Heart Development and Congenital Heart Disease

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four chambered heart

 ascending aorta
 vena cava
 right atrium
 right ventricle

 pulmonay artery

 ascending aorta
 vena cava
 right atrium
 right ventricle

 left atrium
 left ventricle

 pulmonary artery

 left atrium
 left ventricle
Lecture objectives

- Describe how the first and second heart fields contribute to the heart
- Explain how endocardial cushion formation contributes to chamber formation
- Describe the development of primary and secondary atrial septa and the ventricular septum
- Compare prenatal and postnatal blood flow and the changes that occur at birth
- Explain the changes occurring in the outflow tract as it transforms from a single to a double tube
- Describe the major cardiovascular developmental abnormalities.
cardiac crescent and linear heart tube - 20 to 21 days

inner endocardium
outer myocardium
heart tube looping and regionalisation - 23 to 28 days

- **linear heart tube and layers of heart**

  - **pericardium** - covers the heart, formed by 3 layers consisting of a fibrous pericardium and a double layered serous pericardium (parietal layer and visceral epicardium layer).

  - **myocardium** - muscular wall of the heart, thickest layer formed by spirally arranged cardiac muscle cells.

  - **endocardium** - lines the heart, epithelial (endothelial) tissue lining the inner surface of heart chambers and valves.
Constrictions (sulci) and expansions form over 5 weeks as tubular heart lengths. Expansions contribute to the chambers.

- **Rostral**
  - Outflow tract
  - Bulbus cordis
  - Primitive ventricle
  - Sinus venosus
  - Cardinal veins
  - Blood inflow

- **Caudal**
  - Rostral & truncus arteriosus
  - Right ventricle
  - Left ventricle
  - Right & left atrium
  - Sinus venosus
  - Cardinal veins
  - Blood inflow

**Truncus arteriosus**
- Split into ascending aorta & pulmonary artery

**Conus arteriosus**
- Incorporated into ventricle
first and second heart fields - cardiac progenitor populations

first heart field (primary) = linear heart tube

second heart field (secondary) = dorsal to heart tube

How was this worked out?

label cells with lipophilic dye
culture embryo
see where these labelled cells and their progeny end up

first and second heart fields

examine transcript localisation by RNA in situ hybridisation

Waldo et al Dev 2001

Cai et al Dev Cell 2003
growth factor=
Fgf8
Fgf10
BMP
Wnt11
Shh

transcription factors

Nkx2.5 required for deployment of second heart field

Nkx2-5 required for deployment of second heart field
Septation is necessary to separate the systemic and pulmonary circulations.

- Partial separation of definitive atria, ventricles and division of the atrioventricular canal into right and left canals
- Endocardial cushions and muscular septum
Endocardial Cushions

- form initial division of atria and ventricles
- form on dorsal and ventral wall of atrioventricular canals
- grow into canal - meet and fuse to separate atrioventricular canal into right and left channels
- anterior and posterior cushions fuse; lateral cushions remain unfused
**signaling network model for heart valve development and remodeling**

![Diagram showing the signaling network model for heart valve development and remodeling](image)

- **endocardium**
- **myocardium**
- **growth factors**
  - Wnt/β-Cat
  - TGFβ
  - VEGF
  - HA
  - BMP
- **transcription factors**
  - NFATc1
  - ErbB2/3
  - HB-EGF
  - EGFR
  - Ras

**septation- atrial septation**

- Mature interatrial septum is formed by fusion of two muscular septum (primum and secundum). Thus blood does not pass from the right atrium to the left atrium.
- Each has large openings allowing right-to-left shunting of blood throughout gestation.
- Shunting permits oxygenated blood from the umbilicus to bypass the developing pulmonary system and enter the systemic system.
septation - atrial septation

- septum primum
- septum secundum

poor understanding of genes required for atrial septation
septation- atrial septation

septation- atrial septation
postnatal blood flow

de-oxygenated blood
right atrium
right ventricle
pulmonary artery
lungs

oxygenated blood
pulmonary veins
left atrium
left ventricle
ascending aorta
body

prenatal blood flow

oxygenated blood
right atrium
foramen ovale
left atrium
left ventricle
ascending aorta
body

de-oxygenated blood
right atrium
right ventricle
pulmonary artery
ductus arteriosus
ascending aorta
body
changes at birth

- at birth, cutting the umbilical cord and changes in the lungs after the first breaths trigger major functional adaptations in the fetal circulatory system
- blood flow through ductus venosus is eliminated
- pulmonary circulation bed expands - reducing blood flow through ductus arteriosus
- physiological closure of interatrial shunt
- closure of ductus venosus in liver is prolonged
outflow tract septation

- Initially, the outflow tract is a single tube, the bulbus cordis.
- It elongates to form the proximal conus arteriosus and distal truncus arteriosus.
- Two growths (endocardial cushion) form from the wall in a spiral pattern, inferior upwards, separating the tract into two channels.
- Mesenchyme and neural crest contribute to this septation process.
- Fusion of outgrowths separate the aortic and pulmonary outflow.

