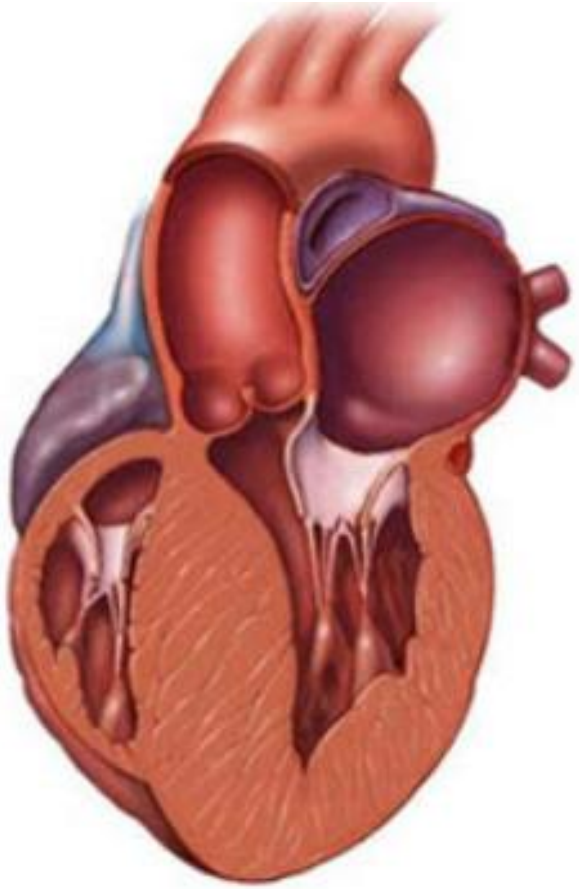
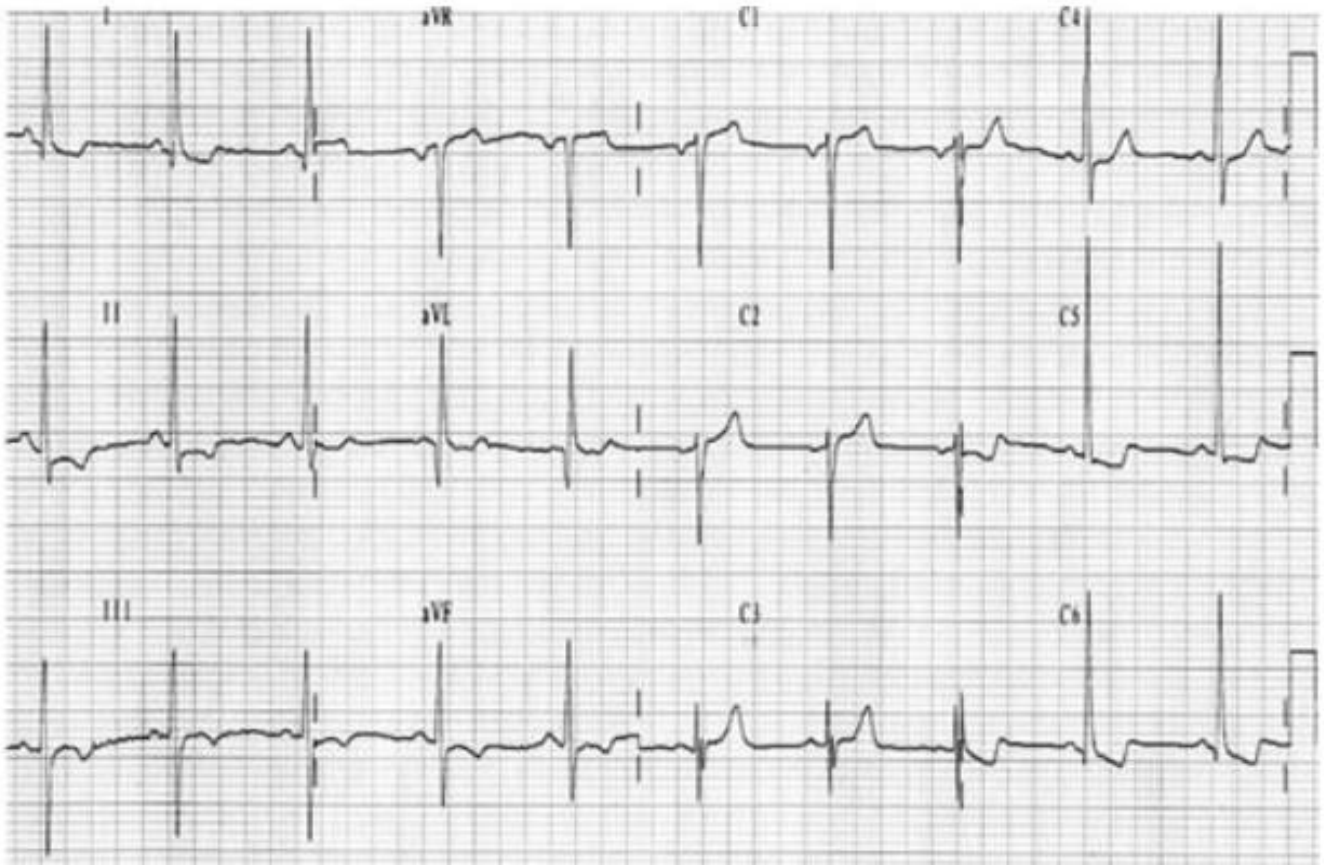
HYPERTROPHIC CARDIOMYOPATHY: WHAT INTERNISTS NEED TO KNOW?

Manasawee Indrabhinduwat, MD



A 18-yr-old man present of pre-participation sport examination.



What is your Dx ?

A. Normal variant
B. Athlete heart
C. HT heart disease
D. Hypertrophic cardiomyopathy

AGENDA

- Definition
- Epidemiology
- Pathophysiology
- Clinical presentation
- Investigation
- Dx
- DDx

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 76, NO. 25, 2020

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CLINICAL PRACTICE GUIDELINE

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society for Cardiovascular Magnetic Resonance. Endorsed by The Pediatric & Congenital Electrophysiology Society

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 79, NO. 4, 2022

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Diagnosis and Evaluation of Hypertrophic Cardiomyopathy

JACC State-of-the-Art Review

Barry J. Maron, MD,[a] Milind Y. Desai, MD,[b] Rick A. Nishimura, MD,[c] Paolo Spirito, MD,[d] Harry Rakowski, MD,[e] Jeffrey A. Towbin, MD,[f] Ethan J. Rowin, MD,[a] Martin S. Maron, MD,[a] Mark V. Sherrid, MD[g]

JACC: CARDIOVASCULAR IMAGING
VOL. 13, NO. 9, 2020

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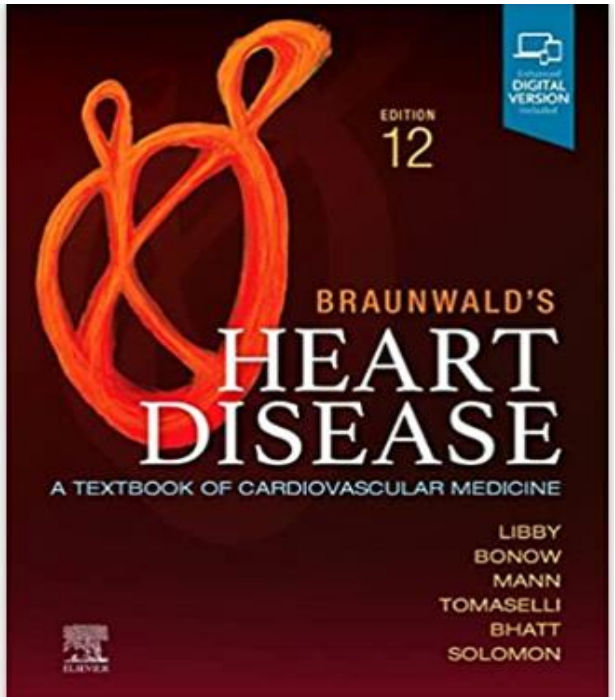
REVIEW

STATE-OF-THE-ART REVIEW

The Hypertrophic Cardiomyopathy Phenotype Viewed Through the Prism of Multimodality Imaging

Clinical and Etiologic Implications

Ethan J. Rowin, MD, Barry J. Maron, MD, Martin S. Maron, MD



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REVIEW TOPIC OF THE WEEK

The Mitral Valve in Obstructive Hypertrophic Cardiomyopathy

A Test in Context

Mark V. Sherrid, MD,[a] Sandhya Balaram, MD,[b] Bette Kim, MD,[c] Leon Axel, MD, PhD,[d] Daniel G. Swistel, MD[e]

DEFINITION: HYPERTROPHIC CARDIOMYOPATHY (HCM)

