Development of Cardiovascular System

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Key Points

- The heart, blood vessels and blood cells develop from splanchnic mesoderm. The cardiac valves and septa are partly derived from neural crest cells.

- Paired endocardial tubes develop in the cranial region of the embryo. Expansion of the brain vesicles results in caudal displacement of the endocardial tubes.

- Lateral folding of the embryo leads to merging of the endocardial tubes, except at their cranial and caudal ends.

- The structures formed, the sinus venosus, atrium, ventricle and truncus arteriosus, differentiate into the chambers of the heart and great vessels (venae cavae, aorta, and pulmonary trunk).

- The primordial heart elongates and bends, forming a cardiac loop, which develops into the four-chambered heart, characteristic of mammals and avian species.

- Formation of interatrial and interventricular septa leads to interatrial and interventricular partitioning. Interatrial septation is completed postnatally.

- Mesenchymal endocardial cushions develop in the atrioventricular region. These structures fuse, dividing the atrio-ventricular canal into two distinct openings. Atrioventricular valves and semilunar valves develop from neural crest cells and mesenchyme.

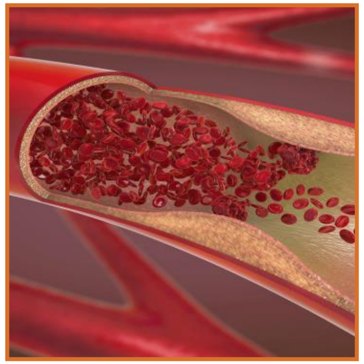
- Prior to birth, the placenta is the organ of gas exchange. The umbilical vein carries oxygenated blood to the foetus. The foetal atria communicate by means of a small opening in the interatrial septum, the foramen ovale, while the ductus arteriosus connects the pulmonary trunk to the aorta. The presence of these shunts means that most of the circulating blood bypasses the non-functional foetal lungs.

- Blood vessels and lymphatic vessels both develop from splanchnic mesoderm. Both sets of vessels are formed by vasculogenesis and angiogenesis.

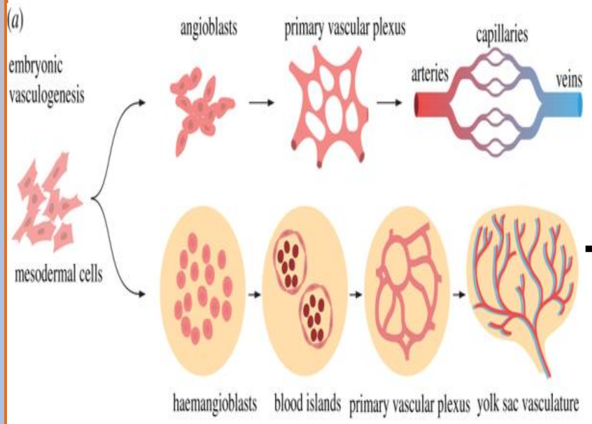
- In the early stages of development, the respiratory, excretory and nutritional requirements of the embryo are provided by simple diffusion.

- As the conceptus increases in size, diffusion is inadequate for its nutritional, respiratory and excretory needs. Consequently, the mammalian embryo requires a system for delivering oxygen and nutrients to its tissues and for removing its waste products. These requirements are supplied by the cardiovascular system.

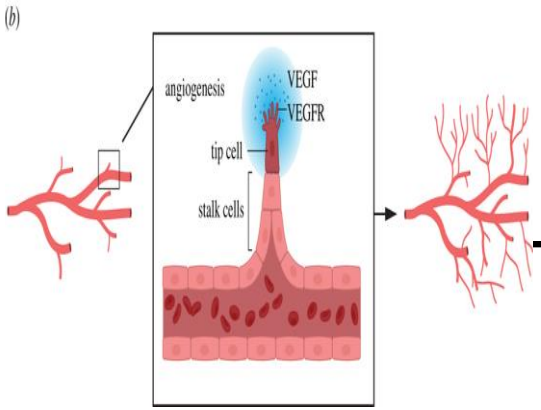
- As one of the first functional systems to develop in the embryo, the cardiovascular system consists of a central pumping organ, the heart, linked to a set of arteries which convey blood to the tissues. Complementary vessels, called veins, carry blood from the tissues back to the heart. An associated network, the lymphatic system, assists in the return of extracellular fluids to the vasculature.



New Blood Vessel Formation



Vasculogenesis



Angiogenesis

- Vasculogenesis, the formation of blood vessels from blood islands, commences during the third week of gestation in domestic mammals, first in the yolk sac and later in the allantois. A number of factors including fibroblast growth factor 2 (Fgf-2), vascular endothelial growth factor (VEGF) and the angiopoietin proteins have an initiating role in vasculogenesis.
- Fibroblast growth factor induces splanchnic mesodermal cells to form haemangioblasts in the yolk sac.
- Vascular endothelial growth factors are a family of proteins which are key to vasculogenesis and are expressed at high levels in areas proximal to active blood vessel formation. These signalling factors act on both haemangioblasts and angioblasts and subsequently promote the differentiation of angioblasts into endothelial vessels. The contribution of haemangioblasts to the formation of blood vessels and to haematopoiesis is outlined in Figure 1.
- Angiopoietins promote the interaction between endothelial cells and smooth muscle cells which eventually surround some developing blood vessels. Development of blood vessels involves a complex series of events during which endothelial cells differentiate, proliferate, migrate and become organised into an orderly vascular network.
- Splanchnic mesodermal cells lining the yolk sac form clusters, referred to as blood islands. With the formation of extra-embryonic vascular channels, a primitive circulatory system becomes established.

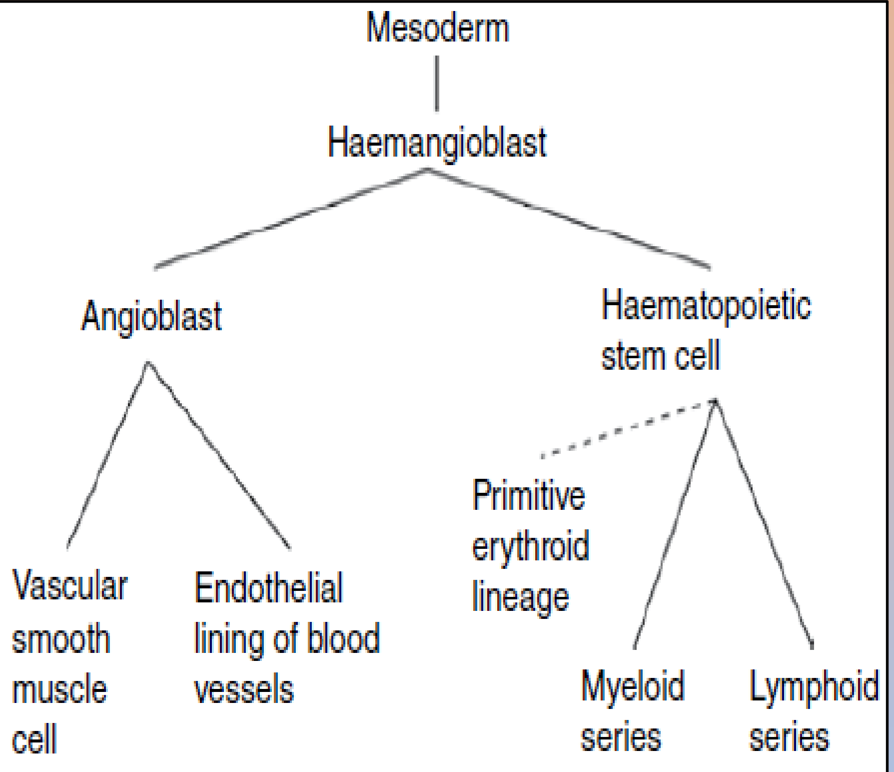


Figure 1 Outline of the origin and differentiation of angioblasts and haematopoietic stem cells from a common mesodermal precursor, the haemangioblast. The haematopoietic stem cell initially gives rise to a primitive erythroid lineage but as maturation proceeds definitive erythrocytes and myeloid cells are produced, along with cells from which the lymphoid lineage develops.

- In contrast to vasculogenesis, Angiogenesis comprises several morphogenic events during which pre-existing endothelial cells sprout, branch and become canalised.
- Other processes that occur during angiogenesis include the remodelling of existing vessels through anastomosis and branching accompanied by increases in luminal diameter.
- This process, a fundamental requirement for embryological development, continues postnatally. VEGF-a is critial to angiogenesis and is produced by mesenchymal cells.
- This factor acts on the endothelial cells at points where new vessel formation commences, termed ‘tip’ cells.
- Endothelial cells release the signalling molecule platelet-derived growth factor (PDGF) which stimulates migration of mesenchymal cells towards the vascular endothelium.
- In response to the release of other growth factors by endothelial cells, differentiation of mesenchymal cells into vascular smooth muscle cells occurs.

- When initially formed, the haematopoietic islands are compact structures. As development progresses, cells at the periphery of the blood islands, under the influence of growth factors, become squamous in shape and surround the centrally located cells. The squamous cells form the endothelial lining of the emerging vascular system and the round, centrally-located cells become the haemoblastic cells or embryonic nucleated erythrocytes (Figure 2).
- Vascular development occurs under the influence of specific growth factors.
- Basic fibroblast growth factor, which binds to receptors on splanchnic mesodermal cells, induces them to form haemangioblasts.
- Vascular endothelial growth factor promotes the differentiation of peripheral haemangioblasts in blood islands into angioblasts which, in turn, differentiate into endothelial cells and form blood vessels.

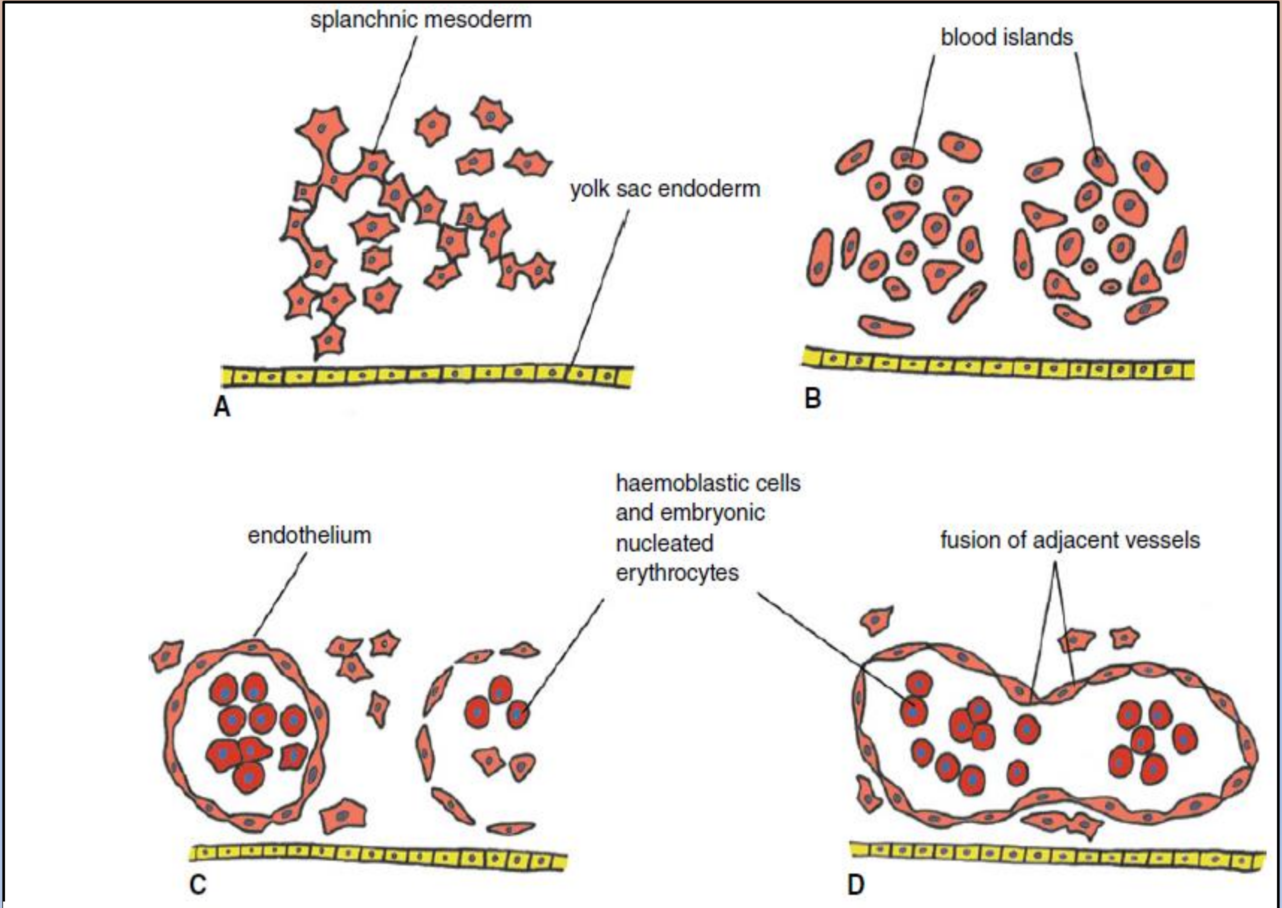


Figure 2 Sequential stages in the formation of blood vessels and blood cells from blood islands in the yolk sac (A to D).

