

The Cardiovascular System

Introduction

- The vascular system begins to develop in the middle of the 3rd week.
- This is the point when simple diffusion is no longer enough to fulfill the embryo's metabolic needs.

◆ Progenitor Heart Cells & Formation of Primary Heart Field (PHF)

- Location of progenitor heart cells:
 - Initially lie in the epiblast, immediately cranial to the primitive streak.
- Migration:

- These cells migrate through the primitive streak → into the splanchnic layer of lateral plate mesoderm.
- Formation of PHF:
 - Cells organize into a horseshoe-shaped cluster called the Primary Heart Field, located cranial to the neural folds.
- Timing:
 - Migration & patterning occur during days 16–18.
- Structures formed by PHF (from lateral → medial):
 - Atria
 - Left ventricle
 - Most of the right ventricle

- ◆ Left-Right (Laterality) Patterning

- Patterning of the PHF occurs simultaneously with establishment of left-right sidedness of the embryo.
 - Importance:
 - Correct laterality is critical for normal heart development.
 - Controlled by a signaling pathway (involving SHH, Nodal, FGF → PITX2).
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◆ Secondary Heart Field (SHF)

- Appears slightly later (days 20–21).
- Location: Splanchnic mesoderm ventral to the posterior pharynx.
- Derivatives:
 - Remaining portion of the right ventricle

- Entire outflow tract (*conus cordis + truncus arteriosus*)
 - Role:
 - Lengthens the outflow tract.
 - Laterality of SHF:
 - Right-sided SHF → left side of outflow tract
 - Left-sided SHF → right side of outflow tract
 - Results in spiraling of pulmonary artery & aorta:
 - Aorta leaves the left ventricle
 - Pulmonary artery leaves the right ventricle
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◆ Induction & Cardiogenic Region

- Once PHF cells are positioned, pharyngeal endoderm induces them to form:
 - Cardiac myoblasts

- Blood islands → form blood cells + vessels via vasculogenesis
 - These islands merge → form a horseshoe-shaped endothelial-lined tube surrounded by myoblasts.
 - This entire area ⇒ Cardiogenic Region
 - The intraembryonic cavity above this region later becomes the pericardial cavity.
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◆ Formation of Dorsal Aortae

- In addition to the cardiogenic region, other blood islands form bilaterally, parallel & close to the midline.
 - These islands form a pair of longitudinal vessels ⇒ dorsal aortae.
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! Clinical Correlate - Laterality & Heart Defects

- Days 16-18 are critical for normal heart development.
- Disruption in the laterality pathway → multiple heart malformations:

Defect	Description
Dextrocardia	Heart located on the right side
ASD / VSD	Atrial or Ventricular septal defects
DORV	Both aorta & pulmonary artery exit right ventricle
Transposition of great vessels	Aorta arises from right & pulmonary artery from left ventricle
Pulmonary stenosis	Obstruction of outflow from right ventricle
Isomerism	Both atria or both ventricles have similar characteristics
Inversion	Reversal of left-right characteristics of chambers

- Serotonin (5HT) is a key molecule in initiating laterality signaling.
 - Higher concentration on left side.
 - MAO (degrades serotonin) is high on the right side.
 - This → increased Nodal & FGF activity on the left → PITX2 expression (master gene for left-sidedness).
 - Clinical note:
 - Selective serotonin reuptake inhibitors (SSRIs) may disturb 5HT signaling → associated with increased incidence of congenital heart defects.
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- ◆ Formation & Position of the Heart Tube
Initial Position of Cardiogenic Area

- At first, the cardiogenic region lies anterior to:
 - the oropharyngeal membrane

- o the neural plate
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- ◆ Cranial Folding → Migration of Heart

- Rapid cranial growth of the CNS + closure of neural tube & brain vesicle formation causes:
 - o CNS to overgrow the cardiogenic region & the future pericardial cavity.
 - Due to cephalic folding:
 - o the oropharyngeal membrane is pulled forward
 - o the heart & pericardial cavity are displaced → from cervical region → thorax
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- ◆ Lateral Folding & Fusion of Cardiac Tubes

- Lateral folding of the embryo causes:
 - Pair of endocardial tubes to approach each other and fuse (except at their caudalmost ends).

- The central part of the horseshoe-shaped tube expands → forms the future outflow tract + ventricular regions.

