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Original Article

The anatomy and development of the cardiac valves*

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Abstract Advances made in the understanding of the molecular biology of the cardiac valves have been truly spectacular. Not all of those investigating these aspects, however, have an appropriate understanding of the underlying anatomy. Partly, this reflects problems in describing the components of the various valves, a difficulty also emphasised by surgeons who repair or replace the valves. In this review, we describe briefly the overall anatomy of the cardiac valves, pointing to their similarities and differences. We then suggest that uniform terms can be developed to account for the components of the valves, treating them as complexes that guard the atrioventricular and ventriculo-arterial junctions. The atrioventricular valvar complex is made up of an annulus, leaflets, tendinous cords, and papillary muscles. The tension apparatus is required to hold the leaflets together against the force of ventricular systole. The ventriculo-arterial complex is also based on the leaflets, but supported within the valvar sinuses, and limited distally by the sinutubular junction. It is the semilunar nature of the leaflets that underscores their snug closure during ventricular diastole. The complexes thus defined can be separated to produce paired valves in the normal arrangement, or to produce common valves in the congenitally malformed hearts. Knowledge of development now permits accurate inferences to be made regarding the origin of the various components, and their relevance to valvar disease. The valvar leaflets are developed from the endocardial cushions formed in the atrioventricular canal and the outflow tract by a process of endothelial-to-mesenchymal transformation. The papillary muscles of the atrioventricular valves are then derived from the trabecular layer of the developing ventricular walls, whereas the sinuses of the ventriculo-arterial valves are formed by additional growth of the non-myocardial tissues, concomitant with excavation of the outflow cushions to form the leaflets.

Keywords: Mitral valve; tricuspid valve; aortic valve; pulmonary valve; atrioventricular valves

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Introduction

It is surprising, at a time when the structure of the heart is beginning to be demonstrated with as much accuracy during life as when visualised in the autopsy room, that there should be so many misconceptions concerning the anatomy of the cardiac valves. Similar misconceptions are then found when considering current notions of valvar development. Some of these problems reflect the ongoing penchant for cardiologists and pathologists to describe the heart as viewed when removed from the body and placed on its apex – the so-called Valentine orientation. This practice ignores the basic rule of anatomy, namely, that structures should be described as they are positioned within the body during life, in other words in attitudinally appropriate manner.[1] Clinicians seem remarkably reticent to accept this concept, despite the fact that the modern-day techniques available for imaging show precisely the location of the valvar structures relative to the body.[2] Further

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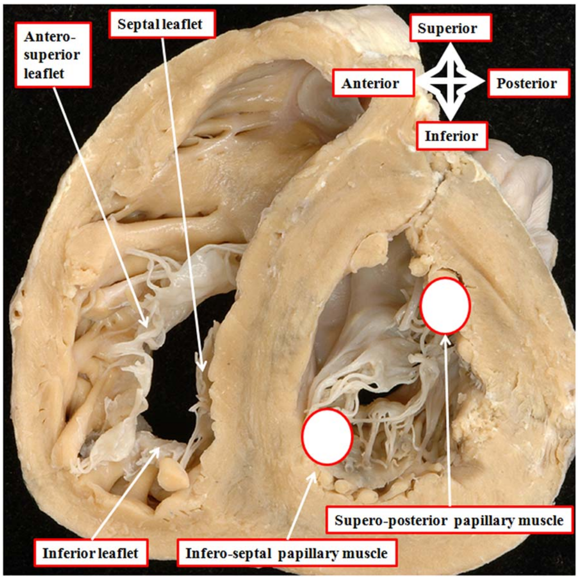

Figure 1.
The short axis of the normal heart has been exposed by removing the ventricular mass, and photographing the atrioventricular junctions from the apical aspect. The heart is positioned as it lies within the chest during life. The compass in the upper left corner of the images shows the anatomic coordinates. As can be seen, the three leaflets of the tricuspid valve are located inferiorly, septally, and antero-superiorly. At the present time, however, it is usually the inferior leaflet of the valve that is described by clinicians as being "posterior". The same problem afflicts the description of the papillary muscles that support the leaflets of the mitral valve. As shown by the superimposed ovals, despite being located infero-septally and supero-posteriorly, they are usually said to be "postero-medial" and "antero-lateral", respectively.

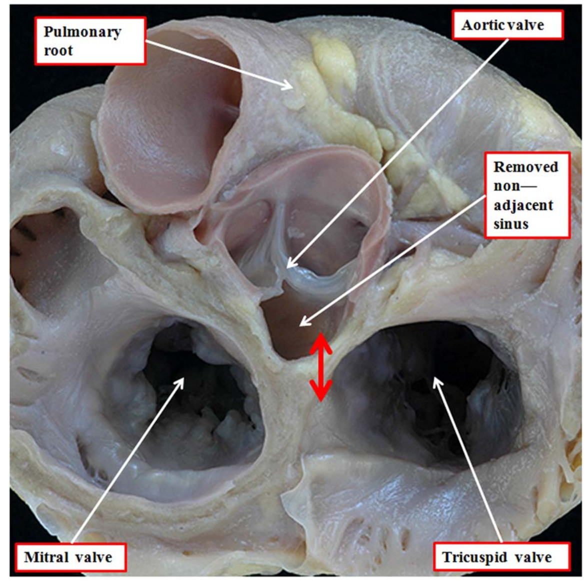

Figure 2.
The cardiac short axis has been exposed by removing the atrial musculature, along with the intrapericardial arterial trunks, and has been photographed from the atrial aspect. The image shows how the mitral and tricuspid valves, guarding the atrioventricular junctions, are located inferiorly within the short axis. The aortic valve, from which the non-adjacent sinus and leaflet have been removed, is centrally located. It overlaps with the mitral valve within the short axis of the left ventricle. The double-headed red arrow shows the short distance needed by the atrioventricular conduction axis to extend from the apex of the triangle of Koch to the crest of the muscular ventricular septum. The pulmonary root, positioned with its long axis at right angles to that of the aortic root, is separated from the tricuspid valve by the supraventricular crest of the right ventricle.

problems then relate to the notions that practitioners gain when first introduced to cardiac anatomy. Well-recognised textbooks of human anatomy, for example, still illustrate the leaflets of all the four cardiac valves as supported by a "fibrous skeleton",[3] despite the fact that evidence is lacking in support of such a structure. The misconceptions regarding anatomy are then magnified by the plethora of terms used to describe the components of the cardiac valves, to the extent that naming of the aortic root by surgeons has recently been compared with the mythical Tower of Babel.[4] In this review, we will show how careful attention to attitudinally appropriate nomenclature, combined with the uniform use of words to describe the parts of the different valves, permits reason to reign where currently there is potential chaos. We then show how the availability of episcopic miscroscopy[5] now permits a comparable approach to be taken to valvar development.

The importance of attitudinally appropriate nomenclature

It was McAlpine, in his stellar atlas published in 1975,[1] who first stressed the importance for clinicians of describing the components of the heart as they are located within the body. The significance of this approach was ignored by one of us (R.H.A.) throughout the larger part of his career, and for many years he described and illustrated the cardiac components as seen with the heart in Valentine orentation. The problems engendered by such an approach came to prominence when electrophysiologists pointed to the nonsense of describing a catheter as moving "anteriorly" when it was seen to progress superiorly through the abdomen as it approached the heart.[6] Despite recommendations made by an expert committee,[7] nonetheless, those investigating the heart using electrophysiological techniques still tend to retain the old incorrect words when describing their findings. Thus far, this is also the case with the cardiac valves. Analysis of the location of the atrioventricular valves within the cardiac short axis as viewed from the cardiac apex (Fig 1) shows that the leaflets of the tricuspid valve are positioned septally, inferiorly, and antero-superiorly. Of the three leaflets, it is the septal one that is closest to the spine, and hence posterior. Clinical cardiologists, nonetheless, continue to describe

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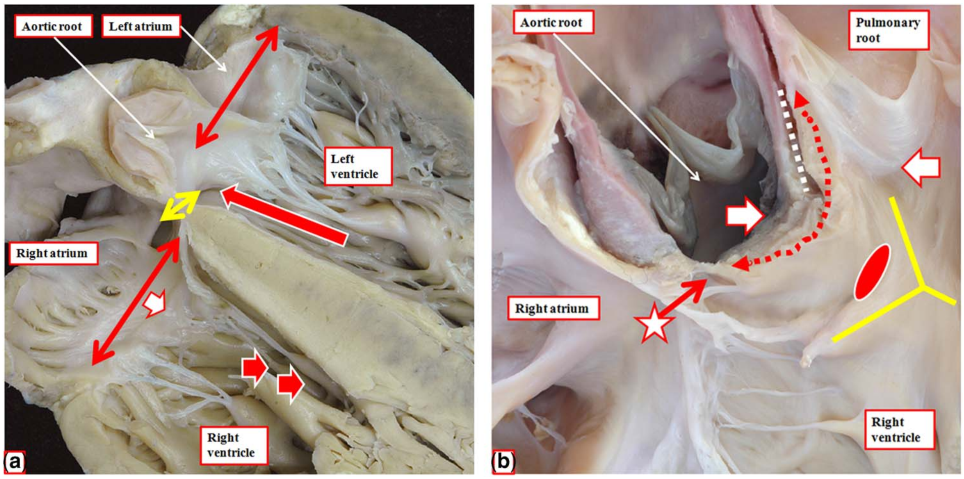

Figure 3.

