

A HEART-TO-HEART CHAT:

Cardiac Involvement in Noonan Syndrome and What Are We Going to Do About It

Bruce D. Gelb, M.D.

Mindich Child Health and Development Institute

Departments of Pediatrics &

Genetics and Genomic Sciences

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Icahn School of Medicine at
Mount Sinai

Jackie Noonan
1928–2020



Maryella Pierpont
1945–2020



“Of particular interest was the recognition of a previously unreported syndrome in 9 patients with valvular pulmonary stenosis. These children were characterized by small stature, hypertelorism, mild mental retardation, and in some instances by ptosis, undescended testes, and skeletal malformations.”

Jacqueline A. Noonan

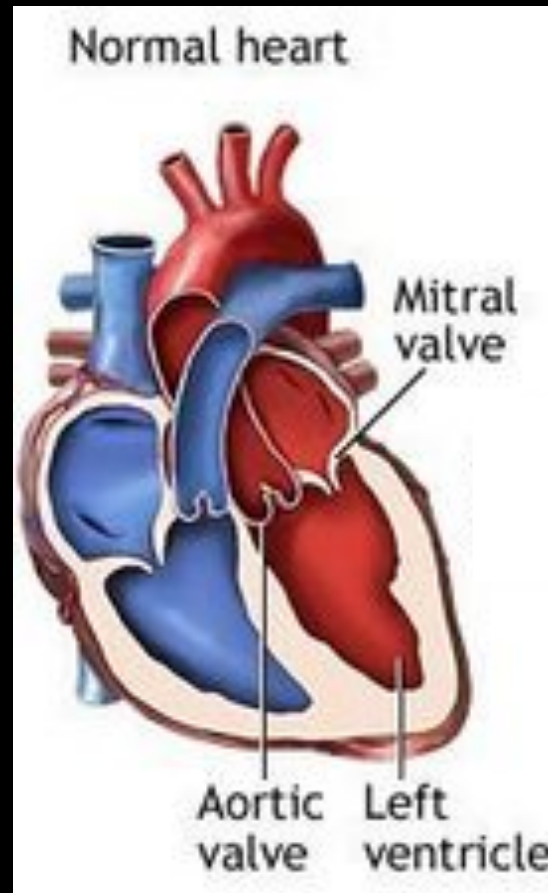
Midwest Society for Pediatric Research

1962

Published: Am J Dis Child, 1968

NS Heart Involvement

HEART 101



NS Heart Involvement ECHOCARDIOGRAM



NS Heart Involvement

FREQUENCY AND FLAVORS

- Frequency
 - 80-90%
- Flavors
 - Congenital Heart Defects
 - Heart Not Formed Correctly
 - Heart Muscle Disease
 - Hypertrophic Cardiomyopathy

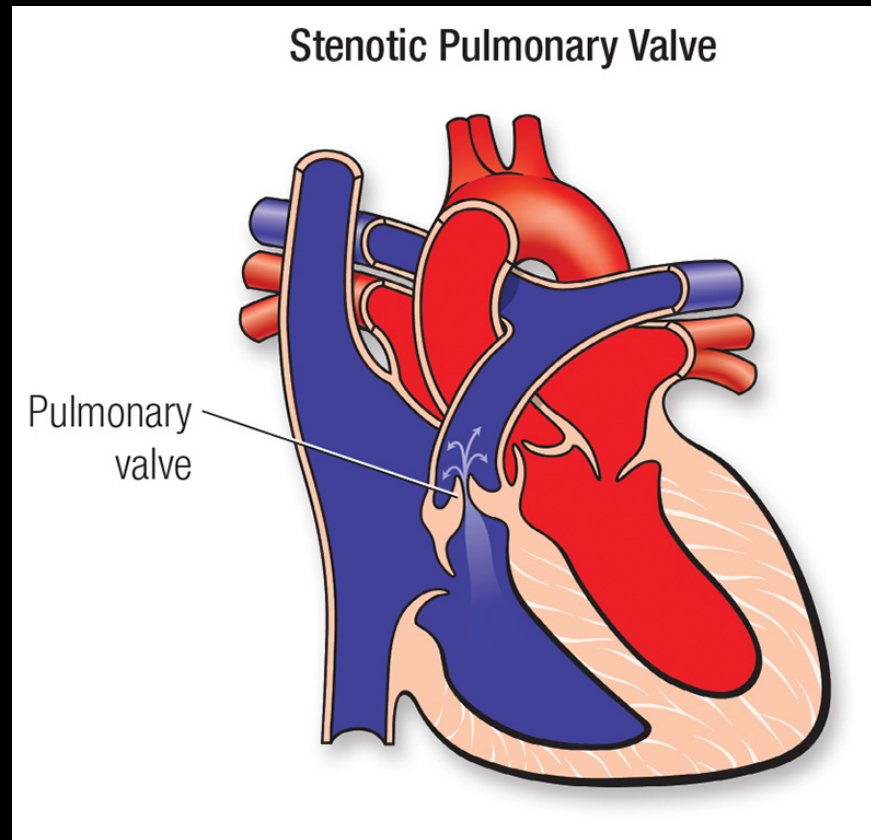
NS Heart Involvement

FREQUENCY OF FLAVORS

- Pulmonary Valve Stenosis 40%
- Hypertrophic Cardiomyopathy 10%
- Aortic Coarctation 9%
- Secundum Atrial Septal Defect 8%

NS Congenital Heart Disease

PULMONIC STENOSIS



NS Congenital Heart Disease

PULMONIC STENOSIS

- Severity
 - Mild
 - Moderate (35-70 mm Hg)
 - Severe (>70 mm Hg)
- Effects
 - Mild: Murmur Only
 - Moderate: Exercise Limitations
 - Severe: Sick Neonates

NS Congenital Heart Disease PULMONIC STENOSIS



NS Congenital Heart Disease

PULMONIC STENOSIS

- Treatment
 - Mild: Observation
 - Moderate-Severe
 - Catheterization
 - Surgery