- Result: A continuous heart tube with:
 - Inner endothelial lining
 - Outer myocardial layer

◆ Polarity of the Heart Tube

Pole	Function
Caudal pole	Receives venous drainage

Cranial pole	Pumps blood out → first aortic arch → dorsal aortae
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◆ Attachment to the Pericardial Cavity

- The heart tube protrudes into the pericardial cavity and stays attached dorsally to the body wall via the dorsal mesocardium.
 - No ventral mesocardium is formed.
 - Dorsal mesocardium disappears, forming the transverse pericardial sinus.
 - This leaves the heart suspended only by great vessels (at cranial & caudal ends).
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◆ Myocardial Differentiation

- Myocardium becomes thicker and secretes extracellular matrix (rich in hyaluronic acid) → separates myocardium from endothelium.
- Mesothelial cells from the septum transversum form the proepicardium, which migrates over the heart → forms most of the epicardium.
- The remaining epicardium derives from mesothelial cells in the outflow tract.

✓ Layers of the Developing Heart Tube

Layer	Origin / Function
Endocardium	Inner endothelial lining
Myocardium	Muscular wall
Epicardium / visceral pericardium	Outer covering (forms coronary arteries, including endothelium & smooth muscle)



Formation of the Cardiac Loop

- Continued elongation of the heart tube (due to SHF cell addition to the cranial end) is essential for:
 - Right ventricle formation
 - Outflow tract (conus cordis & truncus arteriosus)
 - Looping process



If elongation fails → outflow tract defects:

- DORV, VSDs, Tetralogy of Fallot, pulmonary atresia, pulmonary stenosis
- Neural crest cells regulate the SHF, controlling FGF concentrations and later septate the outflow tract.



Bending of the Heart Tube (Day 23 → Day 28)

- Day 23:
 - Cephalic part bends ventrally, caudally & to the right
 - Atrial (caudal) part shifts dorsocranially & to the left
 - This creates the cardiac loop → completed by Day 28
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◆ Cardiac Loop - Regional Differentiation of the Heart Tube - Atrial Region

- Initially paired and located outside the pericardial cavity.
- These paired atria fuse → form a common atrium.
- The common atrium is then incorporated into the pericardial cavity.

◆ Atrioventricular Junction

- Narrow region between the common atrium and the primitive ventricle.
- Remains narrow → forms the atrioventricular (AV) canal.
- Function: Early connection between atrium and ventricle.

◆ Bulbus Cordis - Divisions & Derivatives

Region of Bulbus Cordis	Future Adult Structure
Proximal third	Trabeculated part of the right ventricle

Middle (Conus cordis)	Outflow tracts of both ventricles
Distal part (Truncus arteriosus)	Roots and proximal parts of the aorta & pulmonary artery

- Junction between primitive ventricle and bulbus cordis is marked externally by the bulboventricular sulcus.
- Internally, this narrow connection is called the primary interventricular foramen.

◆ Craniocaudal Organization of the Heart Tube

From cranial → caudal:

Conotruncus → right ventricle → left ventricle → atrial region

→ This regional patterning is regulated by homeobox genes, similar to the general craniocaudal axis of the embryo.

◆ Formation of Primitive Trabeculae

- Once looping is complete, the previously smooth-walled heart tube develops primitive trabeculae (muscular ridges) in two areas:
 1. Just proximal to the primary interventricular foramen → becomes the primitive left ventricle
 2. Just distal to the foramen (proximal bulbus cordis) → becomes the primitive right ventricle


→ The conotruncal part of the tube remains initially smooth.

◆ Final Positioning of Conotruncal Region

- Initially located on the right side, it gradually shifts to a central (medial) position.
 - This is due to transverse dilation (expansion) of the common atrium on both sides, pushing around the bulbus cordis.
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! Clinical Correlate - Abnormal Cardiac Looping

Abnormality	Cause / Mechanism
Dextrocardia	Heart loops to the left instead of right, → heart lies on the right side of the thorax
Situs inversus	Complete reversal of left-right asymmetry (all organs reversed)

 *Important:* These defects may be due to disruption either during gastrulation (when laterality is established) or during cardiac looping itself.

◆ Development of the Sinus Venosus & Septation of the Heart – Sinus Venosus (4th Week)

- Receives blood from right & left sinus horns.

- Each horn has 3 major veins:

1. Vitelline (omphalomesenteric) vein

2. Umbilical vein

3. Common cardinal vein

◆ Rightward Shift of the Sinus Opening

- Initially, wide connection between sinus and atrium.

