Embryology

[rearrangement of dr. Amjad Shatarat's slides]

- The cardiovascular system appears in the middle of the third week.
- It is formed by cardiac progenitor cells in the epiblast with contribution of the neural crest mesenchyme.
- The cardiac progenitor cells migrate into the splanchnic layer of the lateral plate mesoderm

- The atria, left ventricle and part of the right ventricle arise from the primary heart field.
- The remainder of the right ventricle [conus cordis & truncus arteriosus] arises from the secondary heart field.

STAGES OF HEART DEVELOPMENT - LOOPING

1. Two angioblastic cords [a pair of endothelial strands] appear in the cardiogenic mesoderm during the 3rd week of development.
2. The two cords form two heart tubes
3. By the end of the third week, the tubes fuse to form one heart tube as the foetus folds laterally. The heart has a cranial arterial end, and a caudal venous end.

23 days old and 2.2 mm long embryo

Sinus venosus [fixed by septum transversum] -> primitive atrium -> primitive ventricle -> bulbus cordis -> truncus arteriosus [fixed by the pharyngeal arches]

Sinus venosus receives blood from: 1. common cardinal vein [body wall], 2. umbilical vein [placenta], 3. vitelline vein [yolk sac]
Arterial end: tubular truncus arteriosus is continuous with the aortic sac.

* The ***dorsal aortae*** are longitudinal vessels that are formed by blood islands [cardiogenic cells] that appear bilaterally, parallel and close to the midline of the embryonic shield.
* The pericardium at this stage surrounds only the bulbus cordis and the primitive ventricle.

> Small talk:
> basically just understand and remember, blood reaches the hearts by the veins to the smooth part of the atria which will be formed by sinus venosus and then moves to the rough part of the atria which will be formed by the primitive atrium and then, through the atrioventricular canal, it will move to the ventricles, particularly the rough inflow area which will be formed by the primitive ventricles and then to the smooth outflow area [aortic vestibule in the left ventricle, and infundibulum or conus arteriosus in the right ventricle] which will be formed by the bulbus cordis, then eventually to the arteries and out of the heart, this last part will be formed by truncus arteriosus, naturally.

4. The bulbus cordis and the primitive ventricle grow faster than the rest of the heart, so the tube bends to the right with the proximal bulbus cordis lying anterior to the right primitive ventricle forming the u-shaped **Bulboventricular tube**. But they are separated by a deep bulboventricular sulcus.

25 days old, 3.2 mm long embryo

5. The atria and sinus venosus are then freed from the septum transversum and move behind the ventricle forming an **S-shaped heart**.
6. The sulcus separating the bulbus cordis and primitive ventricle becomes shallower and shallower until those two form one chamber communicating with *drum roll* truncus arteriosus

* the ventricles communicate through the interventricular foramen which will be closed later by the interventricular septum, or will it?

7. The atria expand and pop up forward on either side of the truncus, and lie behind and above the ventricles.
8. At the end of looping and rotation of the heart, the arterial and venous ends come closer together.

The heart assumes its definitive shape

ABNORMALITIES OF CARDIAC LOOPING

- Dextrocardia -> the heart loops to the left instead [see point 4] as a part of situs inversus [all organs are flipped] or randomly. Normal physiology, higher risks of cardiac defects [sometimes].

STAGES OF HEART DEVELOPMENT - SEPTATION

- Lasts about 10 days and the formation of the various septa occurs more or less simultaneously with no major changes in the external appearance of the heart.

- The atrioventricular canal: an opening between the atria and the ventricles. Initially it is located on the left side of the heart, but as the tube develops it gets pushed medially.

1. It starts round but then becomes transverse
2. Thickenings on the ventral and dorsal walls of the AV canal appear, forming what we call AV or endocardial cushions. Those cushions are **derived from neural crest cells** migrating from the cranial neural folds to the outflow tract region.
3. The cushions grow and *fuse*, forming a **septum intermedium** dividing the AV canal into left & right. Those canals separate the primordial atrium from ventricles.

