

# Heart Development and Congenital Heart Disease

Gonzalo del Monte Nieto, PhD

[g.delmonte@victorchang.edu.au](mailto:g.delmonte@victorchang.edu.au)

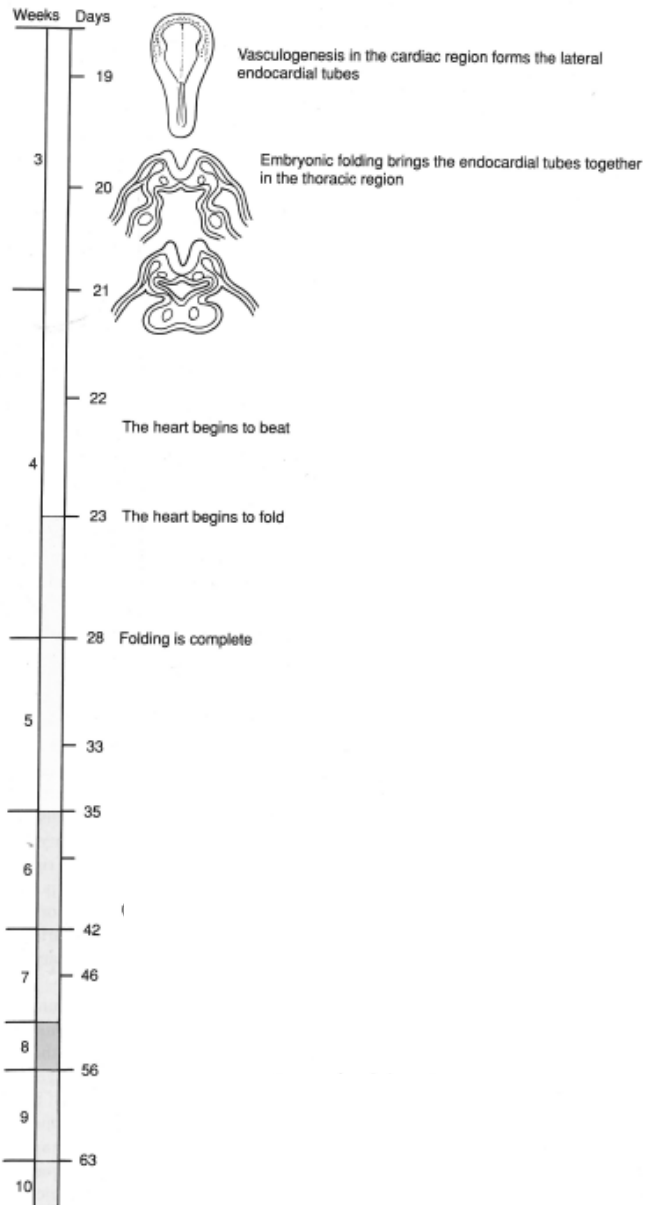
Developmental and Stem Cell Biology Division  
Victor Chang Cardiac Research Institute



# Lecture Index

- 1) Heart Progenitors.
- 2) Cardiac Tube Formation.
- 3) Valvulogenesis and Chamber Formation.
- 4) Epicardium Development.
- 5) Septation and Maturation.
- 6) Changes in Blood Flow during Development.
- 7) Cardiovascular Developmental Abnormalities.

# Summary of Heart development



1) Heart Progenitors.

2) Cardiac Tube Formation.

2) Cardiac Tube Formation. Cardiac Looping

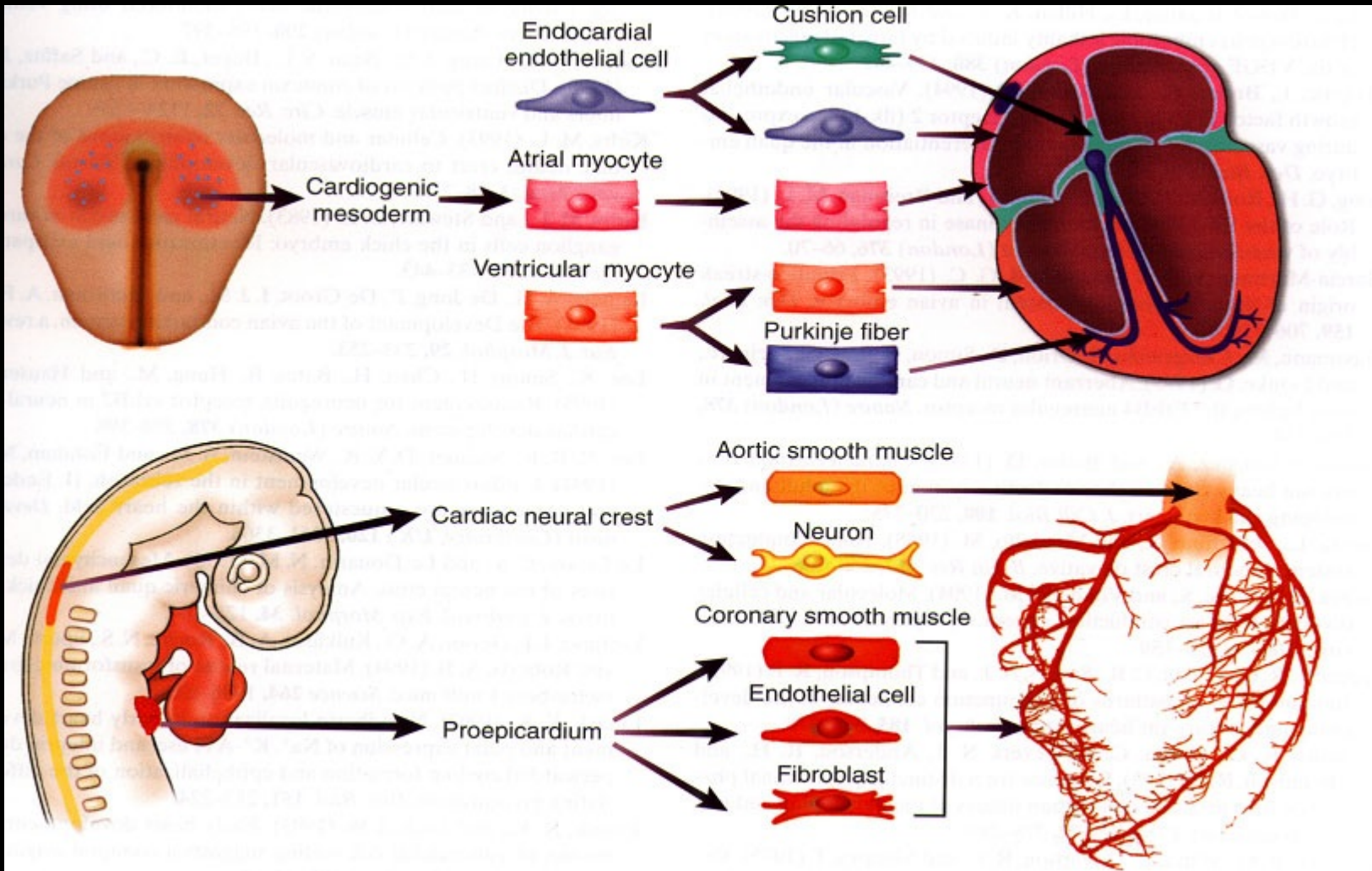
3) Valvulogenesis and Chamber Formation.

4) Epicardium Development.

5) Septation and Maturation.

# 1) Heart Progenitors

## 1.1) Cardiac Progenitors



# 1) Heart Progenitors

## 1.2) Myocardial Progenitors

### Myocardial Progenitors

First Heart Field (FHF)

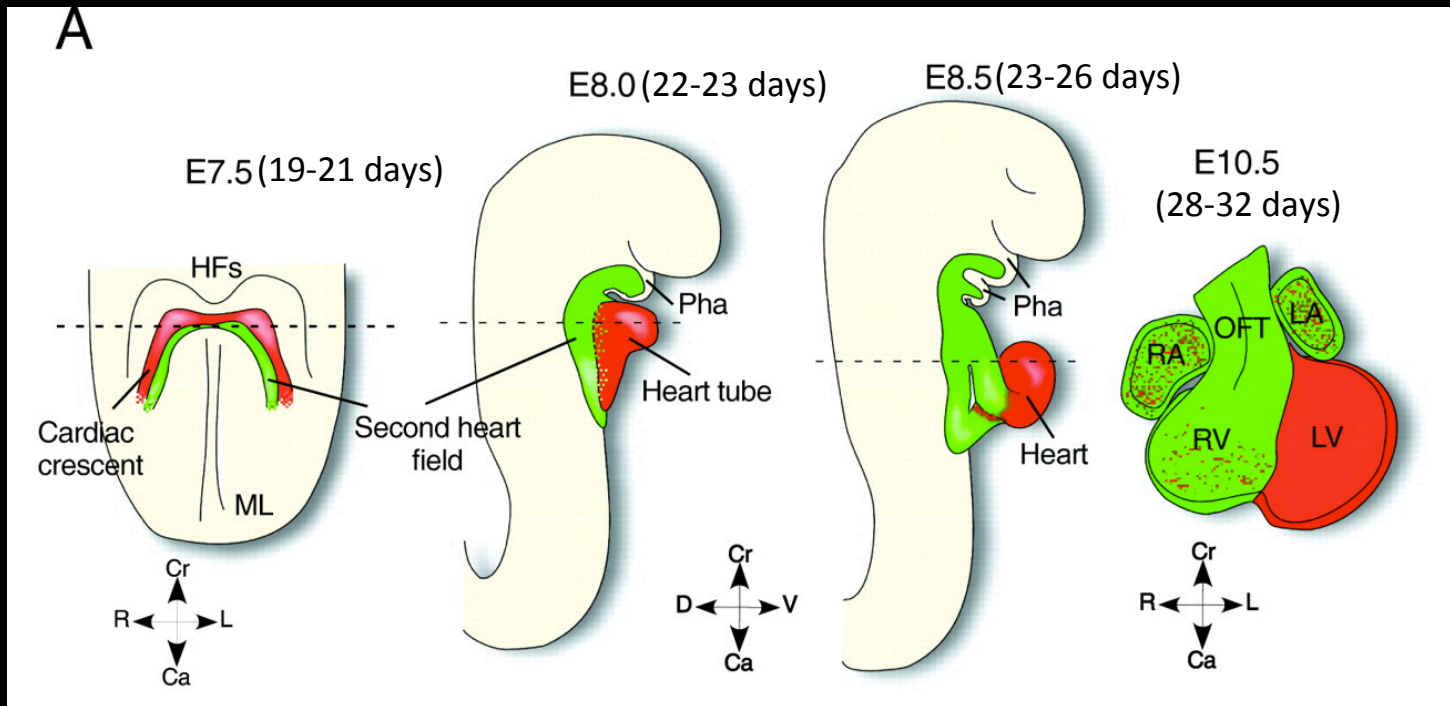
(Nkx2-5)

Atrium, AVC, LV

Secondary Heart Field (SHF)

(Islet1+)

