DEVELOPMENT OF CARDIOVASCUALR SYSTEM

Objectives

1-Appreciate the sources and steps of development of the heart tube and the three layers of the heart.
2-Understand the embryogenesis of septation and formation of valves of the heart.
3-Follow developmental stages of blood vessels and their varieties.
4-Appreciate fetal circulation and its postnatal changes.
5-Overview development, derivatives and anomalies of aortic arches and great veins.
6-State the prevalence, mechanisms, and hemodynamic changes of the common congenital abnormalities of the cardiovascular system.
7-Overview pattern of branches and distribution of great vessels of the body.

Introduction

The cardiovascular system is the first major system to function in the embryo. Primordial heart and vascular system appear in the middle of the 3rd week. The heart starts to function early in the 4th week. The heart begins to beat on day 22. The rapidly growing embryo can no longer satisfy its nutritional and oxygen requirements by diffusion alone.

Development, laterality (right and left sidedness), lengthening of the heart and blood vessels is controlled by regulatory genes and signaling molecules.

Embryonic sources of development of the cardiovascular system

1-***Epiblast cells*** provide progenitor heart cells. These cells migrate during days 16-18 into splanchnic mesoderm where they form horse-shoe cluster of cells cranial to the neural tube. Epiplast cells form the **endocardium.**
2-***Splanchnic mesoderm*** provide myoblasts of the **myocardium**.
3-***Intraembryonic coelom***. Coelom in the lateral mesoderm form the **pericardial** cavity.
4-***Neural crest cells*** are involved in formation of cardiac cushions and **valves** of heart.

Primitive blood vessels and blood cells

Angiogenesis (blood vessel formation)

-Early in week 3, blood vessels form in extraembryonic mesoderm of the yolk sac, connecting stalk and chorion. Mesenchymal cells differentiate into ***angioblasts*** (vessel forming cells) that aggregate to form ***blood islands.*** Peripheral cells flatten to form endothelial lining of blood vessels. These cavities fuse to form networks of channels. Vessels sprout by buddings and fuse with other vessels to form **capillary plexuses.** ***Vitelline vessels*** form in the yolk sac, and ***umbilical vessels*** in the chorion (fig.1&2).
-Embryonic blood vessels develop from intraembryonic mesoderm in a similar way 2 days later. Extraembryonic vessels join intraembryonic vessels. The surrounding mesenchyme differentiates into muscles and connective tissue of blood vessels.

Hematogenesis (blood cell formation)

-Some centrally located cells in the blood islands detach and differentiate into blood cells. Blood formation first occurs in the **liver, spleen, lymph nodes, thymus, and bone marrow.** By the 4th month of pregnancy, the red bone marrow takes over the function of blood cell formation and becomes the main source of blood cells.

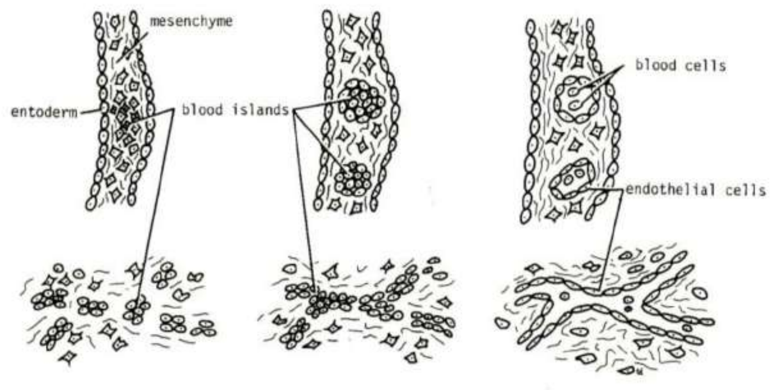

Fig.1. Mesenchymal cells form endothelium-lined blood vessels and blood cells.

