Basics of Cardiac Embryology:

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Goals:

At the end of this lecture you should be able to

- **Understand the embryologic origins of some common cardiac lesions**
- Identify key embryologic events in cardiac development
- Promote integration of developmental process (Embryology) with fetal diagnosis of CHD

Format:

- Simplified overview of cardiac embryology using 3D animations
- Ultrasound images from fetal echocardiograms to highlight the embryologic origins

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Acknowledgement

• Carol Mitchell PhD
Associate Prof in Medicine

• David McDougal/Evan Schultz
Animator and Graphic's Artists
• Sonographers

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Disclaimers

- The Goal of this lecture is to provide a simple easy to understand overview of Cardiac Embryology
- As such it may be an over simplification of some complex processes
- Developmental origins of some structures are hotly debated, and the simplest explanation may be chosen here.

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Etiology

CONGENITAL HEART DISEASE

Multifactorial

Genetic/ environmental

Embryological mishaps

Endocardial cushion Defect(AVC); Double outlet RV; Double inlet left ventricle

Secondary & Flow mediated effects - Progressive chamber hypoplasia and evolution of lesions

PS to PA to HRHS; AS to HLHS, Coarct to Boderline left heart structures

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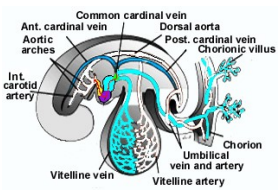
Over-view



- Heart is one of the critical organs necessary for life
- Develops very early in gestation
- **Earliest heart activity appears by about 20-21 days post conception- though still just a tube**
- It starts pumping and effectively aiding in the flow of blood as early as 24 days post conception as it undergoes a complex transformation

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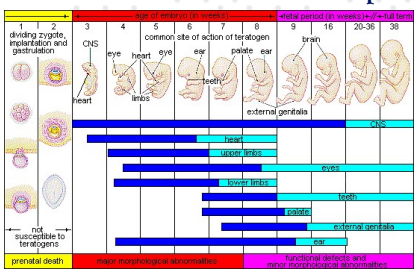
Time line of Fetal Development



Heart develops during a embryologically active period; High association of non-cardiac defects

http://embryology.med.unsw.edu.au/Medicine/images/hcriticaldev.gif

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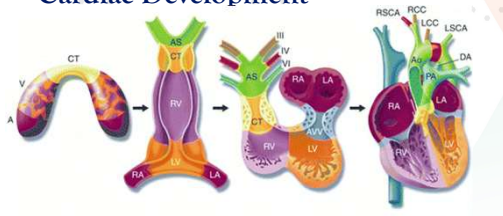
Cardiac Development



Day 15	Day 21	Day 28	Day 50
Paired Endocardial heart tubes	Single Heart Tube	Looping	Septation

Primary Heart Field

Secondary Heart Field

Shrivastava et al

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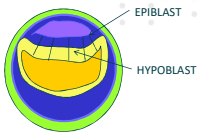
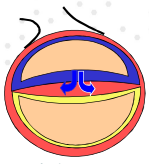
Early Events



BLASTOCYST:
2 Layers
- Epiblast (source of the pro-cardiogenic cells)
- Hypoblast

Implantation



Gastrulation:
3 Layered Embryo
- Ectoderm : Skin and related structures
- Endoderm: Inner lining eg gut and gut related organs
- **Mesoderm: Central layer forming most of skeleton and muscles including heart**

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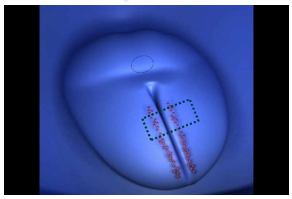
Cardiogenic Fields



Cardiac Cresent

Cardiac progenitor cells are derived from the epiblast emerging from the cranial third of the primitive streak and migrate inward.

Localize in cranial lateral plate mesoderm . In some species they arch cranial to the head fold to form the **Cardiac Cresent or Cardiogenic Fields**

Primitive node has active cilia

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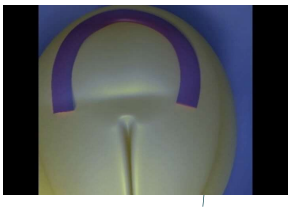
Primary Heart Tube

Cranial End



Vasculogenesis in the area of the primary heart field results in the formation of paired lateral endo-cardial tubes, lined with endothelium and surrounded by jelly where in the myocardial cells develop.