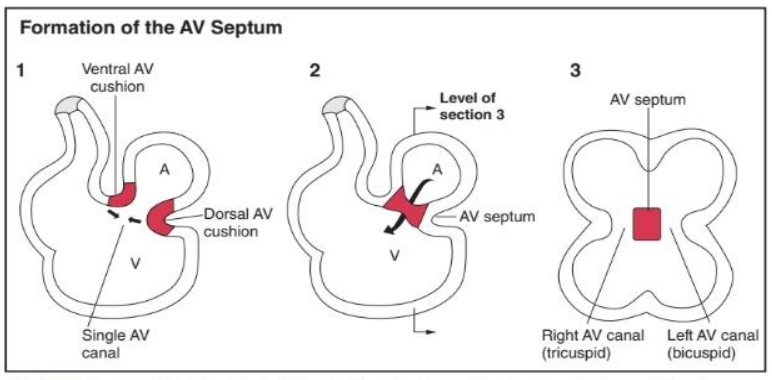


FIGURE 5.11. Formation of the atrioventricular (AV) septum. The AV septum partitions the atrioventricular canal. AV septum = red.

* Those endocardial cushions [point 2] give rise to proliferating mesenchymal tissue, when the blood stream hollows the surface of this tissue, the valves are formed. Initially they are attached to the ventricular wall by muscular cords which will degenerate and get replaced by dense connective tissue -> chordae tendineae.

ATRIAL SEPTATION

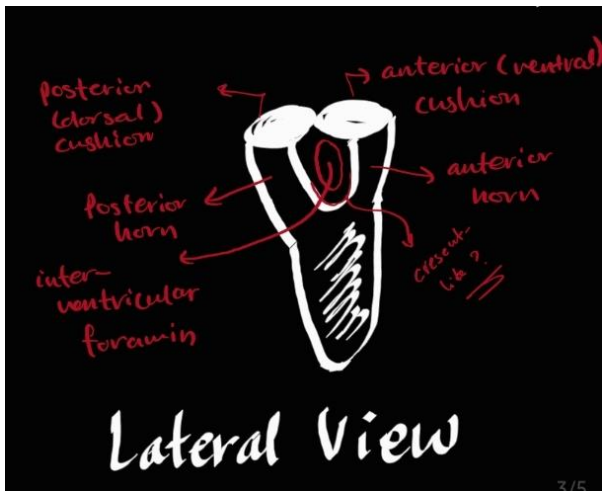
1. Septum primum -> is a *sickle or crescent shaped* septum that appears and extends from the roof of the atria down and **fuses with the endocardial cushions**.
    - *Septum intermedium: formed by the fusion between the septum primum and the endocardial cushions.*
2. Foramen primum -> a large opening *formed between the free edge of the septum primum and the endocardial cushions*. To **shunt oxygenated blood from the right to the left atrium**. Then it progressively disappears as the septum grows.
3. Foramen secundum -> formed just before the foramen primum closes completely, **due to apoptosis and programmed cell death** of the upper part of septum primum. Same function as foramen primum.
4. Septum secundum -> grows *from the ventral-cranial [posterosuperior] wall of the atrium, right to the septum primum* but does not fuse with the endocardial cushions [Forming annulis ovale]. Its lower edge is thick and firm [unlike the septum primum]. And it covers the foramen secundum.
That forms: foramen ovale.
5. Foramen ovale -> *formed near the floor of the right atrium, between the septum secundum and septum primum*.

- The septum primum [thin and floppy] acts like a valve of the foramen ovale. So, **it allows blood to move from the right to the left atrium easily [it bends] but closes if the opposite happens**, so no blood moves from left to right. [سبحان الله]
- When the lungs are formed and the circulation begins, the pressure in the left atrium pushes the septum primum against the septum secundum closing the foramen ovale [بتلزق]. The septum primum forms the floor of a new-not-new structure called Fossa ovalis.

SEPTATION OF THE VENTRICLES

-Starts as a *projection from the base or inferior walls of the ventricle*, then it enlarges and forms two horns, each horn fuses with the corresponding AV endocardial cushion.

My understanding is this: we have ventral and dorsal endocardial cushions [anterior and posterior], as the septum grows it divides or forms two horns [anterior and posterior as well], each horn will fuse with the corresponding cushion and in the middle [the space between the horns] we will have the interventricular foramen. I COULD BE UTTERLY WRONG THO. However, it says in the slides that the upper crescentic border of the septum bounds a temporary connection between the two ventricles called interventricular foramen which in my head looks like this ->



- The IV foramen permits communication between the rt. & lt. ventricles. [till the seventh week].