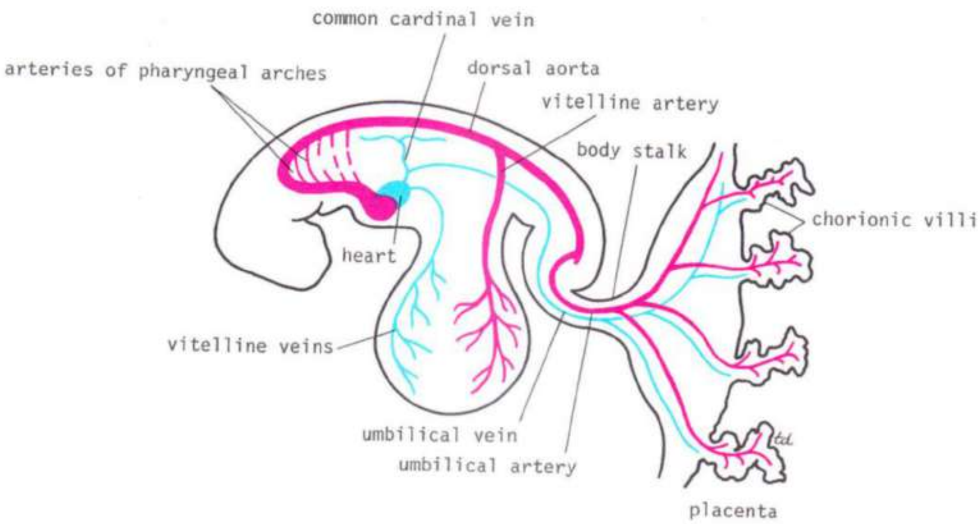

Fig.2. CVS in 21 days embryo shows extra- and intra-embryonic blood vessels.

DEVELOMENT OF THE HEART

CARDIOGENIC AREA

-In the middle of the 3rd week, **progenitor heart cells** in the epiblast migrate into and through splanchnic layer of lateral mesoderm where they form horseshoe cluster of cells called ***cardiogenic area*** (fig.3). The cardiogenic area is in front of the neural tube.
-Other clusters of angiogenic cells appear bilaterally and acquire lumen to form a pair of longitudinal vessels, the ***dorsal aortae.*** Dorsal aortae gain connections with the caudal ends of the heart tubes.
-Cells of cardiogenic area canalize to form two thin-walled ***endocardial heart tubes.***

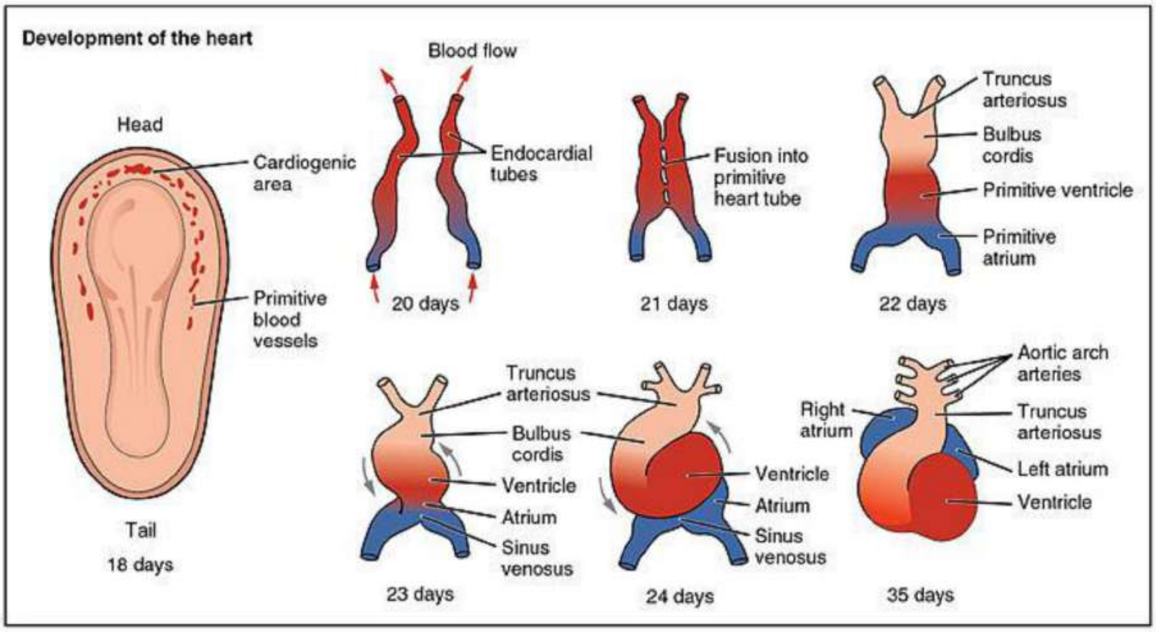

Fig.3. Cardiogenic area and formation of heart tube and primitive vessels.