Atrium, OFT, RV

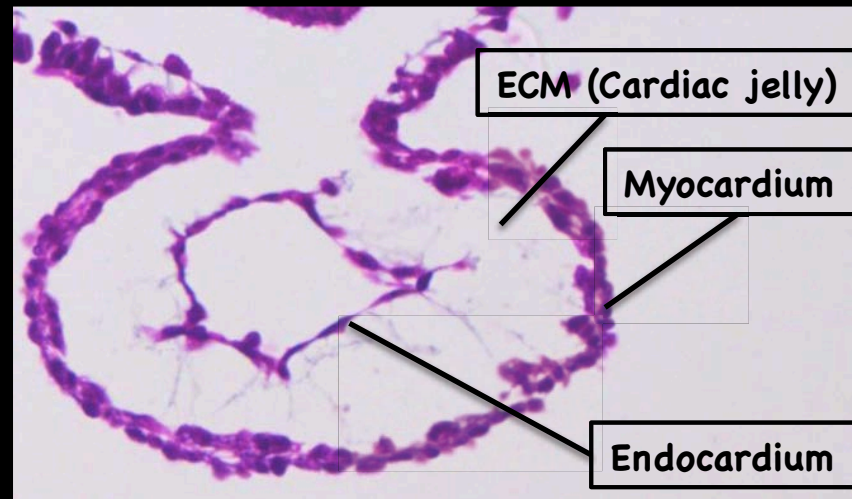
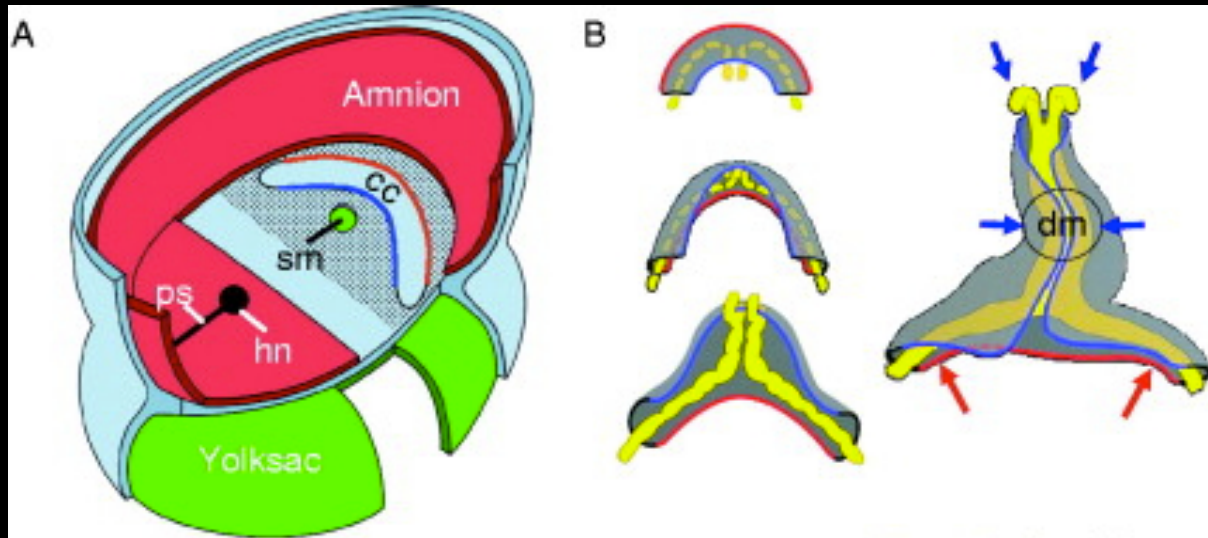


Laugwitz et al., 2008. Development



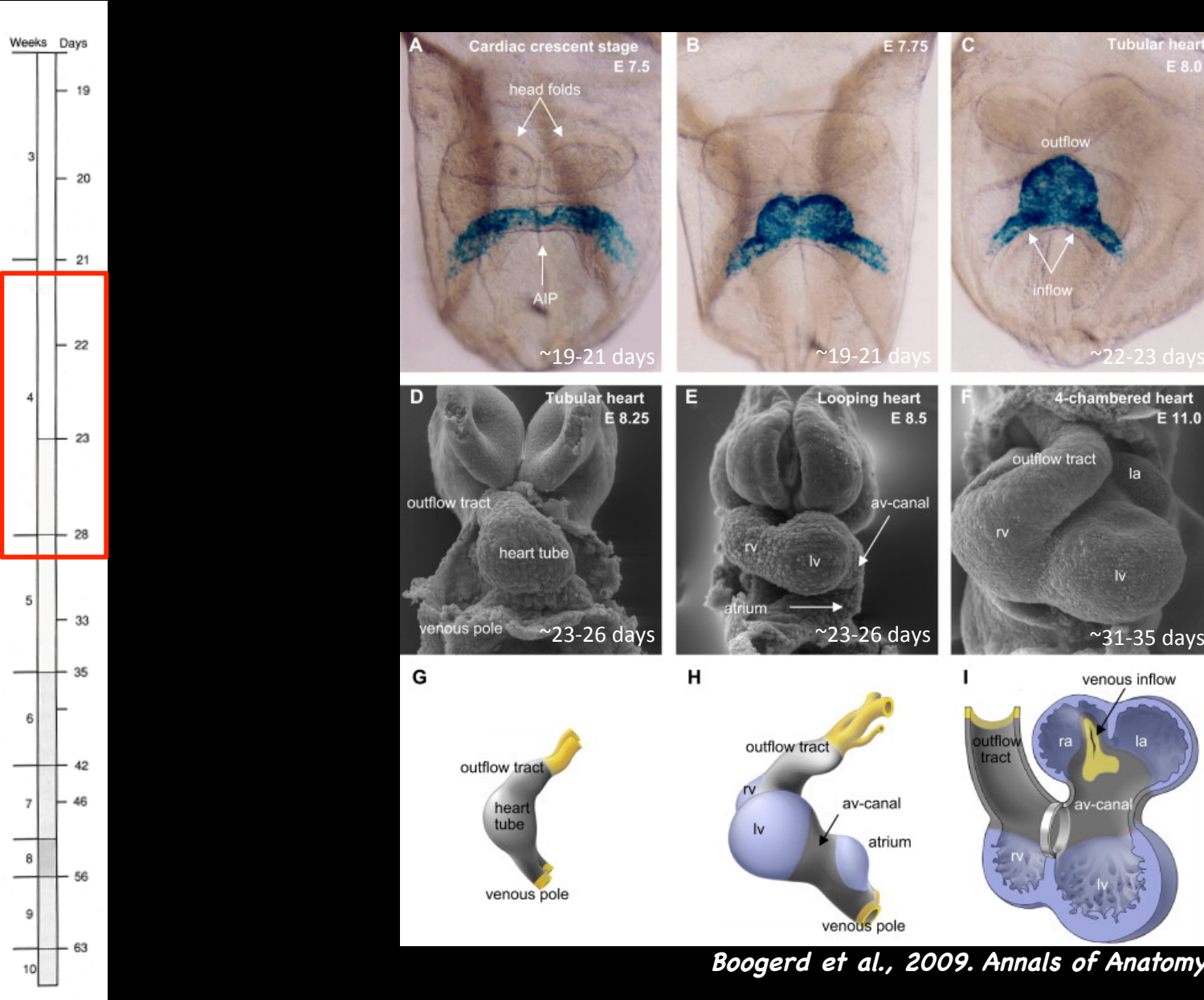
## 2) Cardiac Tube Formation

### 2.1) Linear Heart Tube Formation



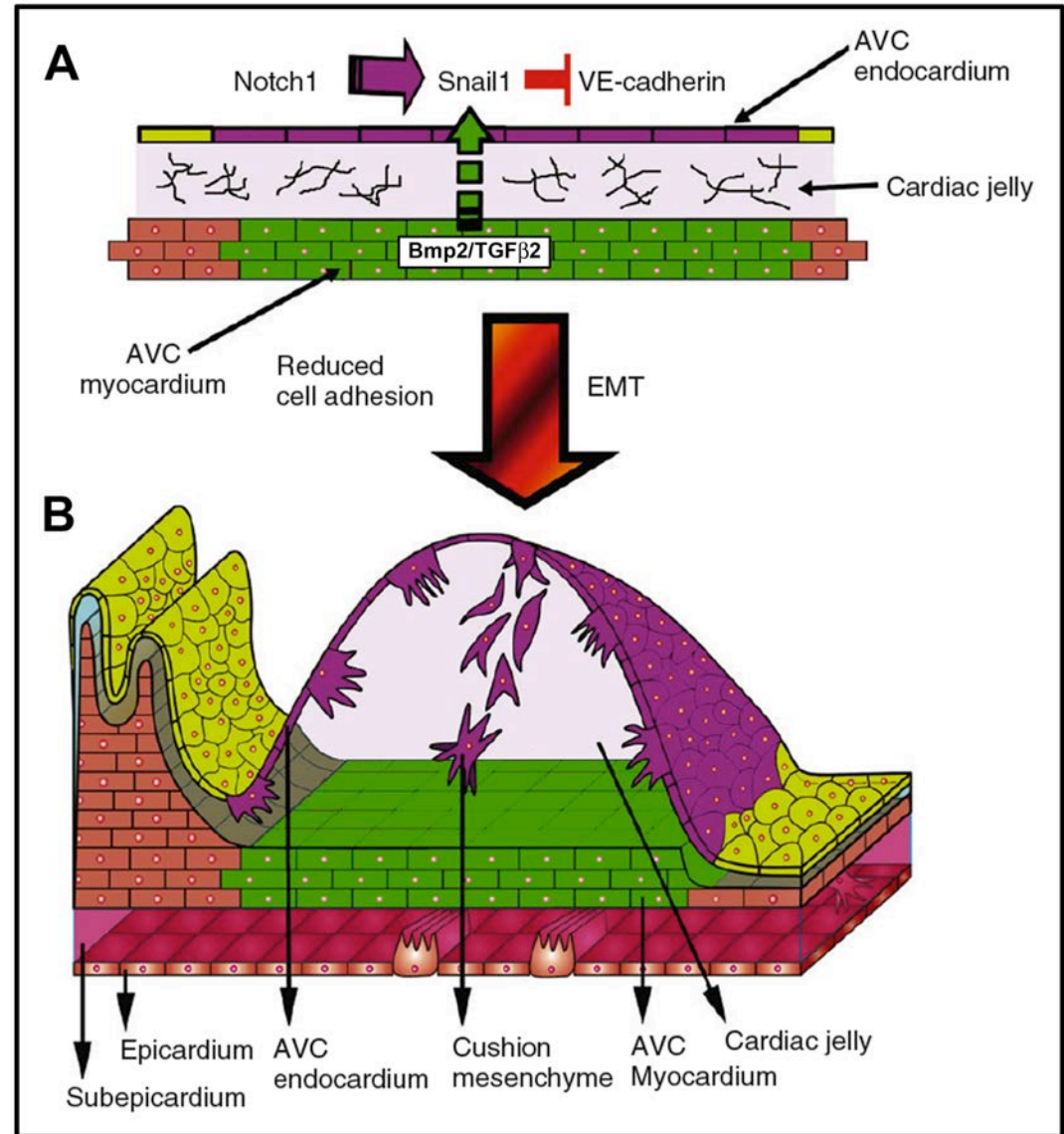
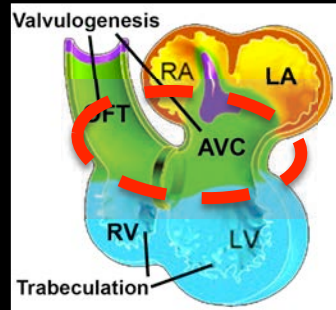
## 2) Cardiac Tube Formation

### 2.2) Cardiac Looping. Inner Curvature-Outer Curvature.



# 3) Valvulogenesis and Chamber Development

## 3.1) Valve Formation

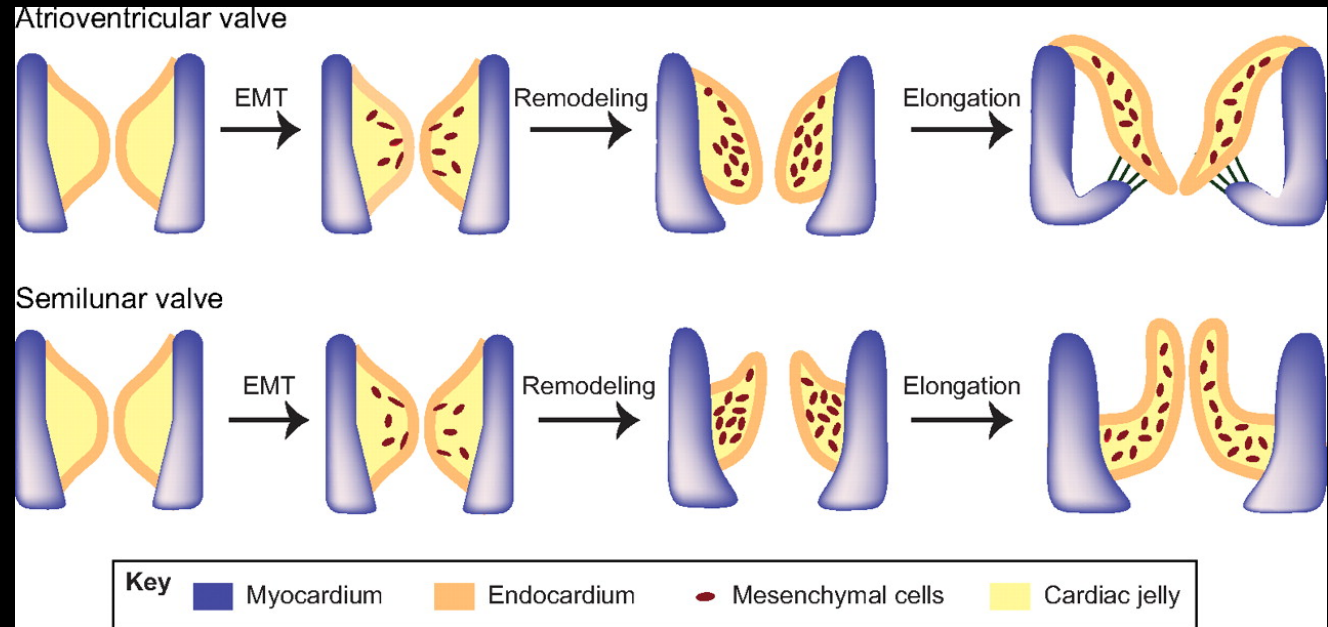
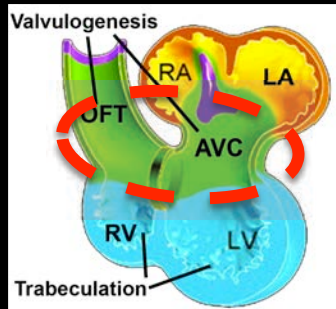


