Development of the heart

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Early Development of the Circulatory System

Appears in the middle of the third week, when the embryo is no longer able to satisfy its nutritional requirement by diffusion alone.

A. Blood Islands

During day 18 of gestation angioblastic blood islands of mesoderm (angiogenic clusters) appear in the yolk sac, chorion and body stalk. The innermost cells of these blood islands are hematopoietic cells that give rise to the blood cell lines. The outermost cells give rise to the endothelial cell layer of blood vessels. A series of blood islands eventually coalesce to form blood vessels.

B. Heart Tube

Cardiac progenitor cells lie in the Epiblast immediately lateral to the primitive streak. They migrate through the streak. Cells that form cranial segment of the heart (the outflow tract) migrate first, this is followed by migration of cells forming more caudal portions, right ventricle, left ventricle and sinus venosus.
Migrated cells position themselves rostral to the oropharyngeal membrane and neural folds in the splanchnic layer of the lateral plate mesoderm. The cardiac myoblast and angioblastic blood islands form blood cells and a plexus of vessels lying deep to the prospective pericardial cavity. These small vessels develop into paired horseshoe-shaped endothelial-lined heart tubes surrounded by myoblast. This region is called the Cardiogenic field. The myocardium thickens and secretes a thick layer of extracellular matrix, rich in hyaluronic acid that separates it from the endothelium. The Epicardium develops from mesodermal cells on the surface of the septum transversum and those adjacent to the outflow tract region. Epicardium also responsible for formation of coronary arteries.

In addition to the cardiogenic region, other blood islands appear bilaterally, parallel and close to the midline of the embryonic shield forming a pair of longitudinal vessels, the Dorsal Aortae. With closure of the neural tube and formation of the brain vesicles, and since the CNS grows so rapidly, it extends over the central cardiogenic area and the future pericardial cavity.
As a result of growth of the brain and the cephalic folding of the embryo, the oropharyngeal membrane is pulled forward, while the heart and pericardial cavity move first to the cervical region and finally to the thorax. The embryo also folds laterally; as a result of that, the paired horseshoe-shaped heart tubes merge except at their caudalmost ends forming the hear tube. The cranial part of the heart tube expands to form the future outflow tract and ventricular regions. The heart receives venous drainage at its caudal pole and begins to pump blood out of the first aortic arch into the dorsal aorta at its cranial pole. The heart tube remains attached to the dorsal side of the pericardial cavity by a fold of mesodermal tissue, called the Dorsal Mesocardium. No ventral mesentry is formed. The Dorsal Mesocardium then disappear and Transverse Pericardial Sinus is formed which connects both sides of the pericardial cavity. The heart is now suspended in the cavity by blood vessels at its cranial and caudal poles.
A. Dorsal view of a late presomite embryo (approximately 18 days) after removal of the amnion. Prospective myoblasts and hemangioblasts reside in the splanchnic mesoderm in front of the neural plate and on each side of the embryo. B. Transverse section through a similar-staged embryo to show the position of the blood islands in the splanchnic mesoderm layer. C. Cephalocaudal section through a similar-staged embryo showing the position of the pericardial cavity and cardiogenic field.

Establishment of Cardiogenic field (Langman’s Medical Embryology)
Establishment of Cardiogenic field (Langman’s Medical Embryology)
Figures showing effects of the rapid growth of the brain on positioning of the heart. Initially, the cardiogenic area and the pericardial cavity are in front of the oropharyngeal membrane. A. 18 days. B. 20 days. C. 21 days. D. 22 days.
Transverse sections through embryos at different stages of development, showing formation of a single heart tube from paired primordia. A. Early presomite embryo (17 days). B. Late presomite embryo (18 days). C. Eightsomite stage (22 days). Fusion occurs only in the caudal region of the horseshoe-shaped tube. The outflow tract and most of the ventricular region form by expansion and growth of the crescent portion of the horseshoe.
Lateral folding apposes paired heart tube primordia and brings dorsal aortae to midline. Heart primordia fuse to form tubular heart.
Formation of the Heart

- Ventral aortic roots
- Ventricular region
- Atrial region
- Ventricular region
- Atrial region
Formation of transverse sinus

- 28 days
- Degeneration of central part of dorsal mesocardium
- Formation of Tr. Sinus
- Three layers of Heart wall.

Apoptosis in the dorsal mesocardium will allow movement of the early heart tube within the pericardial cavity.
Formation of cardiac loop
Heart tube continue to elongate and bend on day 23. Cephalic portion bends ventrally, caudal and to the right. Caudal portion dorsocranially and to the left.
The heart tube is now called the **Cardiac Loop**, it is complete by day 28. Local expansions become visible throughout the length of the tube. Ultimately a **common atrium** and an early **embryonic ventricle** are formed. They are connected by narrow **Atrioventricular canal**. The upper cephalic portion of the cardiac loop is called the **Bulbus Cordis**.

