Lecture - Early Vascular Development

Contents

Introduction

This lecture is an introduction to the events in early embryonic development that relate to mesoderm and early cardiovascular development. Texts frequently separate heart development from vascular development in order to simplify their descriptions of cardiovascular development, although the two are functionally and embryonically connected.

Note that later in the course, the late development of the heart and vascular changes will be further discussed. The complexity of septation, cardiac outflow separation, remodelling of the peripheral vasculature, and the pre- to post-natal changes may also contribute to the relatively large proportion of birth defects associated with this system. These events of vascular development are covered in a later lecture.

It is important to note also that we are just beginning to understand vascular development which involves the careful orchestration of a variety of molecululular mechanisms. Development does appear to be an independent mechanism preceding both skeletal and smooth muscle development and using different regulatory mechanisms. In the next few years, there are certain to be new molecules identified as well as an understanding and appreciation of new roles for known molecules.

(/embryology/index.php/File:Mouse_embryo_va

Image of mouse embryo (19 somite) vascular distribution (about Human stage 12 (/embryology/index.php/Carnegie_stage_11))

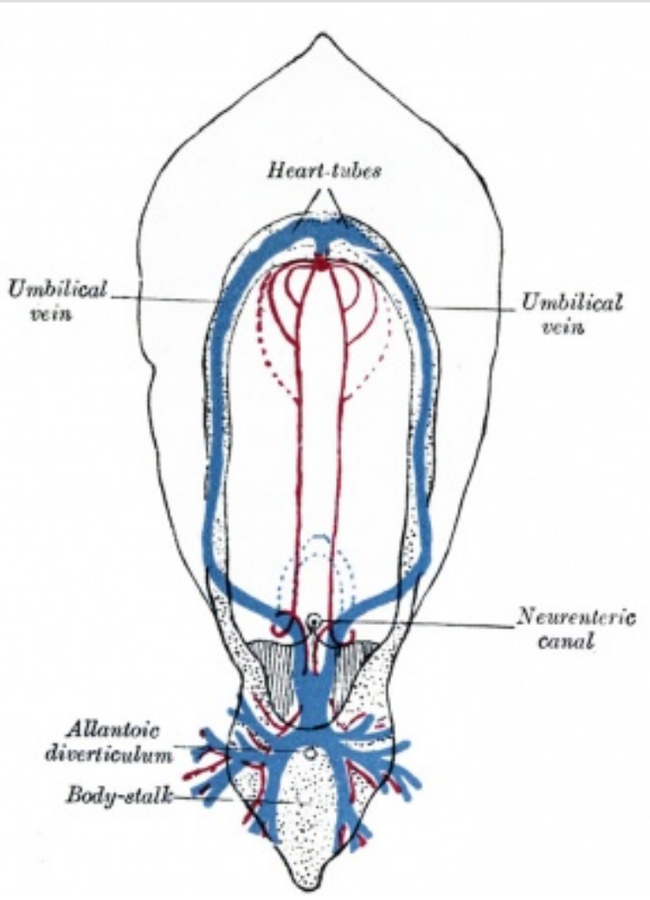
- **Vasculogenesis** - formation of new blood vessels assemble from individual precursor cells.
- **Angiogenesis** - sprouting of new vessels occurs from pre-existing vessels.

Lecture Objectives

- Understanding of mesoderm development
- Understanding of heart tube formation and early development
- Understanding of early blood vessel and blood development
- Brief understanding of vascular growth and regression
- Brief understanding of vascular growth factors

Lecture Resources

Movies[Expand]

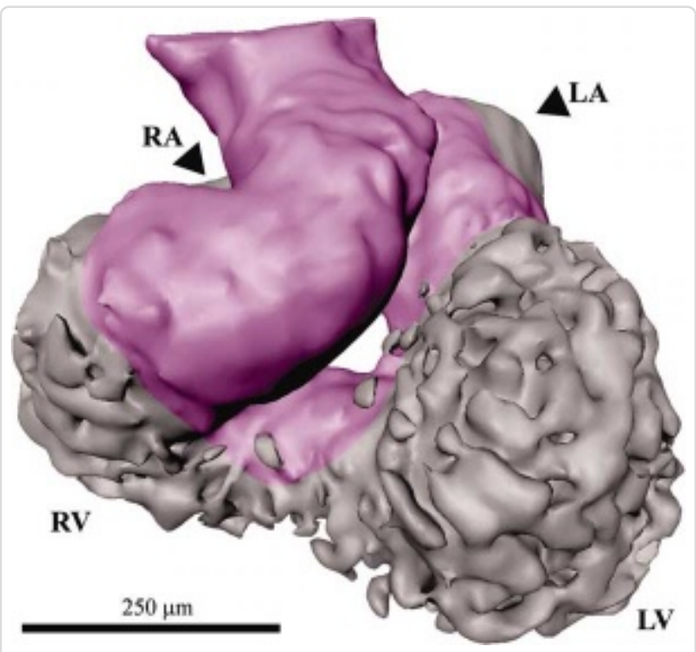


(/embryology/index.php/File:Gray0458.jpg)
Historic image of early human vascular development

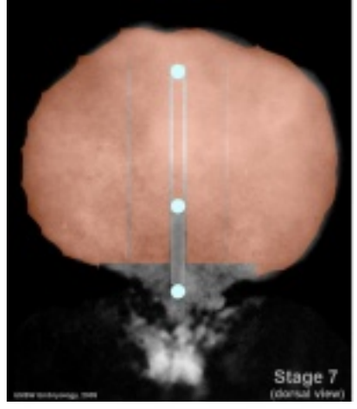
References [Collapse]	
(/embryology/index.php/File:Logo.png) Hill, M.A. (2016). *UNSW Embryology* (16th ed.) Retrieved August 22, 2016, from https://embryology.med.unsw.edu.au (https://embryology.med.unsw.edu.au)	• Week 3 (/embryology/index.php/Week_3) | Gastrulation (/embryology/index.php/Gastrulation) | Implantation (/embryology/index.php/Implantation) | Cardiovascular System Development (/embryology/index.php/Cardiovascular_System_Development) | Placenta Development (/embryology/index.php/Placenta_Development) • Lecture Archive: 2015 (https://embryology.med.unsw.edu.au/embryology/index.php?title=Lecture_-_Early_Vascular_Development&oldid=195358) | 2015 PDF (/embryology/images/7/7d/2015ANAT2341_Lecture_7_-_Early_Vascular_Development.pdf)2014 Lecture 7 PDF (/embryology/images/5/57/ANAT2341_Lecture_7_-_2014_Early_Vascular_Development.pdf)
(/embryology/index.php/Embryology_Textbooks_-_UNSW#The_Developing_Human:_Clinically_Oriented_Embryology) Moore, K.L., Persaud, T.V.N. & Torchia, M.G. (2015). *The developing human: clinically oriented embryology* (10th ed.). Philadelphia: Saunders.	The following chapter links only work with a UNSW connection. • Chapter 7 - Placenta and Fetal Membranes (http://www.unsw.eblib.com.wwwproxy0.library.unsw.edu.au/patron/Read.aspx?p=1430154&pg=131) • Chapter 13 - Cardiovascular System (http://www.unsw.eblib.com.wwwproxy0.library.unsw.edu.au/patron/Read.aspx?p=1430154&pg=311)
Schoenwolf, G.C., Bleyl, S.B., Brauer, P.R., Francis-West, P.H. & Philippa H. (2015). *Larsen's human embryology* (5th ed.). New York; Edinburgh: Churchill Livingstone.	The following chapter links only work with a UNSW UNSW Library subscription (http://er.library.unsw.edu.au/er/cgi-bin/eraccess.cgi?url=http://www.unsw.eblib.com.wwwproxy0.library.unsw.edu.au/patron/FullRecord.aspx?p=2074524) • Chapter 2 - Second Week: Becoming Bilaminar and Fully Implanting • Development of the Heart (http://www.unsw.eblib.com.wwwproxy0.library.unsw.edu.au/patron/Read.aspx?p=2074524&pg=285) • Development of the Vasculature (http://www.unsw.eblib.com.wwwproxy0.library.unsw.edu.au/patron/Read.aspx?p=2074524&pg=322)

