted from Salgo *et al.* 2002).

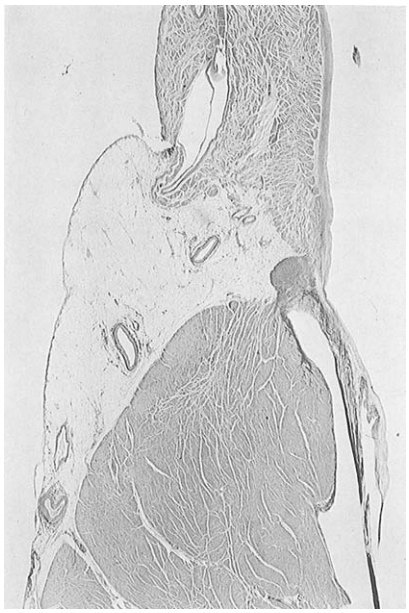

Figure 15. Section through the posterior mitral annulus showing the insertion of the posterior mitral leaflet (adapted from Anderson & Becker 1982, p. 70).

closure of the mitral orifice (figure 16). Interestingly, Kunzelman *et al.* (1994*a*) could demonstrate that the area of each leaflet alone was significantly larger than the calculated mitral valve orifice. Both leaflets meet each other at the two commissures (posteromedial and anterolateral). It is of importance that these commissures are not in the same position as the two fibrous trigones.

(iii) *Chordae tendinae*

Both leaflets are attached to the papillary muscles by the chordae tendinae. They build a functional unit with the papillary muscles and the leaflets. This link is arranged by a sophisticated network of branching of the tendinous chordae which are composed of collagenous and elastic fibres (figure 17). The chordae are able to

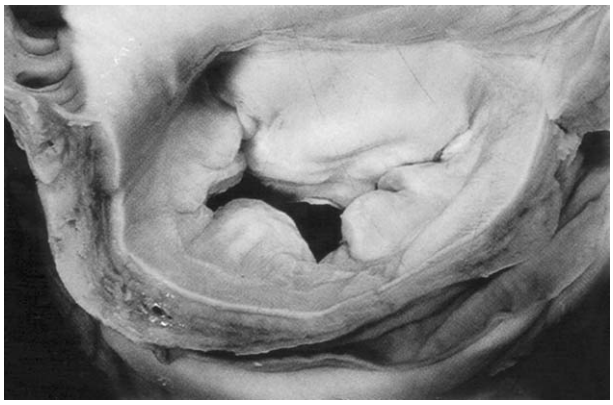

Figure 16. View of the mitral valve leaflets from the atrial side. The three parts of the posterior leaflet and its relation to the anterior leaflet are shown (adapted from Anderson & Becker 1982, p. 68).

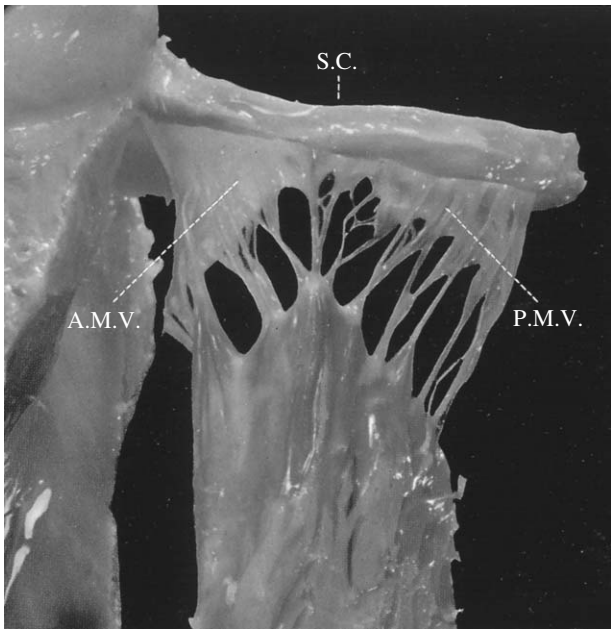

Figure 17. View of the mitral valve apparatus. The lateral papillary muscle and the superior commissure (S.C.) are shown where the anterior (A.M.V.) and posterior leaflet (P.M.V.) confluent (adapted from McAlpine 1975, p. 40).

