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Review

Living morphogenesis of the ventricles and congenital pathology of their component parts

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Abstract Living morphogenetic studies show that each definitive ventricle is constructed from different primitive cardiac segments, and each has its specific anatomical features. These ventricular segments are the atrioventricular junction; the primitive inlet segment, part of the primary heart tube, which initially provides the inlets of each ventricle; the primitive outlet segment, which gives rise to both ventricular outlets; and the apical trabeculated regions of the right and left ventricles which grow from the primary heart tube, respectively. In this review, we describe regional pathology based on the relationship of these primitive ventricular components. We propose that the abnormal morphogenesis of one of these segments gives origin to regional ventricular pathology. For example, abnormal embryogenesis of the atrioventricular canal produces malformations of the atrioventricular junctions, such as double inlet ventricle, absence of one atrioventricular connection, and straddling and overriding atrioventricular valves. Similarly, abnormal morphogenesis of the primitive outlet segment gives rise to malformations of the subarterial region of each ventricle, along with the valves guarding these vessels. The principal anatomical features of these malformations of the ventricular inlets and outlets are described, and their possible morphogenesis is discussed. Due to the fact that the apical trabeculated region of each ventricle arises from a separate primitive segment, each ventricle can be identified according to the pattern of its apical trabeculations. This feature is crucial in the elucidation of complex congenital pathology, such as discordant atrioventricular connections.

Keywords: Regional congenital ventricular pathology; primitive cardiac segments; cardiac defects; congenital cardiac malformation; discordant atrioventricular connections

BASED ON TRADITIONAL STUDIES OF THE developing heart in man[1] and chick,[2–4] it has become conventional wisdom that the heart is derived from different segments, designated as primitive cardiac cavities, and that each of these cavities gave origin to definitive cardiac chambers. Two of these primitive cardiac cavities were described as the "bulbus cordis" and the "primitive ventricle", respectively. It was presumed that they give origin to the definitive right and left ventricles.[1–4] Consequently, it was concluded that the definitive ventricles were discrete units, not only anatomically, but also embryologically. The biological processes of embryological development, however, are essentially dynamic, sequential, progressive and uninterrupted. The only appropriate techniques for examination of these complex processes, therefore, are "in vivo" labeling experiments such as described by de la Cruz and

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Markwald.[5] Using such experiments, we have shown, using the living chick embryonic heart, that the straight tube heart is formed initially by only two primitive cardiac segments. From one of these segments grows the apical trabeculated region of the right ventricle, while the other gives rise to the apical trabeculated region of the left ventricle.[5–6] We have also shown that, at the so-called "C loop stage", two new primitive segments appear. These are the primitive atrioventricular canal,[5,7,8] and the primitive outlet segment.[5,9] The primitive myocardium of the atrioventricular canal, subsequent to development of the fibrous atrioventricular junction, becomes sequestrated within the atrial vestibules.[10] The outlet segment, with ongoing development, gives rise to the definitive subarterial outlets of both ventricles. These facts show that, while the definitive ventricles are discrete anatomical units, they are derived from multiple embryological segments.

Arguing from the premise, therefore, that the normal ventricles are made up from several primitive cardiac segments, each with its specific anatomical expression,[5] we propose that the abnormal embryological development of any of these segments will become manifest anatomically by regional pathology. For example, the anatomical manifestations of congenital pathology of the primitive atrioventricular canal will be abnormal connections between atriums and the ventricles, while the anatomical manifestations of abnormalities of the primitive outlet will be congenital malformations of the subarterial ventricular components.

We believe that the study of regional ventricular pathology enriches and extends the concept of sequential segmental analysis.[11–13] This has already proved its clinical value in the anatomical description of congenital cardiac malformations. It will be equally valuable in examination of those produced experimentally, for example, as seen in transgenic mice. Many of these exhibit complex cardiopathies that prove to be incompatible with postnatal life. In this review, therefore, we establish the link between the primitive embryological segments and regional ventricular pathology.

Primitive cardiac cavities and primitive cardiac segments

In 1927, Davis[1] described the embryological development of the human heart, arguing that, initially, there was a straight tube made up of different segments, which he called primitive cardiac cavities. In his opinion, each of these segments gave rise to a definitive cardiac chamber. He named the primitive cardiac cavities according to their cephalo-caudal order. Thus, he accounted for the aortic bulb, the

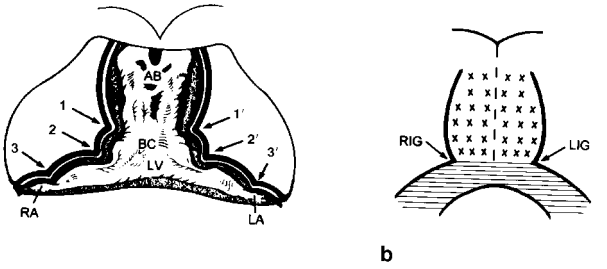

Figure 1.
Diagrams depicting the embryological constitution of the straight tube heart. (a) Postmortem study of the straight tube heart showing the primitive cardiac cavities. (b) Ventral aspect of the straight tube heart using "in vivo" labeling techniques; it shows the two primitive cardiac segments which constitute it. AB, aortic bulb; BC, bulbus cordis; LV, left ventricle; RA, right atrium; LA, left atrium; RIG, right interventricular groove; LIG, left interventricular groove; 1,1′, right and left interbulbar sulcus; 2,2′, right and left bulboventricular sulcus (interventricular groove); 3,3′, right and left atrioventricular sulcus. Crossed area (×'s) represents the primordium of the apical trabeculated region of the anatomic right ventricle. Striped area denotes the primordium of the apical trabeculated region of the anatomic left ventricle.

bulbus cordis, the left ventricle, and the primitive right and left atriums. He thought these gave origin to the great arteries, the right ventricle, the left ventricle and the right and left atriums, respectively (Fig. 1a). By means of "in vivo" labeling experiments in the chick embryo heart, however, we[5] have shown that none of the primitive cardiac cavities identified by Davis[1] becomes a specific chamber in the mature heart. Rather, each definitive cardiac chamber is formed by the integration of multiple primitive cardiac segments.[5] Initially, in fact, the straight heart tube is made up of only two segments (Figs 1b and 2). The cephalic of these, subsequent to looping and ballooning[14] gives origin to the apical trabeculated region of the morphologically right ventricle, while from the caudal one will grow the apical trabeculated region of the morphologically left ventricle[5,6] (Fig. 2). Concomitant with creation of the "C loop" at stage 12, three new segments appear. One is cephalic, called the primitive outlet, which will give origin later in development to the outlets of both ventricles. Initially, however, the primitive outlet is connected exclusively to the segment from which will arise the future apical trabeculated region of the morphologically right ventricle[5,9] (Fig. 2b–d). The other two segments are caudal. One of them is the primitive atrioventricular canal (Fig. 2b–d). When first formed, it is connected cephalically only with the segment which gives rise to the future apical trabeculated region of the morphologically left ventricle. Caudally, it is in communication with the other

