Variants of Hypertrophic Cardiomyopathy?

Steven J. Lester MD, FRCP(C), FACC, FASE

MAYO CLINIC

DISCLOSURE

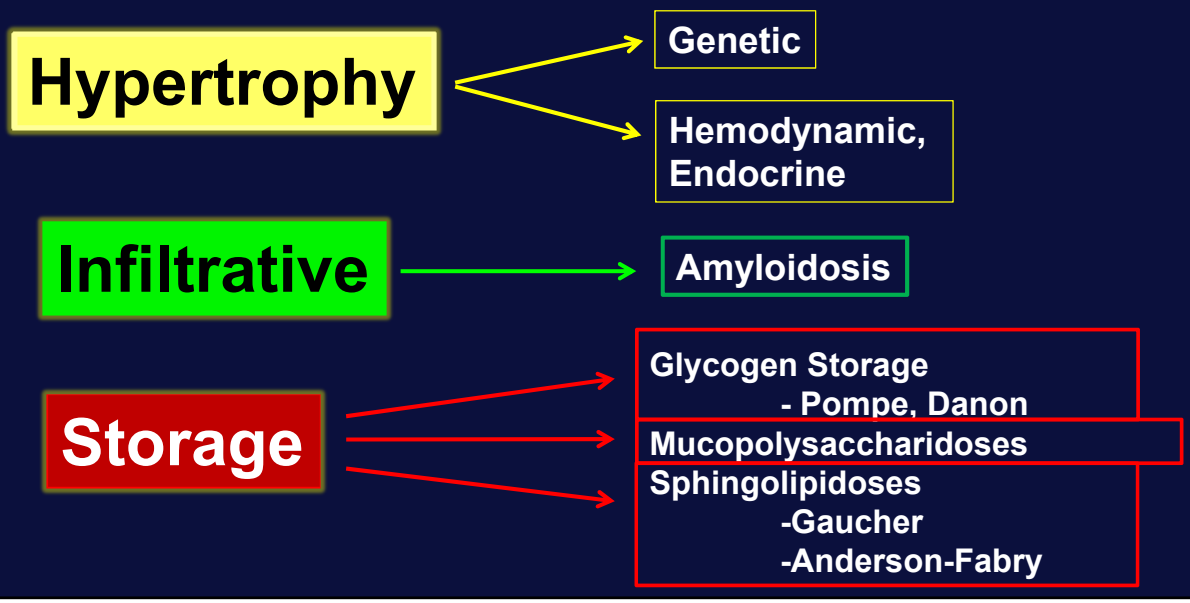
Relevant Financial Relationship(s)

None

Off Label Usage

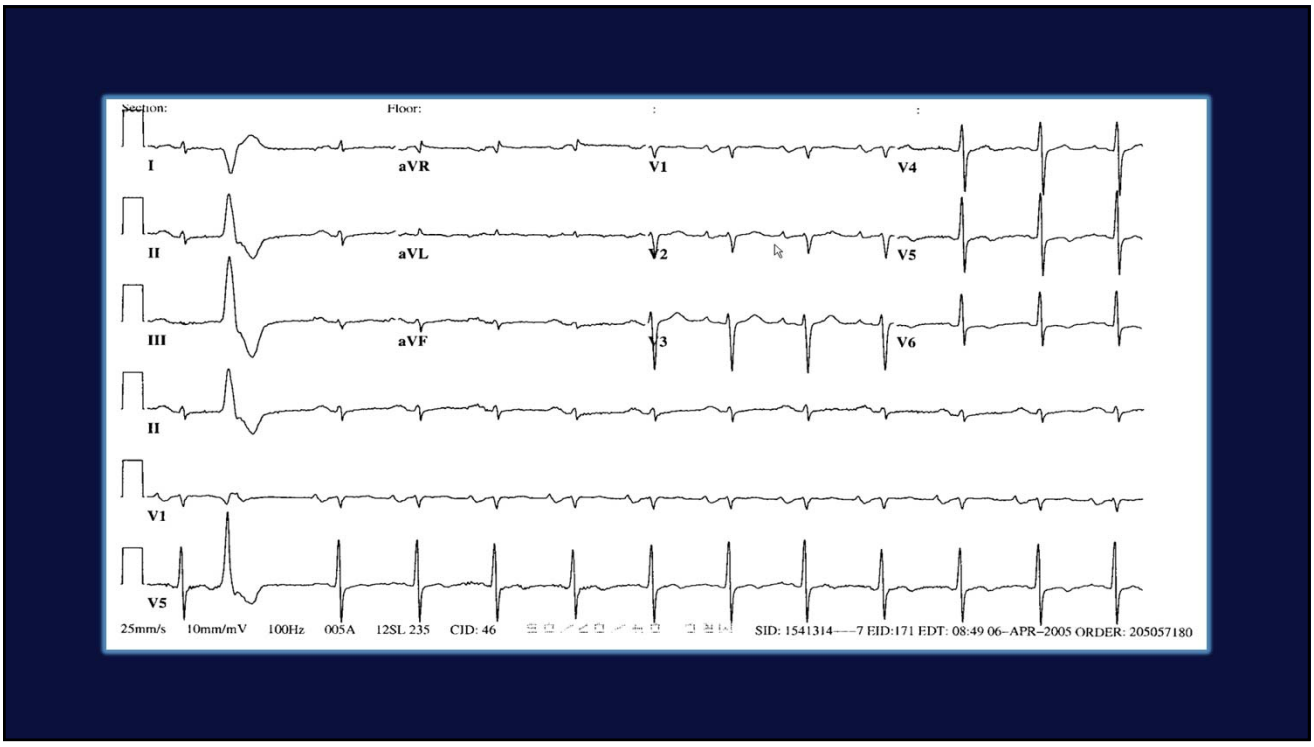
None

Thick Walls Why?



Case

- 47 year old male
- 2005 several near syncope episodes.
- Eventually while at a the Phoenix Suns game had a true syncopal episode.


Section:
Floor:
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
V1
V5
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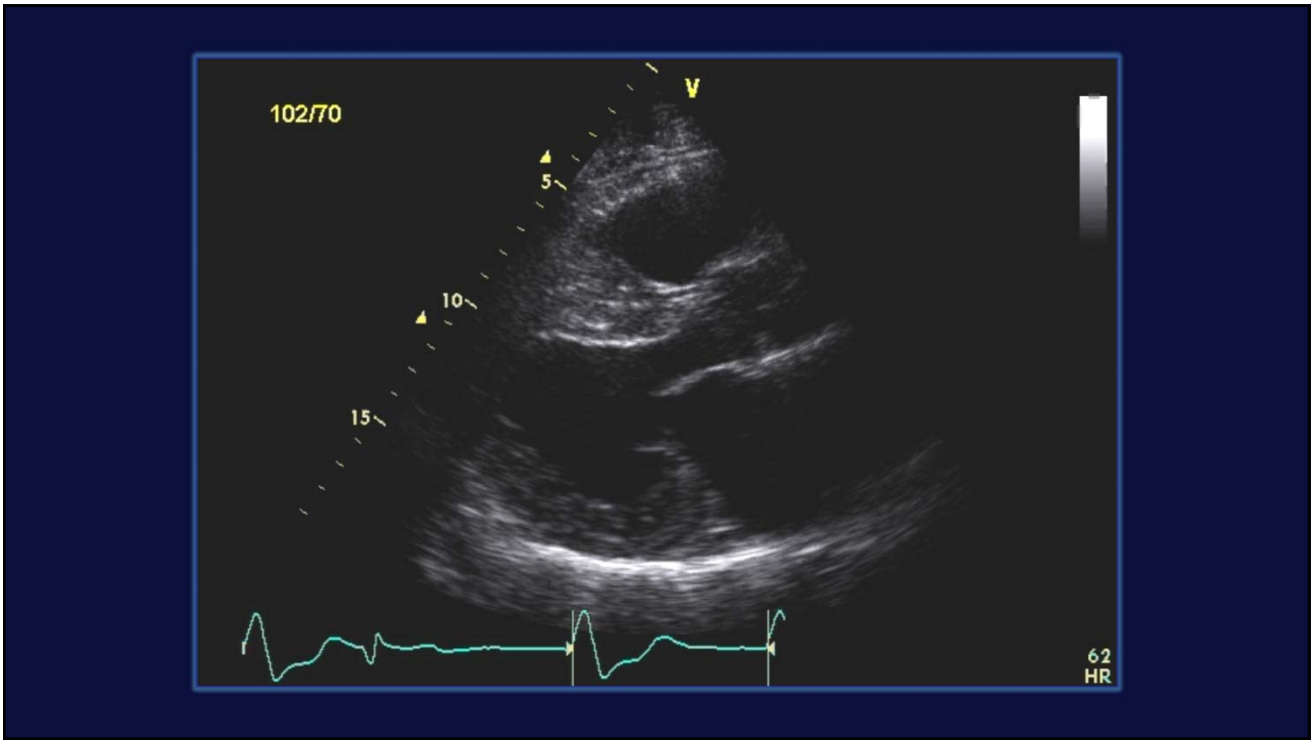
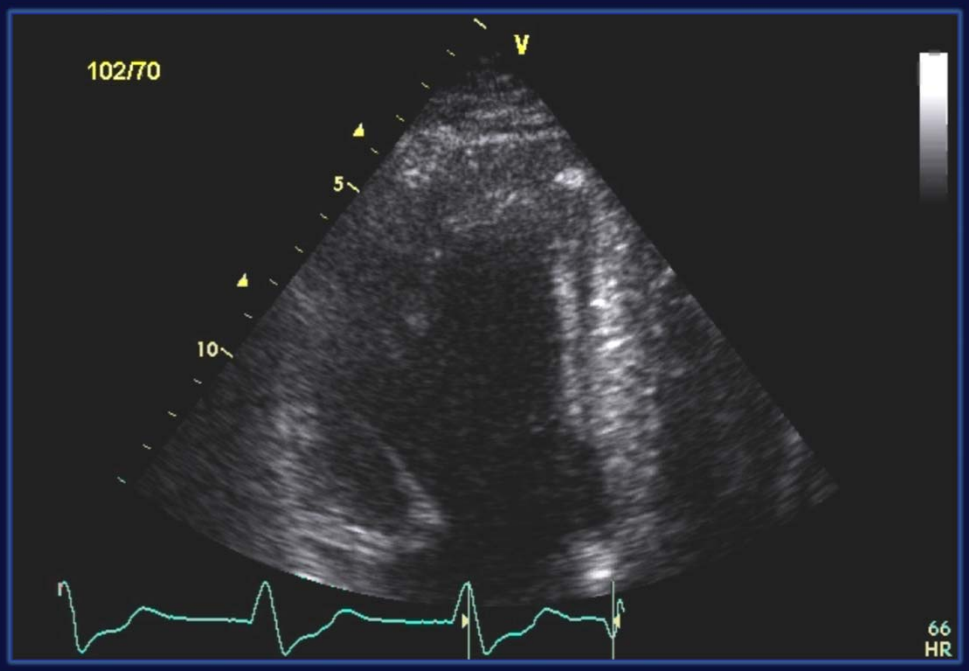

102/70
V
5
10
15
62
HR



Hypertrophic Cardiomyopathy

Echocardiographic Diagnosis

Left Ventricular Hypertrophy ≥ 15mm

The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease is based on presence of unexplained increase in LV wall thickness ≥ 13 mm in one or more LV segments.

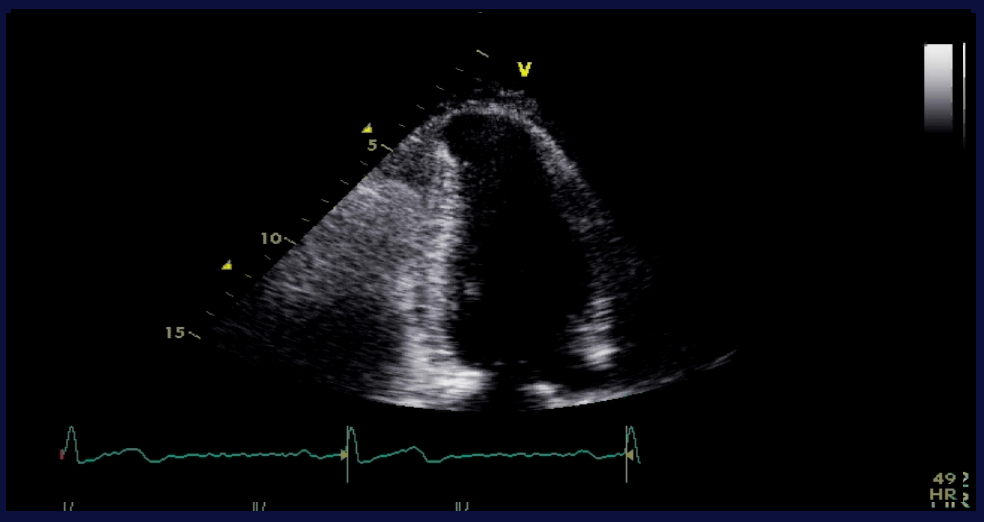
Maron et al. J Am Coll Cardiol 2003;42: 1687

Hypertrophic Cardiomyopathy
Echocardiographic Diagnosis

What is NOT needed for the diagnosis

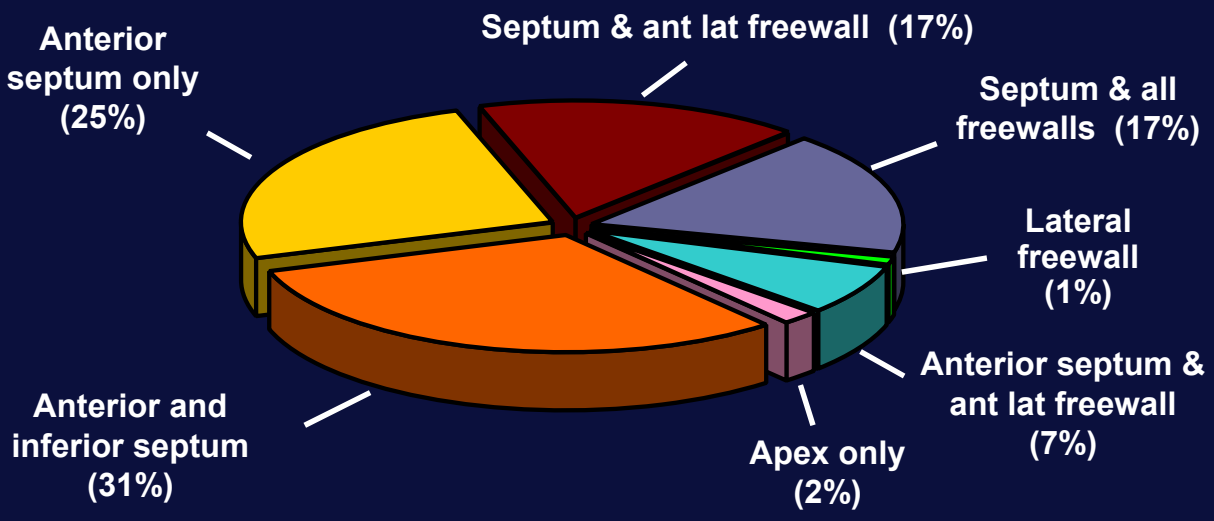
- Asymmetric Septal Hypertrophy (ASH)
- Systolic Anterior Motion (SAM)
- Resting or labile LVOT obstruction

Hypertrophic Cardiomyopathy
Diversity in Phenotype



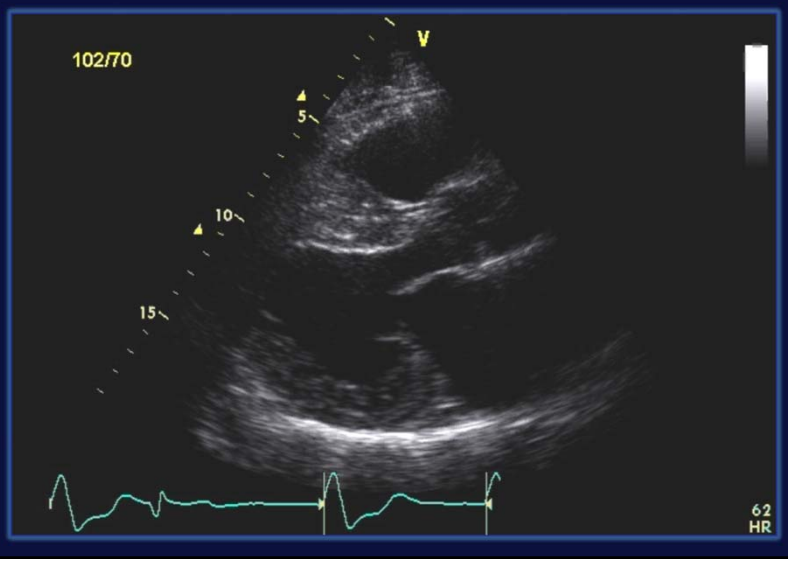
Hypertrophic Cardiomyopathy

Distribution of LVH (600 Patients)



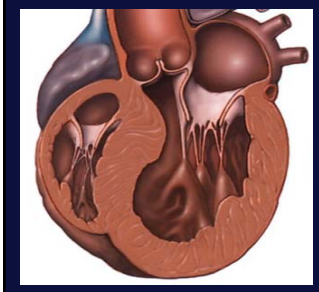
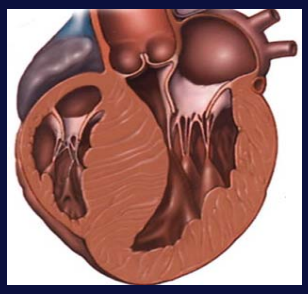
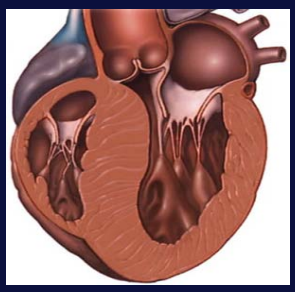
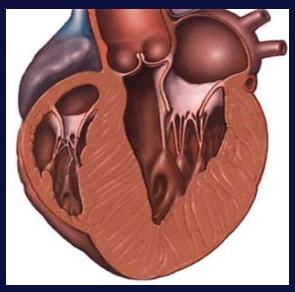
Klues HG, JACC 1995; 26: 1699

Diagnosis:
Hypertrophic Cardiomyopathy



Left Ventricular Morphology in HCM

"Morphogenetics"

Sigmoid Septum	Reverse Septum	Neutral Septum	Apical Variant
			
181(47%) Gene + (8%)	132(35%) Gene + (79%)	32(8%) Gene + (41%)	37(10%) Gene + (32%)

Binder J, et al. Mayo Clin Proc 2006; 81: 459.