*The images compare the alignments of the atrioventricular (**a**) and the ventriculo-arterial (**b**) valves in the human heart. Panel **a** in which the heart has been sectioned in its coronal plane to replicate the echocardiographic four-chamber section that incorporates the aortic root, shows the marked off-setting of the orifice of the tricuspid and mitral valves (double-headed red arrows). Because of the overlapping of the aortic and mitral valves in the left ventricle, the mitral valve has no direct attachments to the ventricular septum (long red arrow with white borders). This is in contrast to the septal leaflet of the tricuspid valve (short red arrows with white borders). The cut also shows how the hinge of the tricuspid valvar leaflets are non-planar (white arrow with red borders). The double-headed yellow arrow shows the site of the fibrous atrioventricular septum. Panel **b** has been prepared by sectioning along the subpulmonary infundibulum, and removing the right coronary aortic sinus. It shows how the supraventricular crest (dotted red double-headed arrow) continues as the free-standing infundibular sleeve, lifting the leaflets of the pulmonary valve away from the cardiac base. This produces off-setting of the orifices of the aortic and pulmonary valves (white arrows with red borders). The yellow lines show the Y of the septomarginal trabeculation, also known as the septal band. The red oval with white borders shows the small part of the supraventricular crest that can be dissected away to create a communication with the left ventricle. There are no anatomic boundaries, however, between this septal component and the free-standing infundibular sleeve. The white star and red arrow show the location of the atrioventricular conduction axis. The white dotted line shows the plane between the arterial roots.*

the inferior leaflet as being posterior. It is a similar conundrum for the naming of the papillary muscles supporting the leaflets of the mitral valve. These are positioned infero-septally and supero-posteriorly. Currently, however, they are usually described, again incorrectly, as being "postero-medial" and "antero-lateral". The increasing use of three-dimensional techniques for imaging, such as CT or MRI, reveals the inappropriate use of these adjectives. With time, sense will surely prevail, and the correct words will be used to describe the location of the cardiac components. At least this is beginning to happen when describing the bridging leaflets of the common atrioventricular valve. Named inappropriately in the past as being "anterior" and posterior", the universal use of echocardiography as the imaging tool of choice has shown that the leaflets are located superiorly and inferiorly. As we will show, it is the attitudinally appropriate descriptions that now permit accurate correlations to be made, with the evidence accruing relative to their development.

How do the valves sit within the cardiac mass?

In Figure 1, we have shown the location of the valves within the cardiac short axis as viewed from the ventricular apex. The valves that guard the atrioventricular and ventriculo-arterial junctions of the heart are located well apart from one another within the right ventricle, but overlap within the short axis of the left ventricle. Their relationship is equally well observed when viewed from the atrial aspect, having removed the atrial musculature and the intrapericardial arterial trunks (Fig 2). When we compare the valves within the same junctions, it is well recognised that the leaflets of the mitral and tricuspid valves are off-set relative to one another when viewed in the coronal, or four chamber, plane of the heart. Echocardiographers use this feature as a means of differentiating the valves, along with the fact that the leaflets of the mitral valve, unlike those of the tricuspid valve, have no direct attachments to the ventricular septum (Fig 3a). It is less well appreciated that there is also marked off-setting of the leaflets of the aortic and pulmonary valves. This is because the free-standing muscular infundibular sleeve lifts the leaflets of the pulmonary valve away from the cardiac base, a feature well demonstrated in the oblique cut that replicates the subcostal section of the right ventricle obtained by echocardiographers (Fig 3b). The cardiac valves are therefore grouped together within the short axis of the heart, guarding the

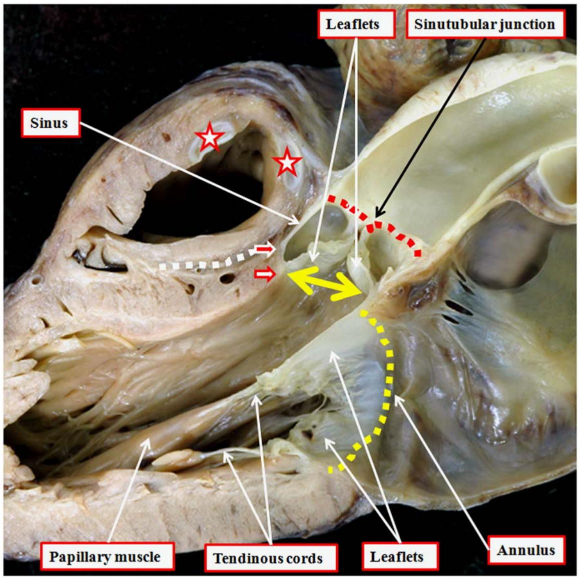

Figure 4.
The image shows a long-axis cut through the ventricular mass that replicates the parasternal echocardiographic section of the left ventricle. It shows well how the mitral valve is a complex entity made up of the non-planar annulus, at the atrioventricular junction (yellow dotted line), the leaflets, the tendinous cords, and the papillary muscles. The aortic valve is also best analysed in terms of a complex, made up of the sinutubular junction, the leaflets, and the valvar sinuses. Note that the entrance to the aortic root (double-headed yellow arrow), usually considered by echocardiographers to represent the valvar "annulus", is a virtual structure in anatomic terms, made by joining together the proximal attachments of the valvar leaflets. Note also that the hinge of the leaflet (white arrow with red borders), by virtue of the semilunar nature of the hinges, can be attached proximal to the ventriculo-arterial junction (red arrow with white borders). This means that crescents of the myocardium are incorporated at the base of the sinuses, as also seen by the stars showing the basal attachments of two of the leaflets of the pulmonary valve. Note also the tissue plane between the free-standing infundibulum and the aortic root (white dotted line).

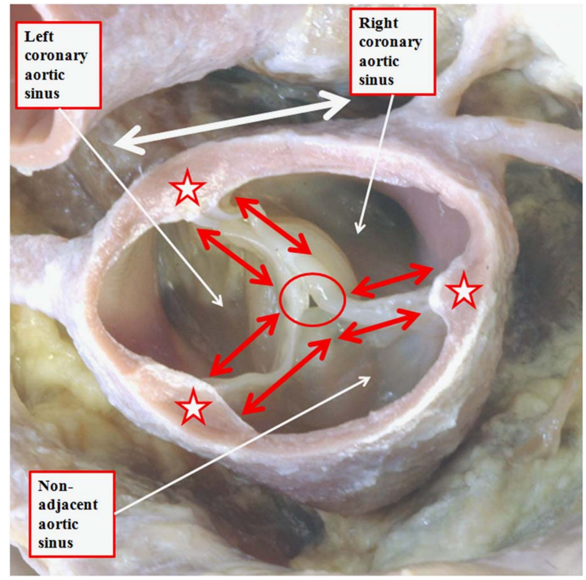

Figure 5.
The image shows the closed aortic valve viewed from the arterial aspect having transected the aortic trunk at the level of the sinutubular junction. The three semilunar leaflets fit snugly together along their zones of apposition (double-headed red arrows), closing at the centre of the valvar orifice (red circle). Note the thickenings at the peripheral attachments of the leaflets at the level of the sinutubular junction (white stars with red borders). These thickenings are conventionally described as the valvar commissures. Dilation at the level of the sinutubular junction results in valvar incompetence.

atrioventricular and ventriculo-arterial junctions. As we will show, they achieve their positions subsequent to cardiac looping, and separation of the right and left components. In the normal heart, although each of the valvar sets has right-sided and left-sided components, the valves themselves are not necessarily located to the right and left relative to each other. In the congenitally malformed heart, furthermore, the valves guarding the junctions can remain as common entities. In the normal heart, the morphologically tricuspid valve, guarding the right-sided atrioventricular junction, is positioned inferiorly, whereas the pulmonary valve, guarding the outlet to the right ventricle, is the most superior of the cardiac valves. It is also located leftwards relative to the aortic valve (Fig 2). The mitral valve is the most posterior of the four, whereas the aortic valve is the centrepiece of the cardiac short axis.

