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Basic Anatomy and Embryology of the Heart

Frank L. Conlon, Christopher E. Slagle, Andy Wessels

ORIGINS OF CARDIAC PRECURSOR POPULATIONS

Heart development begins as the primary germ layers—ectoderm, mesoderm, and endoderm—are induced and progressively changed to various cell types during the morphogenetic process of gastrulation. Combinatorial networks of intercellular signaling events cooperate with massive tissue migrations and internalizations to lay out the basic body plan of the vertebrate embryo. Mesoderm-derived cardiac precursors are among the first cell populations to internalize, coalescing into 2 bilateral populations toward the anterior end of the embryo between 13 and 15 days of human development. The identity of these progenitor pools as cardiac precursors is defined and maintained by expression of a core cohort of developmental gene regulators or transcription factors. These cardiac transcription factors function cooperatively and hierarchically to induce expression of appropriate structural proteins, including components of the specialized cardiomyocyte contractile apparatus and ion channels. Many cardiac transcription factors function not only in the initial specification of cardiac precursors, but also in later aspects of heart morphogenesis, such as establishing chamber identity, chamber-vessel alignment, and conduction system development. Therefore proper spatial and temporal functions of cardiac transcription factors dictate development of a healthy and functional heart. This requirement of correct genetic regulation is exemplified by the numerous congenital heart defects associated with or caused by mutations in cardiac transcription factors.

Even at such early stages of embryonic development, the cardiac precursor pools have been subdivided into two distinct sources of progenitors according to expression of different subsets of cardiac transcription factors. The first, designated as the first heart field, will form the primitive linear heart tube, which will give rise to the left ventricle and most of the atrial tissues. The second heart field, incorporated into the primitive embryonic heart at various stages of development, contributes to the right ventricle and outflow tract. The developing heart receives further contributions from the cardiac neural crest and the mesothelium. The cardiac neural crest is made of ectodermal cells arising outside the heart fields at the lateral borders of the neural plate and because of neural induction from the midline ectoderm. The cardiac neural crest migrates to the heart-forming region, where it contributes to septation of the outflow tract into the arterial and pulmonary vessels. The mesothelium is the embryonic cell source that gives rise to the epicardium, an epithelium that covers the surface of the heart and that plays a role in a number of processes, such as the development of the coronary system and the formation of the annulus fibrosus.

FORMATION OF THE PRIMITIVE LINEAR HEART TUBE

Even before gastrulation has completed, the internalized bilateral cardiac precursor pools continue to migrate in response to signaling cues from neighboring tissues. Remaining as cohesive epithelia, the heart fields

move anteriorly and ventrally between 15 and 20 days of development, fusing at the embryonic midline to form the transient cardiac crescent (Fig. 1.1). Proper midline fusion of the bilateral cardiac primordia is essential for development of the heart. Several cardiac transcription factors are required for this process, and loss of function of any one of them causes extensive defects in further morphogenesis, including cardiac bifida in severe cases.

Newly united as the cardiac crescent, the multipotent cardiac progenitors coalesce further to form a linear tube by 3 weeks of development, segregating into the future endocardial lining and myocardial walls (Fig. 1.2). The linear heart tube consists exclusively of differentiated first heart field cells; the second heart field persists as a mesenchymal population, which is a loose association of rapidly dividing precursor cells adjacent to the heart tube. Although no specialized electrical conduction system has yet arisen, the myocardium of the linear heart tube already exhibits autonomous contractions. Compared with those of a mature heart, these contractions are slow and weak, driven only by the intrinsic depolarizing activity and conductivity of the still-maturing cardiomyocytes. Once the conduction system develops and connects to the mature working myocardium, it will serve as an extrinsic regulator of the electrical impulses within the myocardium. Sufficient contractile force will, in turn, allow the heart to beat at the strength required to circulate blood throughout the body.

LOOPING OF THE LINEAR HEART TUBE

As a consequence of its formation, differentiation, and rudimentary functionality, the linear heart tube is mostly postmitotic. During the fourth week of human gestation, growth and elongation of the linear heart tube occur by means of contribution and division of second heart field cells at both the sinus venosus and truncus arteriosus (posterior and anterior poles, respectively). Concurrently, an embryo-wide genetic program breaks the final axis of symmetry—the left-right axis. Asymmetrical intercellular signaling on the left side of the embryo governs the migration and division of second heart field cells in the lengthening heart tube, leading to two major morphological cardiac asymmetries. First, the entire linear heart tube displaces to the right and rotates 90 degrees about its anterior-posterior axis, so that the original ventral surface of the linear tube is now the left side of a C-shaped tube (Fig. 1.3). Second, asymmetrical mitotic expansion of the second heart field contributions leads to localized “ballooning” of the primitive atrial and ventricular regions of the heart tube, transforming the C-shaped tube into an S-shaped heart (Fig. 1.3).

