

Congenital Heart Disease: Classification Systems

- Anatomic
- Physiologic
- Surgical Procedures
- Familial or causal in which the developmental stage determines the extent of the defect:
Cardiac looping occurs early in development so heterotaxias are associated with multiple, varied defects; VSDs may occur early or late and are, therefore, the most common defects.

Congenital Heart Disease: Prevalence

- 1.5-2.5/1000 live births.
- Bicuspid aortic valve in 1-2% live births.
- Estimated: 20,000 open heart procedures yearly for CHD.
- Post-op secundum ASD, pulmonary stenosis, patent ductus have normal life expectancy.
- Estimated > 500,000 adults in US with CHD.

Congenital Heart Disease: Etiologies

- 70-80% Multifactorial
- 6-12% Gross Chromosomal Anomaly
- 10-15% Single gene defect
- 1% Maternal Disease
- 1% Teratogen Exposure

Congenital Heart Disease: Etiologies

Most cases (70-80%) are “multifactorial”

The Recurrence Risk with:

- 1 sib with CHD: 2-4%
- 2 sibs with CHD: 6-12%
- Mother with CHD: 6-12%
- Father with CHD: 2-4%

In 1/2 of these families the same defect recurs.

Congenital Heart Disease: Etiologies

6-12% have gross chromosomal anomalies

- Trisomy 21 (40% have CHD): AV canal
- Trisomy 18 (100% have CHD): VSD, PS
- Trisomy 13-15: VSD, ASD, TGV
- XO (Turner): Coarc, AS, VSD
- XXY (Klinefelter): Ebstein, Tetralogy

Trisomy 18

100%
have
congenital
heart
disease



Trisomy 18



Trisomy 13



Turner
Syndrome
XO



Cystic
hygroma
(lymphatic
malformation)

Congenital Heart Disease: Etiologies

10-15% Single gene defects

- Williams/elastin (del7q11.23): AS, PS
- Cri-du-chat (del5p15): VSD, AS, PDA
- Connexin 43: PS, heterotaxia
- Holt-Oram/*TBX5* (12q24.1): ASD + limb
- *NKX2.5* (5q35): ASD + heart block
- DiGeorge/velo-cardio-facial syndrome
22q11.2 hemizygous microdeletion

DiGeorge / velocardiofacial syndrome

Cardiac

Abnormal facies

Thymic hypoplasia

Cleft palate

Hypocalcemia

22nd chromosome

22q11.2 **microdeletions** are also found in isolated congenital heart diseases: interrupted aortic arch, truncus arteriosus, Tetralogy of Fallot, transposition, VSD, aortic coarctation, and double outlet RV.

DiGeorge / velocardiofacial syndrome (1 in 4000; 5% of CHD)

- Cardiac anomalies - 75%
- Abnormal facies - 41%
- Thymic hypoplasia – rare (but 75% have some immunodeficiency)
- Cleft palate – 11% (70% have some palatal anomaly)
- Hypocalcemia - 50%



DiGeorge syndrome; deletion of material from long arm of chromosome 22.

Fluorescence In-situ Hybridization (FISH) – normal. Green is an internal control labeling chromosome 22q13; Red labels 22q11.2 and has 2 copies (no deletion)





22q11.2 deletion syndrome

- Autosomal dominant
- 93% of probands have a *de novo* deletion
- 7% inherited from parent
- ***Tbx1*** (but mutations do not have CNS manifestations - cerebellar atrophy, polymicrogyria, neural tube defects, seizures)

22q11.2 deletion syndrome: congenital heart defects in 75%

- Tetralogy of Fallot – 22%
- Interrupted aortic arch – 15%
- Ventricular septal defect – 13%
- Truncus arteriosus – 7%
- Vascular ring – 5%
- Aortic arch anomaly – 3%