How do the cardiac valves fulfil their functions?

It is the role of the valves in guarding the atrioventricular, as opposed to the ventriculo-arterial, junctions that determine the major morphological differences between them, although there are additional subtle differences between the "right-sided" and "left-sided" entities within the subsets.

It was Perloff and Roberts[8] who argued that functional correlations were facilitated by analysing the atrioventricular valves in terms of a valvar complex (Fig 4). A cut taken along the long axis of the left ventricle in a sagittal manner, replicating the echocardiographic parasternal long-axis section, reveals well the components of the atrioventricular valvar complex, exemplified by the structure of the mitral valve. It possesses an annulus, marked by the atrioventricular junction, along with the leaflets, tendinous cords, and papillary muscles (Fig 4). The same components are then to be found in the tricuspid and common atrioventricular valves. The long-axis cut of the left ventricle also reveals how analysis of the ventriculo-arterial valves benefits from an approach in terms of a valvar complex. Thus, the valves guarding the ventriculo-arterial junctions

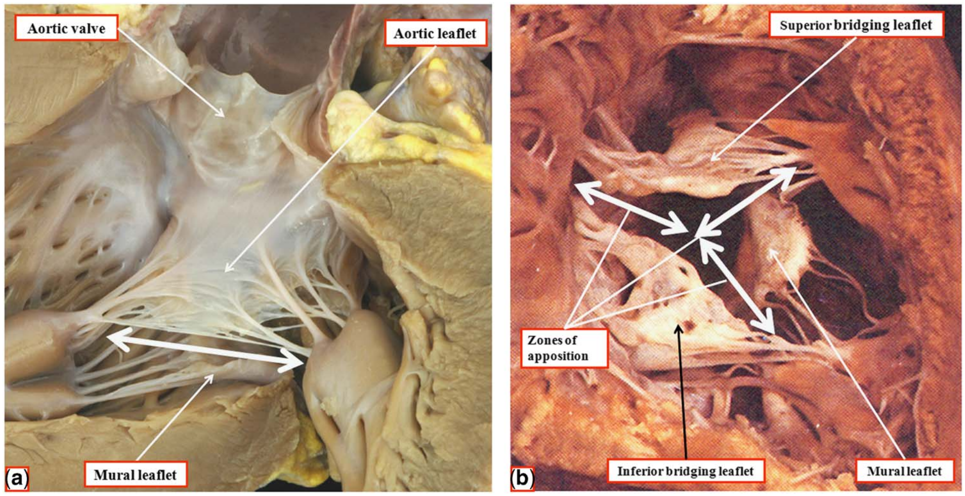

Figure 6.
*The images, viewed from the apex of the left ventricle, show the marked difference in terms of pattern of closure between the bifoliate mitral valve (**a**) and the trifoliate left half of a common atrioventricular valve (**b**). The double-headed arrows show the zones of apposition between the leaflets. Note the resemblance of the valve shown in panel **a** to the episcopal mitre.*

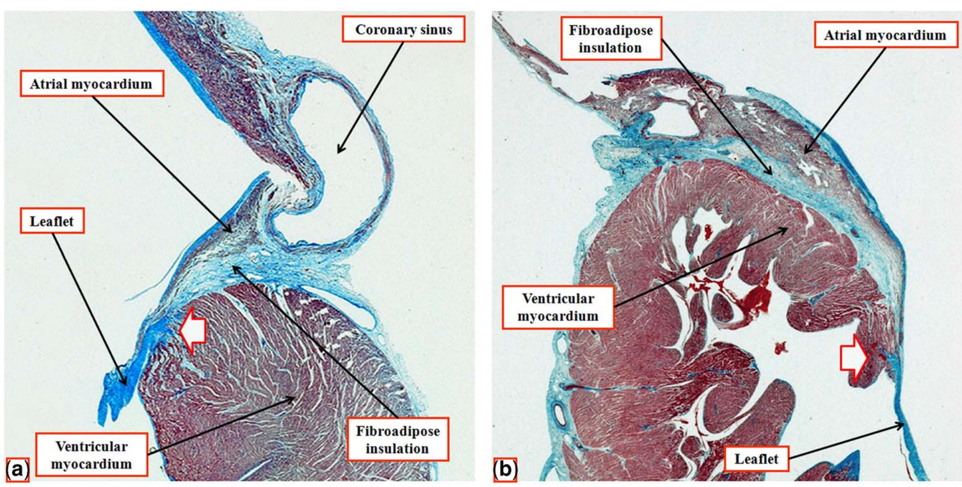

Figure 7.
*The images show histological sections, stained using the trichrome technique, across the left-sided (**a**) and right-sided (**b**) atrioventricular junctions. As can be seen, there is no "fibrous skeleton" as such supporting the leaflets in either junction. The leaflets are hinged from the surface of the crest of the ventricular wall (white arrows with red borders). The fibroadipose tissue of the atrioventricular grooves is responsible for producing the necessary insulation between the atrial and ventricular muscle masses. It is the valvar hinges that produce the "annulus".*

possess the leaflets supported by the valvar sinuses. They extend from the proximal attachment of their semilunar leaflets to the sinutubular junctions (Fig 4). As with the atrioventricular valves, these same components are to be found in the aortic, pulmonary, and common ventriculo-arterial valves.

The presence of the tension apparatus represents the major morphological difference between the atrioventricular and the ventriculo-arterial valves. This reflects the fact that, during ventricular systole, the atrioventricular valves must withstand the full force of ventricular contraction, as the blood is expelled into the intrapericardial arterial trunks. The tension apparatus, therefore, holds the leaflets together in their closed position. When viewed in closed position, the paired leaflets of the mitral valve close along a solitary zone of apposition (Fig 5a). In a similar manner, when viewed in the closed state, the three zones of apposition in the morphologically tricuspid valve are readily recognised. It is when the left ventricular component of a common atrioventricular valve is examined in the closed position that its own trifoliate arrangement is most obvious. Such examination shows clearly that the

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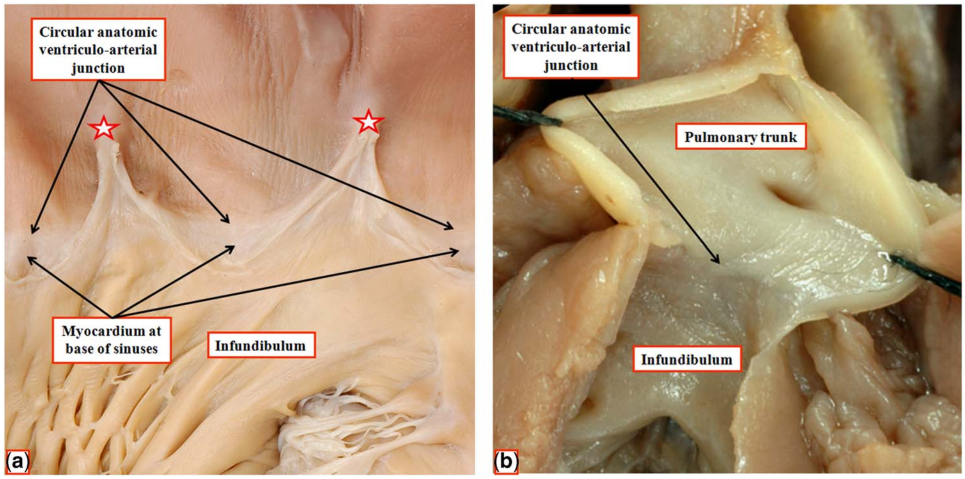