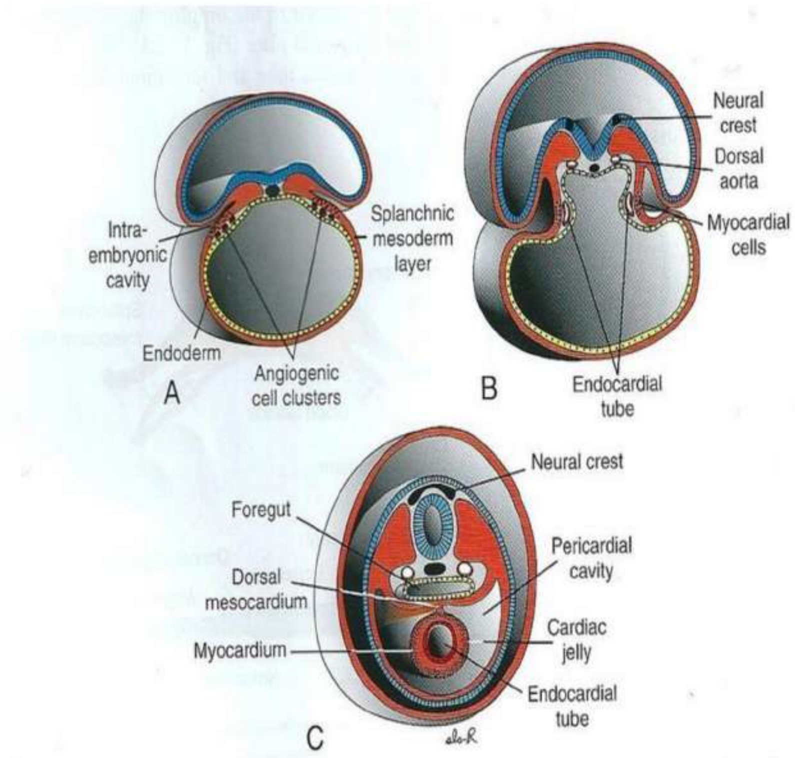

Fig.4. Cross section of 18 days embryo showing fusion of lateral body folds and how the two endocardial heart tubes fuse into one.

HEART TUBE

Effects of folding of the embryo on the heart tube and pericardium

1-As the embryo folds laterally, the two endocardial heart tubes approach each other and fuse to form a single heart tube.

2-When head fold forms, the heart tube is reversed (180 degrees rotation) so that the the dorsal aortae are curved cranially instead of caudally forming the first aortic arches (Fig.5). Venous end of the heart becomes caudal instead of cranial.

3-The heart and pericardial cavity come to lie ventral to the foregut.

4-The pericardial cavity becomes ventral to the heart. The heart and pericardium move to a cervical and finally a thoracic position.

5-The ***septum transversum*** is reversed and becomes caudal to the heart, and eventually will form the diaphragm.