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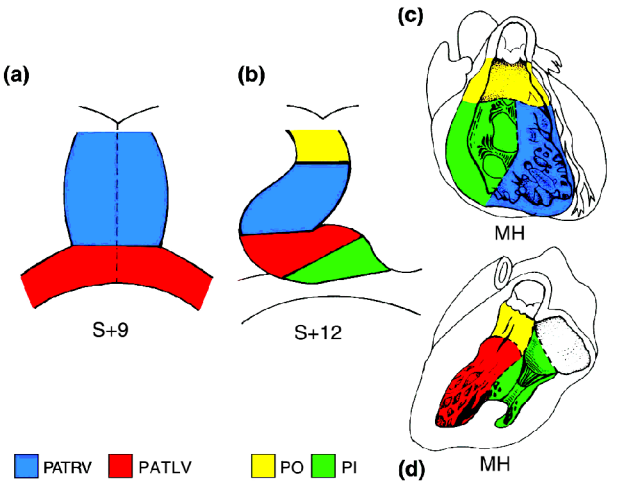

Figure 2.
Diagrammatic representation of the primitive cardiac segments, the developmental stages at which they appear and the anatomical expression of each one of them in the mature heart. (a) Straight tube heart constituted exclusively by two segments, namely which becomes the apical trabeculated region of the morphologically right ventricle (cephalic) and that of the morphologically left ventricle (caudal). (b) C shaped loop heart showing two new ventricular segments, primitive outlet and the primitive inlet. The first one gives origin to the outlet of both ventricles and the second one to their inlet. (c), (d) Internal aspect of the morphologically right and left ventricles respectively showing the anatomical expression of each of the primitive cardiac segments which form them. The broken lines indicate the limits of the three anatomical regions in which the ventricles are divided: the inlet, the outlet and the apical trabeculated region. PATRV, primitive apical trabeculated region of the anatomic right ventricle; PATLV primitive apical trabeculated region of the anatomic left ventricle; PO, primitive outlet; PI, primitive inlet.

new segment, the primitive atrial segment, which is the progenitor of the bodies of both the right and left atriums[5] (Fig. 2b–d). To summarize, our "in vivo" labeling experiments indicate that the heart is formed by five segments which appear in sequence during the formation of the straight tubular heart and its process of looping. Each segment gives origin to a specific anatomical region of a definitive cardiac chamber, but not to the entire cavity (Fig. 2). When considered in the light of the ventricles, this work supports the concept of Goor and Lillehei,[15] who divided the definitive ventricles into three anatomic regions. The fact that each ventricle is constituted by different embryological segments, each of which has its specific anatomical expression, also correlates with the known congenital "regional" pathologies of the ventricles, with pathologies recognized for the inlet, for the outlets, and also for the ventricular apical trabeculated regions. Our results show that abnormalities in the atrioventricular connections reflect abnormal formation of the primitive atrioventricular canal, such as double inlet ventricle, absence of one atrioventricular connection, discordant atrioventricular connections, or common atrioventricular junction.

The ventricular apical trabeculated regions and concordant and discordant atrioventricular connections

The apical trabeculated regions of the morphologically right ventricle and left ventricles are each derived from a separate primitive cardiac segment[5] (Fig. 2). On the other hand, the junction of each ventricle with its atrium is derived from a single primitive cardiac segment, namely the primitive atrioventricular canal. The atrioventricular valves, however, are delaminated from the myocardium of the inlet component of the ventricular loop (Fig. 2b–d).[16] Similar processes occur with the outlet of each ventricle, which originate from a single embryonic cardiac segment, the primitive outlet[17] (Fig. 2b–d). These embryological facts dictate that, in congenital cardiac malformations, we must identify each ventricle according to its specific component, namely the apical trabeculated regions.[8] The morphologically right ventricle is characterized by its coarse apical trabeculation, and by the characteristic septomarginal trabeculation. The morphologically left ventricle, in contrast, has fine apical trabeculations and lacks any septomarginal trabeculation.[18] An example of how this information can be used is seen in atrioventricular septal defect with common atrioventricular junction. In this entity, the morphologically right and left ventricles are readily identified according to their apical characteristics despite the fact that both are joined to the atrium through a common junction. The same is true of double outlet right ventricle, since the morphologically left ventricle is readily identified even though it does not have any outlet, other than the interventricular communication.

These specific features of the apical trabeculated regions of the morphologically right and left ventricles also permit us to determine the identity of these ventricles even in situations that may be abnormal, such as hearts with discordant atrioventricular connections, and the *inversus* mouse mutation.[19] These topics have relevance both to spontaneous congenital cardiopathies, and to those produced experimentally. Because of this, we will give a brief description of these cardiac pathologies.

Concordant and discordant atrioventricular connections are always defined by making reference, first, to the type of atrial arrangement, and second on the basis of the distinctive anatomical features of each ventricle, in other words, their apical trabeculated regions. One of the most important contributions to

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the concept of segmental sequential analysis is the description of the different types of atrial arrangement, namely usual arrangement (situs solitus), its mirror-imaged variant (situs inversus) and the two isomeric arrangements, the latter two being found in the setting of so-called visceral heterotaxy.[13,20] Any type of arrangement is defined with two parameters, first the recognition of each atrium on the basis of the anatomy of its appendage, and second whether the appendages are right- or left-sided. The characteristic features of the morphologically right appendage are the fan-shaped patterns of its pectinate muscles which extend throughout the atrioventricular junction and the terminal crest, whereas the major characteristic of the left atrial appendage is its tubular structure and narrow junction with the smooth-walled venous component. Usual atrial arrangement (situs solitus), by far the commonest pattern, is characterized by the presence of the morphologically right appendage on the right, and the morphologically left appendage on the left (Fig. 3a). So-called "situs inversus", which is less frequent, is the mirror-image of the usual arrangement. Specifically, the morphologically right appendage is situated on the left, and the morphologically left appendage is on the right (Fig. 4a). In visceral heterotaxy, from the stance of the heart, the atrial appendages are isomorphic[20] (usually known as isomerism). This type of arrangement includes two varieties, namely right isomorphism, in which both appendages exhibit the features pertaining to the morphologically right pattern, and left isomorphism, in which both appendage exhibit the features of the left type.[13,20–22]

Concordant atrioventricular connections are found when the atrium with a morphologically right appendage is connected with the morphologically right ventricle, and the atrium with a morphologically left appendage is connected with the morphologically left ventricle (Figs 3a, c′ and 4a, c′). Discordant atrioventricular connections exist when the atrium with the right appendage is connected with the morphologically left ventricle, and the atrium with the left appendage is connected with the morphologically right ventricle (Figs 3a, d′ and 4a, d′). There are two types of concordant atrioventricular connections, being found with either usual (situs solitus) or mirror-imaged (situs inversus) atrial arrangement. In the first case, the morphologically right atrium is situated on the right side (situs solitus), and connects with the morphologically right ventricle, also located on the right side (Fig. 3a, c′). In the second case, the morphologically right atrium is situated on the left (situs inversus) and connects with the left-sided morphologically right ventricle (Fig. 4a, c′). There are also two types of discordant atrioventricular connections, again with usually