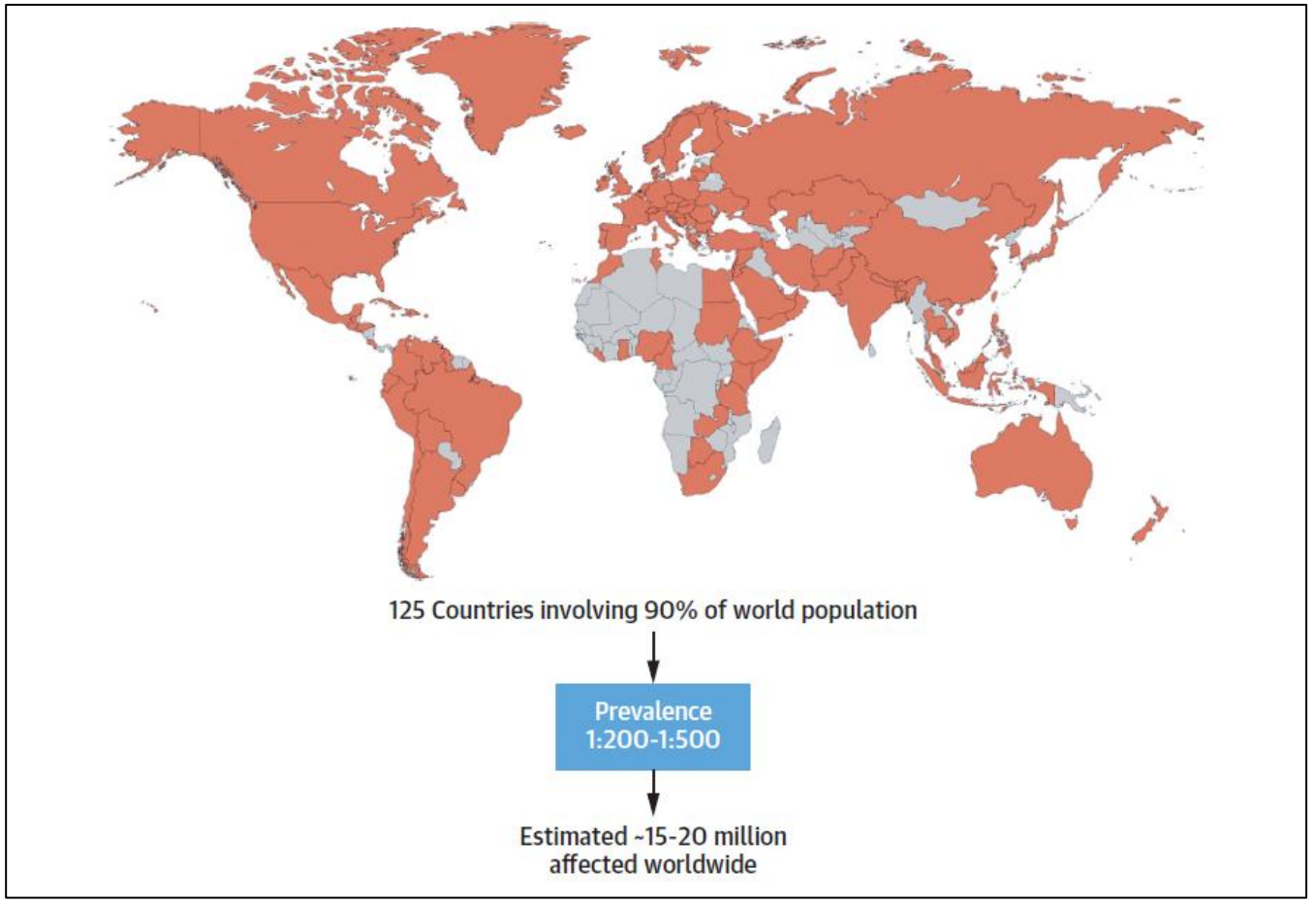
- characterized by LVH in the absence of another cardiac, systemic, or metabolic disease
- morphologic expression is confined solely to the heart

- 2D echo or CMR showing a maximal LV end-diastolic wall thickness **≥15 mm anywhere in LV**, in the absence of another cause of hypertrophy in adults
- More limited hypertrophy (13–14 mm) can be diagnostic when present in family members of a patient with HCM or in conjunction with a positive genetic test

2020 AHA/ACC HCM Guideline

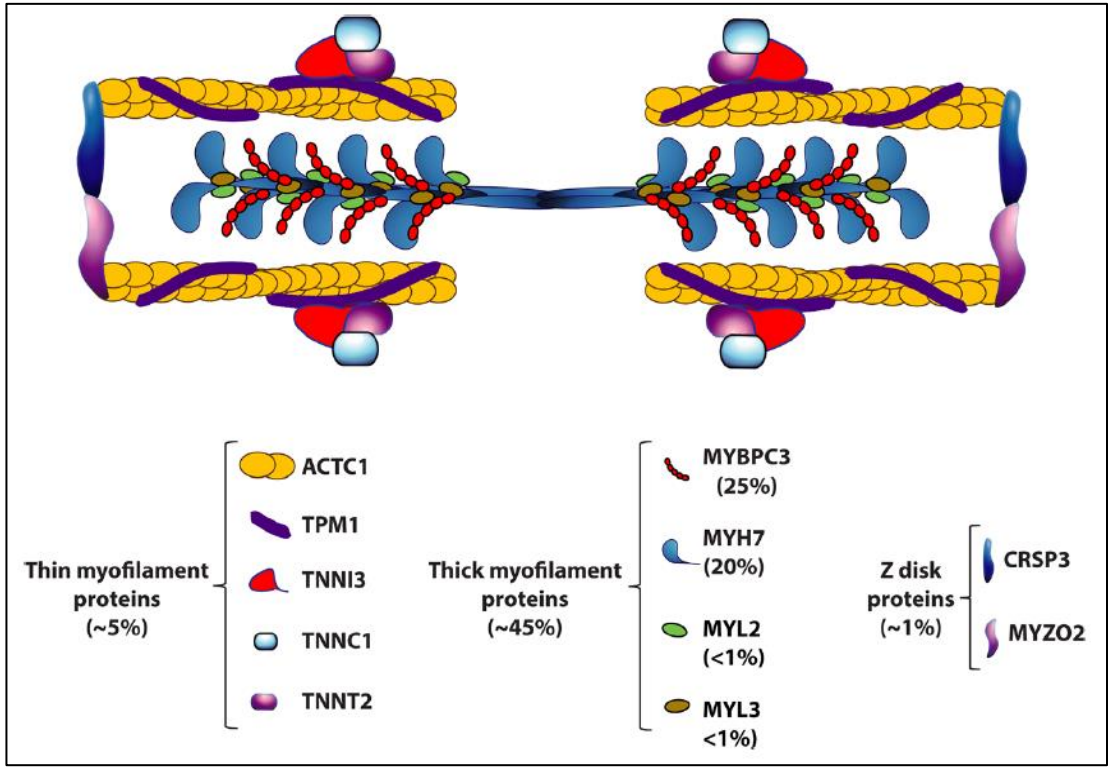
PREVALENCE

- Asymptomatic HCM in young adults in USA has been reported to range from 1:200 to 1:500
- Symptomatic HCM based on medical claims data has been estimated at <1:3,000
- 1/3 of HCM had no LVOT obstruction



J Am Coll Cardiol 2022;79:372–389

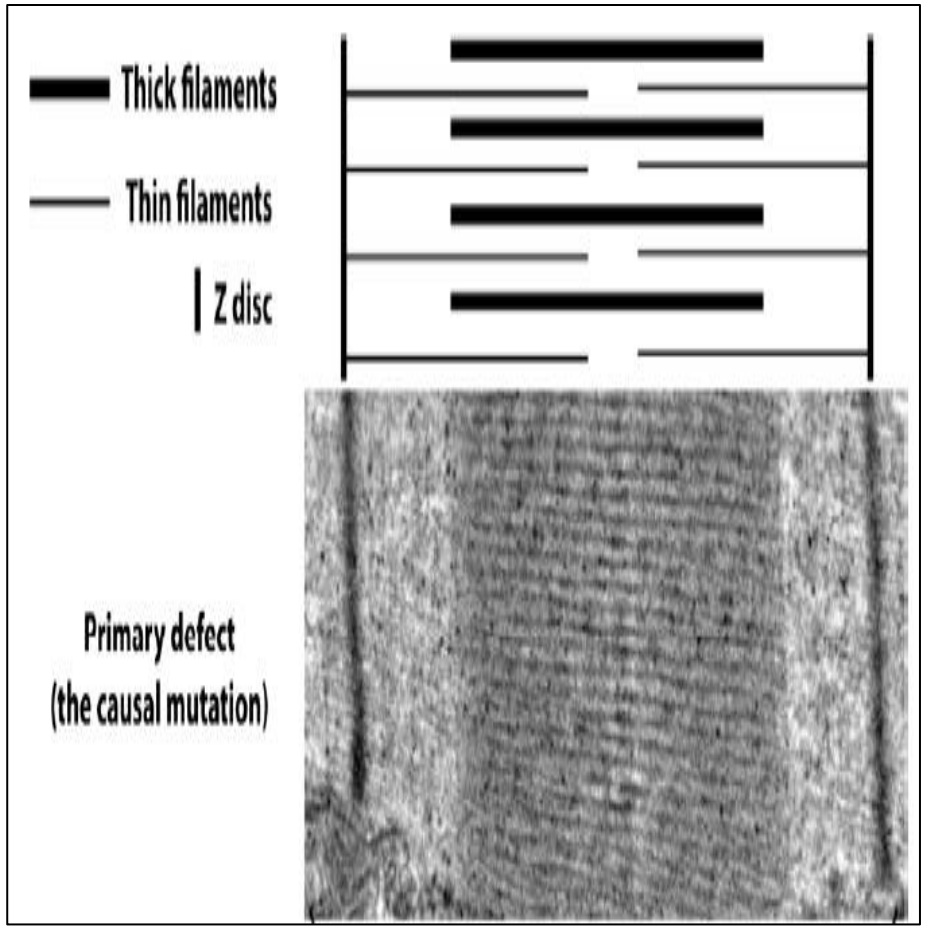
Genetic



Gene	Protein	Function
Established causal gene HCM (large families)		
MYH7	β-Myosin heavy chain	ATPase activity, force generation
MYBPC3	Myosin-binding protein C	Cardiac contraction
TNNT2	Cardiac troponin T	Regulator of actomyosin interaction
TNNI3	Cardiac troponin I	Inhibitor of actomyosin interaction
TPM1	α-Tropomyosin	Places the troponin complex on cardiac actin
ACTC1	Cardiac α-actin	Actomyosin interaction
MYL2	Regulatory myosin light chain	Myosin heavy chain 7–binding protein
MYL3	Essential myosin light chain	Myosin heavy chain 7–binding protein
CSRP3	Cysteine- and glycine-rich protein 3	Muscle LIM protein (MLP), a Z disk protein