3rd Week

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Gastrulation: Fate Mapping of the embryo

- Mesoderm contributes to formation of the CVS, GU, Musculo –skeletal systems
- Abnormalities at this time account for common associations:
  - VACTERL : Vertebral Anal Cardiac TE fistula Renal
  - Cardiac and limb anomalies

Missed Scoliosis: multiple studies and findings may get buried. Update problem list in a timely fashion

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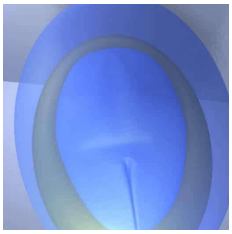
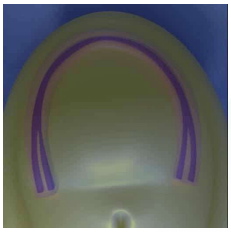
Folding of the Embryo



Head-Tail Folding



Side-Side (lateral) folding

DAY 20-21

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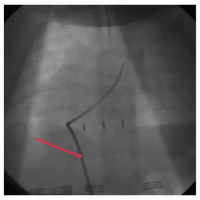
Prenatal diagnosis of Pentalogy of Cantrell

PA Angiogram LV Diverticulum / herniation



Fetal Echo

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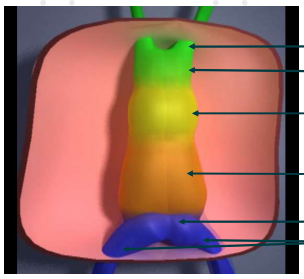
Cardiac Looping (23-28 days)



Arterial Pole

Conotruncus

Outflow tracts/ Vent Outflow area

Bulbus Cordis

Future RV Body

Primitive ventricle

Future LV

Primitive atrium

Horns of Sinus venosus

Venous Pole

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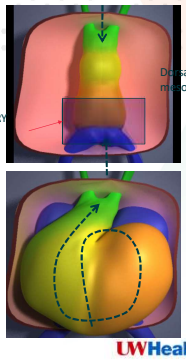
Cardiac Looping

- Critical process that establishes the spatial relationship of the heart
- Normal is looping to right or D – looping: first sign of cardiac Asymmetry
- Inner curvature forms
- Constant addition of cells from both ends as well as Dorsal mesocardium. Primary versus secondary heart fields



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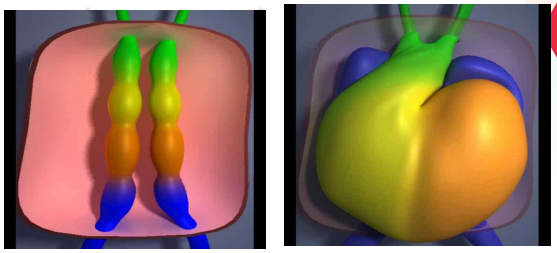
Looping



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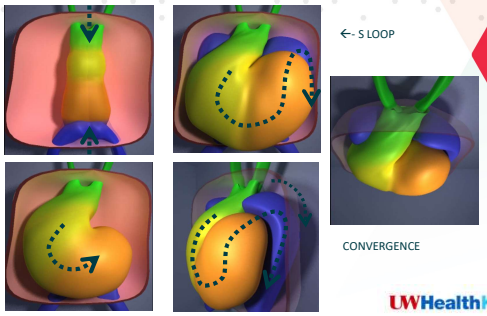
Looping



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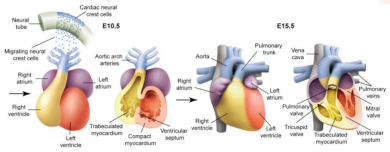
Looping: TAKE HOME message



This Dextro or D looping establishes the basis of normal cardiac topography

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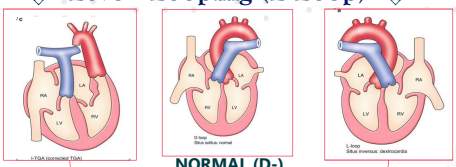
Levo –Looping (L Loop)



NORMAL (D-)

L-TGA: Congenitally corrected TGA
- -Ventricular inversion
- -Systemic right ventricle
- -Associated abnormalities
- -Conduction pathway/ Heart block

Situs- inversus: mirror image dextrocardia: L loop

Image springer link

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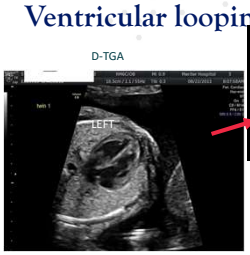
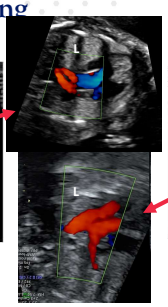
Ventricular looping