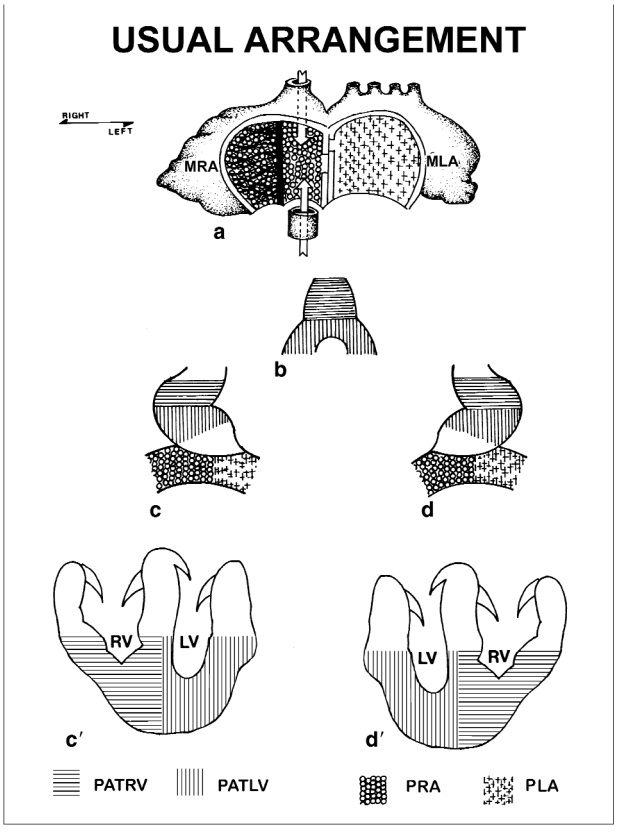

Figure 3.
Graphic representation of the essential anatomic features for the diagnosis of concordant and discordant atrioventricular connections in usual atrial arrangement (situs solitus) and their probable embryogenesis. (a) Anatomical features of usual atrial arrangement, with the morphologically right atrium situated on the right side. (b) Straight tube heart constituted by the primitive cardiac segments of the apical trabeculated region of the anatomic right ventricle and the apical trabeculated region of the anatomic left ventricle. (c) C shape loop convex to the right, the primitive cardiac segment of the apical trabeculated region of the right ventricle situated on the right. (d) C shape loop convex to the left, the primitive cardiac segment of the apical trabeculated region of the right ventricle located on the left. (c′) Apical trabeculated region of the right ventricle situated to the right. (d′) Apical trabeculated region of the right ventricle situated to the left. PATRV, primitive apical trabeculated region of the right ventricle; PATLV, primitive apical trabeculated region of the left ventricle; MRA, morphologically right atrium; MLA, morphologically left atrium; PRA, primitive right atrium; PLA, primitive left atrium; RV, morphologically right ventricle; LV, morphologically left ventricle.

arranged (situs solitus) and mirror-imaged atriums (situs inversus). In the first case, the morphologically right atrium is situated on the right side (situs solitus), and connects with the morphologically left ventricle situated on the right (Fig. 3a, d′). In the second case, the morphologically right atrium is situated on the left (situs inversus), and connects with the morphologically left ventricle situated on the

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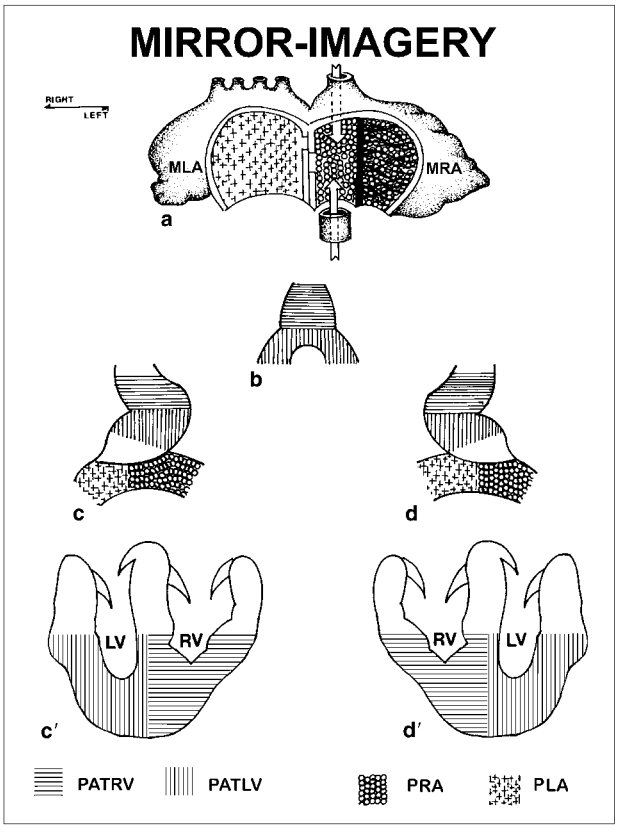

Figure 4.
Graphic representation of the essential anatomic features for the diagnosis of concordant and discordant atrioventricular connections in the mirror-imaged arrangement (situs inversus) and their probable embryogenesis. (a) Anatomical features of mirror-imagery, with the morphologically right atrium situated on the left side. (b) Straight tube heart constituted by the primitive cardiac segments of the apical trabeculated region of the right ventricle and the apical trabeculated region of the left ventricle. (c) C shape loop convex to the left, the primitive cardiac segment of the apical trabeculated region of the right ventricle situated on the left. (d) C shape loop convex to the right, the primitive cardiac segment of the apical trabeculated region of the right ventricle located on the right. (c′) Apical trabeculated region of the right ventricle situated to the left. (d′) Apical trabeculated region of the right ventricle situated to the right. PATRV, primitive apical trabeculated region of the right ventricle; PATLV, primitive apical trabeculated region of the left ventricle; MRA, morphologically right atrium; MLA, morphologically left atrium; PRA, primitive right atrium; PLA, primitive left atrium; RV, morphologically right ventricle; LV, morphologically left ventricle.

left (Fig. 4a, d′). When the atrial appendages are isomorphic (visceral heterotaxy), there are neither concordant nor discordant atrioventricular connections. This is because both atrial appendages are anatomically equal, showing right or left isomorphism.