- Maturation of the capillary network is influenced by PDGF and transforming growth factor-β (Tgf-β). Development of individual channels in the network depends on the volume and direction of blood flow.
- The channels which convey the greatest volume of blood increase in diameter and acquire additional tissue layers from the surrounding mesoderm, becoming thick-walled vessels referred to as arteries; the other vessels, veins, remain thin walled.
- Blood vessels which develop in the foetal membranes, referred to as extra-embryonic vessels, consist of paired vitelline (yolk sac) and umbilical (allantoic) arteries and veins. Intraembryonic formation of blood vessels, which proceeds in a similar manner to extra-embryonic vasculogenesis, commences soon after blood vessel formation begins in the extra-embryonic membranes. Subsequently, the extra-embryonic and intraembryonic vessels anastomose, completing the rudimentary circulatory system of the conceptus (Figure 3).

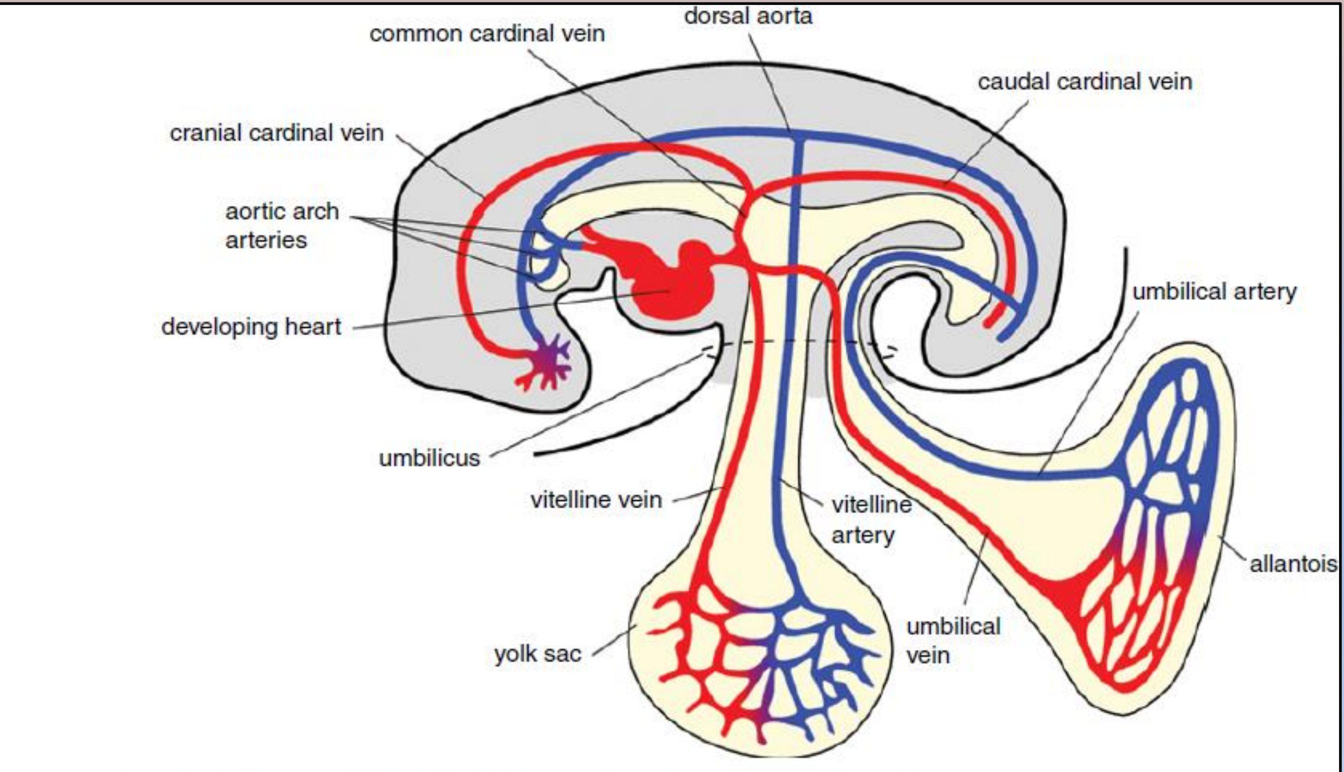


Figure 3 Left lateral view of a mammalian embryo showing the rudimentary cardiovascular system.

Development of the cardiac tubes

- Early in gestation, the embryo has a pear-shaped outline and consists of three layers, namely a dorsal layer of ectoderm, a ventral endodermal layer and a middle mesodermal layer.

- Small discrete spaces in the left and right lateral mesoderm enlarge and coalesce, forming a left and a right intraembryonic coelom, thereby splitting the lateral mesoderm into somatic and splanchnic layers.

- Later, the coelom on the right and the coelom on the left fuse cranial to the developing neural plate, forming an enlarged horseshoe-shaped coelomic cavity (Figure 4).

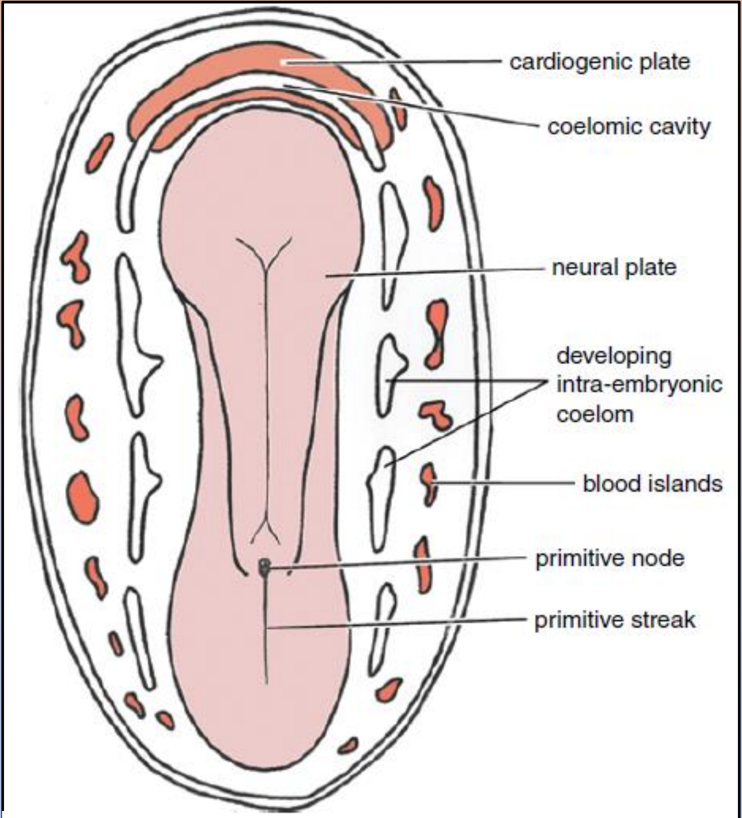


Figure 4 Development of the cardiac tube and the coelomic cavity at the embryonic disc stage.

Development of the cardiac tubes

- Ventral to the coelom, groups of cells in the splanchnic mesoderm form the cardiogenic plate, which is also horseshoe- shaped. Within the cardiogenic plate, angiogenic cell clusters give rise to a horseshoe-shaped structure, the endocardial tube.
- Later, the lateral limbs of the horseshoe-shaped vessel form the left and right endocardial tubes. Splanchnic mesodermal cells, which migrate towards and surround the endocardial tubes, form the myoepicardial mantle.
- At first, this mantle does not attach to the endothelium of the tubes. The intervening space contains a loose, gelatinous reticulum referred to as cardiac jelly.
- Many of the major intra-embryonic blood vessels are formed contemporaneously with the endocardial tubes and extra-embryonic vessels.

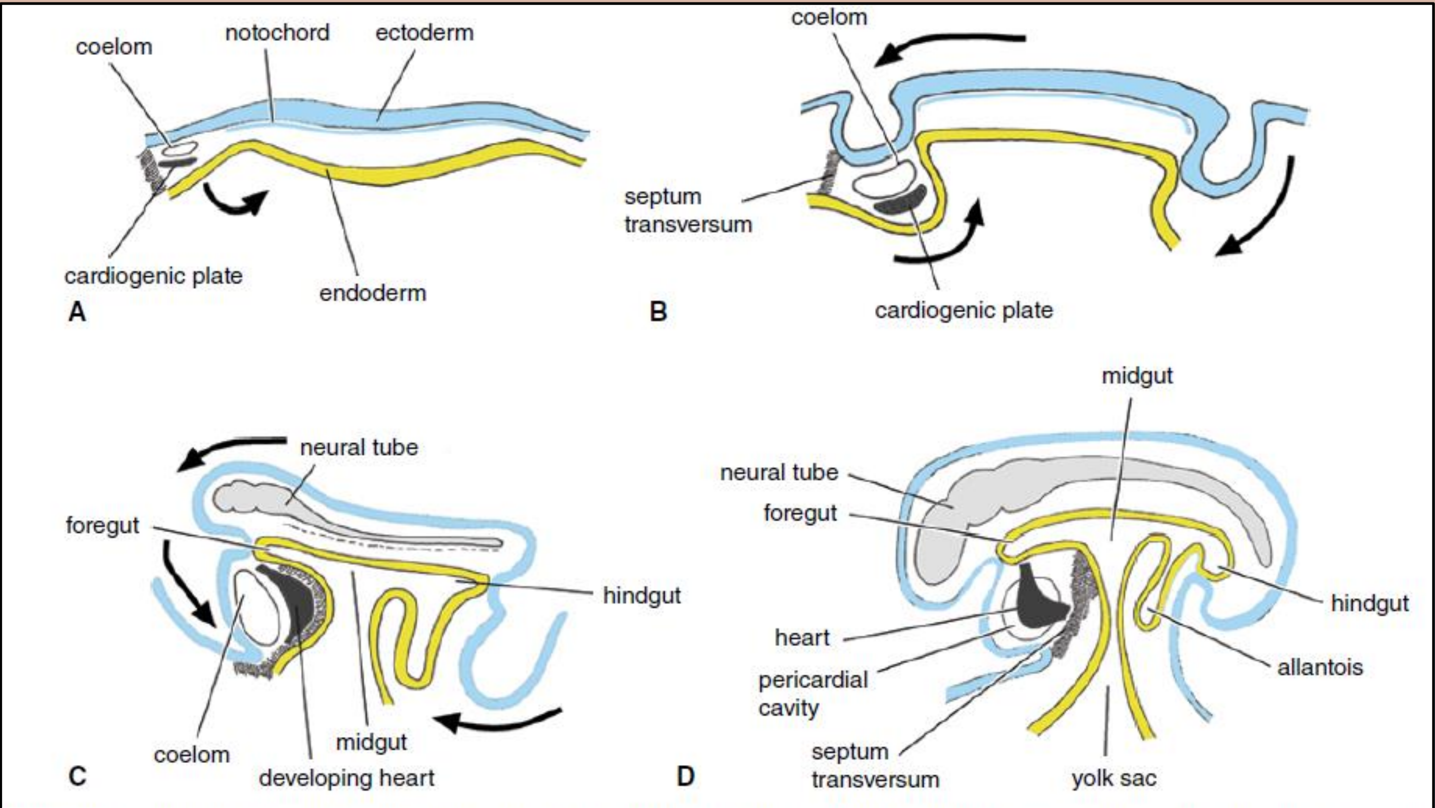


Figure 5 Sequential stages in the cranio-caudal folding of the embryo showing the changed relationship of the developing heart to other embryonic structures (A to D). Arrows indicate the direction of folding of the embryo.

Development of the cardiac tubes

- Mesodermal cells proliferate in a position cranial to the cardiogenic plate and form the septum transversum, which subsequently gives rise to the tendinous part of the diaphragm.
- The developing embryonic disc undergoes cranio-caudal and lateral folding.
- As a consequence of folding of the cranial portion of the embryo, the endocardial tubes and coelom and the septum transversum are displaced caudally.
- Consequently, the endocardial tubes lie dorsal to the coelom, ventral to the foregut and caudal to the oropharyngeal membrane (Figure 5).

