The development of the embryonic cardiovascular system begins during the third week of gestation. The process begins with a straight tube which will eventually differentiate to form a functional heart after several events. Disturbances of any events in the development of the heart, such as cardiac looping, can result in severe congenital disorders. The major clinical presentation of these abnormalities will be cyanosis.

**Derivatives of the Cardiac Tube**

- **First three weeks: primitive heart develops as a straight tube**
  - Truncus arteriosus → Ascending aorta and Pulmonary trunk
  - Bulbus cordis
    - Proximal third of bulbus cordis → muscular right ventricle
    - Conus cordis → smooth outflow portions of right and left
ventricles
- Endocardial cushion → atrial septum, membranous interventricular septum, atrioventricular (AV) valves, and semilunar valves
  - Derived from neural crest cells
  - Endocardial cushion defects: common in Downs syndrome
- Posterior, subcardinal, supracardinal veins → IVC
- Primitive atrium → trabeculated parts of left and right atria
- Primitive pulmonary vein → smooth left atrium
- Primitive ventricle → trabeculated part of left and right ventricles
- Right common cardinal vein (RCCV) and right anterior cardinal vein (RACV) → SVC
- Left horn of sinus venosus → coronary sinus
- Right horn of sinus venosus → smooth RA – sinus venarum

- Smooth portions are found in the areas where the heart connects with the vessels (e.g., below the pulmonic valve)

- **Cardinal veins:**
  - Form superior and inferior venae cavae (that connect to RA)
  - RCCV + RACV = SVC
  - Posterior vein + subcardinal vein + supracardinal vein = IVC

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**Video Gallery**

[Early Development of the Heart](By Peter Ward, PhD)

**Cardiac Looping**

- ** Begins in fourth week: goal to establish left-right polarity**
  - Cranial end bends ventrally and caudally.
  - Then, rotates over to the right (24 days)
  - Atrial end shifts dorso-cranially (posteriorly and cranially) and
moves to the left (35 days).

- Requires cilia and dynein involvement
- Defect in dynein function → dextrocardia (heart on the right side)
  - Seen in Kartagener Syndrome (primary ciliary dyskinesia)

Cardiac Septation

**Atrial septum:** begins with endocardial cushions at the base of the atrial chamber and septum primum

- **Septum primum**
  - Grows toward the endocardial cushions
  - Foramen (ostium) primum narrows → replaced by **foramen (ostium) secundum** (which forms in the septum primum as the ostium primum regresses)
  - Oxygenated blood enters RA from IVC → passes into LA (through foramen secundum) → passes into developing ventricle
  - Poorly oxygenated blood from SVC will be directed to the bulbus cordis (RV)
  - Prenatal and postnatal physiology

- **Septum secundum**
  - Develops on the right side of septum primum
  - Foramen (ostium) secundum maintains right-to-left shunt
  - Expands and covers most of foramen (ostium) secundum → residual opening is the **foramen ovale**
  - RA gets larger → pulls sinus venosus into its wall → move SVC and IVC closer → one opening formed

- **Foramen ovale**
  - Opening between septum primum and septum secundum (shunt between right and left atria)
  - Blood continues to flow right-left, due to ↑↑ pressure in RA
  - After birth: ↑↑ pressure in LA and decreased pressure in RA → septum primum pushed against septum secundum → foramen ovale closed (fused shut during infancy/early childhood) (Defect → *patent foramen ovale*)

**Ventricular septum**
Muscular interventricular septum forms (growing from base of ventricle toward endocardial cushions)

- Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum (closing interventricular foramen)
- Growth of endocardial cushions separates atria from ventricles → contributes to atrial septation and membranous portion of interventricular septum
- Defect → Membranous/muscular Ventricular Septal Defects (VSD)
  - Most common congenital cardiac defect
  - Usually, defect in membranous portion of interventricular septum

**Aorticopulmonary septum**

- Spiral septum that divides the aorta from the pulmonary artery → forms outflow tract
- Neural crest cells migrate to truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → forming ascending aorta and pulmonary trunk.
- Also fuses with muscular portion of ventricular septum → forms membranous interventricular septum
- Defect (due to failure of migration of neural crest cells):
  - Transposition of great vessels (TGV)
  - Tetralogy of Fallot
  - Persistent truncus arteriosus

**Valve development**

- **Semilunar (aortic/pulmonic) valves**: derived from endocardial cushions of outflow tract
- **AV (mitral/tricuspid) valves**: derived from fused endocardial cushions of AV canal
- Defects lead to stenotic, regurgitant, atretic (e.g., tricuspid atresia), or displaced (e.g., Ebstein anomaly) valves