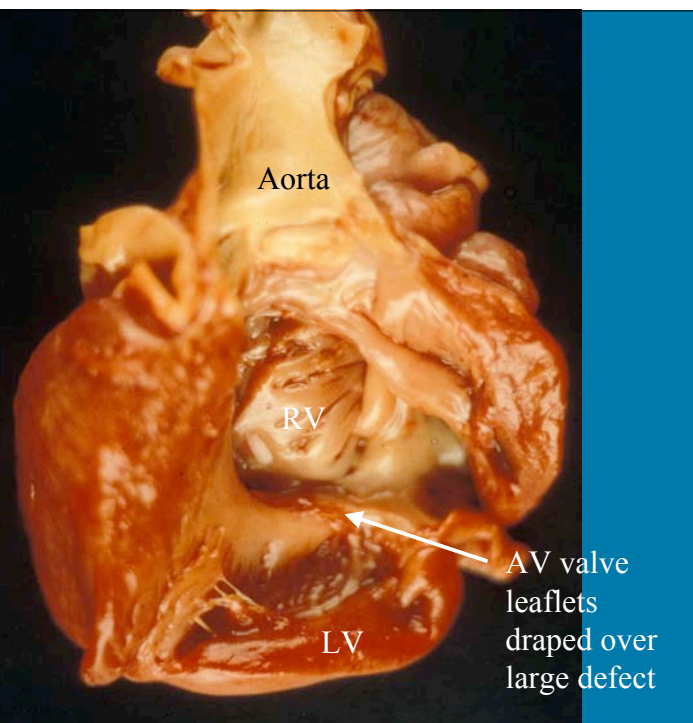
McDonald-McGinn, et al., Genet Couns 10:11-24, 1999

Congenital Heart Disease: Etiologies

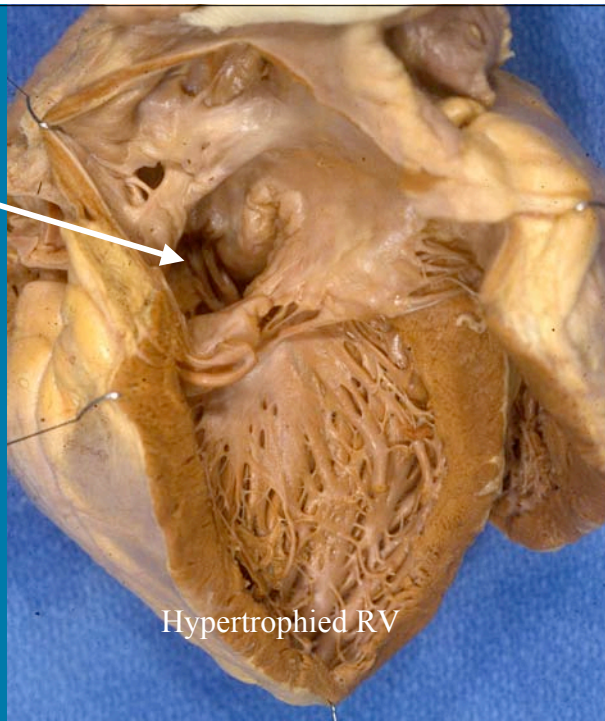
- | | |
|---|---|
| • 1% Maternal Disease | • 1% Teratogen Exposure |
| • Type I diabetes mellitus (2% affected) | • Alcohol (30% have some defect) |
| • Phenylketonuria (if not controlled) | • Anticonvulsants (2-3x increased risk) |
| • Systemic lupus erythematosus (heart block & structural) | • Lithium |
| | • Retinoic acid |
| | • Rubella |