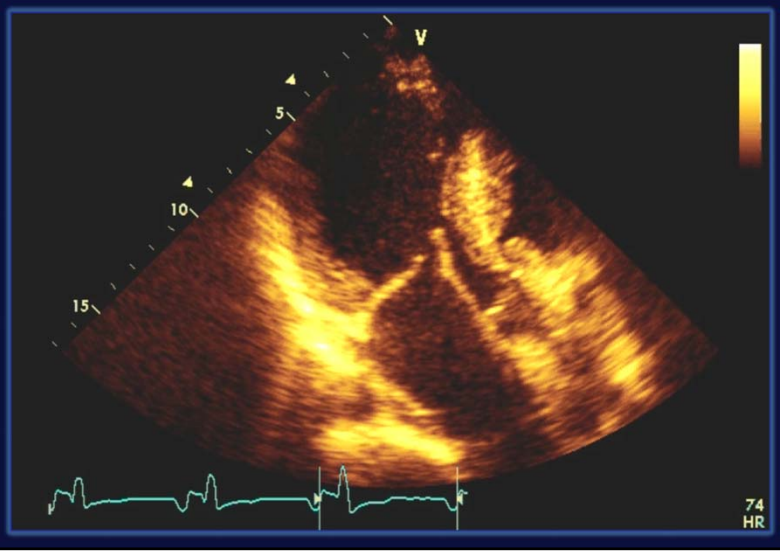
Genetic testing for HCM

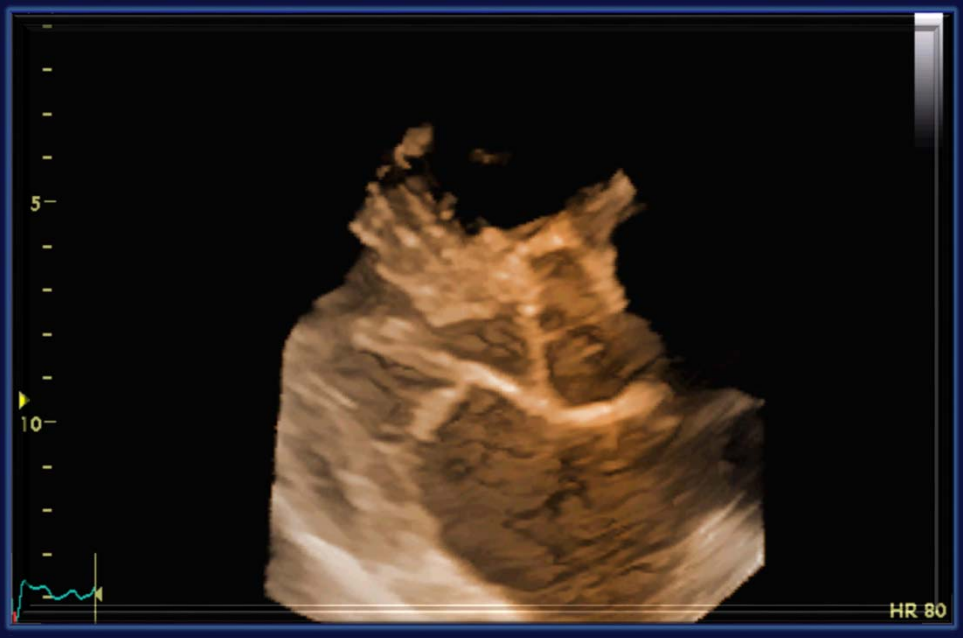
Mayo Clinic Database (389 Patients)

- Echocardiographic anatomic phenotypes are not specific for individual gene mutations
- Specific gene mutations not predictive of prognosis or need for myectomy

Van Driest SL, et al. Mayo Clin Proc 2005; 80: 739

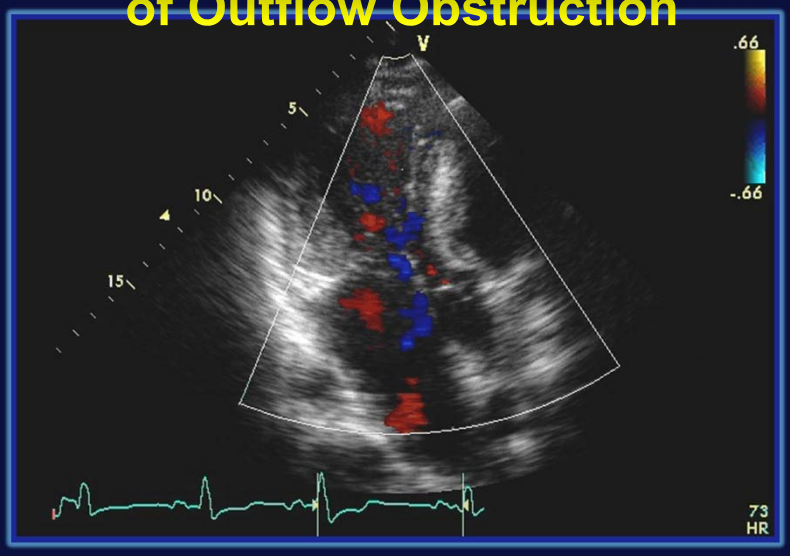
Mitral Valve and Papillary Muscle Anatomy



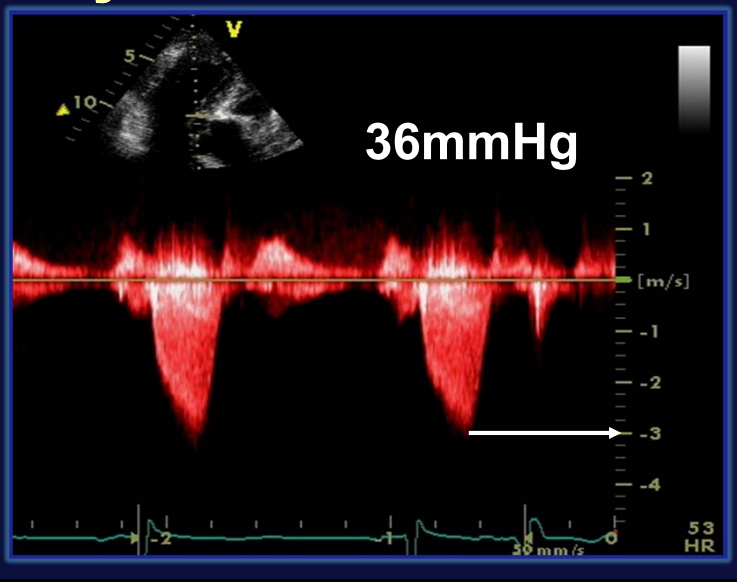


Mitral Regurgitation

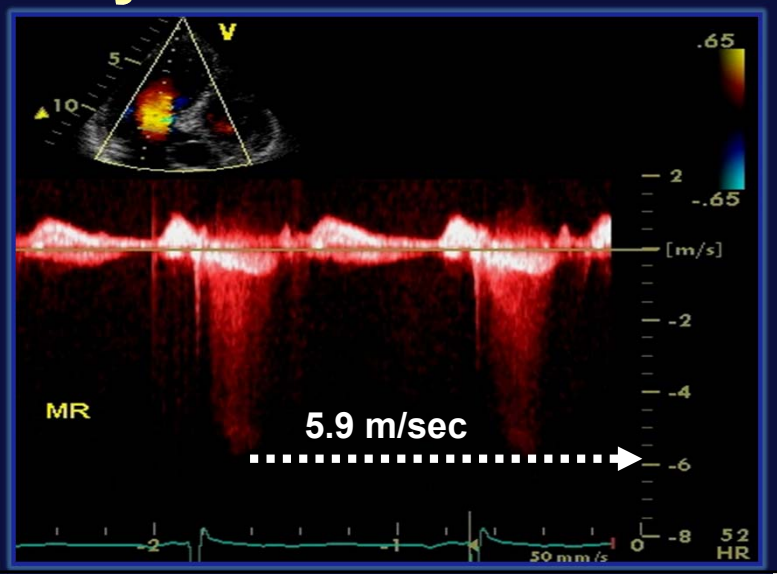
Location, Presence and Severity of Outflow Obstruction



Identify of Location, Presence and Severity of Outflow Obstruction



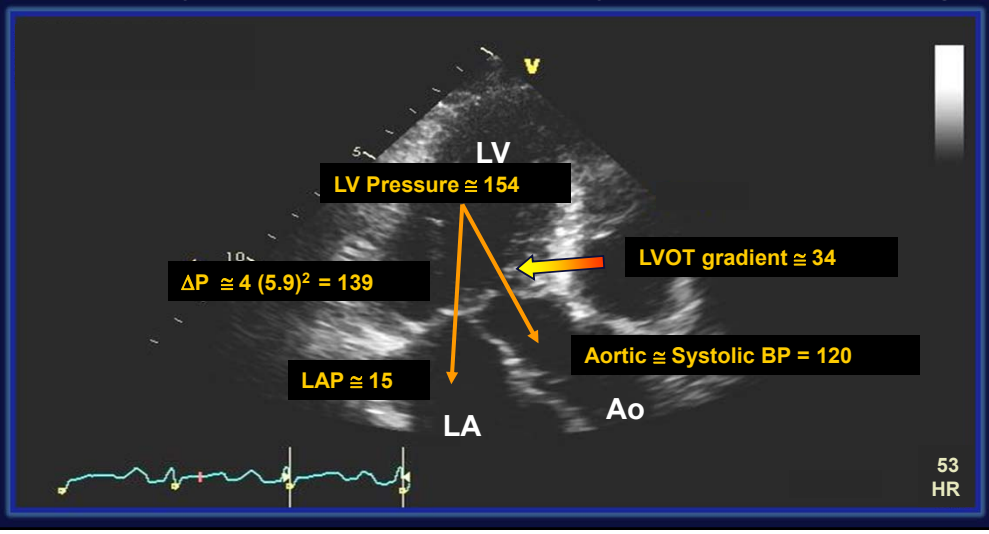
Identify of Location, Presence and Severity of Outflow Obstruction



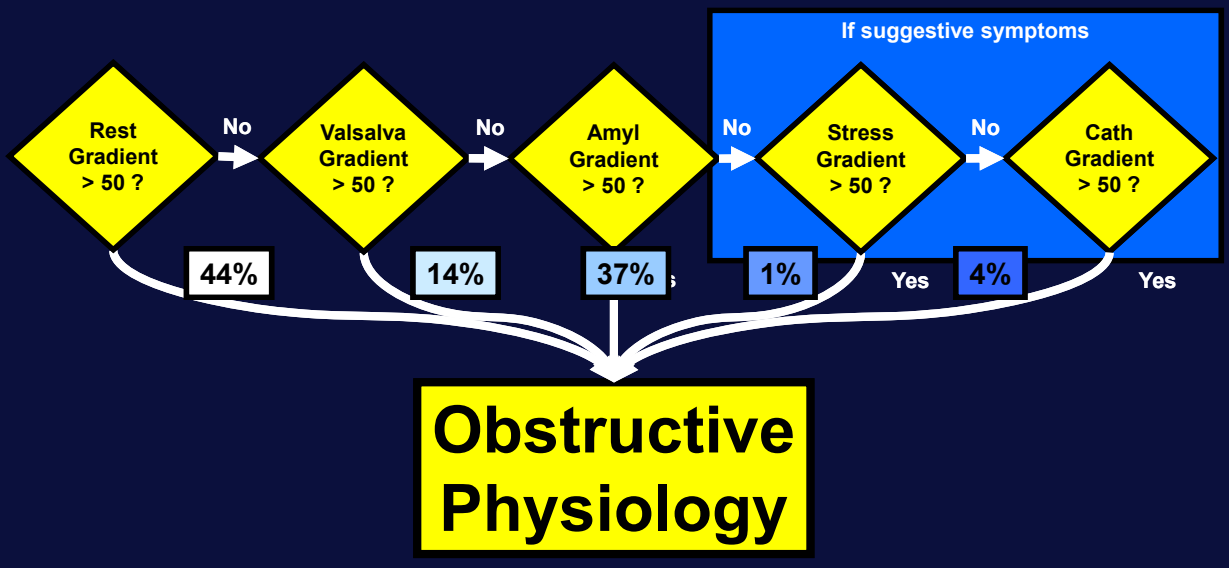
Estimating LVOT Gradient Using MR Peak Velocity

MR Velocity = 5.9 m/sec

Systolic BP = 120 mmHg

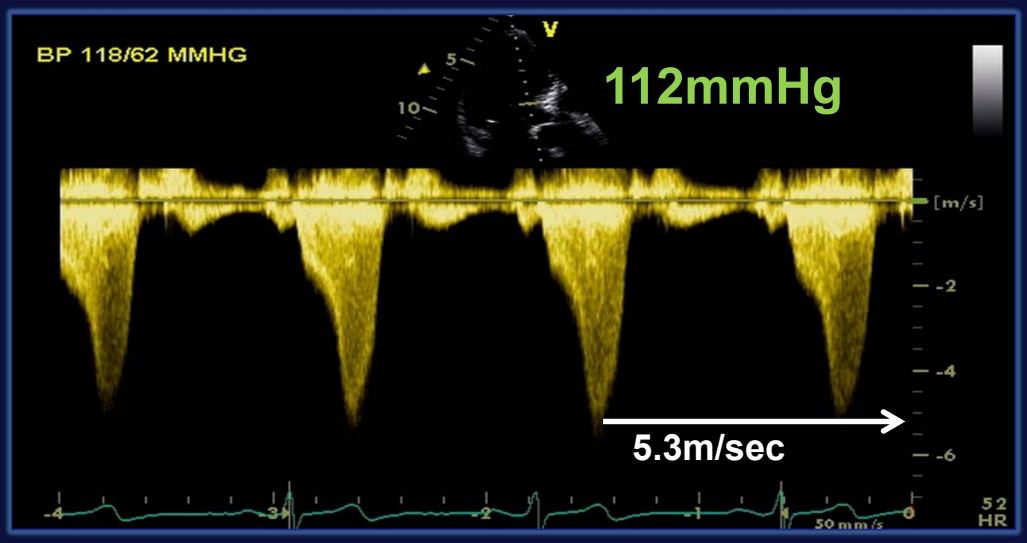


Pursuit of Obstruction



Courtesy of Steve Ommen

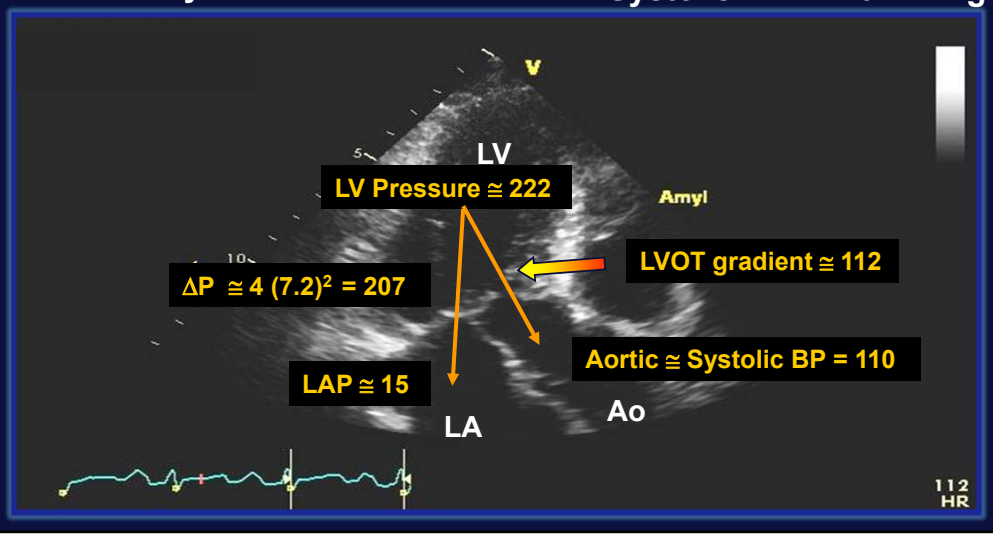
Gradient: Amyl Nitrite



Estimating LVOT Gradient Using MR Peak Velocity

MR Velocity = 7.2 m/sec

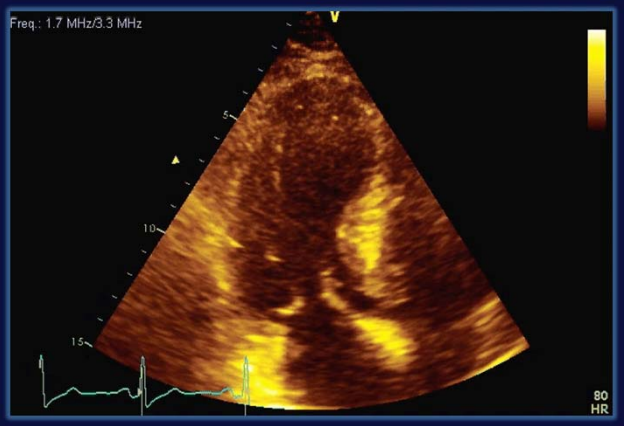
Systolic BP = 110 mmHg

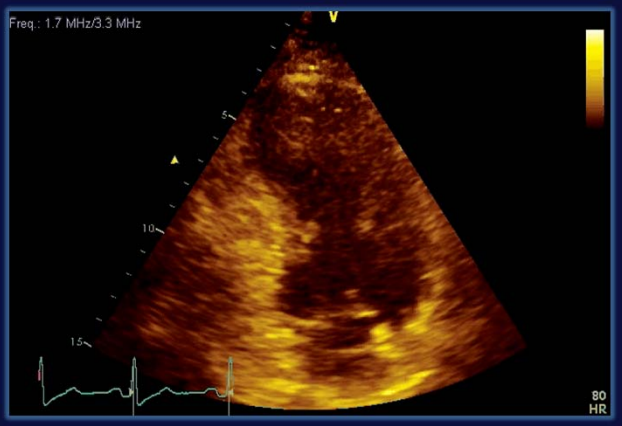


Case
Pursuit of Obstruction

- 58 year old male
- HCM, genotype + (MYH7)
- NYHA II-III; fatigue and SOB

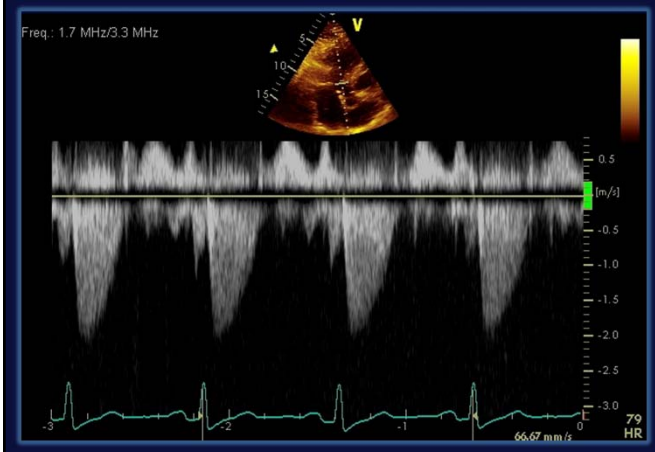
Transthoracic Echocardiogram



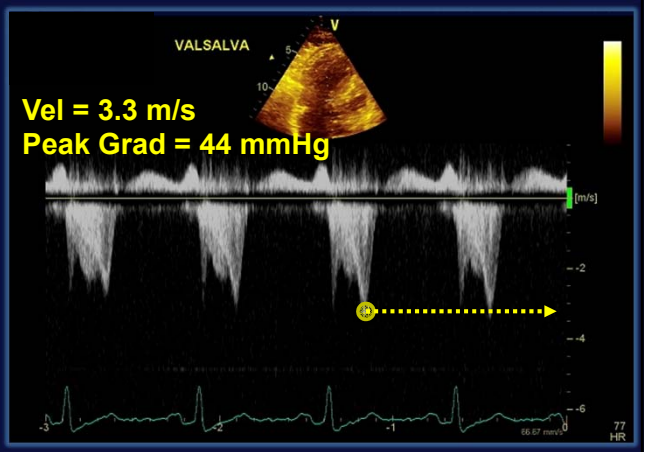


Continuous Wave Doppler

REST

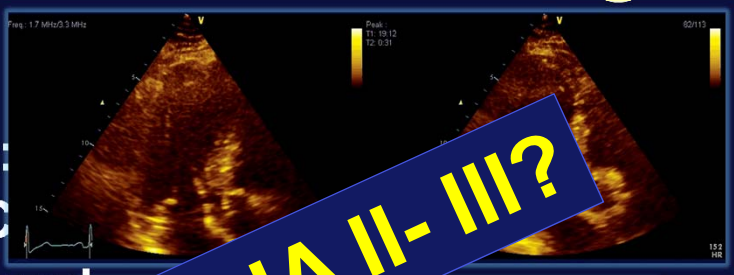


Strain Phase of Valsalva

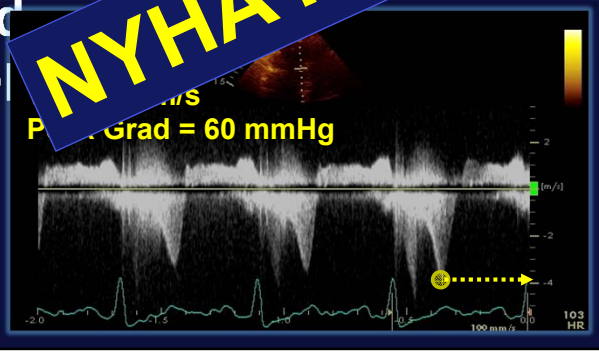


Stress Echocardiogram

- Bruce: 10:
- 118% FAC
- Normal blood pressure res

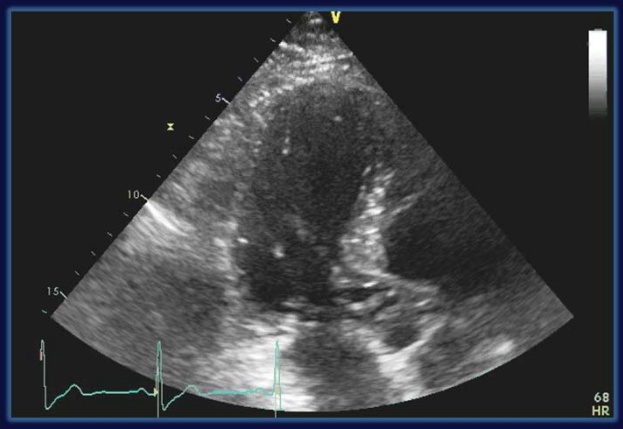


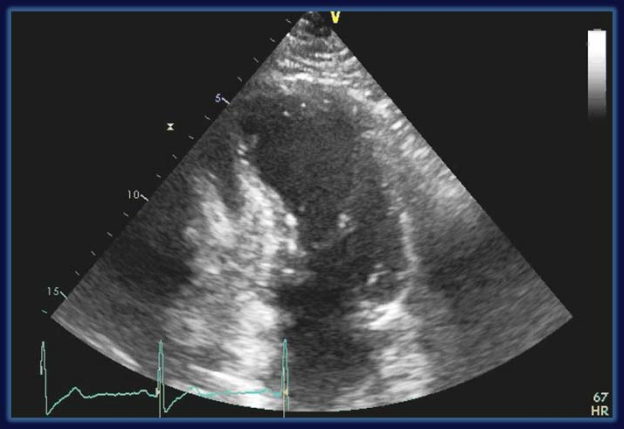
NYHA II- III?