The embryological basis for the interrelationship of the morphologically right and left ventricles within the ventricular mass is determined by the direction of looping. If the heart tube is convex to the right, and concave to the left, the morphologically right ventricle will be placed on the right side, and the morphologically left ventricle on the left side, giving right hand topology (Figs 3c, c′ and 4d, d′). If, in contrast, the loop is convex to the left, and concave to the right, the morphologically right ventricle will be placed on the left, and the morphologically left ventricle will be on the right giving left hand topology (Figs 3d, d′ and 4c, c′). Thus, the existence of concordant and discordant atrioventricular connections depends, first, on the direction of the loop and, second, on the atrial arrangement in which it appears. For instance, in usual arrangement (situs solitus), when the "C loop" is convex to the right, and concave to the left, the combination with right hand topology will produce concordant atrioventricular connections (Fig. 3a, c, c′), rightward looping being normal for this type of arrangement. If, in contrast, the C loop is convex to the left and concave to the right, in other words leftward looping, which is abnormal for this atrial arrangement, there will be discordant atrioventricular connections in usual atrial arrangement (Fig. 3a, d, d′). In mirror-imagery (situs inversus), when the "C loop" is convex to the left, and concave to the right, producing left hand topology which is normal for this arrangement, there will be concordant atrioventricular connections in mirror-imagery (situs inversus) (Fig. 4a, c, c′). If the "C loop" is convex to the right, and concave to the left, giving right hand topology, an abnormal loop for this arrangement, there will be discordant atrioventricular connections with mirror-imaged atrial arrangement (situs inversus) (Fig. 4a, d, d′).

Thus, when the type of loop is concordant with the atrial arrangement, then the atrioventricular connections are similarly concordant, be there usual arrangement (situs solitus) (Fig. 3a, c, c′), or the mirror-imaged variant (situs inversus) (Fig. 4a, c, c′). When the "C loop" does not correspond with the atrial arrangement, then discordant atrioventricular connections are found with either usual arrangement (Fig. 3a, d, d′) or the mirror-imaged variant (Fig. 4a, d, d′).

The atrioventricular canal and its congenital pathology

The atrioventricular canal is the anatomical region which gives rise to the atrial vestibules, and to the fibrous atrioventricular junction from which is hinged the leaflets of the atrioventricular valves. The valvar leaflets themselves, along with their tension apparatus, are derived from the atrioventricular cushions and the myocardium of the ventricular mass (Fig. 2c, d). Thus, the morphologically tricuspid valve is always formed within the morphologically right ventricle, and the mitral valve in the

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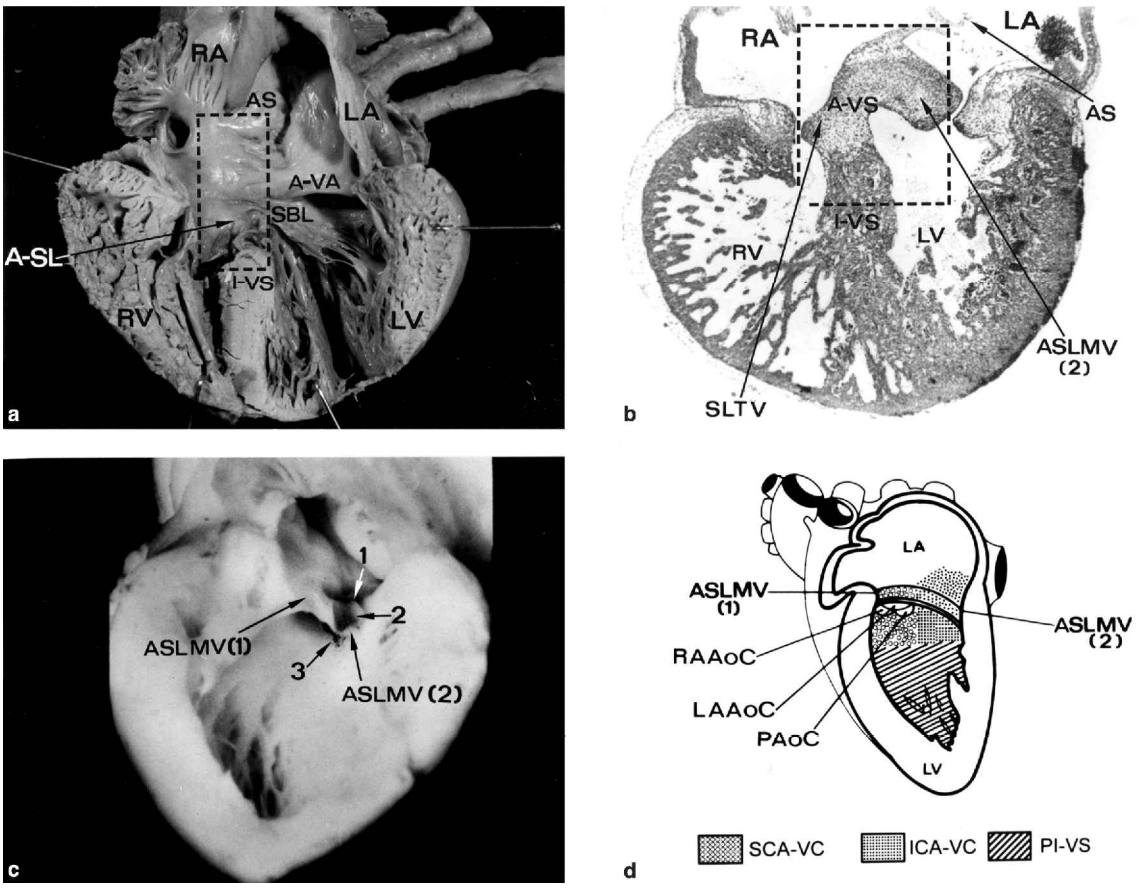

Figure 5.

Embryogenesis of atrioventricular septal defect with common atrioventricular junction based in the possible arrested growth of the inferior cushion of the atrioventricular canal, this being the primary morphogenetic factor. (a) Four chamber cardiac section of an anatomic specimen of atrioventricular septal defect in man. (b) Four chamber histological section of a chick embryo heart at stage 29 showing the contribution of the inferior cushion of the atrioventricular canal to cardiac septation and in the development of the septal leaflets of the tricuspid and mitral valves. (c) Photograph of the left cavities of the mature chick heart showing the results of the "in vivo" labeling of the inferior cushion of the atrioventricular canal in the embryo at stage 18. Notice the label in the interatrial (arrow 1) and interventricular septums (arrow 3), and in the region of the anteroseptal leaflet of the mitral valve that inserts into the septum (arrow 2). (d) Diagram showing the contribution of the superior and inferior cushions of the atrioventricular canal and of the primitive interventricular septum to the definitive ventricular septum in the chick; and the contribution of the superior cushion of the atrioventricular canal in the region of the anteroseptal leaflet of the mitral valve which forms the area of mitroaortic continuity. The inferior cushion of the atrioventricular canal contributes both to the region of the anteroseptal leaflet of the mitral valve which inserts into the septum and also, in the chick, to the atrioventricular septum and the adjacent zone of the atrial septum. The rectangle of the figure b includes the embryological structures which originated, in the bird heart, from the inferior cushion of the atrioventricular canal. Observe that none of the anatomical structures that derive from the embryological structures in the rectangle of figure (b), appear in figure (a). RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; AS, atrial septum; A-VS, atrioventricular septum; I-VS, interventricular septum; SLTV, septal leaflet of the tricuspid valve; ASLMV (1), region of the anteroseptal leaflet of the mitral valve that constitutes the mitroaortic continuity; ASLMV (2), region of the anteroseptal leaflet of the mitral valve that inserts into the septum; SCA-VC, superior cushion of the atrioventricular canal; ICA-VC, inferior cushion of the atrioventricular canal; PI-VS, primitive interventricular septum; RAAoC, right anterior aortic cusp; LAAoC, left anterior aortic cusp; PAoC, posterior aortic cusp; SBL, superior bridging leaflet; A-SL, antero-superior leaflet; A-VA, atrioventricular annulus.

