

Alagille Syndrome: Cardiac Manifestations

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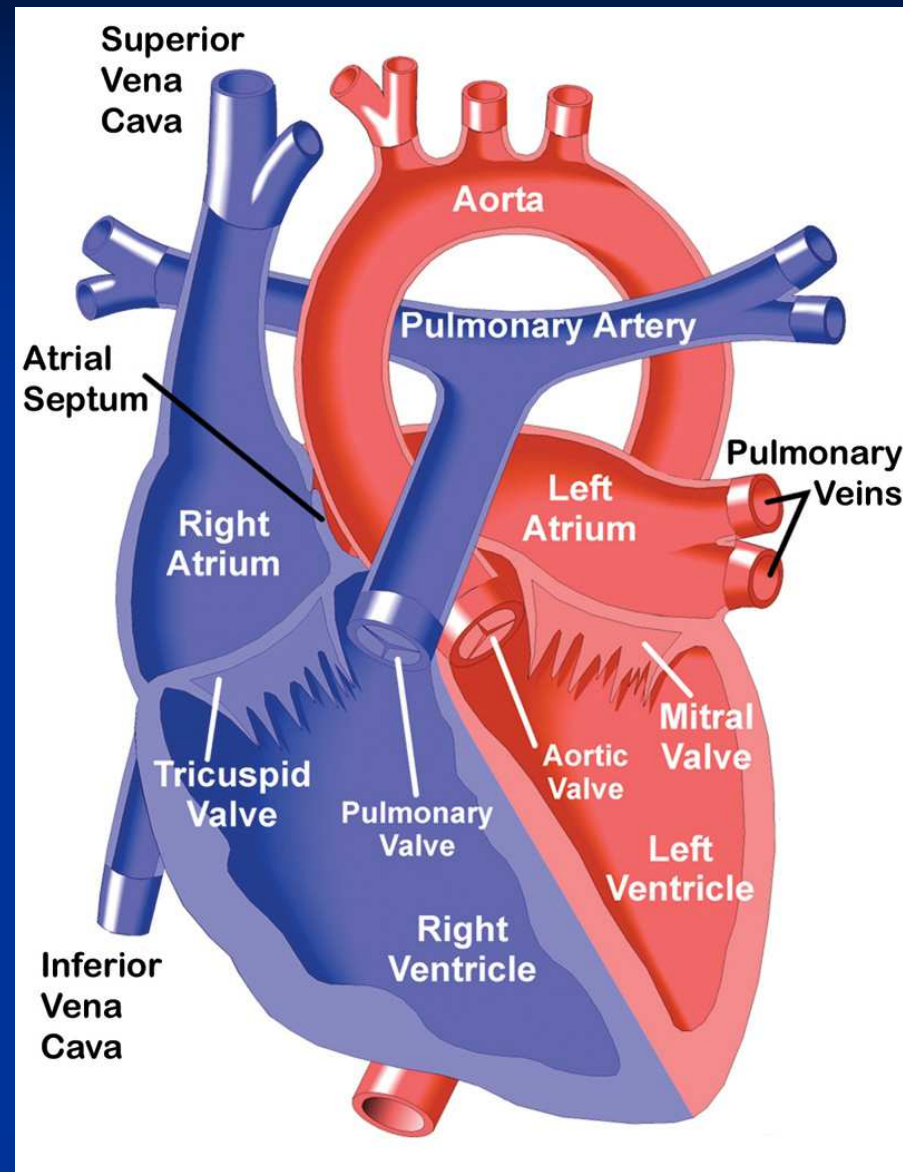
Role of a Cardiologist

- Over 90% have cardiac involvement
- Individuals with documented or suspected diagnosis of Alagille syndrome should be evaluated by a pediatric cardiologist.

Visit With the Cardiologist

- History (including family history)
- Physical exam
 - Vital signs, listen to heart sounds
- Perform an electrocardiogram (EKG)
- Echocardiogram (ultrasound of heart) and/or chest x-ray may be performed
- Additional testing, if necessary, includes heart cath or MRI/CT

Normal Cardiac Anatomy



Common Presentations

- Heart Murmur
- Cyanosis – “blue baby”
- Heart Failure/Shock – in left sided heart lesions secondary to compromise in blood flow to the body

Common Cardiac Defects

- **Peripheral pulmonary stenosis (PPS) most common**
- **Other defects include tetralogy of Fallot, pulmonary valve stenosis, atrial septal defect (ASD), ventricular septal defect (VSD)**

Congenital Heart Disease in Alagille Syndrome

| Diagnosis | % Silberbach | % Emerick |
|-----------|--------------|-----------|
| PPS alone | 71 | 67 |
| Valvar PS | 11 | 2 |
| PA/VSD | 2 | 2 |
| TOF | 8 | 11 |
| VSD | 5 | 8 |
| ASD | <1 | 5 |
| other | 3 | 5 |

- Silberbach et al., 1994 (N=122)
- Emerick et al., 1999 (N=92)

Cardiac Disease In Alagille Syndrome

- McElhinney et al. (2002) examined a large cohort of 200 individuals with JAG1 mutations and/or Alagille syndrome looking at cardiac phenotype
- 94% had cardiac involvement

Primary Cardiovascular Defects in Alagille Syndrome (N=200)

| Cardiac Defect | # Affected |
|----------------------|------------|
| Branch PA stenosis | 70 (35%) |
| PPS murmur | 37 (19%) |
| Tetralogy of Fallot | 23 (12%) |
| Valvar Pulm Stenosis | 15 (8%) |
| Pulmonary Atresia | 1 (1%) |
| Truncus Arteriosus | 1 (1%) |

■(McElhinney et al., 2002)

Severity of PA Anomalies Documented by Imaging (N=111)