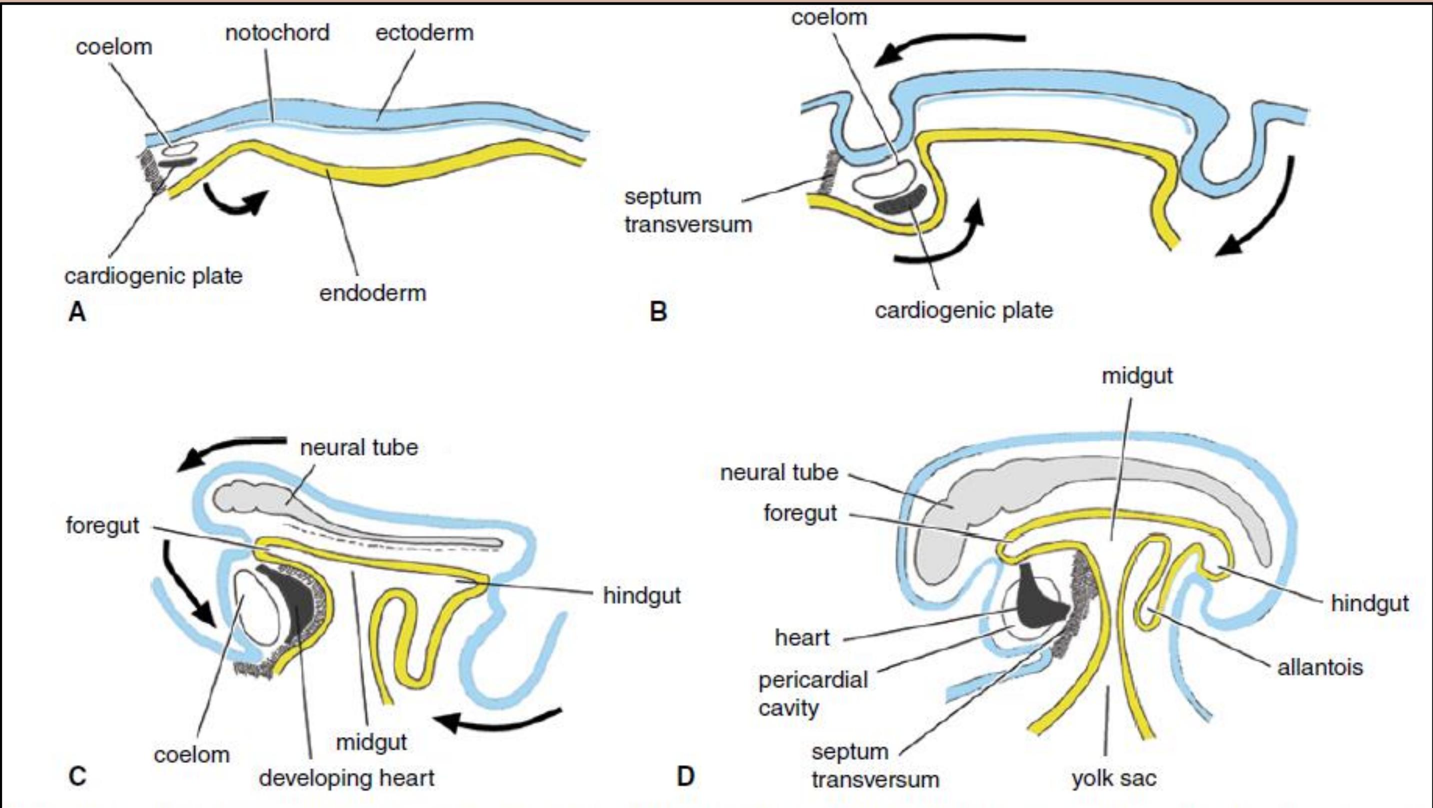


Figure 5 Sequential stages in the cranio-caudal folding of the embryo showing the changed relationship of the developing heart to other embryonic structures (A to D). Arrows indicate the direction of folding of the embryo.

- The caudal displacement of the developing heart is accompanied by rapid growth of the brain in a cranial direction so that it extends over the cardiac area.
- In this position, the convex segment of the fused endocardial tubes anastomoses with the vitelline veins from the yolk sac (Figure 6).
- Before joining the convex segment of the endocardial tube, the vitelline and umbilical veins pass through the septum transversum.
- The cranial portions of the dorsal aortae, which are drawn ventrally, form dorso-ventral loops.
- These loops, the first aortic arch arteries, fuse with the endocardial tubes (Figure 6).

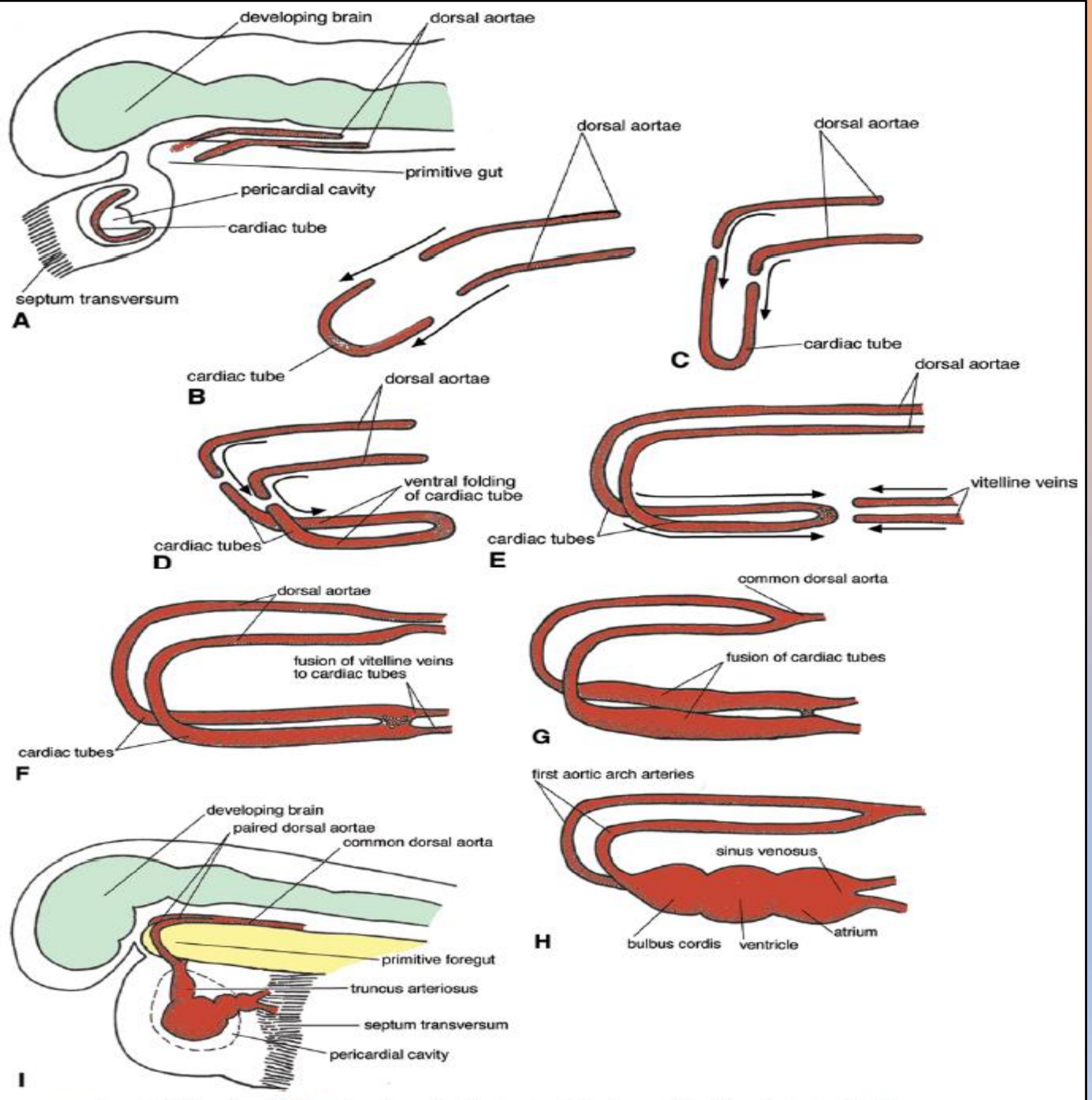


Figure 6 Stages in the formation of the heart from the cardiac tube stage to the development of an S-shaped structure (A to I).

- With lateral folding of the embryo, the left and right endocardial tubes, surrounded by their muscular layers, gradually converge.
- Fusion of the medial walls of the endocardial tubes first occurs midway along their length. Later, fusion extends cranially and caudally until a single cardiac tube is formed (Figure 6 and 7).
- However, as fusion does not extend along the entire length of the endocardial tubes, the cranial and caudal ends remain separated.
- The endothelial lining of the single cardiac tube becomes the endocardium, the myoepicardial layer forms the myocardium and, from the visceral layer lining the pericardial cavity, the epicardium is formed.
- The cardiac tube, which is located in the pericardial cavity, is initially suspended by a dorsal mesocardium and anchored by a ventral mesocardium (Figure 7).

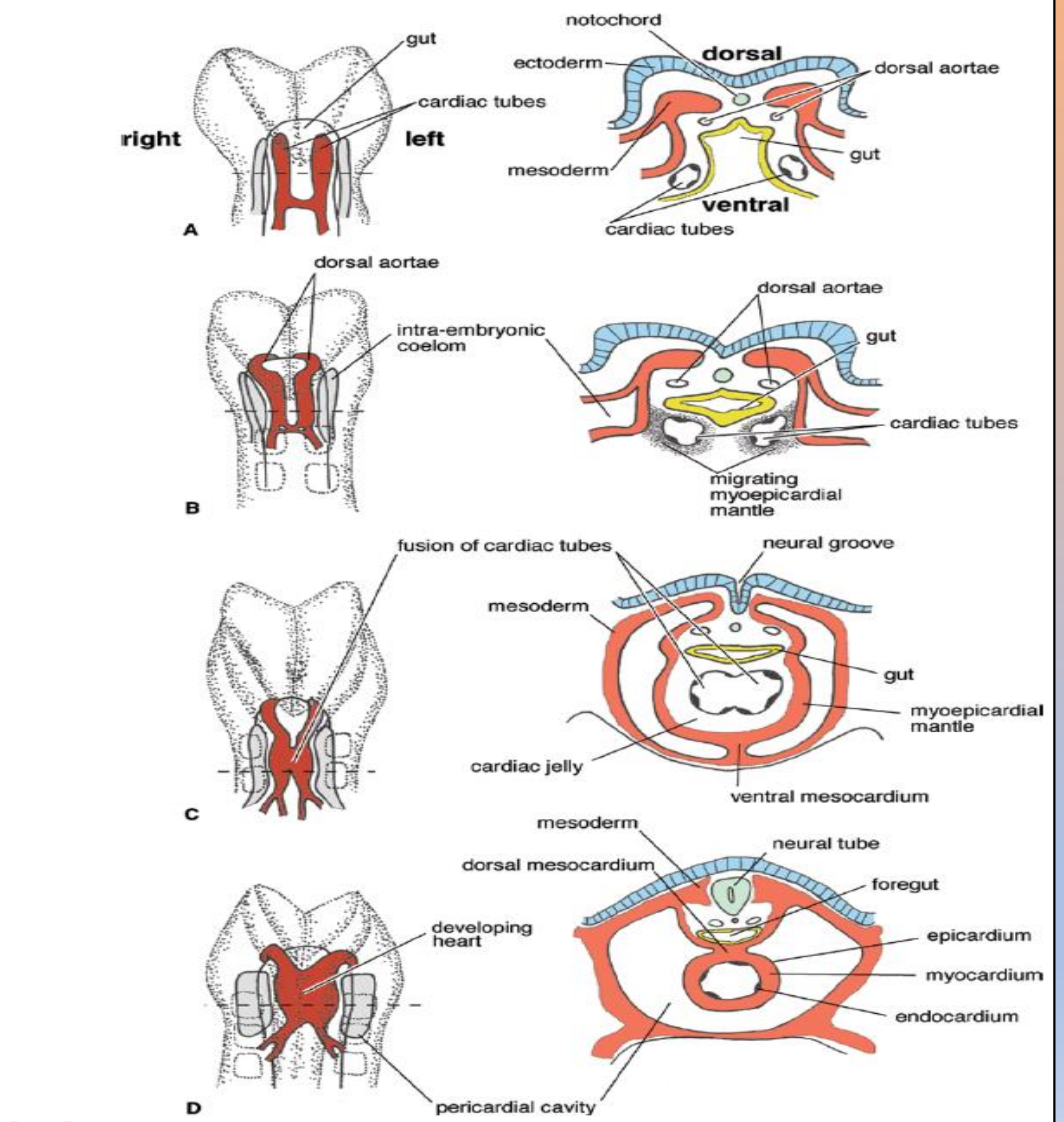


Figure 7 Ventral views of the developing cardiac tubes and coelom with corresponding cross-sections (A to D).

- This cardiac tube undergoes differential growth along its length, which results in expanded portions separated by non-expanded portions. Listed in sequential order from the cranial end, the expanded portions are the truncus arteriosus, the bulbus cordis, the ventricle, the atrium and the sinus venosus (Figure 8).

- The caudal end of the sinus venosus remains bifurcated. The ventral mesocardium persists for only a short period, while the dorsal mesocardium gradually breaks down leaving only the truncus arteriosus and ventricle attached to the pericardium.