- Left→Right shunting of blood (weeks 4-5) → entrance of the sinus shifts to the right side.
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◆ Fate of Left Sinus Horn

Structure	Fate
Right umbilical vein	Obliterates (Week 5)
Left vitelline vein	Obliterates
Left common cardinal vein	Obliterates (≈Week 10)

→ Result: Left sinus horn becomes small and regresses
 → remains as:

- Oblique vein of the left atrium
- Coronary sinus

◆ Fate of Right Sinus Horn

- Enlarges greatly (receives all shunted blood).
- Becomes incorporated into right atrium → forms the smooth-walled part of the right atrium (sinus venarum).
- Its entrance (sinoatrial orifice) is flanked by:
 - Right venous valve
 - Left venous valve
- Dorsocranial fusion of the two valves → septum spurium

➤ Fate of right venous valve:

Part	Derivative

Superior part	Disappears
Inferior part	Valve of the inferior vena cava • Valve of the coronary sinus

→ Crista terminalis separates:

- Smooth-walled sinus venarum (from right horn)
- From trabeculated primitive atrium

◆ Formation of the Cardiac Septa (Days 27-37)

Two ways septa form:

Mechanism	Description
Fusion of growing tissue masses (<i>endocardial cushions</i>)	Actively growing masses approach & fuse → complete division

Uneven regional growth	A ridge remains between expanding regions → partial division (usually closed secondarily)
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Endocardial cushions form in:

- Atrioventricular canal
- Conotruncal region

▼ They contribute to:

- Atrial septum
- Ventricular (membranous) septum
- AV valves
- Aortic & pulmonary channels

→ Cushion defects → VSDs, ASDs, transposition, common truncus, tetralogy of Fallot

- ◆ Septum Formation in the Common Atrium

Step	Event
1	Septum primum grows downward from roof of common atrium (end of week 4)
2	Ostium primum = gap between lower rim & endocardial cushions
3	Endocardial cushions close the ostium primum
4	Ostium secundum forms via apoptosis in upper septum primum
5	Septum secundum forms to the right of septum primum, leaving a gap = foramen ovale
6	Free edge of septum secundum overlaps the ostium secundum

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Remaining septum primum → becomes valve of foramen ovale

→ Before birth: blood flows R → L atrium through the foramen ovale

→ After birth:

- ↑ Pressure in left atrium pushes valve against septum secundum → closes foramen ovale

⚠ In ~20% → probe patency (small cleft remains; no shunt)

◆ Further Differentiation of the Atria & Atrioventricular Canal:

Left Atrium - Incorporation of Pulmonary Veins

- A single embryonic pulmonary vein grows from the posterior wall of the primitive left atrium.

- This pulmonary vein connects to lung bud veins.
- Incorporation of the pulmonary vein and its branches
→ formation of the smooth-walled part of the left atrium.
- Ultimately, 4 pulmonary veins empty separately into the left atrium.
- Adult derivatives:
 - Trabeculated part = original embryonic left atrium (atrial appendage)
 - Smooth part = incorporated pulmonary veins

◆ Right Atrium - Reminder

Region	Origin
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Trabeculated part (pectinate muscles)	Primitive embryonic atrium
Smooth part (sinus venarum)	Right sinus horn of sinus venosus

◆ Septum Formation in the Atrioventricular (AV) Canal

End of Week 4:

- Anterior & posterior endocardial cushions appear in the AV canal → begin projecting into the lumen.

Initially:

- AV canal communicates only with primitive left ventricle (separated from bulbus cordis by the bulbo/conoventricular flange).

Later (Week 5):

- AV canal shifts to the right, allowing blood to flow into both primitive ventricles.

Two additional cushions (right & left lateral) form at the borders of the AV canal.

→ Fusion of anterior & posterior cushions (end of 5th week) → division into:

- Right AV orifice
- Left AV orifice

◆ Atrioventricular Valves

- After the AV cushions fuse, mesenchymal proliferations surround each AV orifice.
- Blood flow hollows the ventricular surface of these proliferations → valve leaflets form.

- Initially attached by muscular cords → later degenerate and are replaced by dense connective tissue
→ Chordae tendineae, attached to papillary muscles

Valve	# of Leaflets
Left (mitral/bicuspid)	2
Right (tricuspid)	3

Clinical Correlates

- Heart/vascular defects are the most common congenital anomalies (~1% of live births; ~10% of stillborns).
- ~1/3 of babies with a chromosomal abnormality have a heart defect.