**Video Gallery**

- [Separation of Ventricles](#) by Peter Ward, PhD
- [Formation of the Right and Left Atria](#) by Peter Ward, PhD
- [Formation of the Outflow Tracts](#) by Peter Ward, PhD
- [Formation of AV Canals](#) by Peter Ward, PhD

Image: “Foramen primum” The opening

Image: “Foramen secundum” Endocardial cushions are derived from the

Image: “Oxygenated blood to the left atrium” The foramen
between the two embryonic atria. By Lecturio.

neural crest. As septum primum approaches the dorsal endocardial cushions, cells in the septum undergo apoptosis, which create the foramen (ostium) secundum. By Lecturio.

(ostium) primum and secundum function together to deliver oxygenated blood to the left atrium, which will then flow to the left ventricle, whereas, poorly oxygenated blood delivered from the SVC will flow to the right ventricle. By Lecturio.

Foramen ovale Secundum will grow to narrow foramen (ostium) secundum and form foramen ovale. In this case, septum primum will function as a valve. By Lecturio.

Blood from IVC pushes septum primum (valve of foramen ovale) to move blood from the right atrium to the left atrium (LA), after which the blood will flow to the left ventricle. At birth, the pressure in LA will increase, which will shut foramen ovale. By Lecturio.

Membranous portion of the interventricular septum grows upward to fuse with conotruncal ridges. Right and left ventricles, as well as the aorta and pulmonary tract become separated from each other. By Lecturio.

Fetal Circulation

- Placenta brings blood through the **umbilical vein** (80% oxygen saturation and PO2 of approximately 30 mm Hg)
  - Umbilical arteries have low oxygen saturation
- **Ductus venosus:**
  - Allows blood to pass the liver
  - Transports blood to IVC from umbilical vein
  - Blood is slightly deoxygenated due to mixing
- **Pathway of oxygenated blood from IVC back to placenta:**
  - Blood hits atrial septum → pushes the valve of foramen ovale → LA
LV → aorta → common iliac arteries → umbilical arteries → placenta
- Remember O for Oxygenated blood as well as for Ovale.

- **Pathway of deoxygenated blood from SVC:**
  - SVC → RA → RV → pulmonary trunk → ductus arteriosus → descending aorta → common iliac arteries → umbilical arteries → placenta
  - This shunt is due to high fetal pulmonary arterial resistance (partly because of low oxygen tension)
  - Remember D for deoxygenated blood as well as for Ductus arteriosus and Descending aorta.

- **Transition from fetal to adult circulation**
  - At birth, infant takes first breath → decreased resistance in pulmonary vasculature → increased left atrial pressure in relation to right atrial pressure leading to the closing of the foramen ovale (becomes the **fossa ovalis**)
  - ↑ in oxygen (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus

- **Fetal-postnatal derivatives:**
  - Umbilical vein → ligamentum teres hepatitis (round ligament - contained in falciform ligament)
  - Umbilical arteries → medial umbilical ligaments
  - Ductus venosus → ligamentum venosum
  - Ductus arteriosus → ligamentum arteriosum (near left recurrent laryngeal nerve)
  - Foramen ovale → Fossa ovalis

- Prenatal and postnatal physiology

**Mnemonics**

*Come In and close the door*
Indomethacin helps close the patent ductus arteriosus → ligamentum arteriosum (remnant of ductus arteriosus)

Prostaglandins **E1** and **E2** $\text{kEEp}$ PDA open

**Video gallery**

*Fetal circulation and Transition to Mature Circulation* by Peter Ward, PhD
Oxygenated blood from the umbilical vein drains into IVC which also collects the blood from the organs and lower portion of our body. Therefore the blood becomes slightly deoxygenated.

Blood from IVC pushes the valve of foramen ovale and flows into the left side of the heart, where it mixes in LA with deoxygenated blood from the pulmonary veins. It leaves the heart through the aorta and flows to the iliac arteries which are connected to the placenta by the umbilical arteries. On the other hand, blood from SVC flows directly into RV and then to the pulmonary trunk, which is connected to the descending aorta through the ductus arteriosus.

After birth, the ductus arteriosus becomes ligamentum arteriosum, as blood is able to enter the lungs to be oxygenated. Foramen ovale closes and becomes fossa ovalis due to the ability of blood to enter the lungs.