3 Months Later

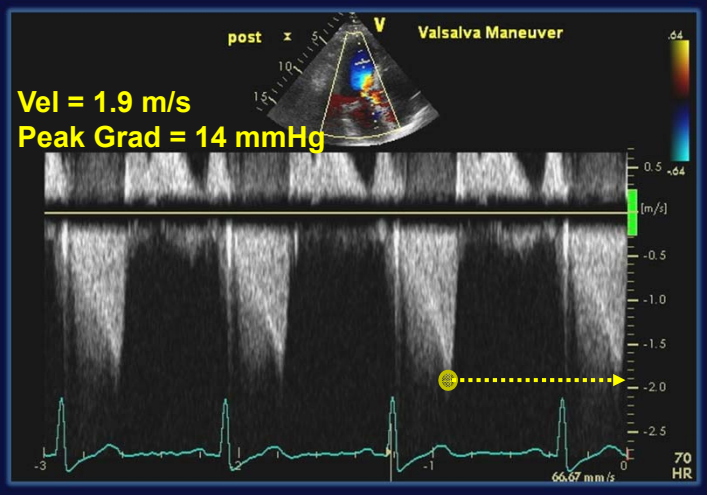
Unable to tolerate beta blocker, NYHA III





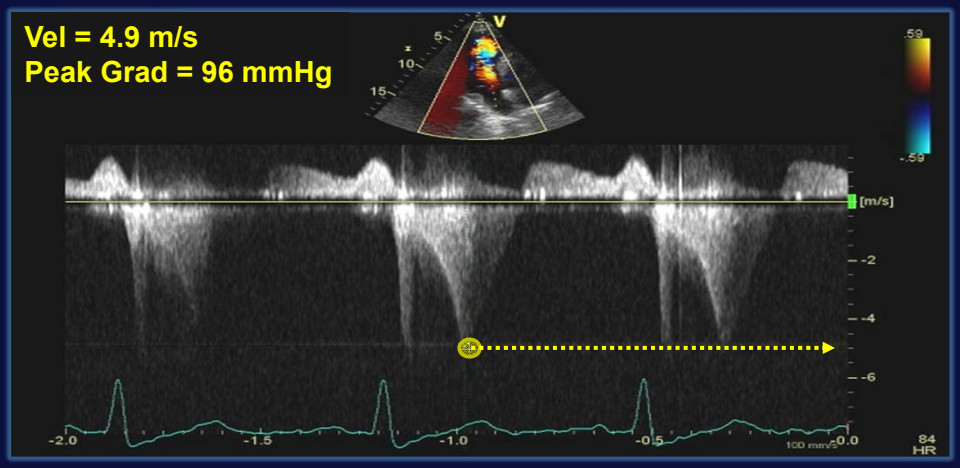
Continuous Wave Doppler

Strain Phase of Valsalva

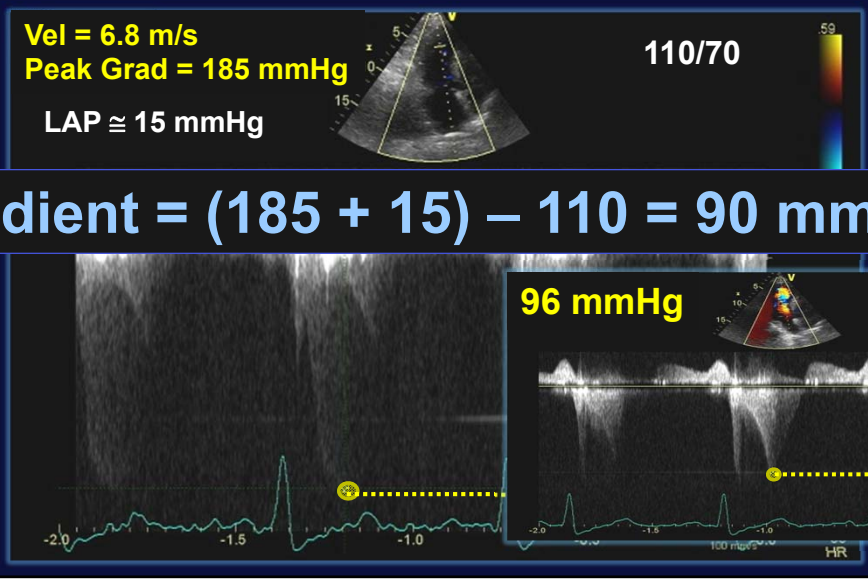


Continuous Wave Doppler
2 Hours Later

Strain Phase of Valsalva: Post Prandial



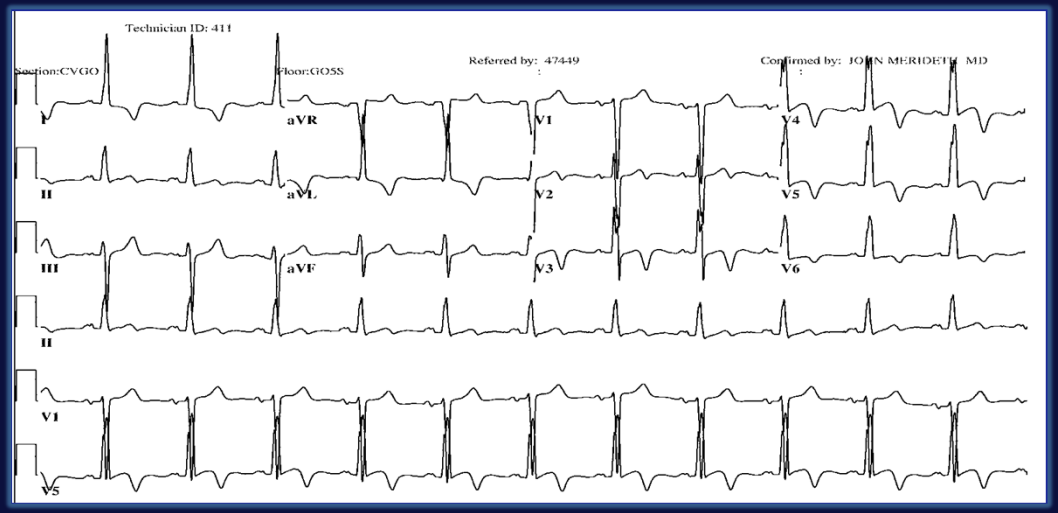
Mitral Regurgitation
2 Hours Later



Gradient = (185 + 15) – 110 = 90 mmHg

Case

- 76 year old male
- Progressive dyspnea and fatigue with minimal exertion; angina when climbing stairs.
- Coronary Angiography: no obstructive epicardial coronary artery disease.


Technician ID: 411
Section:CVGO
Floor:GO5S
Referred by: 47449
Confirmed by: JOHN MERIDETH MD
I
II
III
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V1
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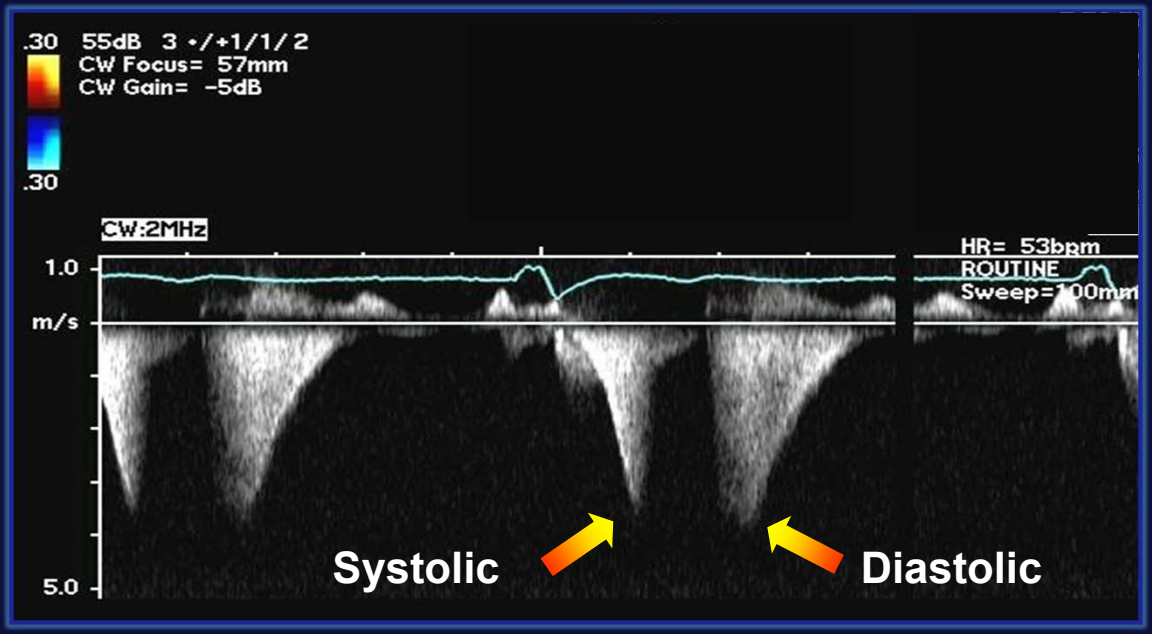
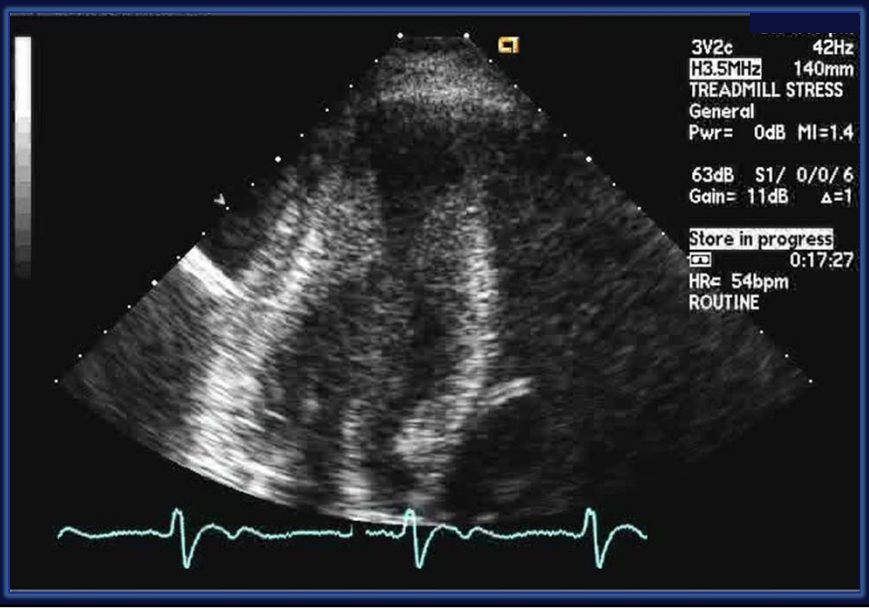
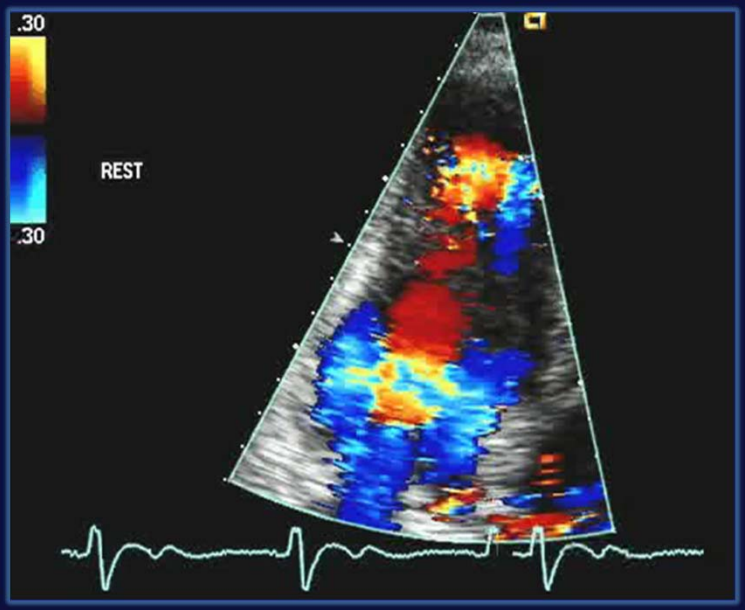
V1
V2
V3
V4
V5
V6

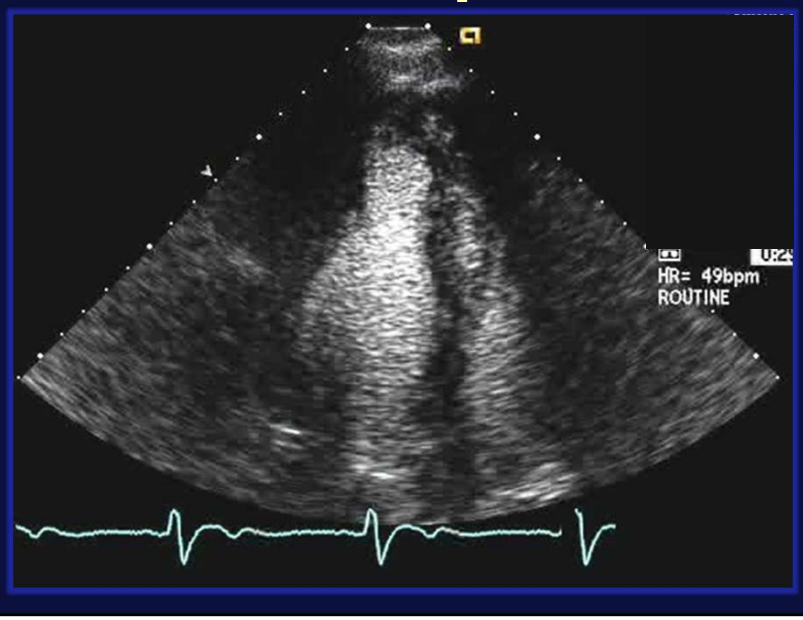

.30
55dB 3 •/+1/1/2
CW Focus= 57mm
CW Gain= -5dB
.30
CW:2MHz
1.0
m/s
5.0
HR= 53bpm
ROUTINE
Sweep=100mm
Systolic
Diastolic

Apical 4 Chamber View



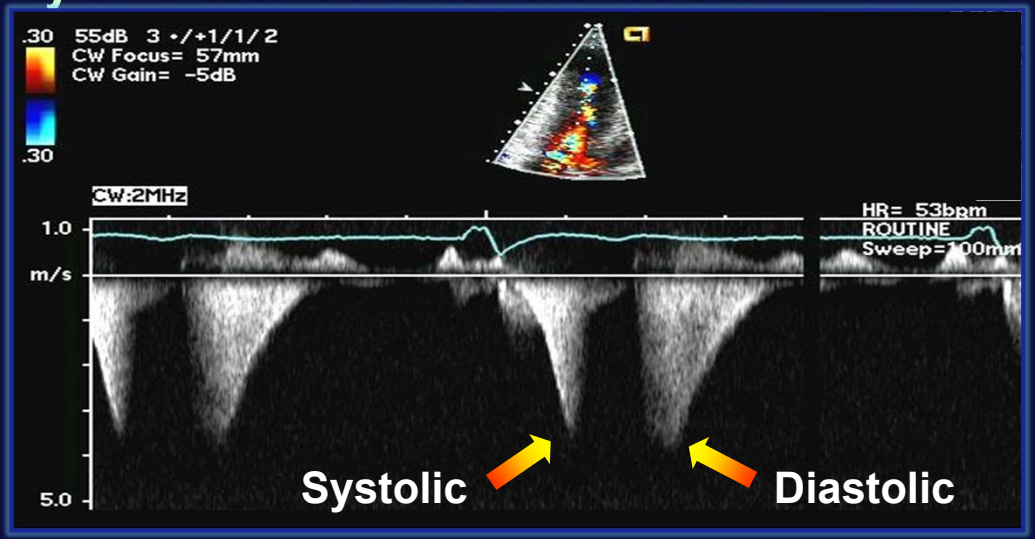


Apical HCM with Apical Aneurysm



Apical HCM with Apical Aneurysm

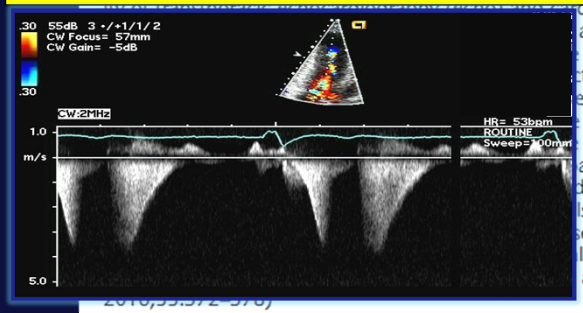
Early and Late Outflow Obstruction ~ 60 mmHg



The Incremental Value of Magnetic Resonance Imaging for Identification of Apical Pouch in Patients with Apical Variant of Hypertrophic Cardiomyopathy

Darko Vucicevic, M.D.,* Steven J. Lester, M.D.,* Christopher P. Appleton, M.D.,* Prasad M. Panse, M.D.,† John William Schleifer, M.D.,* and Susan Wilansky, M.D.*

- **Echo with an without contrast identified 8/17 (47%) of apical those with apical pouch noted on MRI.**
- **Echo missed 2 patients with an apical thrombus.**



diac magnetic resonance imaging (cMRI) to accu-
aneurysm in patients with aHCM. Methods: We
patients that had features of aHCM on imaging.
ted, and the ability of these diagnostic modalities
eurys
four
to accurately identify both aneurysms, but only
atients had apical thrombus that was identified by
dicate that cMRI is superior to echo in identifying
lso suggest that in patients undergoing echo, the
es the diagnostic yield. Further study is necessary
l pouch will be of clinical benefit for patients with
adverse cardiovascular events. (Echocardiography

Echocardiography 2016;33:572-578

Hypertrophic Cardiomyopathy Complicated by Apical Aneurysm

- **Apical abnormalities in apical HCM:**
  Pouch: 15%; Aneurysm: 3%
- **Adverse events associated with aneurysm (not apical pouch)**
  - **Progressive heart failure/death (18%)**
  - **SCD or revived cardiac arrest (14%)**
  - **Appropriate ICD discharge (11%)**
  - **Nonfatal embolic stroke (7%)**

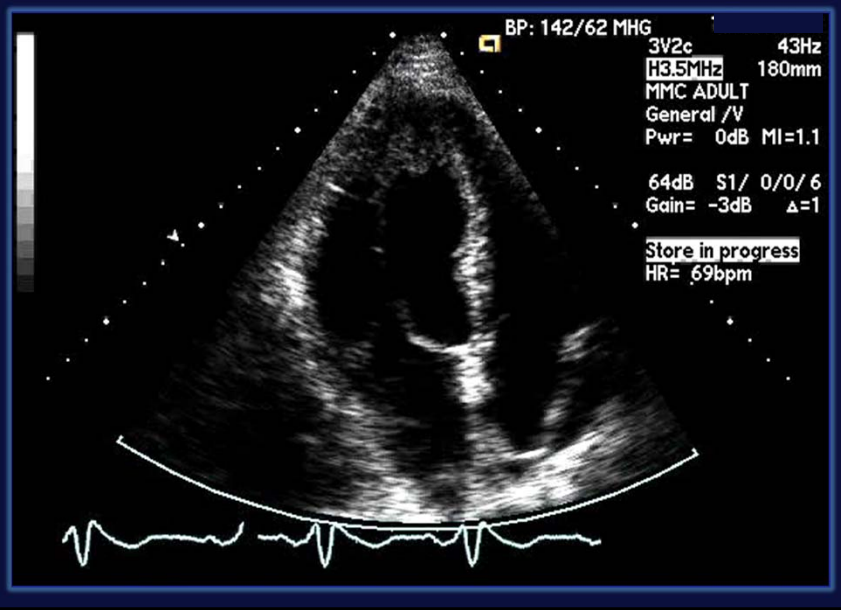
Binder J et al JASE 2011;24:775
Maron MS, et al. Circulation 2008;118:1541

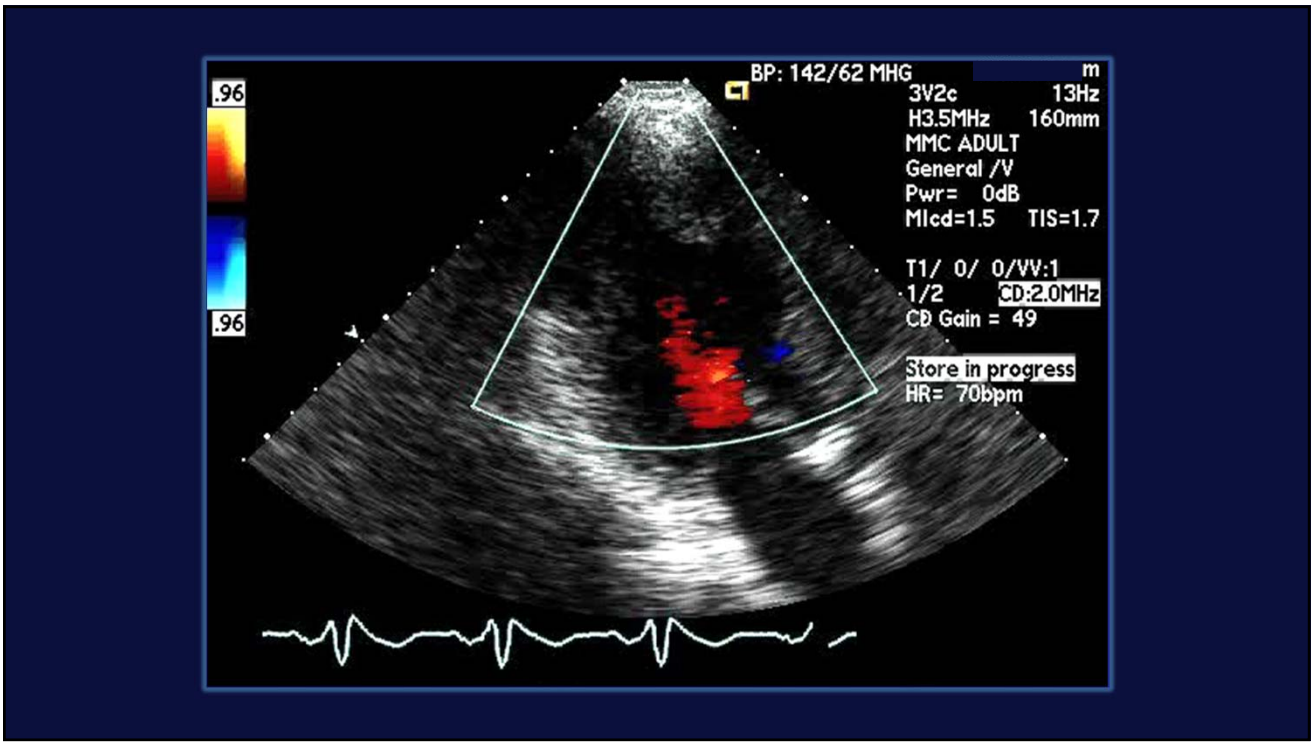
Cardiac Surgery

LV apical ventriculotomy:

Extended mid to apical myectomy, resection of apical aneurysm

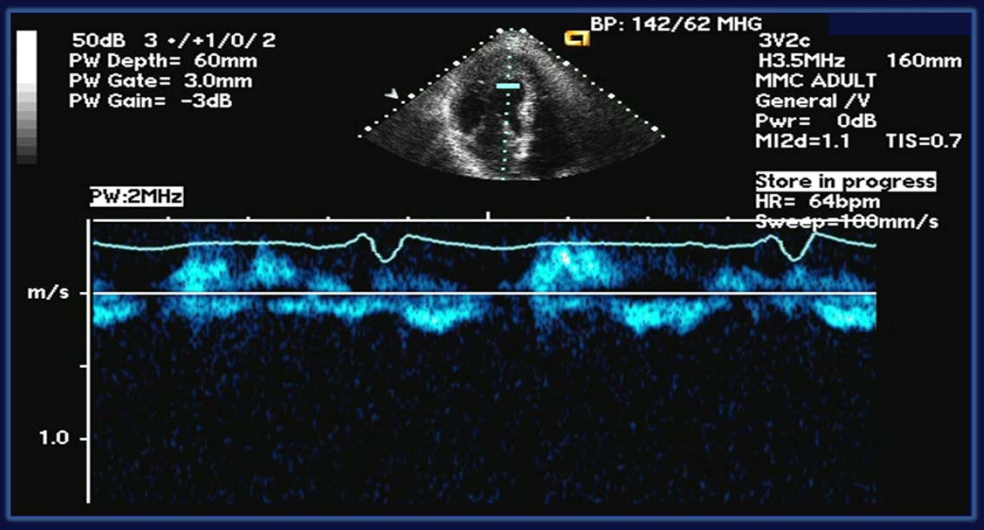
Post Op





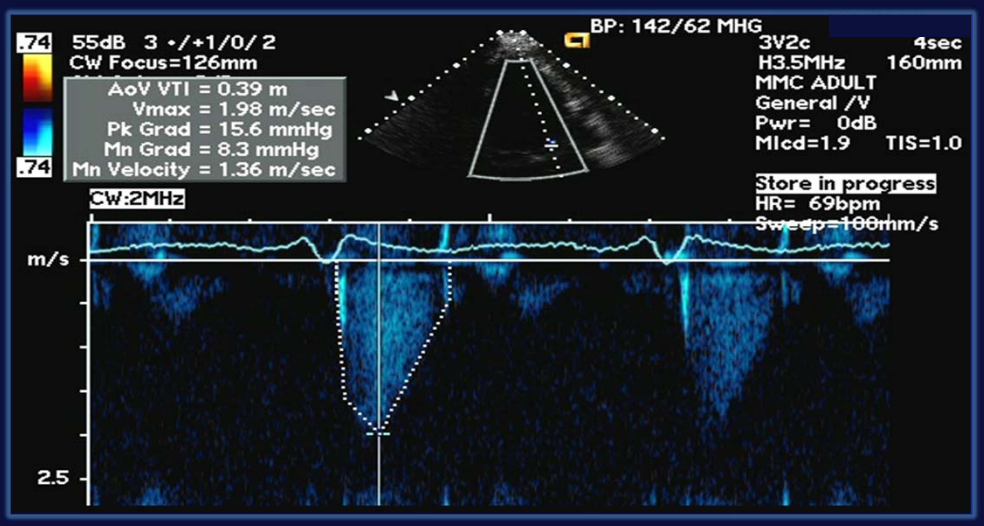
Continuous Wave Doppler

LV Apex



Continuous Wave Doppler

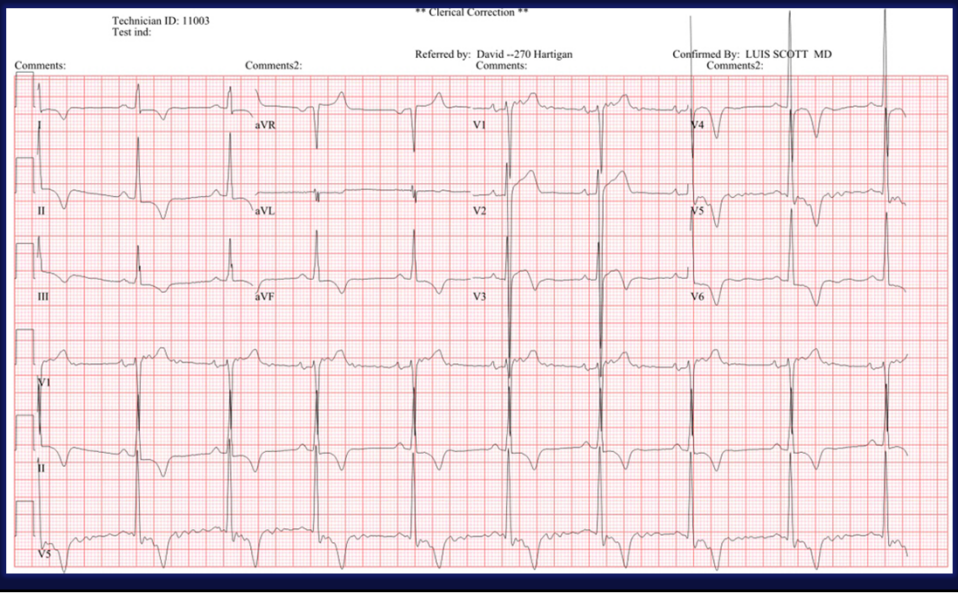
LVOT and Aortic Valve



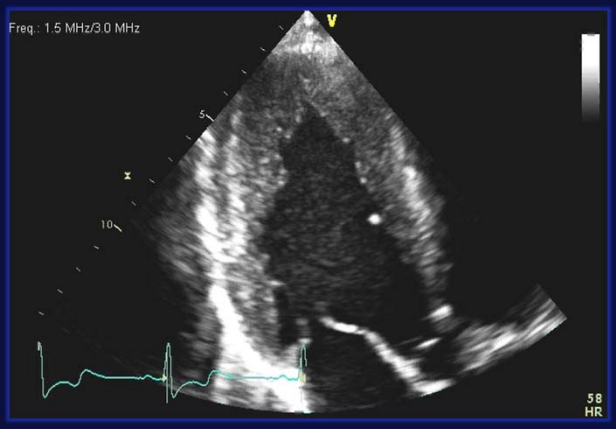
Case

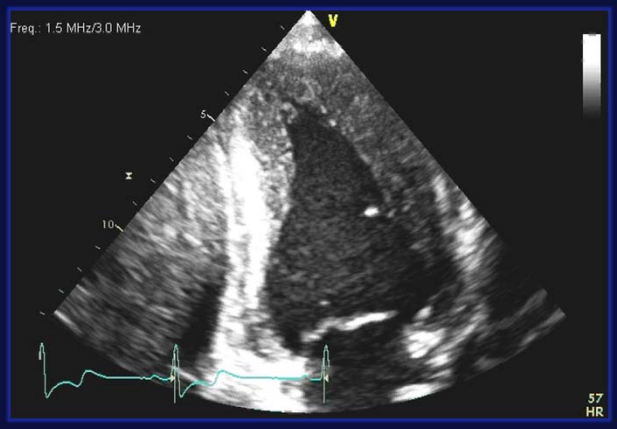
- 31 year old male
- Professional soccer player
- FIFA pre-season examination

Electrocardiogram

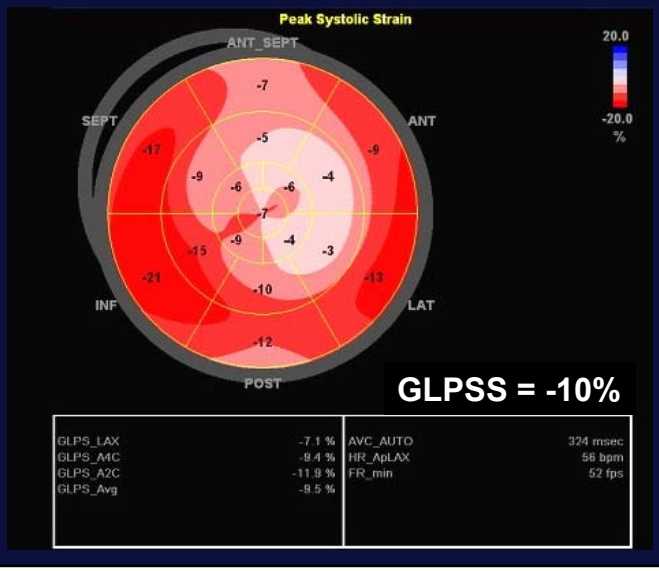


Transthoracic Echocardiogram



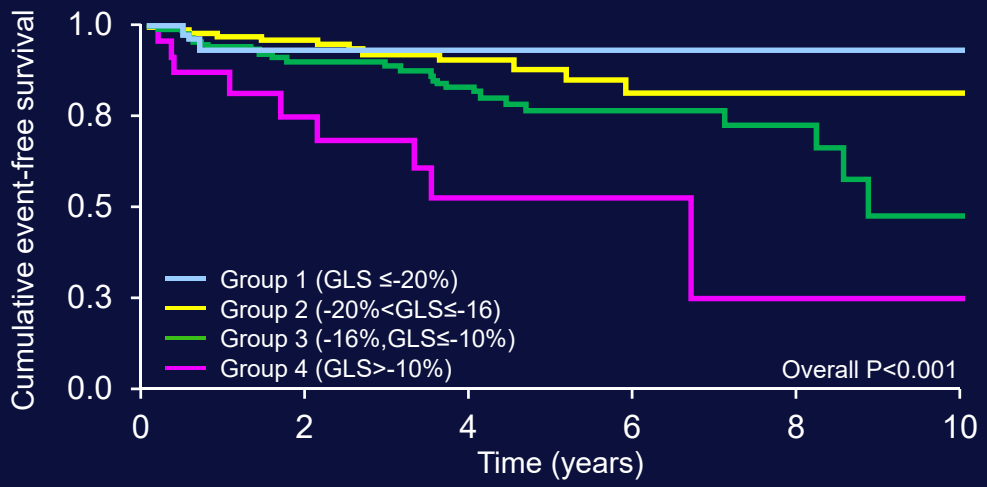


Global Longitudinal Peak Systolic Strain

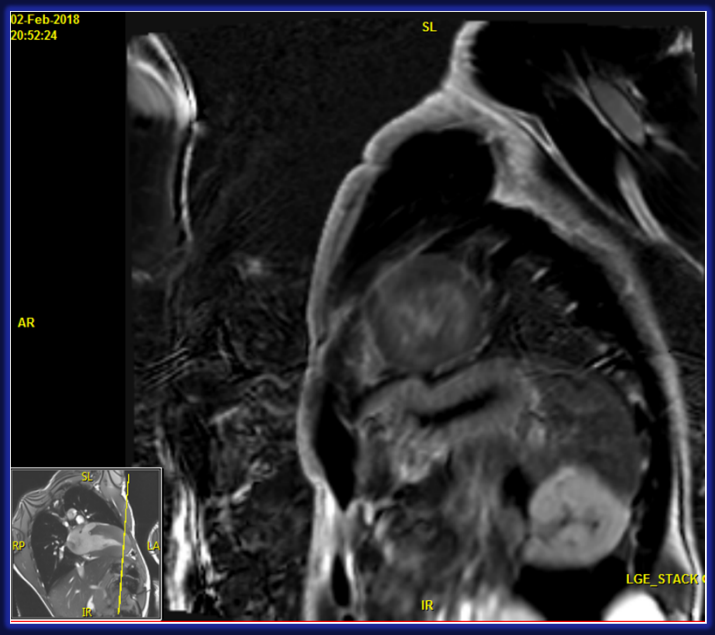


Hypertrophic Cardiomyopathy

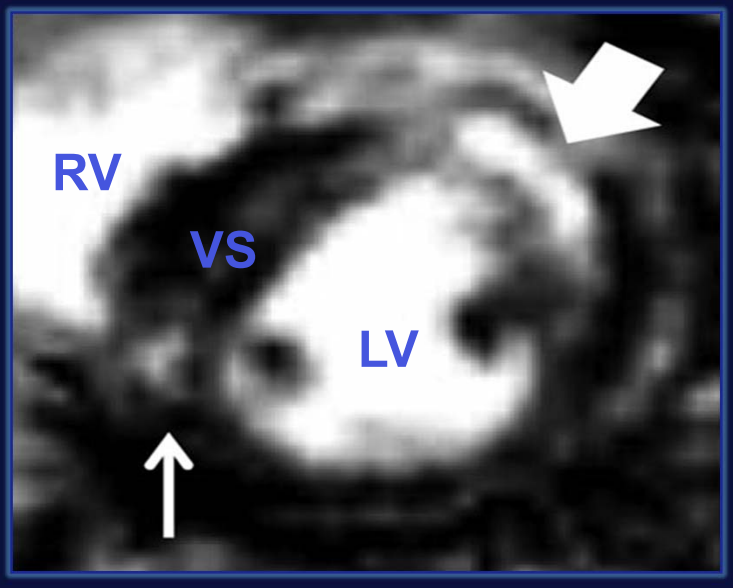
Global Longitudinal Strain and Event Free Survival



Liu et al. Am J Cardiol 2017;120(4):670-675



Late Gadolinium Enhancement



Bravo et al. European Heart Journal-Cardiovasc Imaging 2015

ORIGINAL ARTICLE

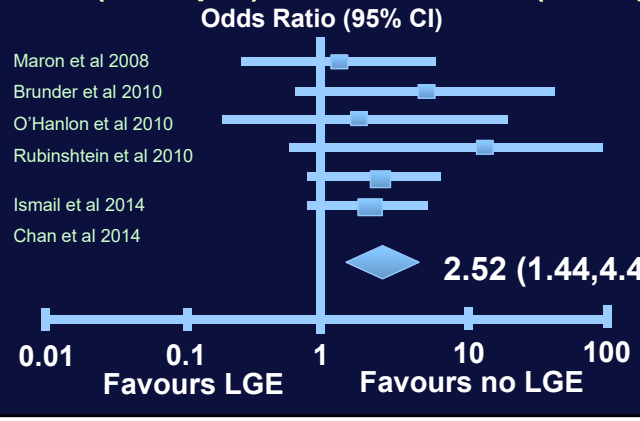
Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis

Alexandros Briasoulis, Sagar Mallikethi-Reddy, Mohan Palla, Issa Alesh, Luis Afonso

Heart 2015;0:1–6

Sudden Cardiac Death

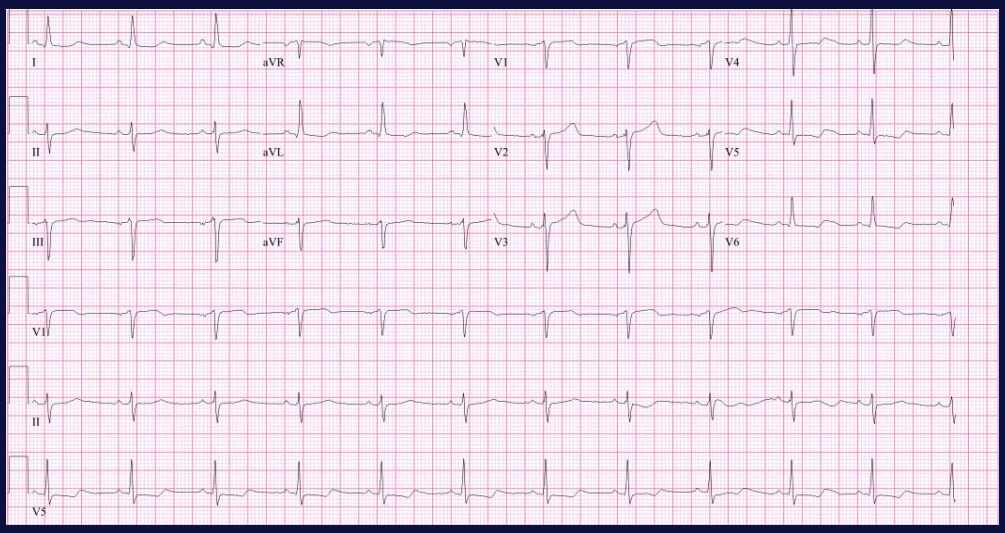
Fibrosis (1653 pts) vs No Fibrosis (1414 pts)



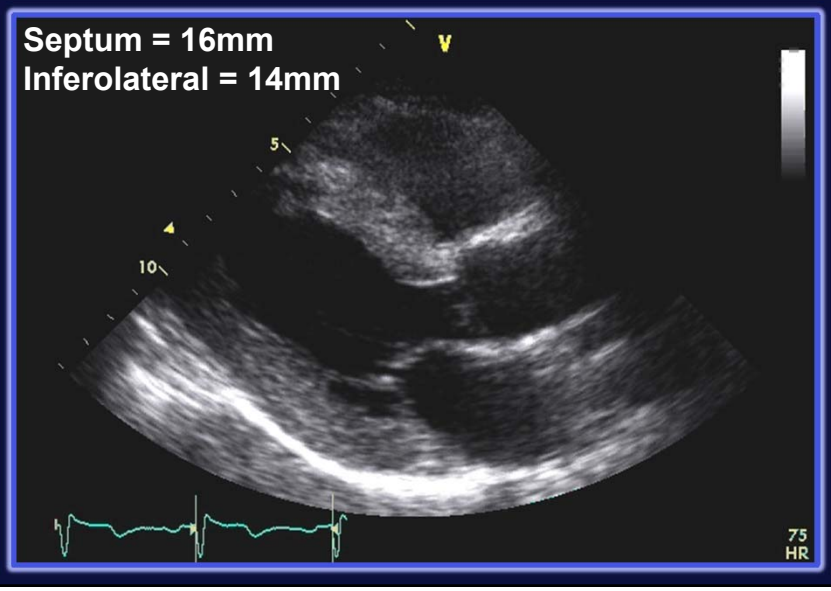
Case

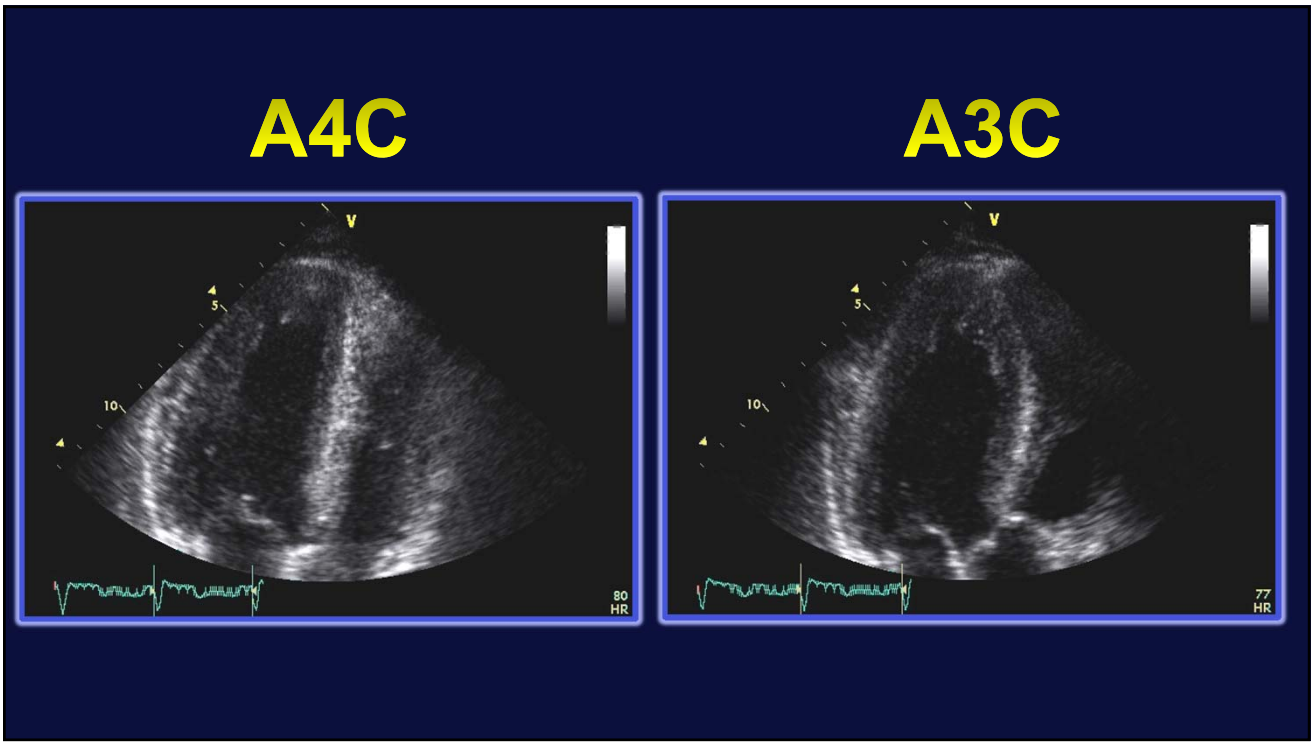
- 42 year old male
- Played football in high school. Continues to exercise and lift weights
- Murmur noted on exam