ECHO360 Recording[Expand]

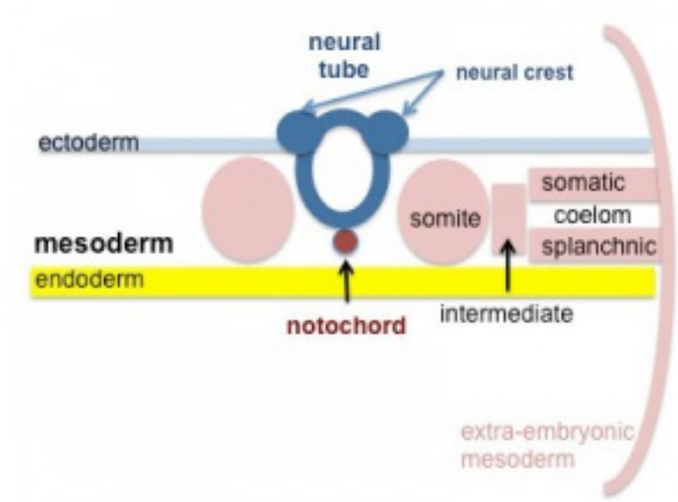
Development Overview



(/embryology/index.php/File:Mouse_heart_E9.5
mouse E9.5 heart (stage 10)



(/embryology/index.php/File:Stage7_mesoderm.jpg)

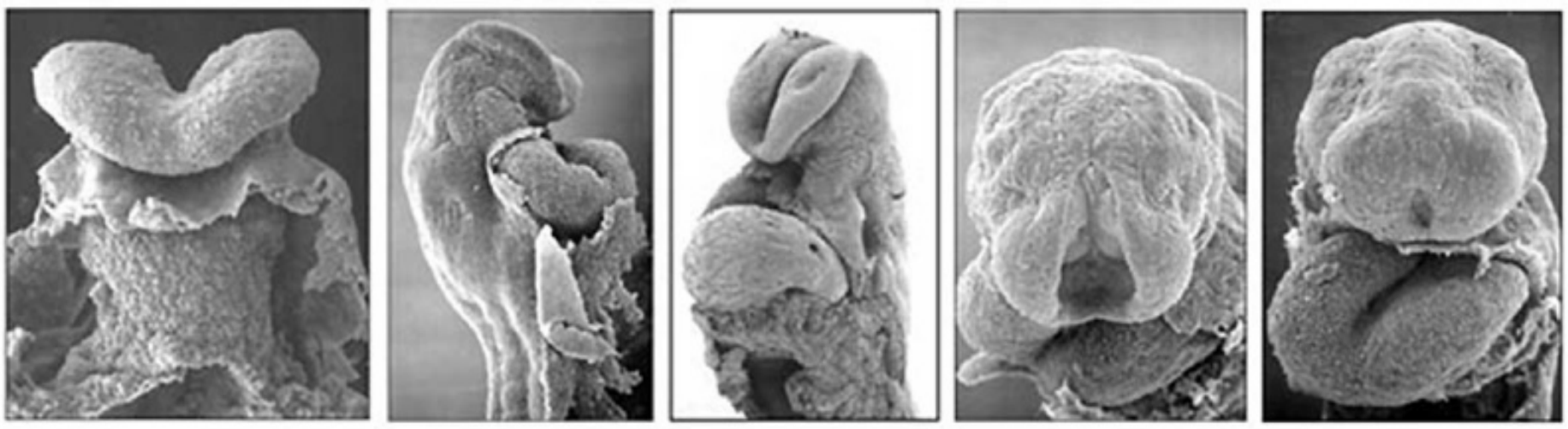


(/embryology/index.php/File:Mesoderm-cartoon4.jpg)

(/embryology/index.php/File:Gray0462.jpg)

The heart develops from cardiogenic mesoderm that originally lies above the cranial end of the developing neural tube. Enlargement of the cranial neural fold brings this region ventrally to its correct anatomical position. The original paired cardiac tubes fuse, with the "ventricular" primordia initially lying above the "atria". Growth of the cardiac tube flexes it into an "S-shape" tube, rotating the "ventricles" downward and pushing the "atria" upward.

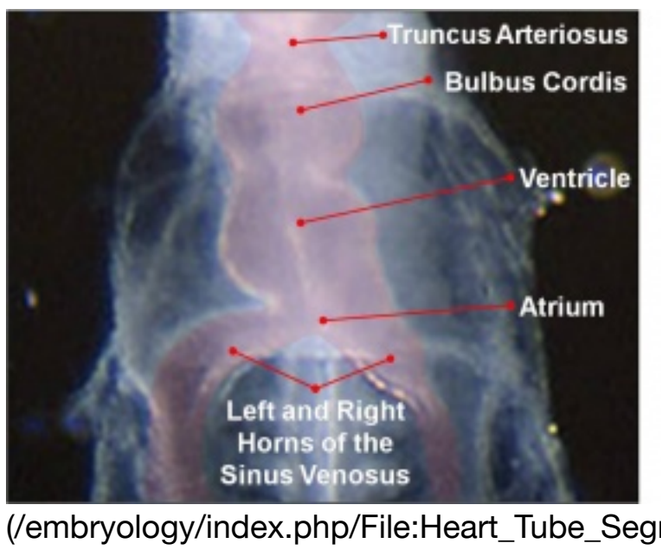
This is then followed by septation, a complex process which converts this simple tube into a four chambered heart and covered in a later lecture and lab. A key part of this process is the separation of cardiac outflow (truncus arteriosus) into a separate pulmonary and aortic arch outflow. During embryonic development there is extensive remodelling of the initially right and left symmetrical cardiovascular system and a contribution from the neural crest to some vessels.



(/embryology/index.php/File:Human_heart_SEM1.jpg)
The Human Heart from day 10 to 25 (scanning electron micrograph)

Timecourse

- forms initially in splanchnic mesoderm of prechordal plate region - cardiogenic region
  - growth and folding of the embryo moves heart ventrally and downward into anatomical position
- heart tube connects to blood vessels forming in splanchnic and extraembryonic mesoderm
- **Week 2-3** pair of thin-walled tubes
- **Week 3** paired heart tubes fuse, truncus arteriosus outflow, heart contracting
- **Week 4** heart tube continues to elongate, curving to form S shape
- **Week 5** septation starts, atrial and ventricular
  - Septation continues, atrial septa remains open until after birth, foramen ovale.
- **Week 37-38** at birth, pressure difference closes foramen ovale leaving a fossa ovals



(/embryology/index.php/File:Heart_Tube_Segments.jpg)
Human early heart tube (Week 4 (/embryology/index.php/Week_4), Stage 10 (/embryology/index.php/Carnegie_stage_10))

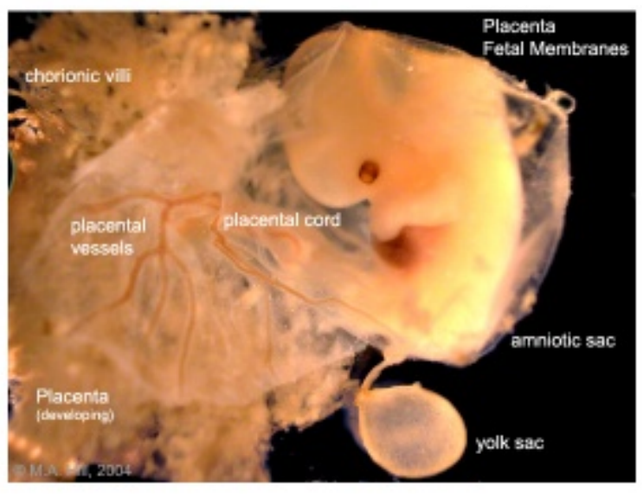
Vasculogenesis and Angiogenesis

Vasculogenesis

formation of new blood vessels
(endothelium from mesoderm)

Angiogenesis
formation of blood vessels from pre-existing vessels
(occurs in development and adult)

- Begins week 3 in **extraembryonic mesoderm** and then **embryonic splanchnic mesoderm**
- Begins as the formation of **blood islands**
- Earliest islands - yolk sac, connecting stalk and chorion (Area vasculosa)
- Growth factors stimulate growth and development - **Vascular Endothelial Growth Factor** (VEGF) and **Placental Growth Factor** (PlGF, PGF)
  - Growing blood vessels follow a gradient generated by target tissues/regions of Vascular Endothelial Growth Factor (VEGF) to establish a vascular bed. Recent findings suggest that Notch signaling acts as an inhibitor for this system, preventing sprouting of blood vessels. Notch is a transmembrane receptor protein involved in regulating cell differentiation in many developing systems.