Figure 8.
*The images show the circular nature of the anatomic ventriculo-arterial junction. Panel **a** shows the normal heart having removed the leaflets of the pulmonary valve. The semilunar hinges of the leaflets cross the junction as they ascend to their distal attachments at the sinutubular junction (stars), thus incorporating crescents of the myocardium at the base of each of the valvar sinuses. The circular nature of the junction is best seen when the leaflets of the valve are congenitally absent, as shown in panel **b**.*

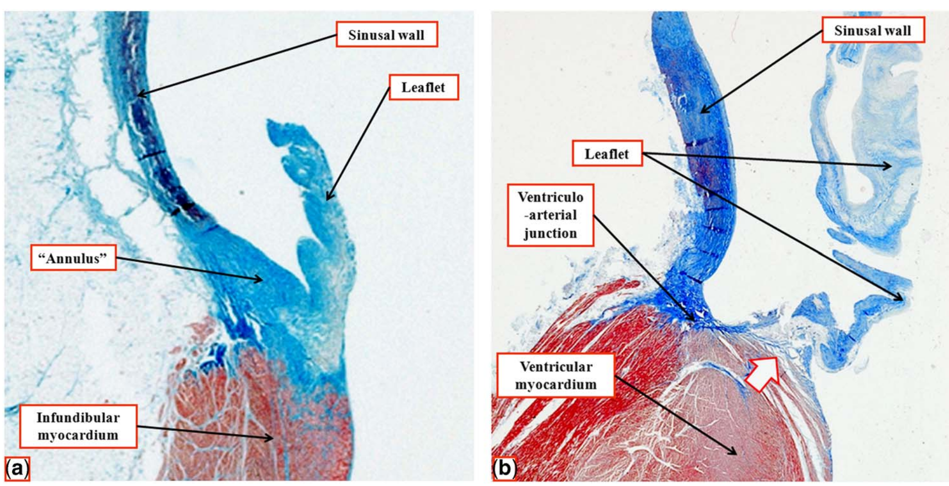

Figure 9.
*The images show sections across the ventriculo-arterial junctions in the pulmonary valve (**a**) and the aortic valve (**b**). At the point sectioned for the pulmonary valve, the hinge is coincident with the ventriclo-arterial junction. Part of the hinge supported the sinusal wall, separating it from the infundibular myocardium. In the aortic valve, however, the hinge takes origin from the crest of the ventricular wall, and is no longer coincident with the anatomic ventriculo-arterial junction.*

so-called "cleft" described previously by many clinicians is no more than the zone of apposition between the left ventricular components of the leaflets of the common atrioventricular valve that bridge the ventricular septum (Fig 5b). The building blocks that come together to produce the mitral valve can fail to fuse properly subsequent to separation of the atrioventricular canal into its right-sided and left-sided components. The cleft that is the consequence of such failure of fusion, however, is markedly different in anatomic terms when compared with the zone of apposition between the left ventricular components of the bridging leaflets seen in the setting of a common atrioventricular valve. The leafets of the ventriculo-arterial valves, unlike those of the atrioventricular valves, are wide open during ventricular systole. Their leaflets are forced together during ventricular diastole by the hydrostatic pressure of the column of blood they then support. It is the semilunar hinging of the valvar leaflets along the valvar sinuses, supported distally at the sinutubular junction, that permits the moving components to close snugly during diastole (Fig 6).

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How can we best describe the valvar components?

There is no concurrent consensus regarding the words to be used to describe the components of the valvar complexes. Our own practise is to use, as far as possible, the same words to describe comparable components of all the valves. We also try to use these words in their vernacular meaning. On this basis, we describe the moving components of all the valves as the leaflets. Some describe the leaflets for the moving parts of the atrioventricular valves, but use "cusp" for this purpose when accounting for the ventriculo-arterial valves. This makes little sense, as the atrioventricular valves themselves are distinguished as being tricuspid and mitral, and the old term for the mitral valve was bicuspid. When describing ventriculo-arterial valves, furthermore, it is frequent to see "cusp" used interchangeably to describe either leaflets or sinuses. Use of the word in either setting is, however, inappropriate, as a "cusp" is a point or elevation. It is properly used to describe the surfaces of the molar or premolar teeth. We prefer to avoid the word when describing the cardiac valves.

Further problems then emerge with the use of "commissure". When used by clinicians, the word typically describes the one end, or both ends, of a zone of apposition between the adjacent leaflets. Thus, clinicians typically describe the mitral valve as having two commissures, yet the valve possesses only a solitary zone of apposition (Fig 5a). When describing the ventriculo-arterial valves, it is the peripheral attachments of the adjacent leaflets at the sinutubular junction that are usually deemed to represent the commissures (Fig 6). It is the adequacy of the zones of apposition that is the major component determining valvar competence. We describe these junctions as such, recognising that clinicians will continue to describe their ends as the commissures. Assessment on the basis of the arrangement of the zones of apposition, nonetheless, makes it an easy matter to distinguish between the trifoliate left valve found in the setting of atrioventricular septal defect with common atrioventricular junction as opposed to the bifoliate morphologically mitral valve (Fig 5), even when the latter valve has a cleft in its aortic leaflet.

The greatest problem in describing the cardiac valves, nonetheless, resides in the use of "annulus".[9] If used in the vernacular sense, an annulus is a little ring, or a ring-like structure. Ring-like structures are found in the atrioventricular junctions, even if these areas are neither directly circular nor annular. By and large, nonethless, the annulus as defined clinically does correspond with the atrioventricular junctions. It is rare, however, to find continuous ring-like

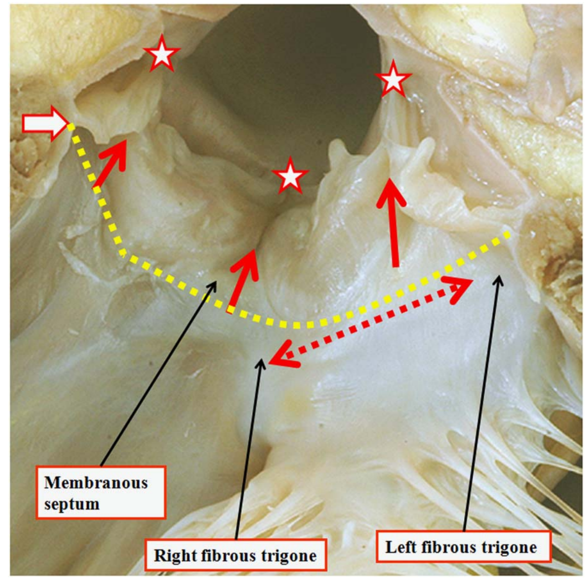

Figure 10.
The image shows the aortic root viewed from the front having opened the left ventricular outflow tract through the left coronary leaflet of the aortic valve. It shows the interleaflet fibrous triangles (red arrows) that extend to the sinutubular junction (white stars with red borders), separating the semilunar hinges of the valvar leaflets. Note that the hinge of the left coronary aortic leaflet is attached to the ventricular wall proximal to the anatomic ventriculo-arterial junction (white arrow with red borders). Also note the fibrous continuity between the leaflets of the aortic and mitral valves (red double headed dotted arrow), thickened at each end to form the fibrous trigones that anchor the aortic-mitral valvar unit in the roof of the left ventricle.

thickenings supporting the valvar hinges that are part of a "fibrous skeleton". Instead, even in the mitral valve, the mural leaflet tends to be hinged from the crest of the ventricular wall, with the fibroadipose tissue of the atrioventricular junction producing the insulation that is essential for normal atrioventricular conduction (Fig 7a). The role of the fibroadipose tissue in producing atrioventricular insulation is even more obvious in the tricuspid valvar orifice, where it is rare to find collagenous entities supporting the valvar hinges (Fig 7b).