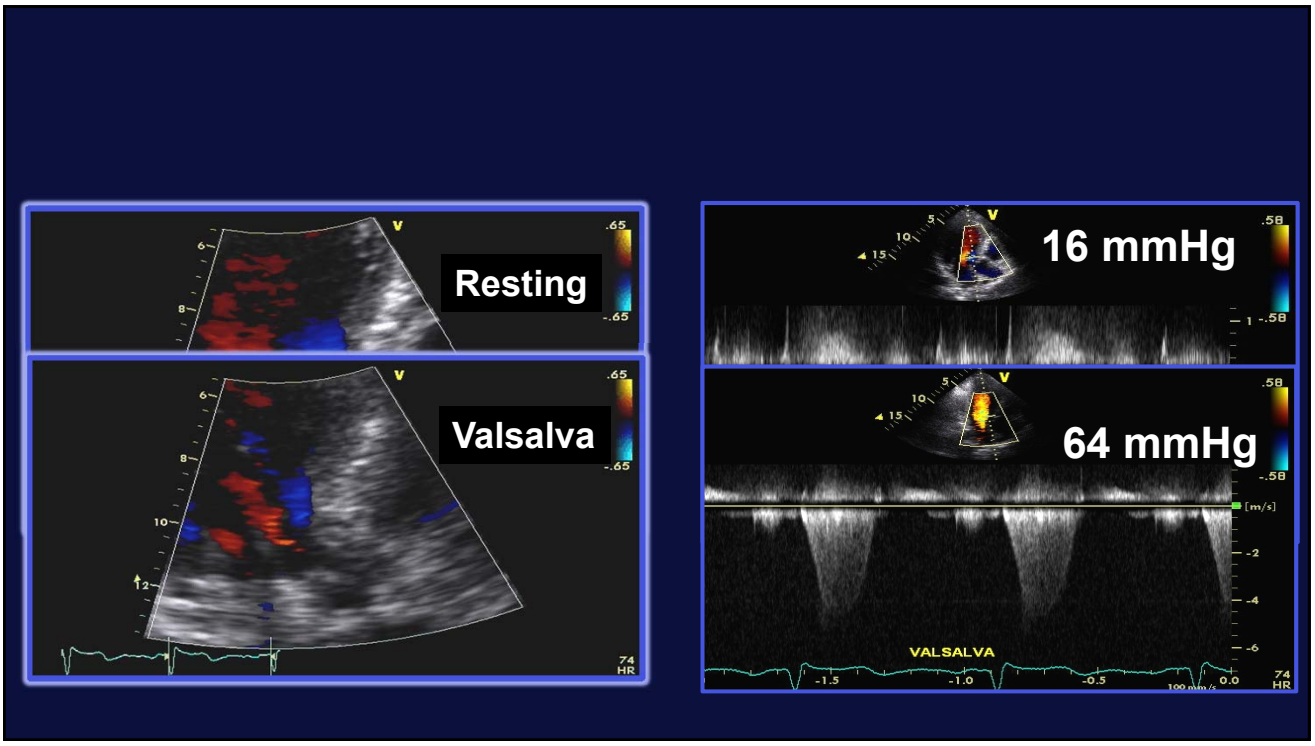
Electrocardiogram



Parasternal Long Axis




A4C
A3C
80
HR
77
HR


Resting
Valsalva
16 mmHg
64 mmHg
VALSALVA
74
HR
74
HR

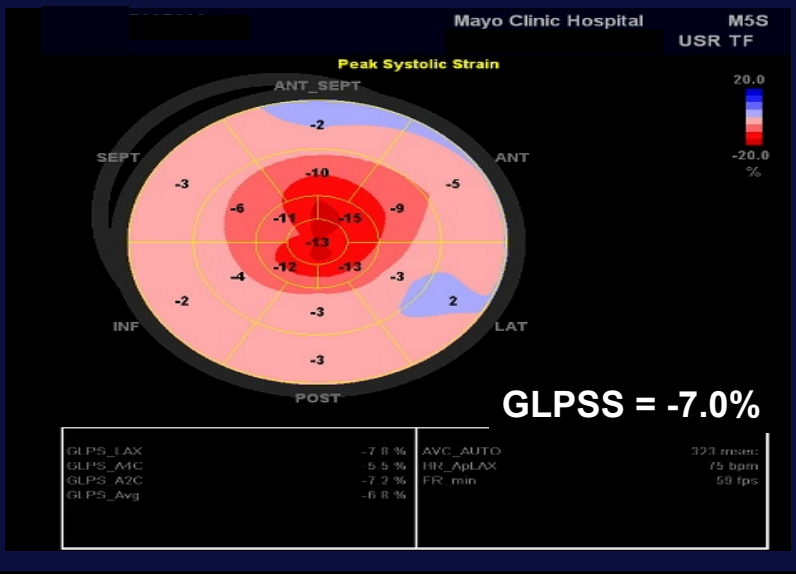
Hypertrophic Cardiomyopathy
Echocardiographic Diagnosis

Left Ventricular Hypertrophy ≥ 15mm

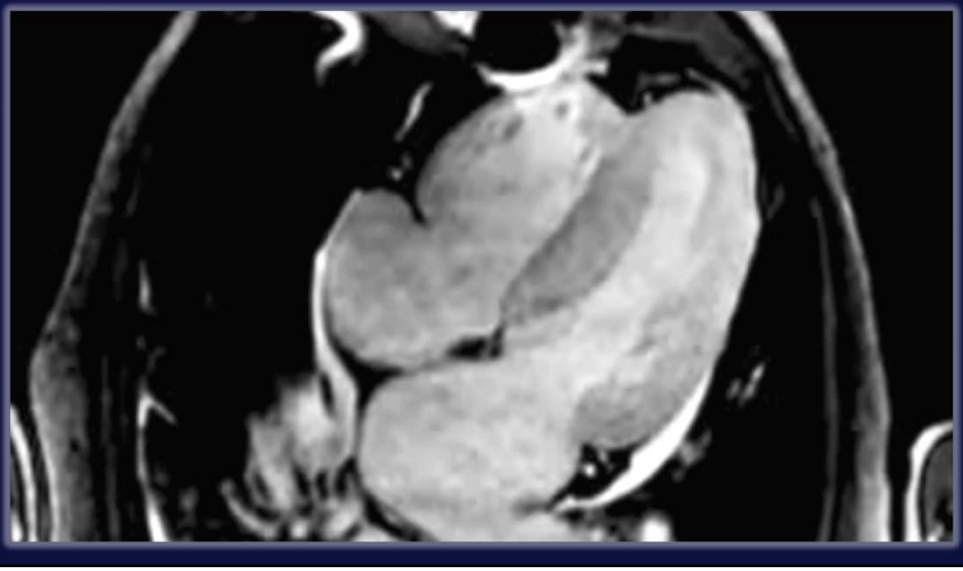
In the absence of another cardiovascular or systemic disease associated with LVH or myocardial wall thickening

Maron et al. J Am Coll Cardiol 2003;42: 1687

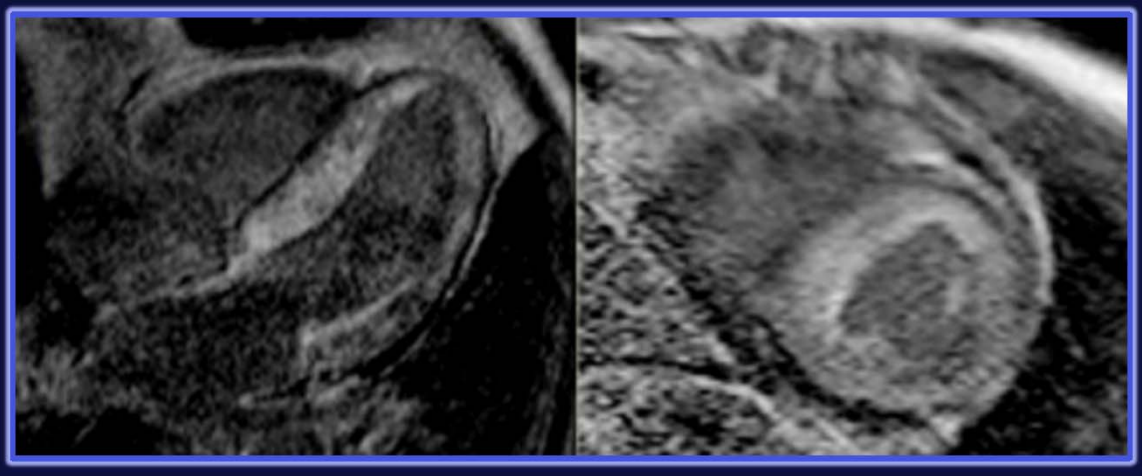
Global Longitudinal Peak Systolic Strain



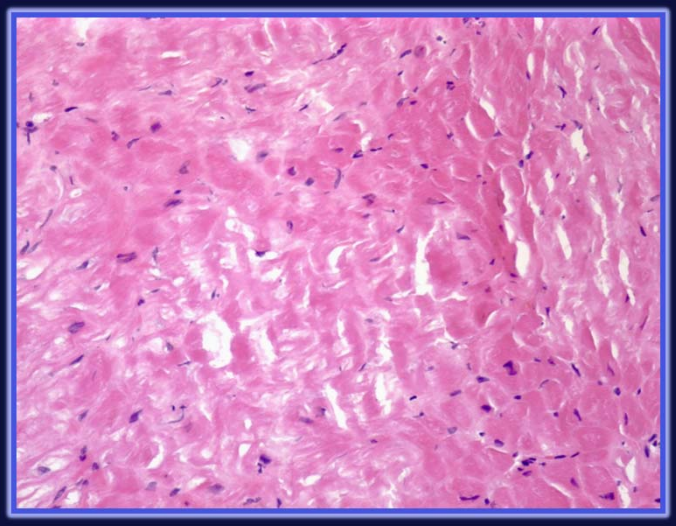
MRI



Late Gadolinium Enhancement

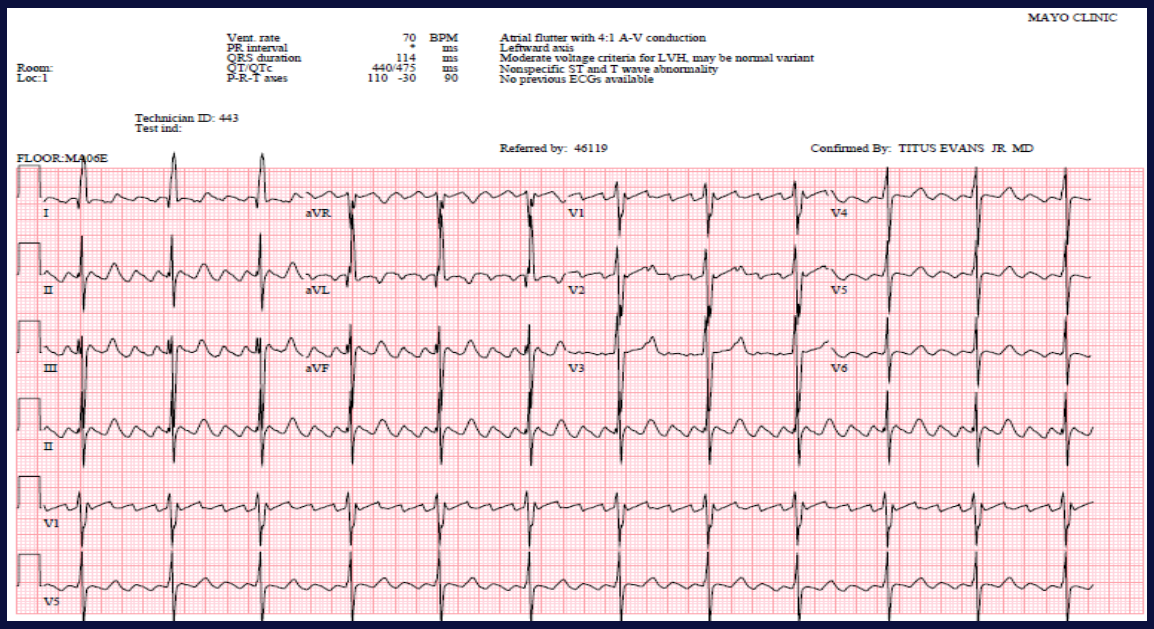


Amyloidosis

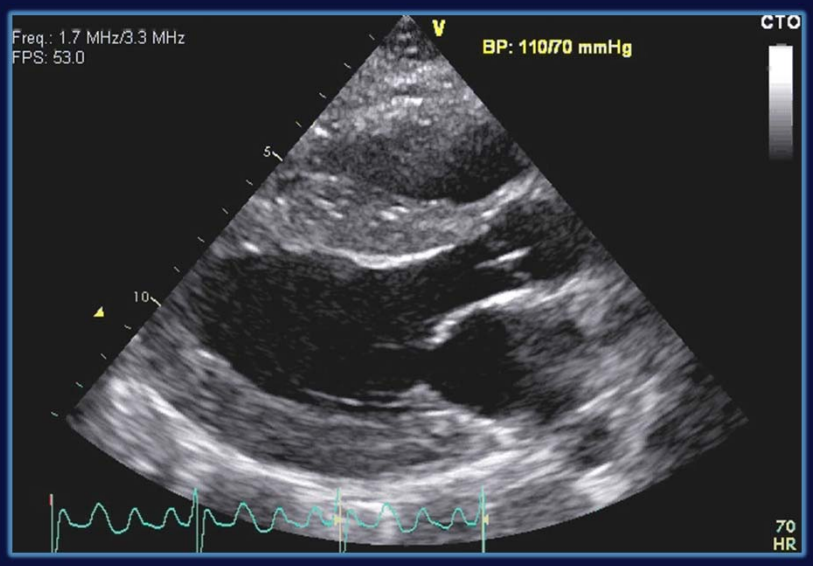


Case

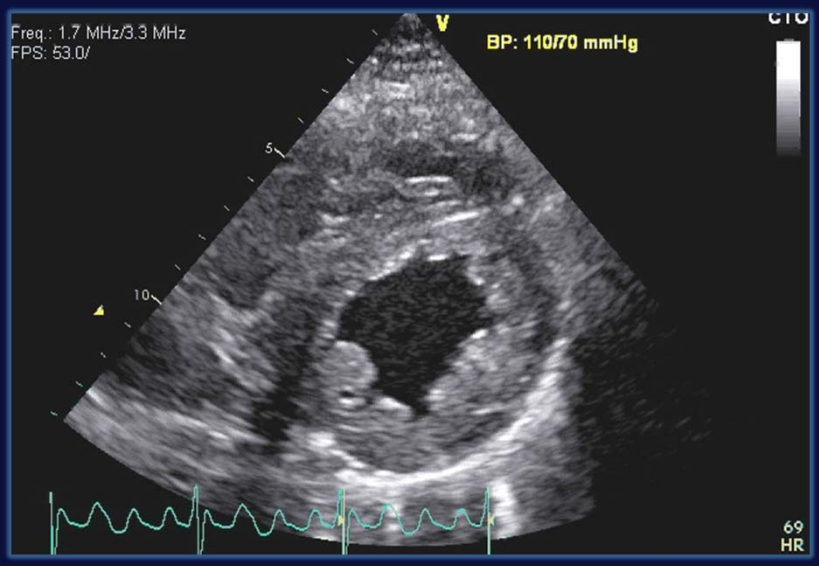
- 19 year old female
- No family history of cardiovascular disease
- NYHA II, shortness of breath and muscle weakness.
- Presents with palpitations



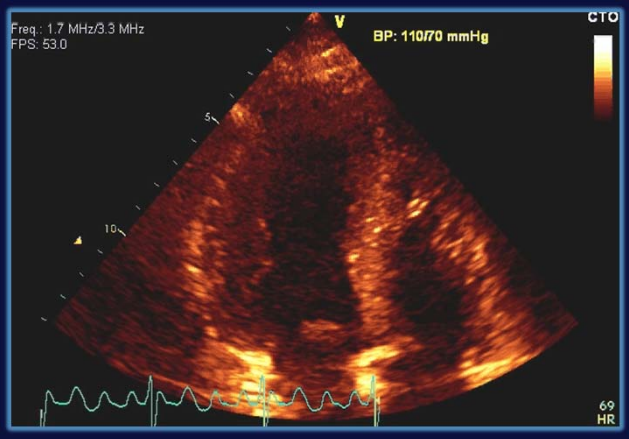
Parasternal Long Axis

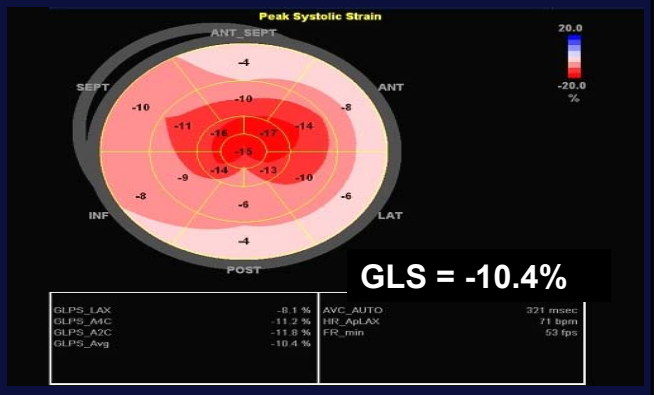


Parasternal Short Axis



Apical 4 Chamber & Global Longitudinal Peak Systolic Strain



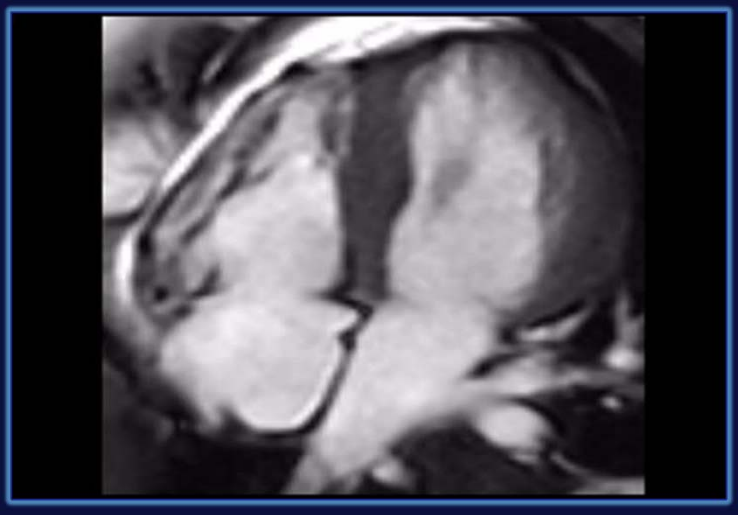


Diagnosis?

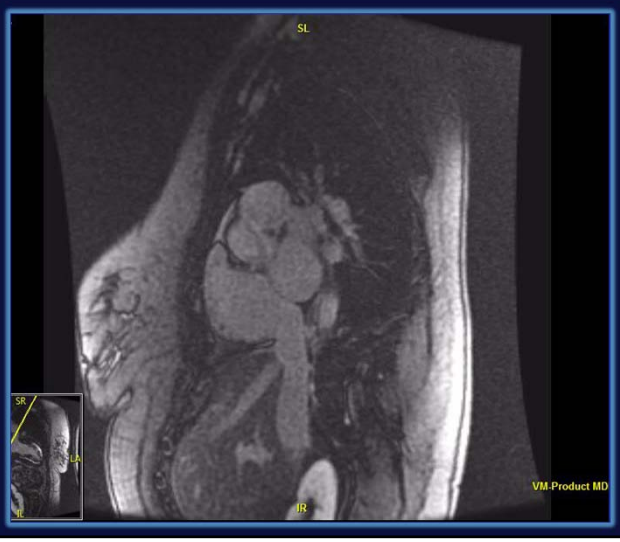
1. Hypertrophic Cardiomyopathy
2. Amyloidosis
3. Glycogen Storage Disease
4. More information needed
5. Ask Dr. Khandheria?