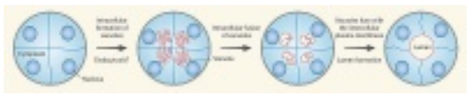


(/embryology/index.php/File:Placental_membra
extraembryonic mesoderm

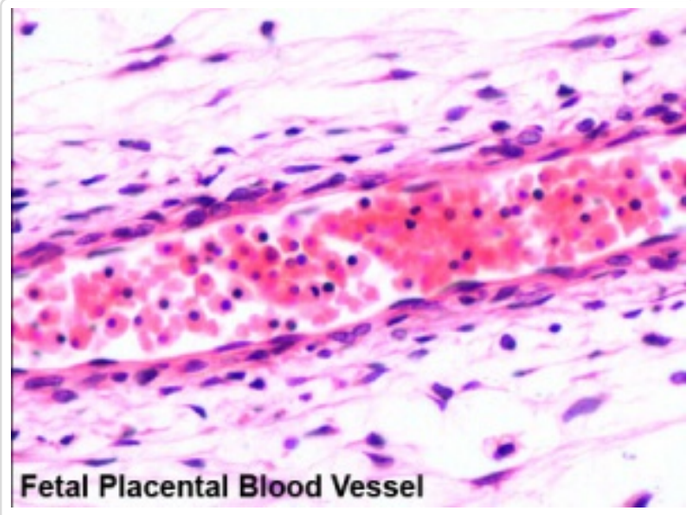
- PIGF is also a VEGF released from the placental trophoblast cells.
- angioblasts form clusters called "blood islands"
- blood islands extend and fuse together to form a primordial vascular network

Blood islands

- Blood islands contain cells (haemangioblasts) which are capable of differentiating into 2 populations of cells
  - Vascular precursors (angioblasts) - form endothelial cells
  - Blood cell precursors (haemocytoblasts)
- These angioblasts migrate, coalesce into cords and form a lumen. This process of vessel formation is called vasculogenesis and is dominant in very early embryogenesis e.g. formation of the dorsal aorta
- Sprouting from pre-existing vessels is called angiogenesis e.g. brain is an organ which is vascularized by this process
- Note: the vascular tree undergoes constant remodeling as the embryo grows.


(/embryology/index.php/File:Blood_vessel_lumen_formation.jpg)

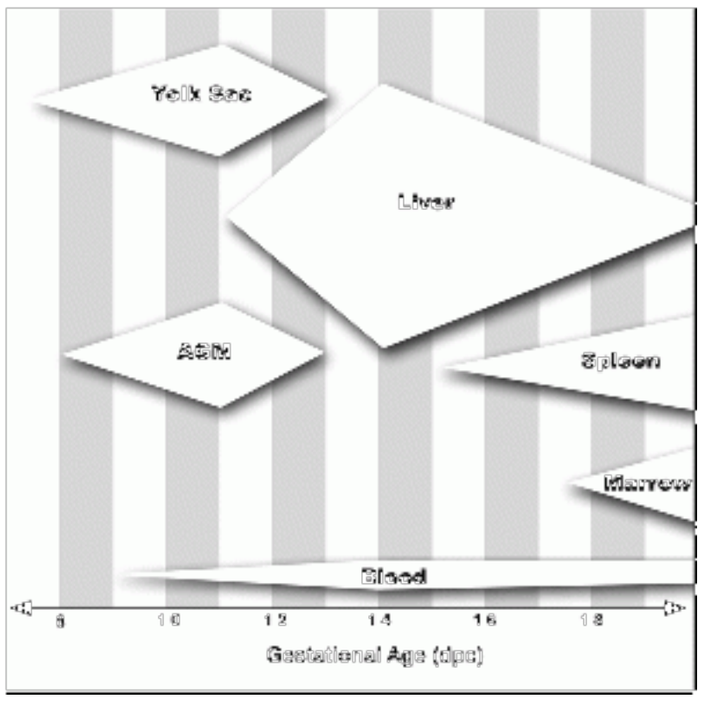
Blood vessel lumen formation



(/embryology/index.php/File:Placenta_blood.jpg
fetal blood

Blood formation

- blood formation from stem cells occurs initially in the extraembryonic mesoderm of the yolk sac
- later (week 5) throughout embryonic mesenchyme
- blood stem cells then migrate into the **liver**
  - then **spleen, bone marrow, lymph nodes**

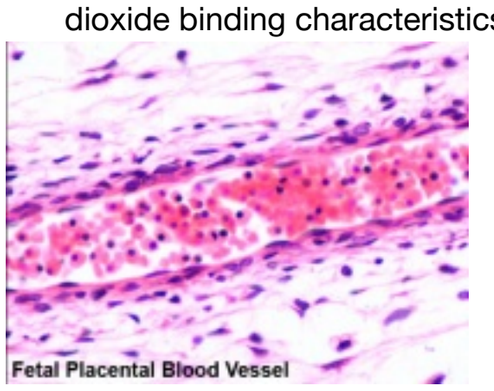


(/embryology/index.php/File:Mouse_hematopoietic_stem_cell.gif)
Mouse hematopoietic stem cell location

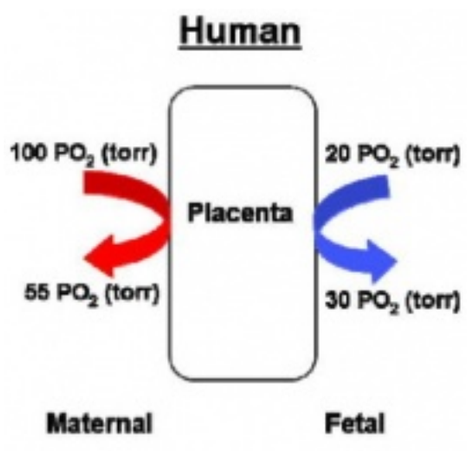
Red blood cells

The only cells in the blood are nearly entirely fetal red blood cells.
These cells differ from adult red blood cells in:

1. often remaining nucleated.
2. contain fetal haemoglobin - which has different oxygen and carbon dioxide binding characteristics.

