Cardiac Embryology and Embryopathy

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As long ago as the beginning of the twentieth century, Abbott [1] argued that knowledge of embryology was essential for interpretation of congenital cardiac malformations. Only recently, however, have the necessary facts regarding the formation of the heart been sufficiently robust to underscore interpretations of the morphology of the lesions themselves. Our knowledge of cardiac development, based as it is on evidence rather than speculation, is now sufficient to help in understanding the morphology, not only of the normal heart, but also most significant congenital cardiac malformations. The advances have been made possible in no small part by the development of techniques that reveal the three-dimensional changes occurring during the processes of cardiac development [2].

Initial Stages of Development

When first recognized as having endodermal, ectodermal, and mesodermal germ layers, the developing human embryo is discoid, and the endodermal and ectodermal layers are continuous at the margins of the disc with the walls of the amnion and the yolk sac, respectively [3]. Already at this early stage, the presence of the primitive streak, with the node at its cranial end, permits recognition of the right and left sides of the developing embryo. During the subsequent stage of gastrulation, cells migrate into the mesodermal region on both sides through the primitive streak, fusing to produce the cardiac crescent. Concomitant with embryonic folding, there is folding of a trough derived from the heart-forming areas that produces the primary linear heart tube. It used to be thought that all the components of the definitive heart were present in the original tube. It is now known that, with ongoing development, new material is added to the tube at both its ends. The material of the initial tube eventually provides no more than the apex of the left ventricle (LV), and part of the muscular ventricular septum [4]. It remains moot as to whether the newly migrating cells are derived from a so-called second heart field, and whether this alleged field itself has cranial and caudal components. Suffice it to say that new cells, both myocardial and non-myocardial, continue to be added at both ends of the heart tube as it loops and separates into its right and left sides [5].

Looping of the Heart Tube

Development of the human heart is usually described using the Carnegie stages, which extend from 1 through 23, although the heart continues to show marked morphologic changes subsequent to stage 23, which is equivalent to about 8 weeks of development. The heart becomes recognizable at stage 9, equivalent to about 20 days of development. The myocardial part is then no more than a strip, anterior to paired vascular channels, with endocardial jelly interposed between the myocardial and endothelial layers [3]. By the next stage, the myocardial component has folded around the vascular elements, which are now fused to produce a tube with a solitary lumen. The connections of the lumen with the developing embryonic circulatory systems then permit recognition of the arterial and venous poles of the tube. At stage 11, representing about 25 days of development, it is possible to recognize the ventricular loop, with the atrioventricular (AV) canal positioned between the developing atrial component and the inlet of the loop. These features are seen in the developing mouse at embryonic day 9.5 (Figure 1.1). Looping is a key feature of development. The tube usually curves to the right, with the apical component of the LV then developing from the inlet part of the loop, and the apical part of the right ventricle (RV) from the outlet (Figure 1.2). The apical components of the ventricles, therefore, develop...
Figure 1.1 The scanning electron micrograph image shows the developing heart of the mouse at E9.5. The heart has been revealed by removing the ventral wall of the pericardial cavity. The ventricular loop extends from the atrioventricular (AV) canal, and supports the outflow tract.

Figure 1.2 The image is prepared using an episcopic dataset from a developing mouse embryo early on embryonic day 11.5. The four-chamber section shows how the atrial appendages are beginning to balloon in parallel fashion from the common atrial chamber, while the apical components of the developing ventricles are ballooning in series from the ventricular loop. The process of ballooning of the apical ventricular components produces the muscular ventricular septum formed between them (star). The AV canal connects predominantly to the developing left ventricle (LV), but already its right wall has provided contiguity between the right atrium (RA) and the developing right ventricle (RV; double-headed white arrow).
in series, unlike the atrial appendages, which develop in parallel from the atrial component of the developing heart. In the setting of visceral heterotaxy, therefore, in which there is isomerism of those features that are usually lateralized, it is only the atrial appendages that show evidence of symmetry [6]. Indeed, isomorphic right atrial appendages are the prime cardiac feature of mice genetically modified by knocking out Pitx2c [7], one of the genes responsible for producing morphologic leftness (Figure 1.3). For the ventricles, however, because the apical part of each ventricle develops from a part of the tube containing both the initial right and left sides, knocking out Pitx2c does not produce evidence of ventricular isomerism. The direction of ventricular looping is random in the syndromes of visceral heterotaxy [8].