transmit the contractions of the papillary muscles to the valve leaflets. They are arranged in an 'arcade'-like fashion. In humans the ratio of origin to insertions has been shown to be 5 : 1 (Kunzelman *et al.* 1994*a*). On the leaflets, the majority of the chordae insert either at the free margin or behind the free margin at the ventricular side (rough zone). They need to be distinguished from the base chordae which insert at the leaflets near their attachment at the annulus originating from ventricular myocardium and they need to be distinguished from the commissural chordae which insert at the free margin of two adjoining leaflets (figure 18). The size, shape, orientation and mode of insertion of the chordae tendinae have been suggested to reflect their function to optimize mitral valve function (Yacoub & Cohn 2004) and to reduce stress on the valve and therefore to preserve valve durability (Millington-Sanders *et al.* 1998). The chordae tendinae also play a key role in the different pathologies of mitral valve disease.

Figure 18. View of the commissural chordae tendinae inserting at the free margin of two adjoined leaflets (adapted from Anderson & Becker 1982, p. 47).

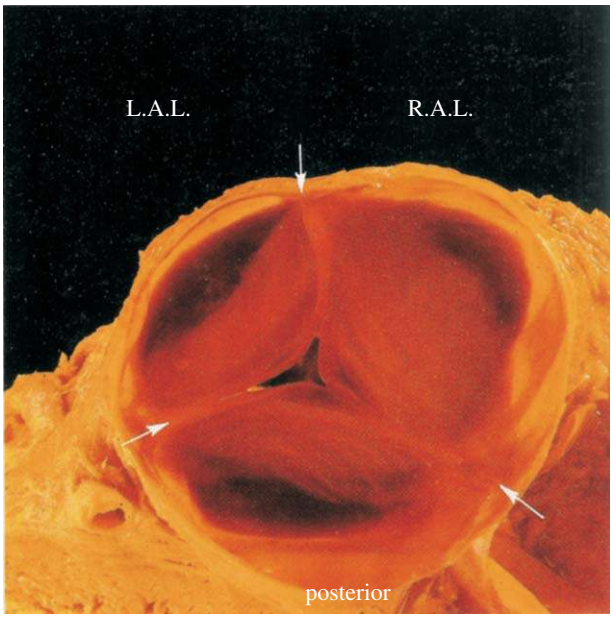

Figure 19. View of the pulmonary valve. L.A.L., left anterior leaflet; R.A.L., right anterior leaflet; Posterior, posterior leaflet; arrows indicate the three commissures (adapted from McAlpine 1975, p. 74).

(**b**) ***Microscopic structure***

(i) *Annulus*

In the last century, the histological structure of the mitral valve annulus has been described before (Puff 1965). Initially, the annulus fibrosus was termed 'annulus fibrocartilagenous'. It was this structure that was thought to contain elastic layers and to be the skeleton of the valves. Other investigators, however, could demonstrate that the lateral part of the mitral annulus consist not of elastic but of collagenous fibres (Puff & Kluemper 1960; Planz 1961). The annulus can be characterized as a transition zone, where the leaflets are anchored to the myocardium. In this zone, the elastic and collagenous fibres radiate into the myocardium (Bargmann 1963). In the 'hinge' zone, the atrial endocardium is thickened. In this area, the number of elastic fibres increases. From the atrial wall, collagenous fibres radiate into the annulus fibrosus and the atrial membrane as a loose three-dimensional network.

(ii) *Leaflets*

The mitral leaflets are composed of a fibrous skeleton with an endocardial surface. The atrial layer has a smooth endocardial cell layer. On the anterior leaflet, this smooth endocardial layer is also present on the ventricular side (Puff 1965). This may be explained by the fact that the posterior aspect of the anterior leaflet is part of the left ventricular outflow tract. Light- and electron-microscopic studies confirm the architecture of the mitral valve leaflet layers of being composed of a lamina spongiosa (facing the atrial side) and a lamina fibrosa (facing the ventricular side; Gross & Kugel 1931; Gross 1961). The endothelium itself consists of a single layer of thin cells which are either simply attached or interlocked with each other (Kühnel 1966). The subendocardial connective tissue of the lamina spongiosa normally consists of fibrocytes, histiocytes and collagenous fibres. The fibrocytes lying in between the fibrils resemble the winged cells of tendons. The diameter of the collagenous fibres varies between 150 and 350 Å and they build in dense layers the 'backbone' of the leaflet. In the zone of leaflet-strut chordae transition geometric changes and collagen fibre angle distribution have been described. The specific stress distribution may play an important role in the durability of valve function (Chen *et al.* 2004).