Ali J. Marian, Eugene Braunwald. *Circ Res*. 2017;121:749-770

HISTOLOGICAL PHENOTYPES



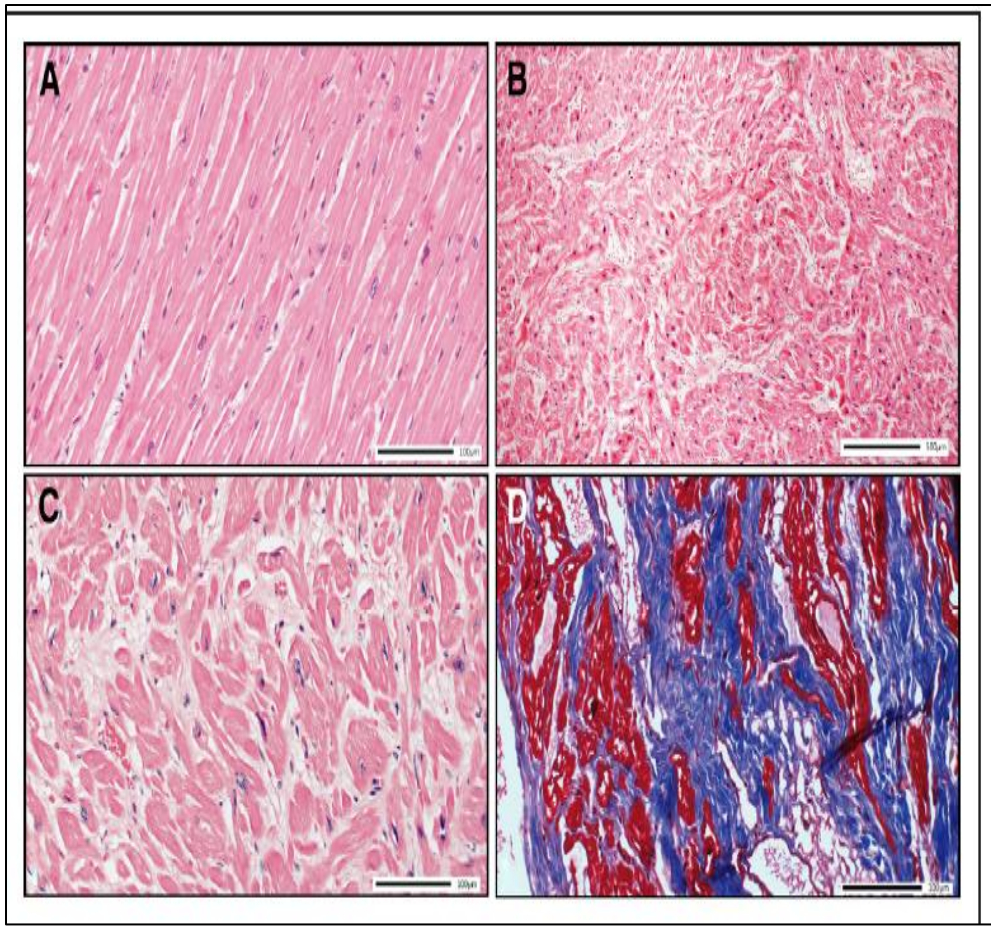
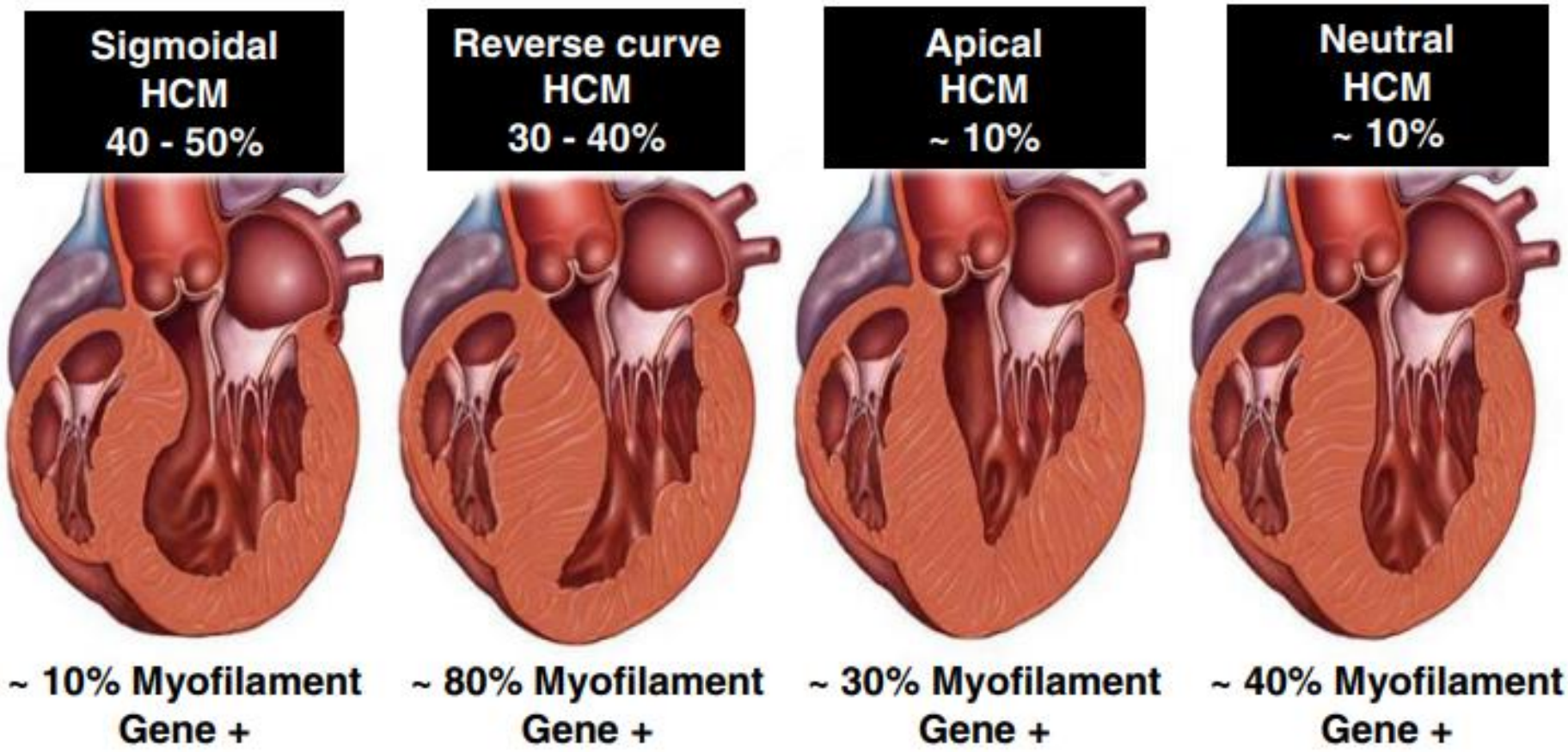


Figure 6. Histological phenotypes. A, A normal thin myocardial section stained with hematoxylin and eosin (H&E). **B,** A low-magnification (×4) H&E-stained thin myocardial section from a patient heart with hypertrophic cardiomyopathy showing disorganized myocardial architecture. **C,** A higher magnification (×20) H&E-stained myocardial section showing myocyte disarray (×). **D,** A thin myocardial section (×20) stained with Masson trichrome in blue showing areas of interstitial fibrosis.