- The muscular part of the interventricular septum is formed by the ventricular septum -.-
- The membranous part is formed by a downward extension from the right margins of the AV endocardial septum [septum intermedium - refer to point 1 in atrial septation].
- The proximal bulbar septum develops when two bulbar ridges fuse together to close the IV foramen along with membranous part [endocardial extensions]

ABNORMALITIES [DEFECTS] OF CARDIAC SEPTATION

- Membranous septal defects are the most common heart defects, why? because the three basic primordia [IV septum, endocardial cushions and spiral septum] need to fuse in an area with **active blood flow**. A lot of work against the blood.
- Postnatal shunts: 1. Right to left: cyanotic conditions, 2. Left to right: non-cyanotic conditions
** Extra: why? right to left shunt decreases the blood flow to the lungs -> decreased oxygenation of blood [hypoxemia] -> cyanosis

1. **Atrial septal Defect [ASD]:** variable openings between the right and left atria in the central part of the septum above the limbus [border]
a. more common in females
b. left to right shunt -> no cyanosis [may you never be blue ladies!]
c. secundum and primum types
    1. secundum is more common
    2. caused by excessive resorption of septum primum or underdeveloped septum secundum or both.
d. if it was small, the symptoms may be delayed till after the age of 30.

* When the fusion between the septum primum and secundum is incomplete, a narrow oblique cleft remains between the two atria, causing **Probe Patency** of the foramen ovale but it doesn't allow intracardiac blood shunting

2. **Ventricular septal defects [VSD]**
a. most common congenital heart defect, more common in males.
b. The most common VSD is a membranous ventricular septal defect caused by failure of neural crest cells to migrate into endocardial cushions.
c. left to right shunting of blood -> no cyanosis but excessive fatigue upon exertion
* blood to the systemic circulation is reduced and when you do something that requires physical effort, your muscles require more blood but there isn't enough, the fatigue now makes sense right?

The excessive left to right shunt causes **pulmonary hypertension eventually**, and that causes marked proliferation of the tunica intima and media of the pulmonary artery -> higher resistance *[physio said Tension = Pressure * Radius, thicker tunica media -> more smooth muscle cells -> higher tension -> smaller radius & higher pressure].*
That would cause right to left shunt and **late cyanosis**. The condition is now called the **Eisenmenger complex**.

SEPTATION OF BULBUS CORDIS
- *Neural crest cells* form two opposing ridges in the walls of the bulbus [conus] cordis called bulbar [conal] ridges. These ridges fuse to form the **Bulbar septum** [proximal and distal].

1. The proximal bulbar septum:
   a. participates in the closure of IV foramen.
   b. forms the outflow, smooth wall of the ventricles.
   - in the right ventricle -> infundibulum [conus arteriosus], gives origin to the pulmonary trunk
   - in the left ventricle -> aortic vestibule, gives origin to the aorta

2. The distal bulbar septum:
   - four endocardial cushions develop in the distal bulbus cordis [anterior, posterior, left and right], then two ridges arise from the middle of the left and right cushions and those ridges fuse dividing the distal bulbus cordis into **pulmonary orifice anteriorly**, and **aortic orifice posteriorly**.

- The cusps of the pulmonary valve are one posterior and two anterior, while those of the aortic are one anterior and two posterior [after the rotation].

SEPTATION OF TRUNCUS ARTERIOSUS
- Neural crest cells form two opposing ridges in the walls of the truncus arteriosus called truncal ridges. These ridges fuse to form the truncal septum.
- THREE PARTS
1. in the lower part -> the ridges are located in the right and left sides of the wall
2. in the middle part -> as the truncus rotates, the right ridge becomes anterior while the left becomes posterior
3. in the upper part -> more rotation, the anterior ridge becomes left while the posterior becomes right.

- The bulbar and truncal ridges undergo 180 -degree spiralling forming **Spiral aortico-pulmonary** septum when the ridges fuse. The truncal septal creates two arterial channels 1. ascending aorta, 2. pulmonary trunk.

TRUNCUS ARTERIOSUS DEFECTS
- Defects in the spiral aorticopulmonary septum are related to failure of neural crest cells to migrate into the truncus arteriosus

1. Tetralogy of Fallot -> **most common *cyanotic* congenital defect**, results when the AP septum fails to align properly and shifts anteriorly to the right.
- Right to left shunt -> cyanosis at birth
- boot-shaped heart -> enlarged right ventricle

The *tetralogy* of Fallot -> 1. pulmonary stenosis, 2. overriding aorta [receives blood from both ventricles], 3. membranous IV septal defect, 4. right ventricular hypertrophy.