D-TGA





L-Loop or CC TGA

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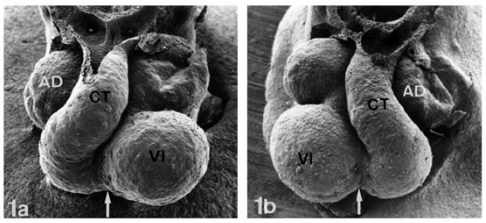

Fig.1. Scanning electron microscopy. Mouse hearts, E10.5. *a)*situs solitus; *b)* situs inversus.

https://www.revespcardiol.org/ Dr Jose Manuel Icardo

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Cardiac Septation (Days 28-37)

- Atrial Septation
- Partitioning of Atrioventricular canal
- Ventricular septation
- Conotruncal (outflow-OFT) septation
- Formation of Systemic venous return
- Pulmonary venous return
- Aortic arches
- Formation of conduction tissue, myocardium, coronary arteries

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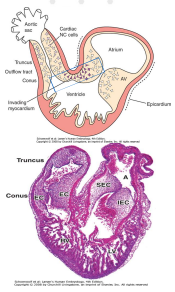
Cardiac Cushion Tissue



Bulges of cardiac jelly appears in area of AV canal and outflow tract

Continuous along inner curvature

Populated by cells that undergo mesenchymal transformation (Epithelial Mesenchymal Transformation)

- Endocardial cells in AV canal
- Neural crest cells (Ectodermal) in outflow tract

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Common denominators in inflow and outflow septation:

- DIVISION: into a right and left inflow/ outflow
- ALIGNMENT: with respective ventricles
  - Rotational
  - Lateral
  - Apoptosis
- VALVE Formation: supported by EMT

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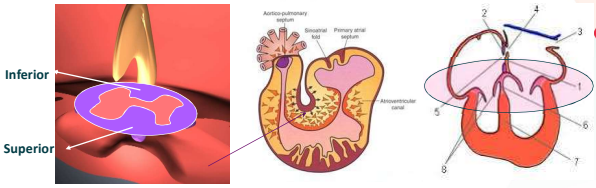
Partition of Atrio-Ventricular Canal



- 4 Cushions: superior, inferior, 2 lateral
- Part of the AV- Valve formation
- Portions of inferior/posterior aspects of atrial septum and ventricular septum.

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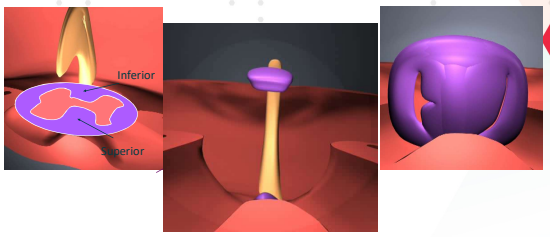
Partition of Atrio-Ventricular Canal



4 Cushions Superior and Inferior and two Lateral Cushions

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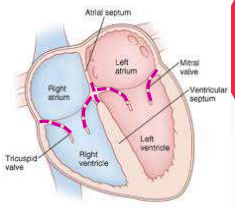
Endocardial Cushions

Contribute to:

- Division of atrioventricular canal
- RAVV and LAVV
- Lower portion of the atrial septum
- The posterior or inlet portion of ventricular septum



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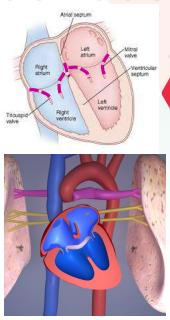
Endocardial Cushion Defects

- Components
  - Common atrioventricular valve/cleft mitral
  - Primum atrial septal defect
  - Inlet ventricular septal defect
- Partial or Complete
- Balanced or unbalanced
- AV conduction abnormalities
- Associated with outflow cushion abnormalities such as Tetralogy of Fallot



Ref: C. Mitchell

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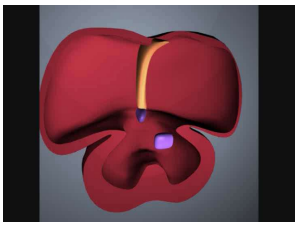
Endocardial Cushion Defe