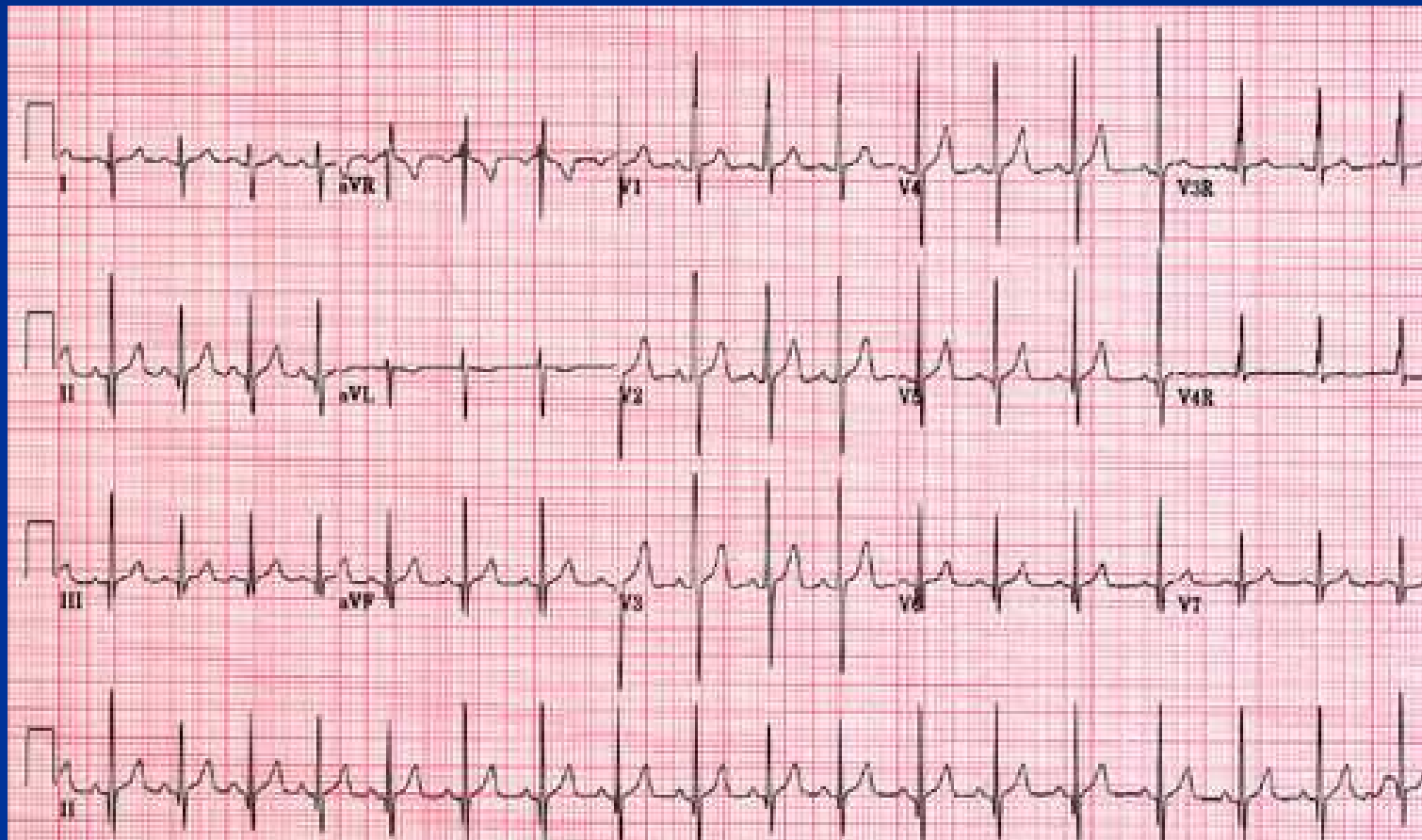
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|-----------------------|----------|
| Isolated PA Anomalies | N = 55 |
| Mild | 27 (49%) |
| Moderate-Severe | 28 (51%) |
| Assoc CVS Defects | N = 56 |
| Mild | 13 (23%) |
| Moderate-Severe | 43 (77%) |

■ (McElhinney et al., 2002)

Peripheral Pulmonary Stenosis (PPS)

- Murmur radiates from top of chest to back
- Many remain asymptomatic and do not require intervention
- Different entity from physiologic or benign PPS of the newborn which typically resolves by 6-8 months of age
- Can have discrete narrowing of pulmonary artery branch or more diffuse hypoplasia which may require intervention

Electrocardiogram (EKG)

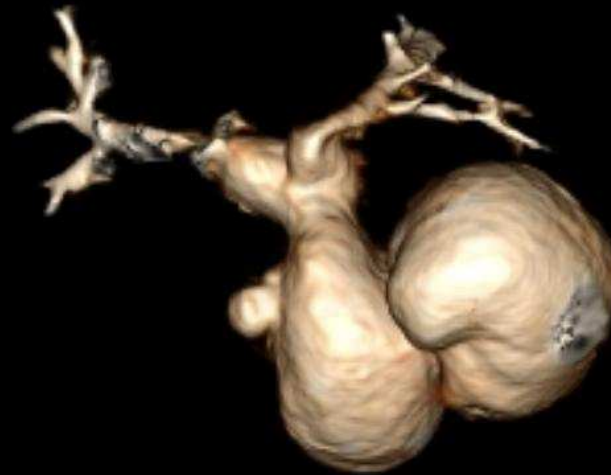


Cardiac CT

27 of 113 LOSSY COMPRESSION 27:1

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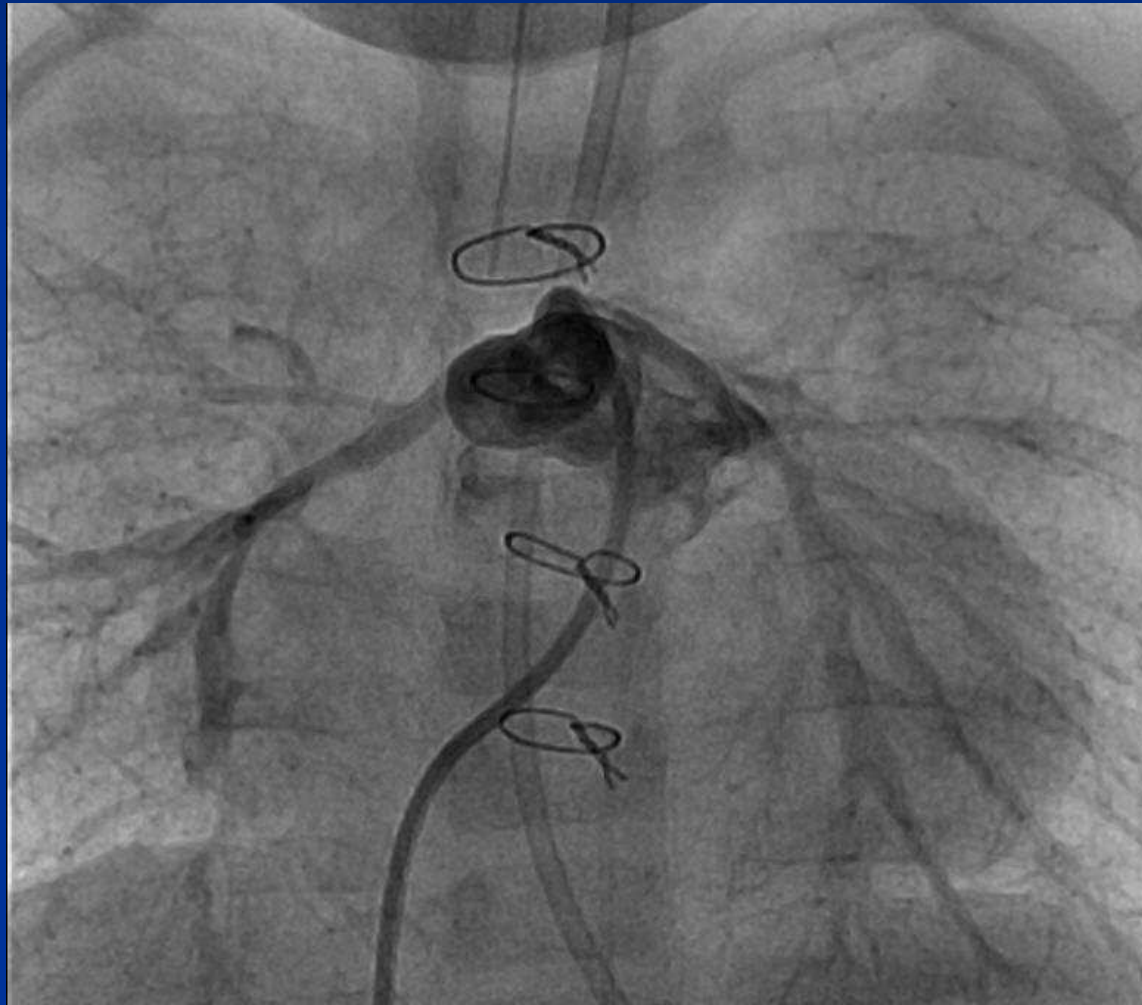