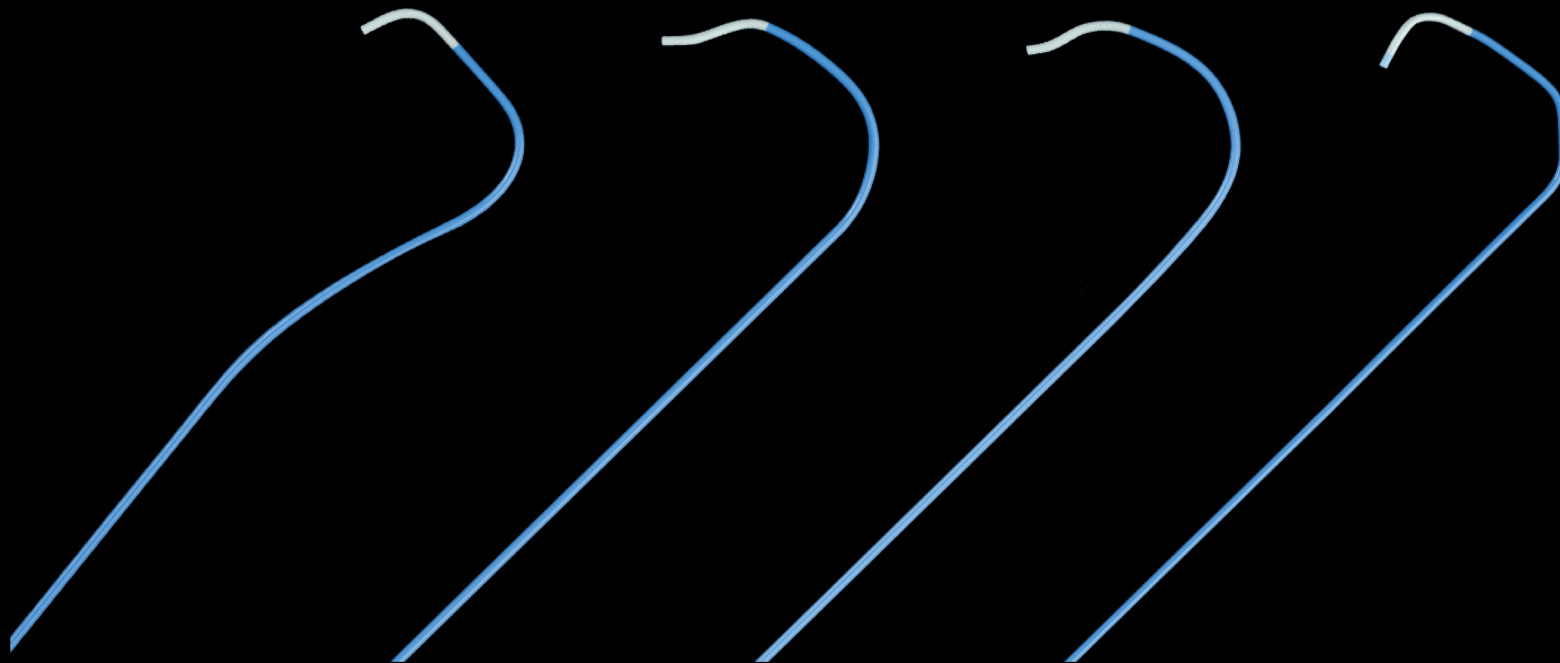
Heart Catheterization



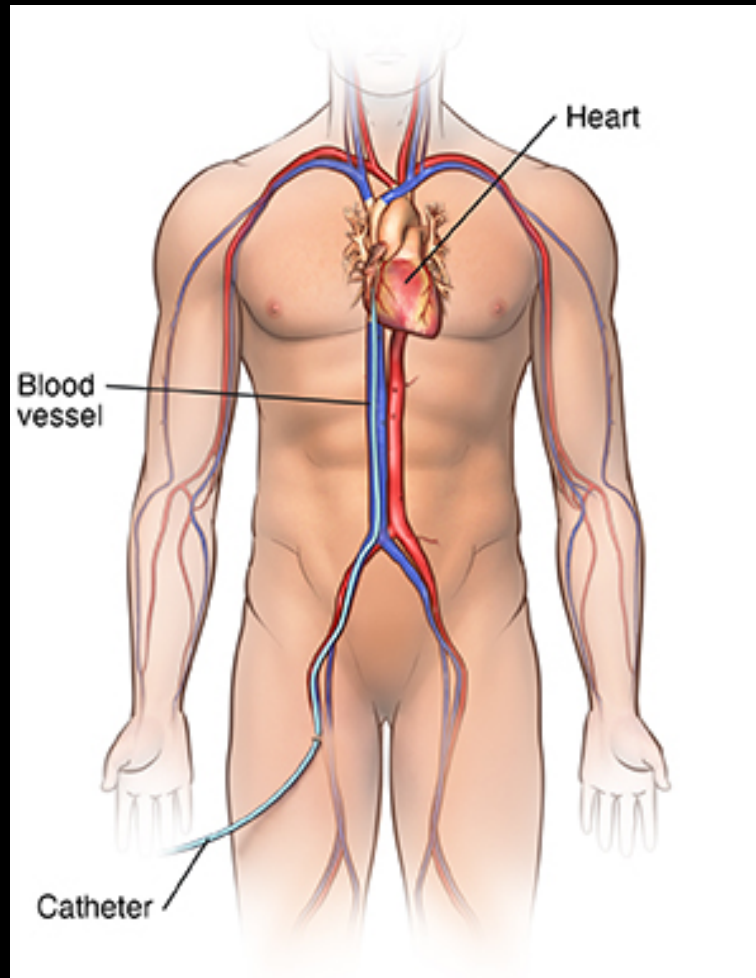
Heart Catheterization



Heart Catheterization



Heart Catheterization



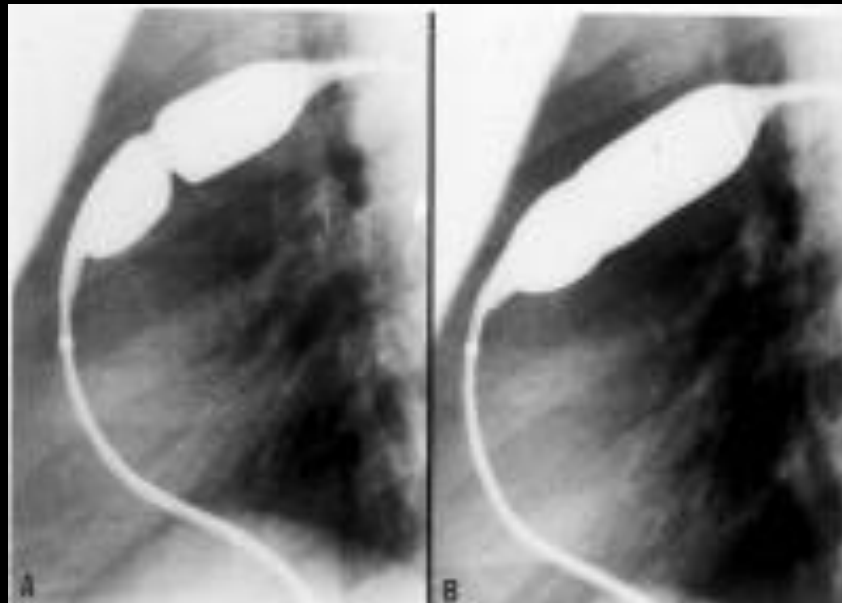
NS Congenital Heart Disease

PULMONIC STENOSIS



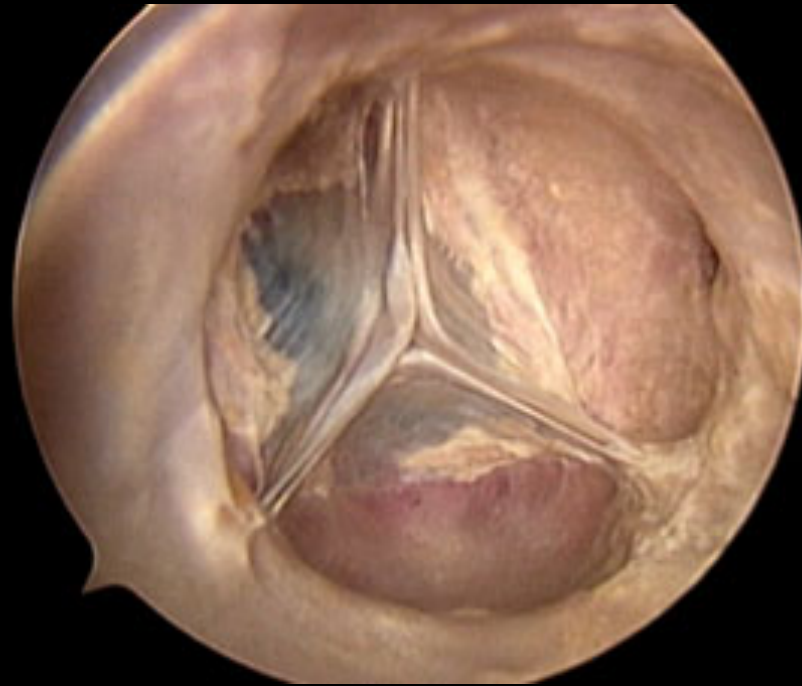
NS Congenital Heart Disease

PULMONIC STENOSIS



NS Heart Involvement