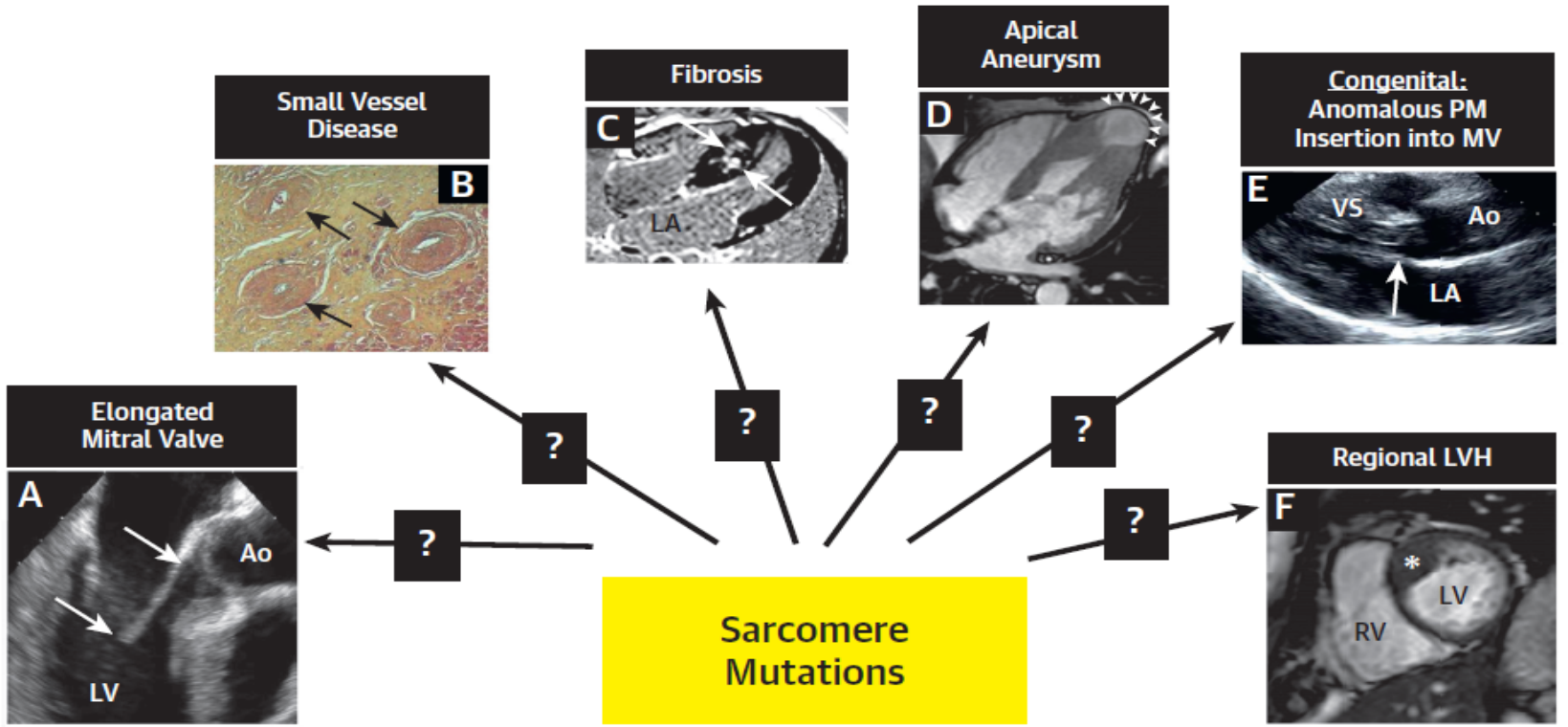
Bruanwald E. Circ Res. 2017;121:749-770

HCM Geometry



Bos et al. Genetic testing in HCM. JACC Vol. 54, No. 3, 2009

CENTRAL ILLUSTRATION Many Features of the HCM Phenotype May Not Be Attributable to Sarcomere Mutations



Rowin, E.J. et al. J Am Coll Cardiol Img. 2020;13(9):2002–16.

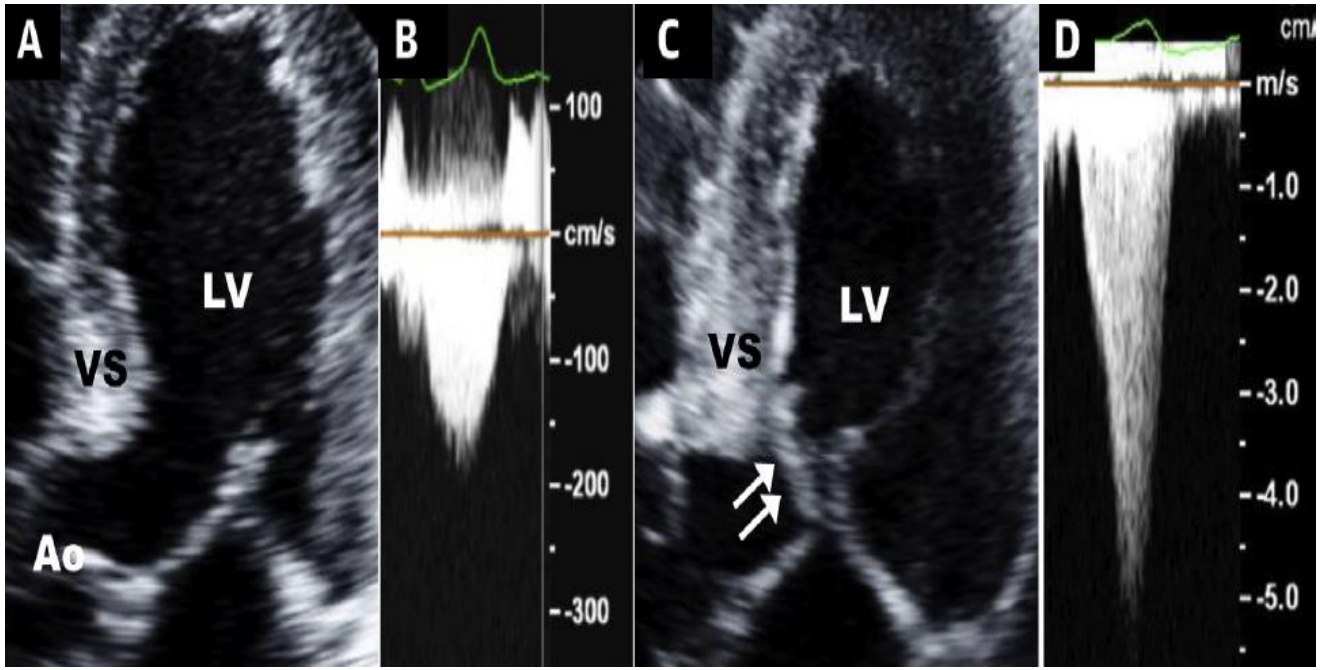
Elongated mitral valve leaflets **(arrows; A)**, structurally abnormal intramural coronary arterioles with medial hypertrophy **(arrows; B)**, myocardial fibrosis **(arrows; C)** and LV apical aneurysms with regional scarring **(arrowheads; D)** are diverse morphologic features of HCM, which do not contain contractile sarcomere proteins or do not appear to be a pathophysiologic consequence of sarcomere mutations. Muscular midcavity obstruction caused by direct papillary muscle insertion into the mitral valve in the absence of chordae tendineae **(arrow; E)** is a congenital morphologic anomaly inconsistent with a single sarcomere gene hypothesis. In addition, patterns of LV hypertrophy, which commonly include regional areas of increased wall thickness **(asterisk; F)**, with normal wall thickness in remainder of the LV chamber, are difficult to attribute solely to sarcomere variants, which are expressed in cardiomyocytes throughout the LV wall. Ao = aorta; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle; VS = ventricular septum.

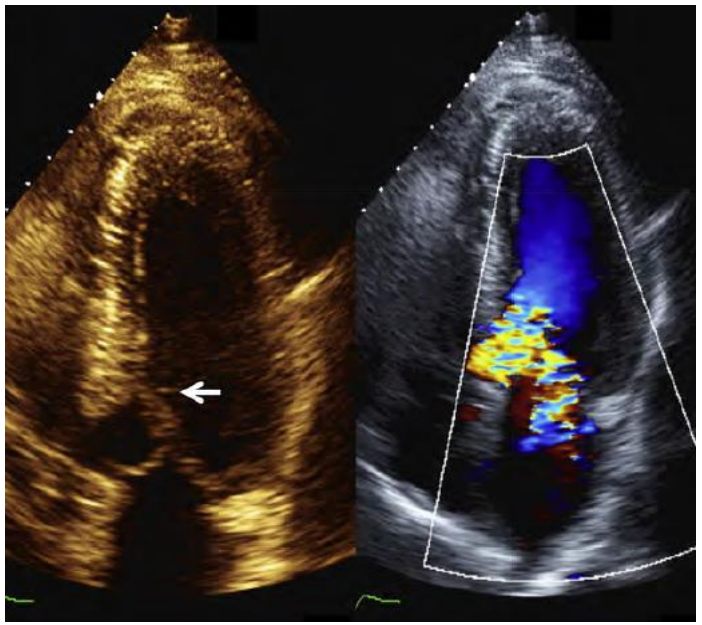
PATHOPHYSIOLOGY

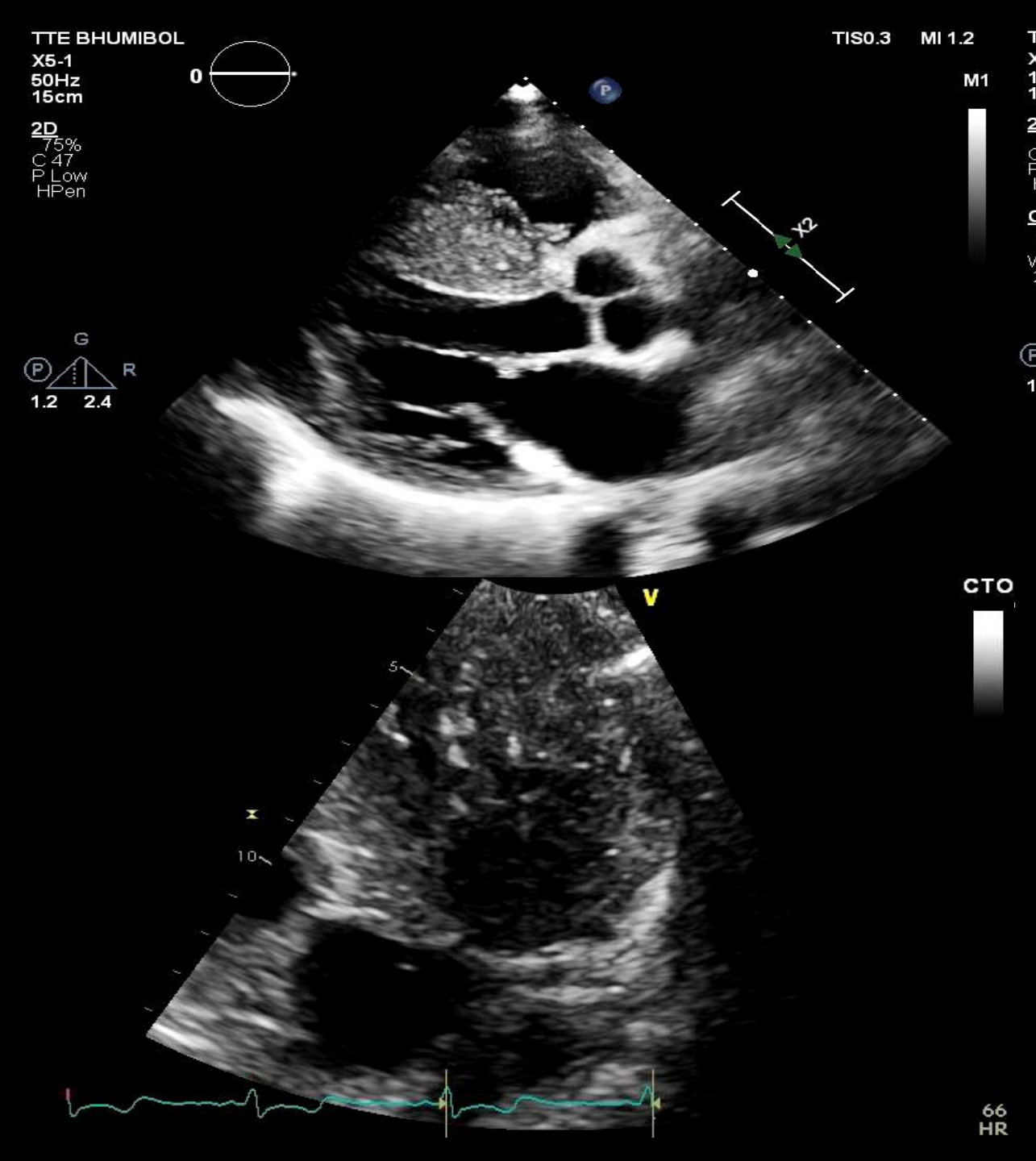
- Dynamic LVOTO,
- Mitral regurgitation (MR)
- Diastolic dysfunction
- Myocardial ischemia
- Arrhythmias