The situation is the more complex at the ventriculo-arterial junctions. At these levels, an obvious ring can be found where the ventricular musculature supports the fibroelastic walls of the arterial valvar sinuses. This ring is most obvious in the right ventricular outflow tract, where all three semilunar leaflets are supported by infundibular musculature. The semilunar hinges of the valvar leaflets, however, cross the circular anatomic ventriculo-arterial junction. They extend distally as far as the sinutubular junction, and incorporate crescents of the ventricular myocardium at the base of each sinus of Valsalva. This arrangement is well seen in

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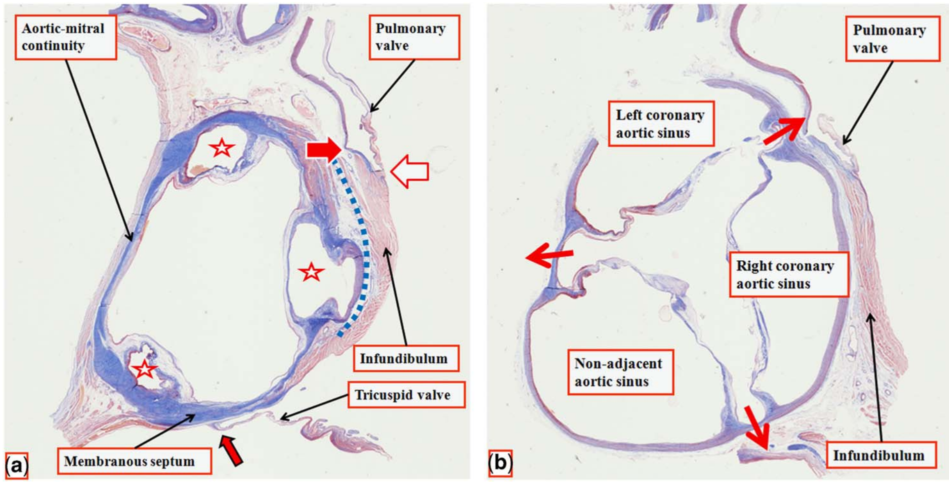

Figure 11.
*The images show cross-sections through the aortic root stained with the trichrome technique. Panel **a** is at the base of the root, and panel **b** is taken just below the sinutubular junction. The basal attachments of the leaflets (white stars with red borders) are seen in panel **a**. The section also shows the tissue plane between the aortic root and the free-standing subpulmonary infundibulum (blue dotted line), along with the hinge of the pulmonary valve leaflet (white arrow with red borders) attached proximal to the ventriculo-arterial junction (red arrow with white borders). The red arrow with black borders shows how the hinge of the septal leaflet of the tricuspid valve divides the membranous septum into its atrioventricular and interventricular components. Panel **b** shows how the interleaflet triangles (red arrows) separate the extensions of the left ventricular outflow tract from the extracardiac space, with the triangle between the two coronary aortic leaflets pointing into the space between the aortic root and the infundibulum. Note the thickenings of the hinges at this site as they approach the sinutubular junction. The other two triangles separate the outflow tract from the transverse pericardial sinus.*

Figure 8a, which shows the attachments of one of the semilunar leaflets of the pulmonary valve, along with its neighbouring leaflets, having removed the leaflets themselves. The circular nature of the anatomic ventriculo-arterial junction, however, is best seen when the valvar leaflets are congenitally absent (Fig 8b). It is the circular area where the sinuses take origin from the musculature of the outflow tract that is illustrated as the valvar "annulus" by molecular biologists.[10,11] A variation can be found in the structure of the ventricular wall at this position (Fig 9a), but the variability does not follow the semilunar hingelines of the leaflets (Fig 9b). It is the semilunar hinges, in contrast, that are identified as the "annulus" of the arterial valves by many surgeons.[12] Other surgeons then follow the lead of echocardiographers in identifying as the "annulus" the diameter of the entrance to the arterial roots (Fig 4).[2] The diameter of the entrance to the arterial roots, which is the measurement taken by clinicians to represent the valvar "annulus", however, has no anatomic counterpart.[9] It is no more than the geometric plane created by joining together the basal attachments of the valvar hinges. The more obvious anatomic ring in the arterial roots is the sinutubular junction. Often considered to be a "supravalvar" entity, in reality it is the area at which the valvar hinges come together at the periphery of the valvar orifice. The integrity of this ring is key to maintaining valvar competence (Fig 6).

The significance of the interleaflet triangles

As we have emphasised, the ventriculo-arterial valves close by virtue of the coming together of the semilunar leaflets at the centre of the valvar orifice (Fig 6). This mechanism of closure is possible only because of the semilunar nature of the hinges of the leaflets. This, in turn, means that there must be spaces on the ventricular aspects of the leaflets. These spaces, best seen in the aortic root, extend to the level of the sinutubular junction. They are walled by the interleaflet fibrous triangles (Fig 10).[13] Serial sections taken across the short axis of the aortic root reveal well the location of the interleaflet triangles, and also reveal the free-standing nature of the muscular sleeve that supports the leaflets of the pulmonary valve (Fig 11). The triangles that interpose between the non-adjacent aortic valvar leaflet and the two coronary aortic leaflets separate the distal extensions of the outflow tract from the transverse pericardial sinus. The triangle interposed between the two coronary aortic valvar leaflets, in contrast, separates the left ventricular outflow tract from the tissue plane that itself separates the free-standing pulmonary infundibulum from the aortic root. The triangle between the non-adjacent aortic leaflet and the right coronary aortic leaflet is continuous basally with the membranous part of the ventricular septum (Fig 11). This triangle is positioned directly cranial to the

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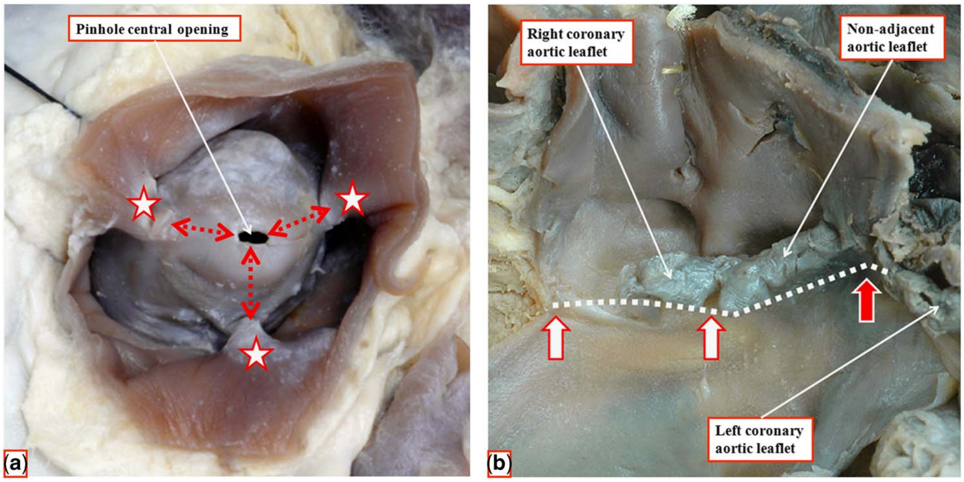

Figure 12.
*The images show critically stenotic arterial valves. Panel **a** shows the critically stenotic pulmonary valve. There is fusion of the zones of apposition normally present between the leaflets (red double-headed dotted arrows) and thickening of the attachments at the sinutubular junction (white stars with red borders). The hinge line, when viewed from the ventricular aspect, is relatively annular, a feature better seen in the critically stenotic aortic valve (**b** – white dotted line). The view of the aortic valve shows failure of excavation of two of the interleaflet triangles (white arrows with red borders), the persisting interleaflet triangle extending to the sinutubular junction along the area of fibrous continuity with the mitral valve (red arrow with white borders).*

point of penetration of the atrioventricular conduction axis.

The importance of the triangles in supporting the normal function of the arterial valves is shown when comparisons are made with the hinges of the leaflets in the setting of critical valvar stenosis. The pulmonary valve, when critically stenosed, assumes a dome-shaped configuration, with uniform fusion of the zones of apposition between the leaflets (Fig 12a). When viewed from the ventricular aspect, there is incomplete formation of the interleaflet triangles, the hinges of the valves being attached in a relatively annular manner. This annular arrangement of the leaflets is also well seen in the setting of the critically stenotic aortic valve. Usually described as being unicommissural and unifoliate, the essence of the lesion is the failure of excavation of the interleaflet triangles that usually interpose between the two coronary aortic leaflets, and between the right coronary leaflet and the non-adjacent aortic leaflet. The only persisting zone of apposition extends from the centre of the valvar orifice towards the area of aortic-mitral valvar continuity, producing the keyhole opening so characteristic of this lesion (Fig 12b). It is a paradox, therefore, that true annular attachment of the valvar leaflets should produce a critically stenotic valvar orifice in both pulmonary and aortic positions. It is also the case that, when formed in rudimentary manner, the valvar leaflets in the so-called absence of the pulmonary valve (Fig 8b) are attached in a truly annular manner.