ABNORMAL

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Endocardial Cushion Defects

- High Association with genetic defects:
  - Trisomy 21 and others: 45% case
  - Other chromosomal : 15% (8pdel, EVC, RAS pathway, Smith-Lemli Opitz)
  - Heterotaxy syndromes: 15%
- Non-syndromic 25%

- Important implications for counseling

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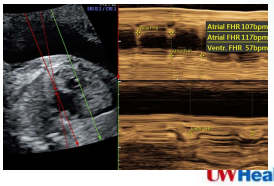
AV Canal : Heterotaxy

1. CHD: AVC, Non-compaction, bilateral SVC, pulmonary stenosis.
2. Complete heart block
3. Non-compaction cardiomyopathy
4. Emergent pacemaker at birth
5. Died of intractable heart failure at 3 weeks.



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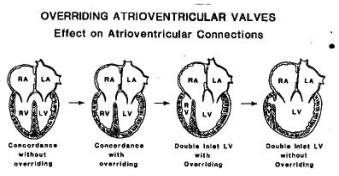
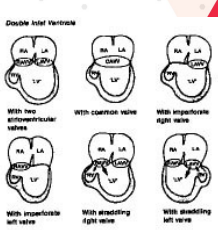
Inflow Abnormalities





Atlas of CHD

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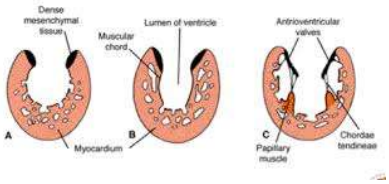
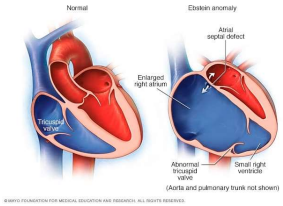
AV Valve Formation



Jaypee Digital

- Partly from endocardial tissue
- Partly from delamination from underlying myocardium.
- Difference in TV versus MV
- Defective delamination: Ebstein's malformation of TV

Ebstein Malformation



Involves the tricuspid valve with varying degrees of downward displacement of the valve

Atrialization of parts of ventricle

Abnormal TV function

RV hypoplasia Variable

Associated left sided abnormalities

1/3rd with WPW / atrial arrhythmias

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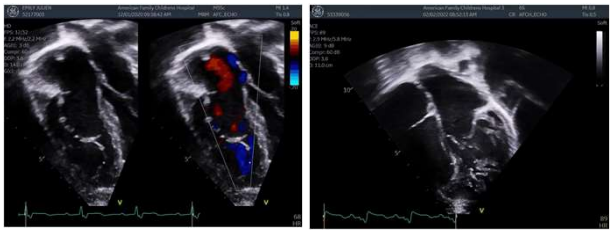
Ebstein Malformation

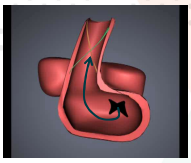


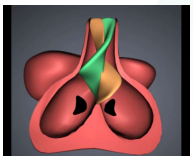
Conotruncal Septation

Divide the outflow part into aorta and pulmonary outflows: Spiral Septum

Form the respective valves

Alignment: Connect to the respective arteries on top and the appropriate ventricles on the bottom (counterclockwise rotation)





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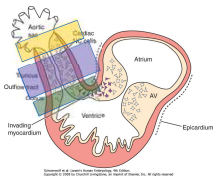
Components of OFT



Various different models available with differing terminology

Broad outline of the process

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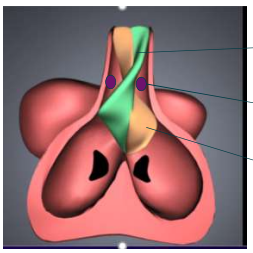
Outflow Septation Spiral Septum



Paired Truncal Ridges
- Dextro superior
- Sinistro -Inferior

Intercalated bulbar swellings / intermediate ridges

Paired Bulbar Ridges
- Dextro-dorsal
- Sinistro-ventral

Intrapericardial Aorta/ Pulmonary artery

Valves

RV
Infundibulum
Aortic vestibule

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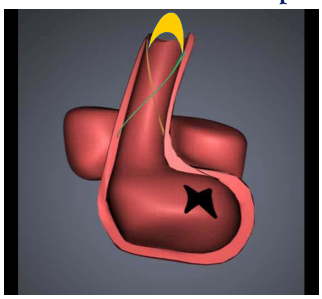
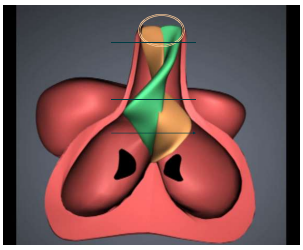
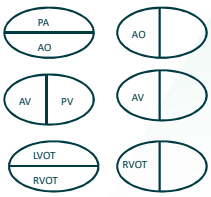
Conotruncal Septation



