Cardiovascular System

Note: The cardiovascular system develops early (week-3), enabling the embryo to grow beyond the short distances over which diffusion is efficient for transferring O₂, CO₂, and cellular nutrients & wastes.

Heart:
Beginning as a simple tube, the heart undergoes differential growth into a four chambered structure, while it is pumping blood throughout the embryo and into extra-embryonic membranes.

Angiogenesis begins with blood island formation in splanchnic mesoderm of the yolk sac and allantois. Vessel formation occurs when island vesicles coalesce, sprout buds, and fuse to form vascular channels. Hematopoiesis (blood cell formation) occurs in the liver and spleen and later in the bone marrow. The transition from fetal to adult circulation involves new vessel formation, vessel merger, and degeneration of early vessels.

Formation of a Tubular Heart:
The first evidence of heart development is bilateral vessel formation within the cardiogenic plate (splanchnic mesoderm situated anterior to the embryo).

The cardiogenic plate moves ventral to the pharynx as the head process grows upward and outward.

Bilateral endocardial tubes meet at the midline & fuse into a single endocardial tube, the future heart.

Splanchnic mesoderm surrounding the tube forms cardiac muscle cells capable of pumping blood.

Primitive Heart Regions:
Differential growth of the endocardial tube establishes five primitive heart regions:

1) Truncus arteriosus — the output region of the heart. It will develop into the ascending aorta and pulmonary trunk.

2) Bulbus cordis — a bulb-shaped region destined to become right ventricle.

3) Ventricle — an enlargement destined to become the left ventricle.

4) Atrium — a region that will expand to become both right and left auricles.

5) Sinus venosus — a paired region into which veins drain. The left sinus venosus becomes the coronary sinus; the right is incorporated into the wall of the right atrium.
Forming a Four-Chambered Heart:
The following are six snapshots of the development process:

A] *Endocardial tube lengthens and loops* on itself—this puts the bulbus cordis (right ventricle) beside the ventricle (left ventricle) and the atrium dorsal to the ventricle.

B] *Venous return is shifted to the right side:*
   - The larger *right sinus venosus* becomes the right atrium. (The embryonic atrium becomes auricles.)
   - The smaller *left sinus venosus* joins the future right atrium as the *coronary sinus*.

   The embryonic atrium expands and overlies the ventricle chamber. A common atrioventricular opening connects the two chambers. A constriction, the future coronary groove, separates atrium and the ventricle.

C] *Atrio-ventricular opening is partitioned:*
   - Growth of endocardial “cushions” partitions the common A-V opening into right and left openings.
   - Ventral growth of the cushions contributes to a septum that closes the interventricular foramen (the original opening between the bulbus cordis & ventricle).

   Incomplete closure of the interventricular septum (ventricular septal defect) results in blood flow from the left to the right ventricle and an associated murmur. Large defects produce clinical signs of cardiac insufficiency.

D] *Right & left ventricles formed:*
   - Ventral growth and interior excavation of the bulbus cordis and ventricle form right & left ventricles, respectively.
   - The interventricular septum, atrioventricular valves, chordae tendineae, papillary muscles, and irregularities of the internal ventricular wall are all sculptured by selective excavation of ventricular wall tissue.

E] *Right and left atria divided by a septum:*
   - Septum formation is complicated by the need, until birth, for a patent (open) septum that allows blood to flow from the right atrium to the left. The septal opening is called the *foramen ovale.*
• Formation of the interatrial septum and foramen ovale:
  Interatrial Septum 1 grows from the dorsal atrial wall toward the endocardial cushions.
  The pre-existing Foramen 1 is obliterated when Septum 1 meets the endocardial cushion. Foramen 2 develops by fenestration of the dorsocranial region of Septum 1 (before Foramen 1 is obliterated). Interatrial Septum 2 grows from the cranial wall of the right atrium toward the caudal wall. The septum remains incomplete and its free edge forms the boundary of an opening called the Foramen Ovale.

NOTE: As long as blood pressure in the right atrium exceeds that of the left, blood enters the Foramen Ovale, flows between the two septae and exits into the left atrium. When, at birth, pressure is equal in the two atria, the left septum is forced against the Foramen Ovale, acting as a valve to preclude blood flow.

An atrial septal defect is not a serious developmental anomaly as long as pressure is approximately equal in the two atria, which is normally the case.