morphologically left ventricle. In the region of the atrioventricular canal, the cushions are found which, in combination with the myocardium, will give rise to the annulus, leaflets and tendinous cords of the atrioventricular valves. These are not associated with the apical trabeculated region of either ventricle, nor with the outlets.[23] By means of a process of endocardium-myocardium induction, as shown by Markwald and his colleagues,[24–26] the cells of the endocardium migrate into the extracellular matrix and differentiate into connective tissue. By means of "in vivo" labeling experiments, de la Cruz et al.[27] showed that, in the chick, the inferior cushion of the atrioventricular canal gives origin to regions of the interatrial and interventricular muscular septums (Fig. 5c, d). In the chick, these cushions divide the

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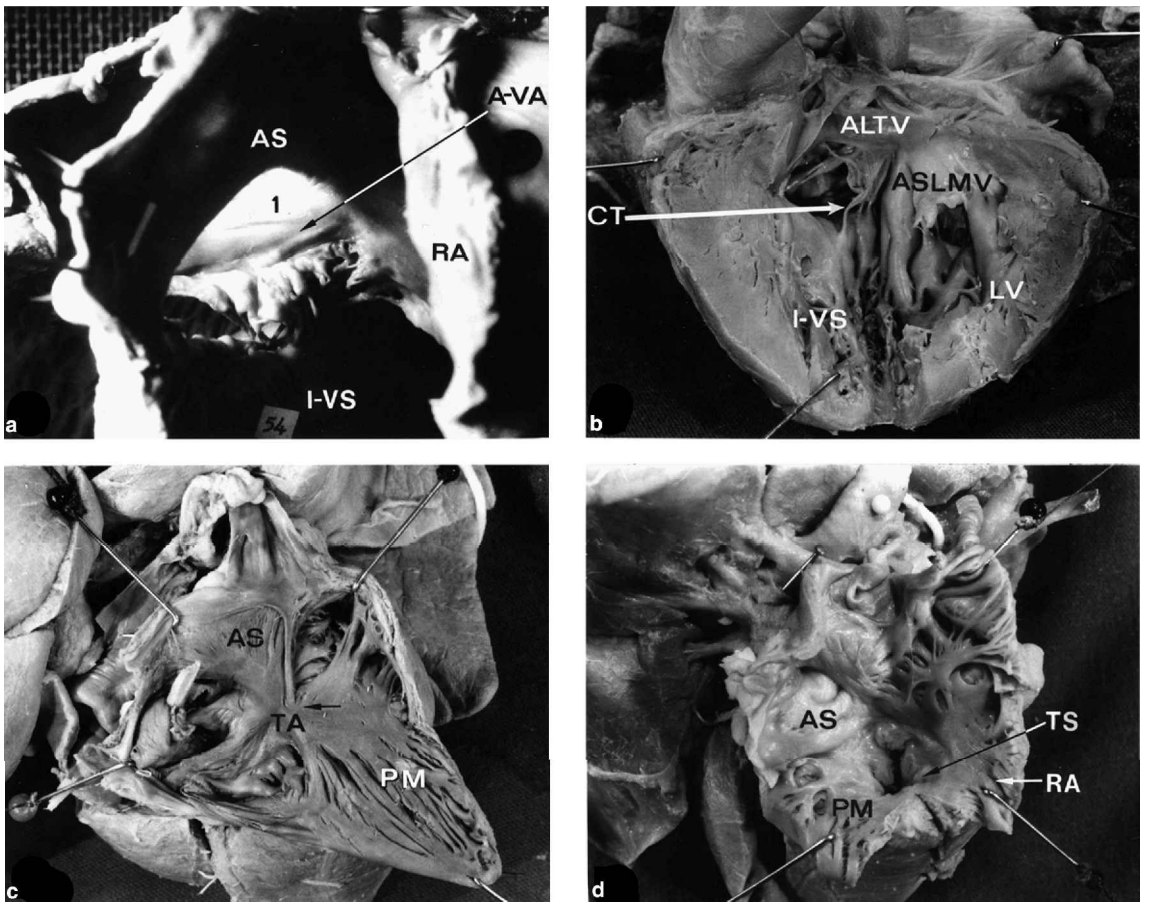

Figure 6.
Photographs of anatomic specimens of human hearts exhibiting congenital malformations of the atrioventricular junctions and ventricular inlets. (a) Posterior aspect of the dissection of the right atrium of a specimen with an atrioventricular septal defect. Notice the septal defect through which the four cardiac chambers communicate, the common atrioventricular junction, and the abnormal leaflets. (b) Internal anterior aspect of the morphologically left ventricle in a specimen with straddling of the tricuspid valve. Notice the septal leaflet of the tricuspid valve partially inserted into the left surface of the muscular ventricular septum. (c) Dissection of the right atrium in a specimen of tricuspid atresia. The arrow indicates the absence of the right atrioventricular connection. (d) Dissection of the right atrium in a specimen of tricuspid stenosis, but with separate atrioventricular junctions. RA, right atrium; LV, left ventricle; AS, atrial septum; I-VS, interventricular septum; ALTV, anterior leaflet of the tricuspid valve; ASLMV, anteroseptal leaflet of the mitral valve; CT, tendinous cords; A-VA, atrioventricular annulus; TA, tricuspid atresia; TS, tricuspid stenosis; PM, pectinate muscles; 1, septal defect through which the four cardiac chambers communicate.

atrioventricular canal into two segments: one for the right and one for the left ventricle (Fig. 5). These septal regions in the avian heart are initially formed by mesenchymal tissue which are eventually converted to cardiac muscle by processes known as myocardialization and transdifferentiation[23,28] (Fig. 5b). Although the process of separation of the atrioventricular canal is the same in mammals, there is no muscularisation of the atrioventricular cushions as occurs in birds. The end result, with formation of separate right and left atrioventricular junctions, nonetheless, is comparable.[29]

Among the most important congenital pathologies involving this region of the atrioventricular junctions is the so-called endocardial cushion defect,[30,31] or atrioventricular septal deficiency with common atrioventricular junction.[32] This group of malformation is characterized by the presence of a single atrioventricular ring, or annulus, and a septal deficiency through which all four cardiac chambers can communicate (Figs 5a and 6a). In this cardiopathy, the muscular ventricular septum is always present, albeit "scooped-out", because it originates from the primitive interventricular septum[5,33,34] (Fig. 5a, d). This malformation is probably the result of arrested growth of the inferior cushion of the atrioventricular canal, since this cushion is the one which participates predominantly in the septation of the atrioventricular junctions[23,27,33,34] (Fig. 5). Failure of fusion of the atrioventricular cushions can be lethal, for example as in the *heart defect* mutant mouse.[35] Other congenital malformations of the