- Shelf in dorsum of aortic sac between 4th and 6th arches separates Aorta from Pulmonary artery
- Pair of Spiral Cono-truncal ridges develop from cushion tissue in truncus and conus
- Grows inwards to meet in midline and divides in Aortic and Pulmonary trunk
- Myocardialization of conal septum / Arterialization of Ao/PA/ resorption of subaortic conus.

Spiral Septation





Normal TGA

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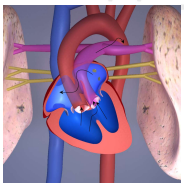
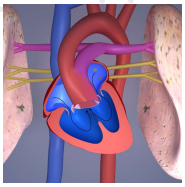
Out-Flow Tract Lesions

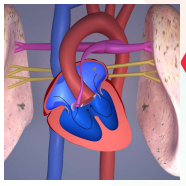
Images: Carol Mitchell



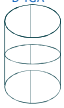
D-TGA



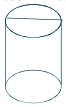
TRUNCUS ARTRIOSUS



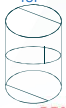
TOF



Abnormal SPIRAL SEPTUM



LACK SEPTATION



UNEQUAL SEPTATION

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22 q 11 Deletion: Di George syndrome

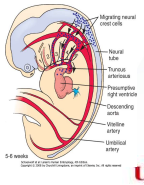
Division of the outflow regulated by cells called the neural Crest Cells that developmentally arise near the brain.

When migration of these cells are affected then outflow division is affected

Arch problems, certain VSD, Tetralogy of Fallot, pulmonary artery problems

Parasympathetic innervation to gut and heart

Associated problems with many midline structures, cleft palate, Parathyroid problems, thymus issues.



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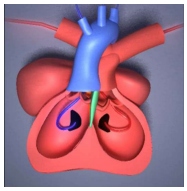
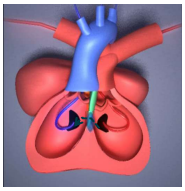
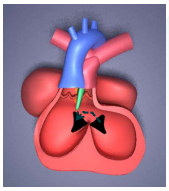
Related defects: Alignment



D-TGA: Transposition of great arteries



D-TGA with VSD



Double Outlet right ventricle (DORV) with D malposed great arteries

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DTGA

Taussig -Bing

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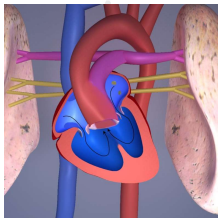
Incomplete spiral septation: Truncus Arteriosus



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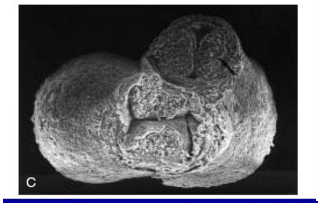
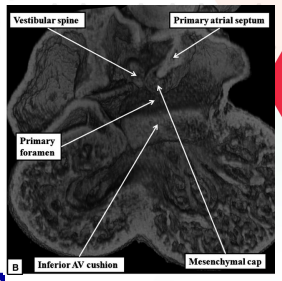
EM Of Cardiac Cushion



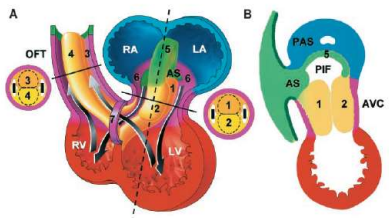
Scanning electron micrograph of heart from mouse embryo, showing growth and fusion of the superior and inferior endocardial cushions in the atrioventricular canal



Dr Robert Anderson

UWHealthKids

Ventricular Development



- Outgrowth from the outer curvature
- Inward growth of muscle at interventricular groove : muscular ventricular septum
- Initially spongy and later compacts as the coronary arteries develop.
- May persist in non-compaction cardiomyopathy

Circ Res. 2009;91:93-103

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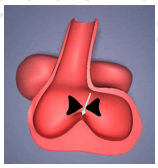
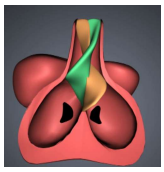
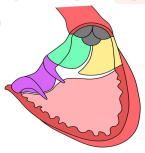
Ventricular Septation