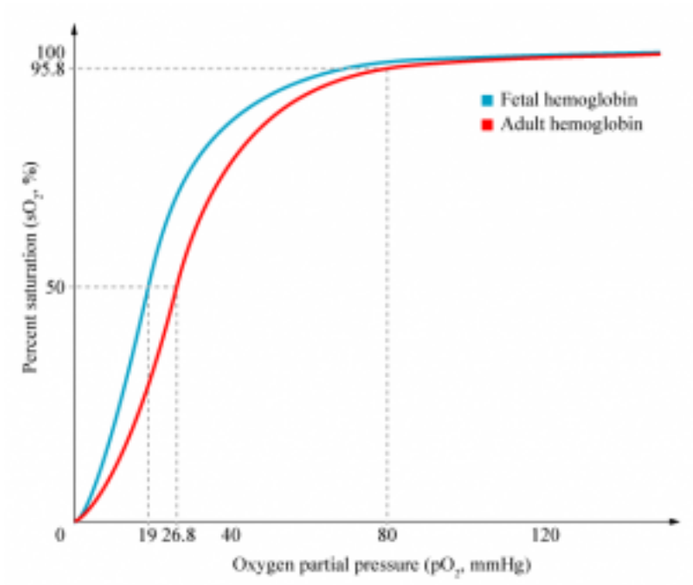


(/embryology/index.php/File:Placenta_blood.jpg)



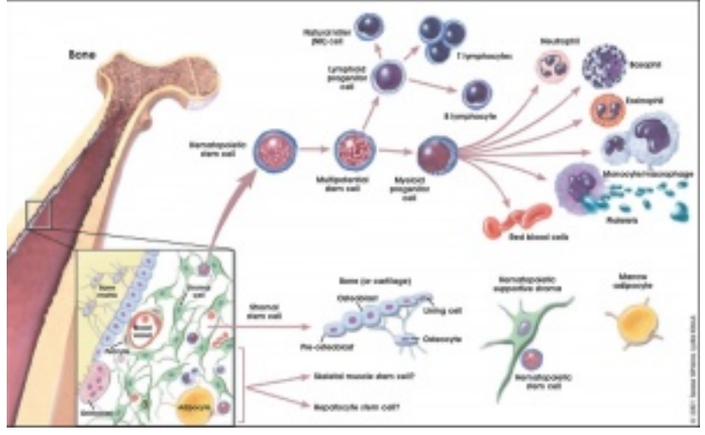
(/embryology/index.php/File:Placenta_oxygen_exchange_levels.jpg)

Fetal Oxygen levels



(/embryology/index.php/File:Haemoglobin_comparison_oxygen_saturation_curve.png)
Red Blood Cell haemoglobin oxygen dissociation curves

Blood stem cells

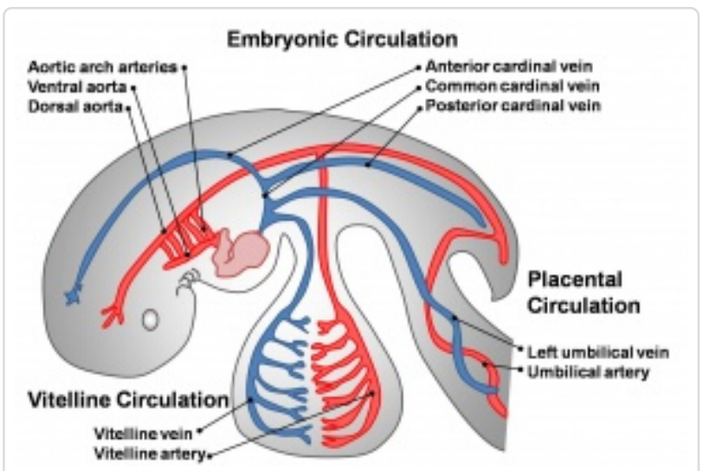


(/embryology/index.php/File:Hematopoietic_and_stromal_cell_differentiation.jpg)

Hematopoietic and stromal cell differentiation (adult)

Early vascular systems

- one vascular system with 3 components - **vitelline, embryonic (system) and placental**
  - each component has own system of artery and vein



(/embryology/index.php/File:Embryonic_Circula

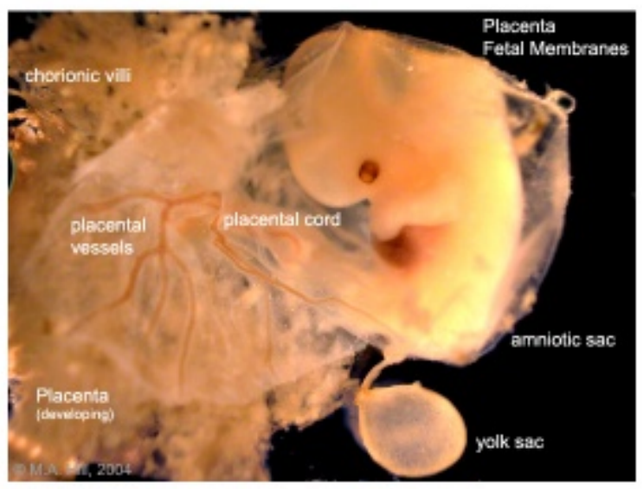
Early vascular systems

Vitelline blood vessels

- Angioblasts form a network of vessels over the yolk sac and connecting stalk
- Join into two main vessels, the vitteline veins (omphalomesenteric)
- Pass through vitello-intestinal duct (yolk sac stalk)
- Enter caudal end of cardiac tube
- **Vitelline Arteries** - arises from dorsal aorta, contribute to adult GIT arteries (fuse to become superior mesenteric artery (midgut)
- **Vitelline Veins** - empties into sinus venosus, contribute to the adult portal system

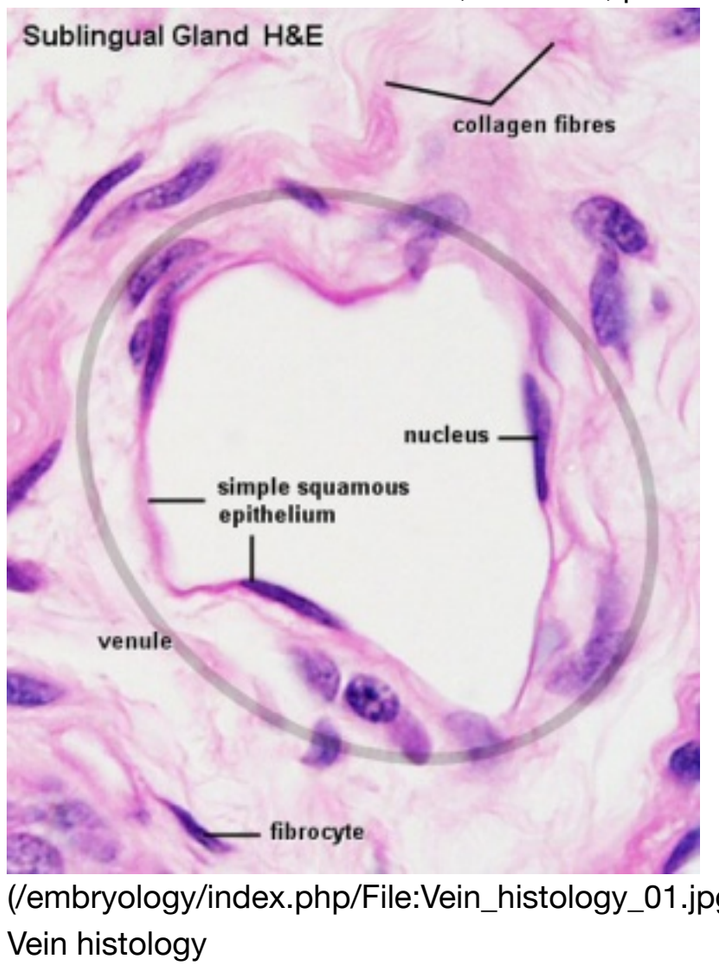
Embryo blood vessels

- (systemic) will form the most of the cardiovascular system
- some vessels have neural crest contribution
- Arterial blood flow - aortic sac → aortic arches → dorsal aorta →umbilical artery
  - dorsal aorta,
    - paired initially , later fuses from T4 to L4 (gives off segmental arteries)
    - connect to ventral aorta via pharyngeal arches arteries.
    - caudally, give rise to umbilical arteries
    - laterally, give rise to intersegmental arteries
- Veins - 3 pairs of veins empty into the sinus venosus of the heart
  - vitelline, umbilical (right and left from developing placenta enter caudal cardiac tube; only left persists)
  - cardinal veins - anterior, common, posterior