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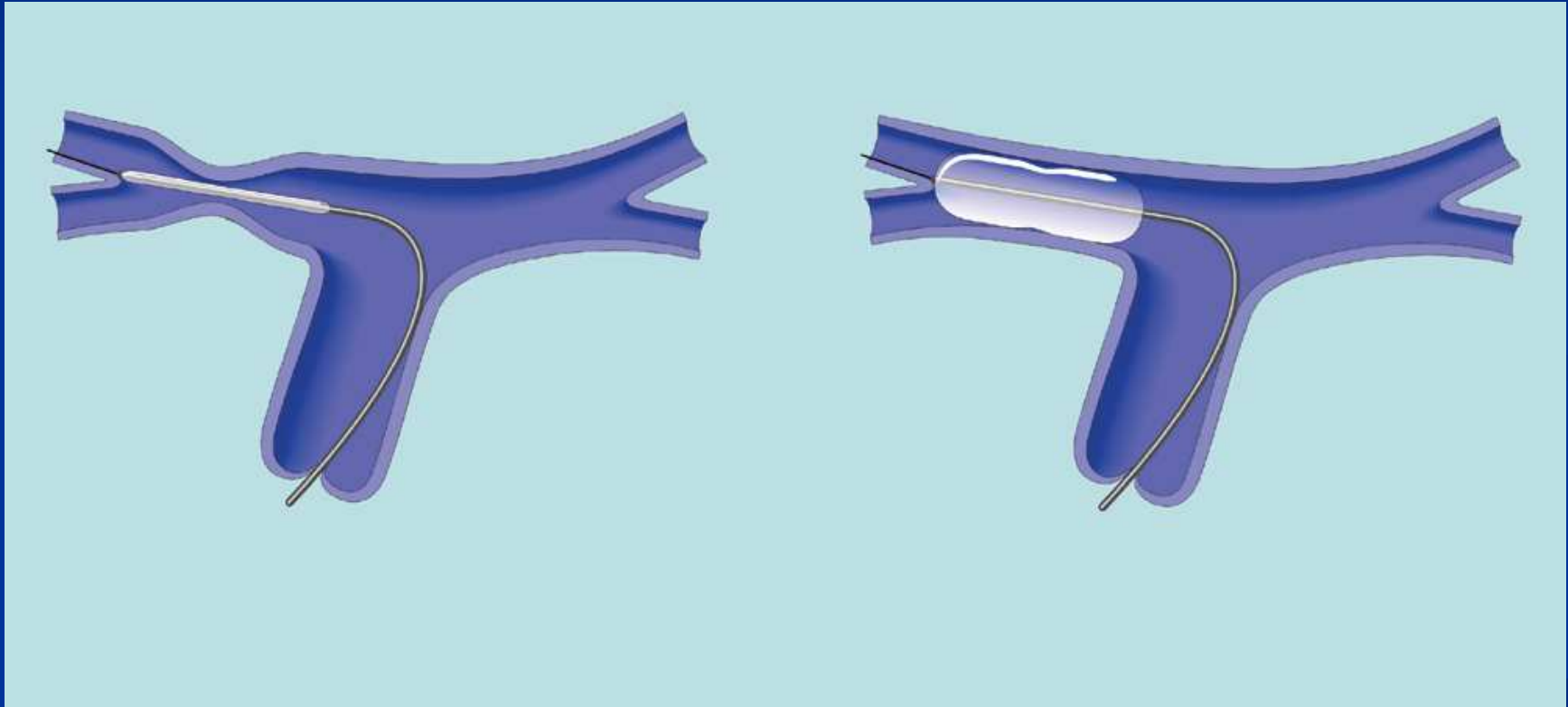
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Cath Image of Peripheral Pulmonary Artery Stenosis



Balloon Dilation of Stenotic Branch Pulmonary Arteries



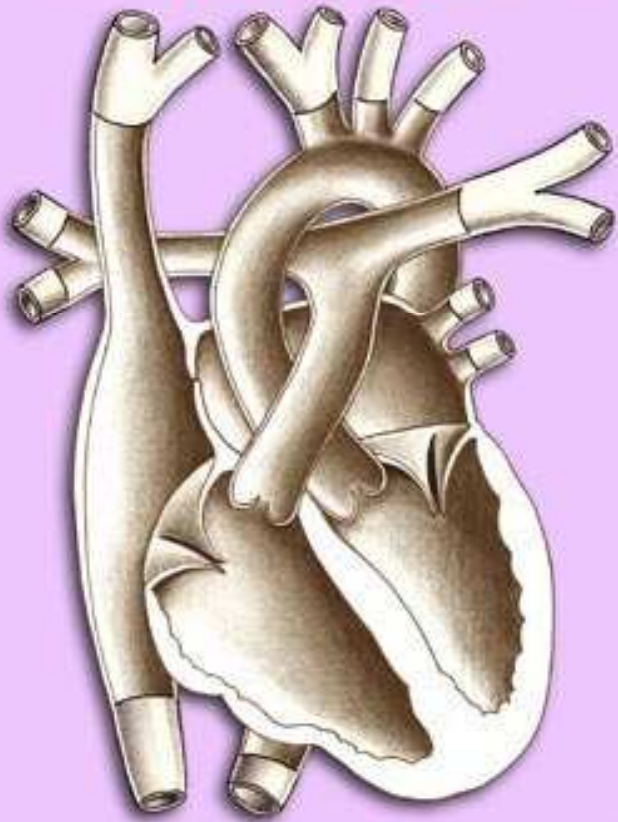
- Illustrations showing (left) uninflated and (right) inflated angioplasty balloon in stenotic branch pulmonary artery

Pulmonary Valve Stenosis

- Murmur loudest at top left side of chest
- Click
- Mild to severe
- May be progressive or can remain stable
- Individuals with a moderate to severe degree of obstruction generally require intervention
- Treatment: Cardiac cath or surgery