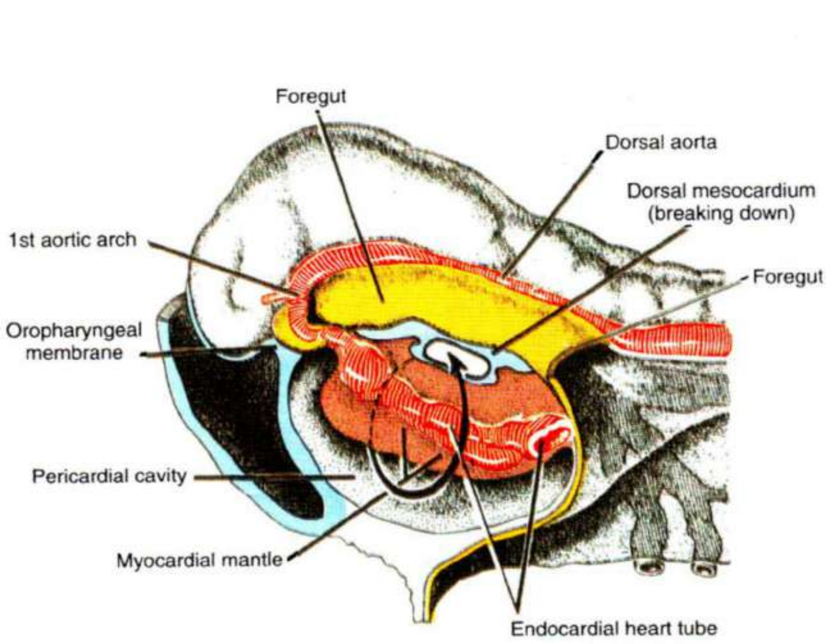

Fig.5. Layers of the heart. Effects of rotation and embryonic folding on heart tube.

Development of the three layers of the heart

a)Endocardium forms endothelial lining of the heart, is derived from ***epiblast cells.***
b)Myocardium forms muscular wall of the heart is derived from ***splanchnic mesoderm.***
c)Epicardium or visceral pericardium covers the surface of the heart, is derived from the wall of sinus venosus and septum transversum. This outer layer shares in formation of coronary arteries.
d)Parietal pericardium and pericardial cavity are derived from cranial part of the ***celomic cavity.*** **Fibrous pericardium** is derived from ***septum transversum.***

Formation of the cardiac loop and its dilatations

The heart tube continues to grow and elongate. This lengthening is essential for formation of the outflow tract and looping process. As the outflow tract lengthens, the cardiac tube begins to bend (fold) on day 23. The cephalic portion of the tube which is the truncus arteriosus and primitive ventricle bends ventrally and to the right (dextral looping). The atrial (caudal) portion of the tube shifts cranially and to the left. The bending creates the cardiac loop which is complete by day 28. The cardiac loop is U-shaped (seen from the side) and S-shaped (seen from above). Looping (folding) places chambers of the heart in their postnatal anatomical position. While the cardiac loop is forming, local expansions become visible and develop alternate dilatations and constrictions (Fig 6).

These dilatations are oriented in a cephalo-caudal order as follows:

1-Truncus arteriosus (TA).
2-Bulbus cordis (BC).
3-Primitive ventricle (V).
4-Primitive atrium (A).
5-Sinus venosus (SV).