**Bulbus cordis** is narrow except for its proximal third, this dilated part forms the trabeculated part of the right ventricle. The mid portion of Bulbus cordis is called **Conus Cordis**, this forms the **outflow tracts of both ventricles**. The distal portion (upper part) of the Bulbus Cordis is called the **Truncus Arteriosus**, this forms the roots and **proximal portions of the Aorta and Pulmonary artery**.
Junction between the ventricle and the Bulbus Cordis is externally indicated by the **Bulboventricular Sulcus.** It is internally called, the **Primary Interventricular Foramen.**

The cardiac tube is now organized by regions along craniocaudal axis.

The cardiac tube can be divided into the following

1- **Bulbus Cordis**
   a- **Truncus Arteriosus + Conus Cordis** (Conotruncal portion)
   form the proximal portions of the Aorta and Pulmonary artery +
   outflow tracts of both ventricles
   b- Right ventricle = is formed by proximal part of Bulbus Cordis

3- **Left ventricle** = is formed by the embryonic ventricle

4- **Atrial region**

The Conotruncal portion of the heart tube initially on the right side of the pericardial cavity, shifts gradually to a more medial position. This is due to the two transverse dilatations of the atrium bulging on each side of the Bulbus Cordis
TA = Truncus Arteriosus
BC = Bulbus Cordis, Rt Ventricle
CC = Conus Cordis
PV = Lt Ventricle
PA = Common Atrium
SV = Sinus Venosus

Parts of the Cardiac Loop

Bulboventricular Sulcus

Conus cordis

NCC migration

Dorsal mesocardium

Blood outflow

Blood inflow

Pericardial cavity

Primary Interventricular Foramen
Cardiac loop

- Bulbus Cordis
- Bulboventricular Sulcus
- Embryonic ventricle = LV
- Common atrium

Bulboventricular Sulcus

Bending of Cardiac Loop

Parts of Cardiac Loop and its Bending

Cardiac Loop

- RV
- CA
- LV
Development of the Sinus Venosus

In the middle of the 4th week the Sinus Venosus receives venous blood from the Rt. And Lt. Sinus Horns.

Each Right and Left Sinus horn receives blood from three veins:
1- Vitelline vein, 2-Umblical vein, 3-Common Cardinal vein

Communication between the Sinus Venosus and atrium is wide but soon the entrance of the sinus shifts to the right. This is caused by left to right shunt of blood because of obliteration of the Rt. Umbilical vein and the left Vitelline vein during the 5th week which is followed by obliteration of the Lt Common Cardinal vein at 10 weeks.

- The Lt. Sinus Horn rapidly loses its importance thus what remains out of it is the Oblique vein of the Lt. Atrium and Coronary Sinus.

The Rt. Atrium and Rt. Sinus Horn with its veins get enlarged.

The Rt. Sinus Horn is incorporated into the Rt. Atrium and forms the smooth part of it. The veins (Right Cardinal system) form Sup. and Inf. Vena Cava
Horns of Sinus Venosus

Sinus Venosus at 24 & 35 Days

- atrium
- sinusatrial junction
- left common cardinal vein
- umbilical vein
- vitelline vein
- right common cardinal vein
- right vitelline vein
- coronary sinus

Left Common Cardinal vein

Right Umbilical vein

Disappear

Coronary Sinus
The left horn change into = Oblique vein of the Lt. Atrium and Coronary Sinus
The Sinoatrial orifice is surrounded by Valvular fold, the Right and Left Venous valve

These valves fuse dorsocranialaly forming Septum Spurium

The left venous valve and the Septum Spurium fuse with the developing Atrial Septum

The superior portion of the Right Venous Valve disappears, the inferior portion develops into
A-Valve of the inferior Vena Cava
B-Valve of the Coronary Sinus
Ventral view of coronal sections through the heart at the level of the atrioventricular canal to show development of the venous valves. 

A. 5 weeks. B. Fetal stage. The sinus venarum (blue) is smooth walled; it derives from the right sinus horn. Arrows, blood flow.

Development of Venous Valves (Langman’s Medical Embryology)
Formation of valves and septa in cavities of the heart in the embryo (27th and 37 days)

1- **Endocardial Cushions** develop in the **Atrioventricular** and **Conotruncal regions**, they assist in formation of
- Atrial and Ventricular septa
- Atrioventricular canals and valves
- Aortic and Pulmonary Channels

2- **Narrow septum of tissue**: These septa (strips) usually develop between two expanding portions of the heart (in the atria or ventricles). Such a septum never completely divides the original lumen but leaves a narrow communicating canal between the two sections. It is usually closed secondarily by tissue from Endocardial cushions.
Formation of Cardiac Septa

**A, B.** Septum formation by two actively growing ridges that approach each other until they fuse. **C.** Septum formed by a single actively growing cell mass. **D-F.** Septum formation by merging of two expanding portions of the wall of the heart. Such a septum never completely separates two cavities.

*Langman’s Medical Embryology*
Septum Formation in the Atrium

• **Septum Primum**, a sickle shaped crest descend from the roof of the atrium dividing the atrium in two but leaves an opening: **Ostium Primum** for communication between the two sides.

• **Osteum primum** is obliterated by fusion of the septum primum with the **Endocardial Cushion** which grow along the edge of the septum primum.