AV Canal or
Endocardial
Cushion
Defect

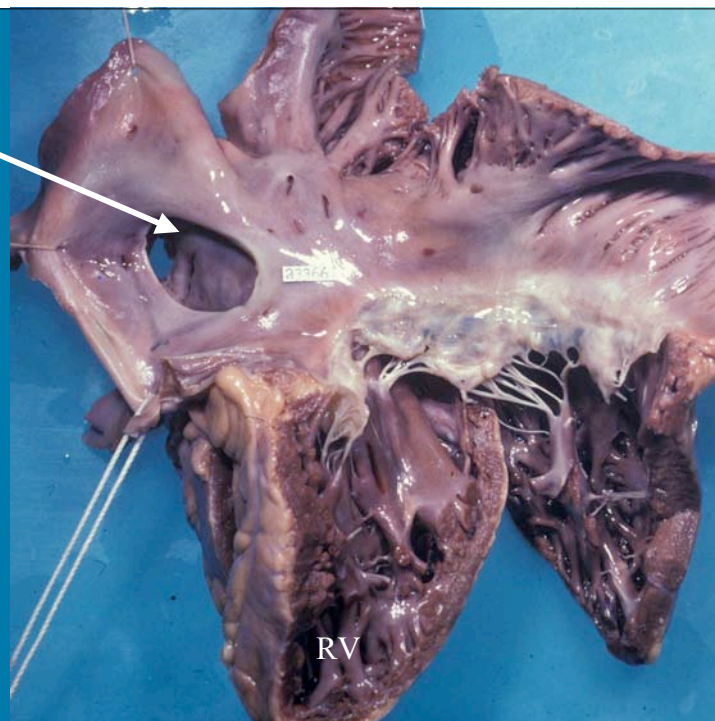


Atrial septal defect - Primum



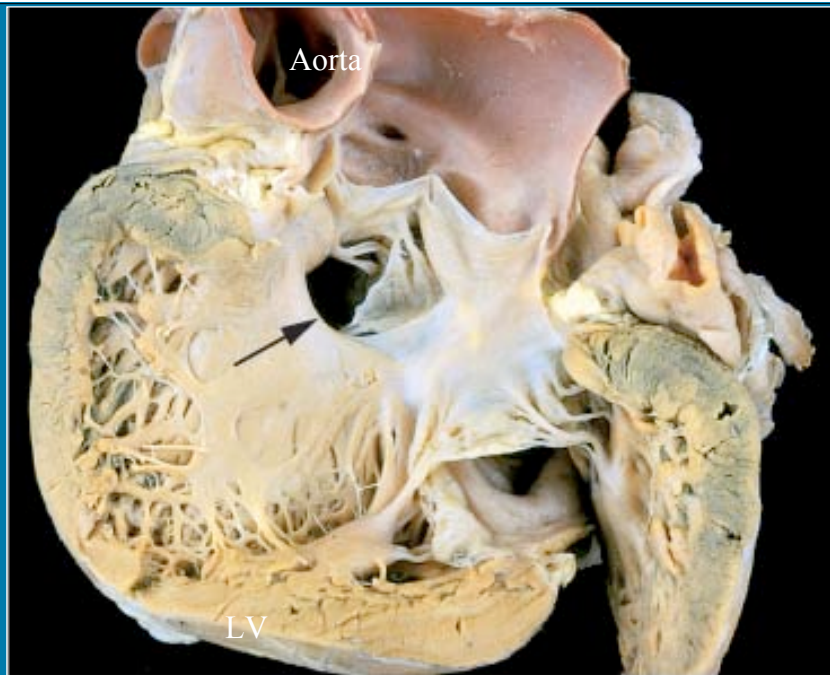