- The atrium and sinus venosus are initially located outside the pericardial cavity in the septum transversum. Because the primitive heart increases in size faster than the pericardial cavity, especially in the bulbo-ventricular region, a U-shaped bend, the bulbo-ventricular loop, forms.

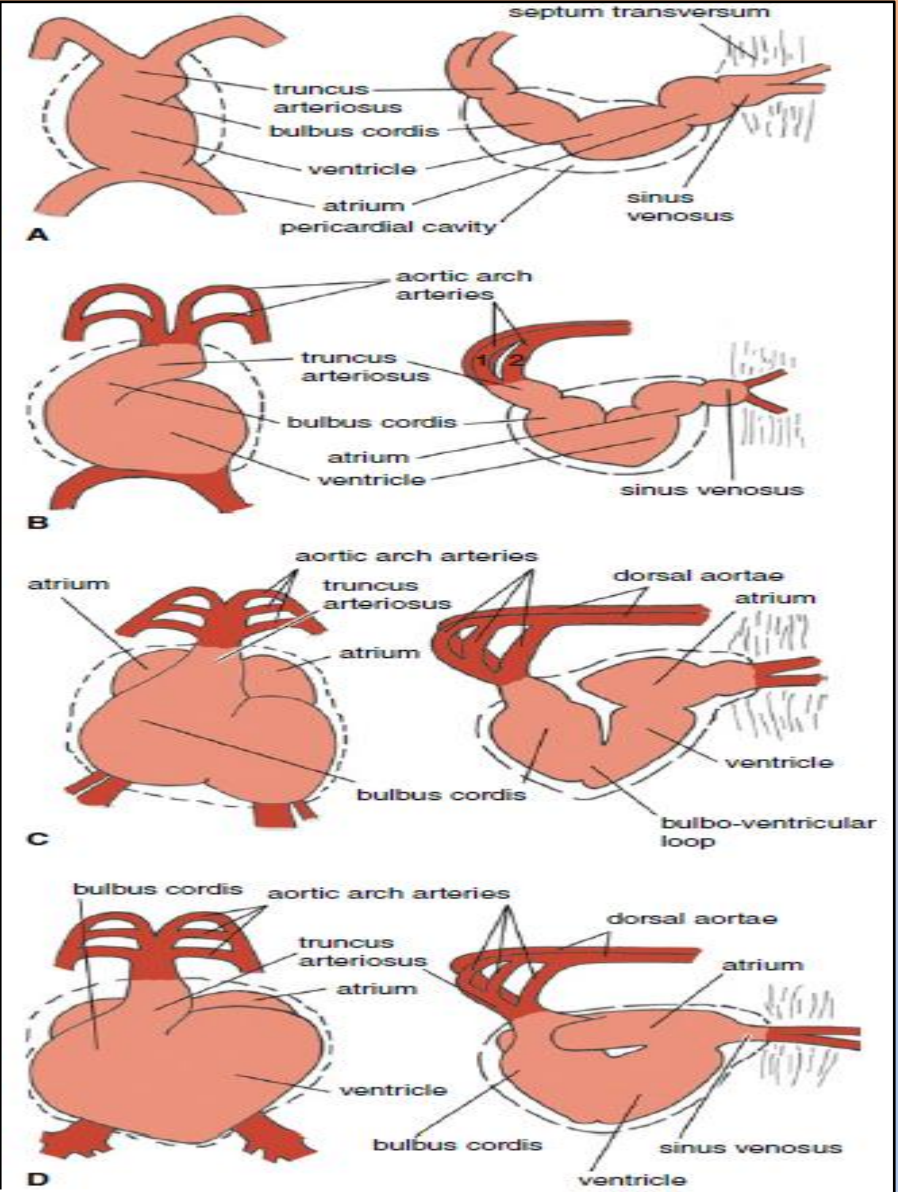


Figure 8 Dorso-ventral and left lateral views of sequential stages in the differentiation of the cardiac tube, from the bulbo-ventricular loop stage to the expansion of the bulbo-ventricular loop ventrally, and the common atrium dorsally (A to D).

➢As a consequence of this development, the atrium and sinus venosus become drawn into the cavity (Figure 8B). The loop occupies a ventral position in the pericardial cavity, to the right of the median plane.

➢Further growth of the developing heart causes the atrium to occupy a position dorsal to the bulbus cordis and ventricle, where it expands towards the truncus arteriosus. The sinus venosus is drawn into the pericardial cavity, and at this stage the developing heart becomes S shaped (Figure 8).

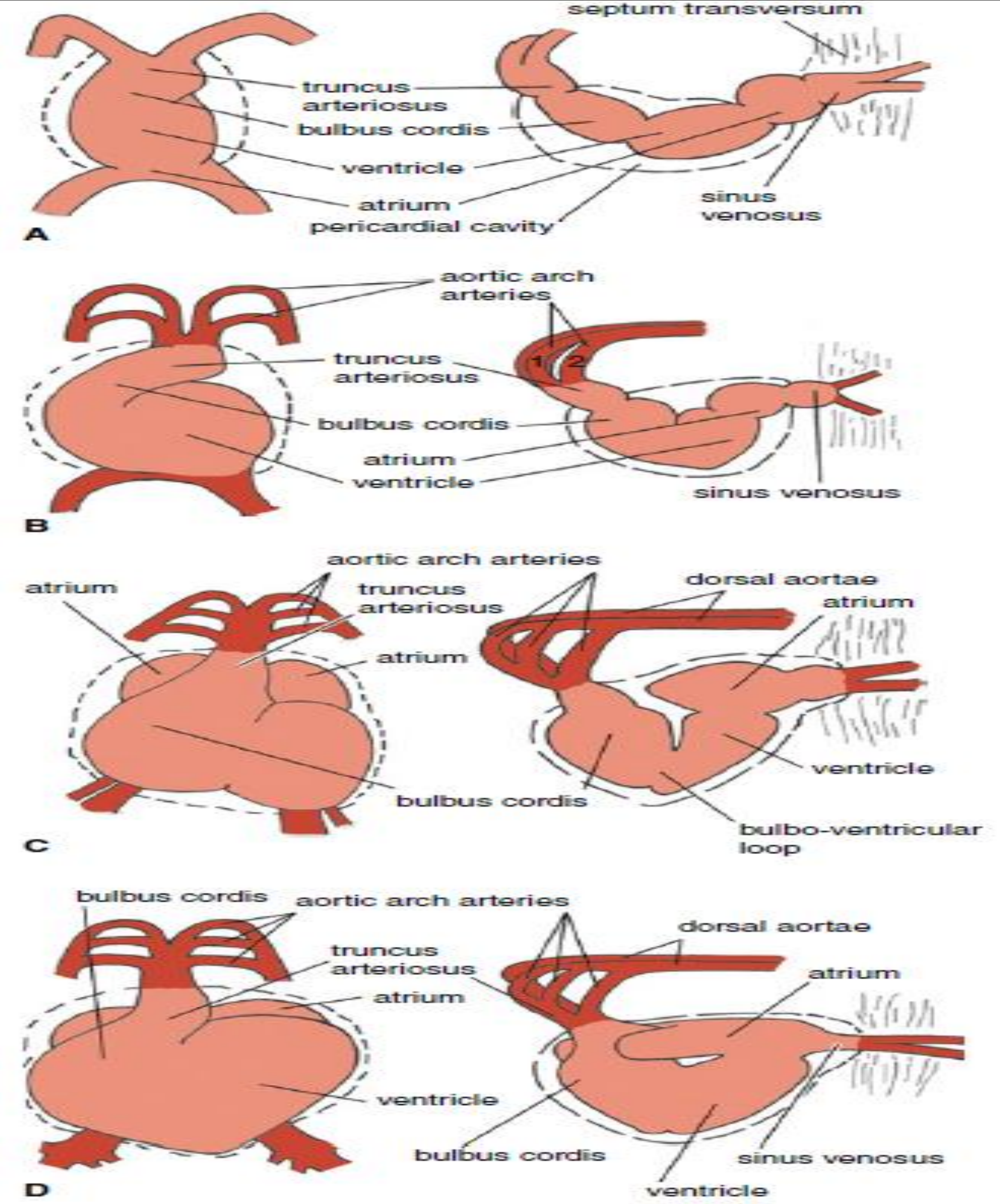


Figure 8 Dorso-ventral and left lateral views of sequential stages in the differentiation of the cardiac tube, from the bulbo-ventricular loop stage to the expansion of the bulbo-ventricular loop ventrally, and the common atrium dorsally (A to D).

- A number of transcription factors have been implicated in the process of bulbo-ventricular loop formation. Differential contraction of the actin cytoskeleton has been proposed as a determining factor in the formation of the bulbo-ventricular loop. During cardiac morphogenesis, blood vessel formation continues within the embryo.

- Two major blood vessels which form ventral to the neural tube become the left and right dorsal aortae. Cranially, they fuse with the left and right limbs of the endocardial tubes. Associated with the lateral folding of the embryo, the dorsal aortae caudal to the developing heart fuse, forming a common aorta. In the mesenchyme adjacent to the truncus arteriosus, an additional series of paired aortic arch arteries develop which join the dilated end of the truncus arteriosus with the dorsal aortae (Figure 8). Branches of the dorsal aortae, the intersegmental arteries, supply the developing somites. Additional branches supply the yolk sac through the vitelline arteries and the umbilical arteries supply the allantois.

- Cranial cardinal veins and the caudal cardinal veins convey venous blood from the head and body wall, respectively. The venous blood is returned to the caudal end of the primitive heart, the sinus venosus (Figure 3). On each side of the developing embryo, the cranial and caudal cardinal veins fuse, forming the common cardinal veins which enter the sinus venosus. At this stage of development, the mammalian cardiovascular system bears a strong resemblance, both morphologically and functionally, to that of the fully formed circulatory system of fish.

Formation of the cardiac chambers

- Partitions which form in the primordial mammalian heart gradually convert the single pulsating cardiac tube into a complex four-chambered organ.

- Although formation of cardiac septa takes place at approximately the same time, for descriptive purposes their formation is described as if they were separate events.

- The foetal heart continues to function effectively as these ongoing major structural changes occur.

Partitioning of the atrio-ventricular canal

- In the equatorial region of the atrio-ventricular canal, two masses of cardiac mesenchymal tissue known as endocardial cushions, which are located between the endocardium and the myocardium, extend towards each other and fuse.

- The fused endocardial cushions form the septum intermedium, which divides the common atrio-ventricular canal into left and right atrio-ventricular openings (Figure 9).

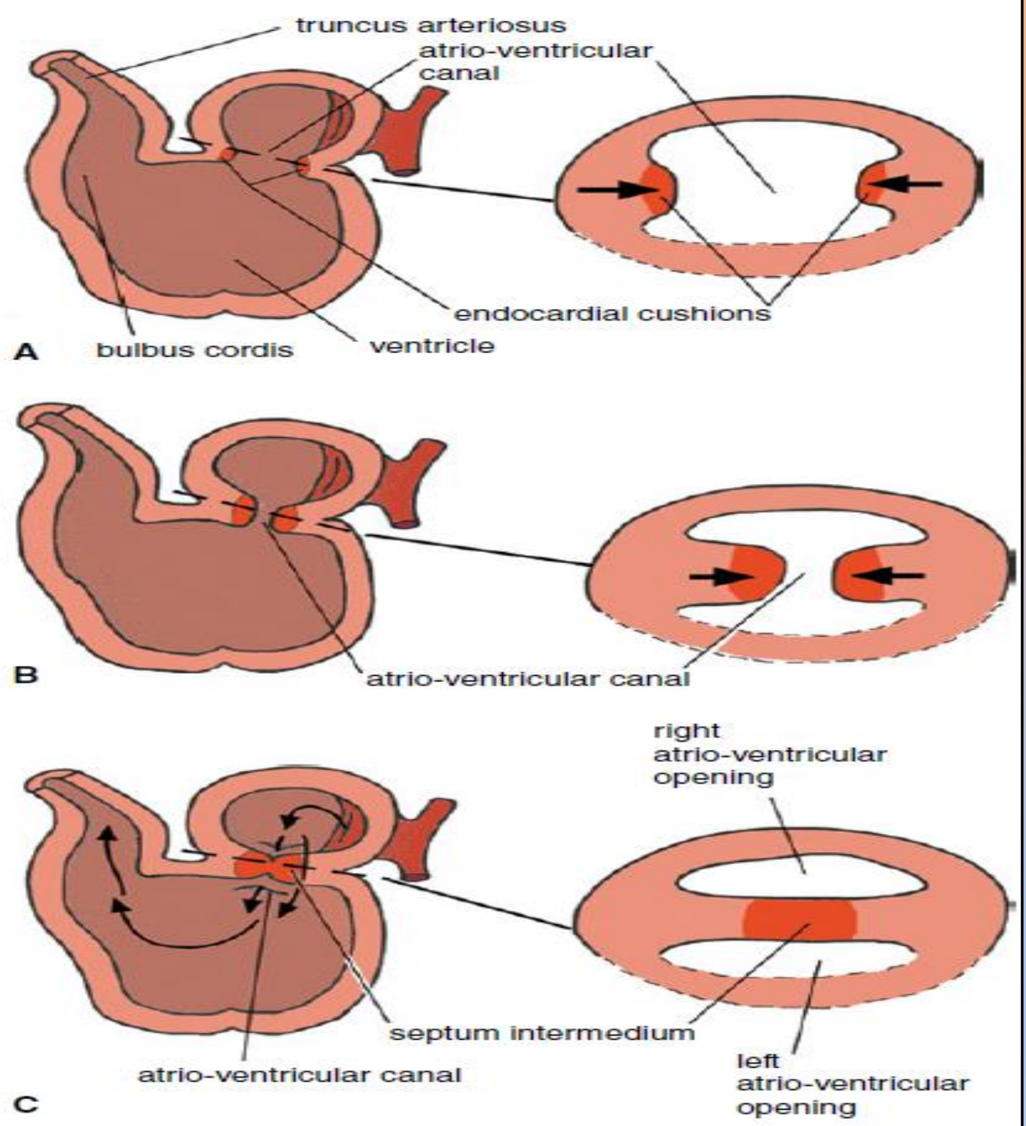


Figure 9 Stages in the division of the common atrio-ventricular canal into left and right atrio-ventricular openings, resulting from the fusion of the endocardial cushions and the formation of the septum intermedium at the level of the endocardial cushions. Arrows in A and B indicate direction of growth of endocardial cushions; arrows in C indicate direction of blood flow.