Further gross morphogenetic movements of the embryo bring the two poles in close apposition, anterior to the primitive chambers. This repositioning prepares the inflow and outflow tracts for appropriate connections to the developing vasculature, thereby contributing to proper segregation of oxygenated and deoxygenated blood flow among the heart, lungs, and body. By 30 days of gestation, the prospective atria

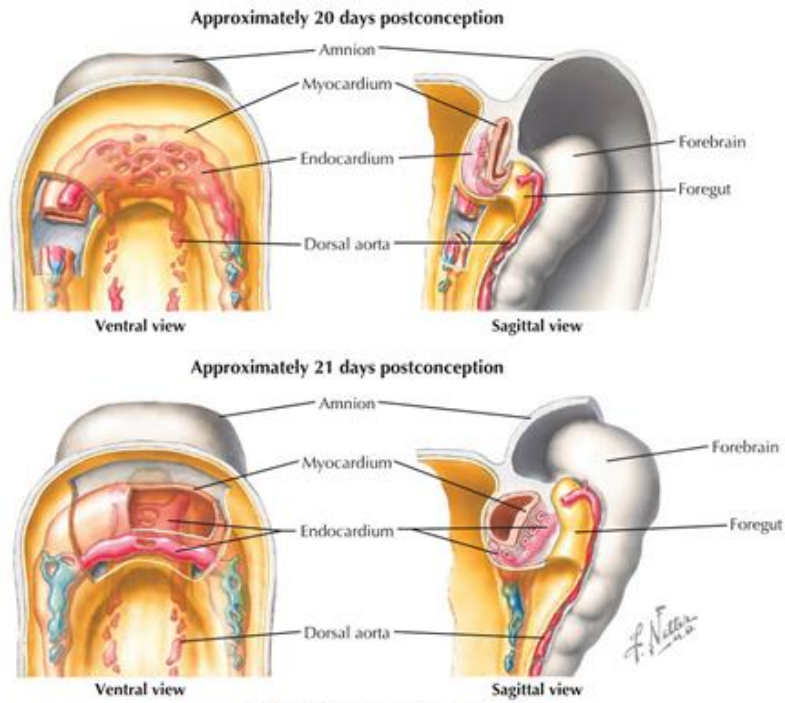


FIG 1.1 Formation of the heart tube.

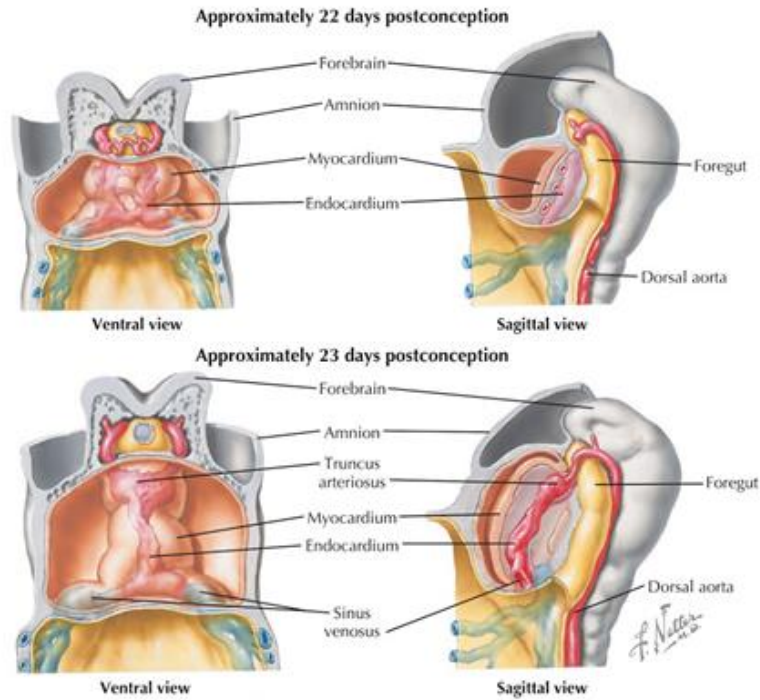


FIG 1.2 Formation of the heart tube (continued).