Additional Testing

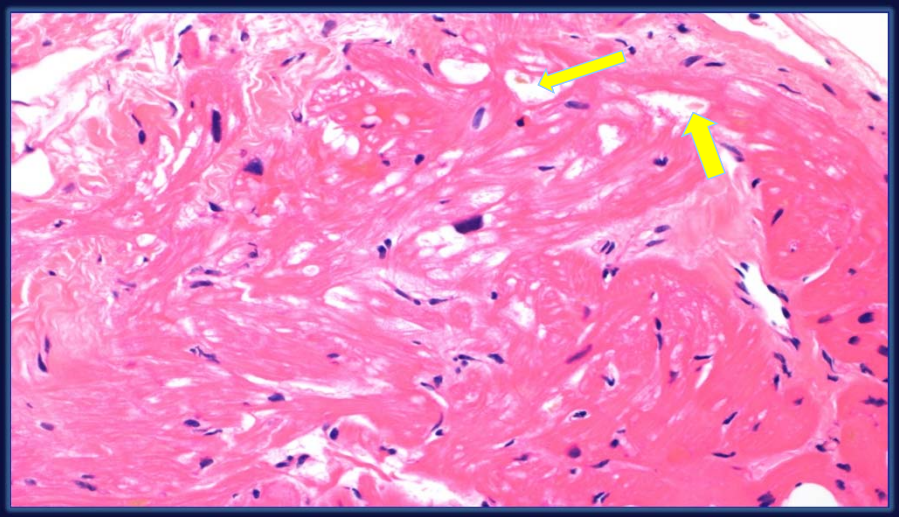
Cardiac MRI



Additional Testing
Cardiac MRI- LGE



Myocardial Biopsy

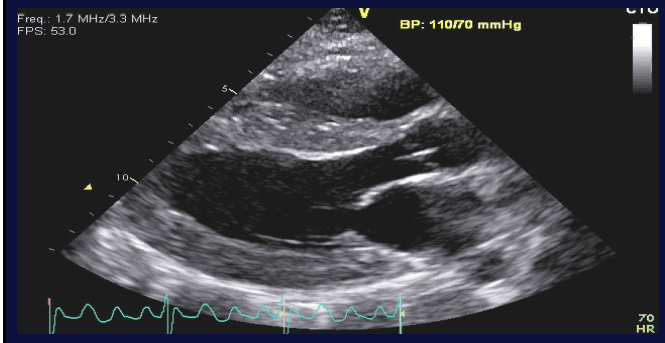


Comprehensive Cardiomyopathy Panel

Disease causing mutation in the LAMP2 gene

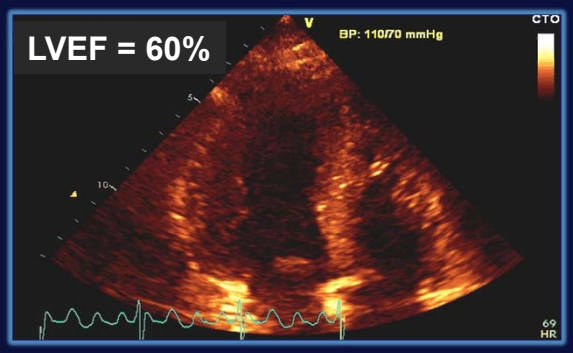
Danon Disease

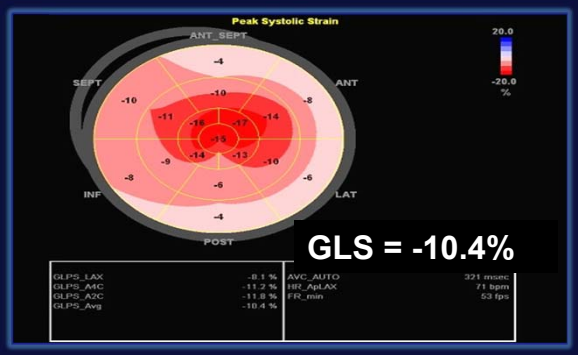
Danon Disease



- Loss of function LAMP2
- X-linked dominant
- Inability to transport cellular material into lysosomes…accumulate autophagic vacuoles in muscles (glycogen storage disease)
- Skeletal myopathy
- Cognitive dysfunction
- Cardiomyopathy (*HCM*, DCM)

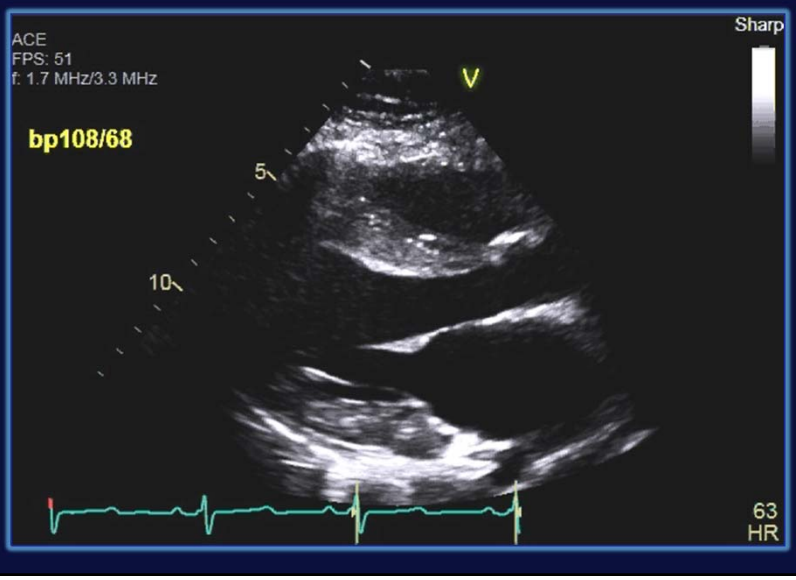
Apical 4 Chamber & Global Longitudinal Peak Systolic Strain





LVEF : GLS ratio 5.8 (> 4.1)
Relative Regional Strain Ratio = 0.74 (< 1!!)

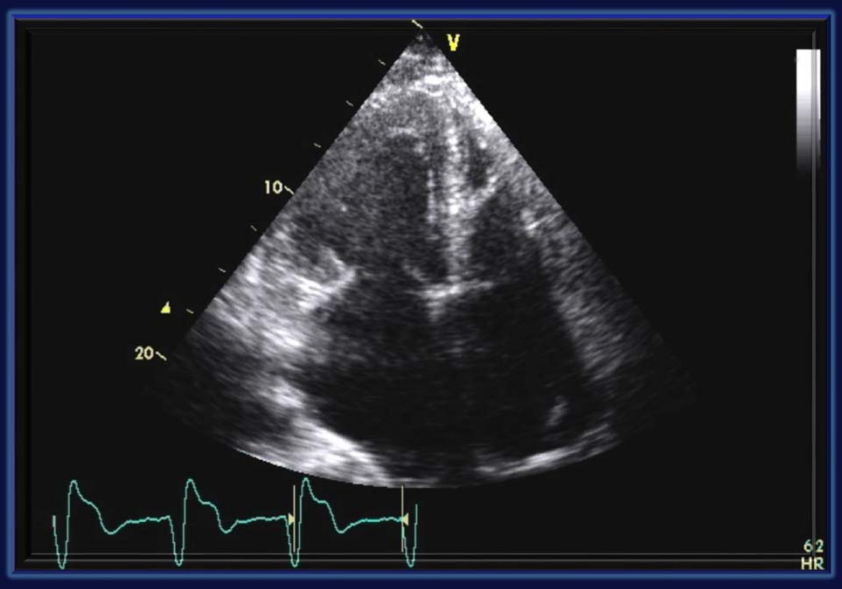
Today at age 23



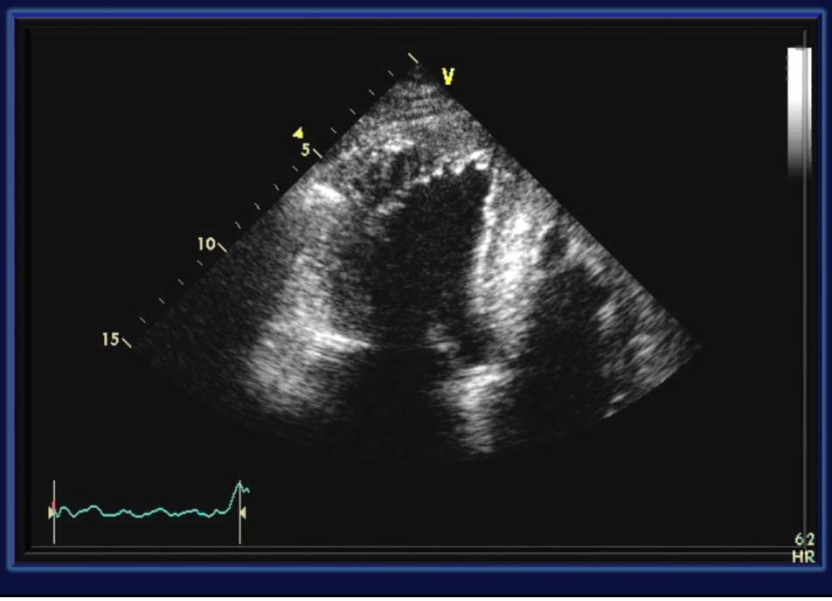
Back to This Case

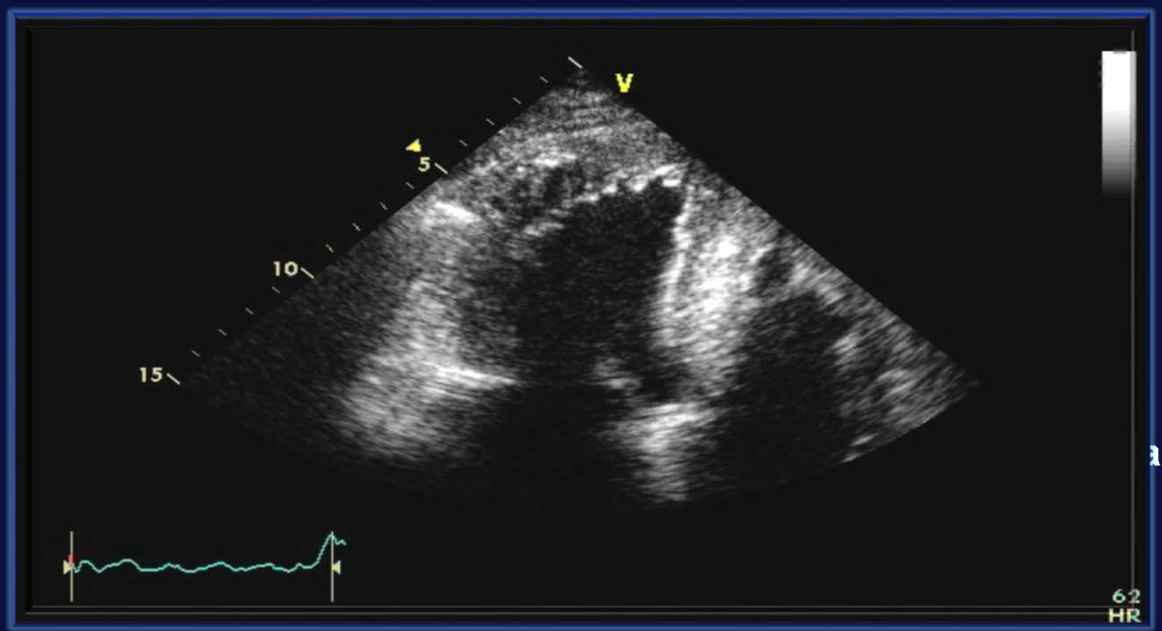
- 47 year old male
- 2005 several near syncope episodes.
- Eventually while at a the Phoenix Suns game had a true syncopal episode.

Echo 2007



Echo 2012





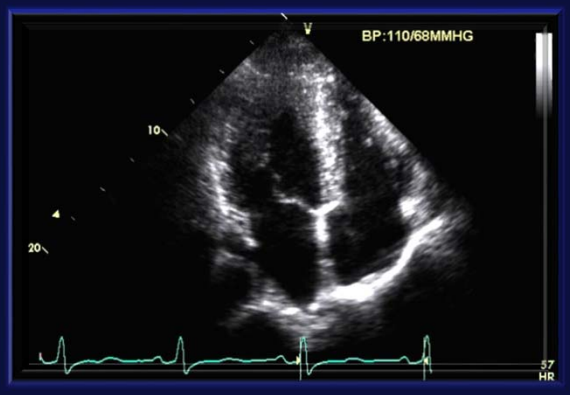
HEART

Apical hypertrophic cardiomyopathy and left ventricular non-compaction: two faces of the same disease

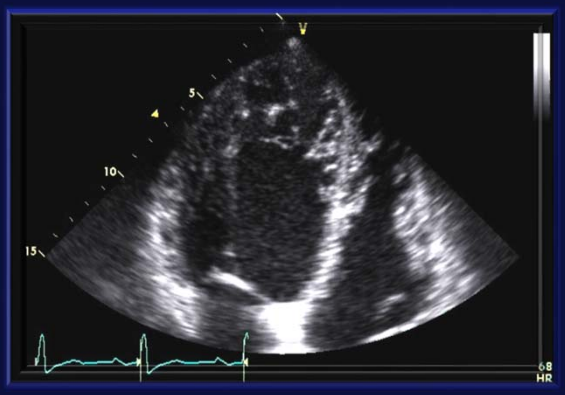
L Monserrat, R Barriales-Villa and M Hermida-Prieto

Heart 2008 94: 1253

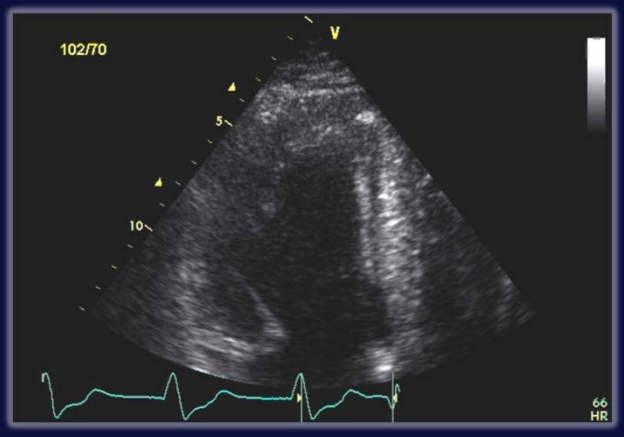
Father

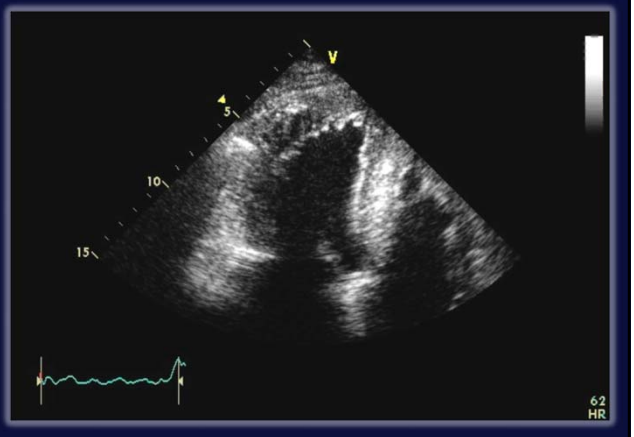


Son



2005-2013





Thick Walls Why?

It's What's on the Inside that Matters

Intragenetic

Individua
Treatme
Strategi

ersity in
HCM
enotype
nocopies)

Dive
Natural H

ssion &
Hemodynamic Profile

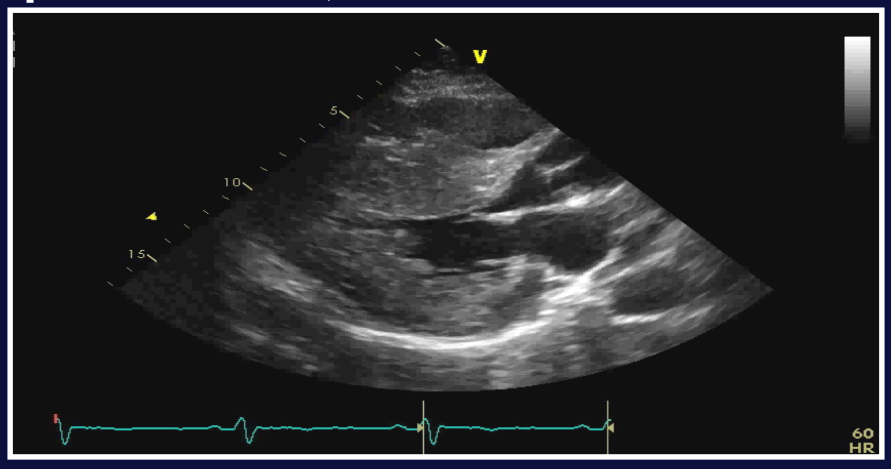

MAYO
CLINIC

Case

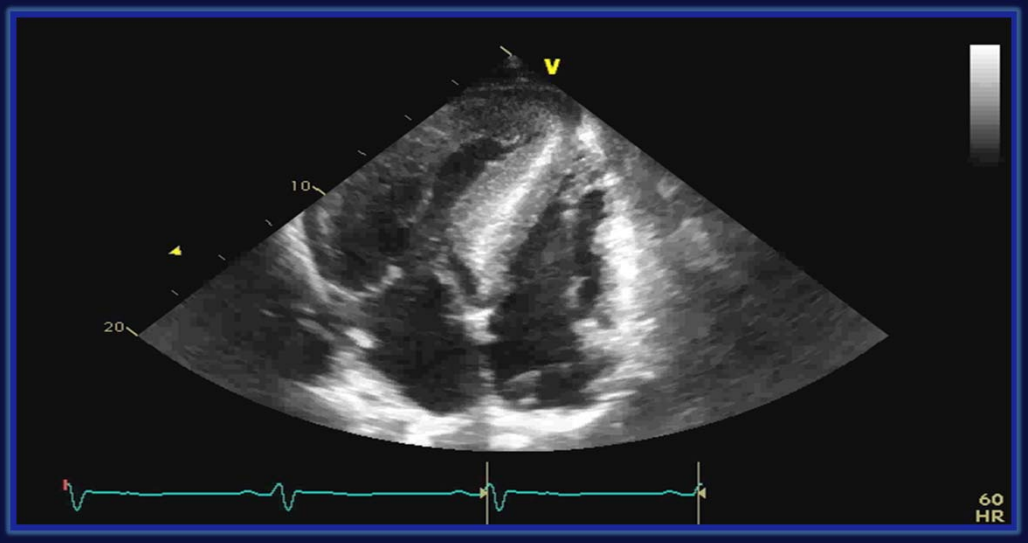
- 53 year old male
- No family Hx of HCM
- NYHA III (SOB and fatigue)
- Effort related presyncope

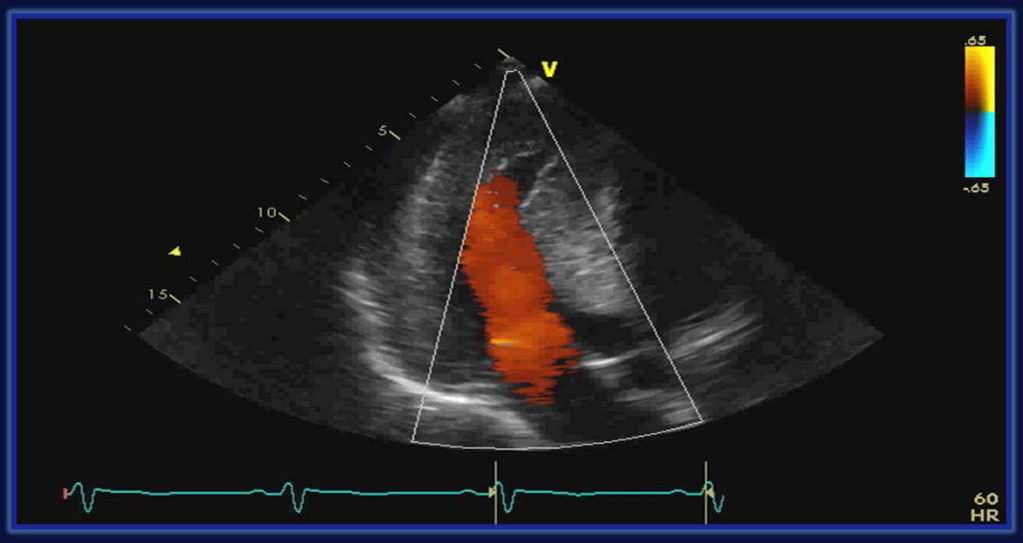
EDD 37 mm; ESD 19mm

Septum 25 mm; inferolateral wall 24 mm

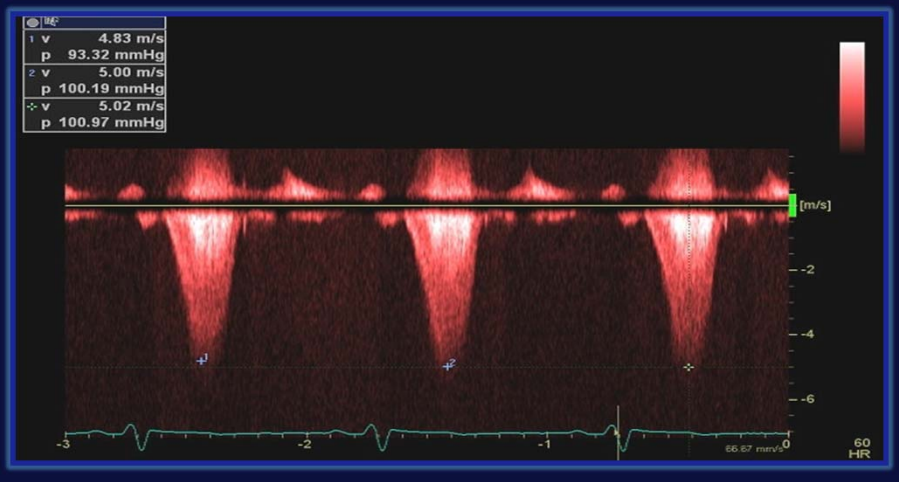


EF 68% LAVI 48 cc/m^2

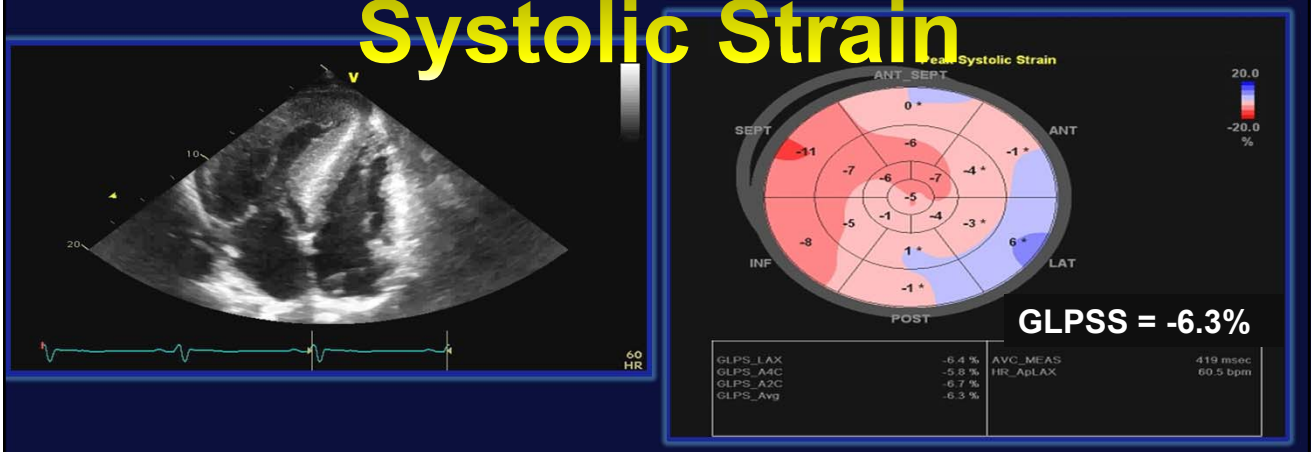




Mid LV gradient 100 mmHg



Apical 4 Chamber & Global Longitudinal Peak Systolic Strain



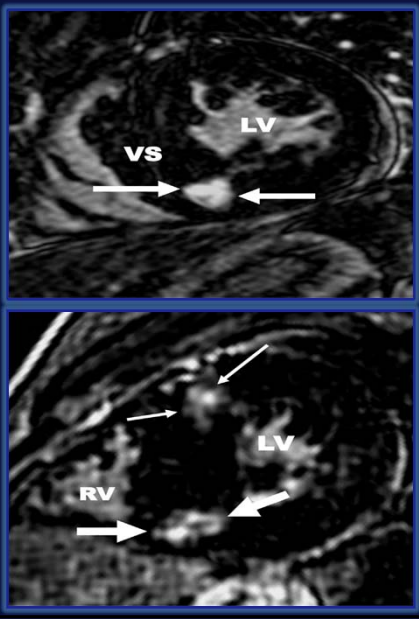
Diagnosis?