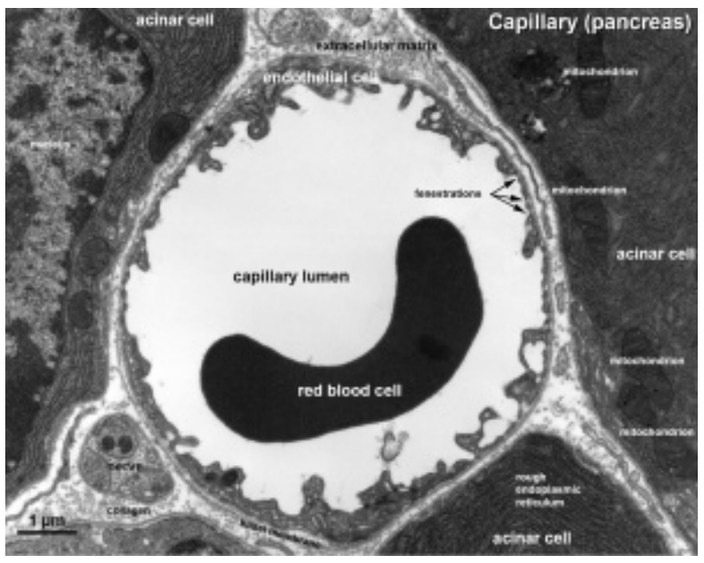
(/embryology/index.php/File:Placental_membra

Week 7 embryo with placenta



(/embryology/index.php/File:Vein_histology_01.jpg)

Vein histology



(/embryology/index.php/File:Blood_capillary_EM_04.jpg)

Blood capillary (EM)

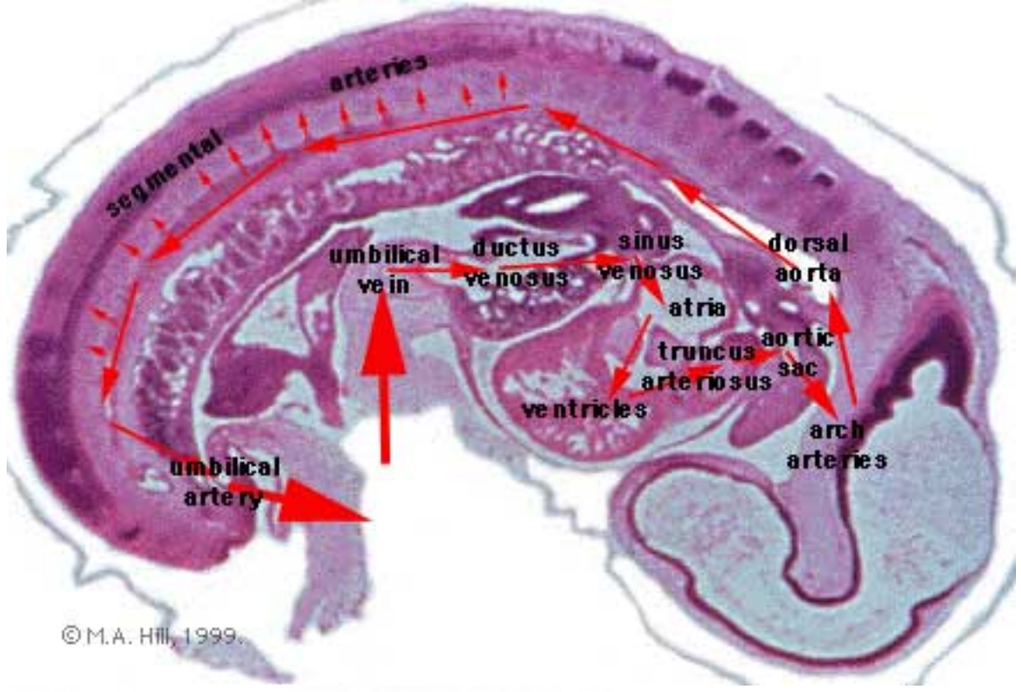
Placental blood vessels

(Placenta development covered in next lecture)

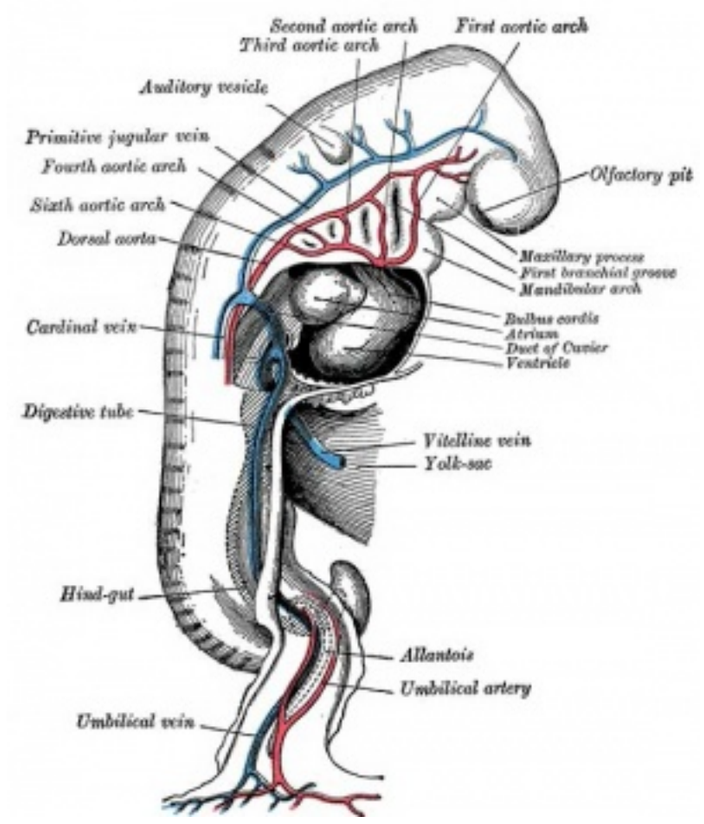
- form initially in the connecting stalk (then umbilical cord) and anastomose in chorion
- extend maternally - toward the chorionic villi
- extend embryonically - toward the sinus venosus and dorsal aorta
- Arteries - paired and carry deoxygenated blood (from dorsal aorta) and waste products to the placental villi
- Veins - paired initially then only left at end of embryonic period and carry oxygenated blood to the embryo (sinus venosus)