LVOT OBSTRUCTION

- Present in 75% of patients with HCM
- Load dependent: preload/afterload
- Mechanism
  - Septal hypertrophy with narrowing of the LVOT, abnormal blood flow vectors that dynamically displace the mitral valve leaflets anteriorly
  - Anatomic alterations in the mitral valve and apparatus, including
    - longer leaflets
    - anterior displacement of the papillary muscles and mitral valve apparatus






TTE BHUMIBOL
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15cm
2D
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C 47
P Low
HPen
TIS0.3
MI 1.2
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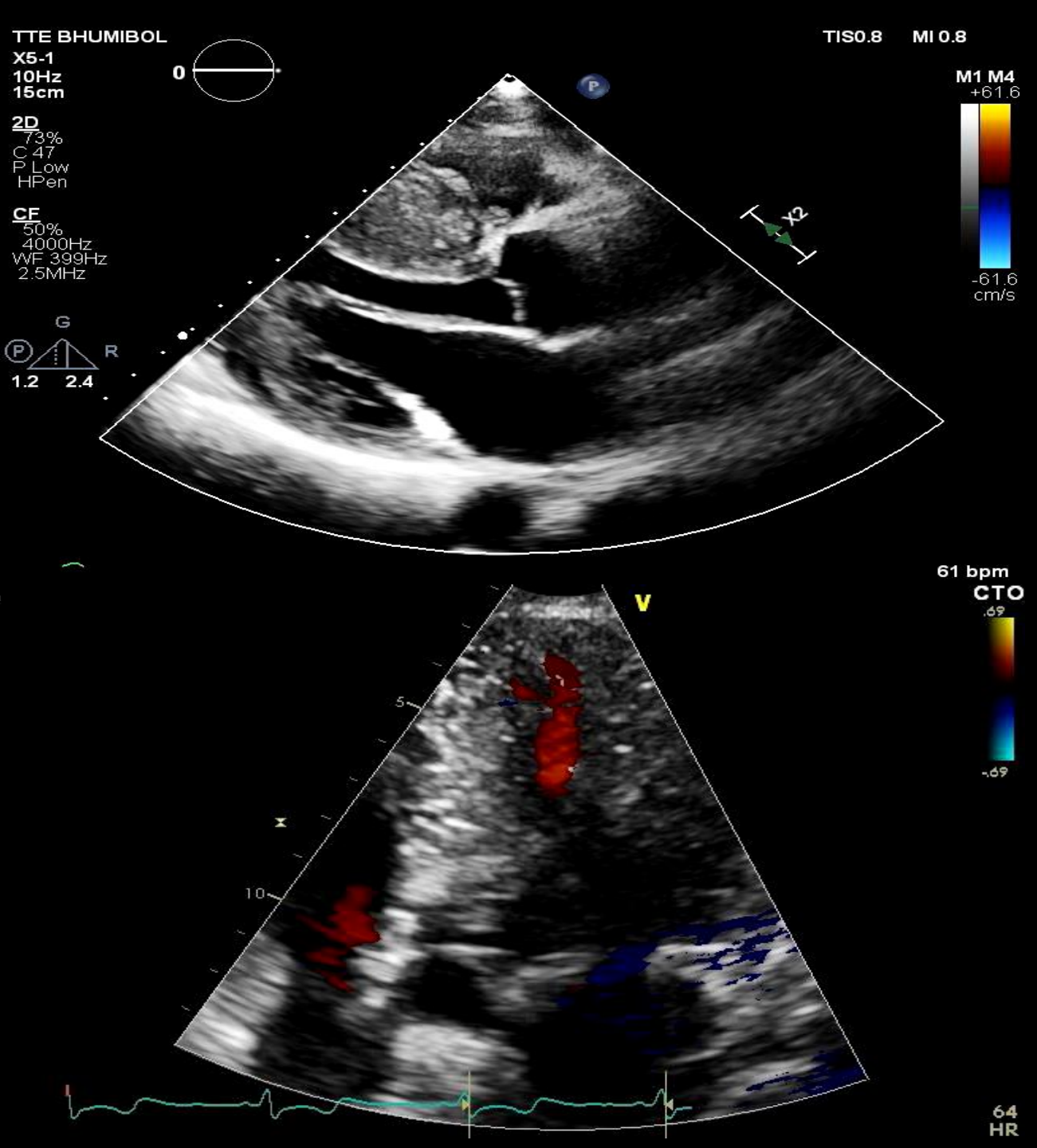
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C 47
P Low
HPen
CF
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4000Hz
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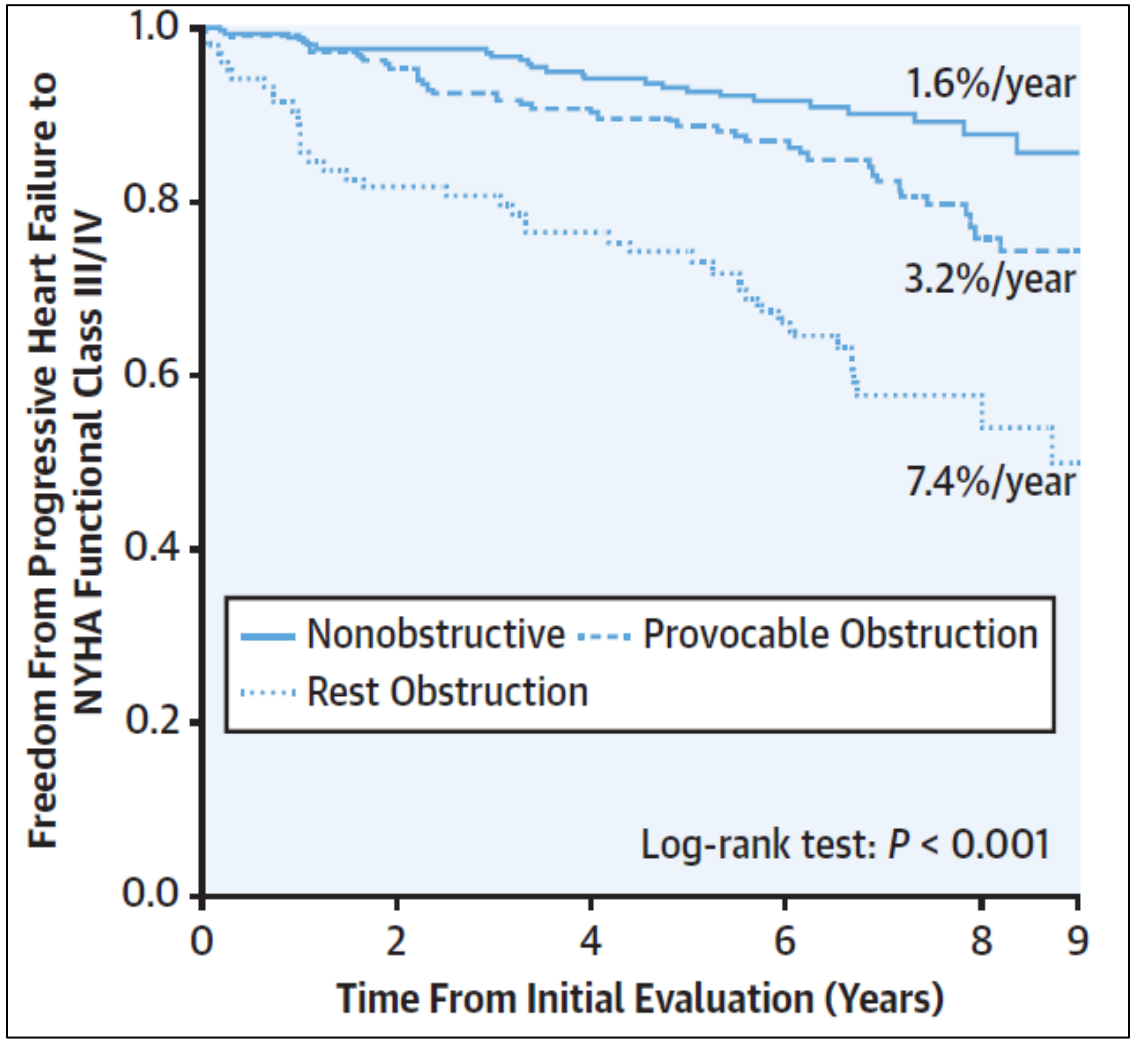
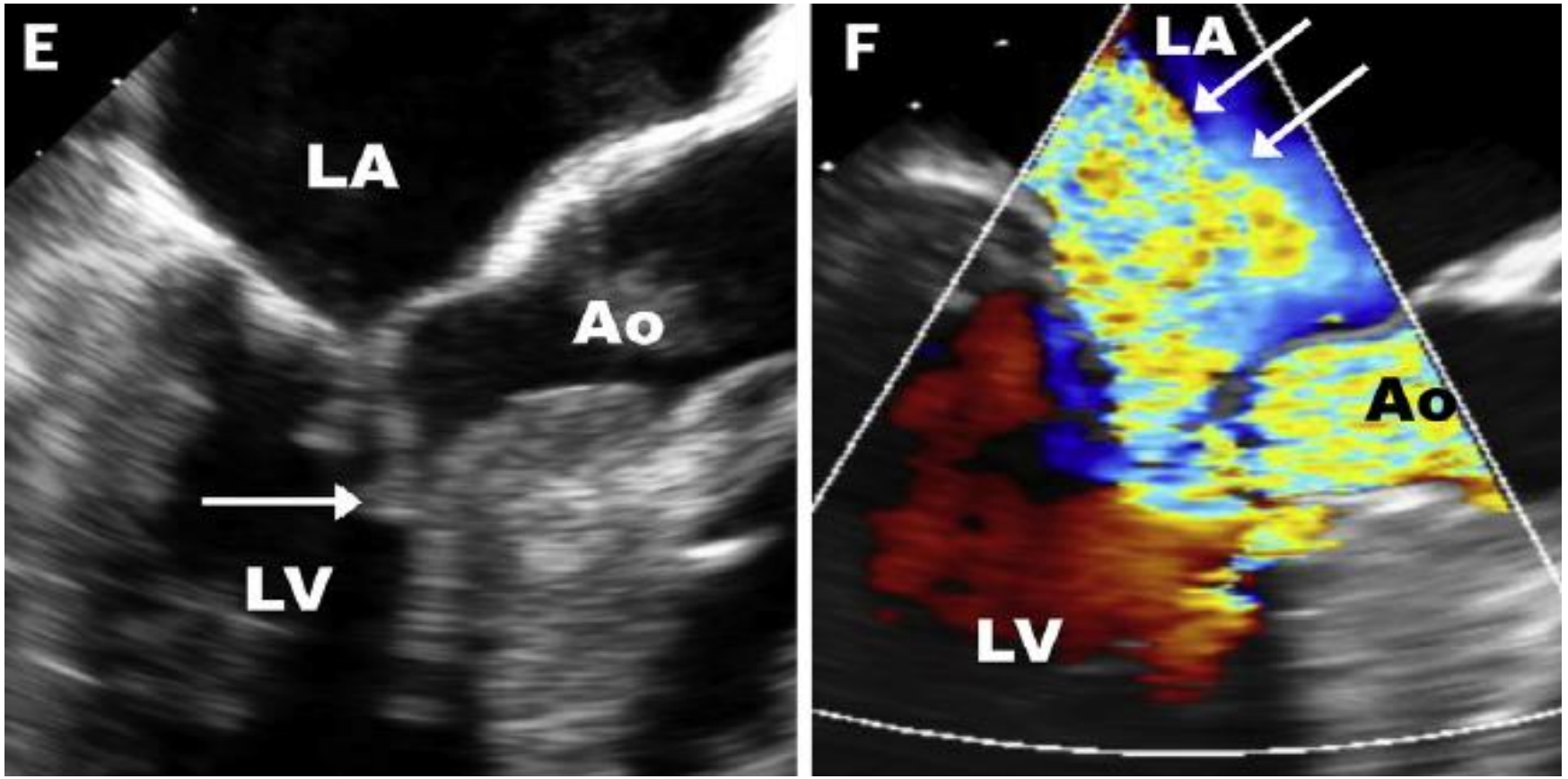
TIS0.8
MI 0.8
M1 M4
+61.6
-61.6
cm/s
X2
G
P
R
1.2
2.4
V
61 bpm
CTO
64
HR