- Causes: multifactorial (genetic + environmental)

Important Teratogens:

- Rubella virus
- Thalidomide
- Retinoic Acid (Accutane)
- Alcohol
- Maternal diabetes

Potential Target Cells:

- PHF / SHF progenitors
- Neural crest cells
- Endocardial cushions



Examples of Gene-related Cardiac Defects

Gene	Defect

NKX2.5	ASDs (secundum), Tetralogy of Fallot, AV conduction defects
TBXS	Holt-Oram syndrome (limb defects + ASDs)
β -myosin heavy chain	Hypertrophic cardiomyopathy

! Example of Laterality Defect

- Ventricular inversion (L-TGA):
Morphologic left ventricle on right side (connected to RA), right ventricle on left (connected to LA).
Great arteries are in normal position, but ventricles are reversed.

! Atrial Septal Defects (ASDs)

Type	Cause
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Ostium secundum defect	↳ Excessive resorption of septum primum ↳ Inadequate formation of septum secundum
Common atrium (cor triloculare biventriculare)	Complete failure of atrial septum formation
Probe patency (oval foramen remains as slit)	Incomplete postnatal fusion (no major shunt)
Premature closure of foramen ovale	Closure before birth → can lead to hypertrophy of right heart and death after birth

◆ Additional Septation & Conotruncal Development

Premature Closure of Oval Foramen

- Before birth: foramen ovale allows R → L shunt
- Premature closure = fusion occurs before birth

- → Right atrium & ventricle hypertrophy
 - → Left-sided chambers underdeveloped
 - → Usually fatal shortly after birth
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◆ Role of Endocardial Cushions in Septation

- AV cushions form the membranous part of the interventricular septum as well as close the ostium primum.
- They intersect with atrial & ventricular septa, forming a "cross" appearance (seen on ultrasound).
- Failure of fusion → persistent AV canal
 - ↓
 - one single AV orifice
 - combined atrial + ventricular septal defect
 - abnormal AV valve leaflets
- Partial fusion → ostium primum ASD

- o Interventricular septum intact
- o Usually associated with a cleft anterior leaflet of the tricuspid valve

◆ Tricuspid Valve Defects

Defect	Features / Associations
Tricuspid atresia	<ul style="list-style-type: none"> • Fusion/absence of tricuspid valve • No connection between RA & RV • Always association with: <ol style="list-style-type: none"> 1. Patent oval foramen 2. VSD 3. Hypoplastic RV 4. LV hypertrophy
Ebstein anomaly	<ul style="list-style-type: none"> • Downward displacement of tricuspid valve toward apex of RV • Enlarged right atrium, small RV

- ◆ Septum Formation in Truncus Arteriosus & Conus Cordis (Outflow Tract)

Week 5:

- Paired truncal swellings (cushions) appear:
 - Right superior
 - Left inferior
- Each cushion grows distally and twists in opposite directions, eventually fusing → forms the aorticopulmonary septum
- Result → Divides the truncus into:
 - Aortic channel
 - Pulmonary channel

Conus Cordis:

- Similar conus swellings develop:
 - Right dorsal wall
 - Left ventral wall
- These fuse and join the truncal septum → divide the conus into:

Region	Future structure
Anterolateral	RV outflow tract (infundibulum)
Posteromedial	LV outflow tract


◆ Role of Neural Crest Cells

- Originate from hindbrain neural folds → migrate through pharyngeal arches 3, 4 & 6 → reach outflow tract
- Contribute to the conotruncal endocardial cushions

- Also regulate SHF signalling (FGF levels) → required for lengthening of the outflow tract

→ Outflow tract defects may result from:

Cause	Examples of Defects
Damage to SHF	DORV, Tetralogy of Fallot
Damage to neural crest cells (conotruncal septum formation)	Persistent truncus arteriosus
Damage to crest cells → disrupt SHF signalling	Transposition of great vessels, pulmonary stenosis

 Note: Neural crest cells also contribute to craniofacial development → therefore, cardiac defects + facial anomalies commonly occur together (e.g., DiGeorge syndrome).

◆ Septum Formation in the Ventricles & Semilunar Valves

Development of the Ventricular Septum


- End of Week 4 → both primitive ventricles enlarge
 - outer growth = myocardial proliferation
 - inner growth = trabeculation / diverticulation
- The medial walls of both ventricles come together and fuse → form the muscular interventricular (IV) septum.
- Incomplete fusion can leave a deep apical cleft → communication persists between ventricles until it closes.
- Above the muscular IV septum is the interventricular foramen — this remains open until the conus septum and endocardial cushions complete closure.