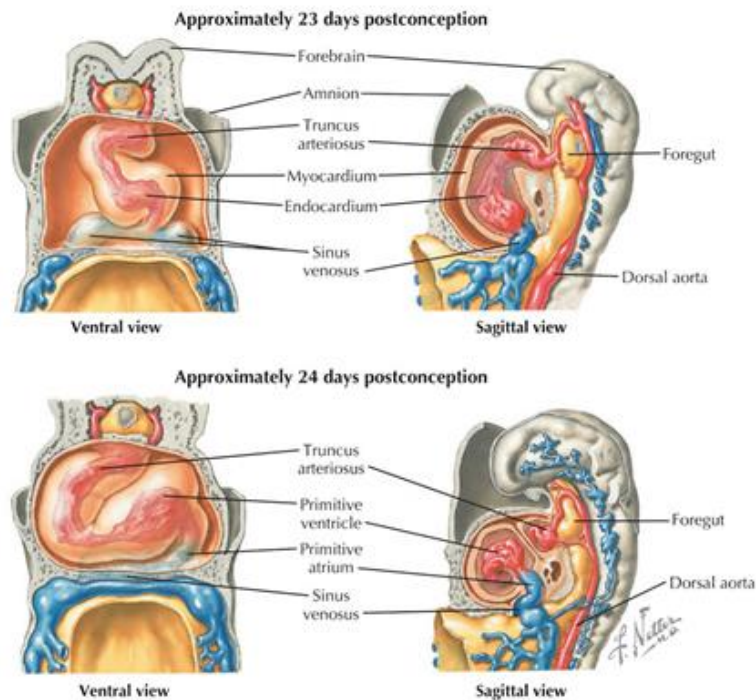


FIG 1.3 Formation of the heart loop.

are repositioned anterior to the ventricular region, marking the first resemblance of the embryonic heart to its future adult structure.

Formation of the S-looped heart overlaps with the beginnings of ventricular and outflow tract septation and valve development as endocardial cushions emerge within the atrioventricular junction and the outflow tract.

CHAMBER FORMATION

During the time of cardiac looping, at approximately 3 weeks of development, the arterial and venous poles of the heart decrease or cease cell division. At the same time, cardiomyocytes at two distinct locations within the intervening tissue reinitiate cell proliferation. This localized expansion of cardiomyocytes gives rise anteriorly to the atria and posteriorly to the left ventricle, with the area separating the two regions giving rise to the atrioventricular canal. Studies in chickens and mice demonstrated that the atria grow not only through proliferation but also by the recruitment of cells to the venous pole of the heart. The left ventricle and the atria are largely derived from a common pool of progenitors termed the first heart field (Fig. 1.4). In contrast, the second heart field gives rise to the dorsal mesenchymal protrusion and primary atrial septum, which are tissues that are critically important for atrioventricular septation, the outflow tract, and the right ventricle. A conserved role for the second heart field is supported by the observations that abnormalities that affect the expansion of the second heart field are associated with congenital heart disease in mouse models and humans, including atrial and atrioventricular defects, as well as outflow tract abnormalities.

Contribution of cells from the second heart field to the heart is complete by the fifth week of human development. At this stage, chamber identity can be established by inspecting anatomic features and/or by the expression of left or right ventricular chamber-specific genes. As the cardiovascular system develops to support postnatal systemic and pulmonary circulations, the heart goes through a series of complex remodeling events. Critical steps in this process are the formation of the septa between individual components of the heart, with the purpose of separating the respective blood flows within the heart, and the formation of valves facilitating unidirectional flow among the respective components. Together, these two events are commonly referred to as valvuloseptal morphogenesis.

SEPTATION

Atrial septation is initiated when the second heart field–derived dorsal mesenchymal protrusion and the myocardial primary atrial septum (or septum primum) extend ventrally into the, yet undivided, common atrium. In the mouse, this process takes place between embryonic day (ED) 9.5 to 10.5; in humans the process occurs around day 30. The space between the leading edge of the atrial septum and the fusing atrioventricular cushions in the atrioventricular canal is the primary atrial foramen. As the primary atrial septum grows toward the mesenchymal atrioventricular cushions, thereby closing the primary interatrial foramen, perforations appear in the upper part of the primary atrial septum. These perforations will eventually coalesce and form the secondary interatrial foramen. As this part of atrial septation process nears completion, the secondary atrial septum (or septum secundum) appears