Mitral valve leaflets, as all other heart valves, have been shown to possess distinct patterns of innervations that comprise both primary sensory and autonomic components (Marron *et al.* 1996). In the anterior leaflet, nerve density is twofold greater than that in the posterior leaflet. The nerves are situated in the atrial layer and extended over the proximal and medial portions of the leaflet. Since fibroblasts (Filip *et al.* 1986), smooth muscle cells (Icardo & Colvee 1995*a*,*b*) and the proximal third myocardial cells have been shown to occur in mitral valve leaflets (Fenoglio *et al.* 1972; Hibbs & Ellison 1973; Basset *et al.* 1976), the functional unit of neuronal structures and contractile elements have been speculated to play a role in mitral valve function (Woollard 1962; Sonnenblick *et al.* 1967; Fenoglio *et al.* 1972; Basset *et al.* 1976). In addition, age-related changes of the nerval innervation may influence valve function over time (Klausner & Schwartz 1985).

(iii) *Chordae tendinae*

The mitral subvalvular apparatus is important to attain the integrity of the left ventricular geometry and systolic pump function of the heart. It has been shown that the distribution of the chordae tendinae varies in the anterior and posterior groups (Bozbuga *et al.* 1999). The functional properties of the chordae

further depend on the link and arrangement between the muscle and the valve. This link is usually arranged in a branching network of the chordae which are composed of collagen and elastic fibres (Millington-Sanders *et al.* 1998). The elastic elements have been shown to return the collagen fibres to its wavy configuration. Collagen fibres itself are composed of a network of collagen fibrils. They are arranged parallel to the long axis of the chordae tendinae. Differences between thin and thick chordae have been investigated by Liao & Vesely (2003). They showed that thinner chordae had a lower average fibril diameter than thick chordae but a greater average fibril density. They concluded that differences in the moduli between thick and thin chordae can be explained by differences in fibril packing and hence fibril-to-fibril interactions. The surface of the chordae has been described to be smooth (Lim & Boughner 1977) and consist of a superficial layer of squamous endothelial cells and an underlying dense layer of elastic fibres (Millington-Sanders *et al.* 1998).

4. PULMONARY VALVE

The pulmonary valve (Valva trunci pulmonalis) connects the Conus arteriosus (infundibulum) of the right ventricular outflow tract and the truncus pulmonalis of the pulmonary artery. It prevents the backstream of blood into the right ventricle during diastole and has principally a comparable design to the aortic valve. As the pulmonary valve is part of the pulmonary root it has also to be seen in the context of the other pulmonary root structures. They are the sinus (sinus trunci pulmonalis), the annulus, the commissures, the leaflets and the sinotubular junction. Principally, the aortic and pulmonary leaflet show similar histological characteristics. Benninghoff and colleagues described the pulmonary leaflets as being thinner and the noduli of Arantii as being smaller compared with the aortic leaflets (Benninghoff *et al.* 1930). Other investigators, focusing on other structures of the pulmonary root showed minor differences in the histological topography of the structures (Gross & Kugel 1931). Both valves have principally the same architecture and their minor differences represent the histological correlate to their location in different physiological environments. However, as mechanical differences of both valves have also been shown to be minimal (Stradins *et al.* 2004), the pulmonary valve is used as an aortic valve substitute in the Ross procedure (Ross 1967).

(a) *Macroscopic structure*

(i) *Annulus*

The annulus of the pulmonary root does not have a circular form but is defined by the line of attachment of the leaflets to the sinus wall, resulting in a 'crown-shaped' annulus, as it has been described in the aortic root (Zimmerman 1969). It is not a well-defined fibrous structure, but it is more a description of the geometrical architecture of the root. The annulus marks the ventriculo-arterial junction between the free-standing right ventricular infundibulum and the fibroelastic walls of the pulmonary sinuses (Stamm *et al.* 1998).

(ii) *Commissures*

The areas where the attachment lines of the leaflets to the pulmonary wall are parallel for a short part are called the commissures. There are three commissures: the one between the left anterior leaflet and the right anterior leaflet, the one between the right anterior and the posterior leaflet and the commissure between the posterior and the left anterior leaflet (figure 19).

(iii) *Interleaflet triangles*

In accordance with the three commissures, there are three interleaflet triangles marking the area under the commissures. These triangles are extensions of the right ventricular outflow tract and play an important role in the opening and closing dynamics of the pulmonary valve.