Partitioning of the common foetal atrium

- During proliferation of the endocardial cushions, a crescentshaped fold, the septum primum, arises from the dorsal wall of the common foetal atrium and extends towards the endocardial cushions.

- The septum primum gradually divides the common atrium into a left and a right atrium (Figure 10). As the septum primum grows towards the endocardial cushions, an opening, the foramen primum, persists between the left and right foetal atria.

- This foramen gradually decreases in size and, when the septum primum reaches the cushions, it eventually closes. Before closure of the foramen primum, however, programmed cell death in the central part of the septum primum results in the formation of a new communication channel between the left and right atria, the foramen secundum (Figure 10D).

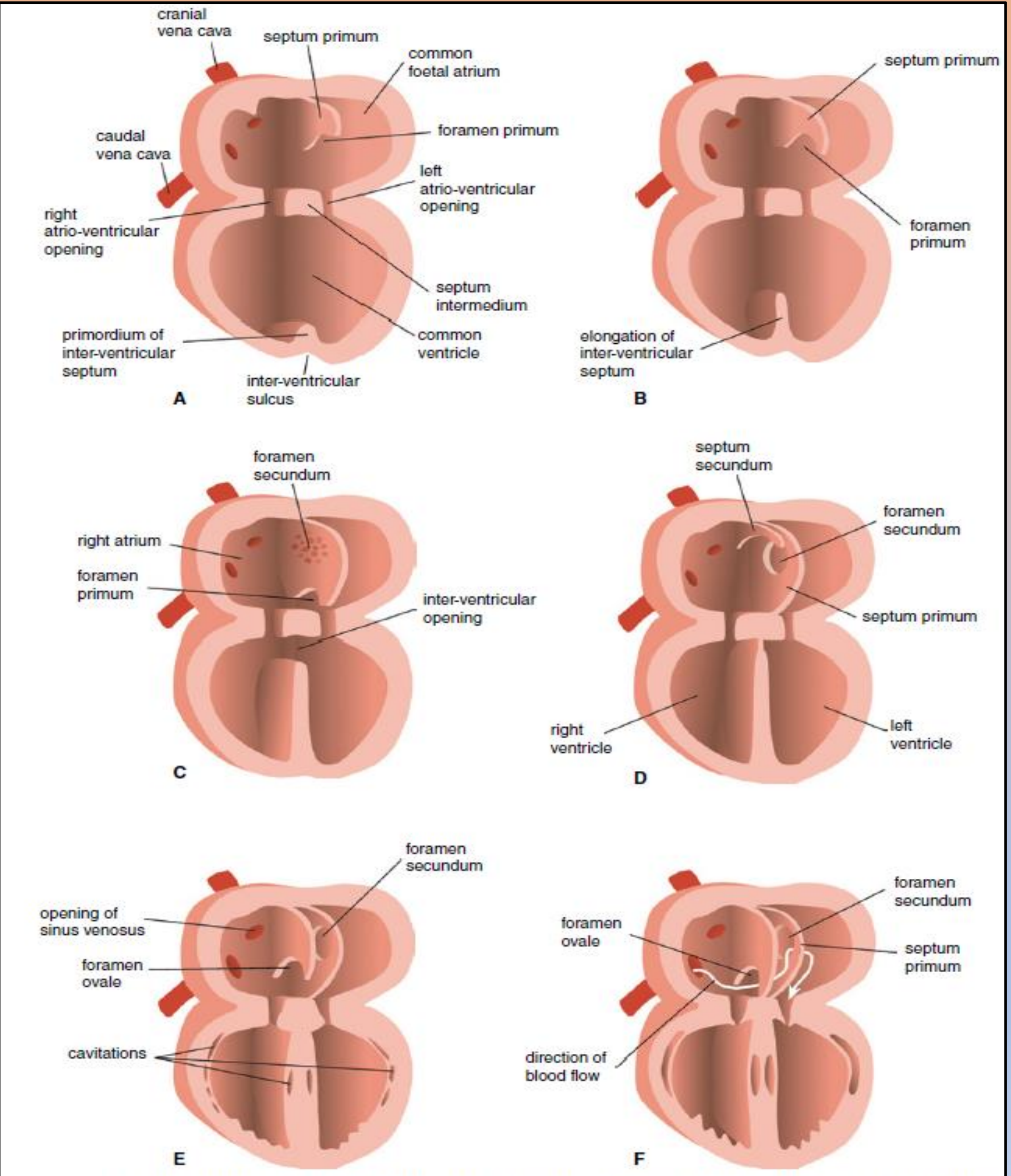


Figure 10 Stages in the partitioning of the developing atrium and ventricle, leading to the formation of left and right atria and ventricles (A to F). The arrow in F indicates the direction of blood flow through the foramen ovale.

Partitioning of the common foetal atrium

- A second membrane, the septum secundum, arises from the dorsal wall of the right atrium, to the right of the septum primum, and extends towards the septum intermedium.
- The central portion of the septum secundum overlaps the foramen secundum, but does not extend as far as the septum intermedium. The opening which persists between the free edge of the septum secundum and the foramen secundum is known as the foramen ovale.
- The upper part of the septum primum fuses with the septum secundum while the remaining portion becomes a valve-like structure for the foramen ovale.
- The lower margin of the septum secundum divides the blood entering the heart via the caudal vena cava into two streams. The greater amount is directed through the foramen ovale into the left atrium, while a lesser amount is directed through the right atrio-ventricular opening into the right ventricle. Due to its functional role, the lower margin of the septum secundum is appropriately named the crista dividens.
- At birth, the foramen ovale closes, completing the separation of the left and right atria.

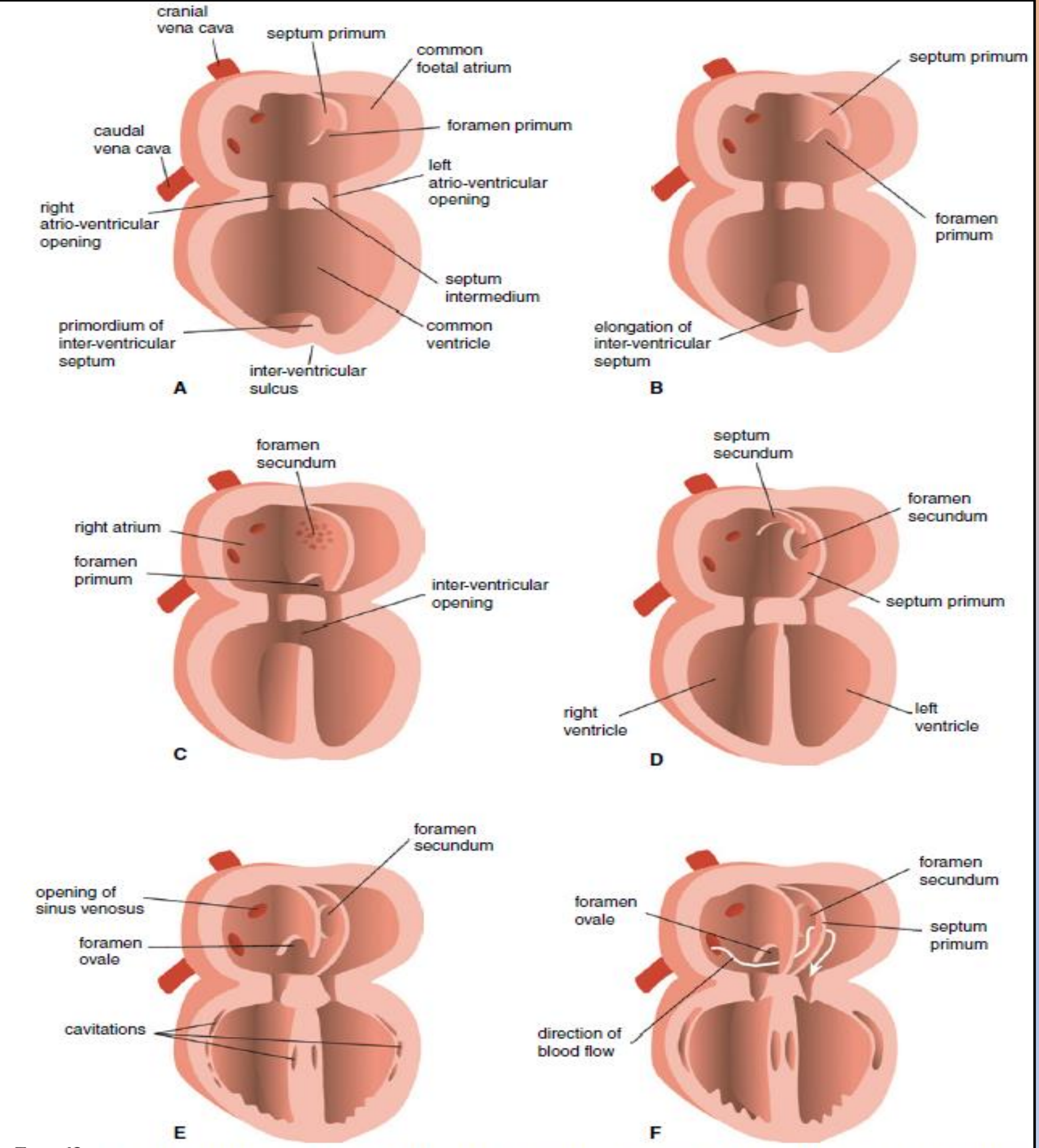


Figure 10 Stages in the partitioning of the developing atrium and ventricle, leading to the formation of left and right atria and ventricles (A to F). The arrow in F indicates the direction of blood flow through the foramen ovale.

Final form of the right atrium

- In the early stages of cardiac morphogenesis, blood returning from the left side of the embryo enters the left horn of the sinus venosus.
- Blood from the right side of the embryo enters the right horn of the sinus. The venous blood entering the sinus venosus enters the embryonic atrium through the sinoatrial opening, which is regulated by the sino-atrial valve composed of left and right components.
- Development of venous shunts between the left and right systemic venous systems leads to the preferential direction of flow to the right side, resulting in enlargement of the right horn of the sinus venosus while the left horn decreases in size.
- As partitioning of the atrium proceeds, the sino-atrial opening occupies a position in the right half of the foetal atrium.