Modified from Macgrogan et al., 2010

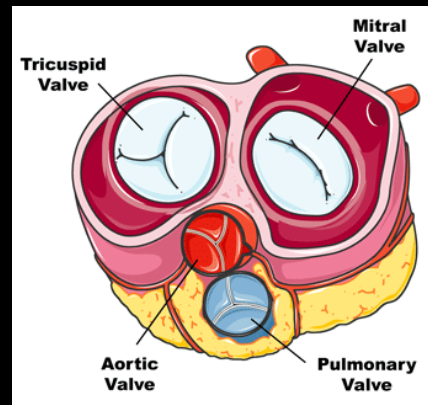


# 3) Valvulogenesis and Chamber Development

## 3.2) Valve Maturation

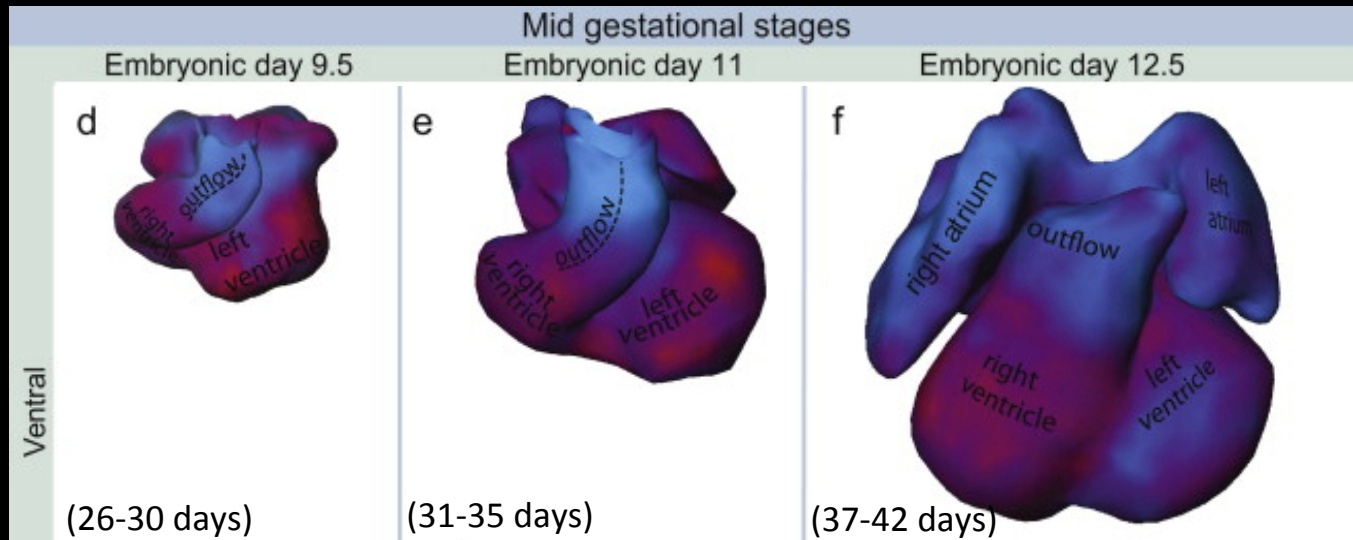
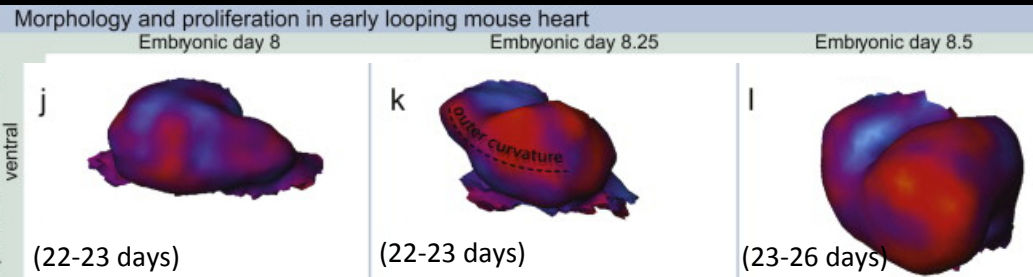
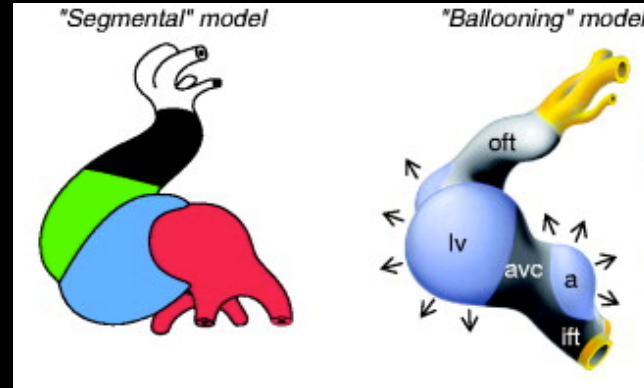
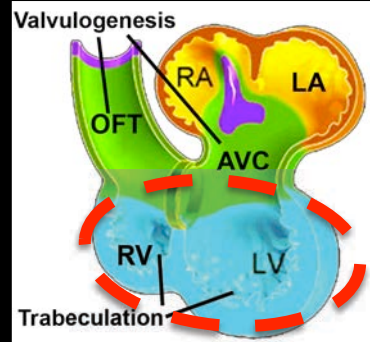


*Chien-Jung et al., 2012. Development*



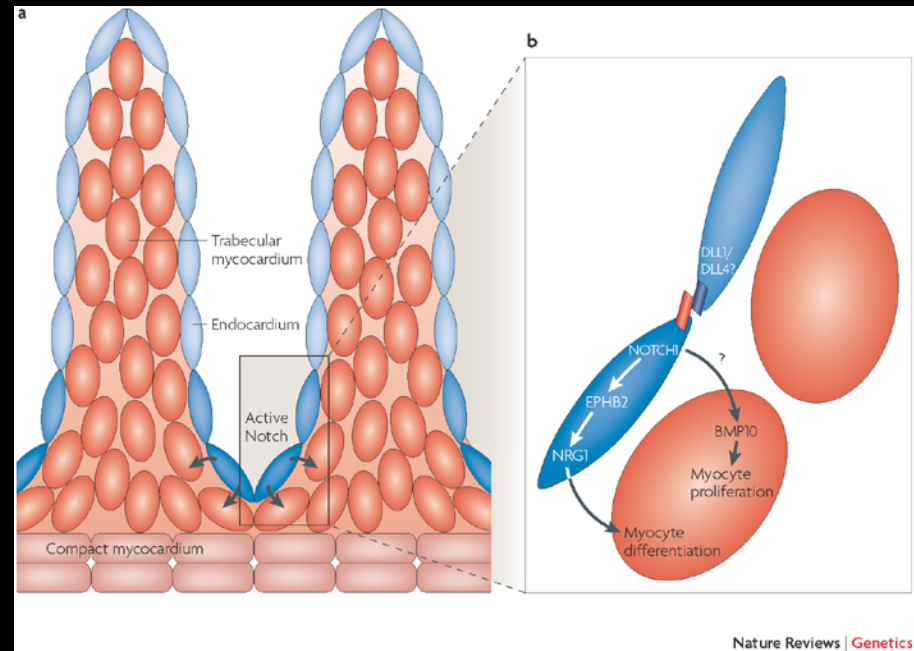
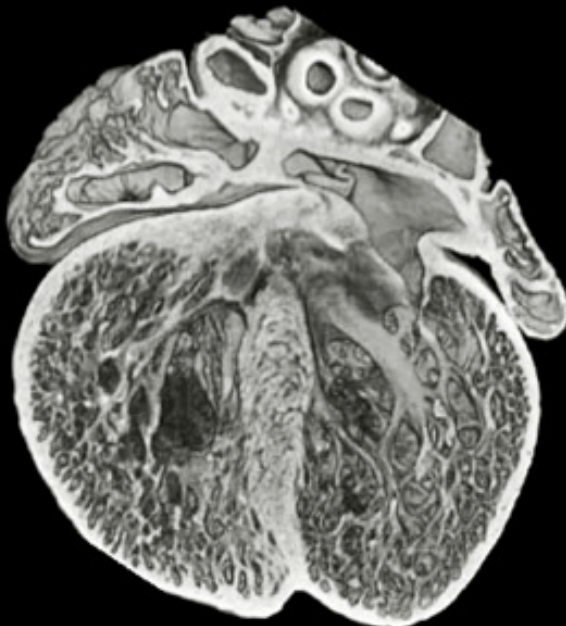
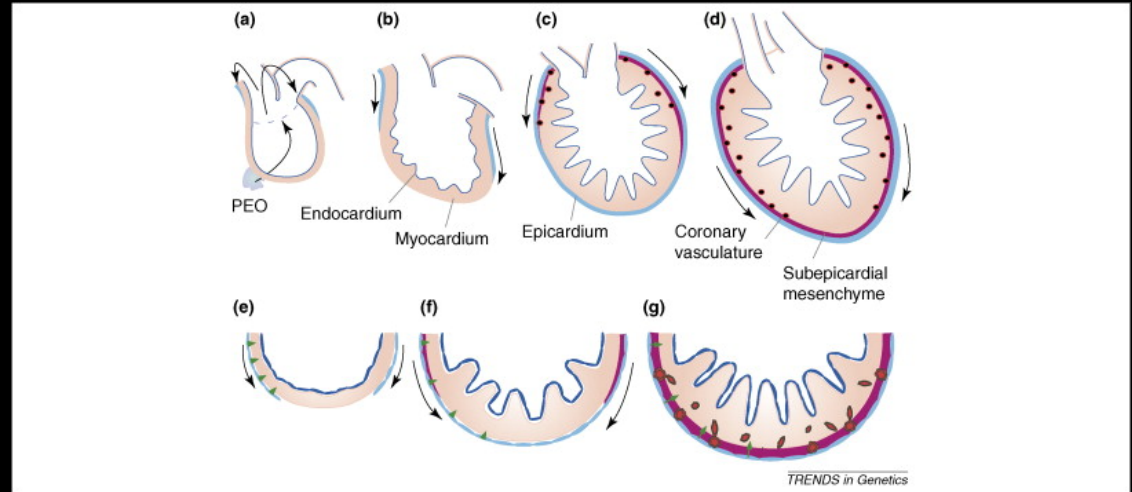
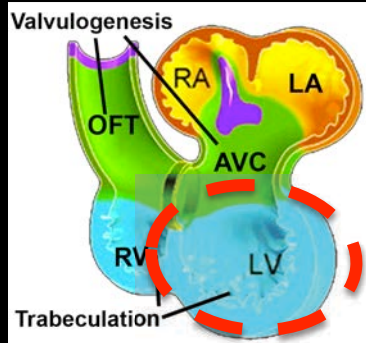
# 3) Valvulogenesis and Chamber Development