- Provoked gradients > 30 mm Hg provide prognostic information including prediction of future HF progression FC class I or II to class III (at a rate of 3% per year)



Maron et al. J A C C VOL . 7 9 , N O . 4 .F E B R U A R Y 1 , 2 0 2 2 : 3 7 2 – 3 8 9

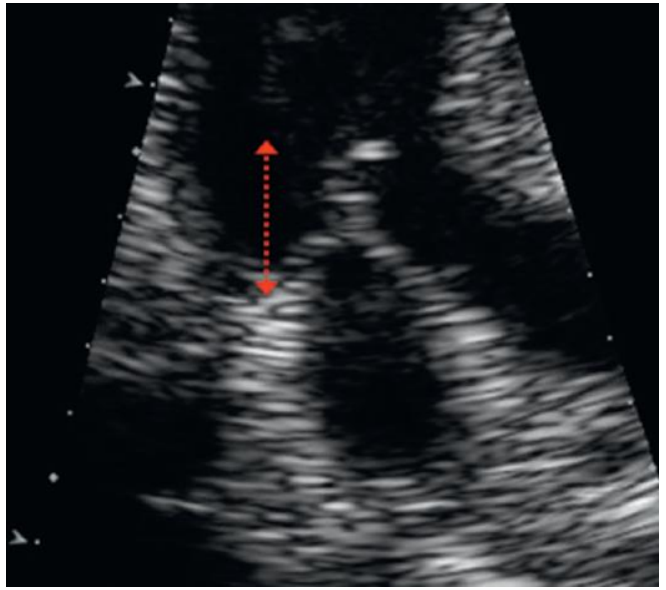
Mitral Regurgitation



J Am Coll Cardiol 2022;79:372–389

MV APPARATUS ABNORMALITY

- MV elongation of both leaflets (In obstructive HCM, the anterior leaflet averages 34 mm VS 24 mm in normal hearts)
- Increased length and area compared with normal controls
- Mitral valve prolapse
- Cleft posterior mitral leaflet
- Calcification of the mitral leaflets or annulus



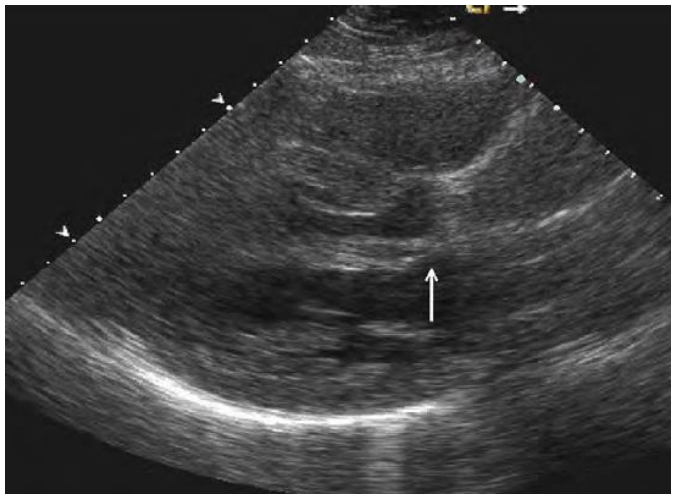
Night "Cap"

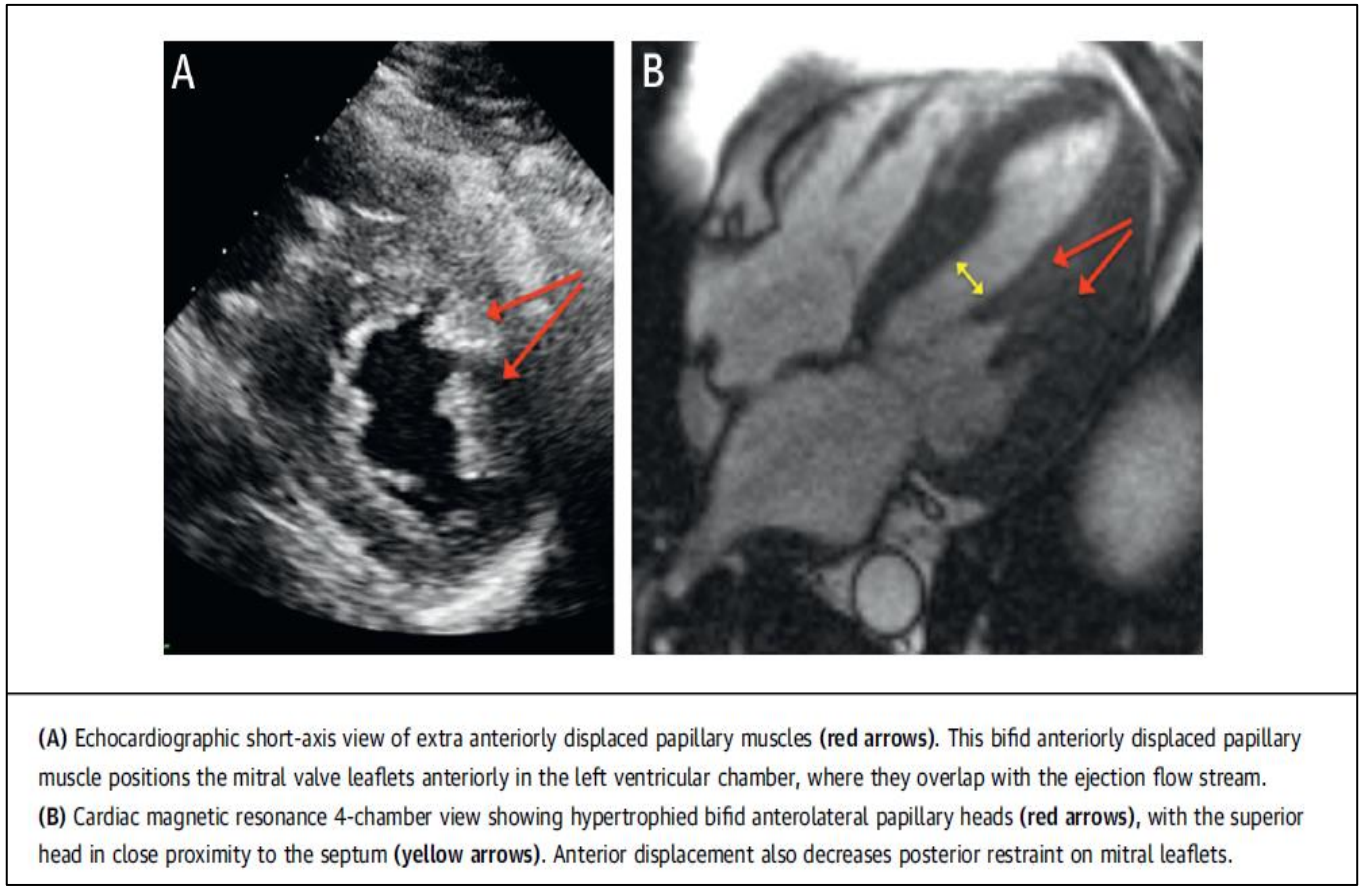
Journal of the American Society of Echocardiography May 2011