F] Aorta and pulmonary trunk formed:
  • The truncus arteriosus (and adjacent bulbus cordis) is partitioned in a spiral pattern in order to form the aorta & pulmonary trunk.
  • Ridges appear along the lumen wall, grow inward and merge to create the spiral septum. As a result, the aorta and pulmonary trunk spiral around one another.
  • Failure of the septum to spiral leaves the aorta connected to the right ventricle and the pulmonary trunk to the left ventricle—a fatal flaw.
  • Growth from the spiral septum and endocardial cushions both contribute to proper closure of the interventricular septum.
  • Aortic and pulmonary semilunar valves are formed like atrioventricular valves, by selective erosion of cardiac/vessel wall.
  • Improper valve sculpturing will produce valvular insufficiency in the case of excessive erosion or vessel stenosis (narrow lumen) in cases of not enough erosion.

Tetralogy of Fallot:
  This is a cardiac anomaly that occurs in number of species, including humans. It involves a combination of four defects all related to a defective spiral septum formation in the truncus arteriosus & bulbus cordis:
  • ventricular septal defect;
  • stenosis of the pulmonary trunk;
  • enlarged aorta that overrides the right ventricle (dextroposition of the aorta); and
  • hypertrophy of the right ventricle, secondary to communication with the high pressure left ventricle.
Arteries:
Paired ventral and dorsal aortae develop in the embryo. Bilaterally, ventral & dorsal aortae are connected by up to six aortic arches. Each aortic arch is situated within a pharyngeal arch.

Caudal to the aortic arches, the paired dorsal aortae merge to form a single descending aorta, as found in the adult. The aorta gives off dorsal, lateral, and ventral branches, some of which persist as adult vessels.

Paired ventral aortae receive blood from the truncus arteriosus and fuse to form the adult brachiocephalic trunk.

Disposition of Aortic Arches:
The third, fourth, and sixth aortic arches become adult vessels. The first two arches degenerate and the fifth arch is rudimentary or absent.

Each third aortic arch becomes an internal carotid artery and proximally the third arch forms a common carotid artery. The dorsal aorta degenerates between the third and fourth aortic arches. Consequently, the third arch supplies the head and the fourth arch supplies more caudal regions. The external carotid artery buds from the third arch.

The left fourth aortic arch becomes the adult arch of the aorta. The right fourth aortic arch becomes the proximal part of the right subclavian artery as the distal connection between the arch and the dorsal aorta normally degenerates. (Persistence of a connection between the fourth aortic arch and the descending aorta results in compression of the esophagus, accompanied difficult swallowing and an enlarged esophagus cranial to the compression.)

The proximal part of each sixth aortic arch becomes a pulmonary artery. The distal part of the arch degenerates on the right side but persists as ductus arteriosus on the left side.

Note: The ductus arteriosus shunts blood from the pulmonary trunk to the aorta, allowing the right ventricle to be exercised in the face of limited blood return from the lungs. At birth, abrupt constriction of the ductus arteriosus shifts pulmonary trunk output into the lungs. Eventually, a ligamentum arteriosum replaces the constricted ductus arteriosus. (A persistent ductus arteriosus results in a continuous murmur during both systole and diastole.)
Subclavian & Vertebral arteries:

Each dorsal aorta gives off intersegmental arteries that pass dorsally between somites. Bilaterally, the seventh cervical intersegmental artery becomes the distal portion of the subclavian artery.

Intersegmental arteries cranial to the seventh cervical form the vertebral artery (by anastomosing with one another and losing connections to the aorta via degeneration). Intersegmental arteries caudal to the seventh cervical become intercostal and lumbar arteries.

When the heart shifts caudally from the neck to the thoracic cavity, positions of aortic arch arteries are changed. In particular, the subclavian arteries become transposed from a position caudal to the heart to a cranial position.

Branches of Dorsal Aortae:

Right and left vitelline arteries arise from right and left dorsal aortae to supply the yolk sac. The right vitelline artery becomes the adult cranial mesenteric artery. The left vitelline artery normally degenerates. (Incomplete degeneration of the left vitelline artery can result in a fibrous band that may cause colic by entrapping a segment of intestine.)

Each dorsal aorta terminates in an umbilical artery that supplies blood to the allantois. In the adult, umbilical arteries persist to the urinary bladder and degenerate distal to the bladder. External and internal iliac arteries develop as outgrowths of the umbilical artery.

Veins:

Bilaterally, the embryonic sinus venosus receives:

— vitelline veins, which drain the yolk sac
— umbilical veins which drain the allantois, and
— cardinal veins which drain the embryo.