## 3.3) Chamber Development



# 3) Valvulogenesis and Chamber Development

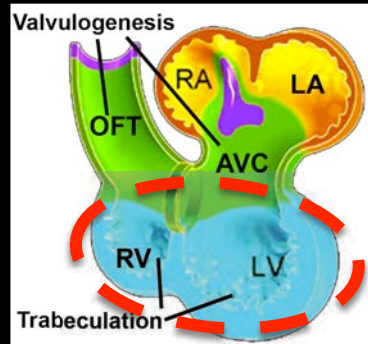
## 3.4) Trabeculation



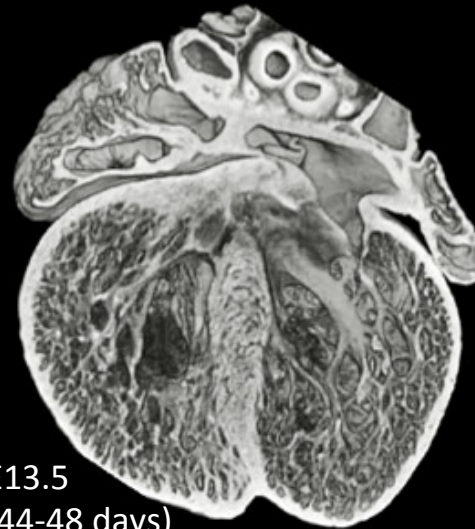


# 3) Valvulogenesis and Chamber Development

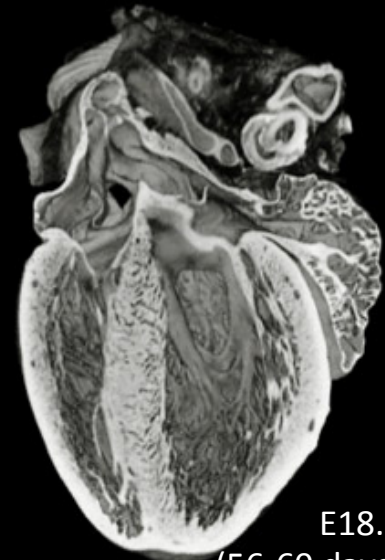
## 3.5) Trabecular Compaction and Papillary Muscle Development



### Trabecular Compaction

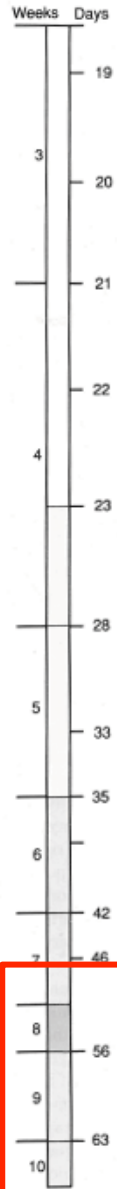
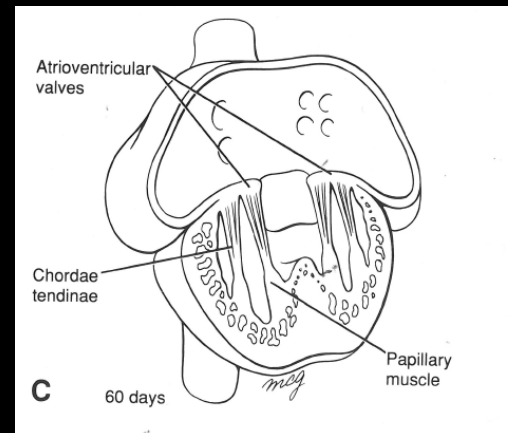
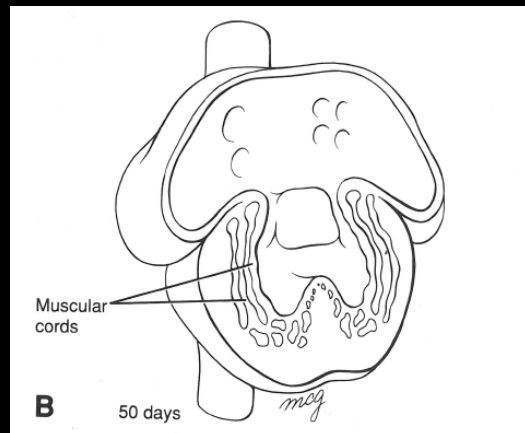
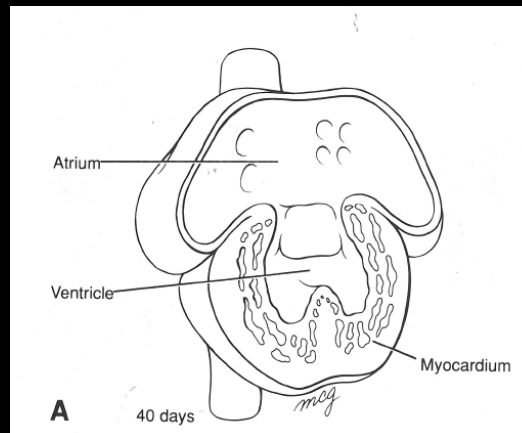


E13.5  
(44-48 days)



E18.5  
(56-60 days)

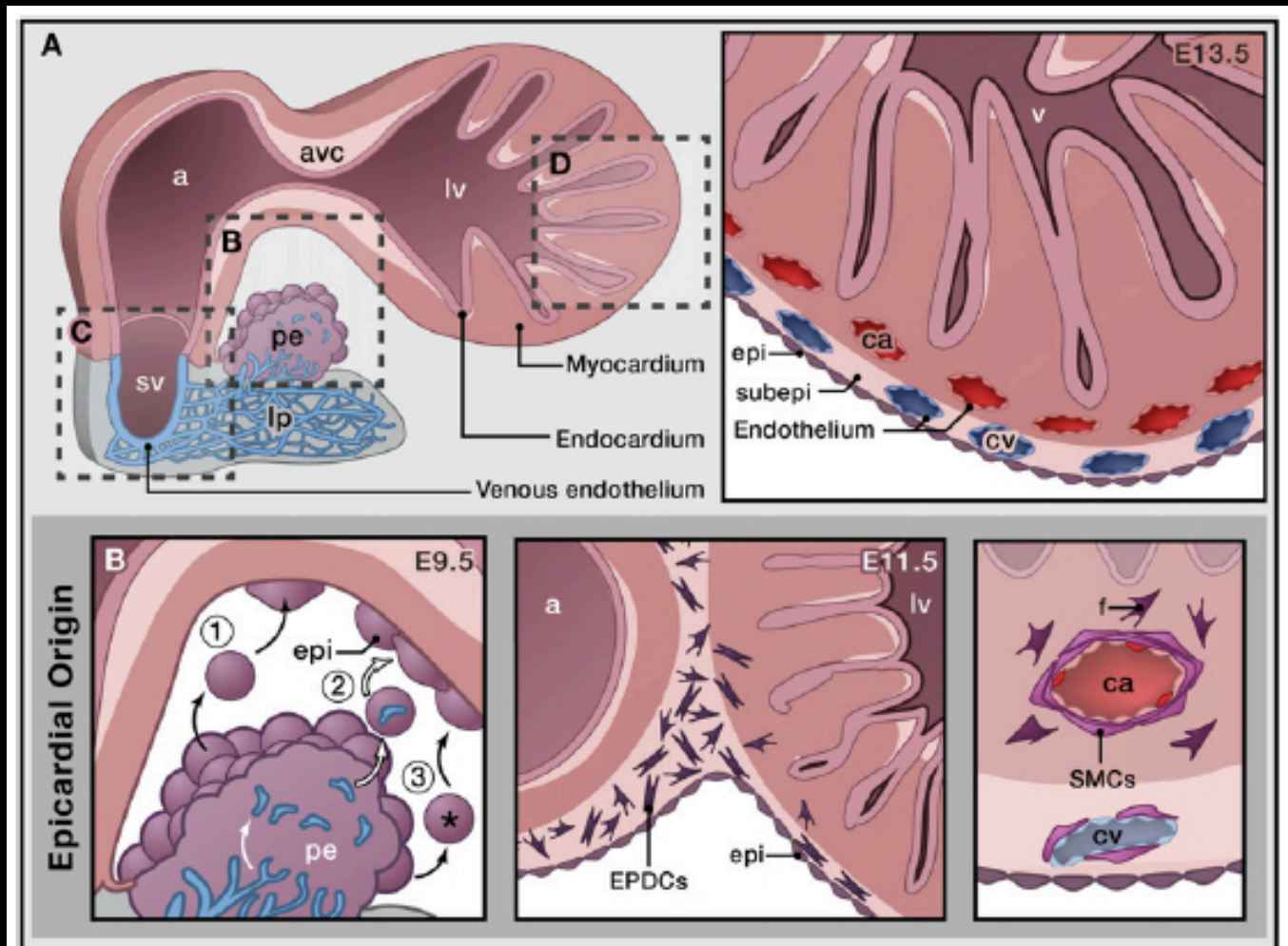
### Papillary Muscle Development





# 4) Epicardium Development

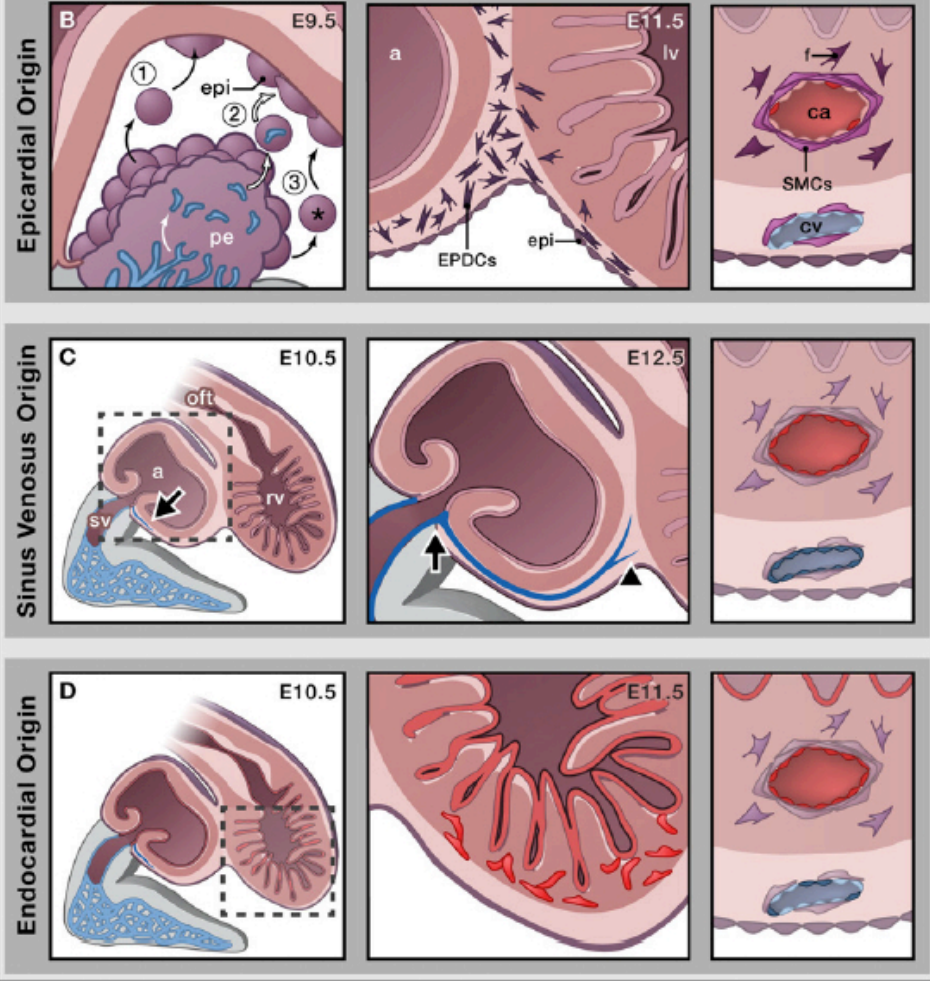
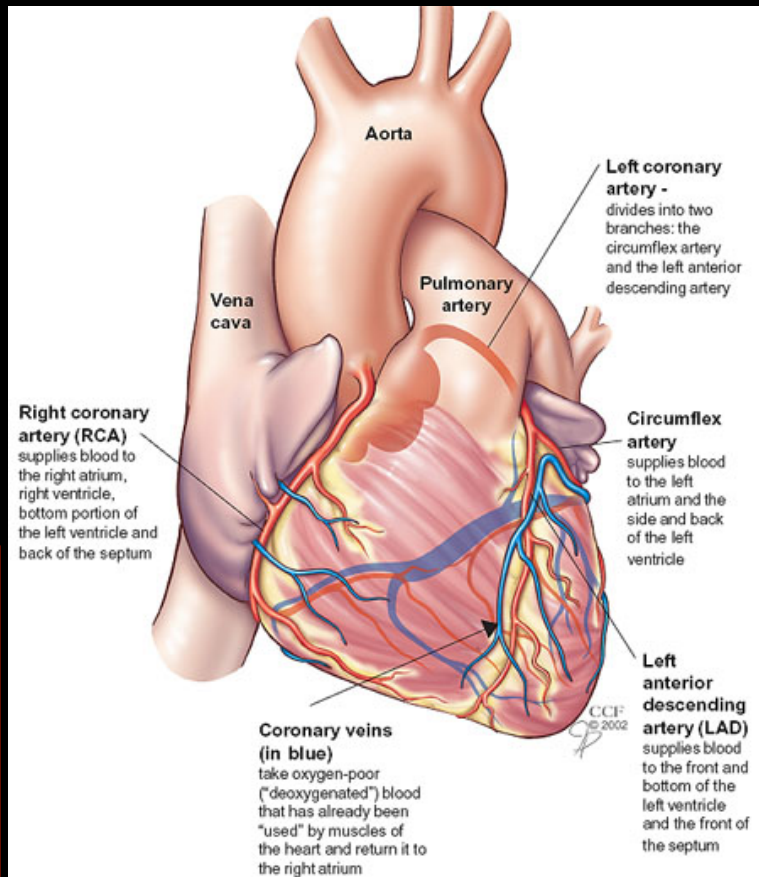
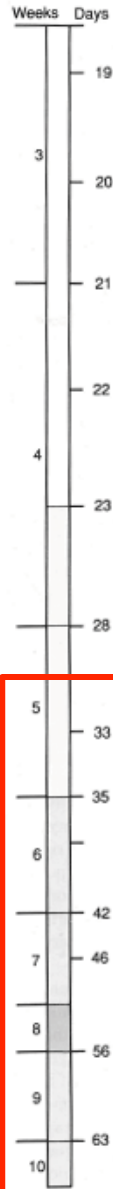
## 4.1) Epicardium Origin