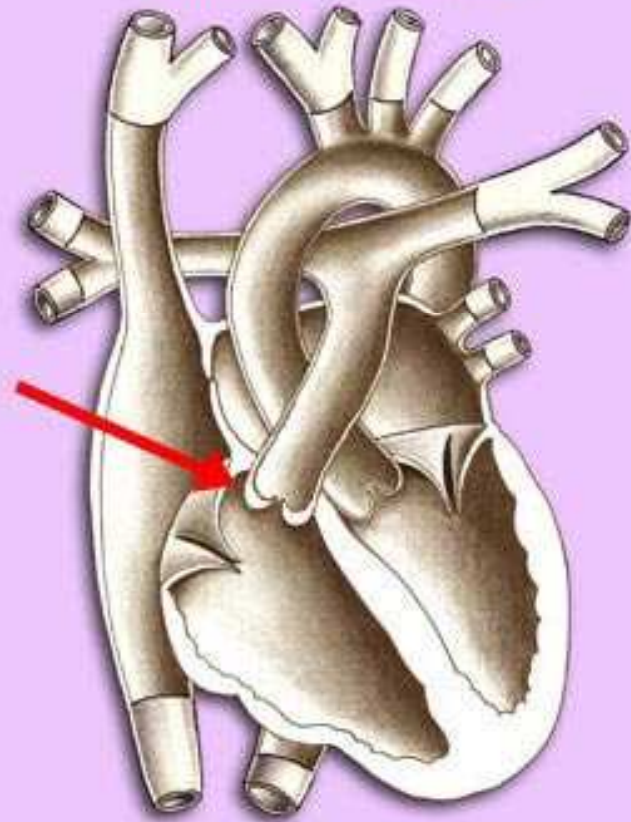
Pulmonary Valve Stenosis

Normal Heart



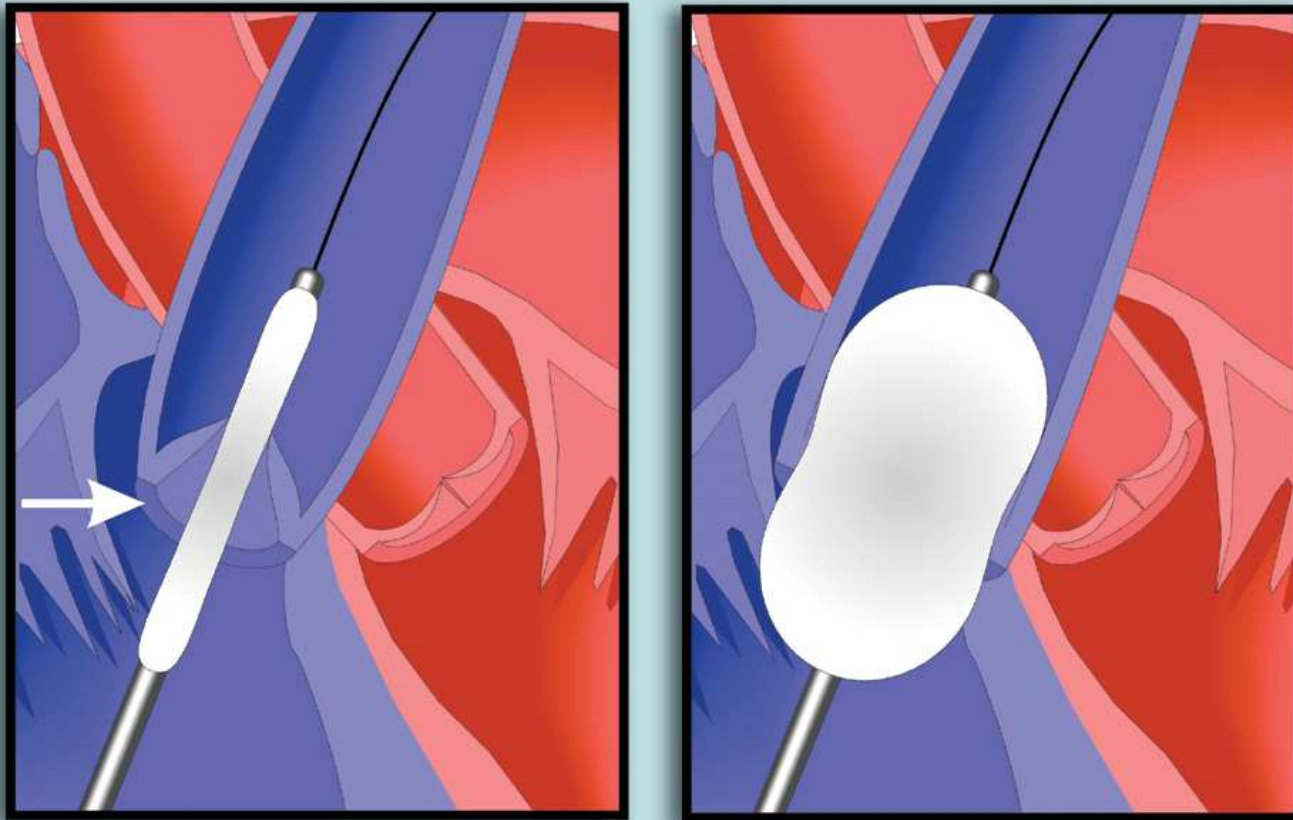
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Pulmonary Stenosis

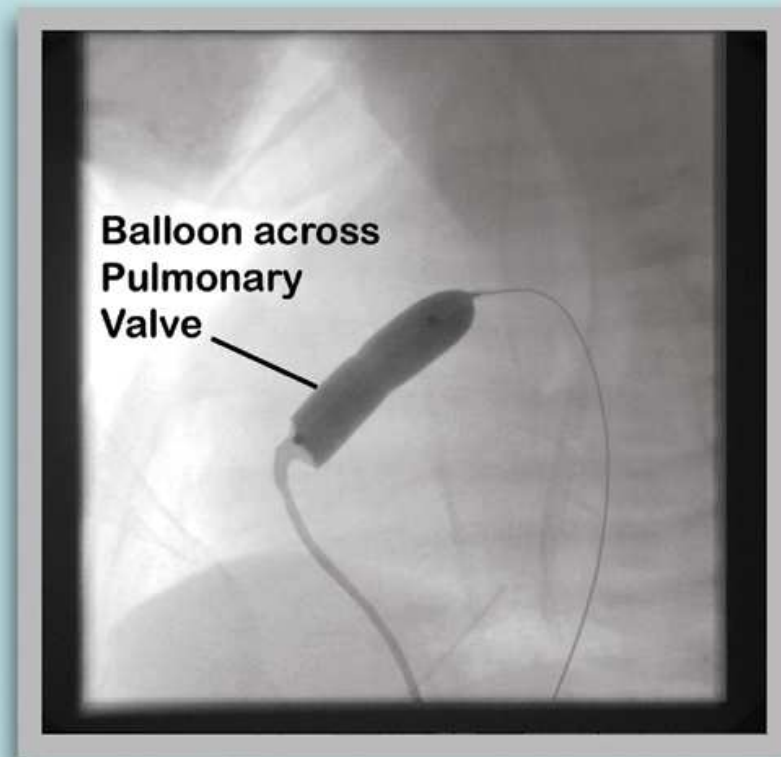
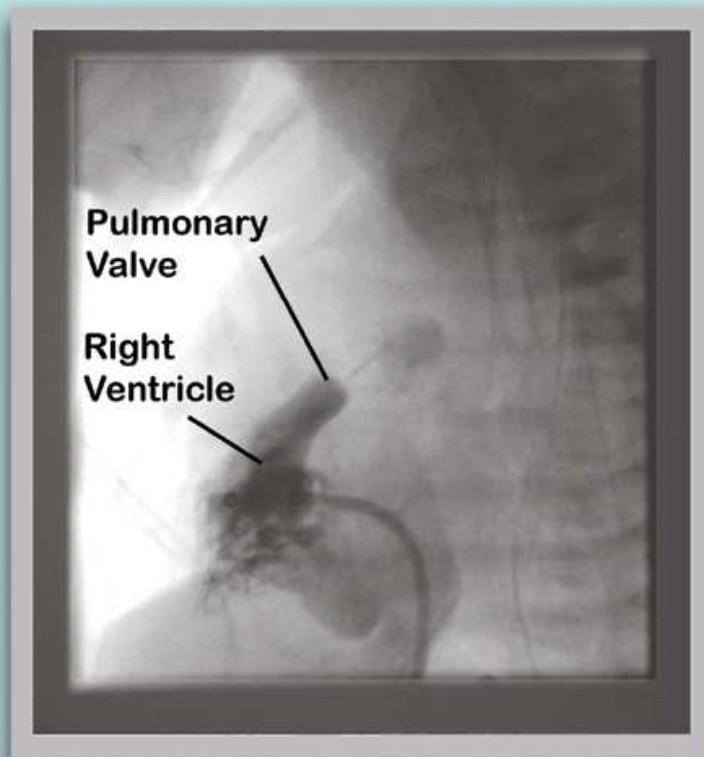