The development of the cardiac valves

When reviewing valvar development, we will concentrate on the observed anatomical changes. In our opinion, these changes need to be taken into account if we are to take full value of the amazing recent discoveries made by molecular biologists, and to understand their relevance to valvar disease.[10] The valvar leaflets are formed by a process of endothelial-to-mesenchymal transformation of the cushions found in the developing atrioventricular canal and outflow tract (Fig 13).[14] The cells within the leaflets are largely derived from the endothelial layer of the original heart tube, although additional cells from the epithelial layer contribute to the mural leaflets of the atrioventricular valves,[15] whereas the cells derived from the neural crest are incorporated within some, but not all, of the leaflets of the ventriculo-arterial valves.[16] When first observed, the cushions themselves are extensive structures, separated by the inner heart curvature. The atrioventricular cushions face each other within the atrioventricular canal, whereas the outflow cushions spiral as they extend through the outflow tract. The latter cushions are positioned septally and parietally in the proximal part of the outflow tract (Fig 13), but have rotated to achieve cranial and caudal locations at the margins of the pericardial cavity.

Development of the atrioventricular valves

At the early stages of development, the atrioventricular cushions are surrounded by a discrete component

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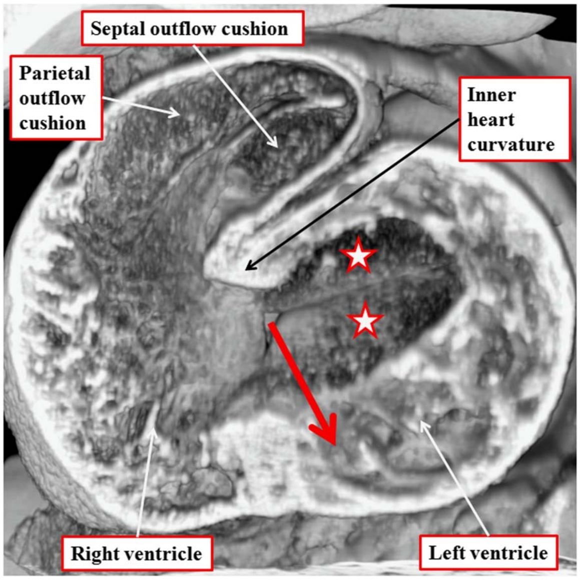

Figure 13.
The image shows a frontal section through the developing ventricular loop from an episcopic data set prepared of an embryonic mouse at day 10.5. The section is viewed from the apical aspect of the developing ventricles. It shows the atrioventricular endocardial cushions (white stars with red borders) lying edge-to-edge in the atrioventricular canal, and the proximal ends of the outflow cushions, which are spiralling through the outflow tract. The two sets of cushions, at this stage, are separated by the inner curvature of the ventricular loop. Note that the right atrioventricular orifice is opening, at this stage, to the apical component of the developing left ventricle (red arrow).

of atrioventricular canal musculature (Fig 14a). As the atrioventricular canal expands so that the right atrioventricular orifice opens directly to the cavity of the developing right ventricle, the atrioventricular canal musculature becomes sequestrated on the atrial aspect of the developing plane of atrioventricular insulation, becoming the vestibules of the newly formed right and left atriums (Fig 14b). At the same time, growth of the vestibular spine through the right margin of the dorsal mesocardial connection cements the primary atrial septum to the atrial surfaces of the fused central atrioventricular cushions, thus separating the right and left atrioventricular junctions (Fig 14b). Once the junctions have been separated, the right orifice is able to expand dorsally (Fig 15a). The developing left atrioventricular orifice at this stage, however, is guarded by cushions with a distinctly trifoliate configuration (Fig 15a). It is only subsequent to the transfer of the aortic root to the left ventricle, which occurs during the 13th embryonic day in the mouse, that the mitral valve achieves its bifoliate arrangement (Fig 15b). Having achieved the bifoliate arrangement subsequent to the transfer of the aortic root to the left ventricle, the line of fusion of the cushions that produce the aortic leaflet of the mitral valve points into the newly transferred outflow tract. It is, therefore, the formation of separate atrioventricular junctions, combined with the transfer of the outflow tract, that changes the trifoliate valve as seen in the hearts with common atrioventricular junction (Fig 5b) to the

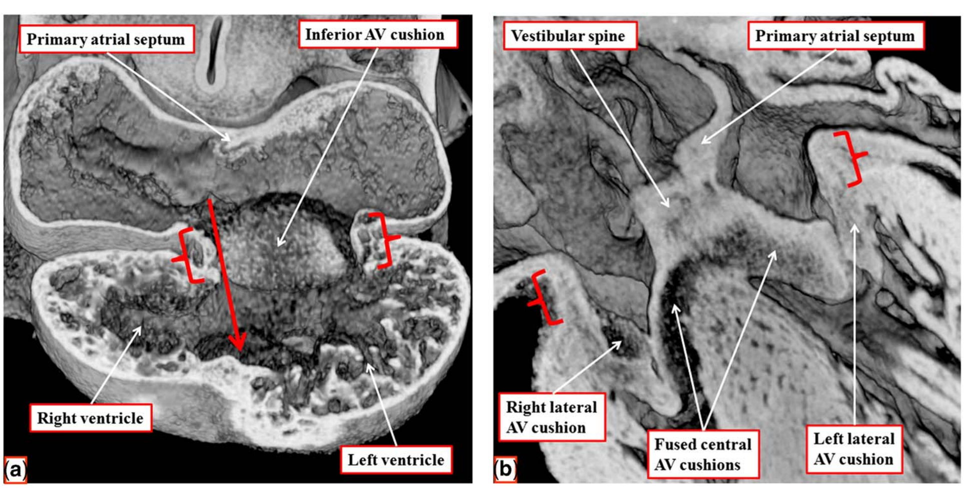

Figure 14.
*The images, in frontal section, are taken from episcopic data sets prepared from embryonic (E) mice at day 10.5 (**a**), and 12.5 (**b**). They show how the atrioventricular canal musculature (red brackets) becomes sequestrated to form the vestibules of the atrial chambers subsequent to rightward expansion of the atrioventricular canal. At E10.5, the right atrioventricular orifice opens to the developing left ventricle (red arrow in panel **a**). By E12.5, lateral cushions have developed on both sides of the expanded canal, which has been separated centrally by the fusion of the central atrioventricular (AV) cushions to the crest of the muscular ventricular septum. The initial canal musculature (red brackets) is now forming the vestibules of the atrial chambers, and will eventually be separated from the ventricular myocardium by formation of the plane of atrioventricular insulation. The vestibular spine has grown from the dorsal pharyngeal mesenchyme to cement the primary atrial septum to the atrial aspect of the fused cushions, thus separating the right and left atrioventricular junctions.*