The transition from embryonic to adult venous patterns involves the formation of new veins, anastomoses between veins, and the selective degeneration of embryonic segments.

Note: Recall that venous return is shifted to the right side and the right sinus venosus is incorporated into the right atrium. The left sinus venosus is reduced and becomes coronary sinus.

Cranial Vena Cava Formation:

Each cranial cardinal vein becomes the adult internal jugular vein. The much larger external jugular and subclavian veins arise by budding from the cranial cardinal vein.

An anastomotic vein develops and runs from left to right cranial cardinal veins, shifting venous return to the right side and becoming left brachiocephalic vein. (Failure of the anastomotic vein to develop results in a double cranial vena cava, the typical condition in rats and mice.)

The caudal segment of right cranial cardinal vein along with the right common cardinal vein becomes the cranial vena cava.

Caudal Vena Cava and Azygos Vein:

Each caudal cardinal vein gives rise to supra-cardinal and sub-cardinal veins with extensive anastomoses among all of the veins. These venous networks, located in intermediate mesoderm, supply embryonic kidneys and gonads.

Selective segments of particularly the right subcardinal venous network, including an anastomosis with the proximal end of the right vitelline vein form the caudal vena cava.

The azygos vein develops from the supracardinal vein as well as the caudal and common cardinal veins of the right side (dog, cat, horse) or the left side (pig) or both sides (ruminants). The azygos vein will drain into the cranial vena cava (or right atrium) on the right side and into the coronary sinus on the left side.
**Portal Vein and Ductus Venosus:**

Proximally, *vitelline veins* form liver sinusoids as the developing liver surrounds the veins. Vitelline veins give rise to the *portal vein*, formed by anastomoses that develop between right and left vitelline veins and enlargement/atrophy of selective anastomoses.

*Umbilical veins*, also engulfed by the developing liver, contribute to the formation of liver sinusoids. Within the embryo, the right umbilical vein atrophies and the left conveys placental blood to the liver. Within the liver, a shunt, the *ductus venosus*, develops between the left umbilical vein and the right hepatic vein which drains into the caudal vena cava.

Postnatally, the left umbilical vein becomes the round ligament of the liver located in the free edge of the falciform ligament.

Because a fetus is not eating & because the placenta is able to detoxify blood & because it is mechanically desirable for venous return to bypass fetal liver sinusoids, the *ductus venosus* develops in the embryo as a shunt that diverts blood away from sinusoids and toward systemic veins.

Postnatally, however, a persistent *portosystemic shunt* allows toxic digestive products to bypass the liver. These toxic agents typically affect the brain resulting in neurologic disorders at some time during life.

A portosystemic shunt can be the result of a *persistent ductus venosus* or a developmental error that results in anastomosis between the portal vein and the caudal vena cava or the azygos vein. Since adult veins are established by patching together parts of embryonic veins, it is not surprising that mis-connections arise from time to time.

**Pulmonary Veins:**

These develop as outgrowth of the left atrium. The initial growth divides into left and right branches, each of which subdivides into branches that drains lobes of the lung. Pulmonary branches become incorporated into the wall of the expanding left atrium. The number of veins entering the adult atrium is variable due to vein fusion.

**Lymphatics:**

Lymph vessel formation is similar to blood angiogenesis. Lymphatics begin as lymph sacs in three regions: jugular (near brachiocephalic veins); cranial abdominal (future cysterna chyla); and iliac region. Lymphatic vessels (ducts) form as outgrowths of the sacs.

Lymph nodes are produced by localized mesodermal invaginations that partition the vessel lumen into sinusoids. The mesoderm develops a reticular framework within which lymphocytes accumulate.

The spleen and hemal nodes (in ruminants) develop similar to the way lymph nodes develop.
Prior to birth, fetal circulation is designed for the *in utero* aqueous environment, where the placenta oxygenates fetal blood.

**Suddenly, at birth...**

The environment is changed:

Stretching and constriction of umbilical arteries shifts fetal blood flow from the placenta to the fetus.

Reduced venous return through the (left) umbilical vein and *ductus venosus* allows the latter to gradually close (over a period of days).

Bradykinin being released by expanding lungs, a loss of prostaglandins generated by the placenta, and increased oxygen concentration in blood, all combine to trigger rapid constriction of the *ductus arteriosus* which, over two months, is gradually converted to a fibrous structure, the *ligamentum arteriosum*.

The increased blood flow to the lungs and then to the left atrium equalizes pressure in the two atria, resulting in closure of the *foramen ovale* that eventually grows permanent.