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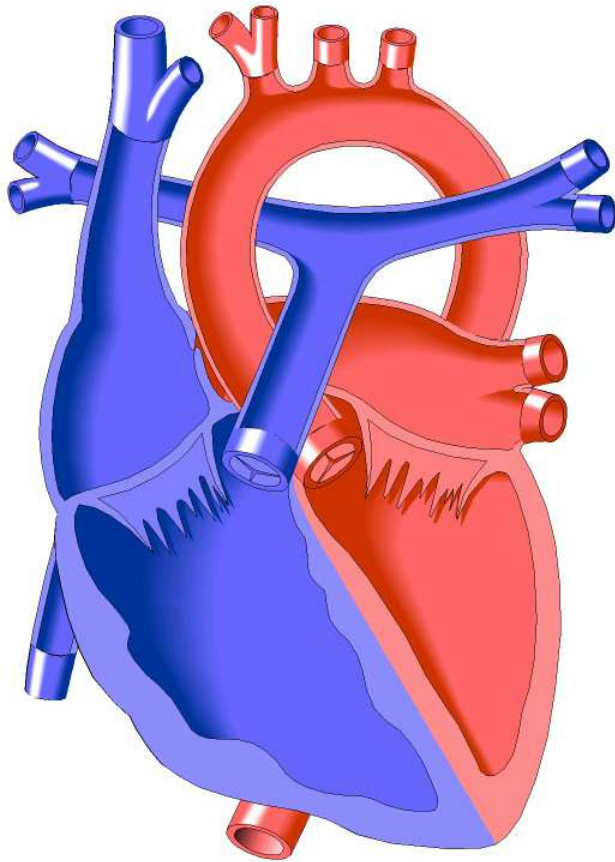
Pulmonary Balloon Valvuloplasty



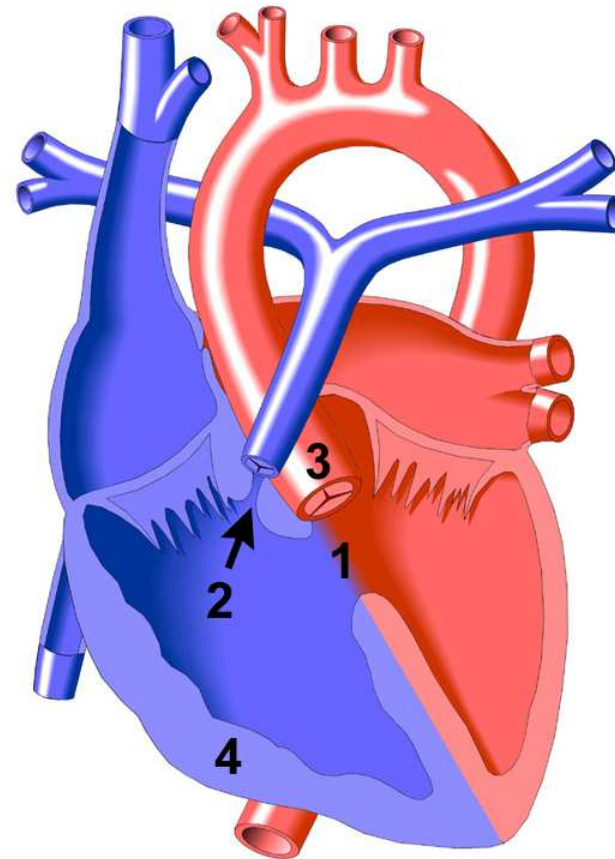
Pulmonary Balloon Valvuloplasty



Tetralogy of Fallot



Normal Heart



Tetralogy of Fallot

TOF

■ Clinical Presentation

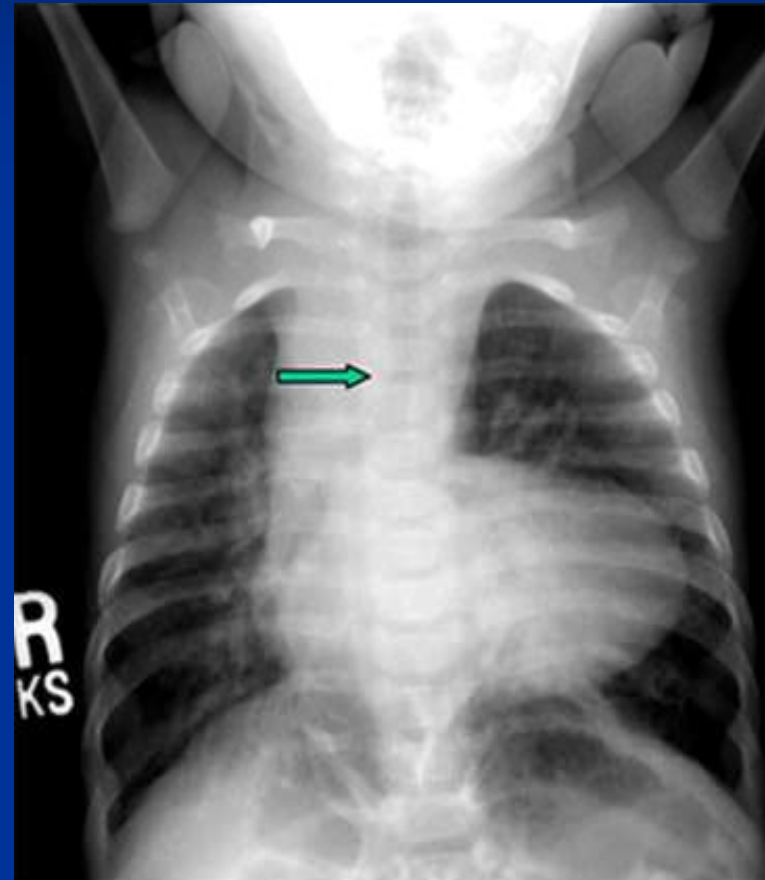
- Often pink and well appearing with a murmur
- May be blue baby
- Occasionally, heart failure symptoms
- Abnormal heart sound (Single S2)