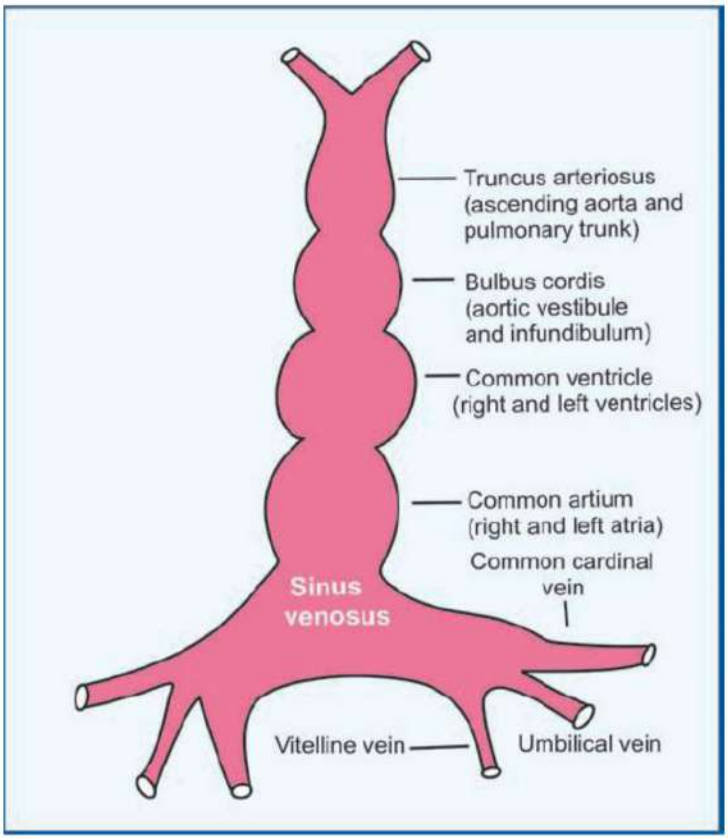

Fig.6.Dilatations of the heart tube.

Development and fate of sinus venosus (4^{th} to 10^{th} week)

-In the middle of the 4^{th} week the sinus venosus receives blood from right and left horns. Each horn receives blood from three veins:

1-**Umbilical vein** carries oxygenated blood from the placenta.

2-**Vitelline (omphalomesenteric) vein** carries deoxygenated blood from the yolk sac.

3-**Common cardinal vein** carries deoxygenated blood from embryo.

Soon the entrance of the SV into the atrium shifts to the right. This results in:

a) The left horn of the sinus venosus decreases in size. All what remains are the **coronary sinus** and **oblique vein of the left atrium.**

b) The right horn enlarges and receives all blood through the superior and inferior vena cava. The right horn becomes incorporated to form the smooth part of the right atrium. The **sinoatrial orifice** is flanked on each side by a valvular fold, the ***right and left venous valves.*** The left valve fuses with the developing **inter-atrial septum.** The cranial part of the right sinoatrial valve is indicated by the **crista terminalis** while the lower part develops into **valve of inferior vena cava** and **valve of the coronary sinus** (fig.7).

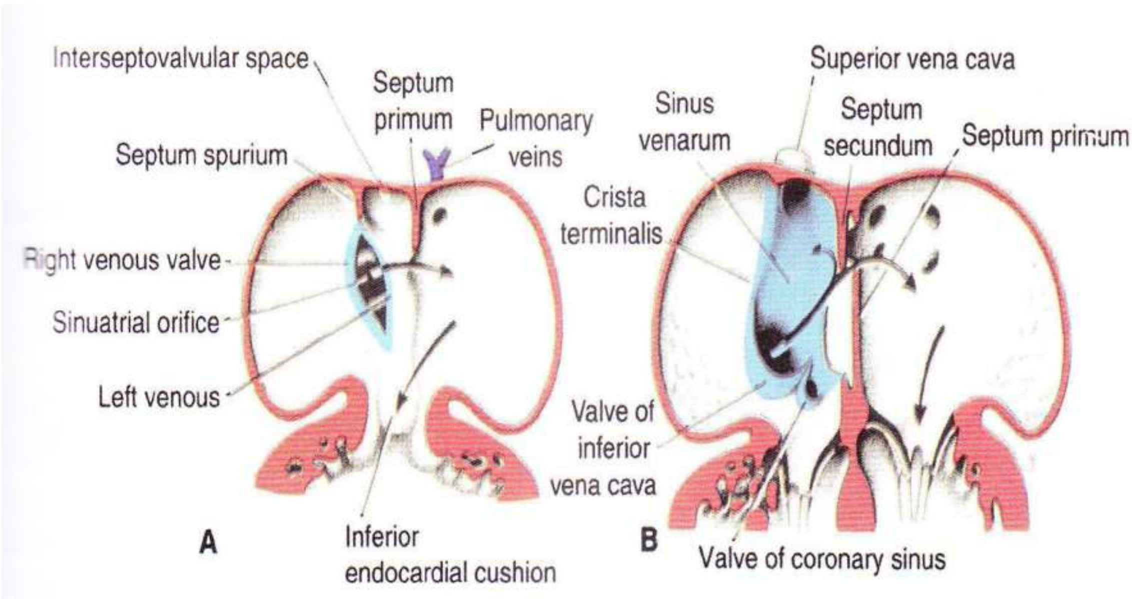

Fig.7. Fate of sinus venosus, heart is open and seen from the front.