- Closure of IV Foramen:
 - Outgrowth from the anterior (inferior) endocardial cushion grows on top of the muscular IV septum.
 - This fuses with the conus septum → forms the membranous part of the IV septum.
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◆ Semilunar Valves (Aortic & Pulmonary)

- When the truncus arteriosus is partitioned, tubercles appear on the truncal swellings.
- One tubercle from each swelling contributes to the pulmonary and aortic channels.
- A third tubercle develops in each channel opposite the fused truncal swellings.
- ➤ These three tubercles → hollow out on their upper surface → form the three semilunar valve cusps.

- Neural crest cells contribute to the formation of these valves.

 **Clinical Correlates**

Ventricular Septal Defects (VSDs) — *Most common congenital cardiac anomaly*

Type	Comments
Muscular VSD (80%)	Often closes spontaneously during growth
Membranous VSD	More serious; typically associated with conotruncal defects

Large VSD → ↑ blood flow through pulmonary circulation (1.2-1.7× aortic output).

Tetralogy of Fallot

Caused by anterior displacement of conotruncal septum

▼ Produces 4 key changes:

1. Pulmonary infundibular stenosis (narrow RV outflow)
2. Large VSD
3. Overriding aorta (over the VSD)
4. Right ventricular hypertrophy

(Occurs in ~9.6 /10,000 births; not immediately fatal.)

Persistent Truncus Arteriosus

- Failure of truncal ridges to form / fuse → no division of outflow tract.

- One common arterial trunk arises from heart and overrides both ventricles.
- Always associated with a VSD
(📉 Incidence \approx 0.8/10,000 births)

Transposition of the Great Vessels

- Conotruncal septum fails to spiral \rightarrow runs straight
 - \rightarrow Aorta exits RV
 - \rightarrow Pulmonary artery exits LV
- Often associated with membranous VSD and patent ductus arteriosus
- Related to defects in SHF or neural crest cells

DiGeorge Sequence (22q11 deletion)

- Neural crest abnormality

- Triad:
 - Facial anomalies
 - Thymic & parathyroid hypoplasia
 - Cardiac defects of outflow tract (e.g., Tetralogy, persistent truncus)

Valvular Stenosis / Atresia

Condition	Description
Pulmonary stenosis	Fusion of pulmonary valve cusps → narrowed or atretic pulmonary artery; right heart empties via oval foramen & ductus arteriosus
Aortic stenosis	Fusion of aortic valve cusps; sometimes only a pinhole remains

Aortic atresia	Complete fusion → marked hypoplasia of LV, LA, and aorta; systemic output maintained via ductus arteriosus
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Ectopia Cordis

- Heart develops outside thoracic cavity
- Caused by failure of ventral body wall closure

Formation of the Cardiac Conducting System & Aortic Arch Derivatives

◆ Formation of the Conducting System

Structure	Origin / Development
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Early pacemaker	Located in the caudal part of left cardiac tube
Later pacemaker (sinus venosus)	Assumes pacemaker role → as it is incorporated into right atrium, pacemaker tissue comes to lie near the opening of the SVC → forms the sinoatrial (SA) node
Atrioventricular (AV) node & Bundle of His	Derived from: <ul style="list-style-type: none"> • Cells in left wall of sinus venosus • Cells from the atrioventricular canal After incorporation → lie at base of interatrial septum

◆ Mechanisms of Vascular Development

Process	Description
Vasculogenesis	De novo formation of vessels by coalescence of angioblasts

Angiogenesis	Sprouting of vessels from existing ones
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→ Major vessels (dorsal aorta, cardinal veins) → vasculogenesis

→ Remainder of vasculature → angiogenesis

Patterning is controlled by VEGF and other growth factors.

◆ Development of the Arterial System - Aortic Arches

- Aortic arches appear during weeks 4-5, one in each pharyngeal arch.
- All originate from the aortic sac (distal truncus arteriosus).

- They terminate in the paired dorsal aortae.
- Five pairs of aortic arches form (I, II, III, IV, VI — the 5th is absent or incomplete).