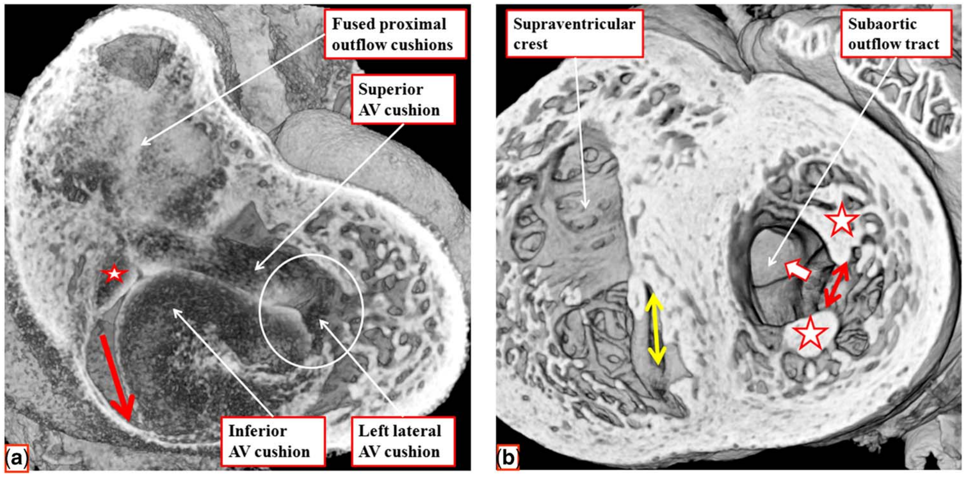

Figure 15.
*The images, taken in short axis across the developing ventricular mass from episcopic data sets prepared from embryonic (E) mice at day 12.5 (**a**) and 14.5 (**b**), show how the mitral valve achieves its bifoliate configuration (red double-headed arrow in panel **b**) only subsequent to the transfer of the aortic outflow tract to the left ventricle. At E12.5, the cushions surrounding the left atrioventricular orifice have a trifoliate configuration (white circle in **a**). The separation of the atrioventricular junctions, however, has permitted the right atrioventricular orifice to extend dorsally (red arrow in panel **a**). The developing tricuspid valve also has a bifoliate arrangement at E14.5 (yellow double-headed red arrow in panel **b**). It is later in development that the septal leaflet of the valve delaminates from the ventricular septum, and further expansion of the inferior margin of the right atrioventricular junction permits delamination of the inferior leaflet. Note that the trabecular layer of the ventricular mass has compacted to form the papillary muscles of the mitral valve (red stars in panel **b**). Also note that the zone of fusion of the central cushions now points into the subaortic outflow tract (white arrow with red borders). These sections should be compared with the images of the postnatal heart shown in Figure 5.*

postnatal arrangement found in the mitral valve (Fig 5a). These changes also show how the zone of apposition found in the left ventricular component of the common valve is comparable in developmental terms to the cleft found in the otherwise normal mitral valve, but is fundamentally different with regard to its anatomical arrangement.[17] The changes occurring over the 12th and 13th days of embryonic development in the mouse also suggest that the trabecular layer of the developing ventricular walls compacts to form the major papillary muscles of the valves, although this possibility requires further study. Ongoing maturation, nonetheless, then converts the junctions between the cushions and the muscular columns into the tendinous cords. Additional delamination from the ventricular walls is needed to form the septal and inferior leaflets of the tricuspid valve.[17]

Development of the ventriculo-arterial valves

The ventriculo-arterial valves are developed in the middle component of the outflow tract. This fact makes it difficult to understand the development when the outflow tract is described in terms of only two components, as was suggested by Kramer.[18] This is the more so, as Kramer introduced the terms "conus" and "truncus". It follows that the ventriculo-arterial valves develop within the middle of the conotruncus. It is surprising, therefore, that abnormalities of these structures are not considered to represent "conotruncal" malformations. Kramer's observations, nonetheless, were crucial in demonstrating the appearance within the central part of the outflow tract of the intercalated cushions. It is the appearance of these additional cushions that makes it possible to distinguish the tripartite arrangement on the basis of the internal morphology (Fig 16). Shortly after the intercalated cushions are formed in the intermediate part of the outflow tract, the distal part is divided into the intrapericardial components of the aorta and the pulmonary trunk by fusion of a ventral growth into the cavity of the protrusion from the dorsal wall of the aortic sac with the distal ends of the outflow cushions. The core of this protrusion, along with the newly formed parietal walls of the intrapericardial arterial trunks, are formed by migration of the non-myocardial cells from the second heart field. The protrusion is covered with a layer of cells derived from the neural crest, with the neural crest cells also filling the septal and parietal cushions that spiral through the outflow tract.[19] It is the fusion of the neural crest populations that divides the tract into its aortic and pulmonary components.[20] The fused cushions, however, do not produce an "aortopulmonary septum", as is still claimed by many who describe development of the arterial valves.[10] Fusion of the distal cushions separates the developing aortic and

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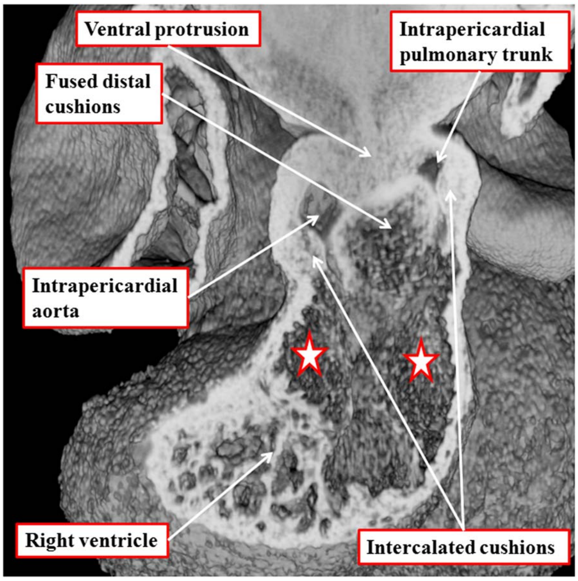

Figure 16.
The image shows a long-axis section, prepared from an episcopic data set, along the developing outflow tract of an embryonic mouse at day 11.5. The appearance of the intercalated cushions make it possible to recognise anatomically the middle part of the outflow tract. The distal part has now become transformed into the intrapericardial arterial trunks, which are separated by the ventral protrusion that has grown into the heart from the dorsal wall of the aortic sac. The proximal cushions (stars) remain unfused in the proximal part of the outflow tract, which is supported by the right ventricle.

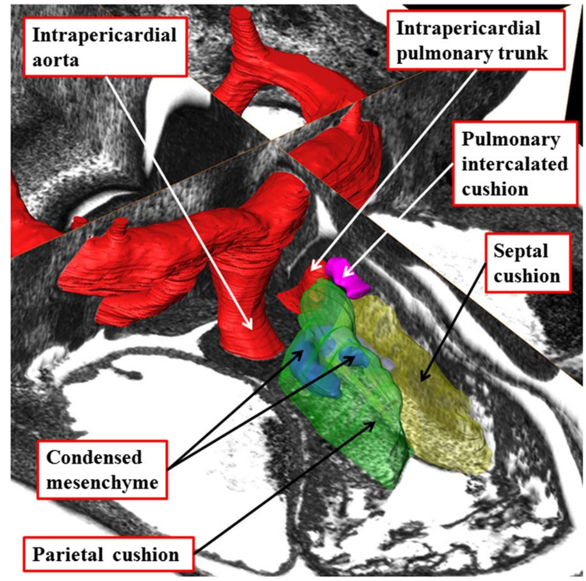

Figure 17.
The image is a reconstruction from an episcopic data set prepared from an embryonic mouse at day 11.5. The location of the major outflow cushions, and the pulmonary intercalated cushion, have been superimposed on the orthogonal sections from the data set. The columns of the condensed mesenchyme, which are often considered to represent the "aortopulmonary septal concept", are shown in blue. They are located within the outflow cushions, and do not interpose between the intrapericardial components of the aorta and the pulmonary trunk. The reconstruction was made by Dr Simon Bamforth, from the Institute of Genetic Medicine, Newcastle University, and our representation of the figure is made with his kind permission.

pulmonary roots, whereas the proximal cushions fuse, and subsequently muscularise, to form the subpulmonary infundibulum. The central parts of the fused cushions, nonetheless, attenuate with ongoing development. There are no septal components found between the infundibulum and the aortic root in the postnatal heart, nor between the two arterial roots themselves.[21] The columns of the condensed mesenchyme often identified as forming the "aortopulmonary septal complex",[10] furthermore, do not appear until after the protrusion from the dorsal wall of the aortic sac has fused with the distal ends of the outflow cushions, thus separating the developing intrapericardial arterial trunks (Fig 17).