Blood flow through the embryo

High pressure pathway

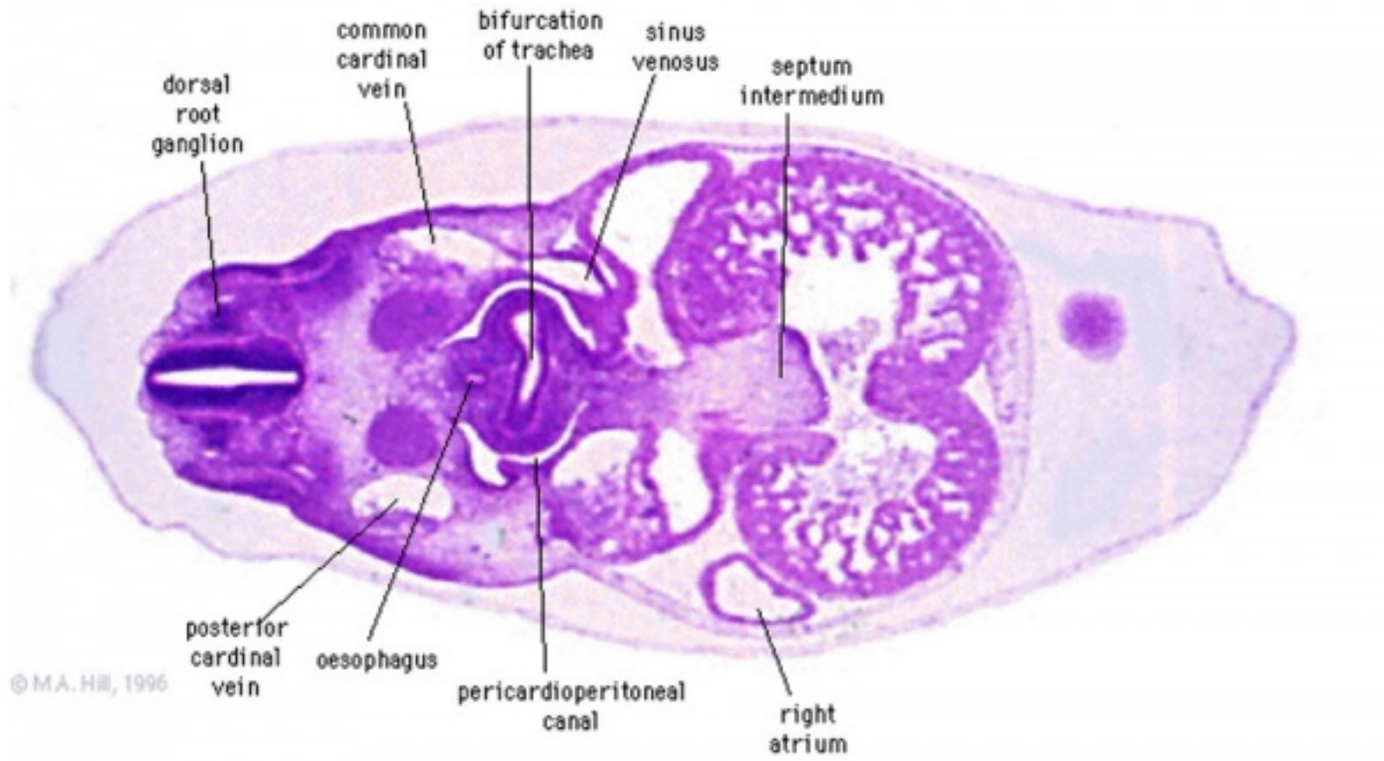


(/embryology/index.php/File:Stage13_bloodflow.jpg)



(/embryology/index.php/File:Gray0472.jpg)

Maternal Blood | -> umbilical vein -> liver -> anastomosis -> sinus venosus -> atria ventricles-> truncus arteriosus -> aortic sac -> aortic arches-> dorsal aorta-> pair of umbilical arteries | Maternal Blood.



(/embryology/index.php/File:Stage_13_image_070.jpg)

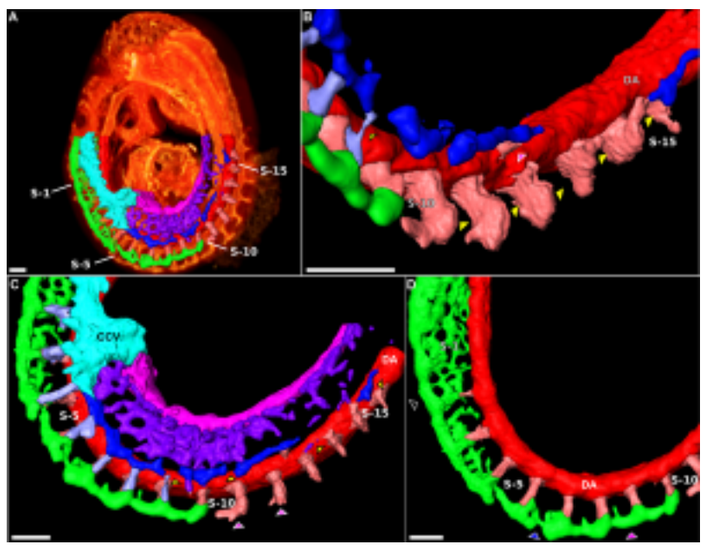
Low pressure pathway

- **Head** - Large veins lateral to dorsal aortae. These are the superior or anterior cardinal veins. Their function is to drain the head region.
- **Body** - Large veins lateral to dorsal aortae. These are the inferior or posterior cardinal veins. Their function is to drain the lower part of the embryo.

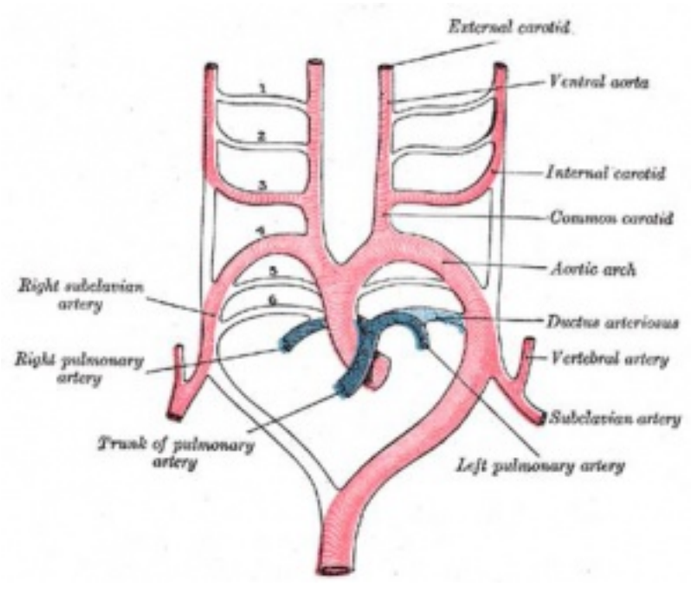
Blood vessel remodeling

Early vascular development is laterally **symmetrical** (paired left and right). With embryo development this scheme is extensively remodelled leading to an **asymmetric** adult system in the body.

Complex balance between Stimulators and Inhibitors of Angiogenisis.



(/embryology/index.php/File:Cervical_intersomitic_vessels.png)



(/embryology/index.php/File:Gray0473.jpg)

Links: Blood Vessel Development (/embryology/index.php/Cardiovascular_System_-_Blood_Vessel_Development)

Vascular Endothelial Growth Factor (VEGF)

- belongs to the platelet derive growth factor (PDGF) family.
- required for early stages of blood vessel patterning.
- required later for endothelial cell maintenance in tissues.
- autocrine VEGF loop from endothelial cell secretion involved in vascular growth.
- 4 protein isoforms generated from a single gene.

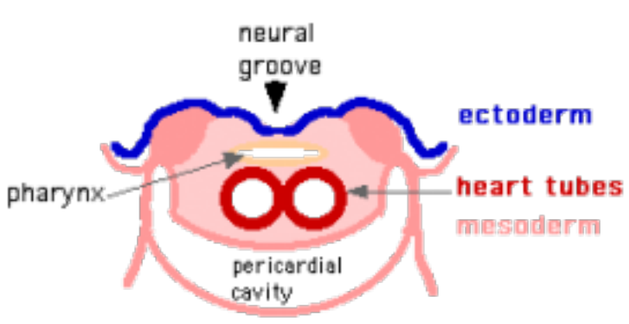
VEGF protein family - VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PGF),

VEGF receptors - VEGFR-1, -2 and -3.

- Cells expressing the receptors are directed in their growth.
- Note that there are other growth factor families (FGF, Tie, TGF-β, netrins, semaphorins) that can also influence vessel growth.
- Some angiogenic factors also involved in organ development (liver).

Links: Vascular Endothelial Growth Factor (/embryology/index.php/Developmental_Signals_-_Vascular_Endothelial_Growth_Factor)

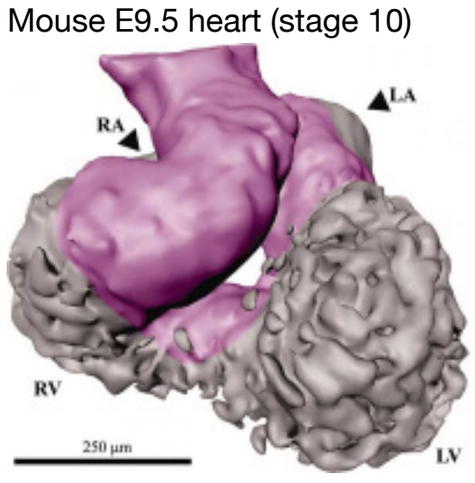
Heart Development



(/embryology/index.php/File:Early_heart_cartoon.png)**MH** - Later development of the heart (septation) will be covered in another lecture.