PULMONARY VALVE



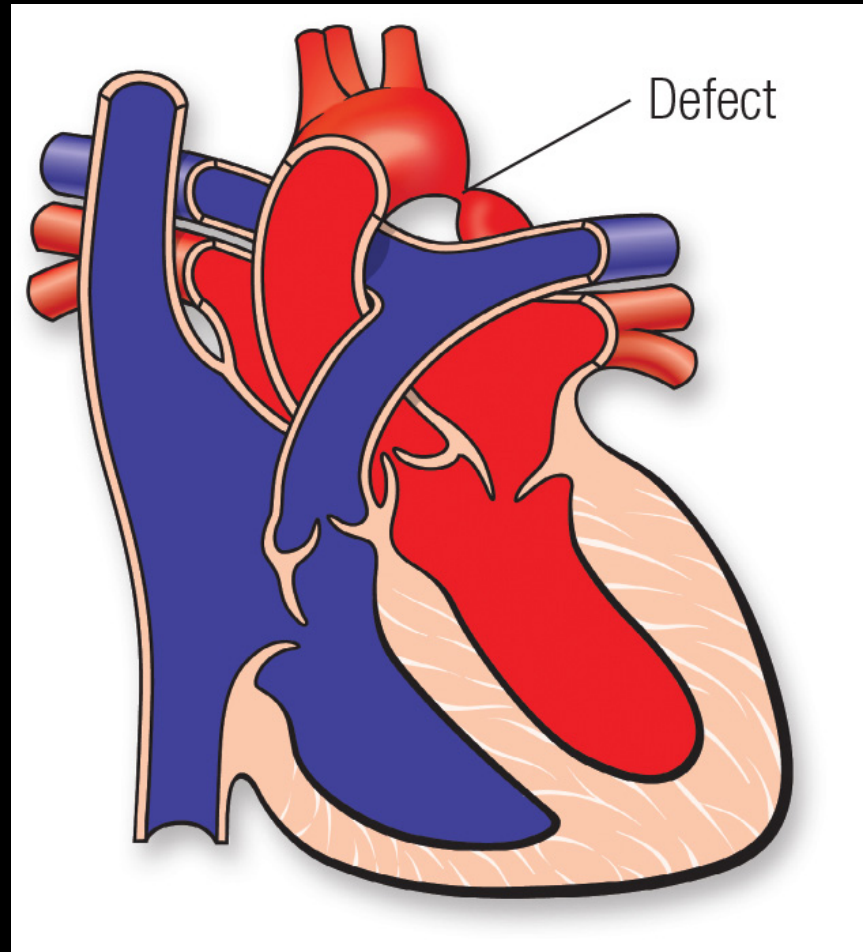
NS Heart Involvement

DYSPLASTIC PULMONARY VALVE



NS Congenital Heart Disease

AORTIC COARCTATION



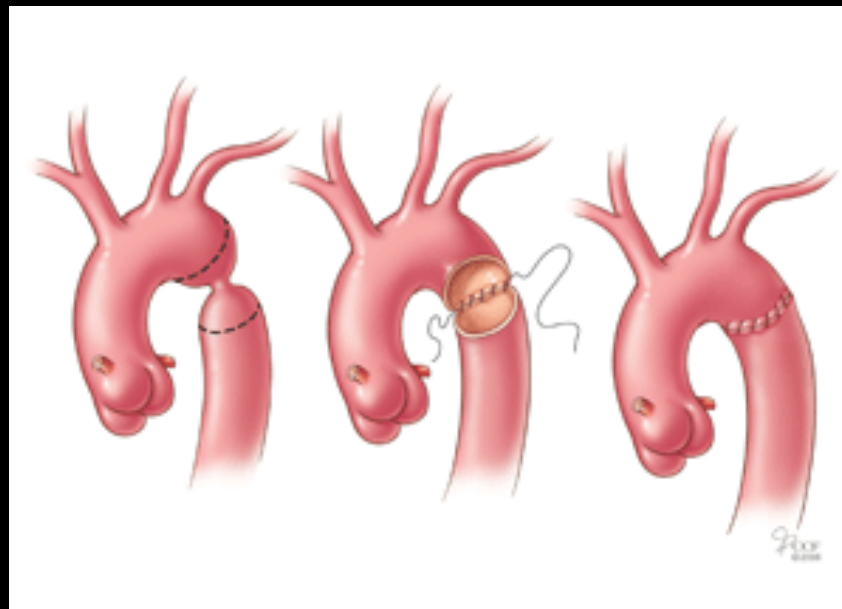
NS Congenital Heart Disease

AORTIC COARCTATION

- Severity
 - Mild-Moderate
 - Variable Presentation
 - Surgery
 - Severe-Critical
 - Present as Newborns
 - Stabilize, Then Surgery