• Before closure is complete, **Ostium Secondum** is formed in the upper portion of Septum Primum, this is formed by cellular death in that septum.

• **Septum Secondum**; crescentic in shape develops, the free concave edge of the septum secondum begins to overlap the ostium secondum. The opening left by the septum secondum is called the **Foramen Ovale**.
At birth when pressure in the Lt. atrium increases, the two septa press against each other and close the communication between the two atria.

Left Atrium initially has single embryonic pulmonary vein which united with veins of the lug. The pulmonary vein and its branches are incorporated within the wall of the left atrium. Ultimately Four Pulmonary veins enters Lt atrium as the branches of the original vein are incorporated into the expanding atrial wall.
Septum Formation in the common Atrium

A.P. View of Embryonic septum (A, C, E, F)

View of embryonic septum From inside of the Rt. Atrium (B, D, G)

Coronary Sinus (Langman’s Medical Embryology)
Septum formation in the Atrioventricular Canal
Initially the primitive atrium empties into the primitive left ventricle through the Atrioventricular canal. As Atrioventricular canal enlarges to the right, the Atrioventricular orifice now has access to the primitive left as well as the right primitive ventricle.

As development progresses, mesenchymal cushions, the Atrioventricular endocardial cushions appear around the edges of the atrioventricular orifice (ant, post and two lateral endocardial cushions). These are the precursors of the atrioventricular valves and function during this early development as primitive valves. The Anterior and posterior endocardial cushions grow toward each other and fuse, separating the atrioventricular canal into two atrioventricular orifices which will eventually become the tricuspid and mitral valves by the end of fifth week.
Development of Atrioventricular valves

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Formation of Atrioventricular Valves

After the atrioventricular endocardial cushions fuse, each atrioventricular orifice is surrounded by local proliferation of mesenchymal tissue. When the blood stream hollows out and thins tissue on the ventricular surface of the proliferations, valves form and remain attached to the ventricular wall by muscular cords. The muscular tissue in these cords is replaced by dense connective tissue, the valves also consist of connective tissue covered by endocardium. The cords are called Chordae Tendineae, they are connected to Papillary muscles in the wall of the ventricle. In this way Mitral valve (bicuspid) and Tricuspid valve are formed between atria and ventricles.

(Langman’s Medical Embryology)
Septum Formation between the Ventricles

By the end of fourth week the two primitive ventricles begin to expand. The medial walls of the expanding ventricles become apposed and gradually merge forming the **Muscular Interventricular Septum** leaving an **interventricular foramen** at top of the septum.

Along the top of the **muscular interventricular septum**, an outgrowth of tissue develops from the Inferior surface of the **Endocardial Atrioventricular cushion**. This component forms a thin membrane called **Membranous Septum** which fuses with the Muscular interventricular septum and a completely closes the interventricular foramen. Failure of union results into an **open interventricular foramen**.
Development of Interventricular Septum
Septum Formation in the cavity of the bulbus cordis

During Fifth week of development, the cavity of the bulbus cordis is divided by a spiral septum into pulmonary and aortic trunks.

The ventricular septum and septum of bulbus cordis unite with each other in a way that the right ventricle leads into the pulmonary trunk and the left ventricle into the aorta.

In their growth the ventricles incorporate the conus cordis, thus forming the smooth walled Infundibulum in the right ventricle and Vestibule in the left ventricle.
Partition of Bulbus Cordis

(Langman’s Medical Embryology)
Development of Semilunar Valve

When Partitioning of the Truncus is complete, three small tubercles appear in both channels. The tubercles hollow out at their upper surface forming Semilunar valves. Neural crest cells play a rule in their formation.
Formation of the Conductive System of the Heart

Initially, the **Pacemaker** for the heart lies in the caudal part of the left cardiac tube. Later, the Sinus Venosus assumes this function. When the **Sinus Venosus is incorporated into the right atrium**, Pacemaker tissue (**Sinuatrial node**) lies near the opening of the superior vena cava.

**Atrioventricular Node and Bundle of His** are derived from 1-Cells in the left wall of the sinus venosus
2-Cells from the atrioventricular canal
When the sinus venosus is incorporated into the right atrium, the **final position of Atrioventricular node** is located at the base of the interatrial septum
Conductive system of the heart
Clinical Correlates - Septal Defects

1- Atrial septal defect
   a) *Ostium secundum* = excess resorption of septum primum or inadequate development of septum secundum (foramen ovale defect)
   b) *Ostium primum* = septum primum fails to fuse with endocardial cushion (low defect with semilunar shape, right above the AV valves)

2- Ventricular septal defect
   a) *Failure* of membranous portion to develop from extension of endocardial cushion to fuse with interventricular muscular septum
   b) *Muscular defect* = resorption of septum

Clinical Correlates - Trancoconal Septation

1- *Truncus arteriosus* = defective fusion of bulbotruncal ridges
2- *Transposition of Great Arteries* = failure of trancoconal spiral
3- *Tetralogy of Fallot* = unequal division of conus cordis
4- *Semilunar valve stenosis* = failure of development of trancoconal swellings or unequal partition
5- Patent ductus arteriosus: failure of closure of the ductus arteriosus