**The Process of Ballooning**

Subsequent to looping, it is possible to recognize the morphologic features of the developing cardiac chambers. The relations of the atrial appendages to the developing AV canal permit distinction of the morphologically right and left atrial chambers, while it is the eventual structure of the apical components that distinguishes between the definitive RV and LV. These parts, the appendages and the apical components, are produced by the process now described as ballooning [9]. Remodeling of the initial cavity of the linear tube then permits the atrial cavities, subsequent to their separation, to become connected directly to their respective ventricles, and the arterial trunks to be brought into union with their appropriate ventricles. When the ventricular loop is first seen, however, the circumference of the AV canal is supported almost exclusively by the developing LV (Figure 1.4), while the developing outlet component, which has a solitary lumen, arises in its entirety from the developing RV. The default options for development therefore are double inlet to the LV, and double outlet from the RV. When first formed, furthermore, the RV possesses only apical trabecular and outlet components (Figure 1.5), although from the outset its wall is continuous through the right side of the AV canal with the developing right atrium (RA; Figure 1.2).

**Formation of the Atrial Chambers**

The systemic venous tributaries drain to the developing atrial component of the heart tube at the venous pole. This situation, established by Carnegie stage 11 in the human heart, is equivalent to embryonic day 9.5 in the mouse. At this early stage, the atrial part of the heart tube is also attached to the pharyngeal mesenchyme through the dorsal mesocardium. The systemic venous tributaries initially open in relatively symmetrical fashion to either side of this area of attachment. The reflections of the pharyngeal mesenchyme in the area of the attachment
Figure 1.4 The image is from an episcopic dataset prepared from a mouse at early embryonic day 11.5. A short axis cut has been made through the ventricular loop, which is then viewed from the aspect of the transected apical components. The star shows the developing ventricular septum. The opening between the AV cushions opens exclusively into the cavity of the developing LV. The outflow tract is supported by the developing RV.

Figure 1.5 The image is from an episcopic dataset prepared from a mouse at early embryonic day 11.5. The apical trabecular component of the RV is beginning to balloon from the outlet component of the ventricular loop. As yet, there is no direct communication between the cavities of the RA and the RV, the blood flowing into the developing RV through the embryonic interventricular communication. Already, however, the right wall of the AV canal (double-headed arrow) provides continuity between the RA and RV walls. The outflow tract arises exclusively from the RV, with the proximal outflow cushions already visible within its lumen (stars).
Atrial Septation

Figure 1.6 The scanning electron micrograph image shows evidence of the initial symmetry of the systemic venoatrial connections at embryonic day 9.5 in the mouse, albeit that the left horn is smaller than the right. The section is taken through the dorsal mesocardium, and shows the pulmonary pit (thick arrow). As yet, there is no formation of the lungs.

enclose a midline pit (Figure 1.6). With subsequent formation of the lungs, and canalization of a venous channel in the mediastinum, the blood from both developing lungs enters the atrial cavity through this pit. By the time the pulmonary vein has canalized and gained its cardiac connection, there has been realignment of the left-sided systemic venous channels. Thus, during E10.5 in the mouse, the left-sided systemic venous tributary becomes incorporated into the developing left AV groove. As it is incorporated within the groove, it retains its own walls (Figure 1.7). Folds then become evident within the developing RA. Known as the venous valves, they guard the entrances of the systemic venous tributaries, now recognizable in the human heart as the superior and inferior caval vein and the coronary sinus, the latter formed from the left sinus horn (Figure 1.8). Should the intrapericardial part of this left-sided channel persist postnatally, it is seen as the left superior caval vein, which is always present in the mouse heart. The pulmonary vein in humans initially has a solitary atrial orifice, which empties into the left atrium (LA) adjacent to the left AV junction (Figure 1.9). Only much later in humans does the pulmonary venous component enlarge in size, with the veins migrating onto the atrial roof so that, eventually, one vein connects at each corner of the definitive LA [10]. A similar expansion in mouse produces a fold dorsally between the connections of the pulmonary veins to the LA, and the wall of the RA (Figure 1.10). Remodeling of the pulmonary venous component is part and parcel of the processes of atrial septation.