*Del Monte et al., Cell 2012*

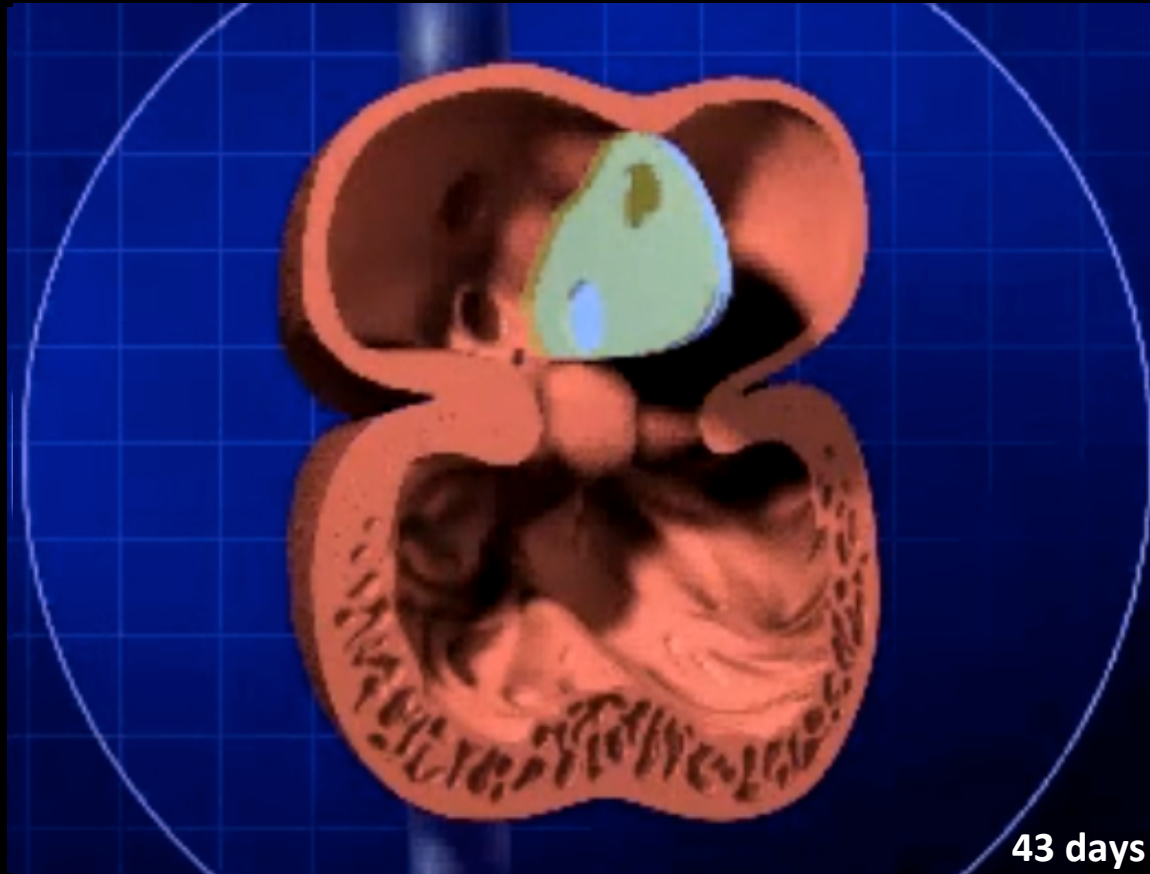
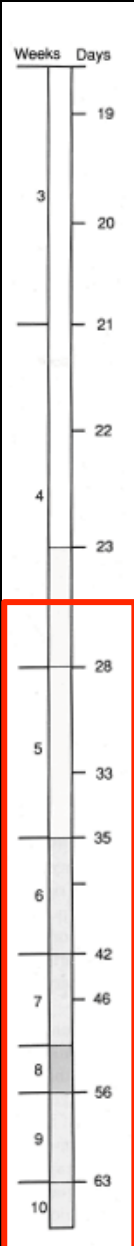
# 4) Epicardium Development

## 4.2) Coronary Vessels

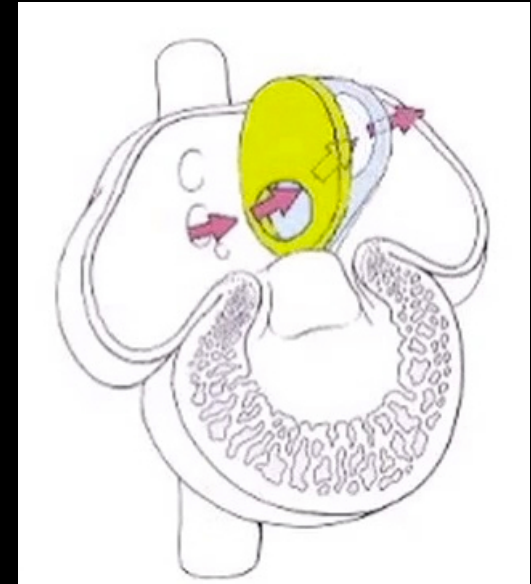


# 5) Septation and Maturation

## 5.1) Atrial Septation



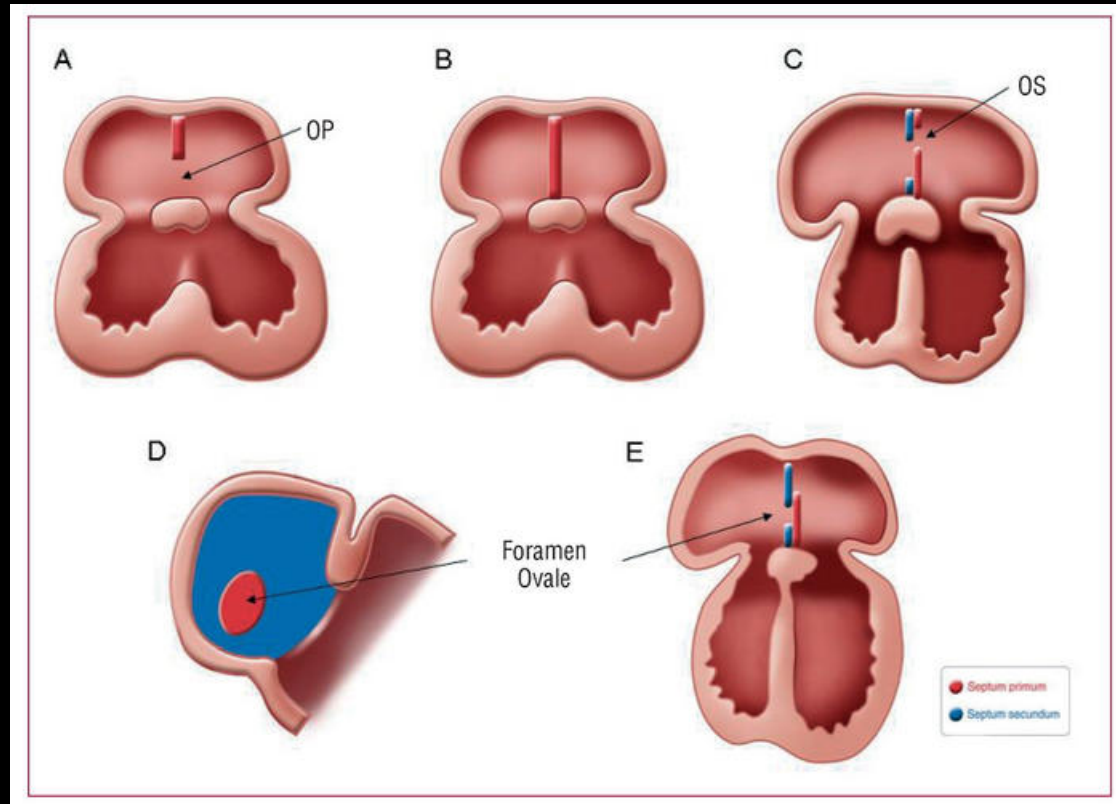
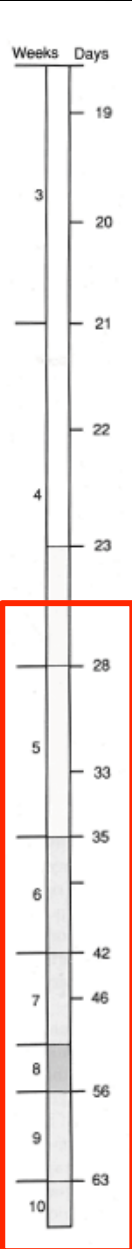
43 days