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inlet are tricuspid atresia (Fig. 6c), mitral atresia, and double inlet ventricle. Malformations of the valves themselves can give tricuspid (Fig. 6d) and mitral stenosis. The latter two defects can also be characterized by a small valvar ring or annulus. These are distinct from acquired stenosis, due to fusion of the leaflets postnatally. The commonest forms of tricuspid and mitral atresia reflect failure of formation of one or other atrioventricular connection, and are manifest by deep atrioventricular grooves interposed between the atrial and ventricular chambers. Flow of blood is an important morphogenetic factor in the normal development of the heart. Thus, the small rudimentary and incomplete right ventricle seen in classical tricuspid atresia may be caused by an abnormal hemodynamic pattern resulting from the absence of the right atrioventricular connection. Straddling and overriding of the tricuspid and mitral valves also reflect abnormal formation of the atrioventricular junctions. Thus, in straddling tricuspid valve, the tension apparatus is partially inserted into the left ventricle, with the atrioventricular junction overriding the crest of the muscular ventricular septum (Fig. 6b). The straddling mitral valve is partially inserted into the right ventricle.[36] In either case, the atrioventricular junction overrides a ventricular septal deficiency, situated inferiorly in the case of straddling mitral valve, but anterosuperiorly when the mitral valves straddles and overrides.[37] Rarely in the setting of overriding of the atrioventricular junction, the tension apparatus of the overriding valve can be inserted exclusively within its own ventricle.[36] Straddling and overriding are due to the fact that the primitive interventricular septum is displaced to the left or right relative to the primitive atrioventricular canal. This is because the last of the three components of the definitive cardiac septums is the primitive interventricular septum (Fig. 7d), which gives origin to the definitive muscular interventricular septum (Fig. 5d).[5,33,34]

The primitive outlet and its congenital malformations

The outlet of the mature heart is the subarterial ventricular regions (Fig. 2b–d). The outlet or infundibulum of the right ventricle has exclusively muscular walls, while that of the left ventricle, the vestibule, has partly muscular and fibrous walls.[17]

To understand congenital malformations of the outlet segment, it is first necessary to review the formation of the primitive cardiac septum. This septum is constituted by the primary septum at the atrial level, by the superior and inferior cushions of the atrioventricular canal in the region of the atrioventricular junctions, and by the primitive interventricular septum at the level of the apical trabeculated region of the ventricles[5,27,34] (Fig. 7d). Initially, there are two orifices within this primitive septum, the primary atrial foramen at the level of the atriums, and the primitive interventricular foramen in the ventricular zone (Fig. 7d). When complete, the septum separates simultaneously both atriums, the apical trabeculated region of both ventricles, and the atrioventricular junctions[23] (Fig. 7b–d). Thus, for the first time, with the completion of septation, the heart becomes four chambered. As the primitive cardiac septum is developing, the primitive outlet is still a simple hollow tube connected entirely to the trabeculated right ventricle (Fig. 7). The outlet cushions form later in development, and ultimately fuse to form the structure which divides the outlet segment into anterolateral and posteromedial components, both of which initially remain connected to the apical trabecular right ventricle.[9,17] We do not yet know the nature of the morphological and molecular changes involved in causing the anterolateral outlet to become incorporated into the right ventricle, and the posteromedial to the left ventricle. The three possible hypotheses are that the process is the consequence of myocardialization,[26,28] apoptosis,[38] or transdifferentiation[39]. It is likely that all three processes are involved, depending on the stage of development. By means of "in vivo" labeling experiments, nonetheless, we know that the anterior wall of the anterolateral outlet contributes to the formation of the anterior wall of the right ventricular infundibulum,[17] and that the superior cushion of the atrioventricular canal participates in the development of the subaortic vestibule.[17,40] The precise contributions of other embryological structures, such as the neural crest and aortic sack, remain to be determined.[41,42]

One of the most relevant features of the normal embryological development of the ventricular outlets is that, over several stages of development, both the anterolateral and the posteromedial outlets are connected with the apical trabeculated right ventricle.[9,17] In addition, the incorporation of the posteromedial outlet to the left ventricle is gradual, and occurs later in development. This fact establishes the pathology of the ventricular outlets as a spectrum in which we can find both outlets connected with the right ventricle, or one outlet arising from the right ventricle and the other almost totally committed to this ventricle. This pathology is designated as double outlet right ventricle[17,43] (Fig. 8b, d). Also, as part of this spectrum, the right ventricle retains its outlet, but the outlet of the left ventricle overrides a ventricular septal defect to varying degree (Fig. 8a, c). There are two important types of overriding of the

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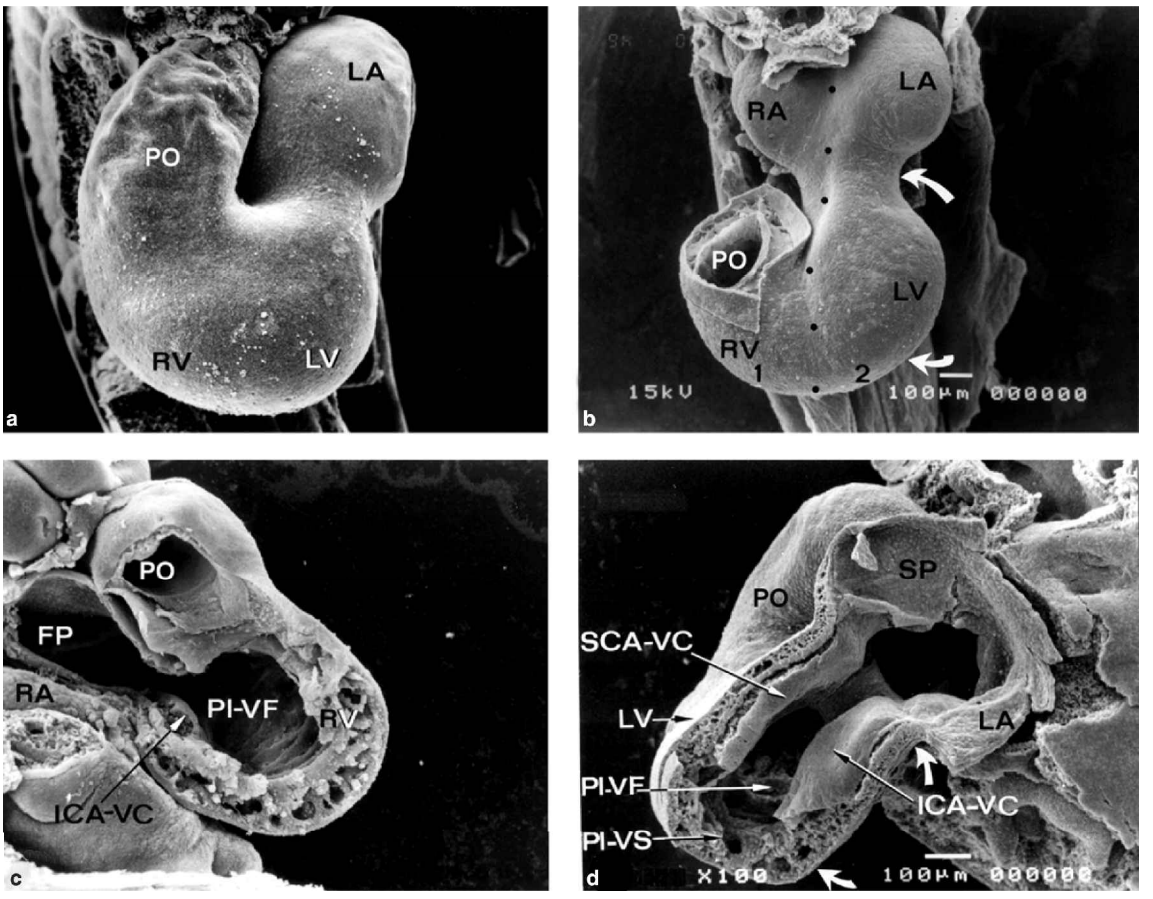