Atrial Septation

Atrial septation is heralded by the appearance of the primary atrial septum, or septum primum, in the atrial roof (Figure 1.7). The primary septum grows towards the AV canal, interposing between the openings of the systemic channels, now committed to the RA, and the orifice of the newly formed pulmonary vein (Figure 1.11). Within the AV canal, the process known as endothelial-to-mesenchymal transformation has already converted the endocardial jelly into superior and inferior AV cushions (Figure 1.10). The space between the leading edge of the primary atrial septum and the atrial surfaces of the cushions is the primary atrial foramen, or “ostium primum.” The cranial border of the foramen is formed by a mesenchymal cap carried on the leading edge of the developing primary atrial septum (Figure 1.11). Continuing growth of the primary septum
Figure 1.7 The scanning electron microscopic image shows the atrial chambers, viewed from the aspect of the removed ventricular chambers, from a developing mouse heart obtained late at E10.5. The dissection shows how the left sinus horn, with its own discrete walls, has become incorporated into the developing left AV junction. Note the secondary atrial foramen.

Figure 1.8 The image is from an episcopic dataset prepared from a human embryo at Carnegie stage 14. It shows the atrial cavities viewed from the ventricular aspect. The left sinus horn has been incorporated in the left AV groove, and the openings of the caval veins are seen within the confines of the venous valves (stars). Note the location of the primary atrial septum, which is growing from the atrial roof.
**Figure 1.9** The image is from the same dataset as shown in Figure 1.8, but is cut in the sagittal plane, replicating the long axis parasternal echocardiographic plane. It shows the AV cushions facing one another in the AV canal, and the outflow cushions (stars) extending the full length of the outflow tract. Note also the ventral protrusion from the dorsal wall of the aortic sac. The section also cuts through the solitary pulmonary vein, and its entrance to the developing LA, which at this stage is adjacent to the developing AV junction. The double-headed white arrow shows the sectioned primary atrial septum, which separated the primary (Foramen 1) and secondary (Foramen 2) atrial foramen. Note the discrete walls of the left sinus horn, now incorporated within the left AV junction.

**Figure 1.10** The four-chamber section is prepared from an episcopic dataset from a mouse heart at embryonic day 18.5. The mesenchymal cap and vestibular spine have muscularized to form the anteroinferior buttress of the oval fossa (double-headed white arrow). The cranial margin of the fossa, however, is a deep fold between the RA wall and the attachments of the pulmonary veins to the LA. The floor of the oval fossa is formed by the primary atrial septum. Note the discrete walls of the left sinus horn, which in the mouse persists as a left superior caval vein.
then reduces the size of the primary foramen. Before
the primary foramen can close, the cranial origin of the
septum breaks down, producing the secondary atrial
foramen, or “foramen secundum.” This second hole is an
essential component of the developing fetal circulation,
because the richly oxygenated blood derived from the
placenta needs to reach the left side of the developing
heart. It is fusion of the mesenchymal cap with the atrial
surfaces of the AV endocardial cushions that obliterates
the primary foramen, with the process reinforced by
additional intracardiac migration of tissues from the
pharyngeal mesenchyme.

The new cells enter the heart through the right margin
of the pulmonary pit, which expands to become the
vestibular spine (Figure 1.12). Expansion of the spine
carries forward the inferior ends of the venous valves,
anchoring them to the right side of the fused endocardial
cushions. The mesenchymal tissues derived from the cap
and the spine (Figure 1.13) subsequently muscularize to
form the anteroinferior buttress of the definitive atrial
septum, with the primary atrial septum forming the
floor of the oval fossa (Figure 1.10). Although the cranial
margin of the oval fossa is often depicted as growing
from the atrial roof, this margin in the postnatal heart is
a fold rather than a muscular ridge. It is not seen during
development until after the right pulmonary veins have
achieved their definitive position on the roof of the LA.