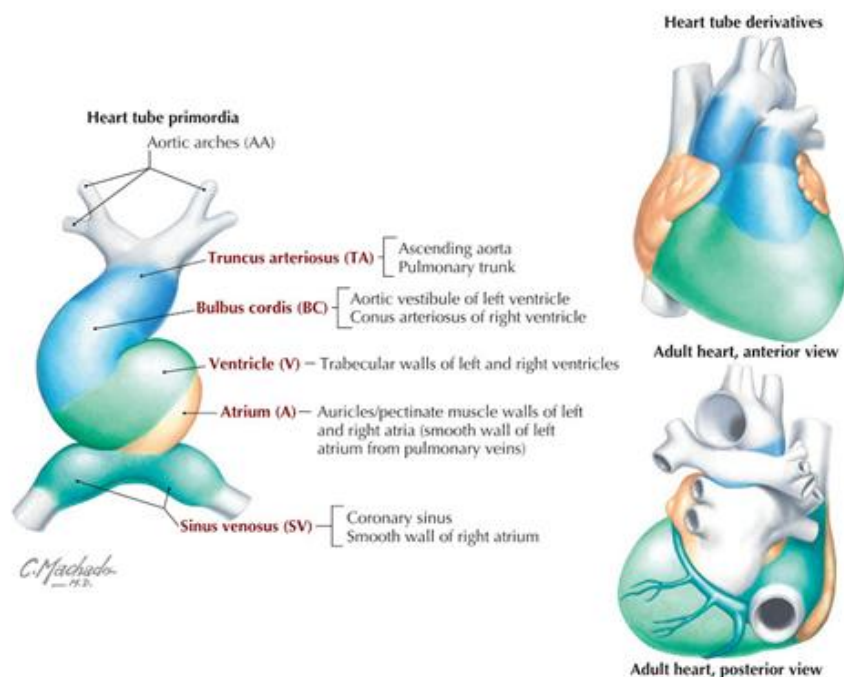


FIG 1.4 Summary of heart tube derivatives.

in the space between the primary atrial septum and the left venous valve in the roof of the right atrium. Eventually, the upper part of the primary atrial septum will fuse with the secondary atrial septum, thereby closing off the secondary atrial foramen and completing the atrial septation process. Failure of fusion of the two atrial septa will lead to the congenital defect patent foramen ovale.

Compared with atrial septation, the creation of the ventricular septum is a rather straightforward process. As the tubular heart expands, undergoes looping, and remodels, distinctive left and right ventricular components appear. During this process, a myocardial ridge, the interventricular septum, emerges between the left and right ventricle. Subsequent outward expansion of the ventricles, a process sometimes referred to as “ballooning,” in combination with upward growth of the interventricular septum and eventual fusion of crest of the septum with the atrioventricular cushions, completes the process of ventricular septation. Cell lineage tracing experiments in the mouse demonstrated that, like the right ventricle, the interventricular septum is largely derived from the second heart field.

The third septal structure that is required for separating the respective blood flows in the heart is found in the outflow tract. After completion of cardiac looping, a single outflow tract can be found connected to the right ventricular component of the yet unseptated heart. Septation of this outflow tract is required for the formation of an aorta, which eventually connects to the left ventricle, and a pulmonary trunk that comes from the right ventricle. Two sets of endocardial ridges are located within the outflow tract, and as a result of their fusion, these will separate the common outflow tract into an aorta and a pulmonary trunk. Failure of fusion can lead to congenital defects, including a double outlet right

ventricle. The cardiac neural crest is also important in the septation process that separates aorta and pulmonary trunk. Abnormal development of the cardiac neural crest specifically affects the formation of the aorticopulmonary septum downstream of the semilunar valves (Fig. 1.5). This can result in the congenital defect common arterial trunk (or truncus arteriosus) or in aorticopulmonary window.

FORMATION OF THE CARDIAC VALVES

The fully formed heart contains two sets of one-way valves. In the atrioventricular junction, the atrioventricular valves facilitate unidirectional flow through the left and right atrioventricular orifices, whereas at the ventriculoarterial junction, the semilunar valves serve the same function at the junction of the left ventricle and the aorta, and at the junction of the right ventricle and the pulmonary trunk.