In several publications, a part of the fibrous skeleton of the heart between the aortic and pulmonary root was called the 'tendon of the infundibulum'. Lal and co-workers, however, could demonstrate that this area is only composed of loose fibroalveolar tissue and therefore, stated that such tendon did not exist (Lal *et al.* 1997).

(iv) *Sinus of Valsalvae*

The three sinuses are called in accordance to their leaflets the left anterior, right anterior and posterior sinus. They are defined by the form of the crown-like annulus, the commissures and the sinotubular junction. Compared to the wall of the pulmonary artery, the wall of the sinuses is much thinner, especially in its middle portion.

(v) *Sinotubular junction*

In accordance with the aortic root, the sinotubular junction of the pulmonary root is characterized by a ridge which defines the upper part of the sinuses and runs through the upper part of the commissures.

(vi) *Leaflets*

The leaflets of the pulmonary valve consist of the same components as the aortic leaflets: the hinge, the belly, the coapting surface and the lannula with the noduli of Arantii. The latter ones are less frequently present than on the aortic leaflets. The lannula participates as the coapting part of the leaflets with each other. Especially in the zone where the lannulae are attached to the pulmonary wall, at the commissures, fenestrations can be present. These fenestrations are without clinical relevance, but they may make this valve unsuitable as an aortic valve substitute in the Ross procedure. The belly, which forms the main area of one leaflet, is almost transparent in its centre. In the zone of the hinge area, the leaflets are attached to the pulmonary annulus.

(b) *Microscopic structure*

(i) *Annulus*

The annulus of the truncus pulmonalis differs from the annulus of the aortic root in as much as its caudal margin adjoins to the myocardium of the right ventricular outflow tract and not a leaflet of an atrioventricular valve or the membranous interventricular septum. There is

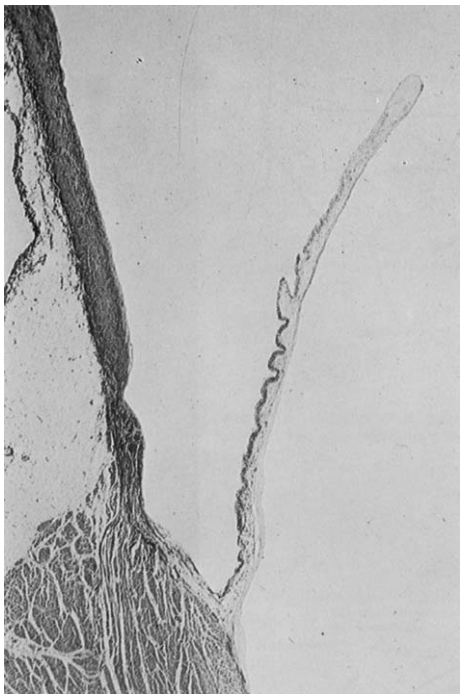

Figure 20. Section through the pulmonary root. The area of attachment of the pulmonary leaflet can be seen (adapted from Anderson & Becker 1982, p. 49).

no well-defined fibrous annulus that characterizes the line of attachment of the pulmonary leaflets (figure 20) and the annulus is only loosely connected to the right ventricular myocardium (Gross & Kugel 1931). It is composed of tight collagenous tissue.

(ii) *Commissures*

Various sections through different heights of the truncus pulmonalis demonstrate the connection of the annulus with the tunica media of the pulmonary artery and the myocardium. The fibres that connect the annulus and the lamina fibrosa of the leaflet mainly radiate in the zone of the commissures into the leaflet (figure 21).

(iii) *Leaflets*

The leaflets of the pulmonary valve are the structures that have been most widely investigated. Their load-bearing components are collagenous and elastic fibres (Broom 1978). Light microscopic investigations show five layers between the ventricular and arterial endocardial layers of the leaflet. They are called: lamina ventricularis, lamina radialis, lamina spongiosa, lamina fibrosa and lamina arterialis, respectively (Gross & Kugel 1931). The layer under the ventricular endothelium is the lamina ventricularis. This layer is composed of a tight network of reticular fibres with only rare thin collagenous fibres and elastic fibres. The thickness of this layer is between 21 and 48 μm. The lamina radialis, as the next layer incorporates radial orientated collagenous and elastic fibres. Between the collagenous and elastic fibres are some reticular fibres. The thickness of this layer is between 58 and 108 μm. This layer proceeds into the endocardium and the subendocardial layer of the ventricle. The lamina spongiosa is composed of loosely arranged reticular fibres with bundles of collagenous