In the mouse, the fold is produced dorsally rather than
cranially. As in humans, it does not become apparent
until after the pulmonary veins have remodeled towards
the end of development (Figure 1.10).

Full anatomic fusion between the flap valve derived
from the primary septum and the rims of the oval
foramen occurs in only three-quarters to two-thirds of
the overall population [11]. Lack of anatomic fusion
results in persistent patency of the oval foramen. A short
primary septum, or perforations within it, produces the
“secundum” defects, which should properly be described
as “foramen secundum” defects, or better considered
as holes within the oval fossa. Inappropriate fusion and
muscularization of the components of the anteroinferior
buttress can also produce holes within the septum,
which are well described as vestibular defects [12]. The
“ostium primum” defect is an AV, rather than an atrial,
septal defect. Its pathognomonic feature is the presence
of a common AV junction, along with a trifoliate left AV
valve. The feature underscoring this, and other AV septal
defects with common AV junction, is failure of formation
of the vestibular spine (compare Figures 1.13 and 1.14)
[13]. The sinus venosus defect is the consequence of
abnormal connection of one or more of the right pul-
monary veins to the superior or inferior caval vein, with
the anomalous pulmonary vein or veins retaining its
or their LA connection [14]. The known spectrum of
**Figure 1.12** The four-chamber section is from an episcopic dataset prepared from a mouse heart at embryonic day 13.5. The mesenchymal cap on the atrial septum has fused with the AV cushions to close the primary atrial foramen. The section is cut more dorsally, and shows how the vestibular spine has reinforced the right side of the area of fusion. The spine is beginning to muscularize to form the anteroinferior buttress of the oval fossa (see Figure 1.10).

**Figure 1.13** The four-chamber section is from an episcopic dataset prepared from a mouse heart at embryonic day 12.5. It shows the vestibular spine growing from the site of the right pulmonary ridge. The arrow shows the connection with the pharyngeal mesenchyme. The spine is carrying forward to inferior zone of apposition of the venous valves that guard the systemic venous sinus. Note the left superior caval vein, derived from the left sinus horn, entering the left AV junction.
Venous valves

Figure 1.14 The four-chamber section is from an episcopic dataset prepared from a Tbx1 null mouse at embryonic day 12.5. The mouse has an AV septal defect, with this section showing the ostium primum defect. There is total lack of formation of the vestibular spine. Note the hypoplastic nature of the right pulmonary ridge.

malformations, which extends from fenestration of the coronary sinus to its complete unroofing, shows that erosion of walls of both the coronary sinus and the LA are required to produce the coronary sinus defect [15].

**Ventricular Development**

Ballooning of the apical trabecular components from the ventricular loop heralds the appearance of the apical muscular ventricular septum. When first seen, the primary interventricular foramen is bounded by the crest of the muscular septum and the inner heart curvature (Figure 1.15). This foramen is never closed. Instead, it is remodeled so that the right half of the AV canal is placed in direct communication with the apical part of the RV, and the developing aortic outlet brought into communication with the apical part of the LV. Prior to remodeling of the foramen, the right AV groove interposes between the cavities of the developing RA and RV (Figure 1.5). Failure of expansion of this groove produces classic tricuspid atresia, which is a result of absence of the right AV connection [16]. With normal remodeling of the AV canal, the apical muscular interventricular septum is brought in line with the underside of the fused AV cushions, the RA then connecting directly with the cavity of the RV (Figure 1.16).

The formation of additional lateral cushions in the newly created ventricular inlets then sets the scene for development of the leaflets of the tricuspid valve (TV) and mitral valve (MV) (Figure 1.17). In the right-sided channel, the lateral cushion forms the primordiums of the anterosuperior and inferior, or mural, leaflets, with the conjoined AV cushions providing the substance for formation of the septal leaflet (Figure 1.18). On the left side, the developing MV initially has a trifoliate configuration [17]. It is only subsequent to transfer of the aorta to the LV that the fused superior and inferior cushions are moved away from the septum to form the aortic leaflet of the MV (Figure 1.19). Failure of complete fusion produces clefting of the aortic mitral leaflet. In both ventricles, the trabecular layers of the myocardium condense to form the papillary muscles, with delamination from the parietal ventricular walls producing the septal and inferior leaflets of the TV, and the mural leaflet of the MV [17]. Abnormal persistence of the myocardial components accounts well for the so-called arcade lesion, in which the leading edge of the valvar leaflets remains myocardial. It is failure of delamination of the inferior and septal leaflets from the myocardium of the RV inlet that produces Ebstein’s malformation [17].