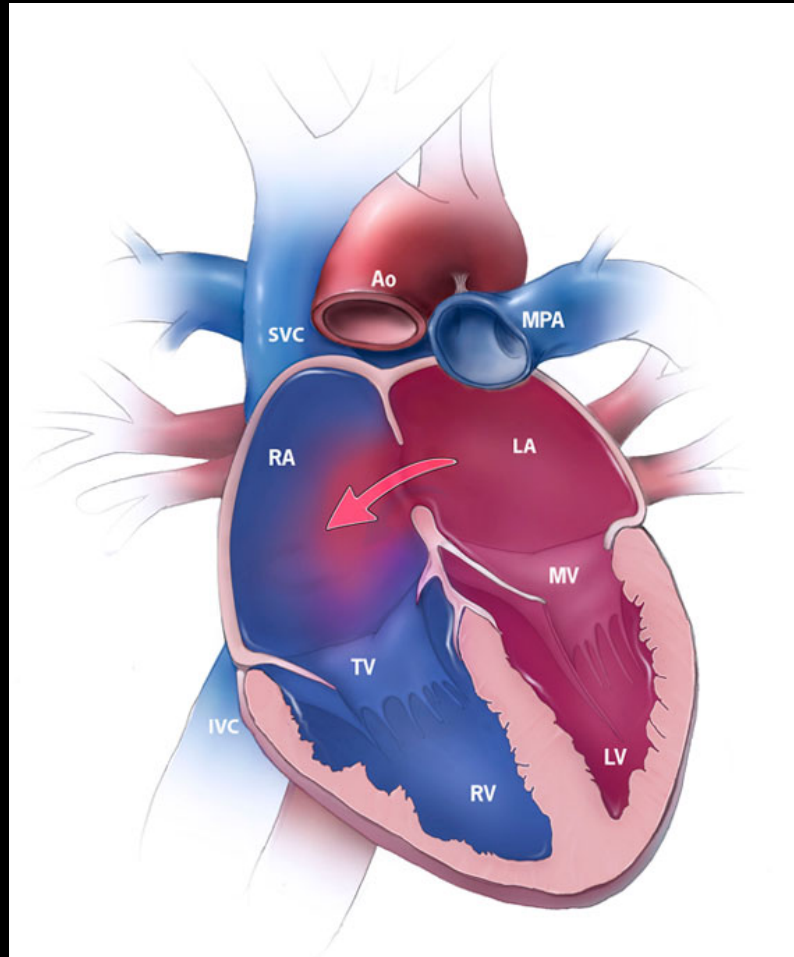
NS Congenital Heart Disease

AORTIC COARCTATION



NS Congenital Heart Disease

ATRIAL SEPTAL DEFECT



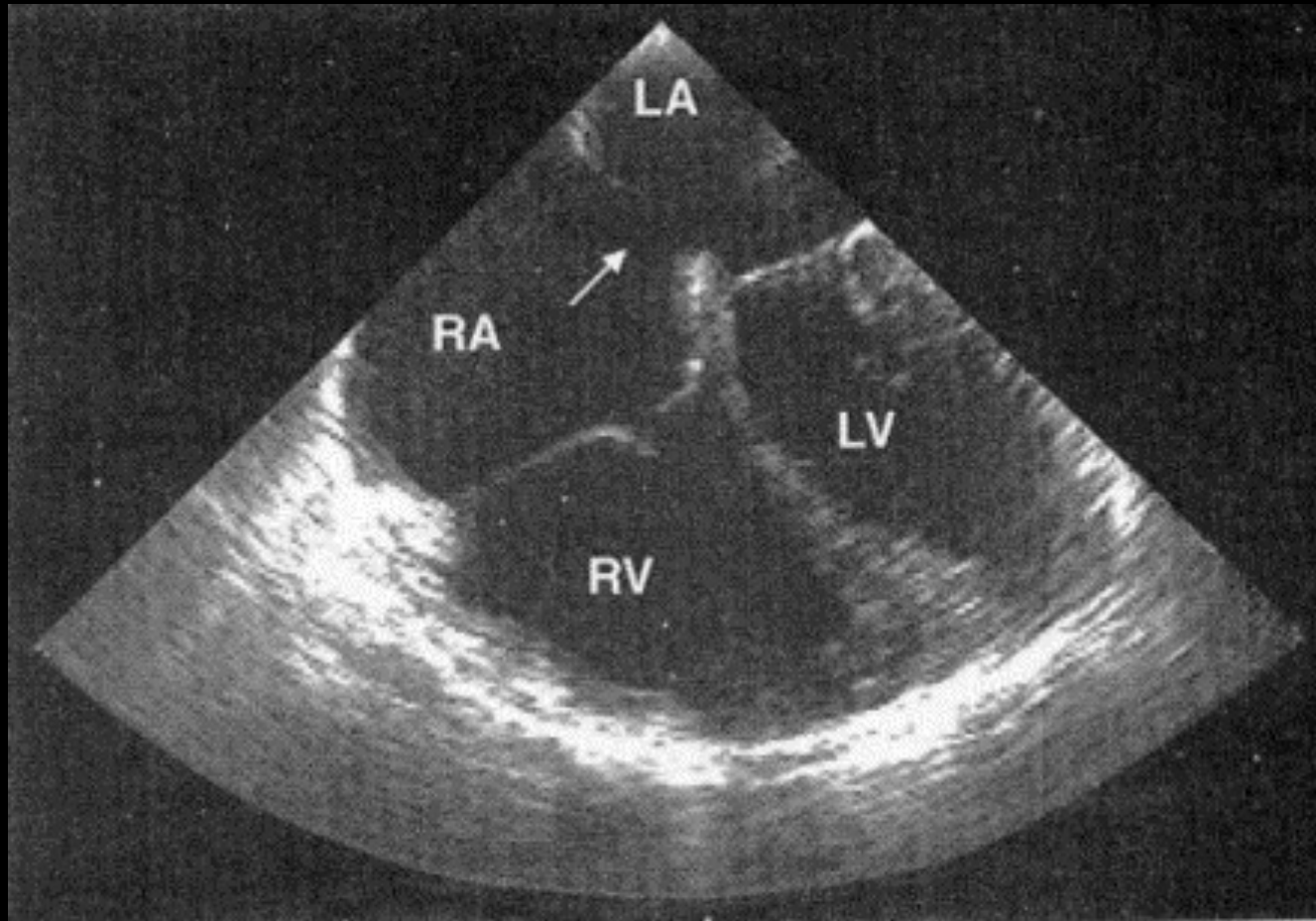
NS Congenital Heart Disease

ATRIAL SEPTAL DEFECT

- Size
 - Tiny- Small
 - No Symptoms
 - Can Close Spontaneously
 - Medium-Large
 - Symptoms Rare in Childhood
 - Need Closure