◆ Fate of Each Aortic Arch

Arch	Adult Derivatives
1st	Maxillary artery (small remnant)
2nd	Hyoid & stapedial arteries
3rd	<ul style="list-style-type: none"> • Common carotid arteries • Proximal internal carotid arteries (distal ICA from dorsal aorta) • External carotid = sprout of 3rd arch
4th	<ul style="list-style-type: none"> • Left side → part of arch of aorta (between L common carotid & L subclavian) • Right side → proximal part of right subclavian artery

Sth	Usually regresses / absent
6th (pulmonary arch)	<ul style="list-style-type: none"> • Right side → proximal right pulmonary artery (distal part regresses) • Left side → proximal left pulmonary artery + distal part persists as ductus arteriosus

◆ Additional Changes

Change	Outcome
Carotid duct (between 3rd & 4th arches)	Obliterated
Right dorsal aorta (between 7th intersegmental and fusion point)	Disappears
Caudal shift of heart	Elongation of carotid & brachiocephalic arteries
	Left subclavian artery shifts cranially to origin close to L common carotid

◆ Recurrent Laryngeal Nerve Paths

- Initially: both hook around 6th aortic arch
- Later:

Side	Final Structure Hooked Around
Right	Right subclavian artery (because distal 6th arch disappears)
Left	Ductus arteriosus / ligamentum arteriosum (distal 6th arch persists)

🔴 Vascular Development - Vitelline, Umbilical & Coronary Arteries

◆ Vitelline Arteries

- Initially: Paired arteries that supply the yolk sac

- Later: Fuse to form gut arteries in the dorsal mesentery
- Adult derivatives:

Artery	Supplies
Celiac artery	Foregut
Superior mesenteric artery (SMA)	Midgut

- Note: Inferior mesenteric artery (IMA) is not vitelline-derived → comes from umbilical arteries

◆ Umbilical Arteries

- Initially: Paired ventral branches of dorsal aorta → run with the allantois to the placenta
- During Week 4:

- o Gain secondary connection to common iliac artery
- o Lose their original origin

- After birth:

- o Proximal part persists → forms internal iliac arteries & superior vesical arteries
- o Distal part obliterates → becomes medial umbilical ligaments

◆ Coronary Arteries

Source	Contribution
1. Angioblasts	Sprout from sinus venosus & cover heart via migration
2. Epicardium	Undergoes epithelial-to-mesenchymal transition (EMT) → forms endothelial & smooth muscle cells
3. Neural crest cells	Smooth muscle cells in proximal segments

4. Aortic invasion	Endothelial cells from coronaries grow into aorta (not from aorta outwards)
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Arterial System Defects

▼ Patent Ductus Arteriosus (PDA)

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- Normally: Functional closure shortly after birth → ligamentum arteriosum
 - Anatomical closure: Takes 1-3 months via intimal proliferation
 - PDA: Persistent shunting of blood from aorta to pulmonary artery
 - Common in preterm infants and those with heart defects

- Pathophysiology: High pressure in aorta causes left-to-right shunt, impairs closure

▼ Coarctation of the Aorta

- Prevalence: 3.2/10,000 births
- Narrowing of aorta below left subclavian artery
- Types:

Type	Description	Ductus arteriosus
Preductal	Above ductus	Ductus persists
Postductal	Below ductus	Ductus usually obliterated

- Collateral circulation via:
 - Intercostal arteries
 - Internal thoracic arteries

- Clinical signs:
 - ↑ BP in right arm
 - ↓ BP in legs
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▼ Abnormal Origin of Right Subclavian Artery

- Cause: Obliteration of right 4th aortic arch + proximal right dorsal aorta
 - New origin: From distal right dorsal aorta + 7th intersegmental artery
 - Crosses behind the esophagus to reach right arm
 - Usually asymptomatic (no significant compression)
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▼ Double Aortic Arch

- Cause: Persistence of right dorsal aorta
 - Result: Vascular ring around trachea & esophagus
 - Symptoms: Difficulty breathing & swallowing
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▼ Right Aortic Arch

- Cause: Obliteration of left 4th arch and left dorsal aorta
 - Aorta arises on right side
 - Can cause esophageal compression if ligamentum arteriosum remains on left
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▼ Interrupted Aortic Arch

- Cause: Obliteration of left 4th aortic arch
 - Often associated with:
 - Abnormal right subclavian artery
 - Patent ductus arteriosus
 - Blood reaches descending aorta via ductus → poorly oxygenated blood supplies lower body
 - Aortic trunk supplies only common carotid arteries
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✨ Summary Tables for Rapid Review

✓ Vitelline vs Umbilical Arteries

Feature	Vitelline Arteries	Umbilical Arteries
Origin	Paired yolk sac vessels	Paired ventral aortic branches