Completion of ventricular formation requires transfer of half of the outflow tract to the developing LV, again achieved by remodeling of the cavity of the initial linear
**Figure 1.15** The image is the same as that used for Figure 1.2, and comes from a developing mouse embryo early on embryonic day 11.5. It is re-labeled to show how, at this early stage, the AV canal connects almost exclusively with the cavity of the developing LV (bracket). The blood then enters the developing RV through the embryonic interventricular communication (double-headed white arrow), which is bounded caudally by the developing muscular ventricular septum (star), and cranially by the right margin of the inner heart curvature (white curve).

**Figure 1.16** The image is a frontal section through an episcopic dataset prepared from a developing mouse early on E12.5. The AV canal has expanded so that the cavity of the developing RA is now in direct continuity with the cavity of the RV, thus producing the RV inlet. The larger parts of the AV cushions, however, remain committed to the LV. The aortic component of the developing outflow tract, in contrast, remains supported by the developing RV, so that the blood entering the aorta must still pass through the embryonic interventricular communication (white arrow). The star shows the crest of the muscular interventricular septum.
Figure 1.17 The image shows a four-chamber section through the AV junctions later on embryonic day 12.5 in the developing mouse heart. The major AV endocardial cushions have now fused to divide the junction into the tricuspid (TV) and mitral valve (MV) orifices. Lateral cushions have now developed in the newly formed right and left junctions, and will form the mural leaflet of the MV, and the anterosuperior and inferior leaflets of the TV (see Figure 1.18). The star shows the muscularizing vestibular spine and mesenchymal cap, which bind the atrial septum to the surface of the cushions.

Figure 1.18 The image shows a short axis section from an episcopic dataset prepared from an embryonic mouse at day 13.5. The bulk of the fused AV cushions remains within the LV and have fused to form what will become the aortic leaflet of the MV. At this stage, however, the aortic outflow tract remains supported by the RV (star). The right lateral cushion and the rightward margins of the fused AV cushions guard the developing TV orifice.
Development and Maldevelopment of the Outflow Tract

When first seen, the outflow component of the linear heart tube extends from the RV to the margins of the pericardial cavity, and has exclusively myocardial walls [18]. Its lumen, at the margins of the pericardial cavity, becomes continuous with the lumens of the bilateral and initially symmetrical arteries that develop within the pharyngeal arches (Figures 1.23 and 1.24). The confluence within the pharyngeal mesenchyme that gives rise to the arteries is known as the aortic sac. The arteries percolating through the arches are never all seen at the same time. By the time the arteries of the fourth and sixth arches have appeared, the arteries of the first three arches have lost their original connection with the aortic sac. Eventually, the right-sided channels disappear, with the artery of the left fourth arch becoming the transverse aorta, and the left sixth arch artery persisting in the fetal circulation as the arterial duct (Figure 1.25).

The multiple variants of vascular rings are well explained on the basis of retention of the various components of the initially bilaterally symmetrical system [19]. As already discussed, the initially common lumen of the...
Figure 1.20  The episcopic section shows the right side of the developing mouse heart at embryonic day 13.5. The proximal outflow cushions have fused to form the cranial margin of the persisting embryonic interventricular communication (white circle).

Figure 1.21  This episcopic section, in the same plane as Figure 1.20, is from a mouse at embryonic day 14.5. The surface of the fused proximal cushions has muscularized to form the margin of the free-standing infundibular sleeve adjacent to the aortic root.
**Figure 1.22** This episcopic section, again from a mouse at embryonic day 14.5, but now in four-chamber projection, shows how the rightward margins of the AV endocardial cushions have fused to close the RV entrance to the subaortic vestibule, thus forming the membranous septum, and completing the process of ventricular septation.