1. Hypertrophic cardiomyopathy
2. Amyloid heart disease
3. Fabry's disease
4. Danon disease
5. Need more information

Additional Testing

1. Cardiac MRI (outside)
   - Corroborated echo morphologic findings
   - "some delayed enhancement at the LV lateral wall in addition to the septum at the RV insertion site".

LGE: At RV Insertion Points

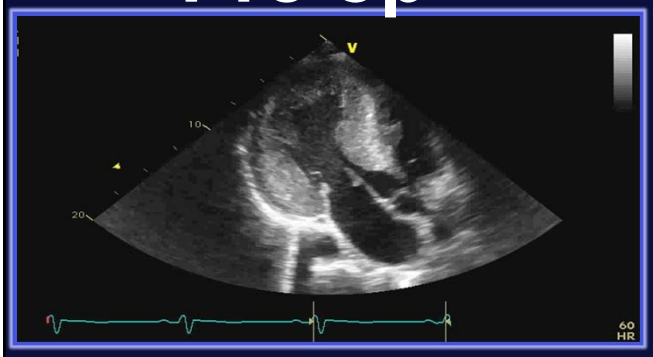


- Seen in isolation in about 10% of pts.
- On average affects only 3% of LV mass.
- Does not represent replacement fibrosis.
- This pattern of LGE in isolation appears to neither be associated with increased risk nor itself a marker for prognostic decision making.

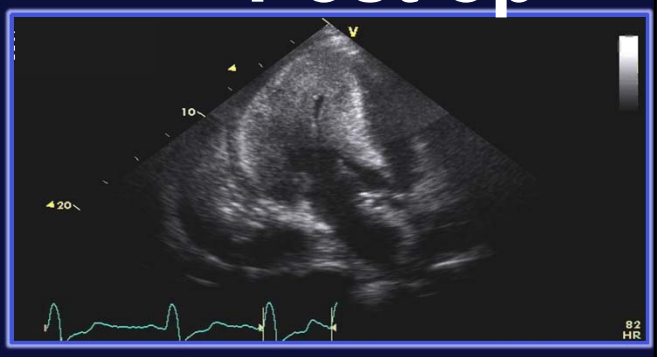
Bravo et al. European Heart Journal-Cardiovasc Imaging 2015
Chan et al. Am J Cardiol 2015;

Surgical Myectomy

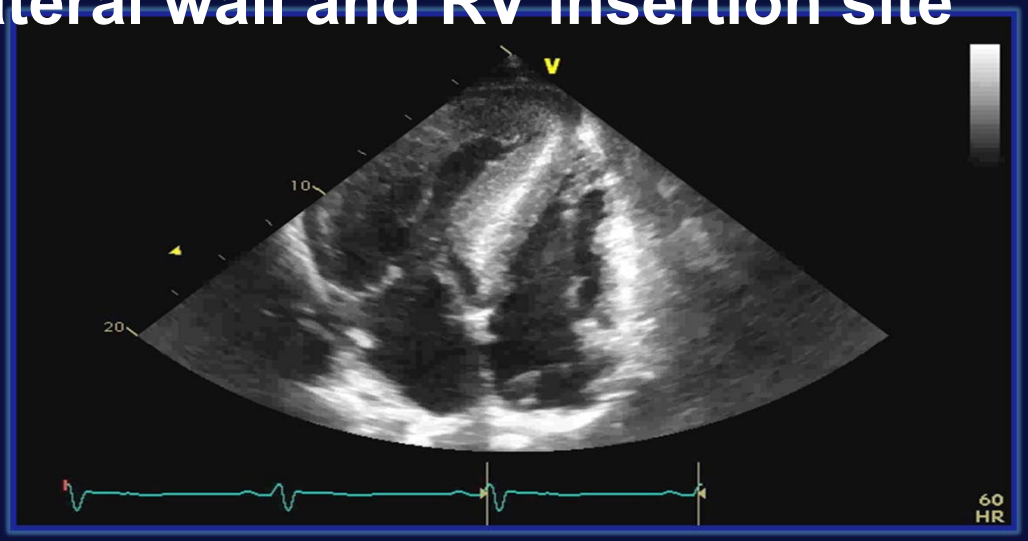
Pre op



Post op



"Some delayed enhancement in the lateral wall and RV insertion site"



Fabry's Disease Additional Testing

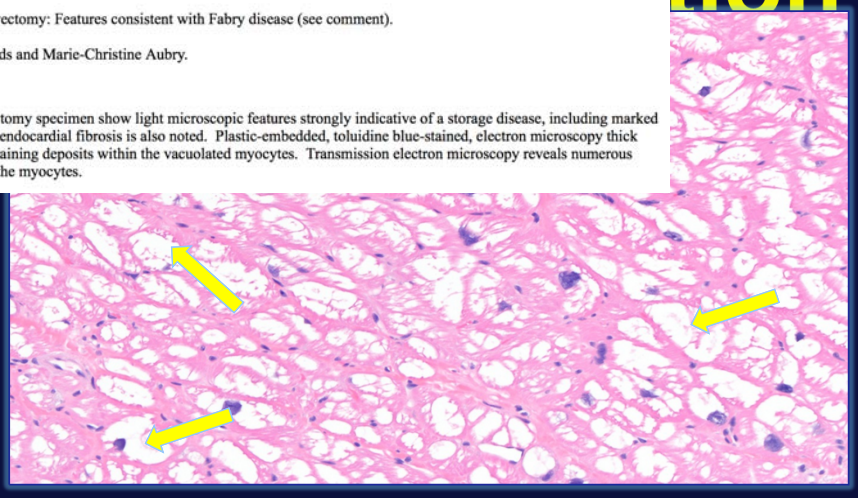
1. Serum alpha-galactosidase level:
   - 0.03 (0.6-3.63)
2. Genetic Testing
   - G373S variant of GLA

Myocyte Hypertrophy and Vacuolization

Final Diagnosis:
A. Heart, left ventricle, septal myectomy: Features consistent with Fabry disease (see comment).

Seen with Drs. William D. Edwards and Marie-Christine Aubry.

Diagnosis Comment:
Tissue sections of the septal myectomy specimen show light microscopic features strongly indicative of a storage disease, including marked sarcoplasmic vacuolization. Mild endocardial fibrosis is also noted. Plastic-embedded, toluidine blue-stained, electron microscopy thick sections show numerous darkly-staining deposits within the vacuolated myocytes. Transmission electron microscopy reveals numerous lamellar bodies contained within the myocytes.



Fabry's Disease

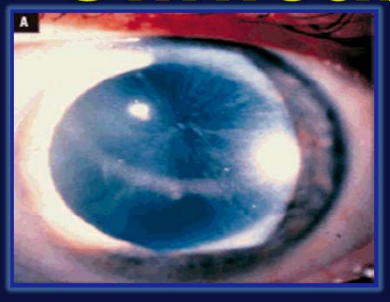
Mutations in the GLA gene

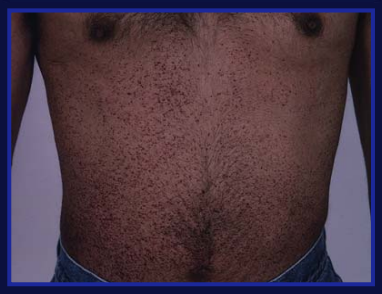
→ Provides instructions for making an enzyme called alpha-galactosidase A (αGLA)

→ αGLA is active in lysosomes and breaks down a fatty substance globotriaosylceramide

→ Globotriaosylceramide builds up in cells throughout the body

Clinical manifestations





- Whorl-like corneal opacifications
- Angiokeratomas
- Progressive renal disease
- CNS (CVA and TIA)
- Acroparesthesias

Ped Neph 2004;19:583

Fabry's Disease

- X-linked
- Often affects women despite being x-linked
- Mutations that decreased but do not eliminate the enzyme activity usually cause the milder, late-onset of disease that affect only the heart

Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

B. Sachdev, MRCP; T. Takenaka, MD, PhD; H. Teraguchi, MD; C. Tei, MD, PhD; P. Lee, MRCP, MD, PhD; W.J. McKenna, MBBS, FRCP, FESC; P.M. Elliott, MBBS, MD, MRCP

Circulation 2002;105:1407-11

- 5 of 79 patients (6.3%) diagnosed at ≥ 40 years had Anderson-Fabry disease.
- 1 of 74 patients (1.4%) diagnosed at < 40 years had Anderson-Fabry disease.

Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

B. Sachdev, MRCP; T. Takenaka, MD, PhD; H. Teraguchi, MD; C. Tei, MD, PhD; P. Lee, MRCP, MD, PhD; W.J. McKenna, MBBS, FRCP, FESC; P.M. Elliott, MBBS, MD, MRCP

Circulation 2002;105:1407-11

Clinical Implications

- Male patients with a concentric increase in left ventricular wall thickness and no family history of HCM or inheritance consistent with X-linked disease should be screened for Anderson-Fabry disease.
- Correct diagnosis is important and treatment may stabilize and even for some

Recombinant α galactosidase *Rx*

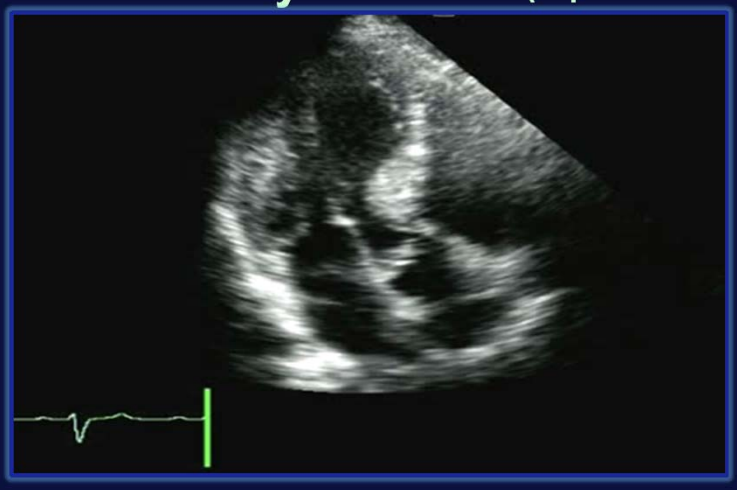
- IV infusion enzyme replacement therapy reduces glycosphingolipid tissue deposition
- Can reverse wall thickness and mass

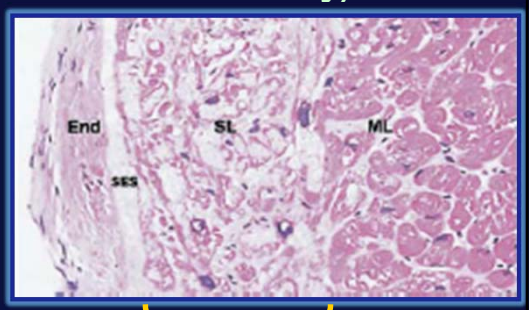
NEJM 2001; Vol345#1:9

Eur J Clin Investig 2004; 34 (12):838.

70 y/o Man: Dyspnea on exertion

Fabry Disease (Alpha-Galactosidase A Deficiency)



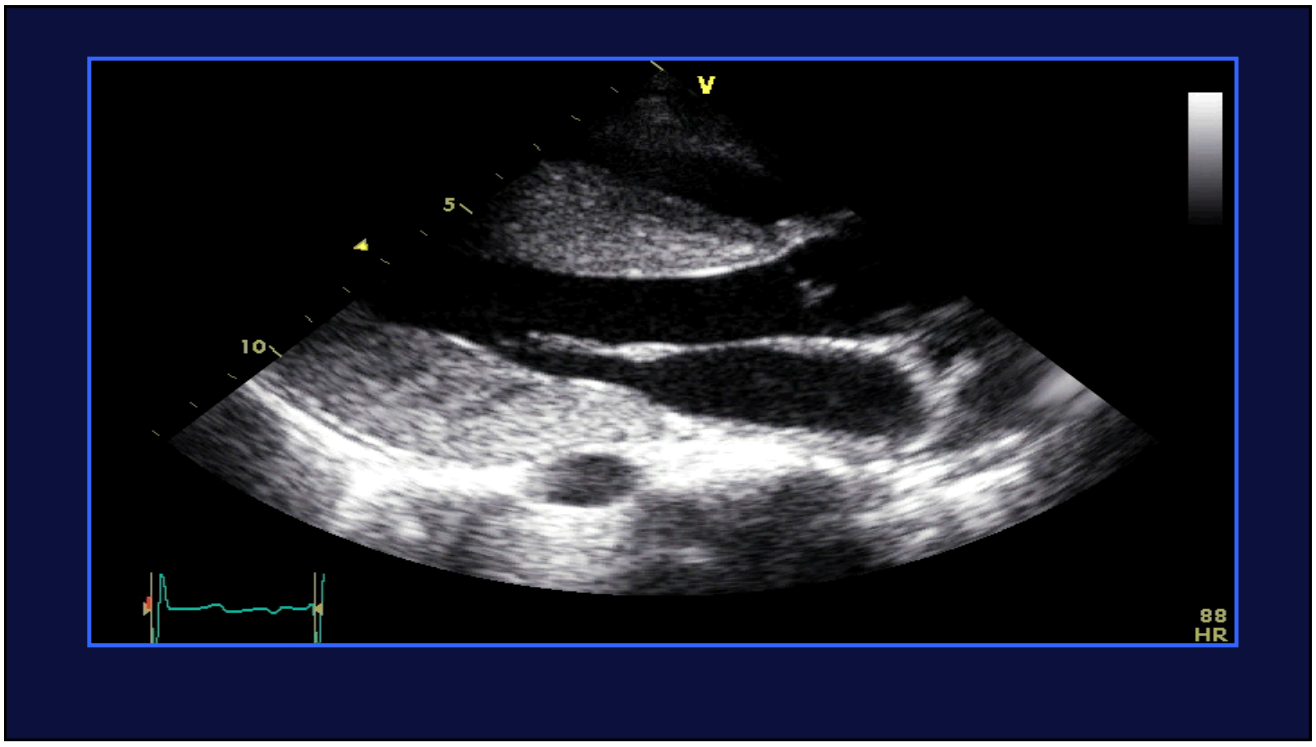


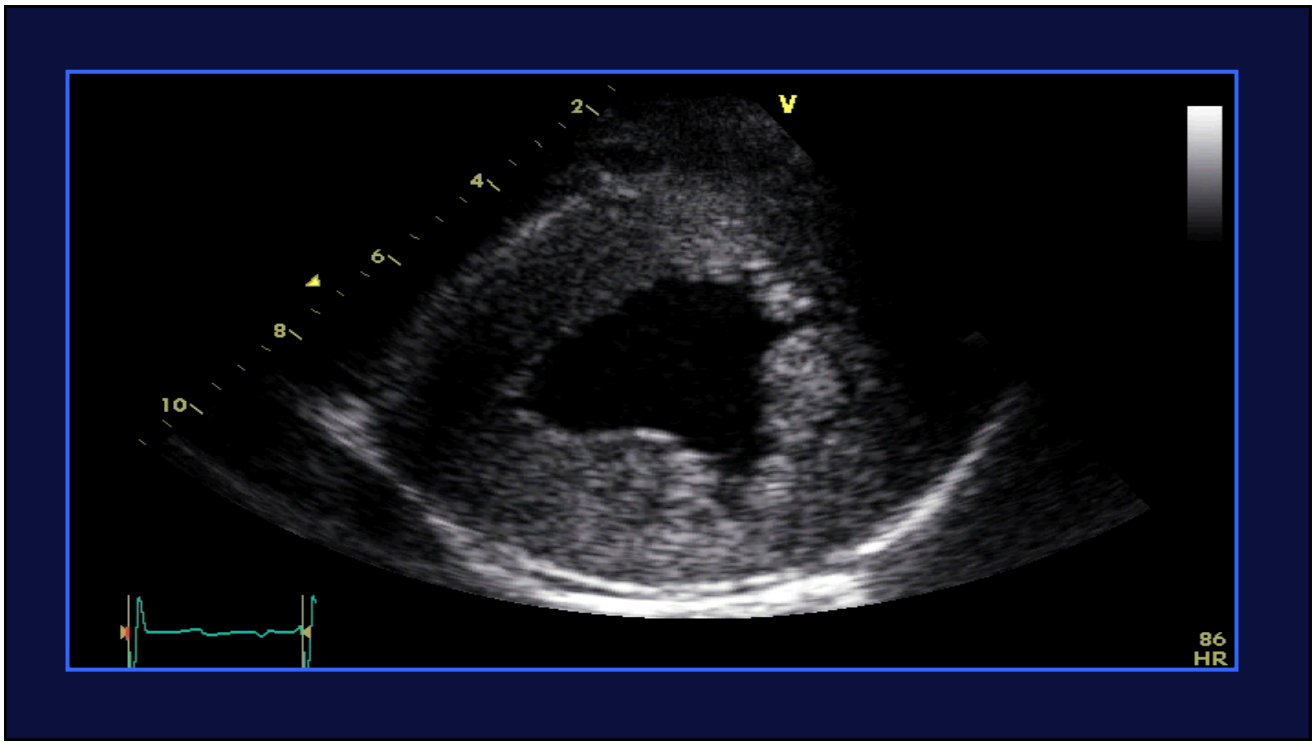
Glycosphingolipid Accumulation
Hyper-refractile subendocardial border:
94% Sensitive
100% Specific

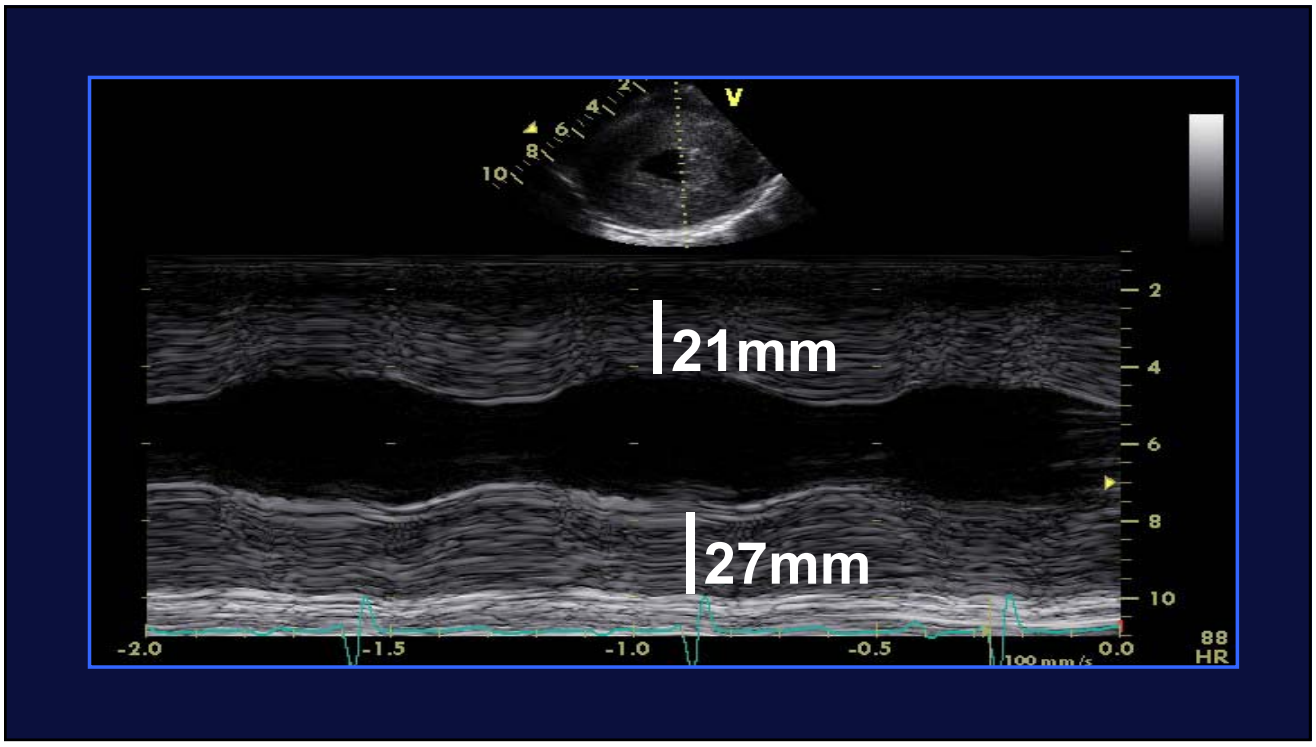
Pieroni M, et al. JACC 2006; 47: 1663
Courtesy Dr Bill Freeman