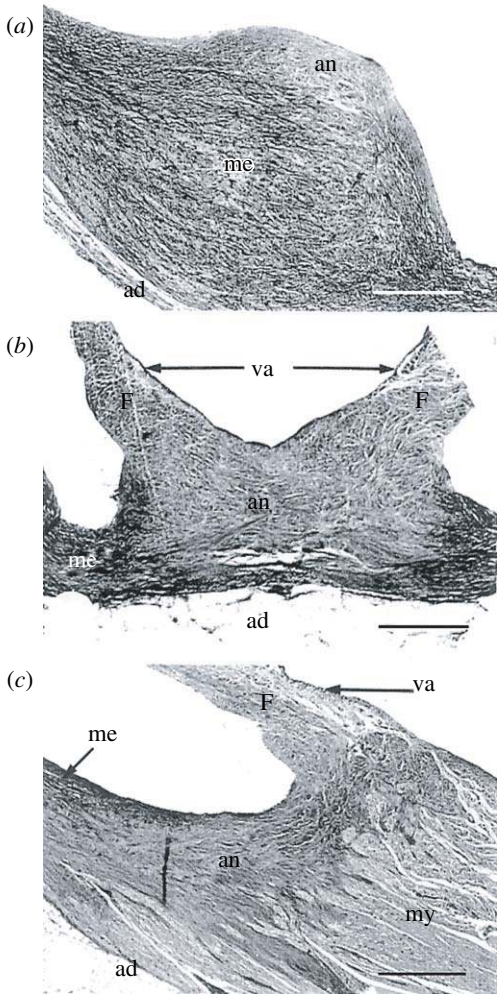

Figure 21. Sections through the annulus of the pulmonary root. (*a*) Upper part of the commissure, (*b*) middle part with the attachment of two leaflets, (*c*) basal part of the annulus. an, annulus; me, tunica media; ad, adventitia; my, myocardium; va, valvula; F, lamina fibrosa. Scale bar, 517 μm (adapted from Fastenrath 1995, p. 65).

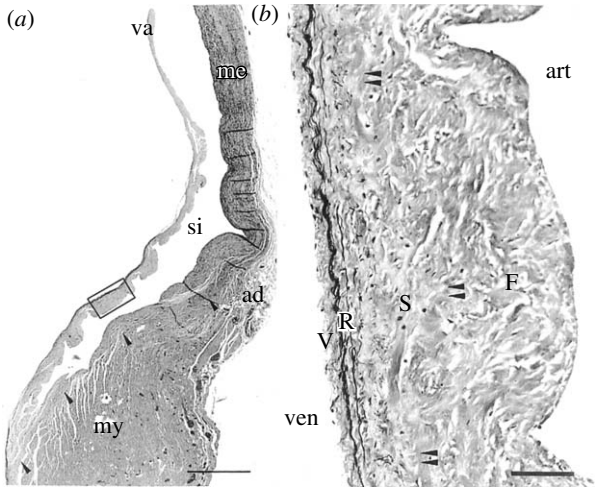

Figure 22. (*a*) Section through the pulmonary root, va, valvula; me, tunica media; si, sinus; ad, adventitia; my, myocardium; arrows, zone of the annulus; scale bar, 1.1 mm. (*b*) Enlargement of the leaflet showing the different layers of the leaflet, ven, ventricular side; art, arterial side; V, lamina ventricularis; R, lamina radialis; S, lamina spongiosa; F, lamina fibrosa; arrows, area between lamina spongiosa and fibrosa. Scale bar, 83 μm (adapted from Fastenrath 1995, p. 35).