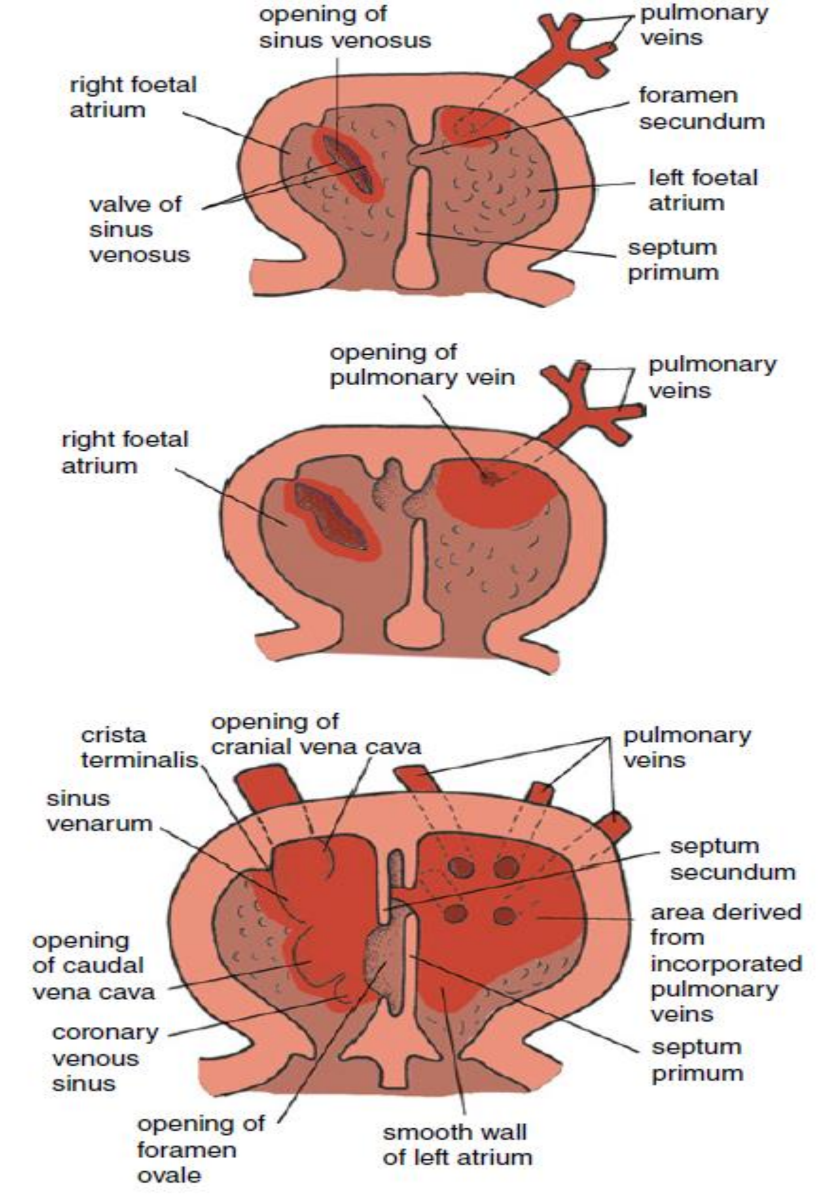


Figure 11 Incorporation of the sinus venosus into the right foetal atrium and incorporation of the pulmonary veins into the left foetal atrium.

Final form of the right atrium

- Gradually, the right horn of the sinus venosus becomes incorporated into the right foetal atrium. In its final form, the right atrium consists of the right foetal atrium which becomes the muscular right auricle, while the right horn of the sinus venosus becomes the thin-walled sinus venarum into which the venous return from the body enters the heart (Figure 11).

- During morphological adaptation, the left portion of the sino-atrial valve fuses with the septum secundum, while part of the right portion forms an internal ridge, the demarcation between the auricle and the sinus venarum, termed the crista terminalis. On the external surface a depression, the sulcus terminalis, marks this division. The remainder of the right portion of the sino-atrial valve contributes to the formation of the valves of the caudal vena cava and coronary sinus. The regressing left horn of the sinus venosus forms part of the coronary venous sinus, which opens into the right atrium.

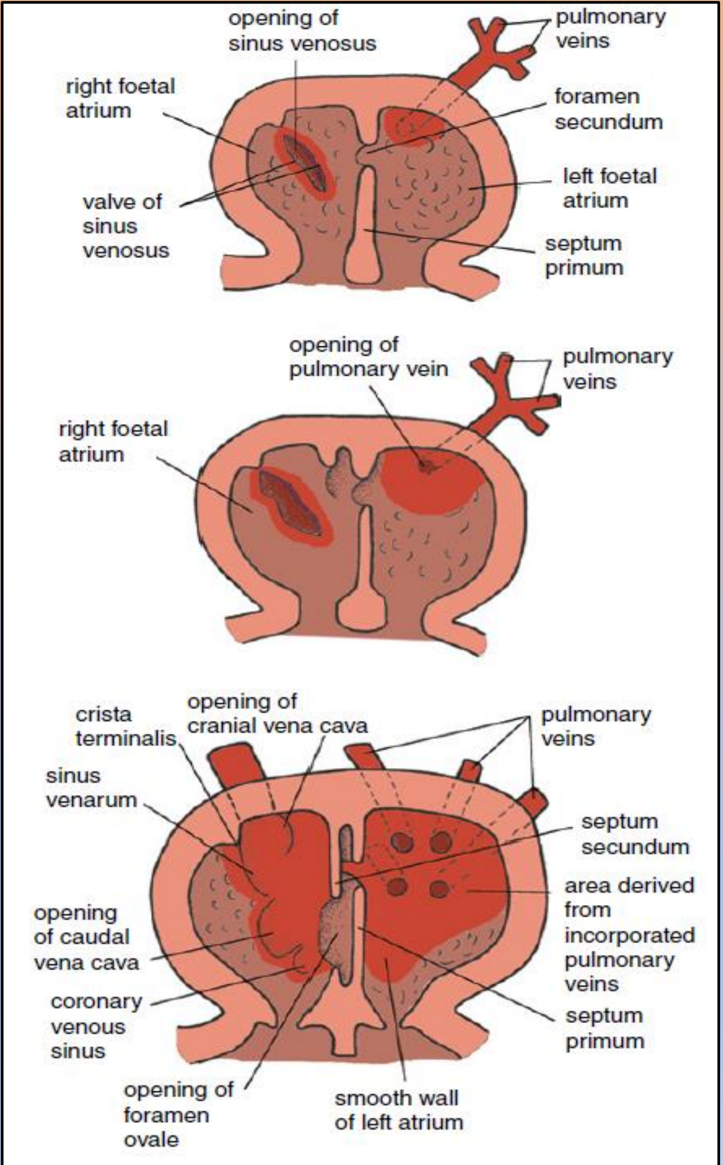


Figure 11 Incorporation of the sinus venosus into the right foetal atrium and incorporation of the pulmonary veins into the left foetal atrium.

Final form of the left atrium

- The embryonic pulmonary vein develops as an outgrowth of the left foetal atrium, to the left of the septum primum.

- The vein divides into left and right branches which supply the developing bronchial buds. Later, the left and right branches subdivide. In a manner similar to the incorporation of the right horn of the sinus venosus into the right atrium, the enlarged pulmonary vein and its branches become incorporated into the left atrium.

- Thus, four pulmonary veins are incorporated into the fully formed left atrium, two from each lung.

- The left atrium therefore comprises the left foetal atrium, which becomes the left auricle, and the integrated pulmonary veins, which form the smooth portion of the wall of this chamber (Figure 11).

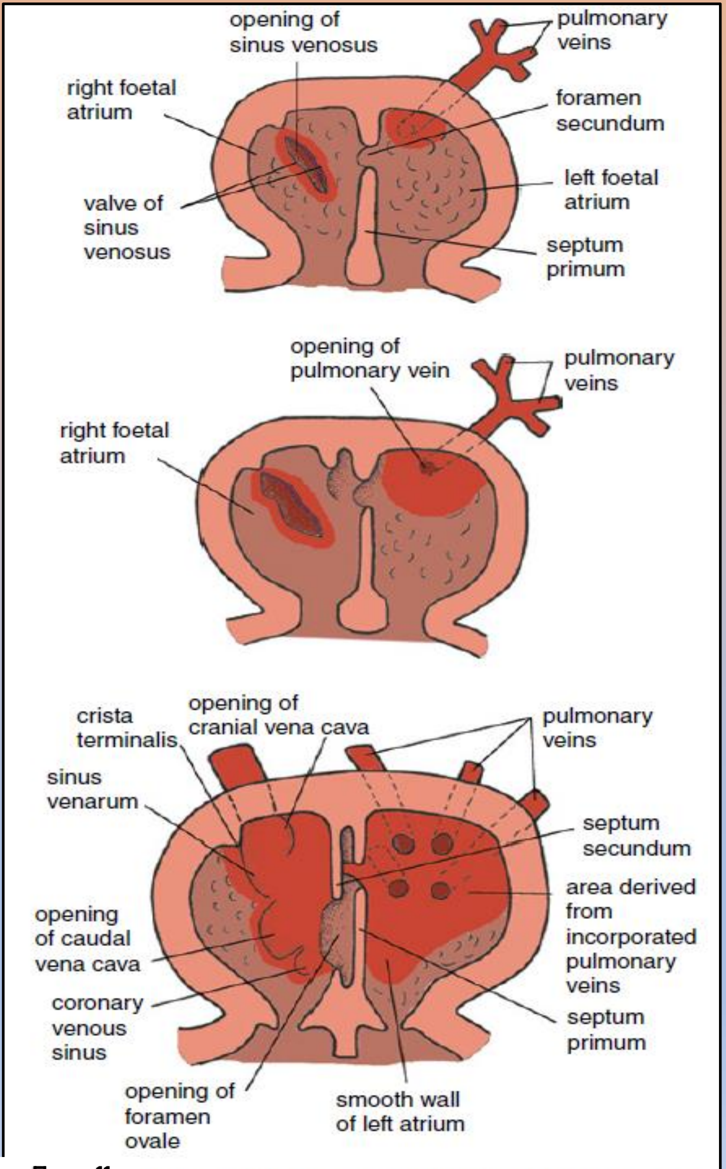


Figure 11 Incorporation of the sinus venosus into the right foetal atrium and incorporation of the pulmonary veins into the left foetal atrium.

Formation of the left and right ventricles

- Following its differential growth, the bulbus cordis consists of a dilated portion adjacent to the ventricle and a non-dilated portion referred to as the conus cordis, which is continuous with the truncus arteriosus.
- The dilated portion of the bulbus cordis and the embryonic ventricle form a common chamber. Externally, the division between the bulbus cordis and ventricle is marked by a groove, the inter-ventricular sulcus, and internally by a muscular fold, the primordial inter-ventricular septum (Figure10).
- As the walls of the ventricle and bulbus cordis increase in thickness, diverticulation of their inner surfaces imparts a trabecular appearance to the myocardium.
- At this stage, the embryonic ventricle can be considered as the primitive left ventricle and the dilated bulbus cordis as the primitive right ventricle.
- The ventricles enlarge by peripheral growth which is closely followed by increased trabeculation of their inner walls.

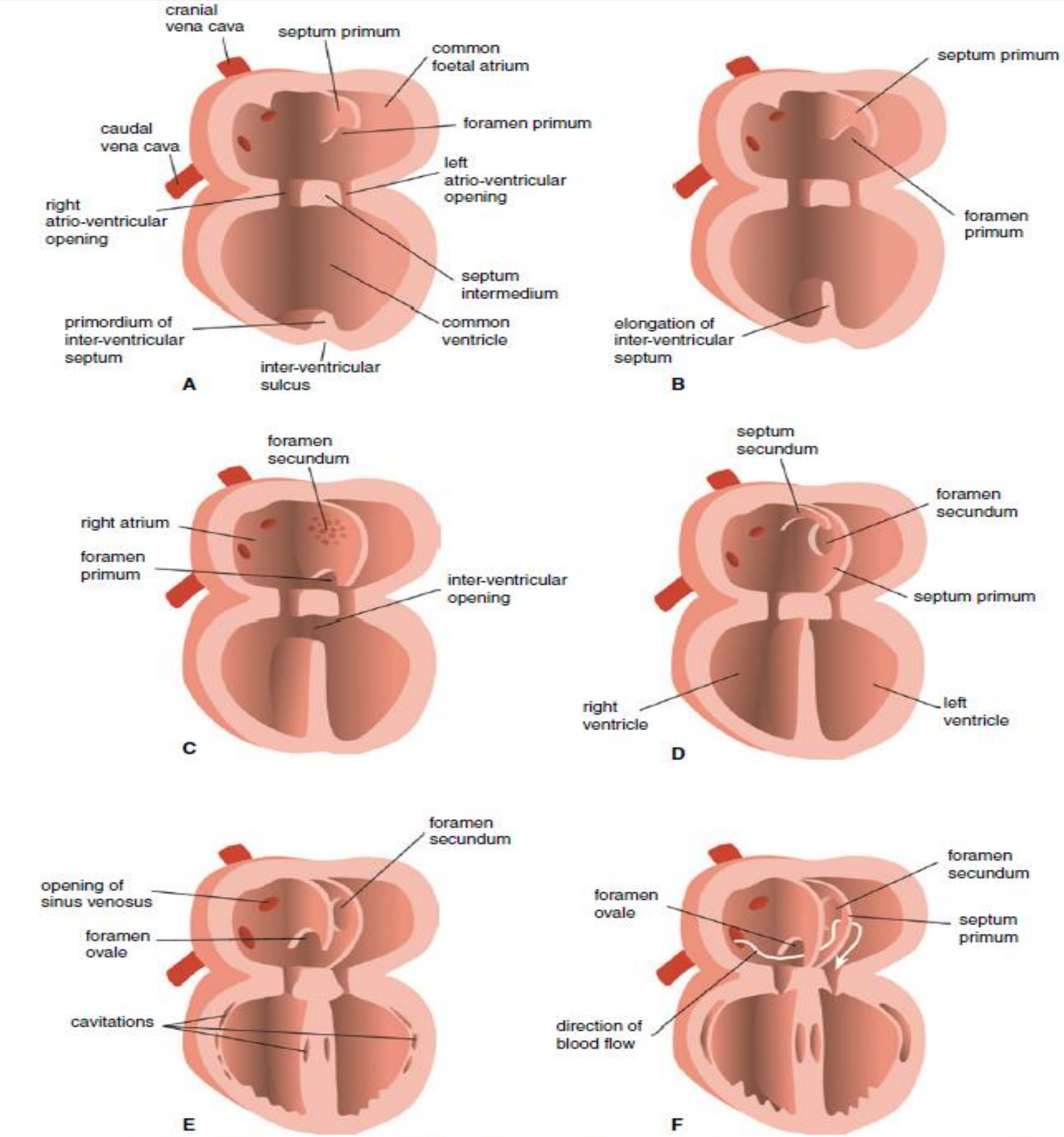


Figure 10 tages in the partitioning of the developing atrium and ventricle, leading to the formation of left and right atria and ventricles (A to F). The arrow in F indicates the direction of blood flow through the foramen ovale.