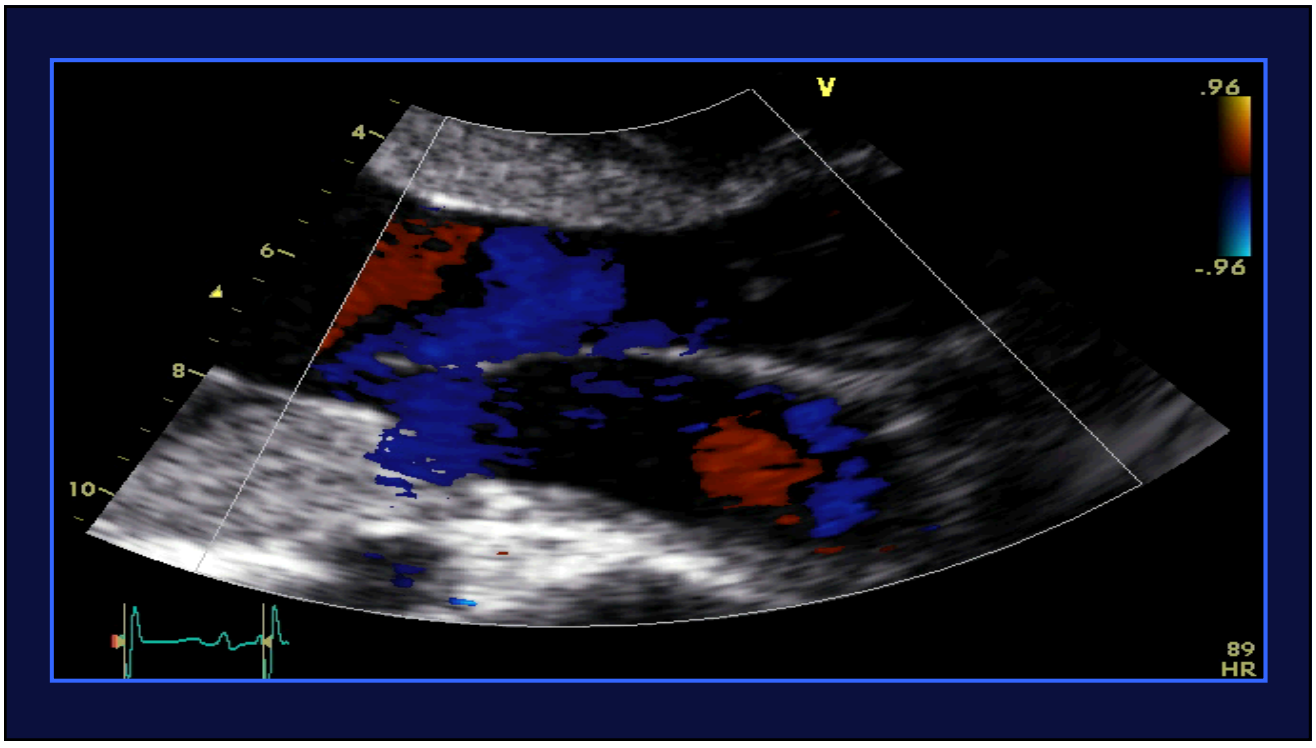
Case

19 y/o male
Wheelchair
Post-prandial chest pain

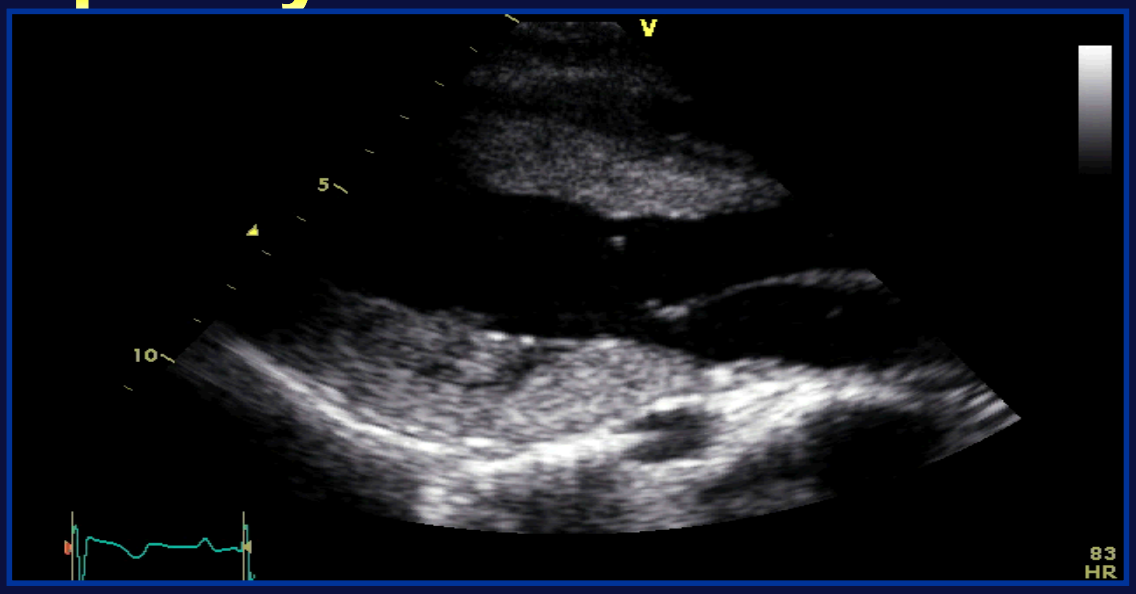

V
5
10
88
HR


V
2
4
6
8
10
86
HR


21mm
27mm
-2.0
-1.5
-1.0
-0.5
0.0
88
HR

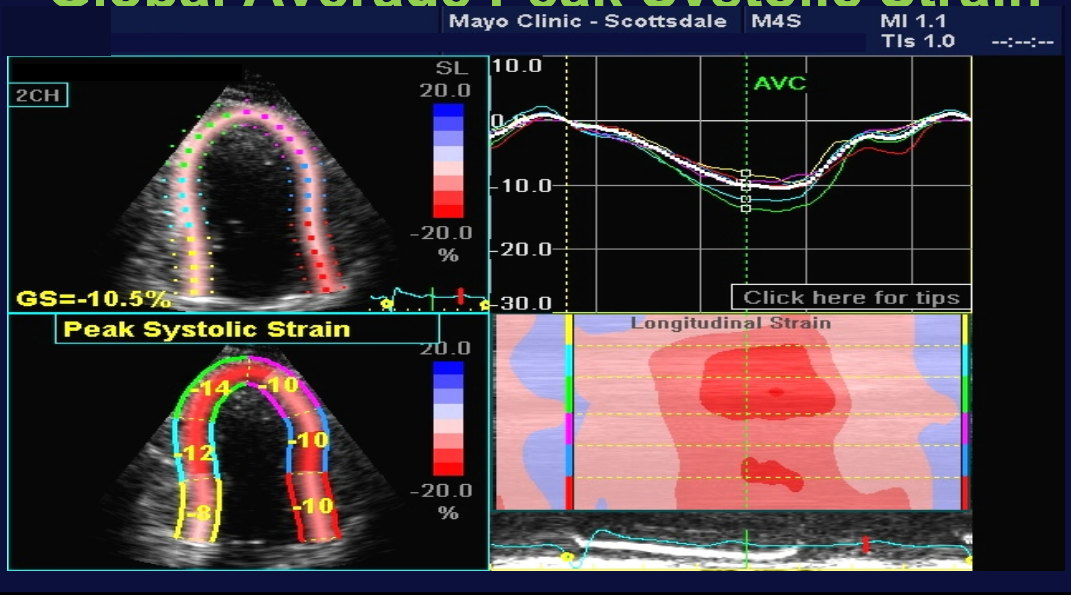

.96
-.96
89
HR

Papillary Muscle Prominence



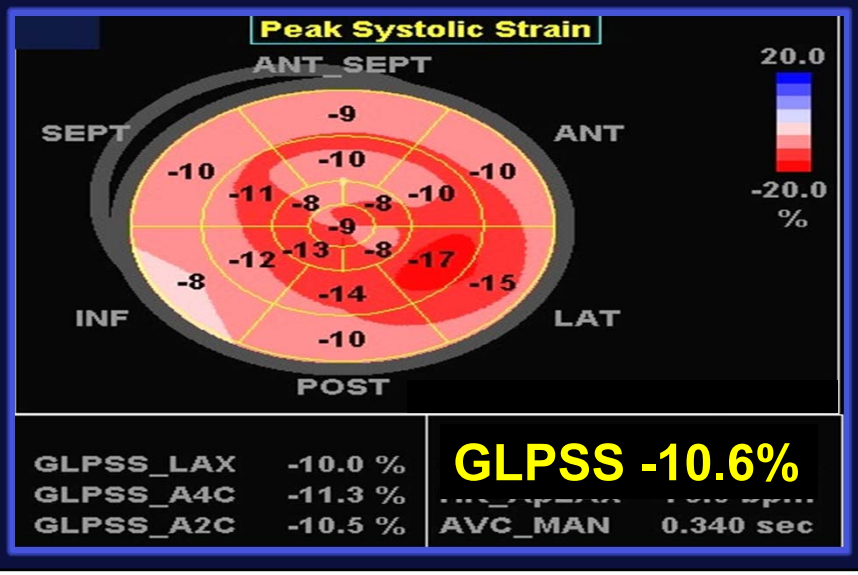
2D Feature Tracking

Global Average Peak Systolic Strain



2D Feature Tracking

Global Average Peak Systolic Strain



Why the Thick Walls?

1. Hypertrophy (genetic)
2. Infiltrative
3. Storage

Friedreich's Ataxia

- Symmetrically hypertrophied LV
- Prominent Papillary Muscle
- Absence of SAM

Clinical/Genetic Abnormalities in Friedrich's Ataxia

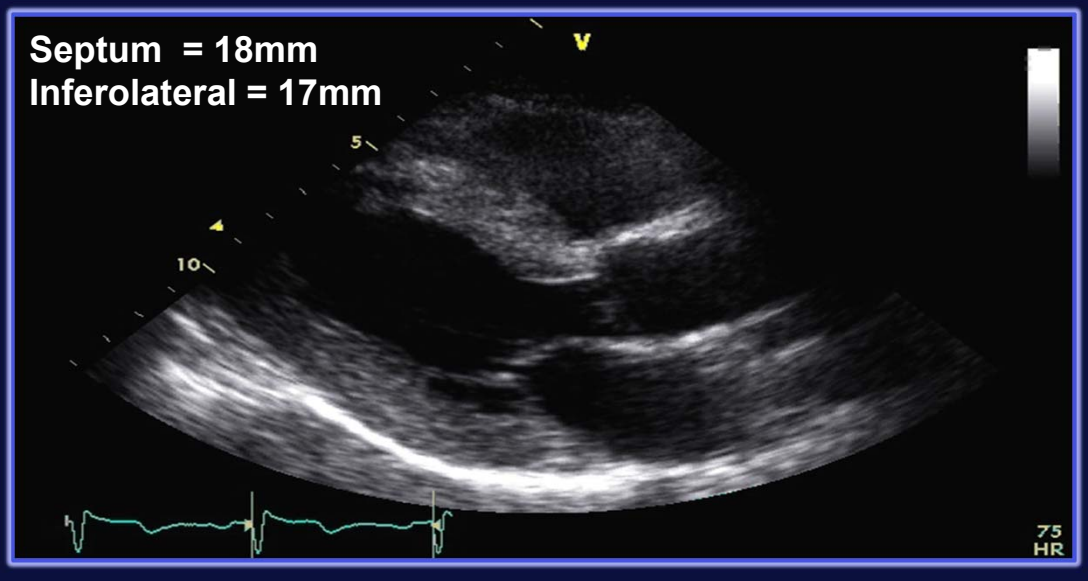
NEJM 1996 335: 1169

- Autosomal recessive neurodegenerative disorder
- 1:50,000
- Ataxia, cerebellar dysarthria, areflexia
- Onset < 20years; relentless course

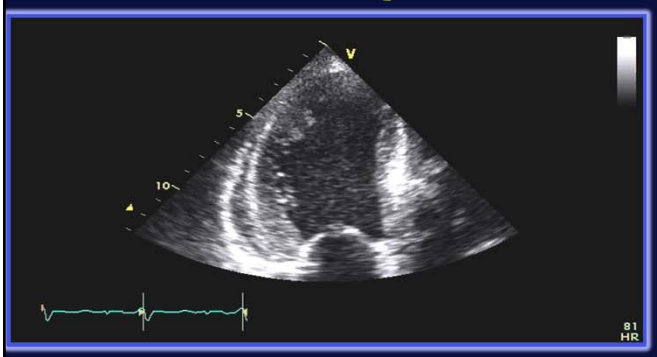
Case

- 67 y/o male status post myectomy 3 years prior
- NYHA III, Neuropathy

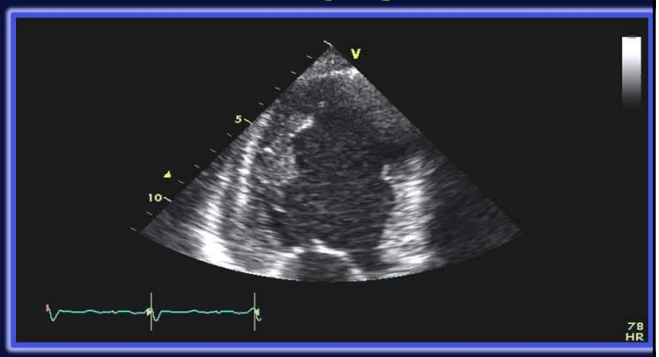
PLAX



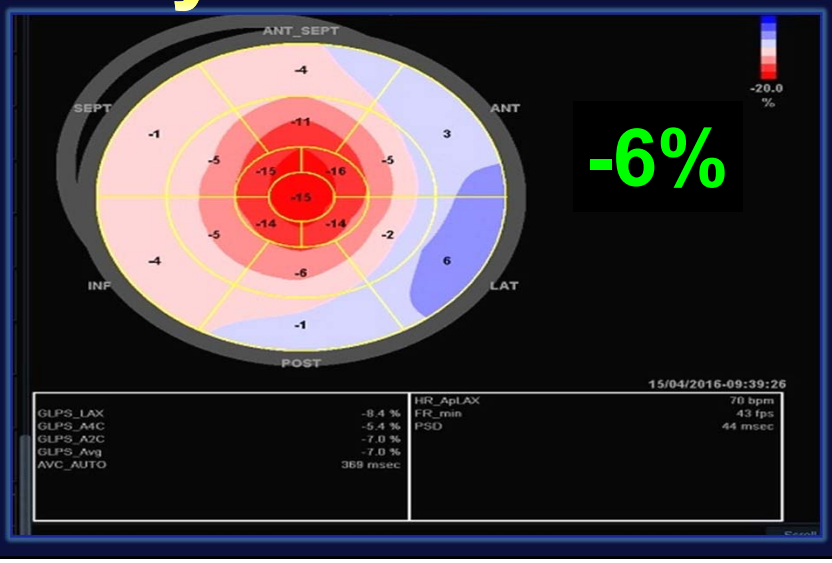
A4C



A3C



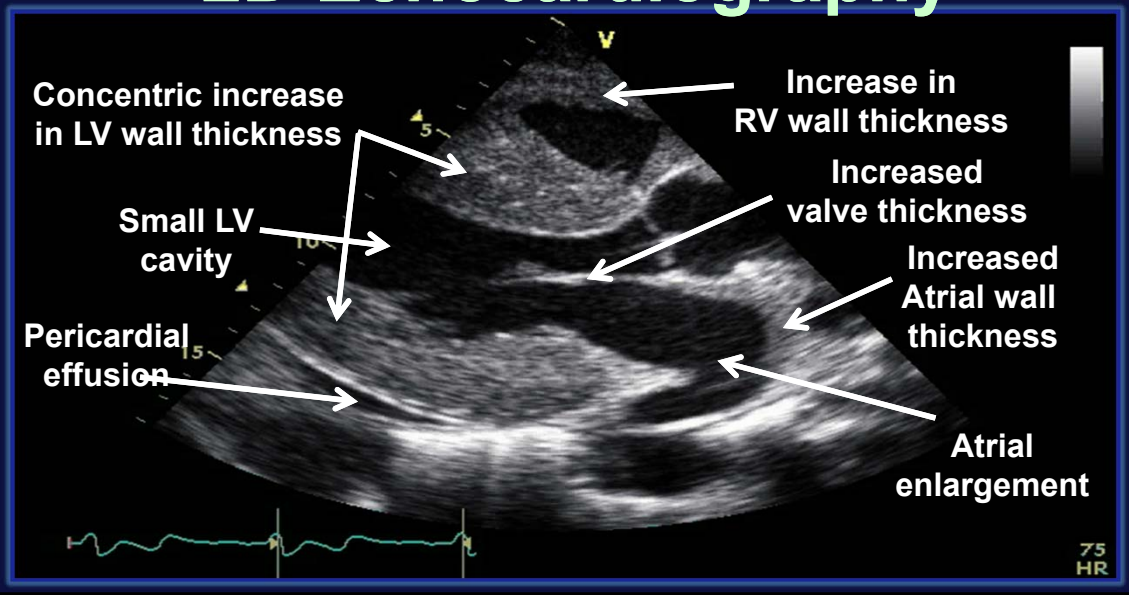
Global Longitudinal Peak Systolic Strain



Pathology Specimen

- Myocyte distribution not consistent with HCM
- Staining ATTR +

Amyloidosis
2D Echocardiography

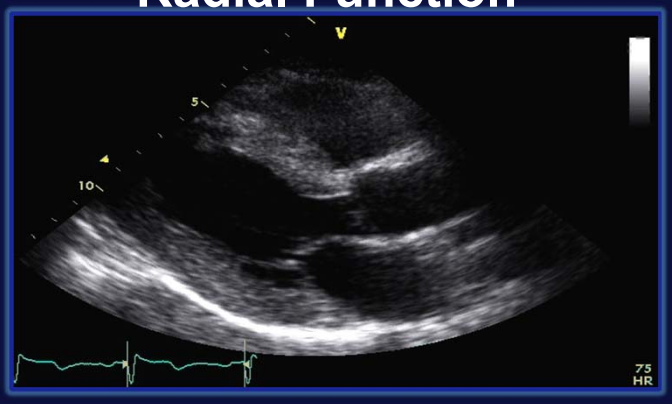


Left Ventricular Function

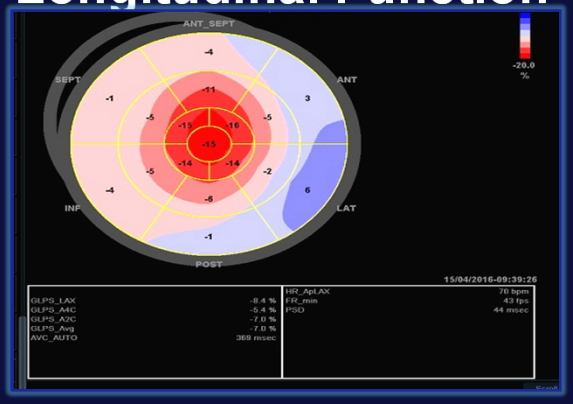
Systole

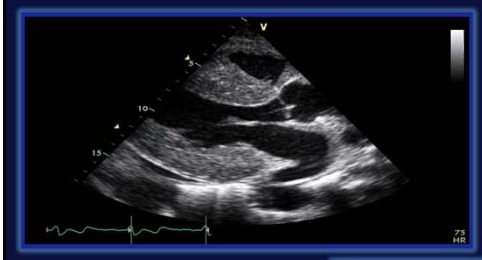
67 year old male post myectomy

Radial Function

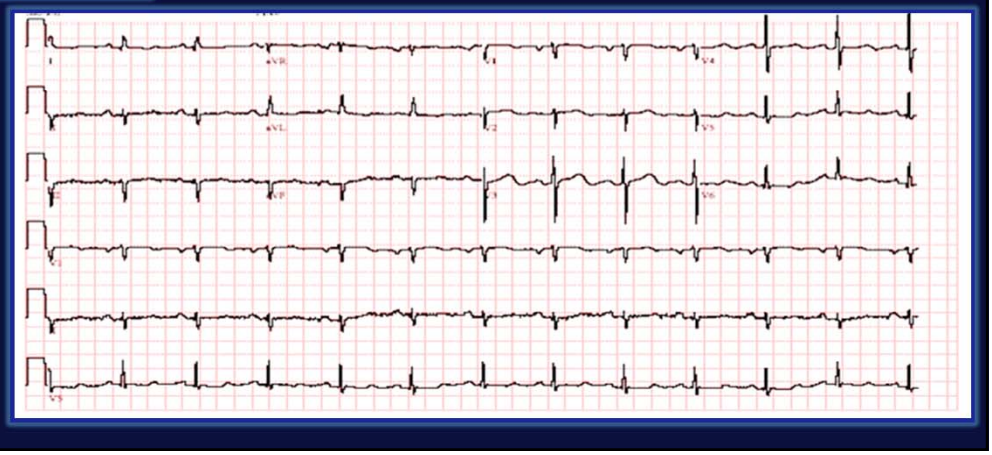


Longitudinal Function





Electrocardiogram



Amyloidosis

Laboratory Approach to Diagnosis

- **Monoclonal Protein Study (Serum and Protein)**
- **Immunoglobulin Free Light Chains (Serum)**
- **Subcutaneous Fat Aspirate (with Congo Red)**

ECHO / MRI
Pyrophosphate Scan
BNP
Troponin

Subcutaneous fat aspirate is negative but clinician still has high index of suspicion

Subcutaneous fat aspirate is positive for amyloid deposits

Specific organ biopsy

Diagnostic for amyloidosis

Negative

Positive

To identify the type of amyloid protein: Consult (hematology / surgical path)

Morphology Not Histology

Phenocopies