# 5) Septation and Maturation

## 5.2) Ventricular Septation and Maturation

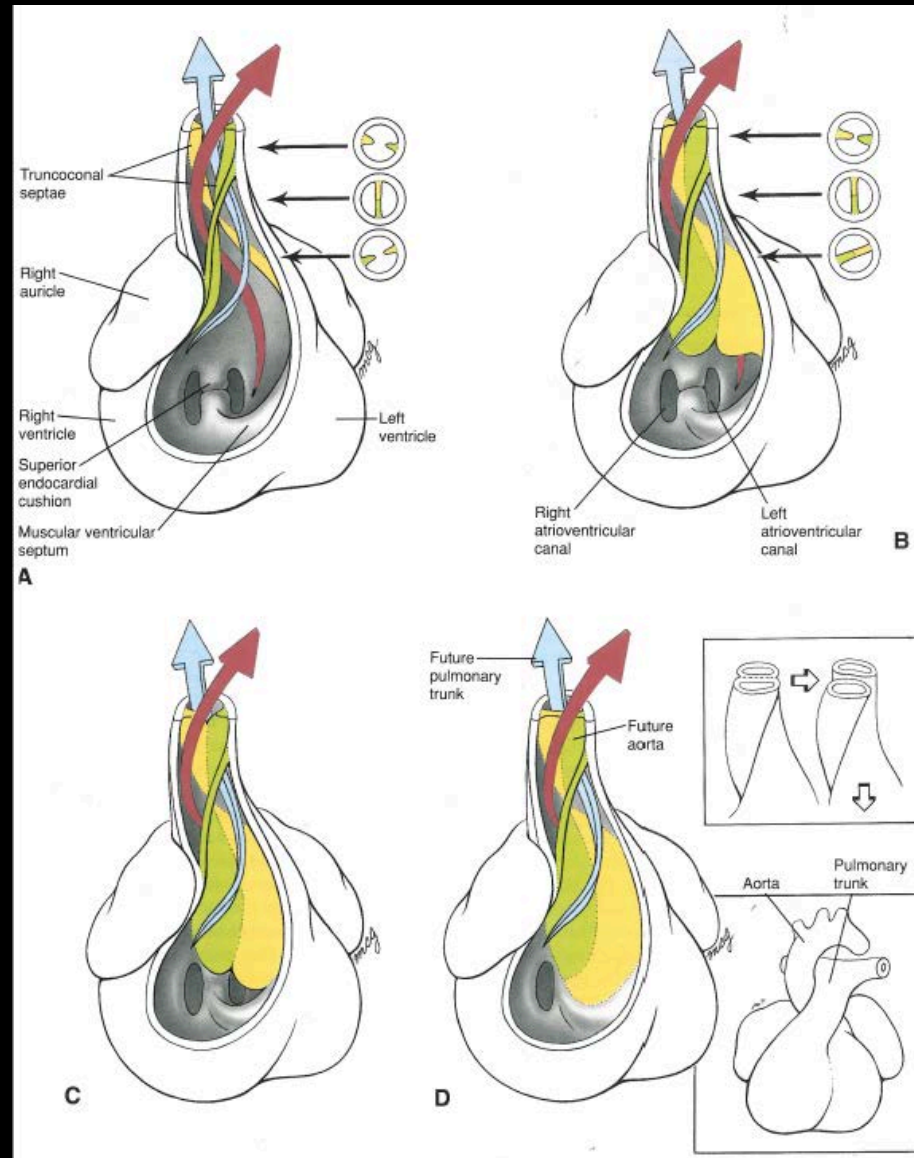
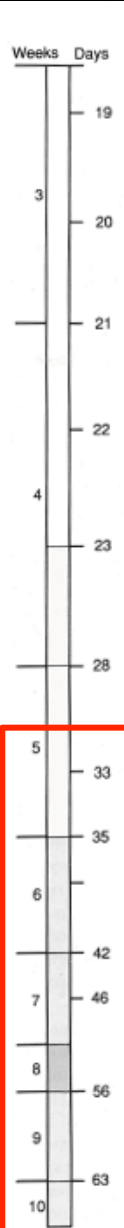


*Cruz-Gonzalez et al., 2008. Rev. Esp. Cardiol.*



# 5) Septation and Maturation

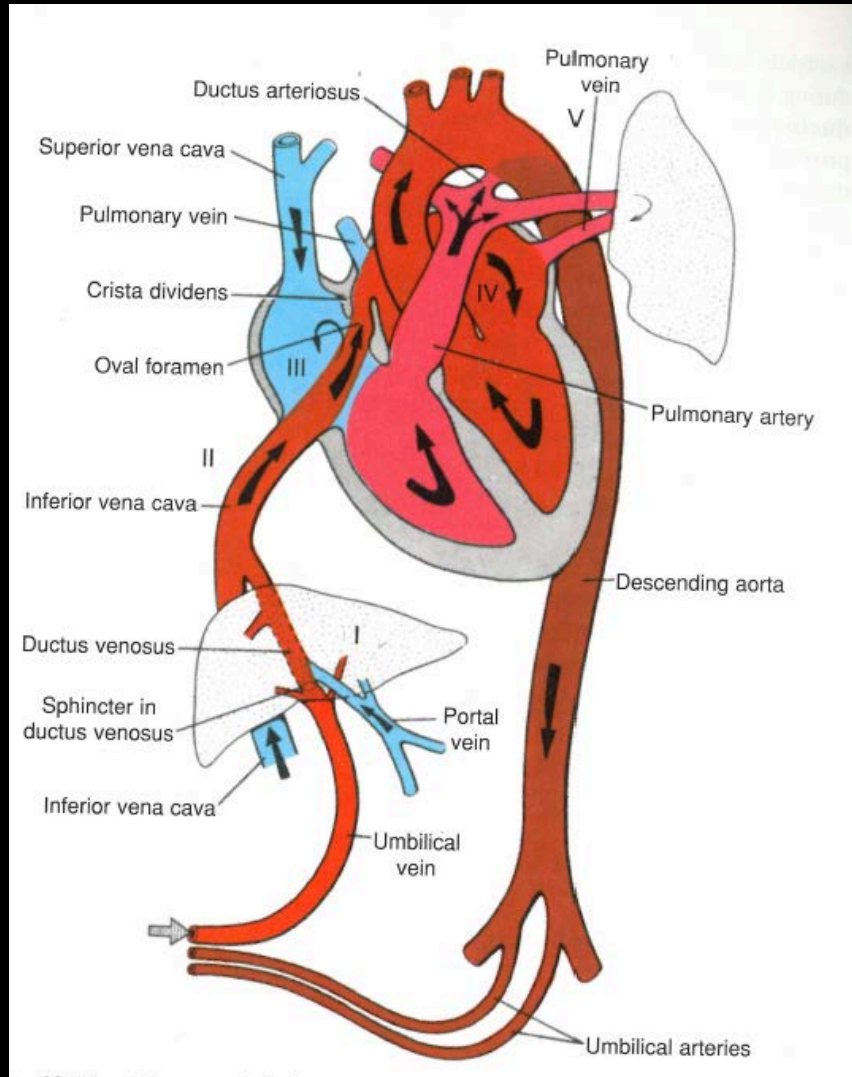
## 5.3) Outflow Tract Septation



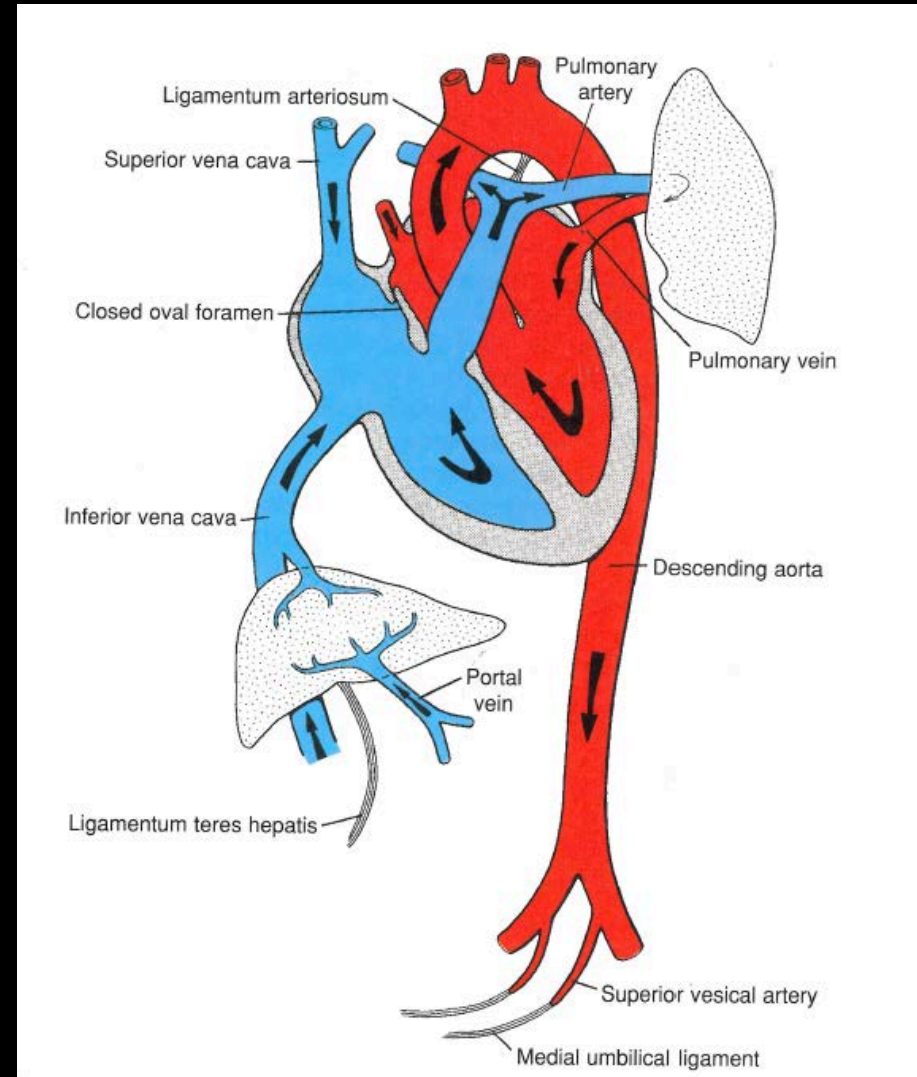
# 6) Changes in Blood Flow During Development

## 6.2) Changes in Blood Flow after Birth

### Before Birth



### After Birth



## **7) Cardiovascular Developmental Abnormalities**

### **Congenital Heart Disease (CHD)**

**ASD: Atrial Septal Defect**

**VSD: Ventricular Septal Defect**

**AVSD: Atrioventricular Septal Defect**

**DORV: Double Outlet Right Ventricle**

**TGA: Transposition of the Great Arteries**

**PDA: Patent Ductus Arteriosus**

**TOF: Tetralogy Of Fallot**

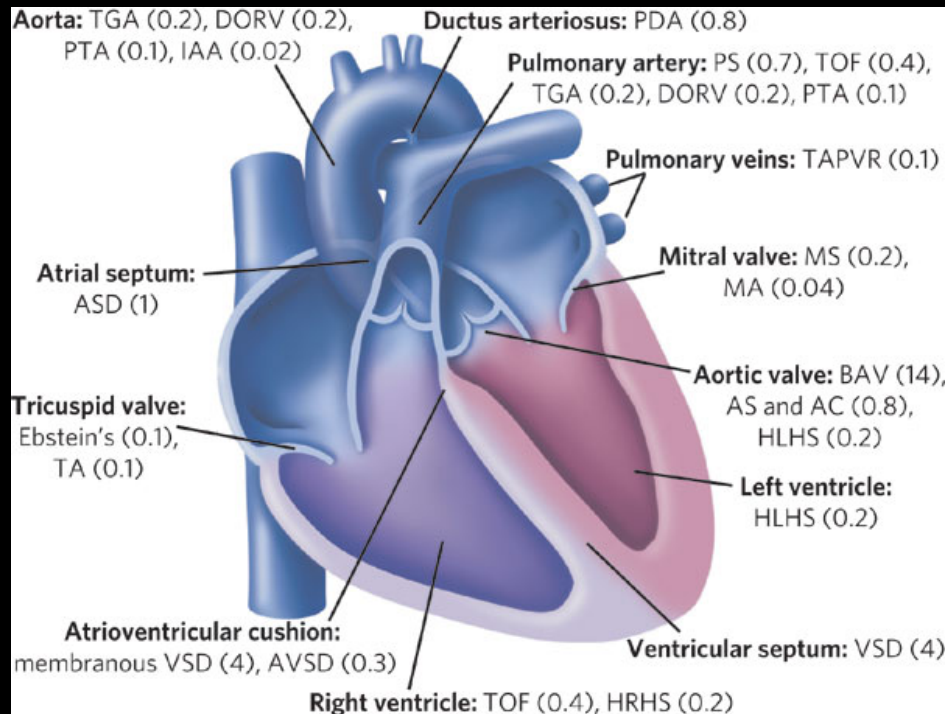
**HLHS: Hypoplastic Left Heart Syndrome**

[http://www.rch.org.au/cardiology/heart\\_defects/](http://www.rch.org.au/cardiology/heart_defects/)

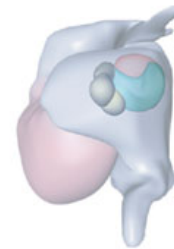
# 7) Cardiovascular Developmental Abnormalities