Atrioventricular valve formation is initiated at the atrioventricular junction of the looping heart (see previous description); two atrioventricular cushions appear as a result of local accumulation of extracellular matrix between the atrioventricular endocardium and myocardium. A process of endothelial-to-mesenchymal transformation leads to the generation of a population of mesenchymal cells that colonize the cushions. As the heart grows, and these major atrioventricular cushions become bigger, they eventually fuse, thereby separating the common atrioventricular junction into the left and right atrioventricular orifices. As this process takes place, on the lateral walls of these respective orifices, two additional atrioventricular cushions form. These are known as the left and right lateral atrioventricular cushions. These lateral cushions also become populated with endocardially derived mesenchyme. Recent

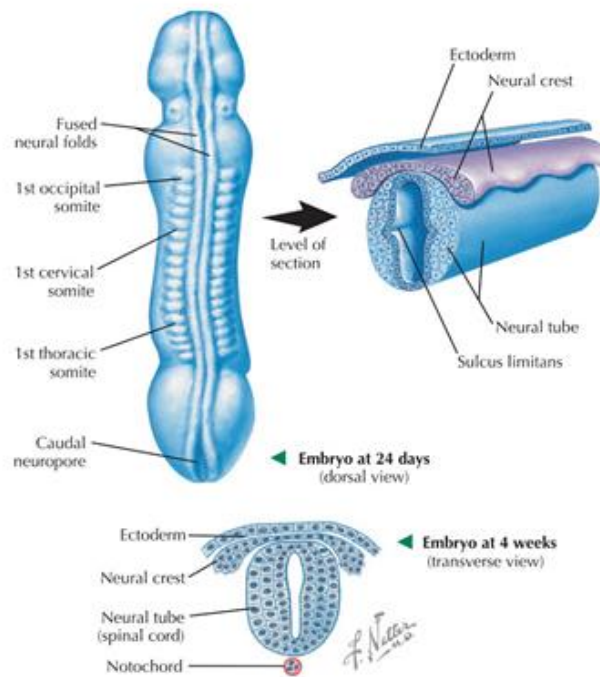


FIG 1.5 Nervous tissue of embryo at 24 days and 4 weeks.

cell fate studies in mice showed that epicardially derived cells migrate into these lateral cushions. Epicardially derived cells do not populate the major cushions. Further remodeling of the cushion-derived tissues eventually leads to the formation of the mitral valve leaflets in the left atrioventricular orifice and the tricuspid valve leaflets in the right atrioventricular orifice.

In many respects, the development of the semilunar valves is similar to that of the atrioventricular valves. It involves the fusion of two mesenchymal tissues, the parietal and septal endocardial ridges, which result in the separation of the left and right ventricular outflows. The emergence of a set of smaller endocardial ridges, the intercalated ridges at the opposite sides of the formed septum, resembles the process of formation of the lateral cushions in the atrioventricular junction. The remodeling of these two sets of mesenchymal ridges will eventually lead to the formation of the semilunar valves.

CARDIAC NEURAL CREST

The neural crest is a transient population of cells that form from the dorsal ectoderm at the time of neural tube closure (Fig. 1.5). The neural crest population arises through a series of inductive interactions with surrounding tissues around the fourth week of development. Once formed, the cells undergo an epithelial-to-mesenchymal transition, migrating ventrally and laterally to contribute to a wide array of tissue types, including the epinephrine-producing cells of the adrenal gland, the parasympathetic neurons, cartilage, bone, connective tissue, and pigment cells. The neural crests themselves are multipotential at the

time of their formation; their ultimate fate is a reflection of their relative position along the anterior-to-posterior axis of the embryo. In the cranial portions of the embryo, classic fate mapping studies showed that a subpopulation of neural crest cells enter the arterial pole or the venous pole of the heart to give rise to all of the parasympathetic innervation of the heart, the smooth muscle layer of the great vessels, and portions of the outflow tract. This population is termed the cardiac neural crest. Ablation studies in chicks and genetic studies in mammals demonstrated not only that the cardiac neural crest cells contribute to these regions of the heart but also that they are also essential for the proper formation of each of these structures.

EPICARDIUM AND EPICARDIALLY DERIVED CELLS

The walls of the developed heart essentially consist of three cell layers: the endocardium, the myocardium, and the epicardium. The endocardium and myocardium are generated early in development during the formation of the primitive linear heart tube (see previous description). However, the epicardium, a layer of epithelial cells covering the heart, is like the cardiac neural crest, a late addition to the developing heart. The source of the epicardium is the proepicardium, a local proliferation of the mesothelium found in association with the sinus venosus at the venous pole. In the mouse, the proepicardium can be seen around ED 9.5; in humans, this happens around day 30. Shortly after its generation, the proepicardium attaches to the myocardial surface in the atrioventricular junction. From there, the cells spread out as an epicardial sheet and eventually cover nearly the entire heart. Cell fate studies in animal