PARTITIONING (SEPTATION) OF THE HEART (4th to 8th week)

Endocardial cushions

By the end of the 4th week, ***endocardial cushions*** form in the atrioventricular. Cushions appear in the dorsal and ventral walls of the atrioventricular canal. AV cushions approach each other and fuse dividing the AV canal into right and left AV canals. The cushions develop from the cardiac jelly where neural crest cells are involved. The cushions contribute to the formation of **valves** and **septa** of the heart.

Septation of the primordial atrium

During the 4th week, a crescent-shaped membrane known as ***septum primum*** grows from the roof of the atrium toward the endocardial cushions and partially divides the atrium into right and left atria. A large opening, ***foramen (ostium) primum*** forms between the free edge of the septum primum and the AV cushions. Foramen primum serves as a shunt enabling oxygenated blood to pass from the right to the left atrium. Foramen primum becomes smaller and disappears as the septum primum fuses with the AV cushion. Before foramen primum disappears, perforations (produced by programmed cell death) appear in the central part of the septum primum. Perforations coalesce to form another opening, -***foramen (ostium) secondum*** near the roof of the atrium (Fig. 8). Foramen secondum ensures flow of oxygenated blood from the right to the left atrium.

A new crescent-shaped fold, - ***septum secomdum*** descends on right side of septum primum. Septum secondum forms an incomplete partition between the atria leaving a foramen below it, - ***foramen ovale (oval foramen).*** The remaining part of septum primum forms ***valve of oval foramen (valvula foramins ovale).*** Foramen ovale and its valve allow most of oxygenated blood entering right atrium from inferior vena cava to pass into left atrium, and prevent passage of blood in an opposite direction.

Primordial pulmonary vein and formation of the left atrium

Most of the wall of left atrium is formed by incorporation of the ***primordial pulmonary vein***. This vein develops as an outgrowth of the posterior atrial wall that gains connection with veins coming of the developing lungs. As atrium expands, the primordial pulmonary vein and its main branches are gradually involved into the wall of left atrium. As a result 4 pulmonary veins form and open in the left atrium.