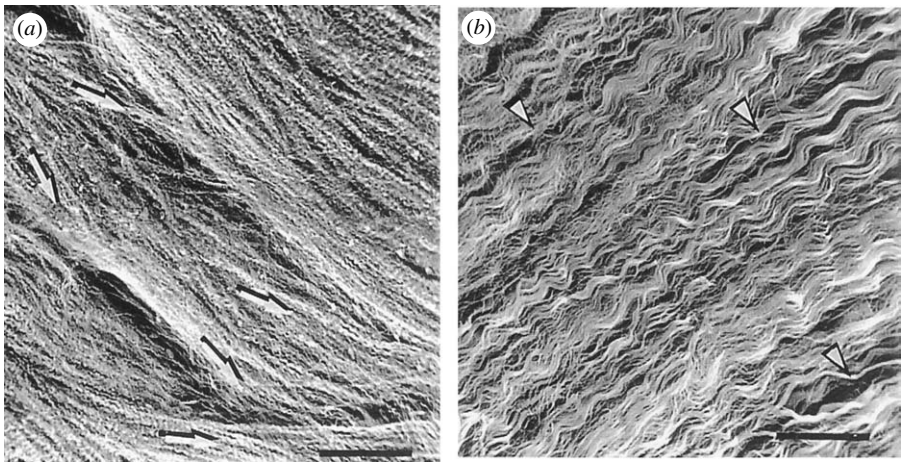

Figure 23. (*a*,*b*) Electronmicroscopic section of collagenous fibrils of the lamina fibrosa of the pulmonary leaflet. The bundles are not strictly arranged in a parallel fashion (arrows on the right), but interweave with each other in an acute-angle (adapted from Fastenrath 1995, p. 53). Scale bars: (*a*) 83 μm, (*b*) 17 μm.

and some elastic fibres. Many of the collagenous fibres radiate from the lamina radialis and lamina fibrosa into this layer, which sometimes make this layer difficult to identify. The thickness of the lamina spongiosa is between 40 and 300 μm. Circular arranged collagen fibres characterize the lamina fibrosa. This layer is connected to the annulus and has a thickness of 80 to 170 μm. Finally, the lamina arterialis is the layer under the endothelium at the arterial side. This layer is composed of a thin layer of reticular fibres and not always present in light microscopic sections (figure 22).

Electron microscopy demonstrates that the endothelial cell layers are bordered by a basal membrane. Endothelial cells of the pulmonary leaflets interdigitate or overlap. They are further characterized by pinocytic vesicles, indicating an active transport system. In the subendothelial reticular tissue collagenous fibrils are scanty, but fibroblasts are abound. The lamina fibrosa consists of tight bundles of collagenous fibrils (figure 23). Fibroblasts lying among these fibrils show multiple long processes (Kühnel 1966).

As in all the other heart valves, the pulmonary valve leaflets have been shown to have distinct patterns of neuronal innervation (Kawano *et al.* 1996; Marron *et al.* 1996). The innervation arises from the ventricular endocardial plexus and is localized to the ventricular layer and lower region of each leaflet.

5. TRICUSPID VALVE

The tricuspid valve (Valva atrioventricularis dexter) is composed of an anterior, anterosuperior, ventral or mural leaflet (Cuspid anterior), a posterior, inferior or dorsal leaflet (Cuspis posterior) and a septal or medial leaflet (Cuspis septalis; figure 24). It is positioned between the right atrium and the right ventricle and builds a structural unit with the annulus, chordae tendinae and the papillary muscles. The latter have shown a great variability in numbers. With a minimum of two and a maximum of nine muscles in the right ventricle, there are usually three papillary muscles present: an anterior, a posterior and a septal muscle, respectively (Aktas *et al.* 2004). Although the tricuspid valve has similar structures compared with the mitral valve, it also has its own specific characteristics. Its orifice is larger than the orifice of the mitral valve and the leaflets are thinner and more translucent. Although the tricuspid valve is located at the atrioventricular border, a well-defined annulus fibrosus as in the mitral valve is not present. Both valves, however, have structural similarities and with these, the ability to open and close rapidly, due to their remarkable mobility, is facilitated by a specific composition of chordae attachment at the leaflets and leaflet anchoring in the annulus. The annulus which undergoes three-dimensional changes in its area, a specific gravity approximating that of blood, a smooth surface minimizing friction, and a large area of coaptation between the leaflets participate in this mobility. Knowledge of the structural components of the tricuspid valve has important implications to restore tricuspid valve function which is predominantly performed by reconstruction procedures.

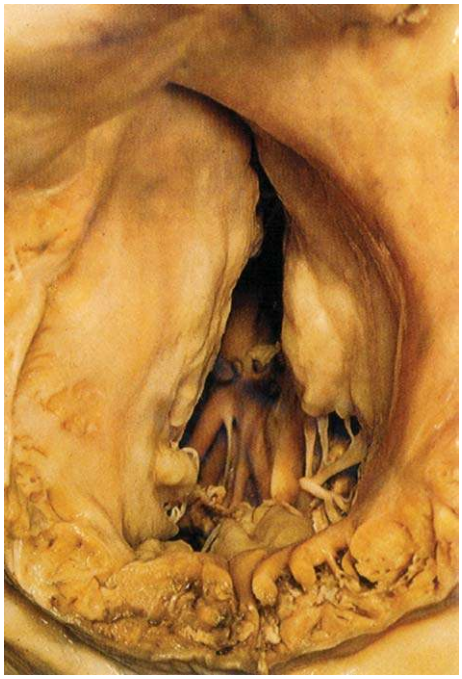

Figure 24. View of the tricuspid valve (adapted from Anderson & Becker 1982, p. 60).