It is the fusion of the distal cushions, combined with the appearance of the intercalated cushions, that sets the scene for the development of the arterial valves within the middle part of the developing outflow tract. When they fuse, the central cushions come together only in the central parts of their facing surfaces. The parietal parts of the adjacent surfaces remain unfused. This, together with their relationships with the intercalated cushions, produces the format for subsequent development of the arterial valvar leaflets (Fig 18a). Excessive fusion of the margins of the cushions provides an excellent explanation for the formation of ventriculo-arterial valves with two as opposed to three leaflets.[22] It is also possible, however, to account for the arterial valves with two leaflets on the basis of hypoplasia or the failure of development of an intercalated cushion. The fact that one of the intercalated cushions is relatively devoid of cells derived from the neural crest provides added strength to this notion.[16] Should the cushions not fuse together, the stage is then set for retention of a common ventriculo-arterial junction, guarded by a potentially quadrifoliate common arterial valve (Fig 18b). Hypoplasia of one of the intercalated cushions in this setting that again provides the potential for the formation of the common arterial valves with three, as opposed to four, leaflets (Fig 18c). The evidence emerging from genetically modifed mice, such as the ones in which the gene for Tbx1 has been knocked out (Fig 18), provides strong evidence to support the concept advanced by Van Mierop et al.[23] to account for the formation of a common arterial trunk, namely, that there has been failure of the fusion of the major cushions formed within the developing outflow tract. The findings

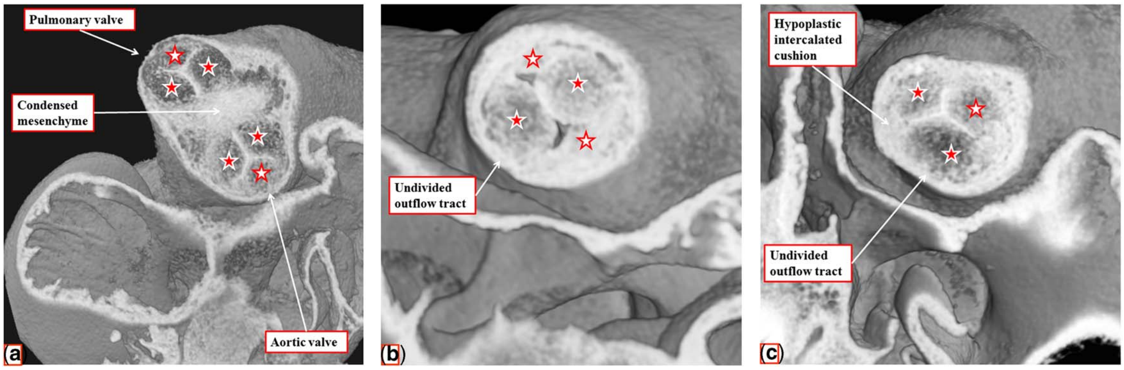

Figure 18.
*The images show how the arrangement of the outflow cushions sets the scene for formation of the leaflets of separate aortic and pulmonary (**a**) as opposed to common ventriculo-arterial valves (**b** and **c**). All images are from embryonic mice killed at day 12.5, but panel **a** shows a wild-type mouse, whereas panels **b** and **c** are from Tbx1 null mice. The major cushions (red stars with white borders) have failed to fuse in the abnormal mice, but have fused along their central parts in the wild-type mouse. Hypoplasia of one of the intercalated cushions (**c**) provides the template for formation of a common valve with three leaflets.*

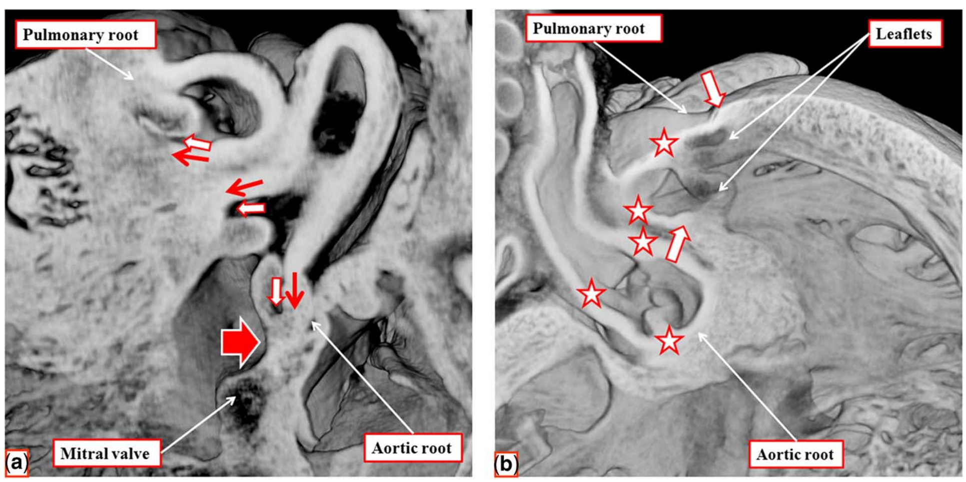

Figure 19.
*The images show the stages in excavation of the leaflets, and formation of the sinuses, of the ventriculo-arterial valves. Panel **a** is from an embryonic mouse killed at day 14.5, whereas panel **b** is from a mouse killed at day 16.5. Panel **a** is viewed from the left, whereas panel **b** is viewed from the right. At E14.5, the excavation of the distal margins of the cushions (white arrows with red borders) has begun, with the parietal margins of the areas of excavation filled by ongoing migration of the tissues from the second heart field to form the walls of the valvar sinuses (red arrows). Note that, at this stage, the myocardium of the inner heart curve separates the developing leaflets of the aortic and mitral valves (red arrow with white borders). By E16.5 (**b**), the excavation of the leaflets and ingrowth of the sinuses has produced the sinutubular junction, with the adjacent margins of the excavated leaflets attached at these points (white stars with red borders). The myocardial turret surrounding the developing leaflets has now regressed (white arrows with red borders) so that only the basal hinges of the leaflets arise from the muscular infundibulum of the right ventricle. Note the tissue plane that now separates the infundibulum from the aortic root.*

provide no support for the alternative notion that the common valve is essentially an aortic valve, the pulmonary valve and conus having failed to form.[24] There is evidence, however, to show that hypoplasia of the pulmonary intercalated cushion, and hypoplastic formation of the pulmonary component of the undivided outflow tract, can account for the formation of common ventriculo-arterial valves with three, as opposed to four, leaflets.[25]

It is, therefore, the fusion of the distal outflow tract cushions, along with the appearance of the intercalated cushions, that produces the template for formation of the leaflets of the ventriculo-arterial valves. The leaflets themselves develop by a process of excavation of the distal margins of the cushions (Fig 19). As the cushions excavate, there is concomitant ongoing ingrowth of non-myocardial tissues from the heart-forming areas to produce the valvar sinuses.

The process of excavation itself initially occurs with the cushions enclosed by the myocardial wall of the intermediate part of the outflow tract. The distal margin of this myocardial wall then involutes in a proximal direction as the valvar sinuses are formed. At the same time, muscularisation of the fused proximal cushions produces the subpulmonary infundibulum, with formation of a tissue plane to separate the developing infundibulum from the aortic root (Fig 19b). Muscular tissue is, therefore, added to the developing pulmonary root, as the distal myocardial boundary of the outflow tract is itself regressing. As the aortic root is confined within the left ventricle, the muscular tissue of the inner heart curve still separates the developing leaflets of the aortic and mitral valves. Additional involution of the myocardial tissues is, therefore, required before the leaflets of the mitral and aortic valves achieve the fibrous continuity, which is a feature of the postnatal heart. As yet, we do not know the mechanisms underscoring formation of the fibrous interleaflet triangles that separate the valvar sinuses.

Comment

The advances made in recent decades in understanding the molecular biology of the developing cardiac valves and the relevance of the observed changes to valvar disease have been truly spectacular.[10] The observations of the molecular biologists, however, have not kept pace with the understanding of valvar anatomy as hopefully demonstrated by our review. For example, the molecular biologists do not seem to recognise the semilunar nature of the hinges of the ventriculo-arterial valves, as they illustrate an "annulus" supporting the hinge of the leaflet at the anatomic ventriculo-arterial junction.[10,11] The anatomic junction itself is unequivocally annular, but this is not the locus defined to represent the "annulus" by either surgeons[4,12] or echocardiographers.[9] Resolution of these ongoing differences in nomenclature is just as important for those investigating the development of the cardiac valves as it is for those diagnosing valvar diseases, or those undertaking surgical or interventional repair or repacement.[4]

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