Work-up

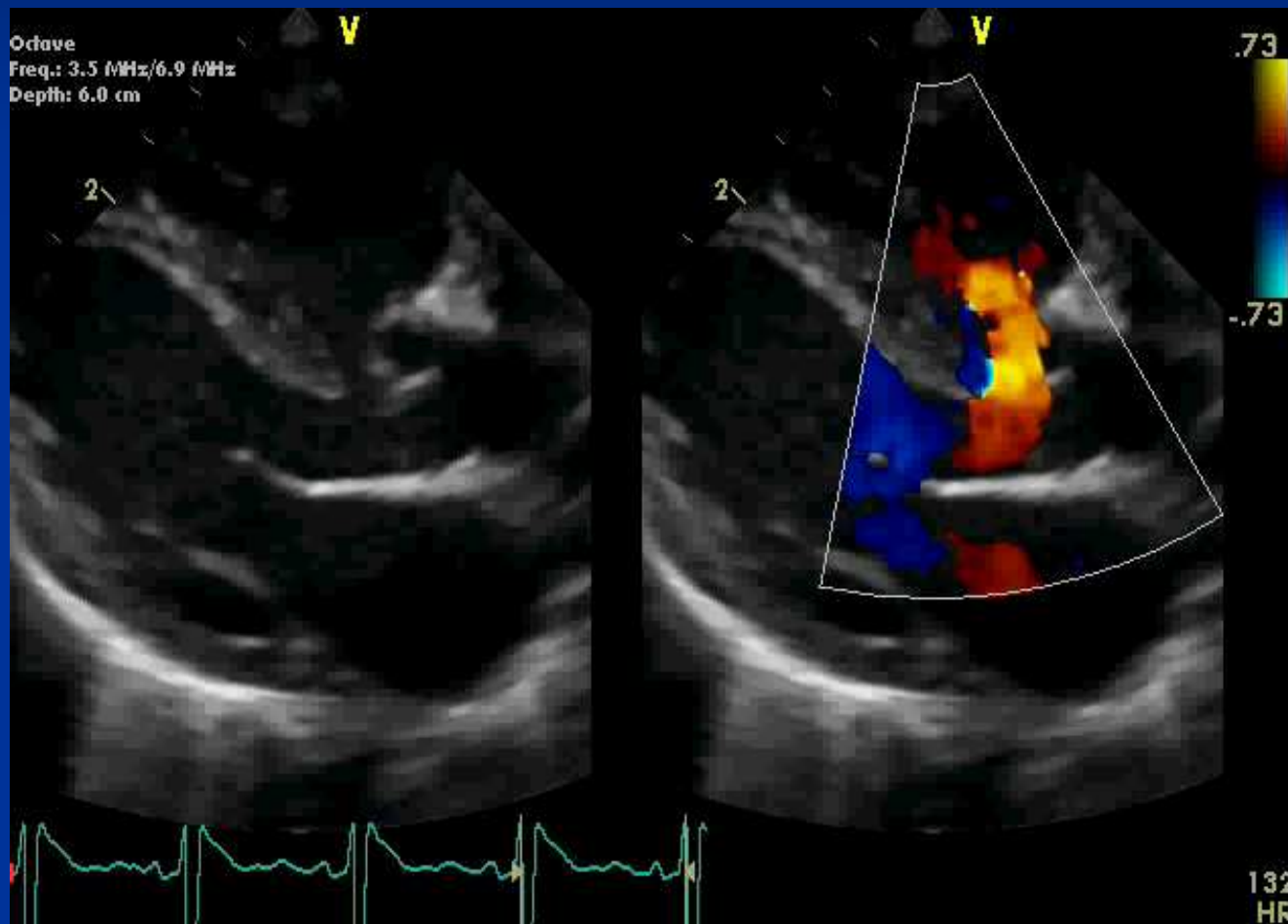
- Echo performed in all individuals with Tetralogy of Fallot
- More complex type may need cardiac cath
- All will undergo heart surgery
- Timing of surgery, procedure performed, and outcome depend on anatomic details

TOF Chest X-ray

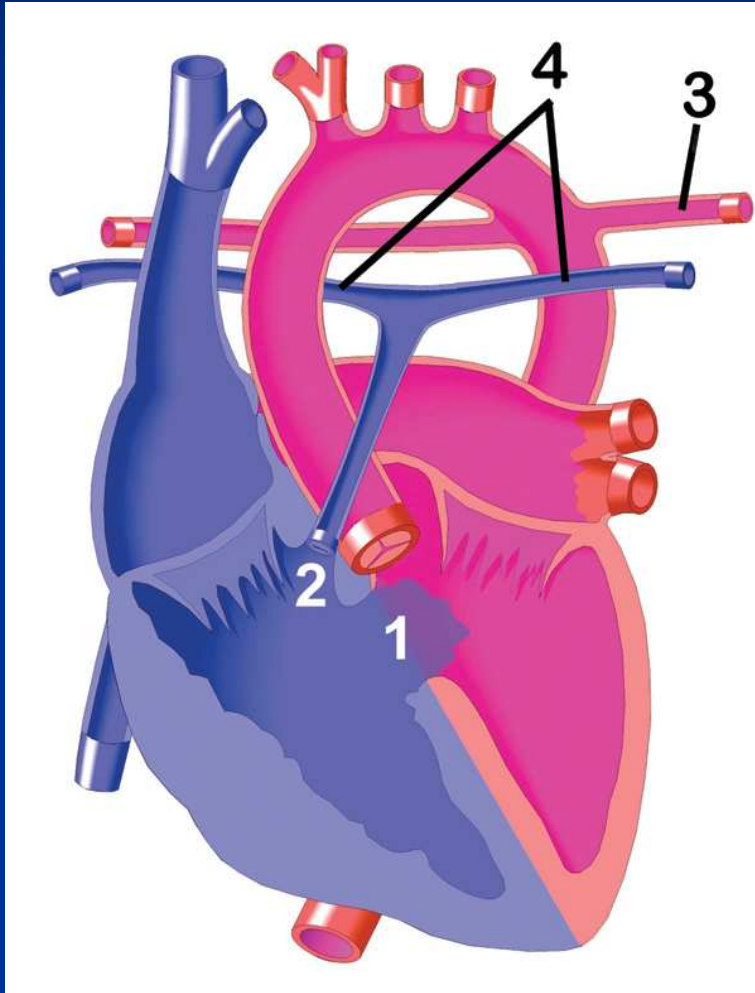
- Boot-shaped heart
- Decreased pulmonary vascular markings



TOF Echocardiogram



Tetralogy with Pulmonary Atresia and AP Collaterals

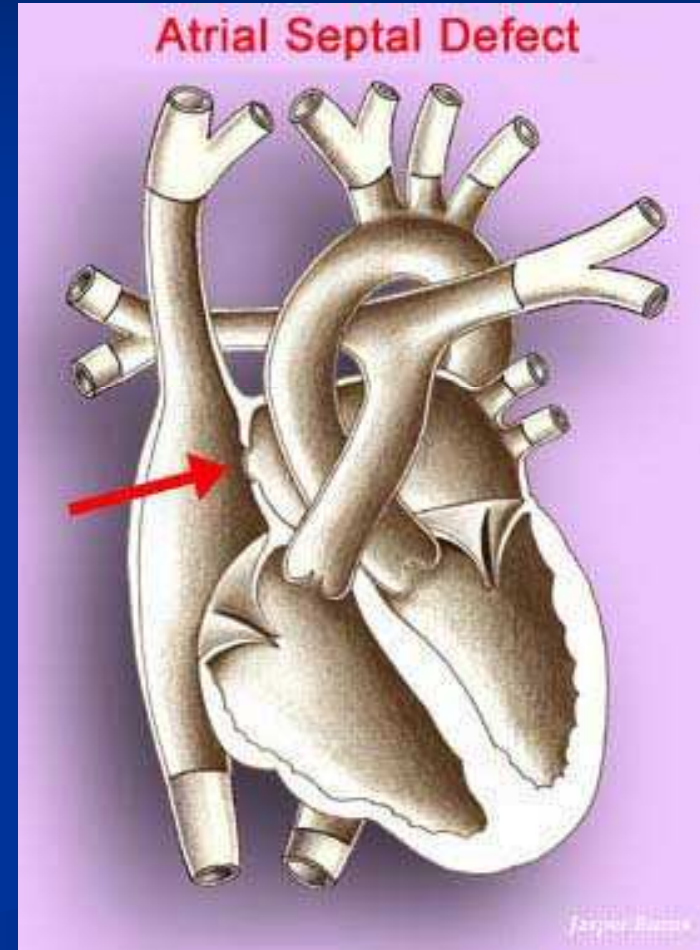
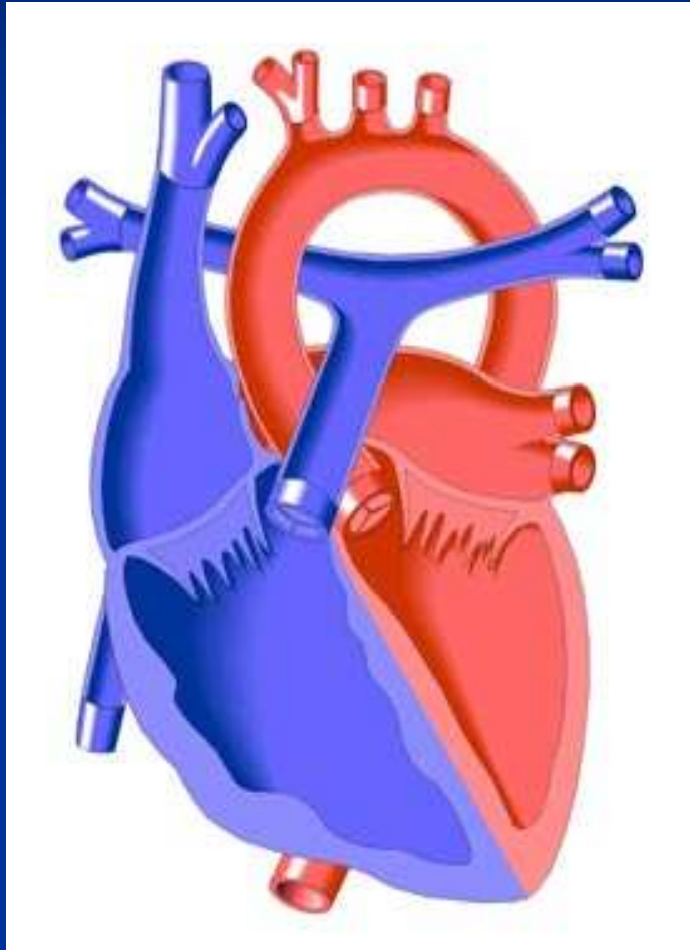