(a) *Macroscopic structure*

(i) *Annulus*

The annulus of the tricuspid valve has a complex three-dimensional shape and does not conform to a flat ring. It undergoes dynamic changes during the cardiac cycle and has a larger orifice compared with the mitral annulus (Yacoub & Cohn 2004). The leaflets are attached to the annulus which has a closed relationship to the right fibrous trigone and the membranous part of the ventricular septum. The annulus also built part of the triangle of Koch together with the coronary sinus and the tendon of Todaro. This triangle has importance in tricuspid valve surgery, because it incorporates the conduction system.

(ii) *Leaflets*

The three leaflets of the tricuspid valve differ in size. The mural or anterior leaflet is the largest. It stretches from the infundibular area downwards to the inferolateral wall of the right ventricle. The septal or medial leaflet is attached to both the membranous and muscular portions of the ventricular septum. The posterior leaflet is the smallest and attached to the tricuspid ring along its posteroinferior border. Sometimes, four leaflets can be identified. The posterior leaflet can be divided or an additional leaflet is positioned between the posterior and the septal one. The free margins of the leaflets show an arcade-like composition and terminate into the chordae tendinae. Similar to the mitral valve leaflets closure of the tricuspid valve is achieved by a plane of attachment of the leaflets to each other, by which the subvalvular apparatus prevent the leaflets from passing into the atrium. The tricuspid leaflets differ from the mitral leaflets in being thinner, more translucent, and less easily separated into well-defined leaflets.

(iii) *Chordae tendinae*

In accordance to the variations of the number of papillary muscles in the right ventricle, the arrangement of the chordae tendinae of the tricuspid valve is not as constant as the ones of the mitral valve. Several chordae supporting the septal leaflet are attached directly to the interventricular septum. The chordae are interconnected before they attach the leaflets (figure 25).

(b) *Microscopic structure*

(i) *Annulus*

Depending on the area of the annulus of the tricuspid valve a fibrous structure can be identified. In some areas, a well-defined cartilage-like structure is not present. Figure 26 demonstrates the zone of attachment of the tricuspid valve to the atrial and ventricular myocardium.

(ii) *Leaflets*

The leaflets of the tricuspid valve are composed of a fibre skeleton and an endocardial surface. The atrial layer of the endocardium shows a smooth surface (Benninghoff 1930). It is a monolayer of endothelium. These cells are interconnected in various fashions. They show either a straight border interlocked with each other or they show 'roof tile'-like overlaps. It has been speculated that these arrangement is of importance to maintain the structural integrity under maximum stretch (Kühnel 1966). The endothelium is underlined by a basal membrane, composed of an osmiophilic lamina densa and an osmiophobic lamina rara. The lamina spongiosa is composed of loosely arranged layer of connective tissue. The lamina fibrosa is composed of dense collagenous fibres which forms a solid plane. Electron microscopic sections through the leaflets reveal the fibres of being arranged parallel and vertical to the free margin of the leaflets (Kühnel 1966).

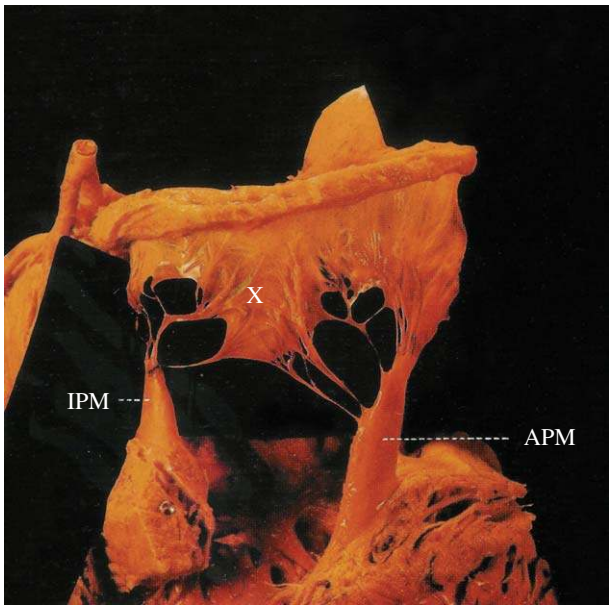

Figure 25. View of an isolated tricuspid valve showing part of the subvalvular apparatus. The septal leaflet (X) is supported by chordae tendinae originating from the inferior papillary muscle IPM and the anterior papillary muscle APM (adapted from McAlpine 1975, p. 74).