Figure 7.
External views and dissections of the chick embryo heart at stage 19 showing the primitive cardiac septum (8-shaped septum) which divides the heart into four chambers. Notice the tubular primitive outlet still connected with but not yet incorporated into the right ventricle. A scanning electron microscope study. (a) Ventral external view of the heart. Notice both atriums are positioned cephalically, the right ventricle to the right and the left ventricle to the left, and the primitive outlet anterior with respect to the right atrioventricular orifice. (b) The same heart in which the primitive outlet was removed. The dotted line shows the groove which corresponds internally to the primitive cardiac septum. The arrows show the limit of the inlet. (c) Dissection of the right cardiac cavities showing the primitive outlet connected exclusively with the right ventricle. (d) Dissection of the left cardiac cavities. Notice the primitive cardiac septum constituted by the septum primum, the superior and inferior cushions of the atrioventricular canal, and an incipient primitive interventricular septum. The segment between the two arrows corresponds to the ventricular inlet. Observe the larger superior and inferior cushions of the canal. PO, primitive outlet; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; FP, foramen primum; PI-VF, primitive interventricular foramen; ICA-VC, inferior cushion of the atrioventricular canal; SCA-VC, superior cushion of the atrioventricular canal, PI-VS, primitive interventricular septum; SP, septum primum; 1, apical trabeculated region of the right ventricle; 2, apical trabeculated region of the left ventricle.

great arteries. In one, the aorta arises from the morphologically right ventricle, and the pulmonary trunk overrides an interventricular communication. This is the Taussig-Bing malformation (Fig. 8c). In the other, the pulmonary trunk arises exclusively from the right ventricle, and the aorta overrides the ventricular septal defect. If there is also infundibular and valvar stenosis of the pulmonary outflow tract, this pathology is designated tetralogy of Fallot (Fig. 8a). In these lesions, it is not possible to find a normal supraventricular crest. Instead, an abnormal structure is present, which is designated as the muscular outlet or infundibular septum (Fig. 8a, b, d).[44–46] It is also important to point out that, in these pathologies of the outlet, the interventricular communication is always located between the two limbs of the septomarginal trabeculation.[44,45] One of these limbs is superior (anterior), and the other one is inferior (posterior) (Fig. 8). Another cardiopathy involving the outlet segment is common arterial trunk, or persistent truncus arteriosus. It is characterized by a single arterial trunk arising from the base of the heart by way of a common arterial valve without an atretic aortic or pulmonary valve.

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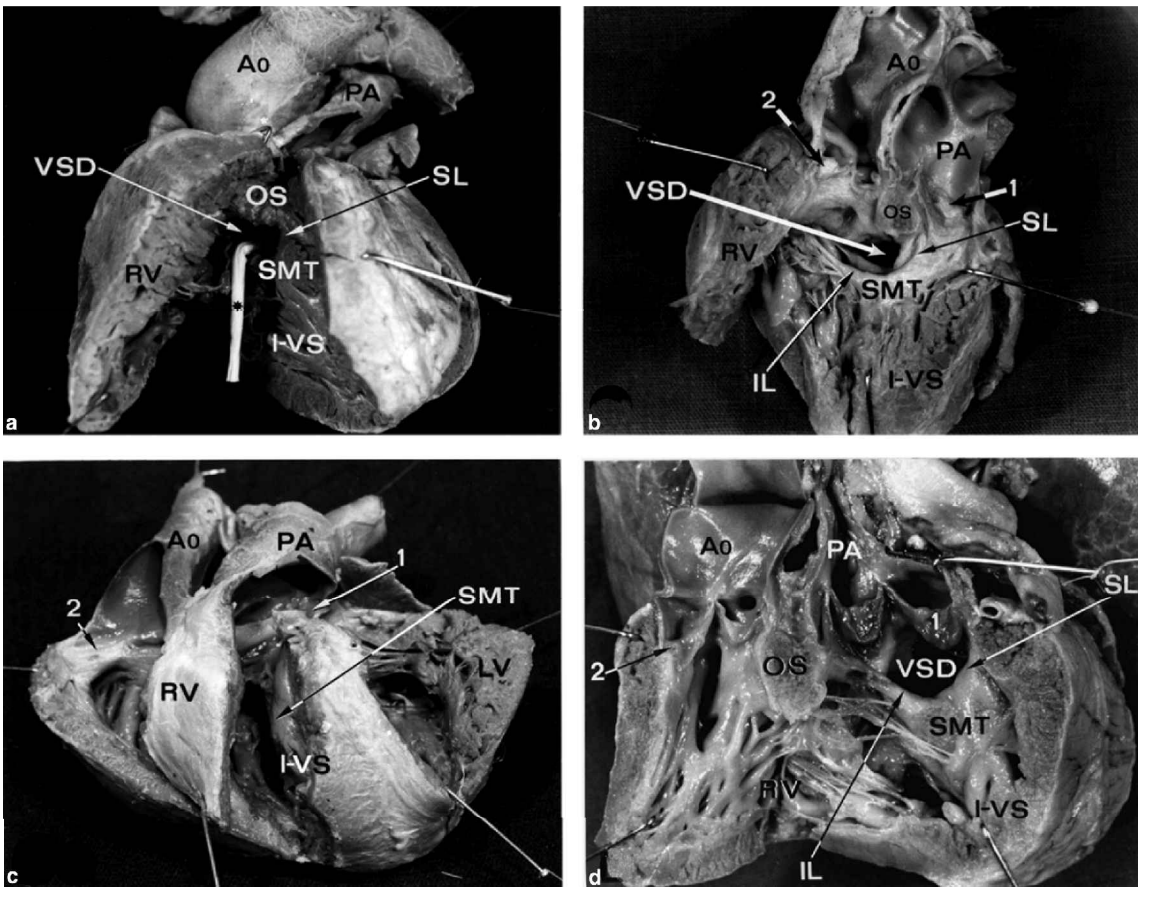