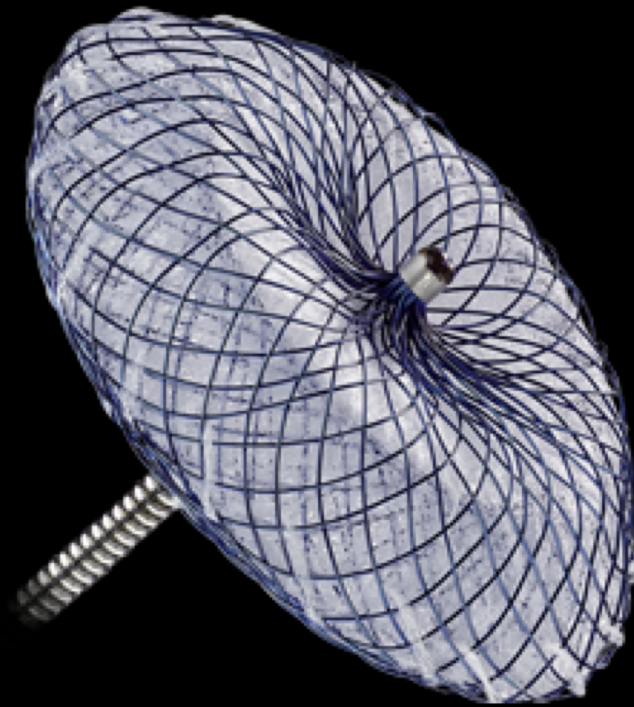
NS Congenital Heart Disease

ATRIAL SEPTAL DEFECT

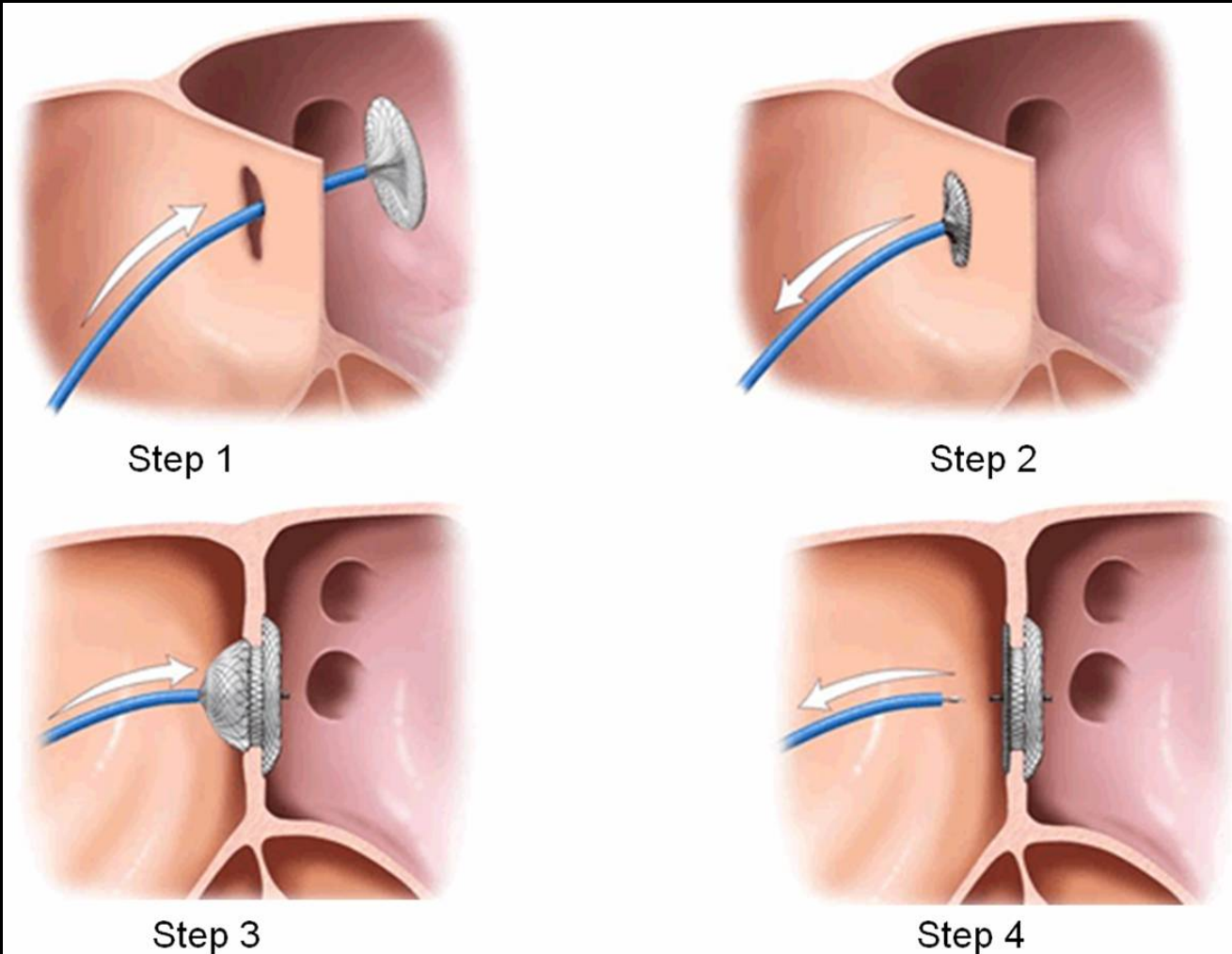


NS Congenital Heart Disease

ATRIAL SEPTAL DEFECT

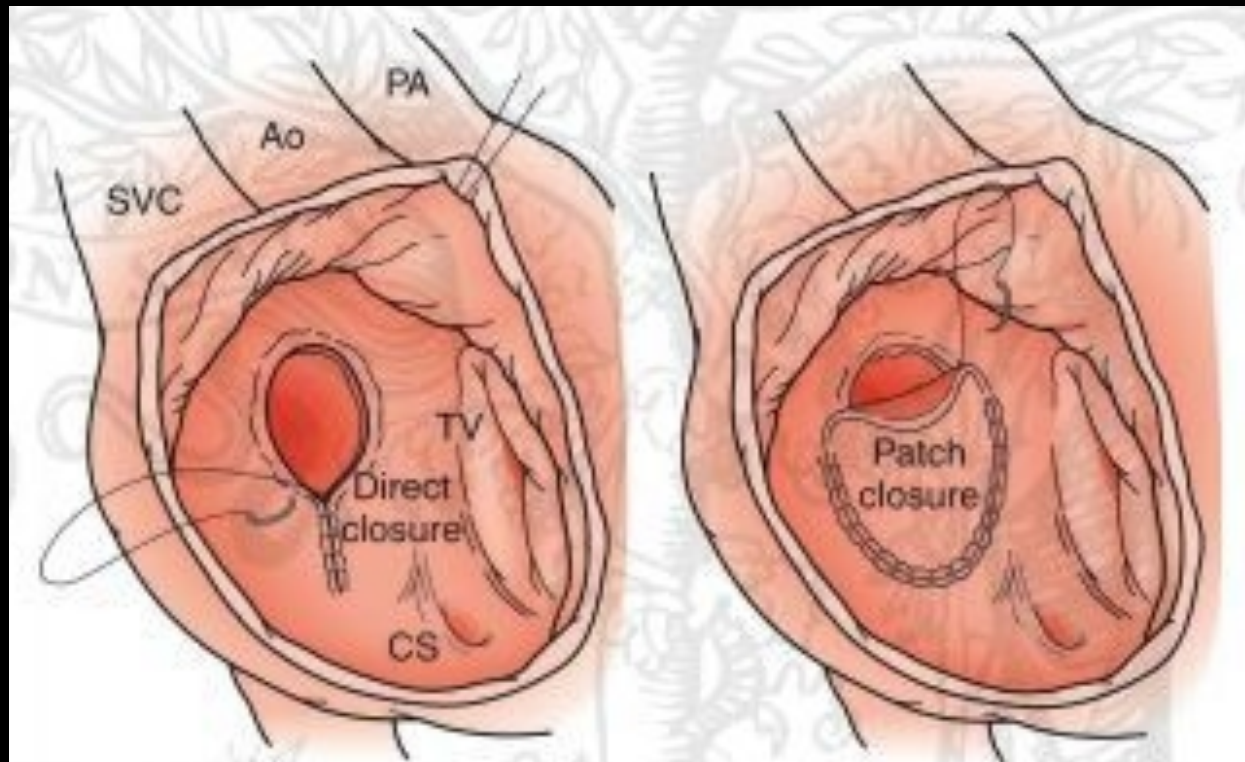


NS Congenital Heart Disease ATRIAL SEPTAL DEFECT



NS Congenital Heart Disease

ATRIAL SEPTAL DEFECT



NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY



Normal heart
(cross section)



Hypertrophic
cardiomyopathy

NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY

- Severity
 - Variable
 - No Symptoms
 - Congestive Heart Failure
 - Onset
 - Newborn
 - Adolescence

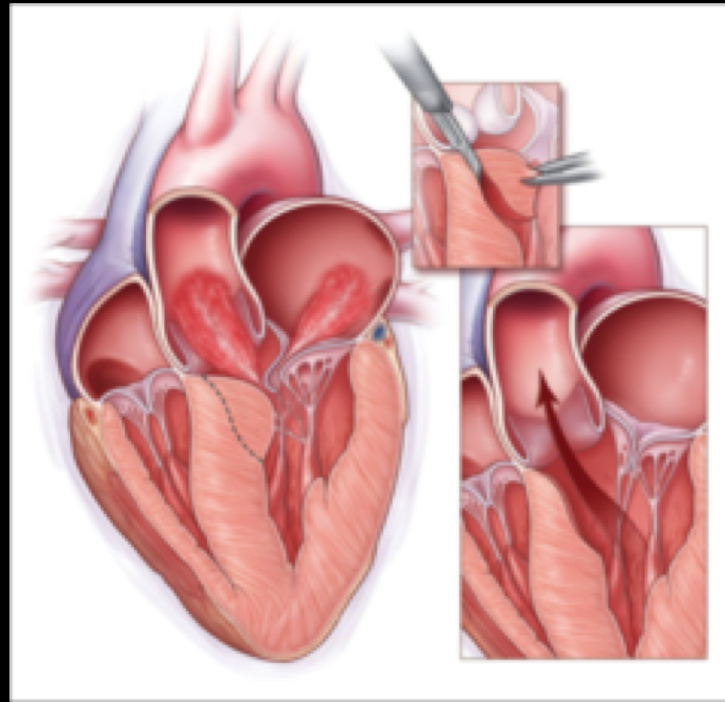
NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY

- Treatment
 - None
 - Medical
 - Various Types of Drugs
 - For Symptoms, Not Cure
 - Surgical
 - For Symptoms, Not Cure

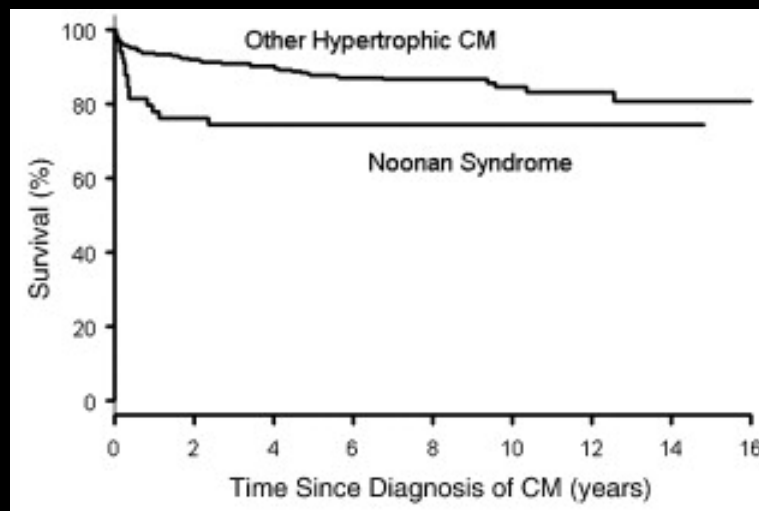
NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY



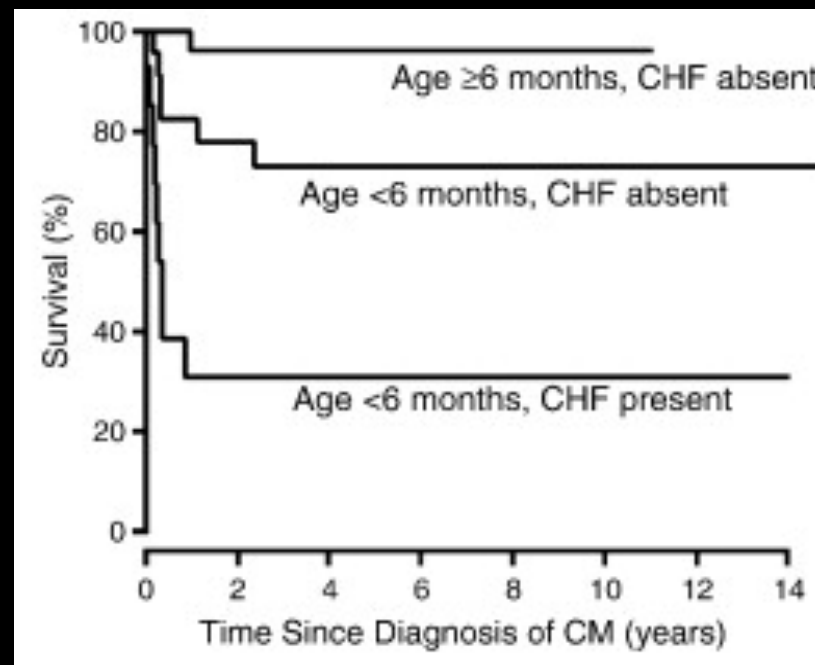
NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY



NS Heart Muscle Disease

HYPERTROPHIC CARDIOMYOPATHY



NS Heart Involvement

TYPICAL FOLLOW-UP

- Baseline
 - Exam, ECG, Echocardiogram
- Normal Baseline
 - Annual until 3, then 5, 10, 15
- Hypertrophic Cardiomyopathy
 - Infants- Carefully
 - Older- Annually
- Congenital Heart Disease
 - Variable

NS Heart Involvement

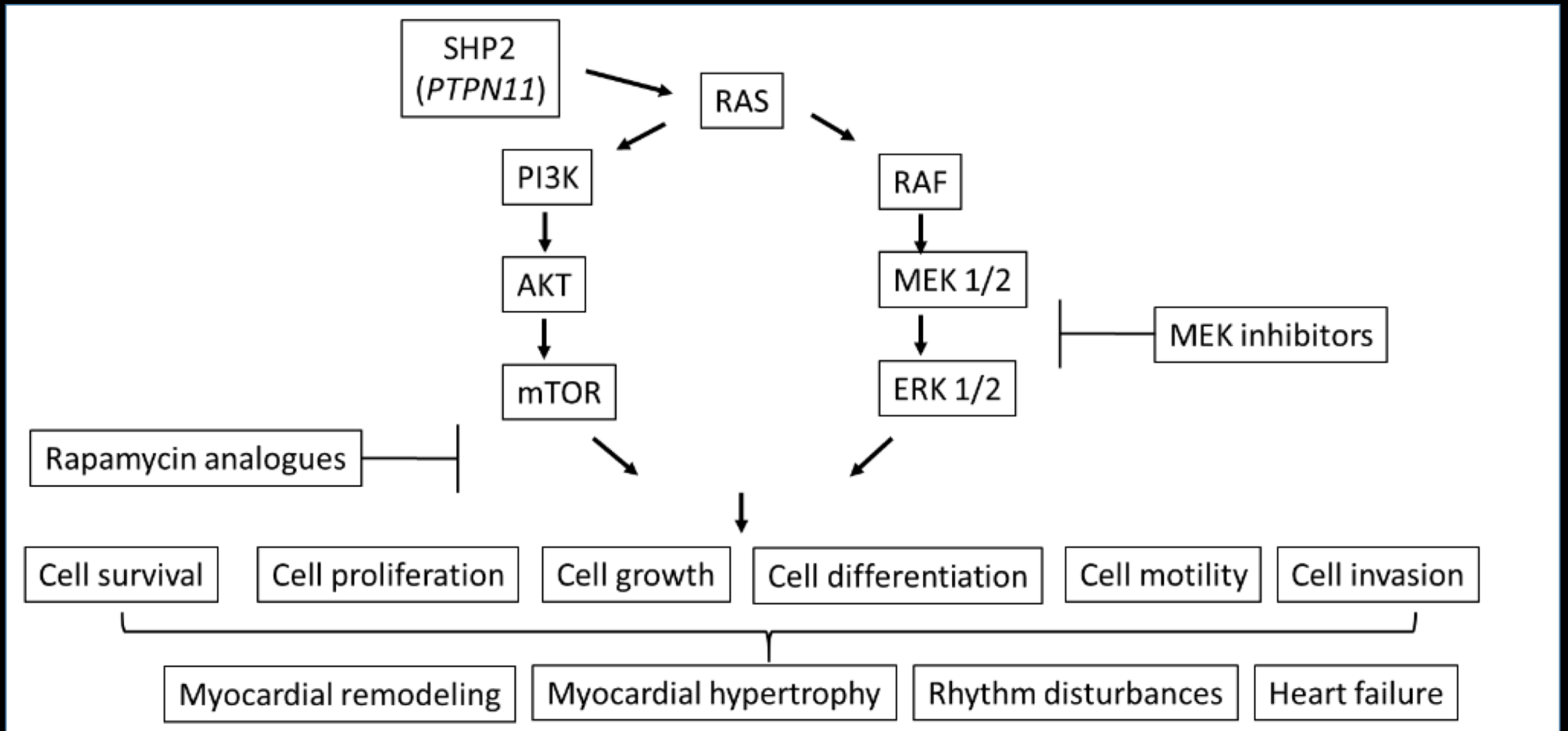
SPECIAL CONSIDERATIONS

- Pediatric Cardiology
 - “Noonan Expert” Not Necessary
- Pulmonary Valve Stenosis
 - Later Progression
- Hypertrophic Cardiomyopathy
 - Not Typical, Particularly for Infants
- Pre-Procedure
 - Evaluation for Bleeding
- Anesthesia
 - Typical Risk