2. Transposition of the great vessels -> develops when the AP septum fails to develop in a spiralling manner, the aorta arises from the right ventricle, and the pulmonary arises from the left.
- **most common cause of severe cyanosis**, immediately after birth.
- two closed circulation loops
- infants born with those defects usually have other defects that allow the mixing of oxygenated and deoxygenated blood [PDA, VSD, ASD].

CHANGES IN SINUS VENOSUS
- The sinus venosus has two horns -> left and right

The Left horn loses its importance **due to left-to-right shunts of blood** [as a result of the transformation of both vitelline and umbilical veins and when the left common cardinal vein gets obliterated at 10 weeks].
All that remains of the left sinus horn is: 1. oblique vein of the left atrium, & 2. the coronary sinus.

The right horn is a party. It communicates with the primordial atrium through the sinoatrial orifice. Initially, the sinus opens into the centre of the posterior wall of the primordial atrium.

- Week four -> the right sinus horn becomes larger than the left and the sinoatrial orifice moves to the right and opens in the part that will later form the adult!right atrium.
-At first the communication between the sinus and the atrium is wide but then it shifts to the right because of the left-to-right shunting of blood that occurs in week 4 and 5.

- The right sinus horn **receives blood from the head and neck through SVC**, and **from the placenta and the caudal region through IVC**.
- The right horn will form the smooth wall of the right atrium [**THE SINUS VENARUM**]. The sinoatrial orifice is surrounded by two valvular folds -> right and left venous valves. Dorso-cranially the valves fuse and form septum spurium.

1. The right valve ->
    a. the cranial part will develop into crista terminalis
    b. the inferior portion develops into: the valve of IVC & the valve of the coronary sinus [look both are located on the inferior aspect of the atrium, so being related to the inferior portion of the right valve kinda makes sense] ;/
2. The left valve -> along with septum spurium, they fuse with the developing atrial septum.

NOW, what happens in the left atrium? Most of its wall is smooth, we have four pulmonary veins!
- Initially though, we have a **primordial pulmonary vein that develops as an outgrowth of the dorsal wall** of the left atrium [left to septum primum] and it has branches. As the atrium expands, the branches get incorporated into its wall as well.
- The small left auricle is *remnants of the primordial atrium and it has a rough, trabeculated surface.*

THE VEINS TRANSFORMATION

The sinus venosus represents the venous end
* it receives blood from three veins:
    1. Vitelline veins -> from the tolksac
    2. Umbilical veins -> from the placenta
    3. Common cardinal vein -> from the body wall

* It has right and left sinus horns. The left sinus horn loses its importance due to left-to-right shunts of blood -> blood is **rechanneled** toward the right. When do these shunts occur?
    a. the first is a result of the transformation of the vitelline and umbilical veins
    b. the second occurs when the left anterior cardinal vein becomes connected to the right anterior cardinal vein by an oblique anastomosis *[left brachiocephalic]*

1. The vitelline [omphalomesenteric] veins

- The veins form a *plexus around the developing duodenum* then it enters the sinus venosus. Then, this anastomotic network develops into the **Portal vein.**
- The course of the veins is interrupted by the growing liver and forms an extensive vascular network called **Hepatic sinusoids**.
- At the same time, the left sinus horn starts losing its importance so blood gets rechanneled from the left side of the liver toward the right which results in the enlargement of the right vitelline vein which gets called the Right Hepato-cardiac channel. This channel forms **the hepato-cardiac portion of the IVC**.
- The proximal part of the left vitelline vein disappears.
- The right vitelline vein gives origin to the **Superior Mesenteric vein** as well. [it's called omphaloMESENTERIC, and the right one because the left disappeared]
- The proximal and distal parts of the left vitelline vein disappear.

2. The umbilical veins

- The umbilical veins pass of each side of the liver, some connect to the hepatic sinusoids
- The proximal part [initially connected to the sinus venosus] disappears -> no connection to the sinus venosus.
- The remainder [distal] part of the right umbilical vein disappears
- The left umbilical vein carries blood from the placenta to the liver.
- When the placental circulation increases, a direct connection between the left umbilical vein and the right hepato-cardiac channel is formed -> **Ductus venosus.** It bypasses the hepatic sinusoids and connects the left umbilical vein to the hepatic portion of IVC.
- After birth, the **ductus venosus and the left umbilical vein are obliterated forming ligamentum venosum and ligamentum teres hepatis**, respectively.