Formation of the left and right ventricles

- As the inter-ventricular sulcus deepens and the walls of the expanding ventricles meet medially at the sulcus, the walls become apposed and fuse, contributing to the elongation of the inter-ventricular septum.

- Continued peripheral growth of the myocardial tissue of each ventricle accounts for the progressive increase in length of the inter-ventricular septum. At this stage, the septum does not completely separate the two ventricles, which communicate through the inter-ventricular foramen. As a consequence of differential cellular proliferation, the inter-ventricular foramen subsequently closes (Figure 10D).

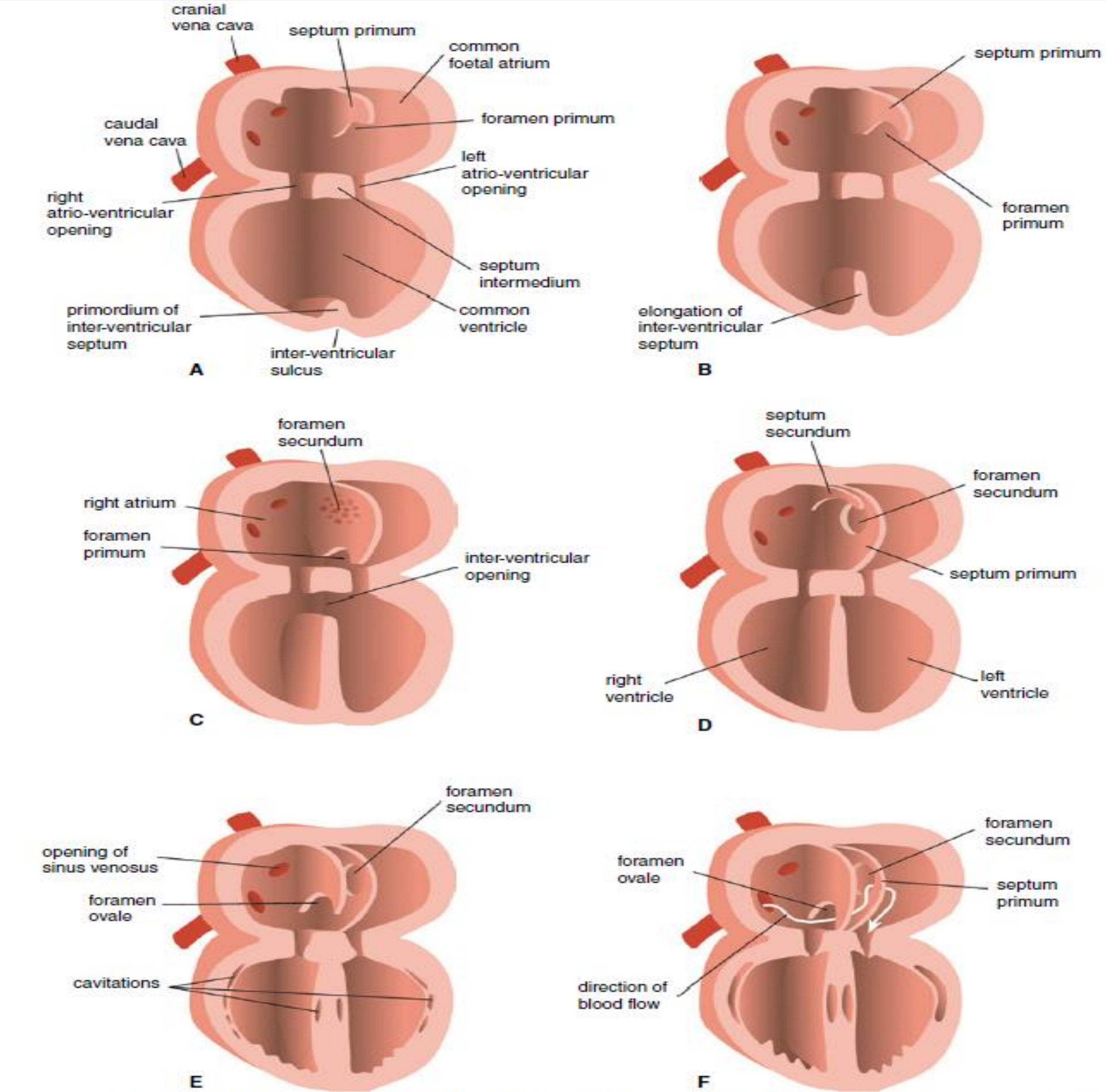


Figure 10 Stages in the partitioning of the developing atrium and ventricle, leading to the formation of left and right atria and ventricles (A to F). The arrow in F indicates the direction of blood flow through the foramen ovale.

Partitioning of the conus cordis and truncus arteriosus

- Two subendocardial thickenings, the bulbar ridges, which fuse forming the aortico-pulmonary septum, divide the conus cordis and truncus arteriosus into an aortic trunk and a pulmonary trunk (Figure 12).

- The spiral form of the aortico-pulmonary septum ensures that the aortic trunk becomes continuous with the fourth aortic arch arteries and that the pulmonary trunk communicates with the sixth aortic arch arteries.

- Mesenchymal cells of neural crest origin, which migrate from the cranial region, contribute to the formation of the aortico-pulmonary septum.

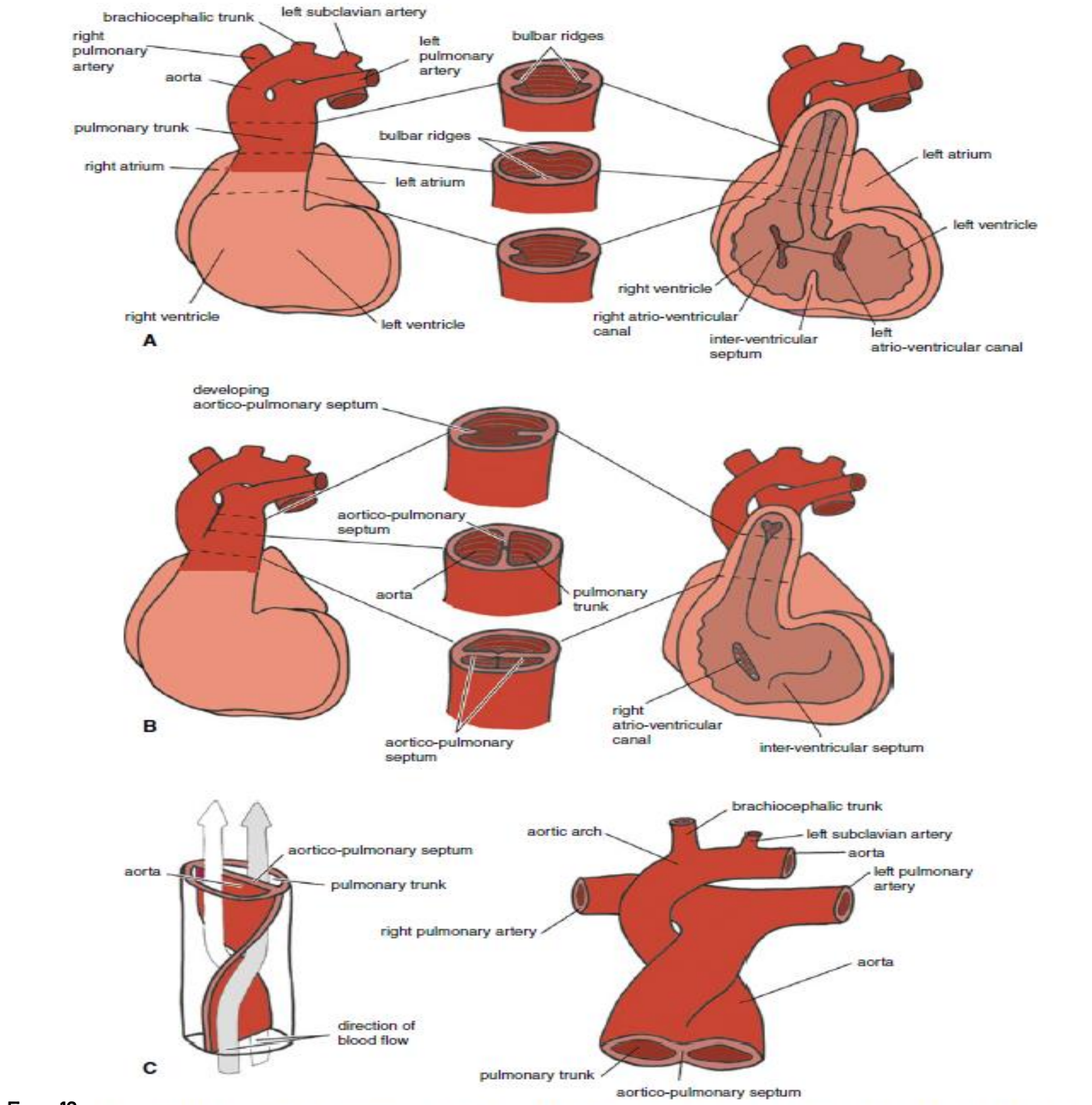


Figure 12 Partitioning of the conus cordis and truncus arteriosus into the aortic and pulmonary trunks respectively. The spiral arrangement of the aortico-pulmonary septum and the final relationship of the aortic and pulmonary trunks is also illustrated (A to C).

Closure of the inter-ventricular foramen

- The developmental changes which lead to the closure of the inter-ventricular foramen are complex.
- The membranous portion of the inter-ventricular septum, which causes closure of the inter-ventricular foramen, is formed from proliferation of tissues derived from the bulbar ridges of the aortico-pulmonary septum, the septum intermedium and the muscular inter-ventricular septum (Figure 13).
- Following closure, the pulmonary trunk carries blood from the right ventricle and the aorta conveys blood from the left ventricle.

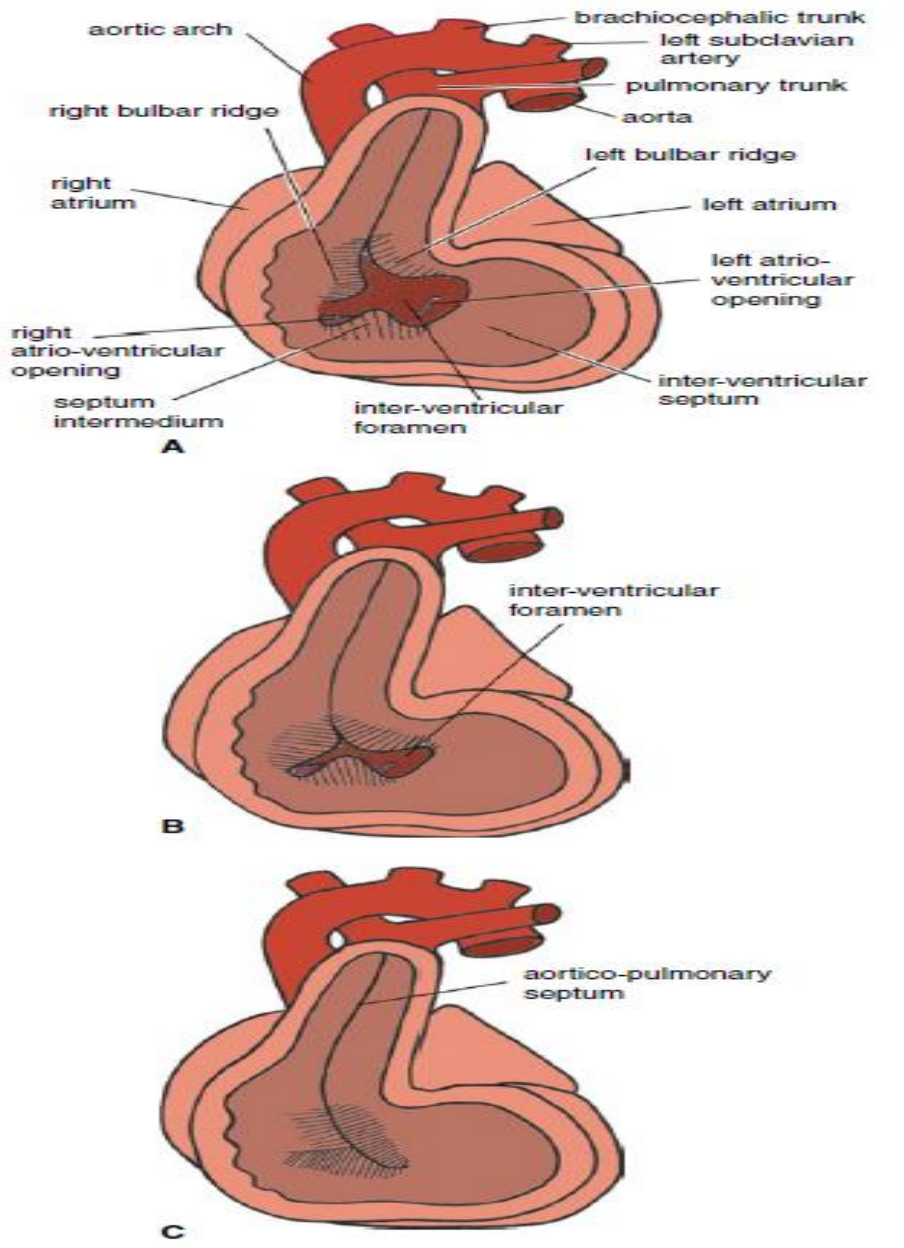


Figure 13 Stages in the closure of the inter-ventricular foramen (A to C).