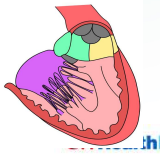




Components:

- Protrusion of muscular interventricular septum (4-5 wks)
- Endocardial Cushions (6 wks)
- Outflow Cushions
- Membranous Septum (6-8 wks)



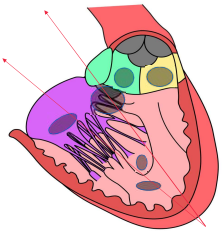


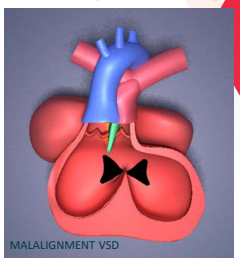
VSD

Ventricular Septum: Sinusoidal

The position of VSD is related to its embryologic origin

Define the VSD by its relationship to nearby structures and flow patterns.





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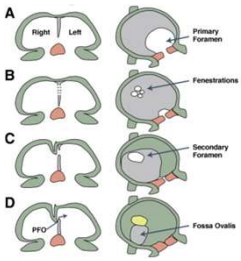
Atrial Septation (Weeks 4-5)



- Day 26: Septum Primum arises as a curtain from the top
- Initial communication at inferior edge : FORAMEN PRIMUM
- Foramen SECUNDUM arises as perforations
- Secundum septum arises to the right of the primum septum
- Septation completed by Endocardial Cushion Tissue (end of 6th week)

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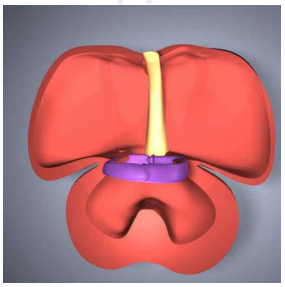
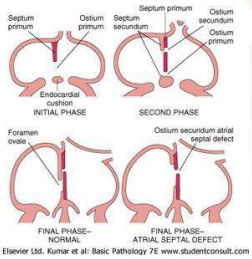
Atrial Septation





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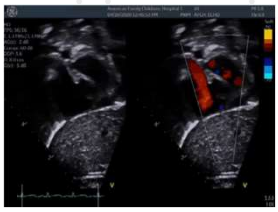

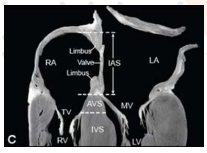

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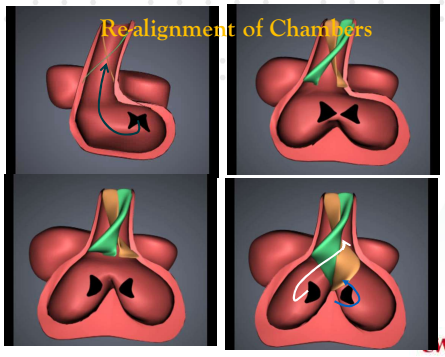
Realignment of Chambers

DOUBLE INLET LV

DOUBLE OUTLET RV



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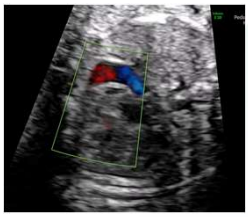
Early arrest development: TA DORV



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Double INLET LV

CAVC with DORV

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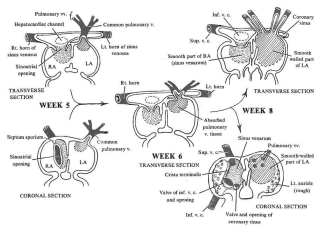
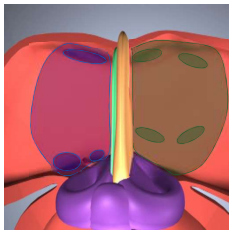
FORMATION OF ATRIA





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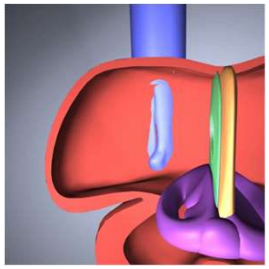
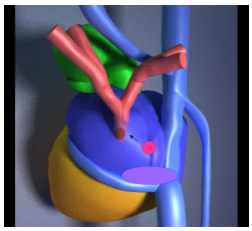
Formation of the Right Atrium



- Right Sinus Horn: intussusception and absorption into the posterior right atrial wall
- Left Sinus horn Coronary sinus
- Left sinus valve involutes
- Right Valve: valve of IVC and valve of CS
- Primitive atrial tissue persists in the trabeculated atrium and appendage demarcated by CRISTA TERMINALIS