NS Heart Disease

TREATMENT POSSIBILITIES

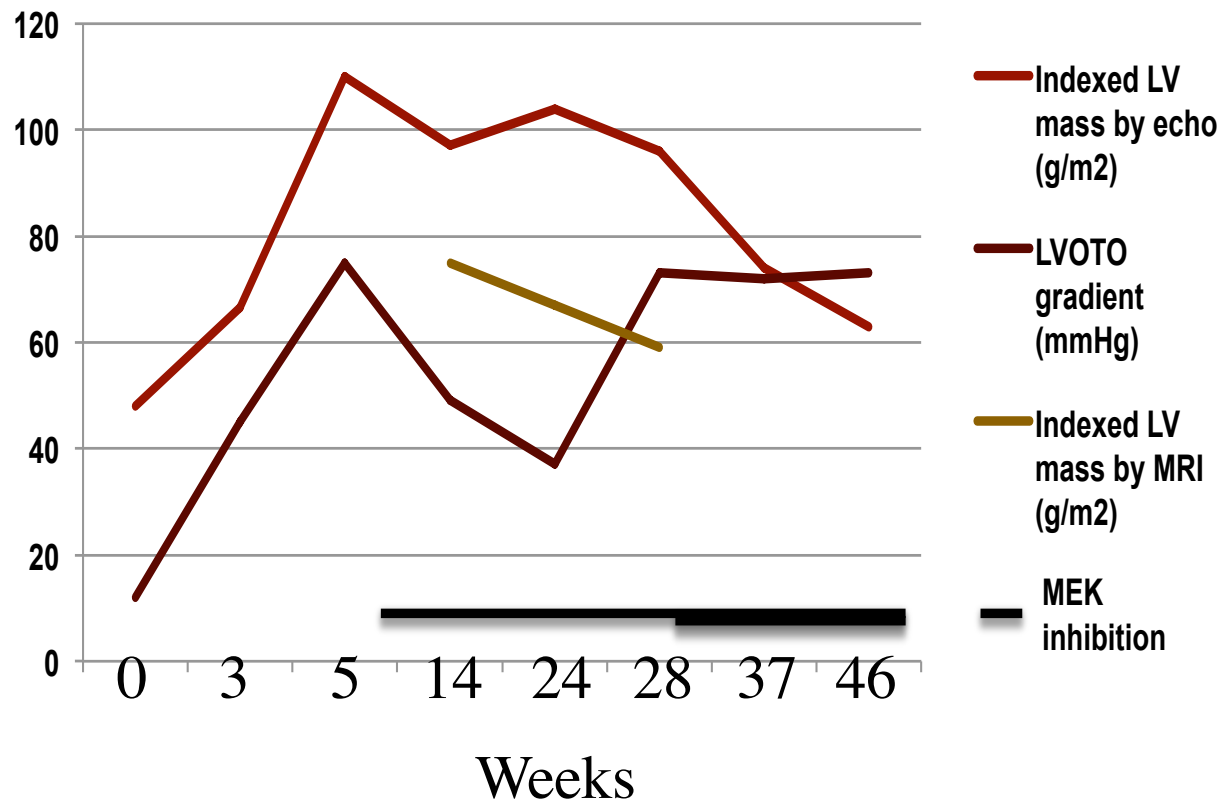


NS HCM TRAMETINIB

- 2 Infants with NS with Severe HCM
 - Both with *RIT1* Mutations
- High-Dose Beta Blockers
- Oral Trametinib
- Compassionate Usage Basis
- Results: Both Survived and Improved

NS HCM TRAMETINIB

Left ventricular mass and gradient



NS Lymphovascular Disease

TRAMETINIB TREATMENT

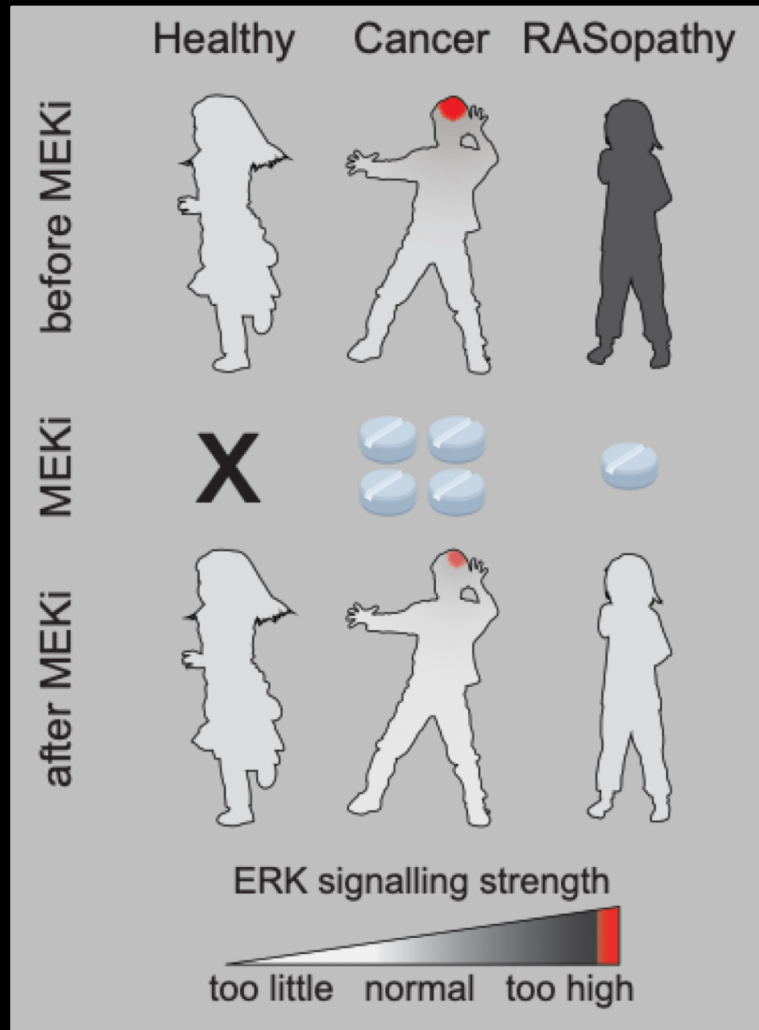
- 16-Year-Old with NS (*SOS1*)
 - Leaking Lymphatic Fluid in Gut and Lungs
 - Dilated Lymphatic Vessels in Gut and Lungs
 - Failed Medical and Interventional Approaches
- Trametinib
 - Symptoms Resolved by 8 Weeks
 - Remained Well on Treatment at 6 Months

NS MEKi Treatment Questions

- Does it really work?
- For whom does it work?
 - Ages?
 - Genes?
- Do what aspects of NS does it work?
- What are the side effects in patients with NS?

MEKi Treatment

NS \neq CANCER



NS Treatment PATH FORWARD

- Interest from Pharmaceutical Company
- Interact with the FDA
- Clinical Trial(s)
 - HCM
 - Lymphatic
- Build on Success and Insights
- Develop Additional Drugs