Papillary Muscle Abnormality

The 2 most common pathogenic abnormalities

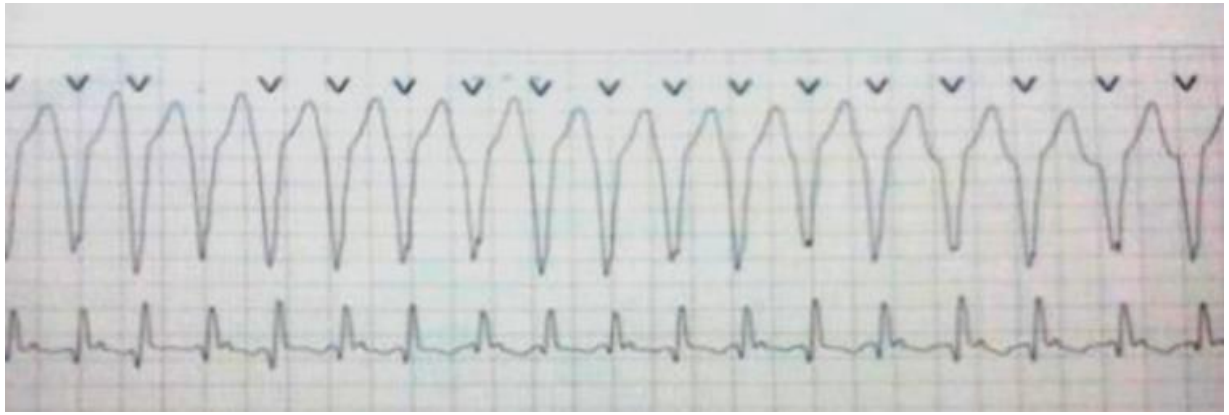
1) Anterior and basilar displacement of the base of the anterolateral papillary muscle
2) abnormal muscular connections between its head and the anterolateral wall, inserting into or near the A1 scallop

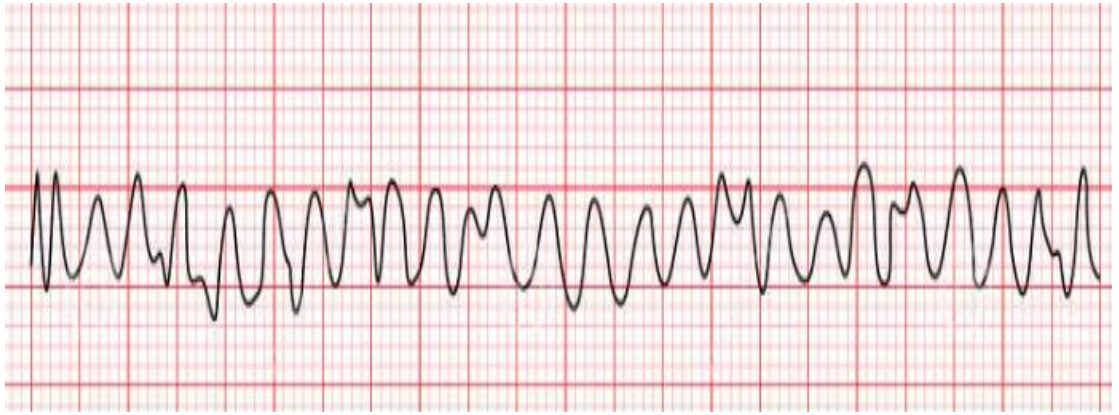




(A) Echocardiographic short-axis view of extra anteriorly displaced papillary muscles **(red arrows)**. This bifid anteriorly displaced papillary muscle positions the mitral valve leaflets anteriorly in the left ventricular chamber, where they overlap with the ejection flow stream. **(B)** Cardiac magnetic resonance 4-chamber view showing hypertrophied bifid anterolateral papillary heads **(red arrows)**, with the superior head in close proximity to the septum **(yellow arrows)**. Anterior displacement also decreases posterior restraint on mitral leaflets.

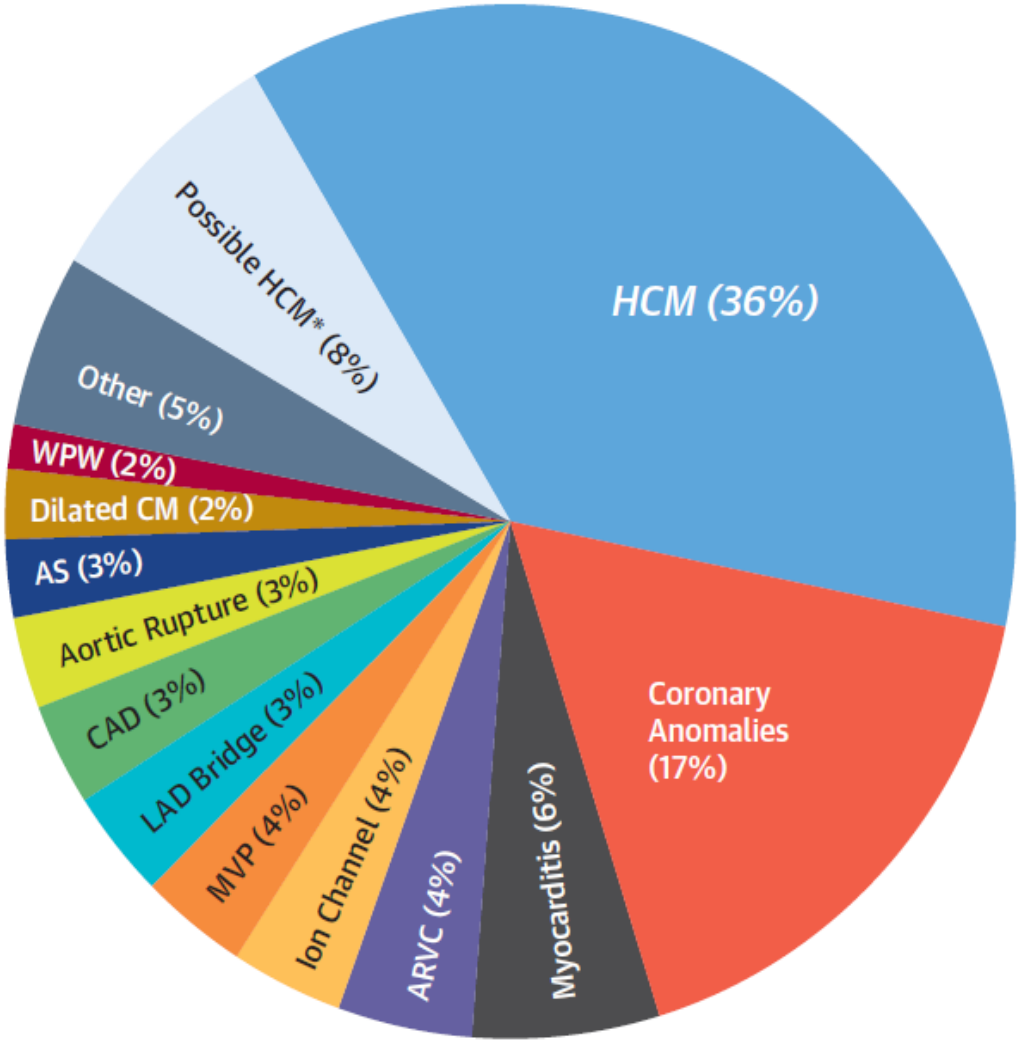
Sherrid et al. Mitral Valve in Obstructive Hypertrophic Cardiomyopathy. JACC. Vol 6 7 , NO . 1 5 , 2 0 1 6





VENTRICULAR ARRHYTHMIA

Causes of Sudden Death in Competitive Athletes



Maron et al. J A C C V O L . 7 9 , NO . 4 , 2 0 2 2. : 3 7 2 – 3 8 9

Established Clinical Risk Factors for HCM Sudden Death Risk Stratification

Family history of sudden death from HCM	Sudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 years of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.
Massive LVH	Wall thickness ≥30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable.
Unexplained syncope	≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 months of evaluation (events beyond 5 years in the past do not appear to have relevance).
HCM with LV systolic dysfunction	Systolic dysfunction with EF <50% by echocardiography or CMR imaging.
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.
Extensive LGE on CMR imaging	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been established in children).
NSVT on ambulatory monitor	It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥3), longer (≥10 beats), and faster (≥200 bpm) occurring usually over 24 to 48 hours of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by >20% is considered significant.