Adult Derivatives	Celiac & SMA	IMA, Internal iliac, Superior vesical
After birth	—	Distal part → medial umbilical ligaments

✓ Aortic Arch Derivatives

Aortic Arch	Adult Arterial Derivative
1st arch	Maxillary arteries
2nd arch	Hyoid and stapedial arteries
3rd arch	Common carotid arteries and proximal portion of the internal carotid arteries
4th arch (Left)	Arch of the aorta (portion between the left common carotid and left subclavian arteries)
4th arch (Right)	Proximal part of the right subclavian artery
6th arch (Left)	Left pulmonary artery + Ductus arteriosus
6th arch (Right)	Right pulmonary artery

5th arch	Does not form or regresses early
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- Remainder of the internal carotid arteries are derived from the dorsal aorta.
- The proximal part of the aortic arch comes from the left horn of the aortic sac; the right horn forms the brachiocephalic artery.
- The distal portion of the right subclavian artery and the entire left subclavian artery come from the 7th intersegmental arteries on their respective sides.

Development of the Venous System

◆ Overview - Week 5

Three pairs of major veins drain into the sinus venosus:

Vein	Function
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Vitelline (omphalomesenteric)	Carry blood from yolk sac to the heart
Umbilical	Carry oxygenated blood from placenta
Cardinal	Drain embryo body wall and organs

◆ Vitelline Veins

- Form a plexus around duodenum, pass through septum transversum
- Hepatic cords interrupt the vitelline veins → form hepatic sinusoids
- Left vitelline vein regresses → blood re-routed to the right side
- Right vitelline vein enlarges → becomes hepatocardiac segment of IVC

- Plexus around duodenum → portal vein
 - Superior mesenteric vein also arises from right vitelline vein
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◆ Umbilical Veins

- Initially paired, passing on each side of liver and connecting to hepatic sinusoids
- Right umbilical vein & proximal left portion disappear → Only left umbilical vein carries oxygenated blood from placenta
- Formation of the ductus venosus (connects left umbilical vein to hepatocardiac channel → bypasses liver sinusoids)
- After birth:

Structure	Adult Derivative
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Left umbilical vein	Ligamentum teres hepatis
Ductus venosus	Ligamentum venosum

◆ Cardinal Veins

Type	Drains
Anterior cardinal veins	Head and upper body
Posterior cardinal veins	Lower body
These two join to form	Common cardinal veins (drain into sinus venosus)

Additional venous systems (Weeks 5-7):


Vein	Function
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Subcardinal veins	Drain kidneys
Sacrocardinal veins	Drain lower limbs
Supracardinal veins	Drain body wall/intercostals (replacing posterior cardinals)

◆ Key Anastomoses & Final Structures

Anastomosis / Transformation	Adult Structure Formed
Left ↔ right anterior cardinal veins	Left brachiocephalic vein
Right common cardinal + proximal right anterior cardinal	Superior vena cava
Distal anterior cardinals	Internal jugular veins
Facial venous plexus	External jugular veins
Subcardinal vein anastomosis	Left renal vein
Right subcardinal vein	Renal segment of IVC

Sacrocardinal anastomosis	Left common iliac vein
Right sacrocardinal vein	Sacrocardinal segment of IVC
Right vitelline vein (hepatic segment) + renal + sacrocardinal	✓ Inferior vena cava
Right supracardinal vein (with posterior cardinal remnant)	Azygos vein
Left supracardinal (4th-7th intercostals)	Hemiazygos vein
Terminal left posterior cardinal	Left superior intercostal vein

 Clinical Correlates - Venous System & Overview of Fetal Circulation

Venous System Defects

Because venous return is initially bilateral and then gradually shifts to the right, abnormal persistence or

disappearance of certain venous channels is common, especially in patients with laterality defects.

- Double Inferior Vena Cava:

- Cause: Persistence of the left sacrocardinal vein

- Result: Two inferior vena cavae are present. The left IVC may drain either into the left common iliac vein or directly into the left renal vein.

- Absent Inferior Vena Cava:

- Cause: The right subcardinal vein fails to connect to the liver, so blood is diverted into the right supracardinal vein.

- Result: Blood from the lower body reaches the heart via the azygos vein → superior vena cava. (The hepatic vein still drains directly into the right atrium.)

- Left Superior Vena Cava:


- Cause: Persistence of the left anterior cardinal vein, combined with obliteration of the right anterior and right common cardinal veins.