Hypertrophied RV

ASD – Secundum type

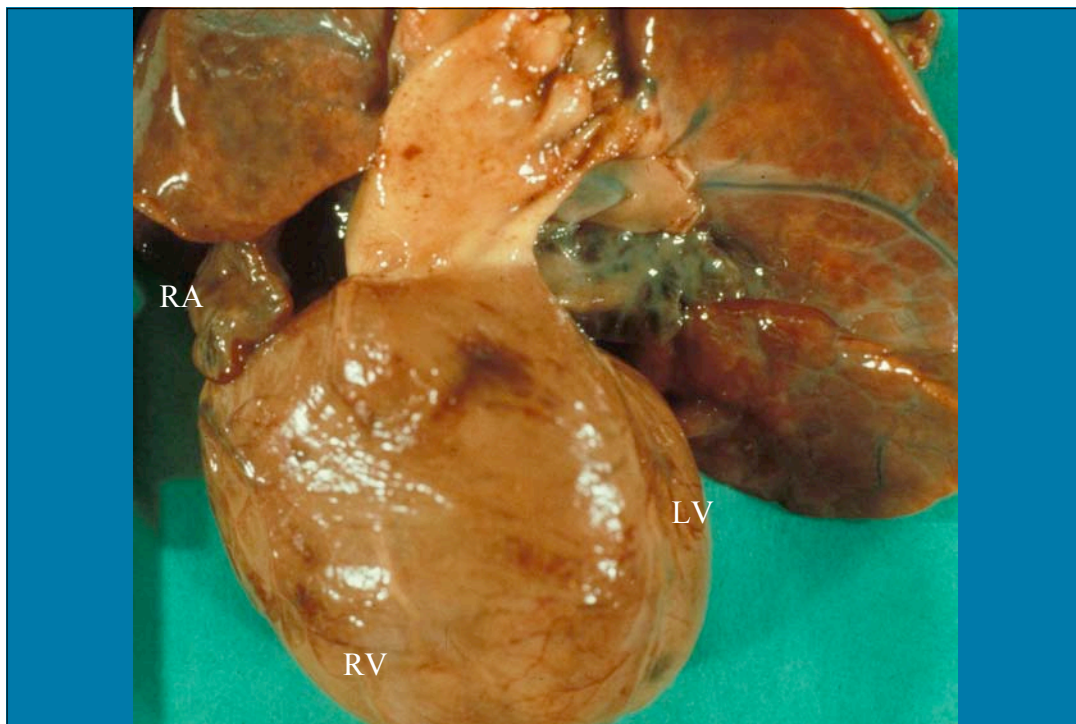


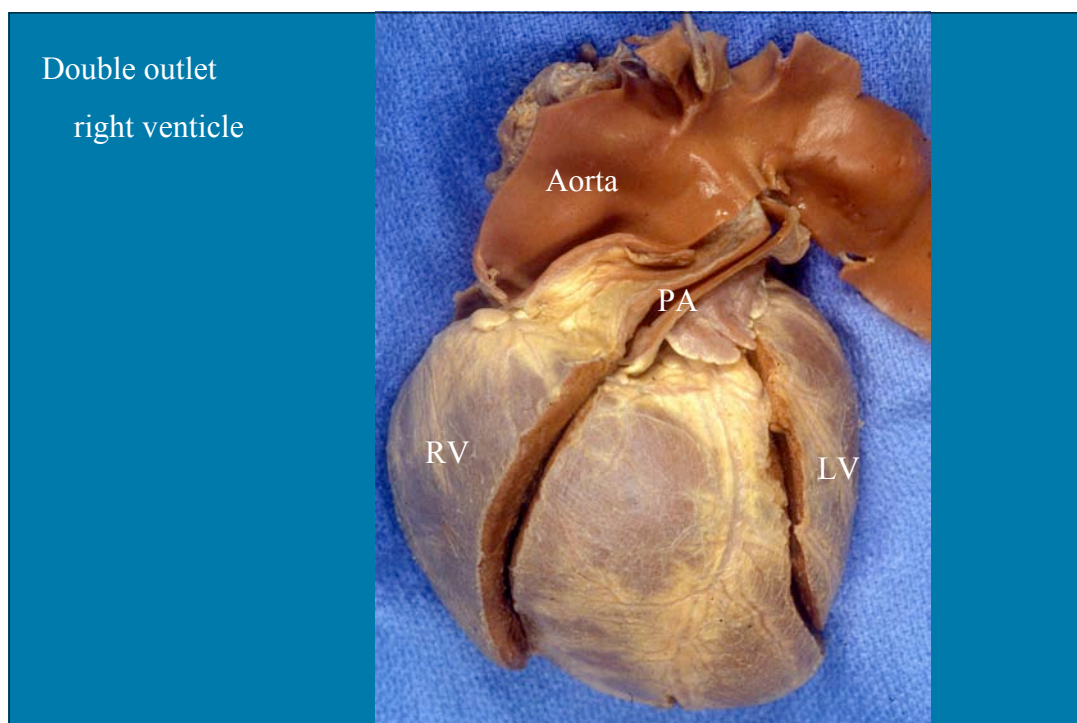
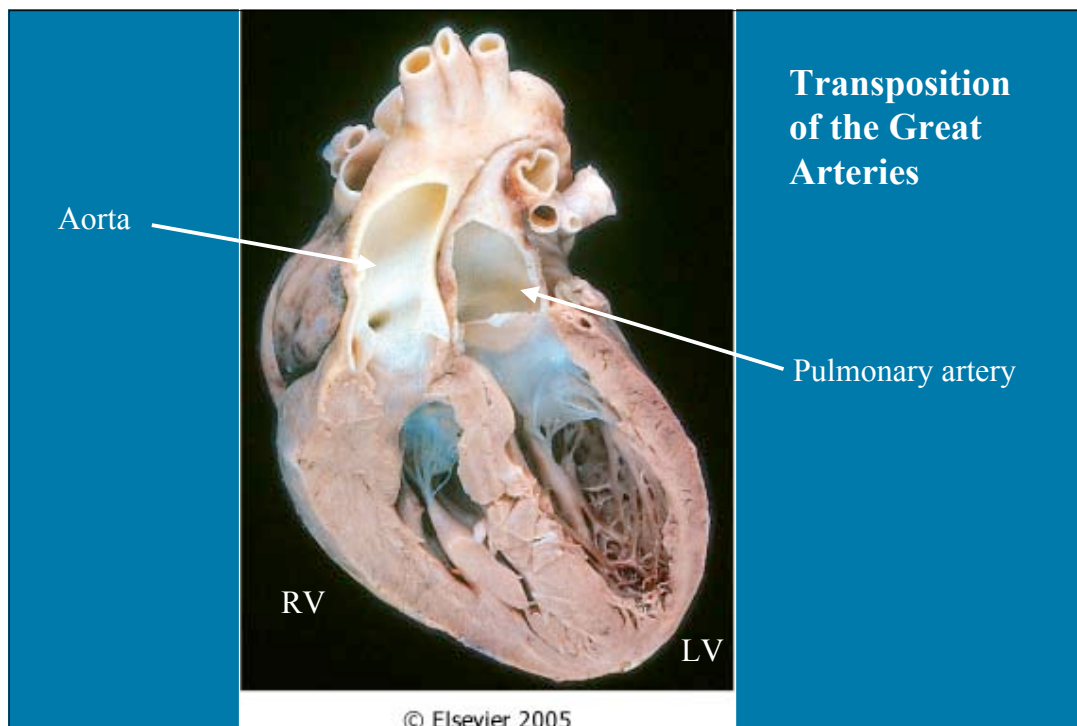
RV

**VSD-
membranous
type**

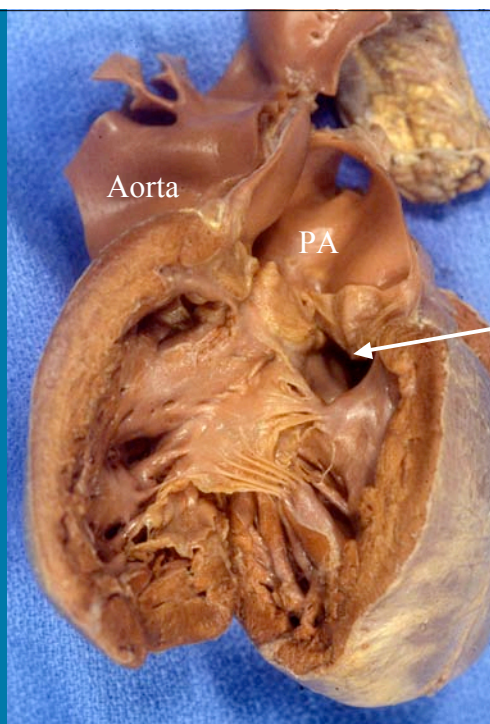


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**Double
outlet right
ventricle**



VSD