Figure 8.
Photographs of anatomic specimens of human hearts exhibiting congenital pathology of the outlets. (a) Dissection of the right ventricle of a specimen with tetralogy of Fallot. Notice the infundibular and valvar stenosis of the pulmonary outflow tract, and the aorta overriding the ventricular septal defect located between the two limbs of the septomarginal trabeculation, with a stick positioned in this defect. (b) Dissection of the right ventricle in a specimen with double outlet right ventricle with anterior and posterior infundibulums. Observe both outlets in the right ventricle, and the outlet septum inserted into the superior limb of the septomarginal trabeculation. Both outlets are abnormal, and there is an infundibular and valvar pulmonary stenosis. The aorta is related with the ventricular septal defect located between the two limbs of the septomarginal trabeculation. (c) Dissection of both ventricles of a specimen with the Taussig-Bing defect. Observe the aortic outlet in the right ventricle and the aorta emerging from it. The pulmonary trunk overrides the ventricular septal defect, arising from both ventricles. (d) Dissection of the right ventricle in a specimen with double outlet right ventricle with side by side infundibulums. Observe both outlets in the right ventricle and the outlet septum inserted into the inferior limb of the septomarginal trabeculation. Both outlets are abnormal; the pulmonary trunk is related with the ventricular septal defect located between the two limbs of the septomarginal trabeculation. Ao, aorta; PA, pulmonary artery; OS, outlet septum; VSD, ventricular septal defect; SMT, septomarginal trabeculation; SL, superior limb of the septomarginal trabeculation; IL, inferior limb of the septomarginal trabeculation; I-VS, interventricular septum; RV, right ventricle; LV, left ventricle; 2, aortic cusp; 1, pulmonary cusp.

The common arterial trunk emerges from a single undivided outlet, with no formation of a muscular outlet septum (Fig. 9). This cardiopathy exhibits the same spectrum described above in that the common trunk may arise entirely from the right ventricle, it may override a ventricular septal defect located between the two limbs of the septomarginal trabeculation, or it can arise almost entirely from the morphologically left ventricle. The malformation is almost certainly due to persistence of the primitive undivided outlet. But, in addition, the septal structures of the outlet segment and the aortic sack are either partially or completely absent. Consequently, although it is a cardiopathy of the region of the ventricular outlet, it is also a malformation of the arterial pole. The arrangement which is characterized by the aorta arising from the morphologically right ventricle, and the pulmonary trunk from the morphologically left ventricle, has also frequently assumed to be a malformation of the ventricular outlets. The most frequent type of such discordant ventriculo-arterial connections, usually known as

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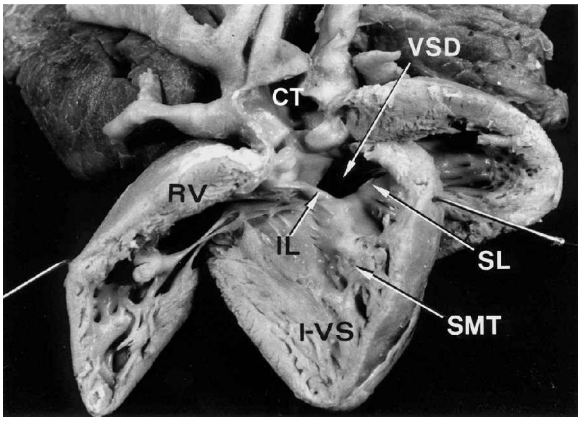

Figure 9.
Photograph of a human specimen with common arterial trunk (persistent truncus arteriosus) showing the congenital pathology of the region of the outlet. Dissection of the morphologically right ventricle exhibiting a single outlet from which arises a single arterial trunk, related with the ventricular septal defect which is located between the two limbs of the septomarginal trabeculation. CT, common arterial trunk; VSD, ventricular septal defect; RV, right ventricle; I-VS, interventricular septum; SMT, septomarginal.

transposition, has an anterior aorta and a posterior pulmonary trunk.[47] This lesion, however, is probably due to abnormal formation of the aorto-pulmonary septum,[41,42,47] but not of the primitive outlets, although the discordant ventriculo-arterial connections often co-exist with ventricular septal defects.

Complex congenital cardiopathies and transgenic models

We have reviewed those ventricular regional congenital pathologies in which only one of the primitive cardiac segments is abnormal. It should be remembered, nonetheless, that two or more of these segments can be abnormal. In this event, the anatomical manifestation is a complex congenital cardiopathy which is characterized by two or three abnormal ventricular regions. An example with two abnormal primitive cardiac segments is the combination of atrioventricular septal defect with double outlet right ventricle. An example with three abnormal primitive cardiac segments is the hypoplastic left heart syndrome, which usually exhibits mitral atresia or stenosis, a hypoplastic left ventricle, and atresia or stenosis of the outlet from this ventricle. There can also be complex congenital cardiopathies in which any of the ventricular regions may be abnormal, and the atrial or the arterial segments, or both, may also be involved. An example of the latter group is isomorphism of the right atrial appendage, which usually exhibits abnormal venoatrial connections, deficient atrioventricular septation, common atrioventricular junction, discordant or double outlet ventriculo-arterial connections, and infundibular and valvar stenosis of the pulmonary trunk. The majority of transgenic animal models also present complex congenital cardiopathies. Their study requires a special analysis, because many die during prenatal life, and those that do survive are used to investigate genetic mechanisms. Bearing these facts in mind, we emphasize the need to establish the stage of development at which the embryo died, because a single anatomical picture may be normal or abnormal depending on the developmental stage. For example, in the chick embryo, stenosis of the right atrioventricular orifice is normal at stages 18 to 22, but abnormal from stage 22 and beyond. It is also essential to know if circulation of blood existed in the development stage at which the molecular genetic action occurred, since the hemodynamic process is itself a morphogenetic factor. Thus, the primary molecular genetic action, and its subsequent anatomical expression, can give origin to a secondary abnormal hemodynamic pattern. The second feature, in turn, is manifested by malformations of other structures which appear in subsequent stages of development. A possible example of this is atrioventricular septal defect with common atrioventricular junction, in which the possible morphogenesis was caused by a molecular genetic action, the primary morphogenetic factor. This may produce an arrest in the development of the inferior cushion of the atrioventricular canal, resulting in an anatomical manifestation such as a single atrioventricular annulus (Compare b, c, d with a in Fig. 5), and a septal defect which allows communication between the four cardiac chambers (Fig. 5). This hypothetical picture of morphogenesis could then be modified by abnormal hemodynamic patterns, the secondary morphogenetic factors. These, in turn, give origin to abnormal leaflets, tendinous cords, and papillary muscles, all of which could appear in the subsequent developmental stages (Fig. 5).

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