Myocardial energy is stored as creatine phosphate (CP), which is in equilibrium with ATP, the immediate source of energy. In states of reduced energy availability, the CP stores decline first. Cardiac hypertrophy, fibrosis, tachycardia, increased wall tension resulting from ventricular dilation, and increased intracytoplasmic [$Ca^{2+}$] all contribute to increased myocardial energy needs. When coupled with reduced coronary flow reserve, as occurs with obstruction of coronary arteries or abnormalities of the coronary microcirculation, an imbalance in myocardial ATP production relative to demand may occur, and the resulting ischemia can worsen or cause heart failure.

**Developmental Biology of the Cardiovascular System** The heart is the first organ to form during embryogenesis (Fig. 265e-12) and must accomplish the simultaneous challenges of circulating blood, nutrients, and oxygen to the other forming organs while continuing to grow and undergo complex morphogenetic changes. Early progenitors of the heart arise within very early crescent-shaped fields of lateral splanchnic mesoderm under the influence of multiple signals, including those derived from neural ectoderm long before neural tube closure. Early cardiac precursors express genes encoding regulatory transcription factors that play reiterated roles in cardiac development, such as *NKX2-5* and *GATA4*. Mutations in these genes are responsible for some forms of inherited congenital heart disease. Cardiac precursors coalesce to form a midline heart tube composed of a single cell layer of endocardium surrounded by a single layer of myocardial precursors. The caudal, inflow region of the heart tube, which is destined to adopt a more rostral final position, represents the atrial anlagen, whereas the rostral, outflow portion of the tube forms the truncus arteriosus, which divides to produce the aorta and the proximal pulmonary artery. Between these extremes lie the structural precursors of the ventricles.

The linear heart tube undergoes an asymmetric looping process (the first gross evidence of left-right asymmetry in the developing embryo), which positions the portion of the heart tube destined to become the left ventricle to the left of the more rostral precursors of the right ventricle and outflow tract. Looping is coordinated with chamber specification and ballooning of various regions of the heart tube to produce the presumptive atria and ventricles.

Relatively recent work has demonstrated that significant portions of the right ventricle are formed by cells that are added to the developing heart after looping has occurred. These cells, which are derived from what is called the second heart field, migrate to the heart from the ventral pharynx and express markers that allow for their identification, including Islet-1. Different embryologic origins of cells within the right and left ventricles may help explain why some forms of congenital and adult heart diseases affect these regions of the heart to varying degrees.

After looping and chamber formation, a series of septation events divide the left and right sides of the heart, separate the atria from the ventricles, and form the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, the single layer of myocardial cells secretes an extracellular matrix rich in hyaluronic acid. This extracellular matrix, termed "cardiac jelly," accumulates within the endocardial cushions, precursors of the cardiac valves. Signals from overlying myocardial cells, including members of the transforming growth factor β family, trigger migration, invasion, and phenotypic changes of underlying endocardial cells, which undergo an epithelial-mesenchymal transformation and invade the cardiac jelly to cellularize the endocardial cushions. Mesenchymal components proliferate and remodel to form the mature valve leaflets.

The great vessels form as a series of bilaterally symmetric aortic arch arteries that undergo asymmetric remodeling events to form the mature vasculature. The immigration of neural crest cells that arise in the dorsal neural tube orchestrates this process. These cells are required for aortic arch remodeling and septation of the truncus arteriosus. They develop into smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries. Smooth-muscle cells within the descending aorta arise from a different embryologic source, the lateral plate

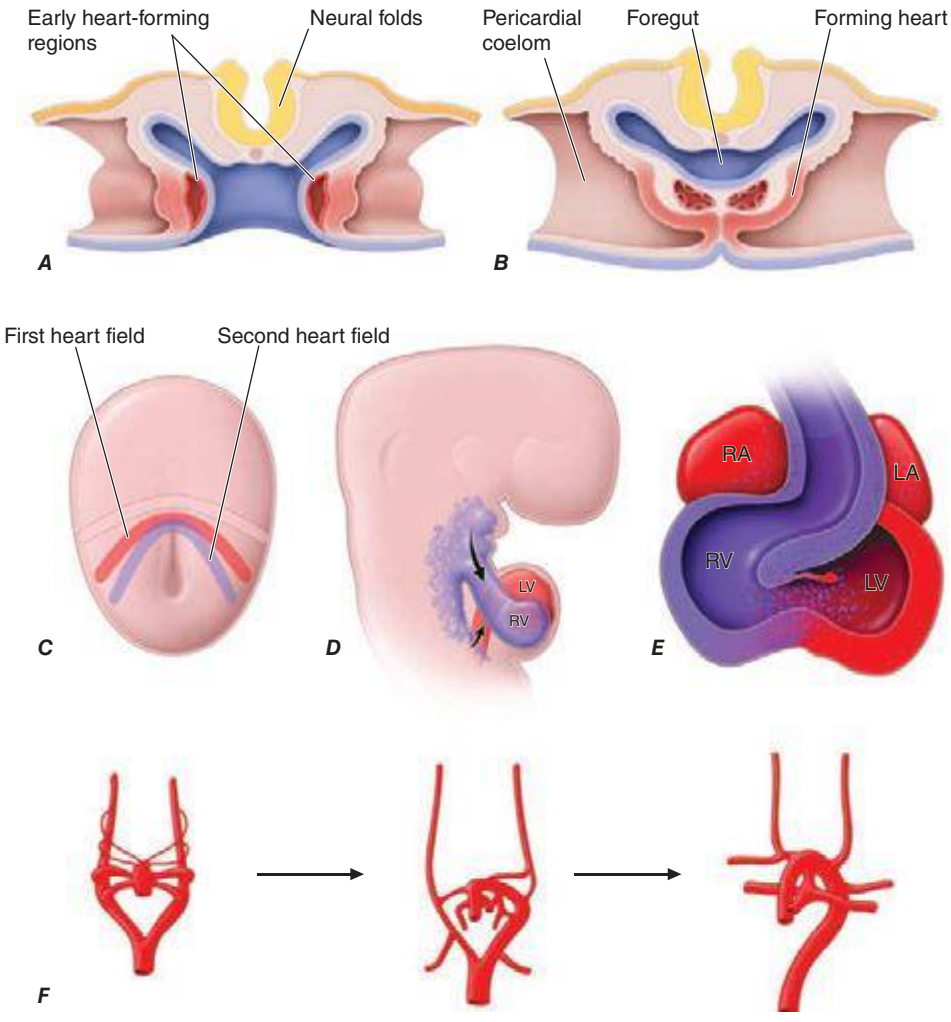


**FIGURE 265e-12** ***A.*** Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. ***B.*** The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. ***C.*** At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. ***D.*** Second heart field cells populate the pharyngeal region before subsequently migrating to the maturing heart. ***E.*** Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. ***F.*** The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.