## Congenital Heart Disease (CHD)

Estimated incidence of each disease per 1,000 live births



Atrial septation



**ASD:** NKX2-5  
GATA4  
TBX20  
MYH6  
TBX5

Ventricular septation and  
atrioventricular cushion  
formation

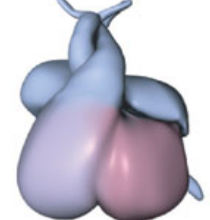


**VSD:** NKX2-5  
GATA4  
TBX20  
TBX1  
TBX5

**AVSD:** PTPN11  
KRAS  
SOS1  
RAF1  
CRELD1

**Ebstein's, TA:** NKX2-5

Great vessel formation  
and valvulogenesis



**DORV, TGA:** NKX2-5  
THRAP2

**PTA:** TBX1

**TOF:** NKX2-5,  
NOTCH1  
TBX1  
JAG1  
NOTCH2

**AS and AC:** NOTCH1  
PTPN11

**PS:** PTPN11  
JAG1  
NOTCH2

**BAV:** NOTCH1

**HLHS:** NOTCH1

**PDA:** TFAP2B

*Bruneau et al., 2008.Nature*

Australia 2009

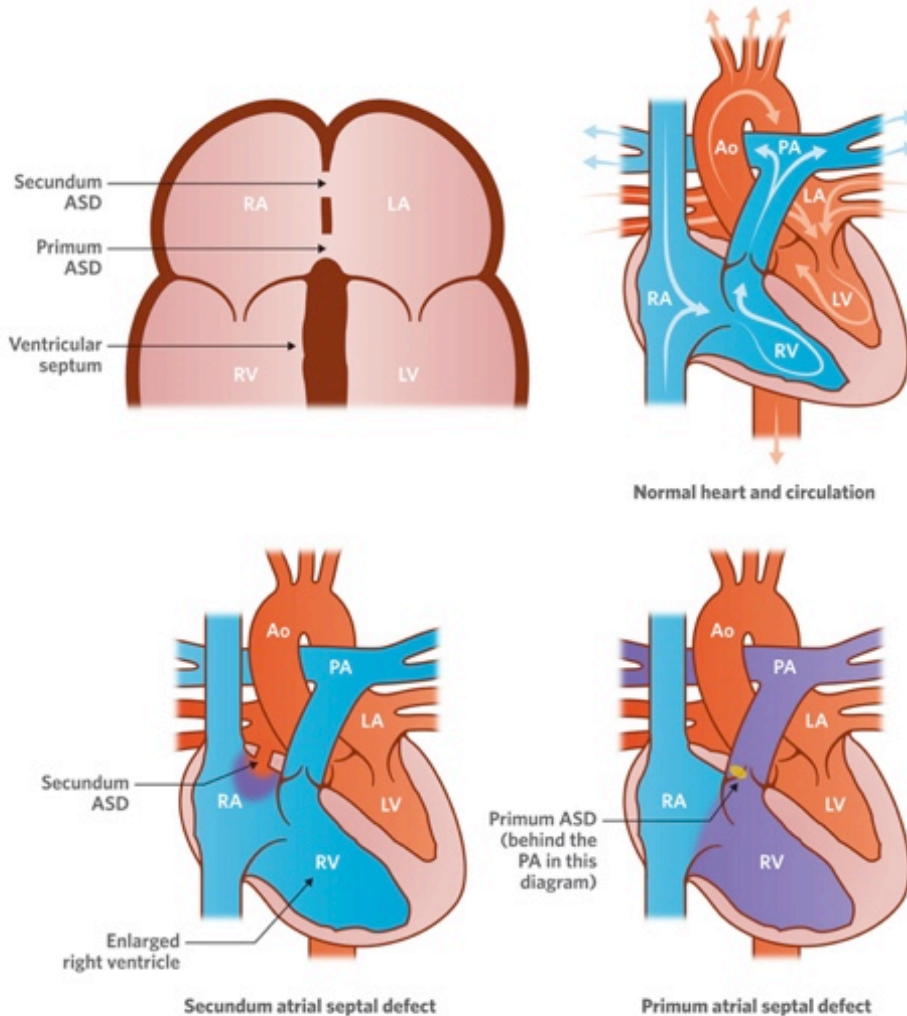
72800 fetal deaths / 3066 CHDs  
274000 live births / 1650-7400 CHDs



# 7) Cardiovascular Developmental Abnormalities

## Atrial Septal Defect (ASD)

Atrial septal defect (ASD)

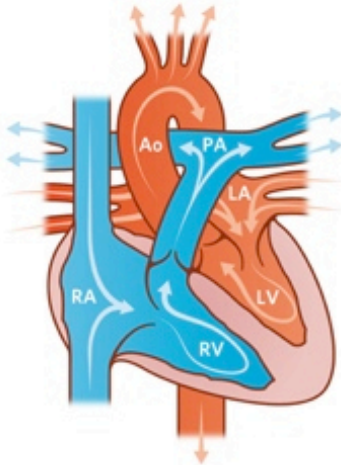


- 1/1000 live births. More often in females.
- ASD allows red blood to pass through into the right side of the heart, leading to enlargement of the Right Ventricle and excessive flow in the lung circulation.
- Types:
  - Patent Foramen Ovale
  - Secundum ASD
  - Primum ASD
  - Common Atrium
- Closed by a Catheter Procedure

# 7) Cardiovascular Developmental Abnormalities

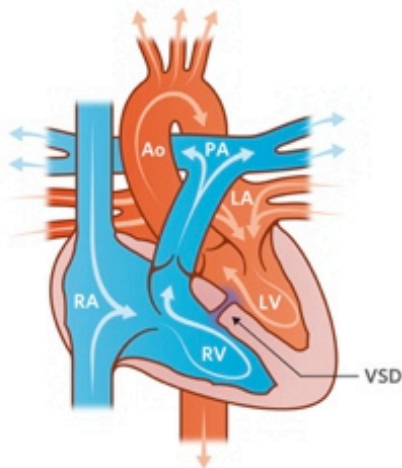
## Ventricular Septal Defect (VSD)

Ventricular septal defect (VSD)

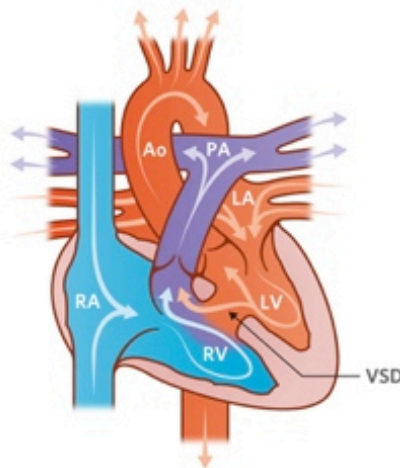


Normal heart and circulation

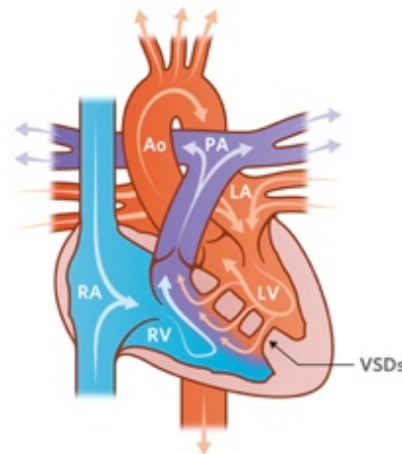
- 8/1000 live births. More frequent in males.
- VSD usually occurs in the membranous component rather than the muscular component.
- Closed by a Catheter Procedure



Small VSD



Large VSD

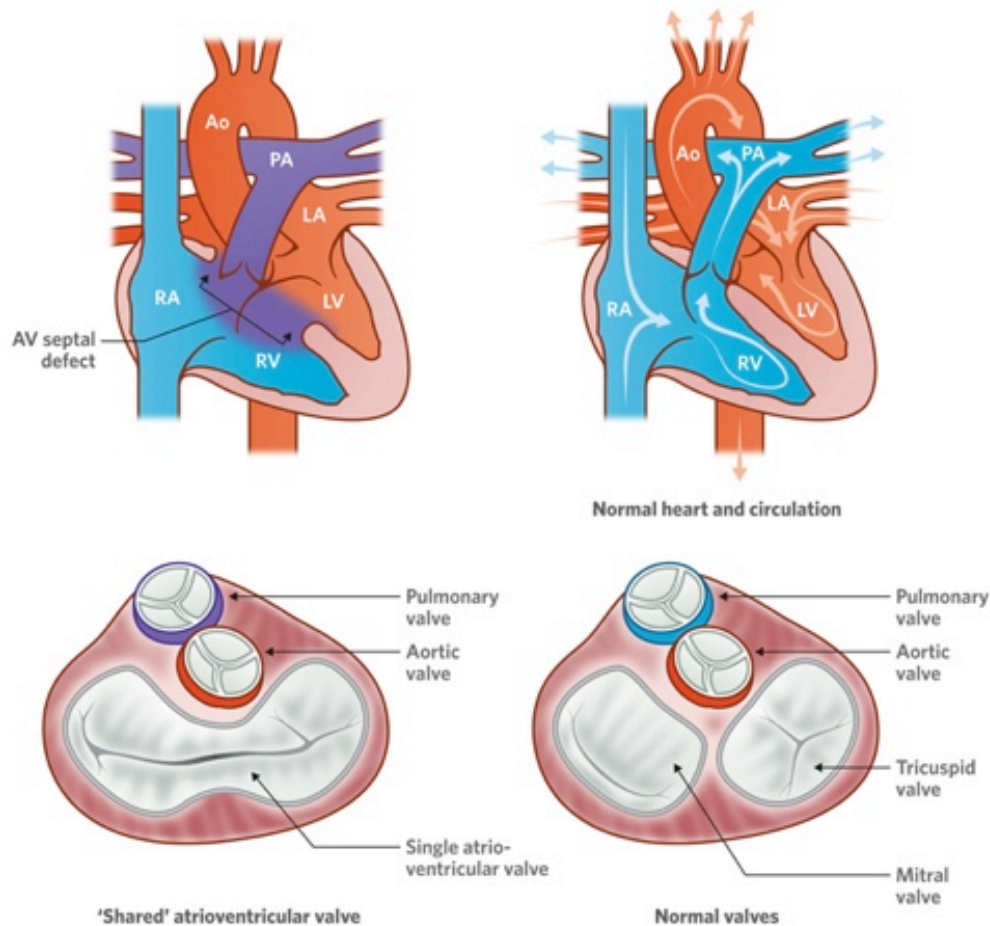


Multiple VSDs

# 7) Cardiovascular Developmental Abnormalities

## Atrioventricular Septal Defect (AVSD)

Atrioventricular septal defect



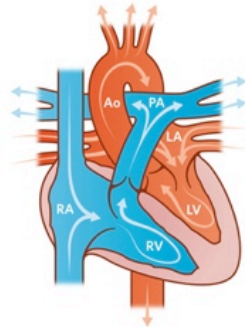
© The Royal Children's Hospital, Melbourne, Australia

- Common in babies with Down syndrome.
- A large defect involving both the atrial (ASD) and the ventricular (VSD) septums allows blood to pass freely between the two ventricles and the atriums.
- Repair performed by surgery in the first 3 to 6 months of life.

# 7) Cardiovascular Developmental Abnormalities

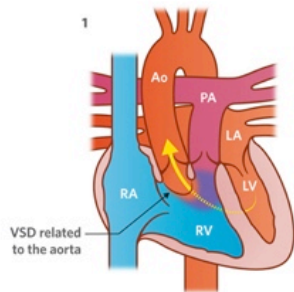
## Double Outlet Right Ventricle (DORV)

Double outlet right ventricle (DORV)

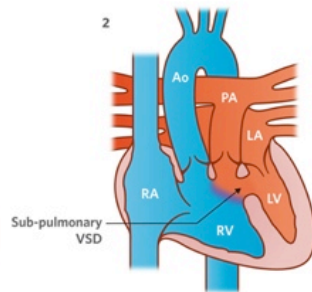


Normal heart and circulation

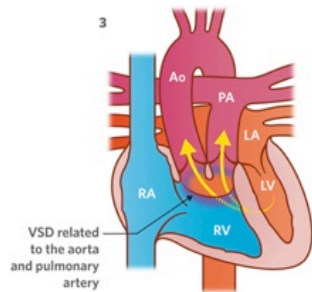
- 0.1/1000 births
- The two great arteries (Aorta and Pulmonary Artery) originate from the right ventricle and blood from the left ventricle passes across a VSD into the RV to reach the great arteries.
- Repair performed by surgery.