Formation of cardiac valves

- The aortic and pulmonary valves, which are necessary for prevention of backflow of blood into the left and right ventricles, arise from three swellings of subendothelial mesenchymal tissue at the origins of the aorta and pulmonary trunk.

- Mesenchyme of neural crest origin contributes to the formation of these valves.

- As a consequence of hollowing out, these ridges undergo remodelling, forming three thin-walled cusps, each composed of a connective tissue core covered by endothelium (Figure 14).

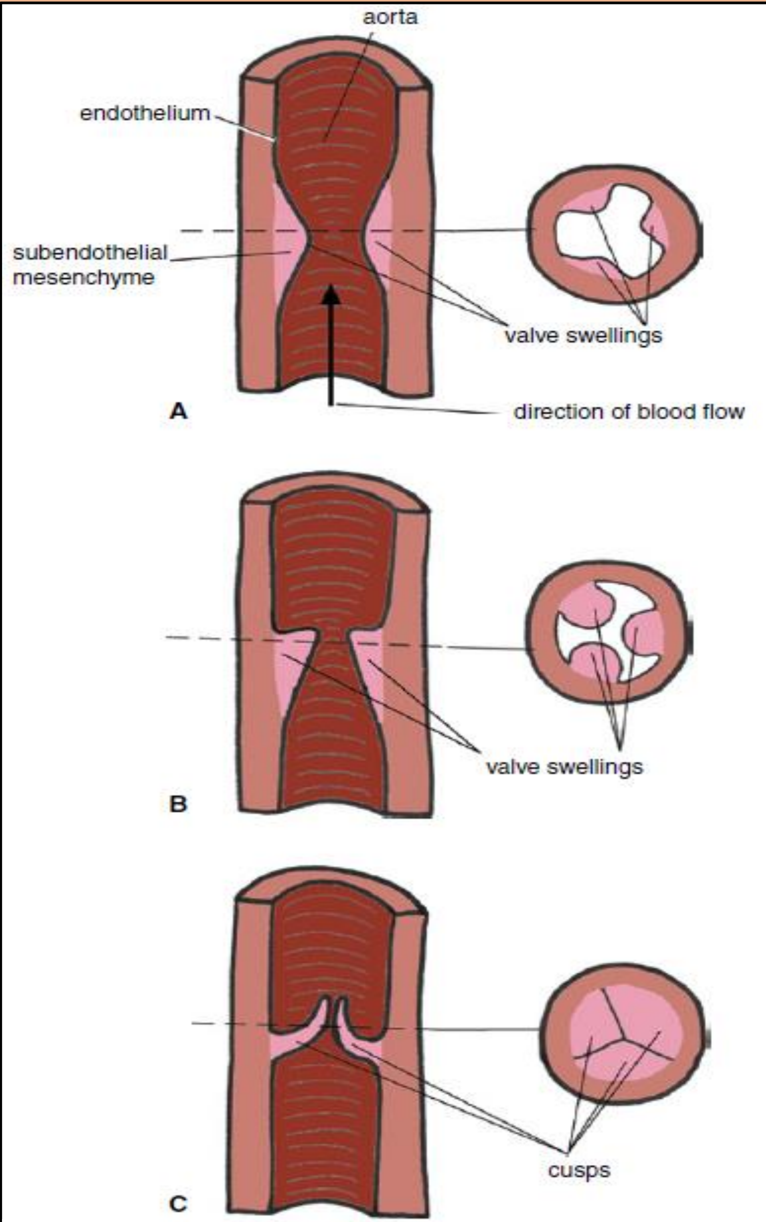


Figure 14 Sequential stages in the formation of the aortic valve. The valve of the pulmonary trunk forms in a similar manner (A to C).

Formation of cardiac valves

- As the endocardial cushions fuse and divide the common atrio-ventricular opening into left and right openings, the left and right atrio-ventricular valves form at these openings.

- The left atrio-ventricular valve is composed of two cusps and is referred to as bicuspid, while the right atrio-ventricular valve is composed of three cusps and is referred to as tricuspid.

- Mesenchymal tissue proliferates around the rim of each orifice.

- Cavitation of the muscular layer immediately beneath the mesenchymal thickening, and remodelling of the associated tissue, contribute to the formation of the cusps of the atrio-ventricular valves (Figure 15).

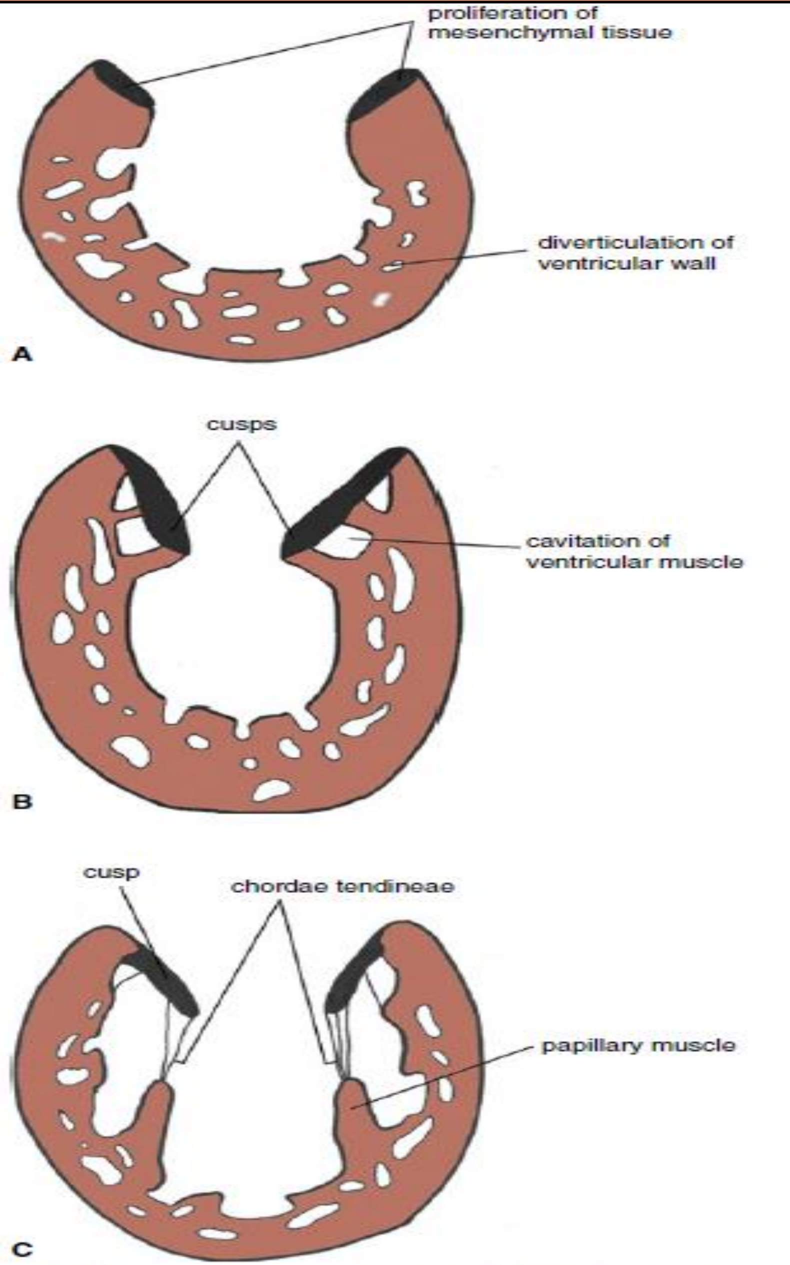


Figure 15 Stages in the formation of an atrio-ventricular valve, showing diverticulation of the ventricular musculature, formation of papillary muscles and attachment of chordae tendineae to valve cusps (A to C).

Formation of cardiac valves

- Because the valves are partially derived from mesenchymal tissue which was originally attached directly to the myocardium at the orifices, the valves remain anchored by muscular strands to the ventricular walls.

- With diverticulation and resultant thinning of the ventricular walls, muscular strands remain attached along the ventricular surface of the valve cusps.

- These thin muscular structures are gradually replaced by dense connective tissue, the chordae tendineae, which connect the valve cusps to muscular projections of the ventricular walls referred to as papillary muscles (Figure 15).

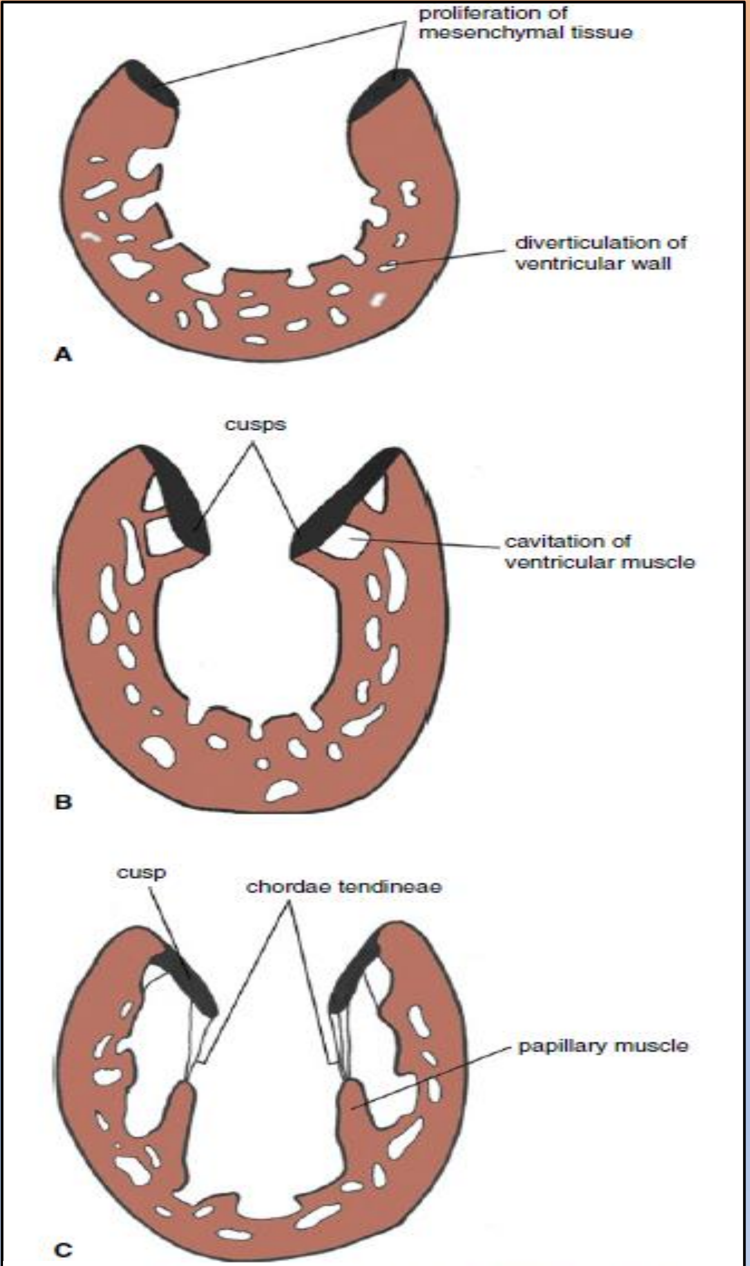


Figure 15 Stages in the formation of an atrio-ventricular valve, showing diverticulation of the ventricular musculature, formation of papillary muscles and attachment of chordae tendineae to valve cusps (A to C).

Thank you for your attention.