1. Ventricular septal defect
2. Atretic pulmonary valve
3. Aortopulmonary collaterals
4. Hypoplastic, confluent pulmonary arteries

Less Common Cardiac Defects In Alagille Syndrome

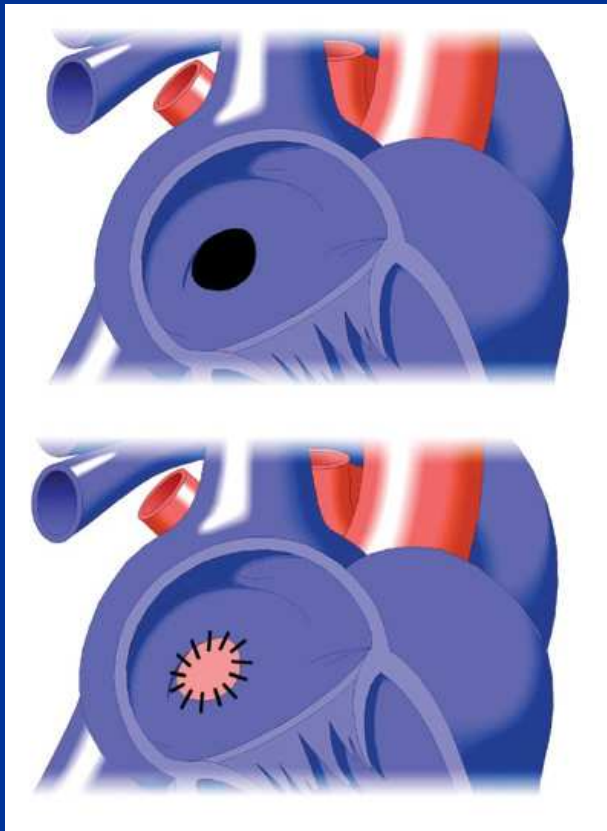
- McElhinney and colleagues (2002) demonstrated a high percentage of left-sided heart defects (11%)
- Examples include coarctation of the aorta, aortic valve stenosis
- Other lesions include ASD and VSD
- No cardiac involvement in 7%

Atrial Septal Defect (ASD)