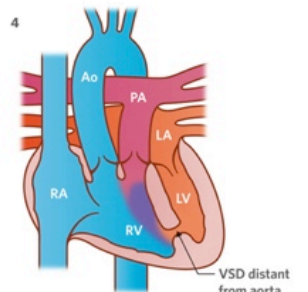
Sub-aortic VSD



Sub-pulmonary VSD



Doubly committed VSD

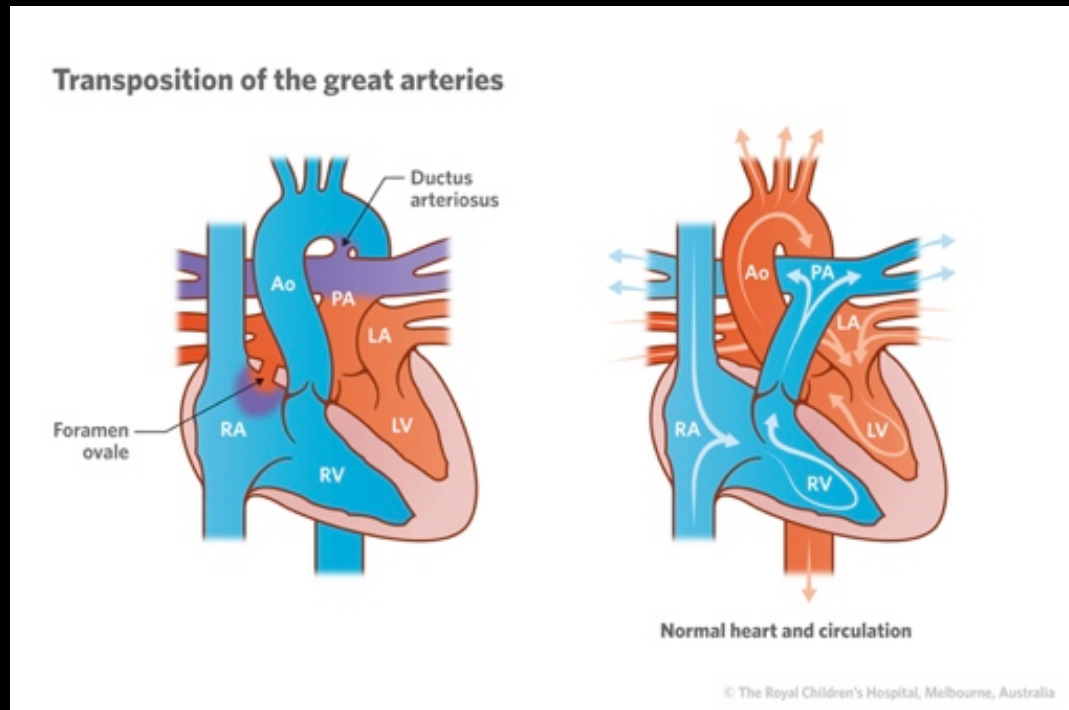


Non-committed VSD



# 7) Cardiovascular Developmental Abnormalities

## Transposition of the Great Arteries (TGA)

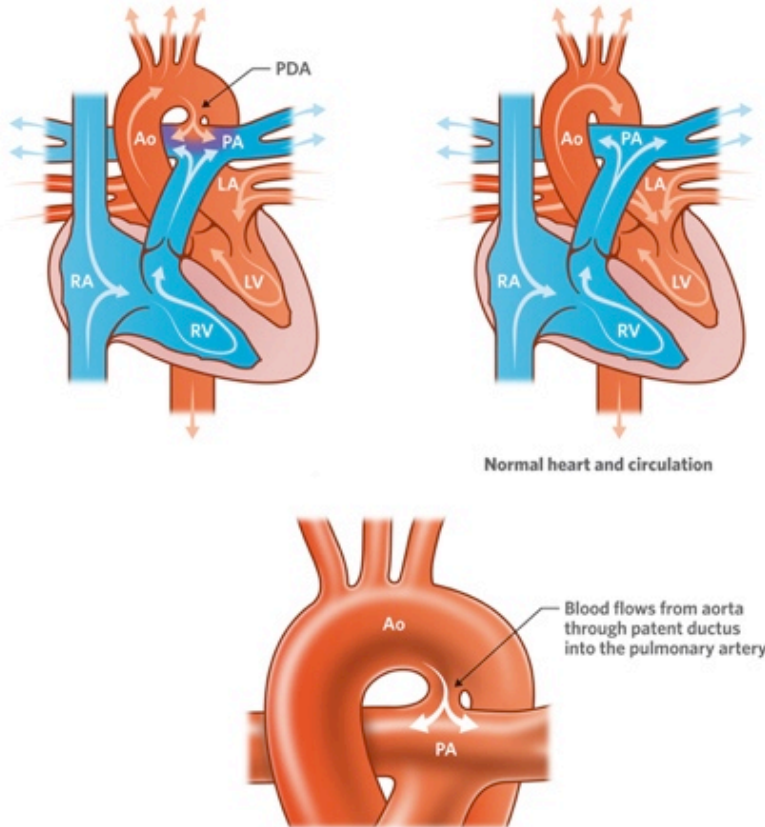


- 0.28-0.2/1000 births
- The Aorta arises from the right ventricle, whilst the Pulmonary Artery arises from the left ventricle.
- Early surgery is essential and involves the "Arterial Switch Operation", which is carried out in the first week or two of life and corrects the abnormality. The coronary arteries, which feed the heart muscle with blood, need to be transferred as well.

# 7) Cardiovascular Developmental Abnormalities

## Patent Ductus Arteriosus (PDA)

Patent ductus arteriosus (PDA)

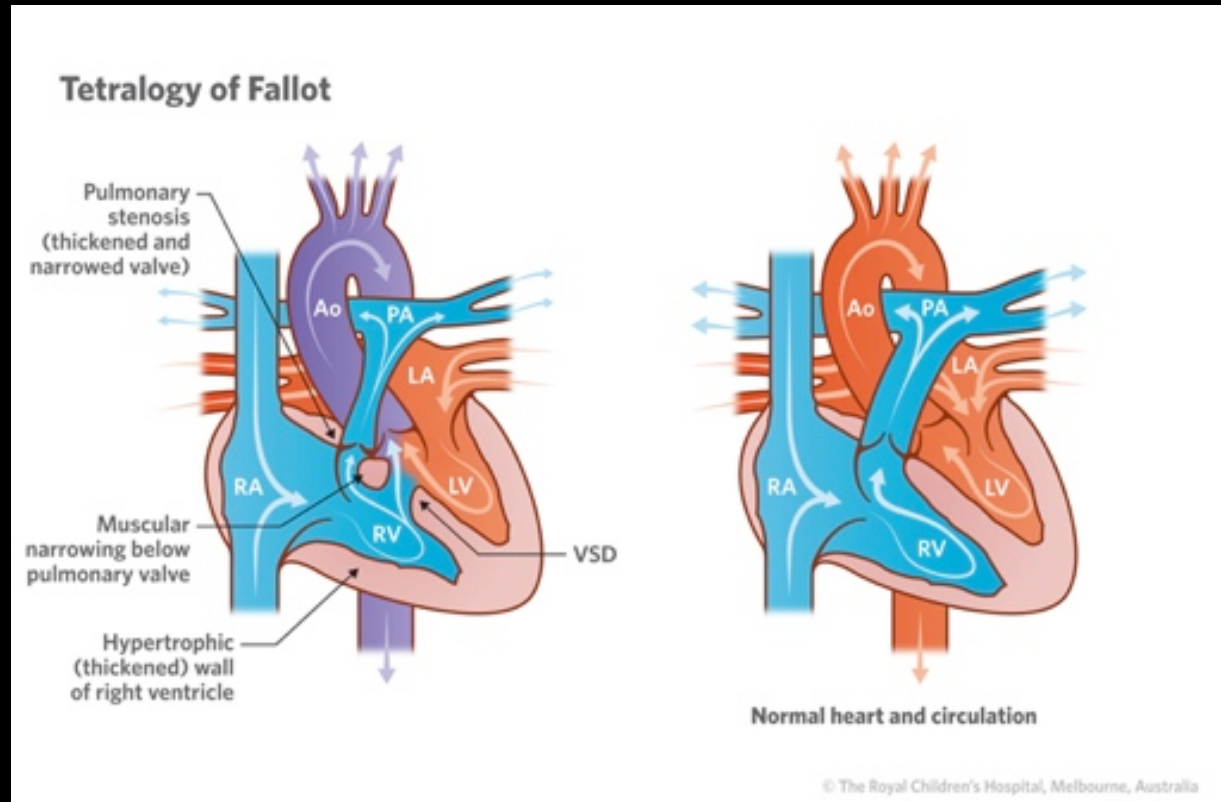


© The Royal Children's Hospital, Melbourne, Australia

- 0.81/1000 Births
- Failure of the ductus to close in the early weeks of life. This allows blood to flow between the aorta and the pulmonary artery, leading to an increase in flow in the lung circulation.
- PDA can be treated with both surgical and non-surgical methods. Surgically, the Ductus Arteriosus may be closed by ligation. Non-surgical methods include intravascular coils or plugs.

# 7) Cardiovascular Developmental Abnormalities

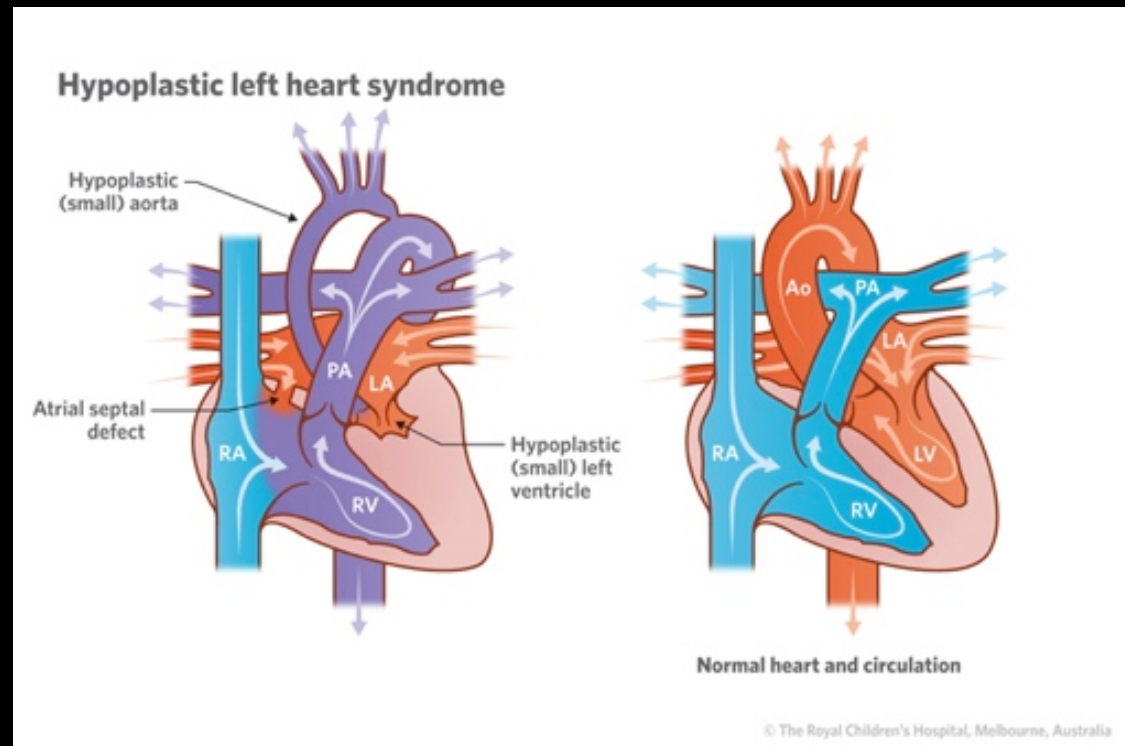
## Tetralogy of Fallot



- 0.4/1000 Births
- Combination of 4 defects: Ventricula Septal Defect, Pulmonary Stenosis, Overriding Aorta and Right Ventricle Hypertrophy.

# 7) Cardiovascular Developmental Abnormalities

## Hypoplastic Left Heart Syndrome



- 0.23/1000 Births.
- The left side of the heart is very poorly formed and cannot support the main circulation. The left ventricle and aorta are abnormally small (hypoplastic). This is amongst the most severe forms of heart defect.
- Recently described to be caused by abnormal blood flow conditions during development.



# Heart Development and Congenital Heart Disease

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[g.delmonte@victorchang.edu.au](mailto:g.delmonte@victorchang.edu.au)

Developmental and Stem Cell Biology Division  
Victor Chang Cardiac Research Institute