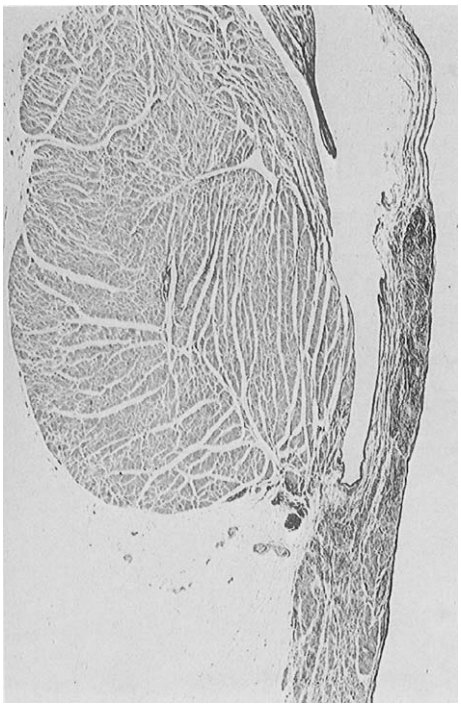

Figure 26. Section through the tricuspid valve (adapted from Anderson & Becker 1982, p. 60).

Marron *et al.* (1996) also investigated the innervation of human tricuspid valve leaflets and found their distribution relatively frequently in all leaflets of the tricuspid valve in contrast to mitral leaflets. It has been speculated that this findings may play a role in the control of valve function.

(iii) *Chordae tendinae*

The chordae tendinae of the tricuspid valve show a similar composition as the chordae tendinae of the mitral valve. They are also composed of a network of collagen fibrils which built the collagen fibres. Arranged parallel to the long axis of the chordae, these fibrils secure valve competence. Abnormalities in the arrangement of the collagen bundles as in myxomatous tricuspid valves have been found to cause less breaking stress compared with normal chordae (Lim *et al.* 1983). This fact has been suggested to be the cause of chordal rupture, a common complication in myxomatous valve disorders.

6. CONCLUSIONS

Heart valve disease has been shown to be increasing in numbers. In developing countries due to inflammatory disease (WHO Study Group 1988), and in industrial countries due to mainly degenerative valve disease (Schneider & Guralnik 1990; Otto *et al.* 1999). Approximately more than 150 000 heart valves are implanted annually world-wide and it has been shown that ageing of the population and advances in preoperative and postoperative care are increasing the number of older patients undergoing valve surgery (Asimakopoulos *et al.* 1997; Edwards & Taylor 1999, 2003; Sahar *et al.* 1999).

Besides valve replacement, reconstructive techniques try to preserve the physiological conditions of the heart valve to ensure durability and reduce potential side effects of valve substitutes. There is also an increasing interest in tissue engineered valve substitutes to replace diseased valves.

Various histological studies have described the macro and microstructure of heart valves. Surprisingly, some non-uniformity still exists with regard to the nomenclature of valve structures. This may be explained by the fact that with advanced histological techniques, closer insights into the ultrastructure of the heart valves become apparent. Most analyses of the heart valves focus on leaflets. Other valve structures have been of interest in accordance with their pathological or surgical relevance. There is no study that has systematically analysed all structures that compose the human heart valves and some histological investigations have described histological structures of other species.

Macroscopic and microscopic analyses of heart valve structures reveal specific characteristics of each valve. Each heart valve itself consists of a sophisticated 'cross-talk' between the components that compose the valve. The complexity of structural elements and the individual histological profile enable this system a unidirectional flow under different physiological conditions and optimize stress distribution. Interference with the integrity of the valves will lead to valve degeneration and thus to valve dysfunction. Understanding the composition of the structural elements of the heart valves will have important implications in understanding normal valve function and its difference in pathological states. It will further provide information for therapy of valve dysfunction, not only for surgical, especially reconstructive techniques, but also for the design and development of valve substitutes, i.e. artificial chordae tendinae. In addition, analysis of the structural elements of the heart valves will give important inputs into tissue engineering principles.

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