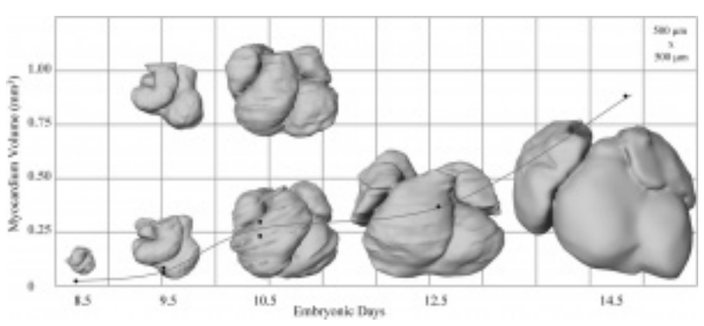
Mouse Model

Mouse E9.5 heart (stage 10)



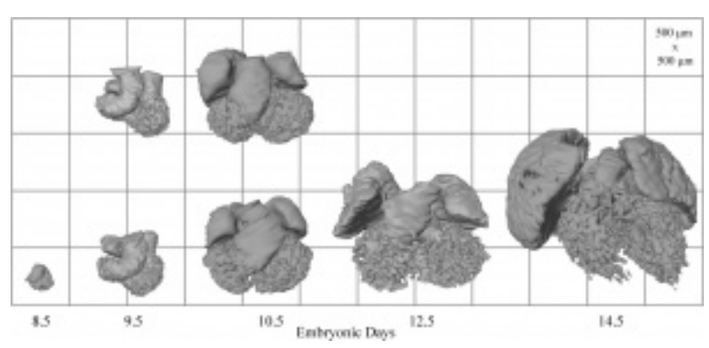
(/embryology/index.php/File:Mouse_heart_E9.5.jpg)

Mouse E8.5 - 14.5 heart (external)



(/embryology/index.php/File:Mouse_3D_Heart_external_E8.5-14.5.jpeg)

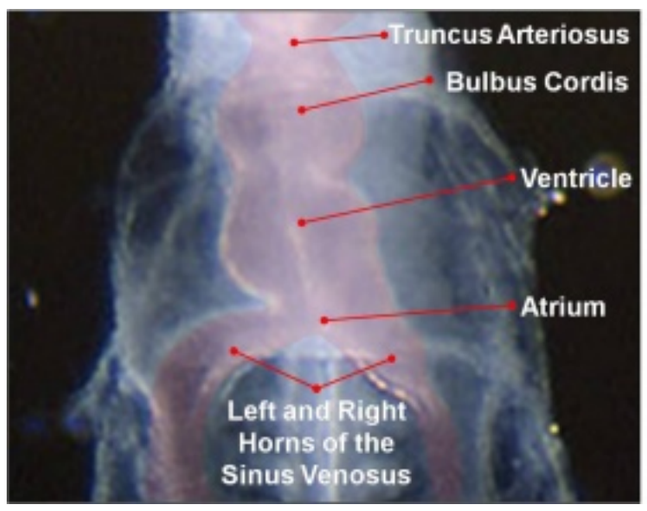
Mouse E8.5 - 14.5 heart (internal)



(/embryology/index.php/File:Mouse_3D_Heart_internal_E8
14.5.jpeg)

Early Human Heart Development

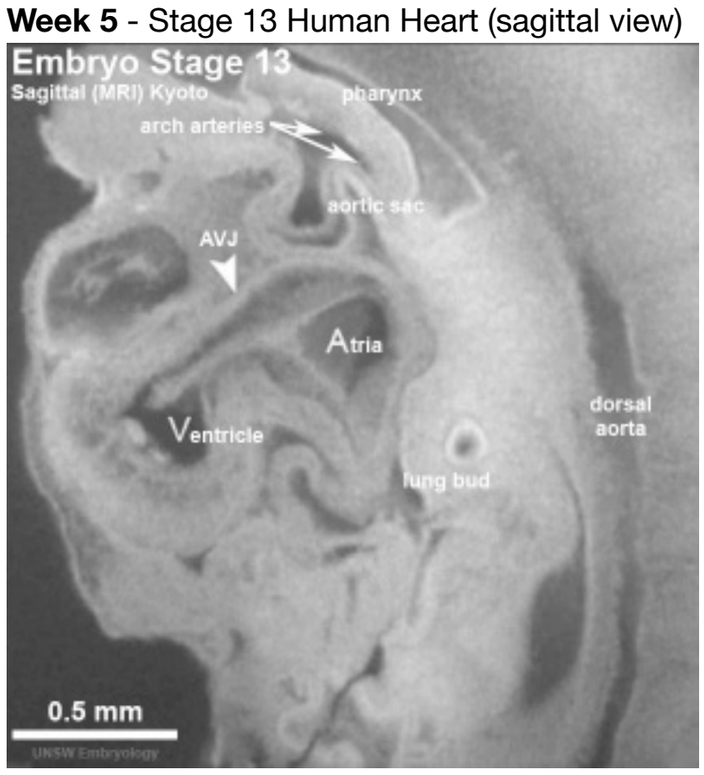
Week 4 - Stage 10 Human Heart tube



(/embryology/index.php/File:Heart_Tube_Segments.jpg)

from a pair of heart tubes

Week 5 - Stage 13 Human Heart (sagittal view)



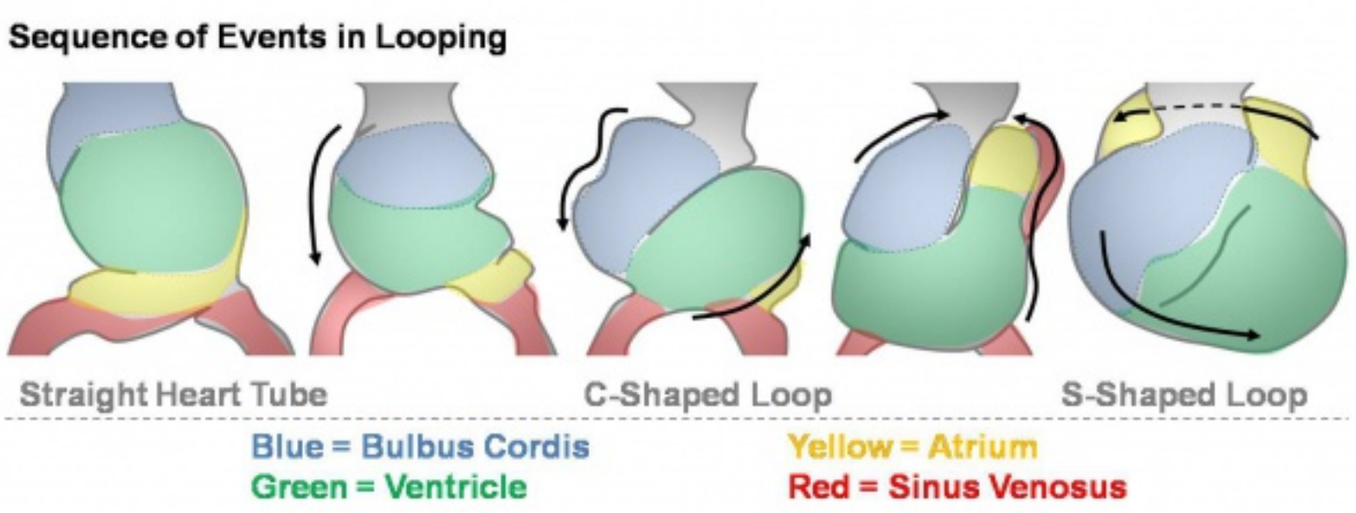
(/embryology/index.php/Stage_13_MRI_Movie_1)
to the heart forming chambers

- Mesenchymal condensation in splanchnic mesenchyme = cardiogenic plate
- Following bending and folding, the plate comes to lie dorsal to pericardial coelom
- Plate undergoes bilateral canalisation to form 2 cardiac tubes:
  - cranial part of cardiac tubes = ventral aortae which will later join the existing dorsal aortae
  - Caudally the tubes will join vitelline and umbilical veins
- Cardiac tubes fuse to form single heart tube that sinks into coelom (= future pericardial sac)
- At this stage, the heart is an endothelial tube surrounded by visceral layer of pericardium (epicardium)
- From the time of the fusion of cardiac tubes, the walls undergo fibrillary movements (forerunner of cardiac contraction)
- Later, space between epicardium and cardiac endothelium fills with jelly-like material (cardiac jelly), which becomes invaded by cells of deep layer of epicardium. These are the myoblasts (future cardiac muscle)
- Combined layer of epicardium and invaded jelly = myoepicardial mantle.
- Epicardial layer also gives rise to blood islands which form vascular network (future coronary vessels)
- Heart tube (now within the pericardial coelom) begins to undergo internal and external changes.