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
PTA: persistent truncus arteriosus
TOF: tetralogy of Fallot
HLHS: hypoplastic left heart syndrome

http://www.rch.org.au/cardiology/heart_defects/

congenital heart disease (CHD)

6-27 per 1,000 live birth

Australia
2009
72,800 fetal deaths
3066 CHDs
274,000 live births
1650-7400 CHDs
4 children die each week

44 per 1,000 fetal deaths

Australia
62,000 with CHD
50% >18yo
recurrence risk to offspring up to 6.7%

Hoffman (1995) Pediatr Cardiol


**genetic causes of CHD**

- Chromosomal (11.9%) and Mendelian syndromes (7.4%) account for CHD
- Non-syndromic large families with Mendelian inheritance patterns have identified CHD genes: ZIC3 (heterotaxy), NOTCH1 (aortic stenosis and bicuspid aortic valve), NKX2.5 (ASD), NKX2.6 (PTA/CAT), MYH6 (ASD), MYH11 (PDA), JAG1 (TOF), ACTC1 (ASD) and GATA4 (ASD)
- Non-Mendelian/non-chromosomal “sporadic” CHD account for the remaining 80%, the increased risk of CHD recurrence in siblings and offspring indicates a genetic component

**congenital heart disease (CHD)**

How do we identify the genes associated with these defects?

- familial: gene mapping
- non-familial: candidate gene
  - 316 genes associated with heart defects in mice
  - 276 genes associated with ASD in mice
  - 143 genes associated with VSD in mice
- understand developmental processes eg. SHF – OFT – aorta + pulmonary artery
congenital heart disease (CHD)

**Gene Expression**
- CITED2
- CRELD1
- EVC
- FOXH1
- FBN1
- GATA4
- GDF1
- HRAS
- CFC1
- ACVR2B
- ALK2
- ANKRD1
- BRAF
- ZIC3
- ACTC1
- TLL1
- THRAP2
- TCFAP2B
- TBX20
- TBX5
- TGFBR2
- SOS1
- RAFL
- PTPN11
- NOTCH1
- NOTCH2
- MYH6
- TOF
- TDGF1
- TGFBR2
- SOS1
- PTPN11
- NOTCH1
- NOTCH2

**Gene Expression**
- CITED2
- GATA4
- ZIC3
- MYH6
- NKX2-5
- TBX20
- TBX5
- ASD
- TOF

**Gene Expression**
- CITED2
- GATA4
- NOTCH2
- NOTCH1
- NKX2-5
- TBX1
- JAG1
- FOG2
- GDF1
- NODAL
congenital heart disease (CHD)

NKX2-5

DORV
TGA
PTA

ASD
Ebstein’s anomaly
tricuspid atresia

interrupted aortic arch
coarctation of the aorta

aortic stenosis
TOF
HLHS
VSD

congenital heart disease (CHD)

NKX2-5 R25C

DORV
TGA
PTA

ASD
Ebstein’s anomaly
tricuspid atresia

interrupted aortic arch
coarctation of the aorta

aortic stenosis
TOF
HLHS
VSD

no defect
Atrial Septal Defects (ASD) are a group of common (1% of cardiac) congenital anomalies defects occurring in a number of different forms and more often in females.

- patent foramen ovale - allows a continuation of the atrial shunting of blood, in 25% of people a probe patent foramen ovale (allowing a probe to bypassed from one atria to the other) exists.
- ostium secundum defect.
- endocardial cushion defect involving ostium primum
- sinus venosus defect - contributes about 10% of all ASDs and occurs mainly in a common and less common form. Common ("usual type") - in upper atrial septum which is contiguous with the superior vena cava. Less common - at junction of the right atrium and inferior vena cava.
- common atrium

1/1,000 live births

The Ventricular Septal Defect (VSD) usually occurs in the membranous (perimembranous) (70%) rather than muscular interventricular septum, and is more frequent in males than females.

- Perimembranous defects are located close to the aortic and tricuspid valves and adjacent to atrioventricular conduction bundle.
- The defect allows left-right shunting of blood, this shunting depends upon the size of the defect.
- Small defects may close spontaneously, larger defects result in infant congestive heart failure.
- Clinically repaired by coils or tissue-adapted devices like muscular or perimembranous occluders.

8/1,000 live births

http://fromyourdoctor.com/topic.do?title=Atrial+Septal+Defect+ASD&t=7958
**Patent Ductus Arteriosus**

Patent Ductus Arteriosus (PDA) occurs commonly in preterm infants, can close spontaneously (by day three in 60% of normal term neonates) the remainder are ligated simply and with little risk.

The operation is always recommended even in the absence of cardiac failure and can often be deferred until early childhood.

0.81/1,000 live births

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**Tetralogy of Fallot**

Named after Etienne-Louis Arthur Fallot (1888) who described it as "la maladie blue" and is a common developmental cardiac defect.

The syndrome consists of a number of a number of cardiac defects possibly stemming from abnormal neural crest migration.

The basic defect in a tetralogy of Fallot is an asymmetrical fusion of the truncoconal ridges and a malalignment of the aortic and pulmonary valves. This results in the typical 4 features seen in this defect:

1. pulmonary stenosis,
2. overriding aorta,
3. ventricular septal defect
4. right ventricular hypertrophy.

0.4/1,000 live births
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