Pulmonary Veins



- Lung: outgrowth from foregut. Venous plexus drains initially to cardinal system.
- 4th week Single midline pulmonary vein in dorsal mesocardium: Grow out to establish connection with pulmonary venous plexus. Connections to cardinal system regress
- Shifts to left with growth of primum atrial septum
- Absorbed into the LA by intussusception to second major division: 4 separate openings

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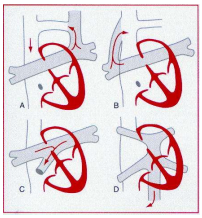
Pulmonary Venous Anomalies



Failure of pulmonary vein development → persistence of connections to the cardinal system: TAPVR or PAPVR to different sites

Incomplete absorption of pulmonary vein into the left atrium: Cortriatrium.

A combination of the two might be present with variable levels of atrial/ extracardiac communications

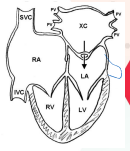


Image Source www.med.[illegible]

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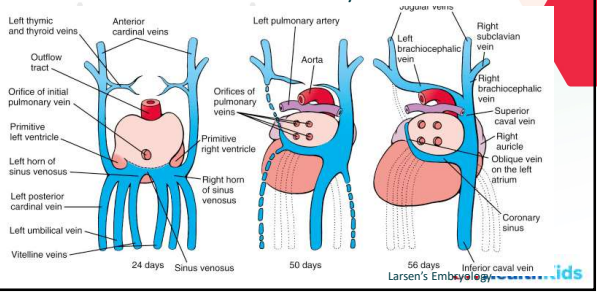
Systemic Veins (24-56 days)

Formation of SVC and Coronary Sinus



Larsen's Embryology

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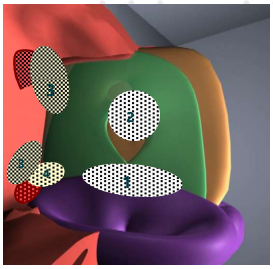
ATRIAL SEPTAL DEFECTS



1. Primum ASD: failure of fusion of septum primum with endocardial cushion (ECD)
2. Secundum: Foramen secundum too big, deficiency of septum secundum, extra fenestrations
3. Sinus Venosus : defective absorbtion of right horn sinus venosus superior and inferior
4. Coronary sinus : defective absorption of left horn of sinus venosus

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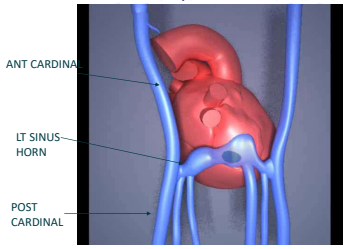
Systemic Veins (24-56 days)



- Lt ant cardinal Oblique vein if Marshall/ LSVC
- Left Sinus Horn : Coronary Sinus
- Rt Ant cardinal : RSVC
- Vitelline Veins
  - Left disappears
  - Right: terminal IVC, portal system, SMV
- Umbilical Veins
  - Right disappears
  - Left connects placenta to Ductus Venosus

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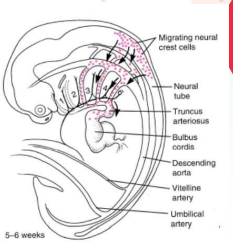
Development of the aortic arch

- Paired Aortic Arches develop with in the pharyngeal mesoderm.
- These connect anteriorly with the aortic sac and posteriorly with the paired dorsal aorta
- Precursors of mature aortic arch/ prox pulmonary artery



(Modified from Kirby ML. 1988.

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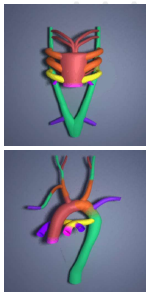
Paired Aortic Arch Derivatives



Arch	Left	Right
1st	small part of maxillary art.	
2nd	small part -stapedial art.	
3rd	CCA, ICA and ECA	
4th	Part of AA	Part of RSCA
6th	PDA, prox LPA	Prox RPA
7thinterseg Art	LSCA	Part RSCA
D.Dorsal Ao.	Desc Ao	Part RSCA, Regress