After birth, the umbilical artery becomes the ligamentum teres.
Congenital Abnormalities

Right-to-left shunts (cyanotic lesions)

- **Truncus arteriosus**: A single large vessel arises from both ventricles due to failure of formation of the aorticopulmonary septum to divide into the pulmonary trunk and aorta. Most times it is accompanied by VSD. Danger of irreversible pulmonary hypertension.

- **Transposition of the great vessels** (TGV): Failure of aorticopulmonary septum to spiral. Pulmonary artery arises from LV (posterior), whereas the aorta comes out from RV (anterior). It is unsuitable for life without a shunt. In 65% of cases, TGV is accompanied by patent ductus arteriosus or patent foramen ovale. In 35% of cases, it is accompanied by a ventricular septal defect. Radiologically will have an “egg on string” appearance on chest X-ray. Need surgical intervention or else most infants die within first few months of life.

- **Tricuspid atresia**: Tricuspid valve is absent which impedes the development of the right ventricle leading to a hypoplastic right ventricle. Requires ASD and VSD for viability. Blood will flow from RA to LA through atrial septal defect or patent foramen ovale. To get to the lungs, blood will flow from RA to LA through patent foramen ovale, and then from LV to RV through ventricular septal defect.

- **Tetralogy of Fallot**: Most common cause of early childhood cyanosis. Accompanied by pulmonary stenosis, right ventricular hypertrophy, overriding aorta, and a ventricular septal defect.

- **Total anomalous pulmonary venous return (TAPVR)**: All pulmonary veins drain into the right heart circulation (i.e., SVC, coronary sinus, etc.). Defect is similar to the shunt from LA to RA. RA and RV causing oxygenated blood to mix with deoxygenated blood and spread throughout the body. Associated with an ASD and sometimes a PDA to allow for right-to-left shunting to maintain cardiac output.

Left-to-right shunts (acyanotic): listed in order of decreasing frequency

- **Ventricular septal defect (VSD)**: Most common congenital anomaly, associated with fetal alcohol syndrome. The defect causes communication between LV and RV. Clinical presentation is harsh, holosystolic murmur that is heard best in the tricuspid area.

- **Atrial Septal Defect (ASD)**: Communication between LA and RA. Can lead to pulmonary hypertension. Clinically characterized by wide splitting of S2. There are four types of ASD: primum, secundum, sinus venosus, and coronary sinus. The most common being a secundum type ASD.

- **Patent ductus arteriosus (PDA)**: Normally, ductus arteriosus shunts blood from the left pulmonary artery to the aorta, this should stop after birth due to decreased level of prostaglandin E2. Clinical presentation of PDA is a continuous machinery-like murmur on auscultation, blue toes and normal fingers, and a widened pulse pressure.
Other congenital abnormalities

- **Coarctation of the aorta:** The aorta narrows in the area around the ductus arteriosus to a certain point and then widens to its normal diameter. Postductal coarctation (occurring after the ductus arteriosus) is clinically silent and only present in adults. Preductal coarctation (occurring before the ductus arteriosus) is an infantile type, where clinical presentation involves cyanosis in the toes.

- **Patent foramen ovale (PFO):** Present in 25% of adults. Failure of fusion of septum primum with septum secundum after increased left atrial pressure. Clinically detected with bubble test in evaluation of syncope and strokes.

- **Hypoplastic left heart syndrome:** High-grade stenosis or atresia of the aortic and/or mitral valve in addition to severe hypoplasia of the left ventricle, ascending aorta, and aortic arch.

- **Ebstein anomaly:** Defect of tricuspid valve, which is displaced towards the right ventricle. Tethering of septal leaflet causes tricuspid regurgitation, which will result in right-sided heart failure.

- **Double aortic arch:** Embryonic vascular malformation resulting in a double aortic arch. This can lead to subsequent constriction of the trachea and esophagus.

- **Endocardial cushion defect:** Defect of the atrioventricular valves as well as the atrial septum and/or ventricular septum. Can present as a complete form (ASD, VSD, and severe abnormalities in the AV valves, leading to severe mixing of blood) or a partial form (only ASD and minor AV valve abnormalities). Commonly seen in patients with Downs syndrome.

**Mnemonics**

**Right-to-left shunts (cyanotic lesions), the 5Ts:**

- Truncus arteriosus: 1 vessel
- Transposition of the great vessels: 2 switched vessels
- Tricuspid atresia: 3 (Tri)
- Tetralogy of Fallot: 4 (Tetra)
- Total Anomalous pulmonary venous return (TAPVR): 5 letters in the name

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