3. The cardinal veins

- Form: 1. right and left anterior [drain the cephalic area]. The anastomosis between them develops the **left brachiocephalic vein**. When this oblique anastomosis occurs, blood from the left side of the head and left upper extremity gets channelled to the right. The second left-to-right shunt.
    2. right and left posterior [drain the rest of the embryo] cardinal veins.

- Before entering the sinus venosus, the veins join together forming the right and left common cardinal veins.

- The right common cardinal vein and the proximal portion of the right anterior cardinal vein form the **Superior vena cava**.

CLINICALLY ->
1. failure of right brachiocephalic vein to form -> left SVC.
2. persistence of left anterior cardinal vein -> double SVC.
3. Left sacro-cardinal vein remains connected to the left subcardinal -> double IVC.
4. right subcardinal vein fails to make connection with the liver -> absence of IVC

THE ARTERIEs TRANSFORMATIONS

- **Ductus arteriosus** ->
  - *Functional* closure of DA is usually completed 10-15 hours after birth
  - *Anatomical* closure of DA and formation of Ligamentum arteriosum occurs by the 12th postnatal week.

Patent ductus arteriosus -> a common birth defect, more common in females than males [two or three times]

- Functional closure of a PDA occurs soon after birth but it *remains open*, and it fails to form ligamentum arteriosum, so -> the aortic blood is shunted into the pulmonary artery.
- causes:
  1. rubella infection in early stages of pregnancy -> the most common birth defect associated with this infection
  2. hypoxia -> in preterm babies or those born at high altitudes

Coarctation of the aorta -> congenital *narrowing* of the aorta just proximal, opposite or distal to the site of attachment of the ligamentum arteriosum. More common in males [two times more than females]. It occurs in 10% of children with CHDs.

- Most defects occur distal to the left subclavian artery [branch of the arch], at the entrance of DA [juxtaductal coarctation].
- In 90% of the cases, it occurs opposite to the DA.
- causes: this condition is believed to result from an unusual quantity of ductus arteriosus muscle tissue in the wall of the aorta. When the ductus arteriosus contracts, the ductal muscle in the aortic wall also contracts, and the aortic lumen becomes narrowed. Later, when fibrosis takes place, the aortic wall also is involved, and permanent narrowing occurs.

- clinical signs: **absent or diminished pulses in the femoral arteries of both lower limbs**. To compensate for the diminished blood flow, an enormous collateral circulation develops with the dilation of: *internal thoracic, subclavian and posterior intercostal arteries*. The dilated intercostal arteries erode the lower borders of the ribs producing **characteristic notching** seen on radiographic examination.
- treatment: surgery.

FOETAL CIRCULATION

- Oxygenated blood reaches from the placenta to the foetus through the umbilical vein. Three vascular shunts develop to bypass blood flow around the liver and lungs.
- ductus venosus allows oxygenated blood in the umbilical vein to bypass the hepatic sinusoids into the IVC and to the right atrium.
- from the right atrium, blood flows through the foramen ovale to the left atrium -> left ventricle -> systemic circulation [right-to-left shunt]
- SVC drains deoxygenated blood from the upper limbs and head into the right atrium and most of it gets directed to the right ventricle and into the pulmonary trunk.
- ductus arteriosus opens into the underside of the aorta, distal to the origin of the subclavian artery and shunts deoxygenated blood from the pulmonary trunk to the aorta, to bypass the pulmonary circulation.

Oxygenated blood from the placenta -> umbilical vein -> ductus venosus -> IVC -> right atrium -> through foramen ovale shunts to -> left atrium -> left ventricle -> systemic circulation
SVC -> right atrium -> right ventricle -> pulmonary trunk -> ductus arteriosus -> aorta

** *All in all, the main goal is to avoid pulmonary circulation because .. er .. there are no lungs*.

CHANGES AT BIRTH

1. after birth, the lungs take on gas exchange instead of the placental circulation
2. ductus arteriosus, foramen ovale, umbilical vein and ductus venosus close.
3. the umbilical arteries for the medial umbilical ligaments.