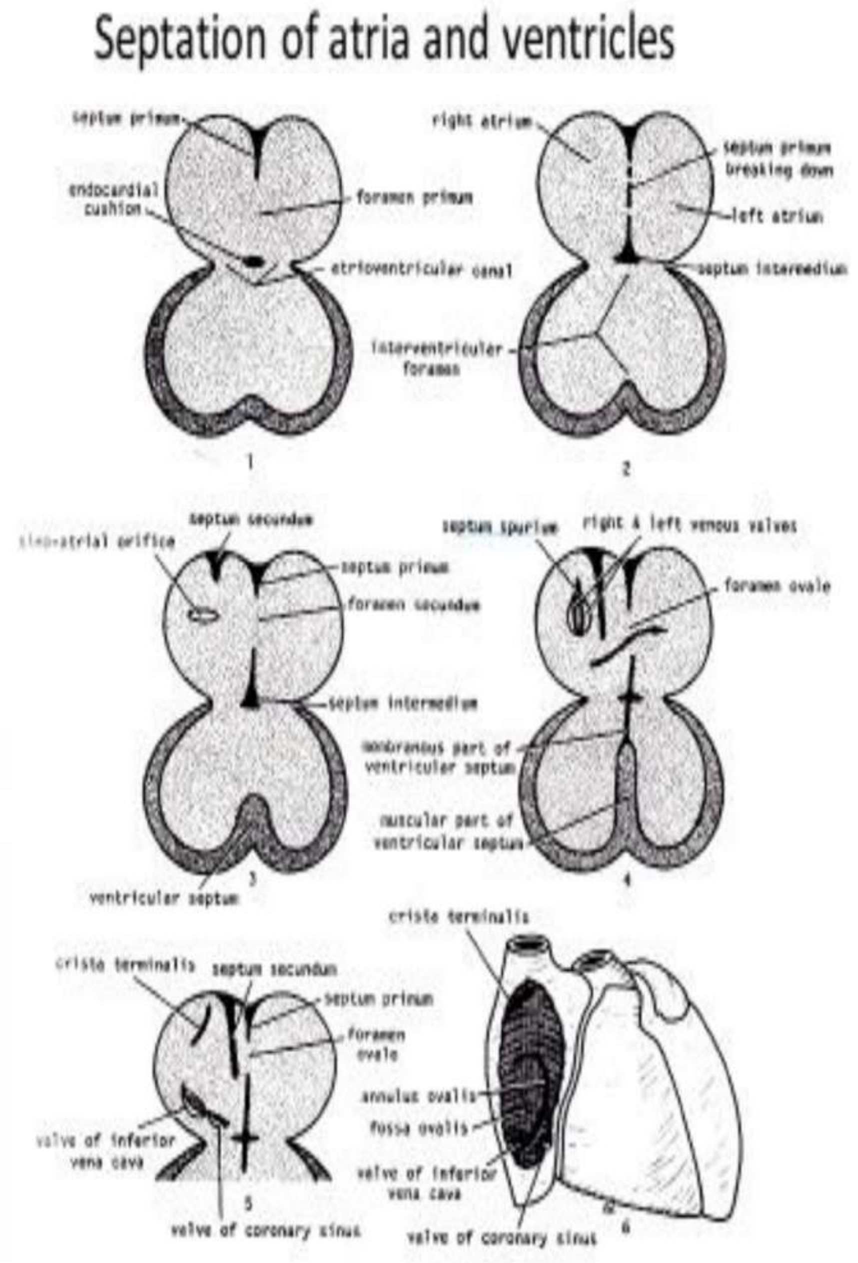

Fig. 8. Steps of septation of the heart.

Septation of the ventricles

By the end of the 4th week, the two primitive ventricles expand. Medial walls of the expanding ventricles become apposed and fuse forming the ***muscular interventricular septum.*** The ***interventricular foramen*** is reduced. A down growth from the AV cushion forms the ***membranous part of the interventricular septum*** which fuses with the muscular part of the IV septum closing the interventricular foramen. IVS closes completely by the end of the 7th week. Cavitation of the inside of the ventricular walls forms as a sponge of muscular bundles called **trabeculae carnae.** Some of these muscular bundles become the **papillary muscles** and **chordae tendineae.**

Partitioning of bulbus cordis and truncus arteriosus (5th to 8th week)

During the 5th week, proliferations of mesenchymal cells (derived mainly from neural crest cells) form ridges in the common tube of BC and TA. These ridges (cushions) are right superior and left inferior. Cushions grow to fuse in a spiral way. Spiraling is caused by the pattern of stream of blood coming from the ventricles. Fusion of these cushions results in formation of the ***spiral aorticopulmonary septum*** (Fig. 9). This septum divides the BC and TA into two channels, - **ascending aorta** and **pulmonary trunk.** Because of the spiraling of the aorticopulmonary septum the pulmonary trunk twists around the ascending aorta.
Proximal third of BC is incorporated into the walls of the definitive ventricles to form:

a) **Infundibulum** of the right ventricle which gives origin of the pulmonary trunk.
b) A**ortic vestibule** of the left ventricle just below the aortic valve.

Semilunar valves

Two minor cushions, one dorsal and one ventral, grow inwards from the wall of the common tube (BC&TA). As the spiral aorticopulmonary septum separates the ascending aorta from the pulmonary trunk and as a result of development of the dorsal and ventral cushions, each of the two arteries will have three cusps for their valves (fig.10). Also, as a result of 45-degree rotation of the common trunk, the pulmonary trunk will have two anterior and one posterior cusps for its valve, whereas the ascending aorta will have one anterior and two posterior cusps for its valve.

Atrioventricular valves

Atrio-ventricular valves develop from localized proliferations of mesenchymal tissues around the A-V canals. Two valve leaflets form the **mitral (bicuspid) valve** and three leaflets form the **tricuspid valve.** This region has the appearance of a cross with the atrial and ventricular septa forming the vertical bar, and the atrioventricular cushions the crossbar. Integrity of this cross is an important sign in ultrasound of the heart.