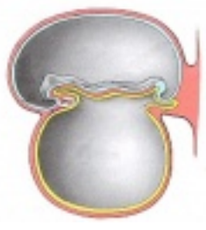
Heart layers

- **pericardium** - covers the heart. Formed by 3 layers consisting of a fibrous pericardium and a double layered serous pericardium (parietal layer and visceral epicardium layer).
- **myocardium** - muscular wall of the heart. Thickest layer formed by spirally arranged cardiac muscle cells.
- **endocardium** - lines the heart. Epithelial tissue lining the inner surface of heart chambers and valves.

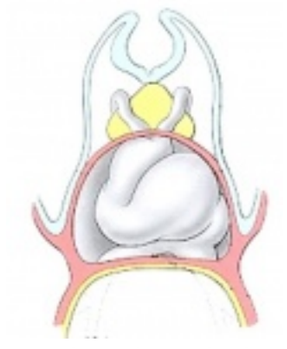
Heart looping



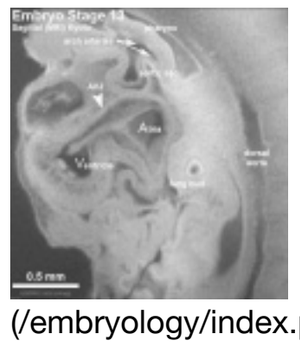
(/embryology/index.php/File:Heart_Looping_Sequence.jpg)



(/embryology/index.php/Week_3_Development_Movie) **Week 3** Page (/embryology/index.php/Week_3_Development_Movie) | Play (/embryology/images/2/27/Week3_folding.mp4)



(/embryology/index.php/Heart_Looping_Movie) **Heart Looping** Page (/embryology/index.php/Heart_Looping_Movie) | Play (/embryology/images/0/07/Heart1_looping.mp4)



(/embryology/index.php/Stage_13_MRI_Movie_1) **Heart Sag MRI** Page (/embryology/index.php/Stage_13_MRI_Movie_1) | Play (/embryology/images/6/60/Stage_13_MRI_S02.mp4)

Transverse section- Heart is 2 tubes that fuse in the midline anterior to pharynx.

The pericardial cavity can be imagined as the top of the "horseshoe" of the intraembryonic coelom. (where the arms become the pleural cavity and the ends fuse anteriorly to form a single peritoneal cavity).

This view shows the initial positioning of the ventricles above the atria. The ventricles are rotated into their correct anatomical position by the growth of the heart tube, bending into an "S" shape.

Initially...

- Heat tube develops a series of constrictions:
  - Truncus arteriosus – ventral aortae meet - **OUTFLOW**
  - Bulbus cordis
  - Ventricle
  - Atrium
  - Sinus venosus – caudal end of tube, receiving 4 veins - **INFLOW**
- Rapid growth – 'buckling' and 'twisting'
- Heart tube bends ventrally into pericardial coelom
- Ventricle enlargens, absorbs lower part of bulbus cordis (bulboventricular loop)
- Ventricle also twists to left- atrium and sinus venosus come to lie dorsal to bulbus cordis and lower part of truncus arteriosus
- Venous inflow comes to lie directly dorsal to the arterial outflow.
- Possible abnormality – dextro-rotation, the heart bends or twists to the right. Maybe associated by other abnormalities.
- Later, sinus venosus becomes absorbed into atrium

Heart neural crest

- The mouse model shows that the heart also has contributions from neural crest E8.5 mouse neural crest (http://dev.biologists.org/cgi/content/full/131/14/3367/FIG1)
  - between the levels of post-otic hindbrain to somite 4, with the most contribution from somite 2 level.
- 7 somite stage - Migration of cardiac neural crest from the neural tube begins. (level post-otic hindbrain and somite 4)
  - Pathways dorsolateral, medial, and between somites.
  - Then through peri-aortic mesenchyme (lateral to pharynx), through pharyngeal arches (3, 4, 6) into the aortic sac.
- 32 somite stage: Colonisation of the outflow tract mesenchyme.

Data from: Chan WY, Cheung CS, Yung KM, Copp AJ. Chan WY, Cheung CS, Yung KM, Copp AJ. Cardiac neural crest of the mouse embryo: axial level of origin, migratory pathway and cell autonomy of the splotch (Sp2H) mutant effect. Development. 2004 Jul;131(14):3367-79. PMID: 15226254 (http://www.ncbi.nlm.nih.gov/pubmed/15226254)

Embryonic heart rate

- Ultrasonographic measurement of embryonic heart rate (EHR) shows a steady increase from Stage 9-10 (75 beats/minute) to Stage 18 (130 beats/minute) and on to Stage 20, following which a gradual decrease in EHR occurs
- Maximal EHR is reached when morphological development of the embryonic heart is completed.

Links: Embryonic Heart Rate (/embryology/index.php/Cardiovascular_System_-_Heart_Rate_Development)

Internet Links

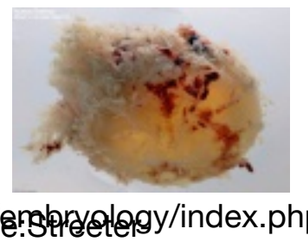
Embryo Images Unit: Embryo Images Online (http://www.med.unc.edu/embryo_images/) Early Cell Populations (cardiogenic section) | Cardiovascular Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardevtoc.htm) | Week 3 Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev001.htm) | Week 4 Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev007.htmhttp://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev007.htm) | Heart Chambers and Outflow Tract (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev018.htm) | Atrioventricular Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev022.htm) | Outflow Tract Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev028.htm) | Ventricular Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev035.htm) | Atrial Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev036.htm) | Atrial Walls (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev040.htm) Aortic Arch Vessels (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev041.htm) | Changes at Birth (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev042.htm)

References

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 The Heart (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3693#3695) | Figure 15.6. Cascade of heart development} | [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3698 Figure 15.3. Formation of the chick heart from the splanchnic lateral plate mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3702) | Figure 15.4. Fusion of the right and left heart rudiments to form a single cardiac tube (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3699) | Figure 15.5. Specification of the atrium and ventricles occurs even before heart looping (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3701)
- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Figure 21-35. The vertebrate body plan as a dorsoventral inversion of the insect body plan (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3860) Figure 22-40. The four classes of muscle cells of a mammal (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.4167)

(/embryology/index.php/File:Streeter-plate02.jpg)



(/embryology/index.php/File:Stage13_bf11.jpg)

Stage 13

Stage 12

Terms

Cardiovascular Terms (/embryology/index.php/Cardiovascular_System_Development) [Expand]

Other Terms Lists [Expand]

ANAT2341 Course Timetable (/embryology/index.php/ANAT2341_Course_Timetable_2016) [Expand]

Categories (/embryology/index.php/Special:Categories): Heart (/embryology/index.php/Category:Heart)
Cardiovascular (/embryology/index.php/Category:Cardiovascular) | 2016 (/embryology/index.php/Category:2016)
Science-Undergraduate (/embryology/index.php/Category:Science-Undergraduate)