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Normal Arch

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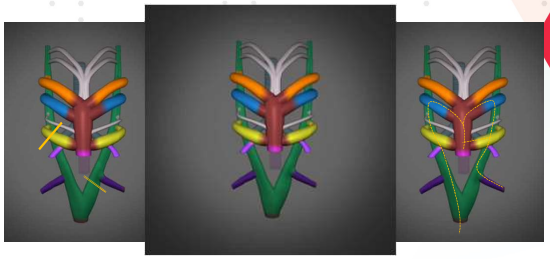
Right Arch/ Left PDA

MIRROR IMAGE BRANCHING



Or, one can have a right PDA (mirror image) with this anatomy

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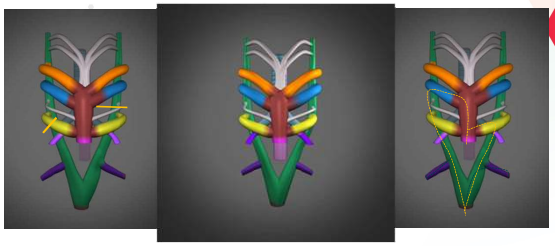
Rt Arch/ Lt PDA/ ALSCA

VASCULAR RING



Rarely one can have a left PDA WITHOUT ALSCA

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Double arch

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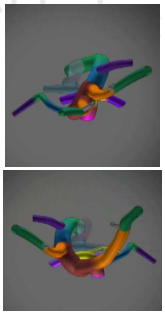
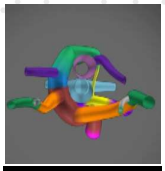
SUPERIOR VIEW

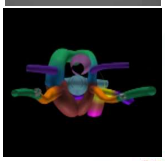
CONOTRUNCAL lesions may be associated with arch abnormalities and variations in PDA anatomy
- Role for PGE1
- Release of vascular ring substrate with surgery

LEFT ARCH/ left PDA

RT ARCH: Mirror Image with Left PDA/ RT PDA







VASCULAR RINGS

RT ARCH: ARSCA and LEFT PDA

Double Aortic Arch

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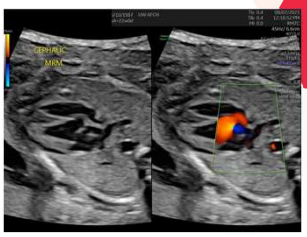
Double Arch

Rt Arch ALSCA



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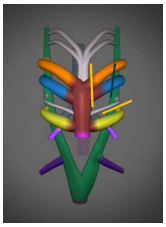
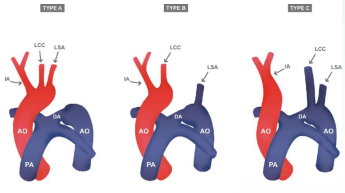
Interrupted Aortic Arch





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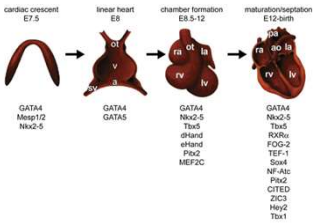
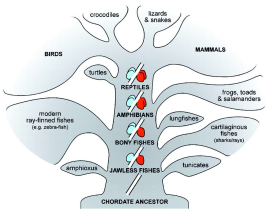
Genetic Control

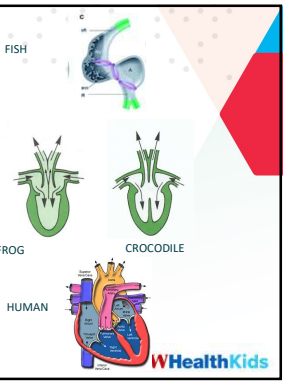


- Several genes now identified that play a role in cardiac development
- Tightly regulated expression with several modifiers and regulators
- Same gene defect may result in different defects
- A single defect may arise from different gene defects

Evolution



Physio.rev. 2003 vol 83



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Reading list:

- Larsen's human embryology
- Basics of cardiac development: Ped Research vol 57, no 2 2005
- Development of the human heart Am J Med Genet.2020;184C:7–22 https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajmg.c.31778
- Moorman AFM, Webb S, Brown NA, et al. The development of the heart: (1) Formation of the cardiac chambers and arterial trunks. Heart 2003;89:806–14.
- Robert H Anderson, Sandra Webb, Nigel A Brown, Wouter Lamers, Antoon Moorman. DEVELOPMENT OF THE HEART: (2) SEPTATION OF THE ATRIUMS AND VENTRICLES Heart 2003;89:949–958
- https://www.karger.com/Article/Fulltext/501906; more physiologic transition review not addressed this talk

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