- Result: Venous return from the right side is diverted to a left SVC, which then drains into the coronary sinus → right atrium.

• Double Superior Vena Cava:

- Cause: Persistence of the left anterior cardinal vein AND failure of the left brachiocephalic vein to form.

- Result: Two SVCs are present; the left SVC drains into the coronary sinus, and both SVCs enter the right atrium separately.

 Fetal Circulation
Oxygenation Source

- Blood from placenta ($\approx 80\%$ oxygenated) returns via the umbilical vein
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Liver Bypass Mechanism

Structure	Function
Ductus venosus	Shunts most oxygenated blood bypassing the liver \rightarrow directly to IVC
Sphincter in ductus venosus	Closes during uterine contractions to prevent cardiac overload

Heart Circulation in Fetus

Chamber	Blood Source	Fate
Right atrium	IVC (oxygenated) + SVC (deoxygenated)	Most IVC blood \rightarrow foramen ovale \rightarrow left atrium

Left atrium	Mostly from foramen ovale + some pulmonary veins	→ Left ventricle → Ascending aorta
Right ventricle	Blood from SVC → pulmonary trunk	Most blood bypasses lungs → ductus arteriosus → descending aorta

🔑 Well-oxygenated blood supplies brain & heart (via carotid and coronary arteries - early branches of ascending aorta)

🔗 Major Fetal Shunts and Their Functions

Shunt	Function	Adult Remnant
Ductus venosus	Umbilical vein → IVC (liver bypass)	Ligamentum venosum
Foramen ovale	Right atrium → Left atrium	Fossa ovalis
Ductus arteriosus	Pulmonary trunk → Aorta	Ligamentum arteriosum



Mixing of Blood in Fetus - Key Sites


Site	Mixing of Blood
(I) Liver	Umbilical vein blood + portal venous blood
(II) Inferior vena cava	Umbilical vein blood + venous return from lower limbs, pelvis, kidneys
(III) Right atrium	IVC blood + SVC blood (from head/upper limbs)
(IV) Left atrium	Foramen ovale blood + small amount of pulmonary venous blood
(V) Descending aorta	Blood from ductus arteriosus + blood from proximal aorta



Oxygen Saturation Summary

Vessel	O ₂ Saturation

Umbilical vein	~80%
Left atrium / ventricle / ascending aorta	~65%-70%
Umbilical arteries	~58%

 Exam Tip: Always associate the bypass mechanisms (3 shunts) with fetal oxygen priorities — brain and heart receive most oxygen-rich blood.

Circulatory Changes at Birth

Triggered by loss of placental circulation + first breath

Structure	Physiological Change	Adult Remnant
Umbilical arteries	Smooth muscle constriction → closure within minutes	Medial umbilical ligaments (distal) Superior vesical arteries (proximal)
Umbilical vein	Closure shortly after arteries	Ligamentum teres hepatis

Ductus venosus	Closure shortly after birth	Ligamentum venosum
Ductus arteriosus	Bradykinin-mediated constriction → closes within hours (anatomical closure in 1-3 months)	Ligamentum arteriosum
Foramen ovale	↑ LA pressure & ↓ RA pressure press septum primum → septum secundum	Fossa ovalis (complete fusion ~1 year)

- ◆ *Note:* Foramen ovale closure can be reversible in first days → crying may cause transient R→L shunt → cyanosis
- ◆ Probe patent foramen ovale remains in ~20% of individuals

Lymphatic System Development

Stage / Structure	Details
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Begins	Week 5 (later than CV system)
Origin	Endothelial outgrowths from veins
Primary lymph sacs	<ul style="list-style-type: none"> • 2 jugular (< subclavian + anterior cardinal) • 2 iliac (< iliac + posterior cardinal) • 1 retroperitoneal (root of mesentery) • 1 cisterna chyli (dorsal to retroperitoneal sac)
Main channels	Right & left thoracic ducts connect jugular sacs to cisterna chyli
Final thoracic duct	<p>Formed from:</p> <ul style="list-style-type: none"> - Distal right thoracic duct - Anastomosis between R & L ducts - Cranial left thoracic duct
Right lymphatic duct	Cranial portion of right thoracic duct
Fate	Both ducts drain into junction of internal jugular & subclavian veins
Molecular control	PROX1 transcription factor specifies lymphatic lineage → upregulates VEGFR3 (receptor for VEGFC) → endothelial sprouting from veins

-> The End <-