**Figure 1.23** The image is from an episcopic dataset prepared from a human embryo at Carnegie stage 13. The cavity of the distal outflow tract becomes continuous with the lumen of the aortic sac at the level of the pericardial reflections (thick arrows). Arising from the aortic sac are the arteries running through the fourth and sixth pharyngeal arches. The fourth arch arteries will become the systemic channels, while the sixth arch arteries will supply the developing pulmonary arteries, so at this stage the dorsal wall of the sac (star) is the putative aortopulmonary septum.
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Figure 1.24 The image shows orthogonal sections from an episcopic dataset from a mouse at embryonic day 11.5, with reconstruction of the arteries running through the pharyngeal mesenchyme. At this stage, the arteries of the fourth arch are dominant, and bilaterally symmetrical, as are the arches of the first through third arches, which are diminishing in importance, and those of the sixth arches, which are still developing.

Figure 1.25 The image is a reconstruction made from an episcopic dataset prepared from a mouse at embryonic day 14.5. It shows how, because of regression of the right-sided components of the initially bilaterally symmetrical arteries coursing through the pharyngeal pouches, the system has been transformed into the arch of the aorta and the arterial duct. The seventh intersegmental arteries (stars), however, have still to migrate cranially to become the subclavian arteries. PT, pulmonary trunk.
Development of the Coronary Circulation

The coronary arteries, which supply blood to the various tissues within the walls of the heart, and the coronary veins, which return the deoxygenated blood, are epicardially derived. Most of the cells are derived from the epicardial organ, which grows over the entire epicardial surface of the heart as far as the distal outflow tract [21]. An additional population of cells then forms around the distal outflow tract [22]. The proximal coronary arteries bud out from the aortic wall, with the openings initially seen distal to the junction between the developing sinuses and the intrapericardial component of the aorta (Figure 1.27). The buds growing from the aortic trunk make contact with the plexuses forming around the distal outflow tract, which in turn communicate with the overall epicardial plexus [22]. Subsequent to the separation of the aortic and pulmonary roots by fusion of the outflow cushions, the origins of the coronary arteries however, require straight as opposed to spiraling formation of the outflow cushions. Inappropriate transfer of the pulmonary trunk in this setting, as opposed to the aorta, then explains well the spectrum known as the Taussig–Bing malformation [20].

Figure 1.26 The image is from an episcopic dataset prepared from a developing mouse heart at embryonic day 11.5. It shows a long axis cut through the developing outflow tract. The parietal walls of the aorta and pulmonary trunk have grown into the heart from the second heart field. The distal outflow tract is now undergoing separation by fusion of a ventral intraluminal protrusion from the pharyngeal mesenchyme enclosing the aortic sac (star) with the distal ends of the cushions that extend through the outflow tract.
Figure 1.27 The image is from an episcopic dataset prepared from a developing mouse heart at embryonic day 13.5. It is a frontal section showing the part of the aortic root adjacent to the newly separated pulmonary root. Note the fused mass of the proximal outflow cushions that produced the separation. The bud of the left coronary artery, arising from the aortic trunk distal to the ends of the outflow cushions, which will cavitate to form the aortic valvar leaflets. The bud has joined with the epicardial component of the developing left coronary artery.

Figure 1.28 The image, this time in short axis, and viewed from above, is from an episcopic dataset prepared from a mouse heart at embryonic day 15.5. The origins of the coronary arteries, which were originally formed distal to the junction between the developing sinuses and the intrapericardial aorta (see Figure 1.27), have now been incorporated within the aortic valvar sinuses adjacent to the pulmonary root. Dashed line, transient aortopulmonary foramen.
are incorporated within the two aortic valvar sinuses formed adjacent to the pulmonary trunk (Figure 1.18). Inappropriate connection with a pulmonary valvar sinus provides the explanation for anomalous origin of a major coronary artery from the pulmonary trunk, while abnormal incorporation within the developing aortic sinuses explains well the various lesions seen in which the coronary arteries arise from inappropriate sinuses.

Acknowledgments

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References