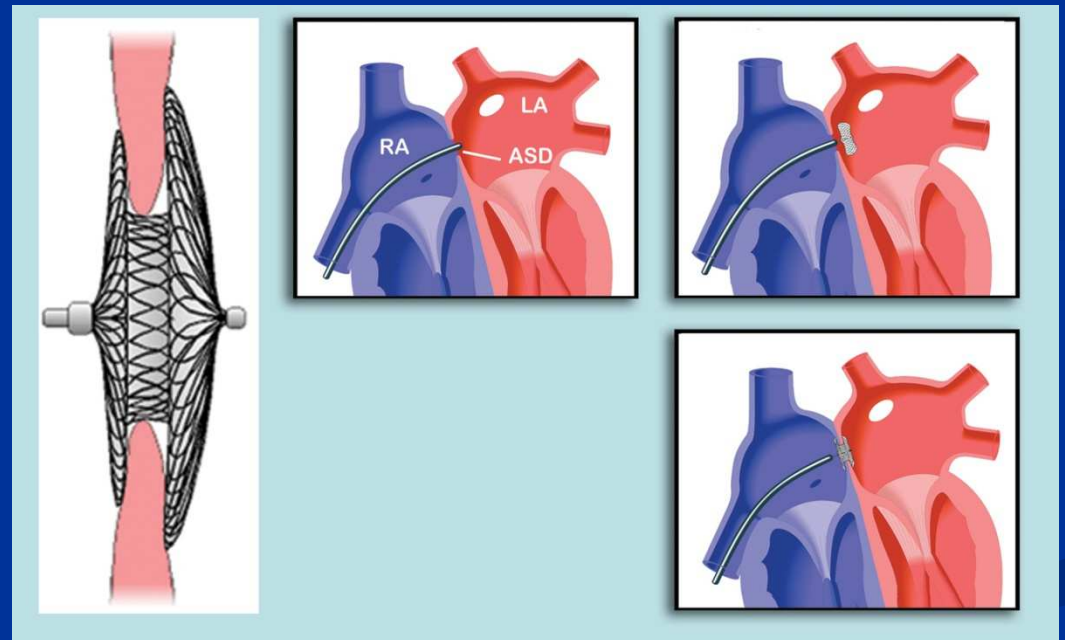


ASD Treatment Options

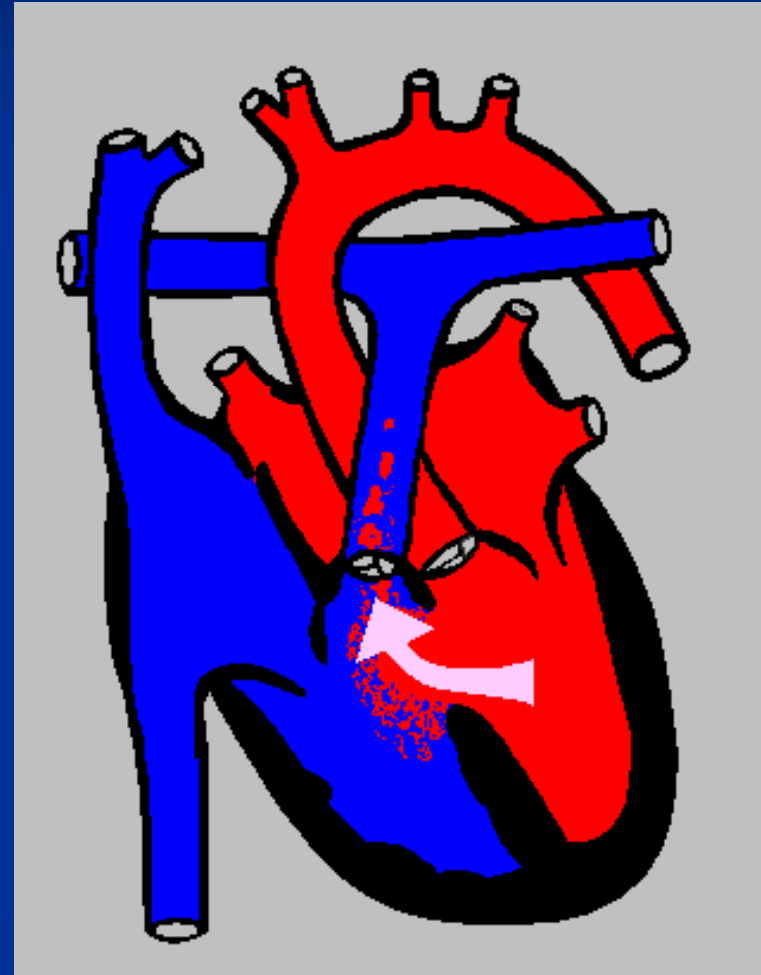
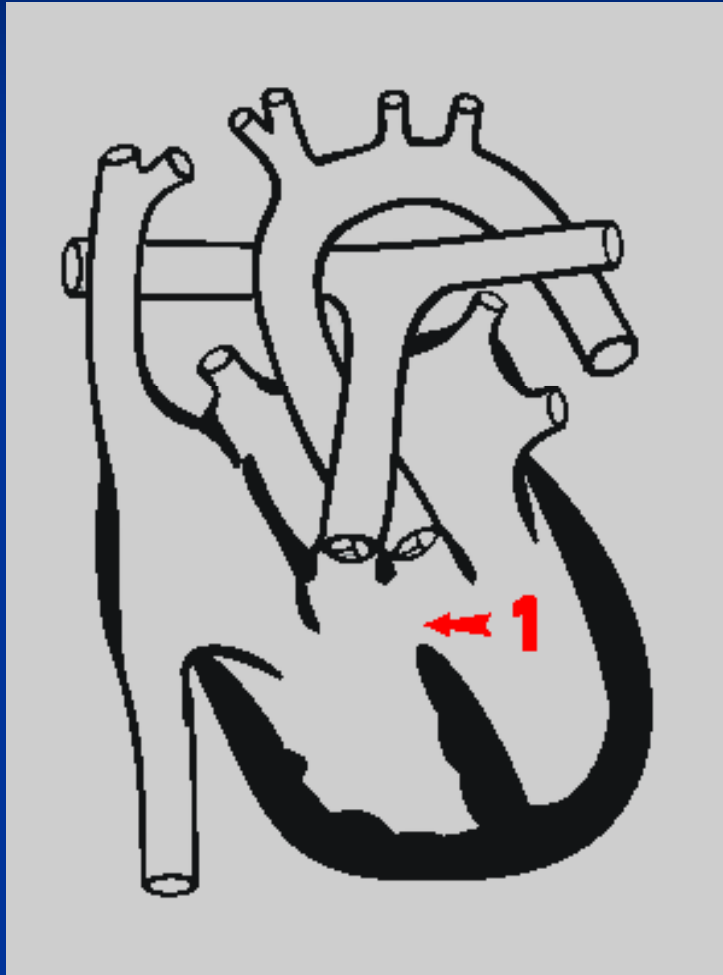
Surgical Repair



Device Closure In Cath Lab

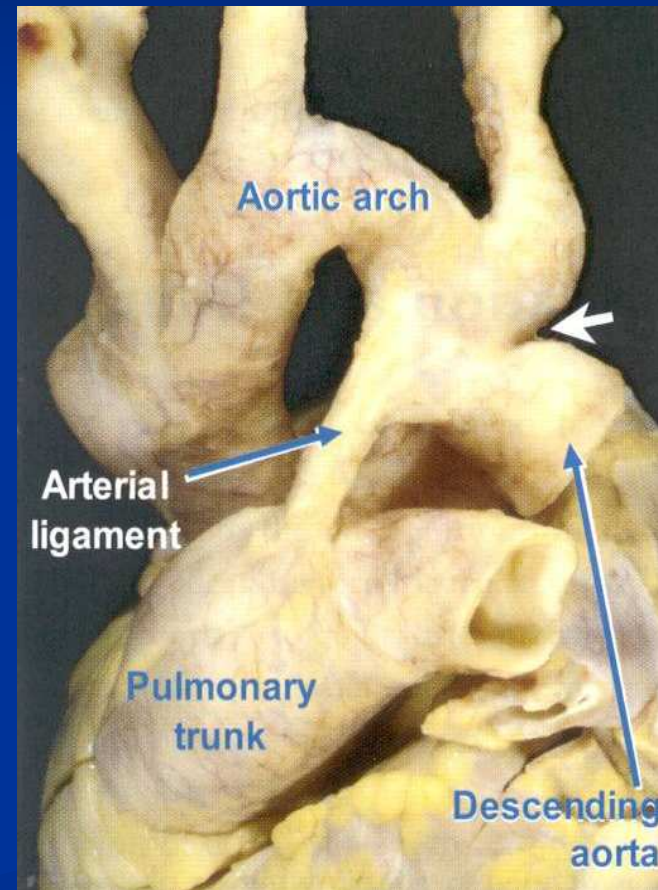


Ventricular Septal Defect (VSD)



Coarctation of the Aorta

- Narrowing of the artery that delivers blood to the body
- Often present in shock during 1st week of life
- Poor feeding, breathing fast
- Decreased/absent lower extremity pulses



Alagille Syndrome, Heart Disease and Clinical Outcome

- Emerick et al. (1999) reported 7/22 (32%) with structural heart disease were deceased.
 - 2/6 with TOF/PS
 - 3/4 with TOF/PA
 - 1/2 with PA/VSD
- Associated PPS present in 4 of 7 deceased individuals
- Complex congenital heart disease contributed significantly to mortality.

Alagille Syndrome, Heart Disease and Clinical Outcome

- 14 of 200 subjects known to be deceased
 - 10 of 23 (43%) with TOF
 - 2 with severe isolated PA stenosis
 - 1 with truncus arteriosus
 - 1 with sinus of valsalva aneurysm
- 10 deceased subjects with TOF
 - 6 had TOF/PA
 - 3 had TOF/PS
 - 1 with TOF/Absent PV
- Frequency of severe forms of TOF (particularly with PA and collaterals) in this study was significantly higher

■ (McElhinney et al., 2002)

Alagille Syndrome, Heart Disease and Clinical Outcome

- Limited follow up data (148 of 200)
- Serial echo data for 55 subjects with branch pulmonary artery stenosis demonstrated no significant progression in degree of stenosis (TOF with branch PA stenosis excluded)
- Cardiac intervention (cath or surgery) performed in 46 (23%)
 - (McElhinney et al., 2002)

Genotype-Phenotype Correlation

- Within the group of individuals with a JAG1 mutation, there was no correlation between the type or location of mutation and the frequency or type of cardiac malformation.
- Cardiac expression can vary between family members with same mutation

JAG1 Mutations in TOF/PS

- Bauer et al (2010) evaluated the frequency of JAG1 mutation in individuals with right sided heart defects
- Did not otherwise have diagnosis of Alagille syndrome
- Significant mutations identified in 3% (2/94) in TOF and 4% (2/50) in PS/PPS/PA with IVS
- Remember to look for features of Alagille syndrome or FH of cardiac lesions

Summary

- Right sided cardiac lesions most common in Alagille syndrome.
- Many will have asymptomatic changes (PPS).
- Some will have more complex heart defects detected within the first week to year of life.
- All should be evaluated by a cardiologist, especially if liver transplantation is being considered.
- Intracardiac defects may be the single most important determinant of survival.