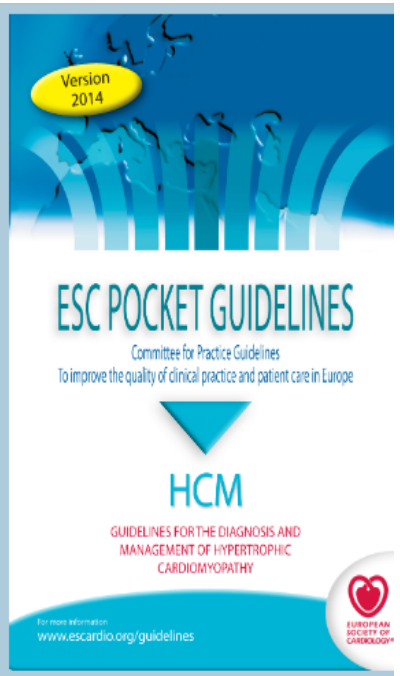
CMR indicates cardiovascular magnetic resonance; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NSVT, nonsustained ventricular tachycardia; and SCD, sudden cardiac death.

EUROPEAN SOCIETY OF CARDIOLOGY®

HCM Risk-SCD Calculator

Age		**Years**	*Age at evaluation*
Maximum LV wall thickness		**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size		**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient		**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes		*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes		*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes		*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	
ESC recommendation:	



5-yr SCD risk < 4% → no indication for ICD implantation

PHYSICAL EXAMINATION

- Apical systolic thrust
- Medium-pitch SEM at LLSB; increases with the Valsalva maneuver, during or immediately after exercise, or on standing
- Lack of radiation of the murmur to the neck (differentiating dynamic subaortic obstruction from fixed aortic stenosis)
- Most HCM patients with loud murmurs of at least grade 3/6 are likely to have LV outflow gradients of more than 30 mm Hg
- Arterial pulses may rise rapidly with the spike and dome pulse contour.

Investigations

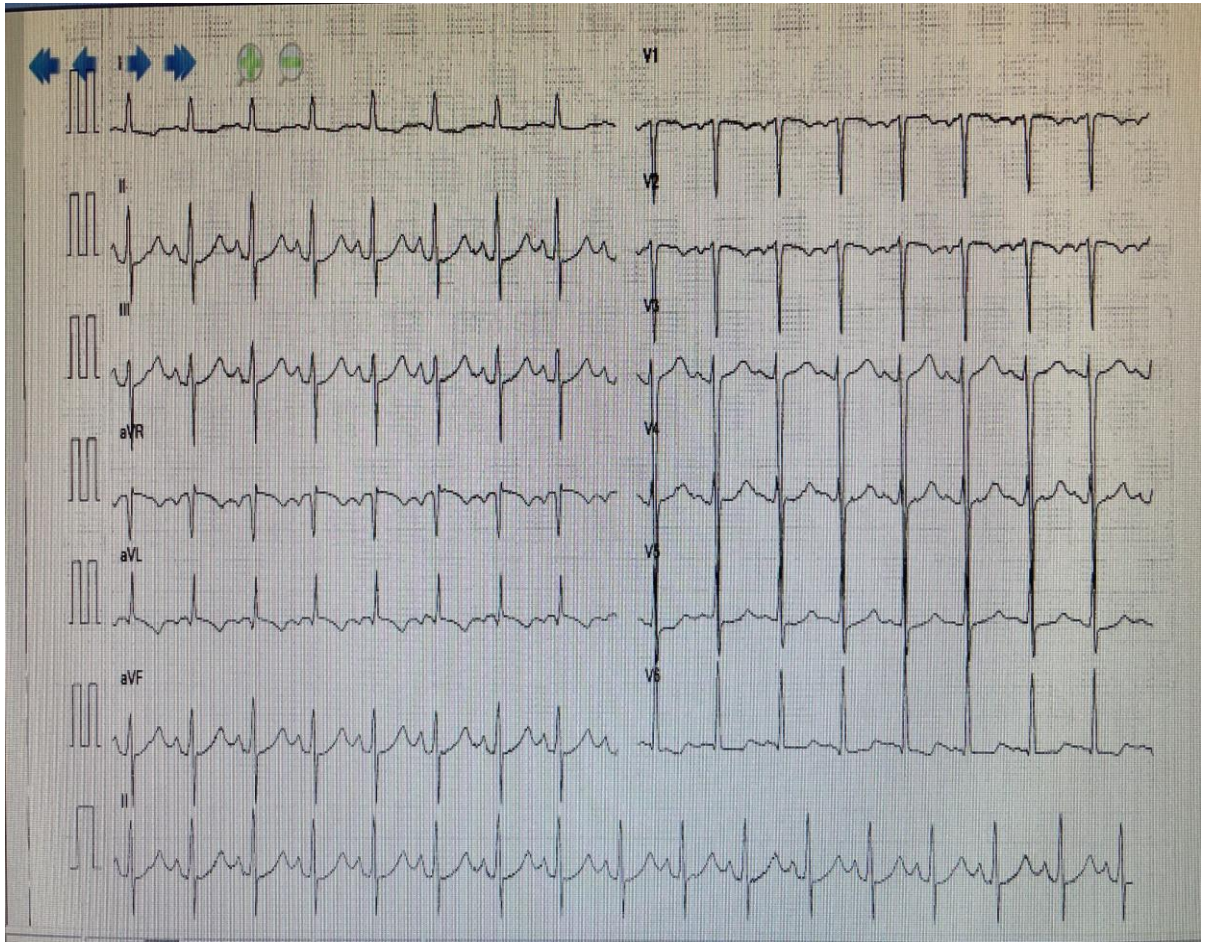
-EKG
-Holter
-Echocardiography/ exercise echocardiography
-CMR

Common Diagnostic Criteria for LVH

MEASUREMENT	CRITERIA
Sokolow-Lyon voltages	$SV_1 + RV_5 > 3.5$ mV
	RaVL > 1.1 mV
Romhilt-Estes point score system*	Any limb lead R wave or S wave > 2.0 mV (3 points)
	or SV_1 or $SV_2 \geq 3.0$ mV (3 points)
	or RV_5 to $RV_6 \geq 3.0$ mV (3 points)
	ST-T wave abnormality, no digitalis therapy (3 points)
	ST-T wave abnormality, digitalis therapy (1 point)
	Left atrial abnormality (3 points)
	Left axis deviation ≥ −30 degrees (2 points)
	QRS duration ≥ 90 msec (1 point)
	Intrinsicoid deflection in V_5 or $V_6 \geq 50$ msec (1 point)
Cornell voltage criteria	$SV_3 + RaVL > 2.8$ mV (for men)
	$SV_3 + RaVL > 2.0$ mV (for women)
Cornell regression equation	Risk of LVH = $1/(1 + e^{-exp})$†
Cornell voltage duration measurement	QRS duration × Cornell voltage > 2436 mm-sec‡
	QRS duration × sum of voltages in all leads > 1742 mm-sec

Sensitivity ranging from 10.5% to 21% and Specificity of 89% to 99%

EKG in HCM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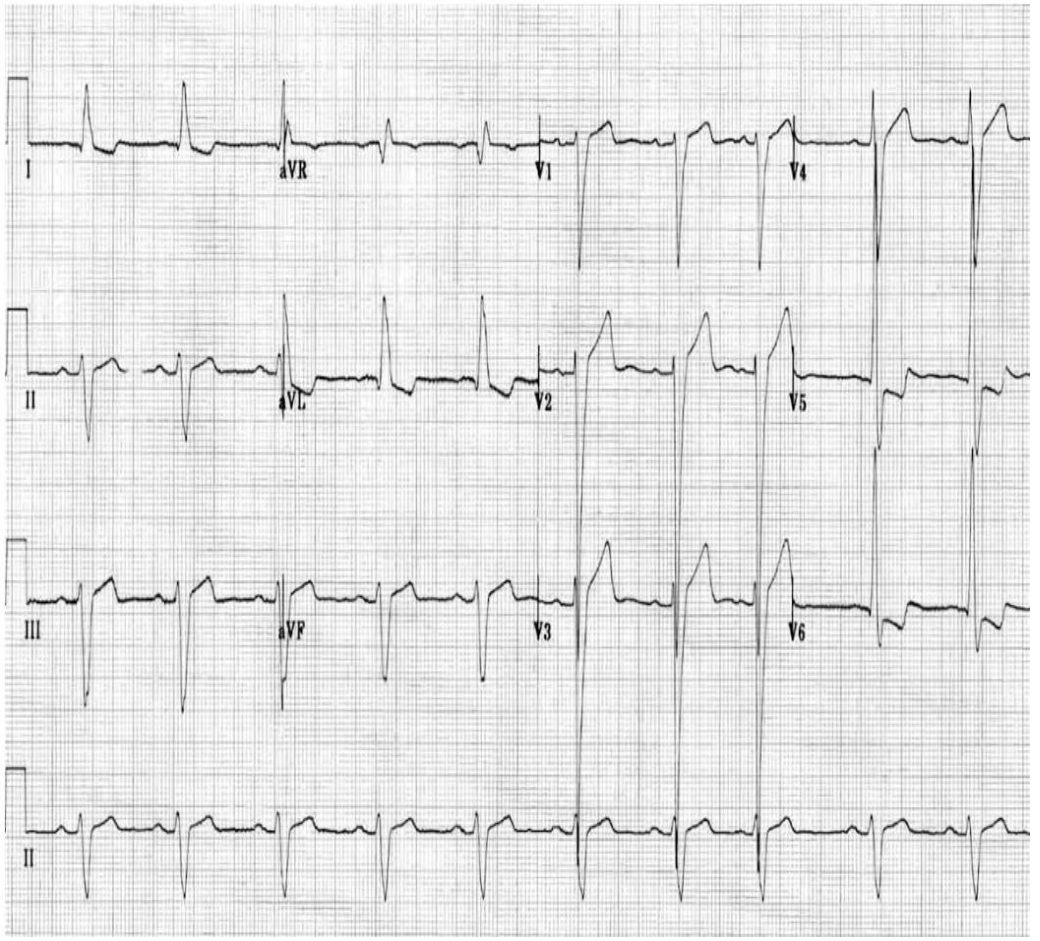
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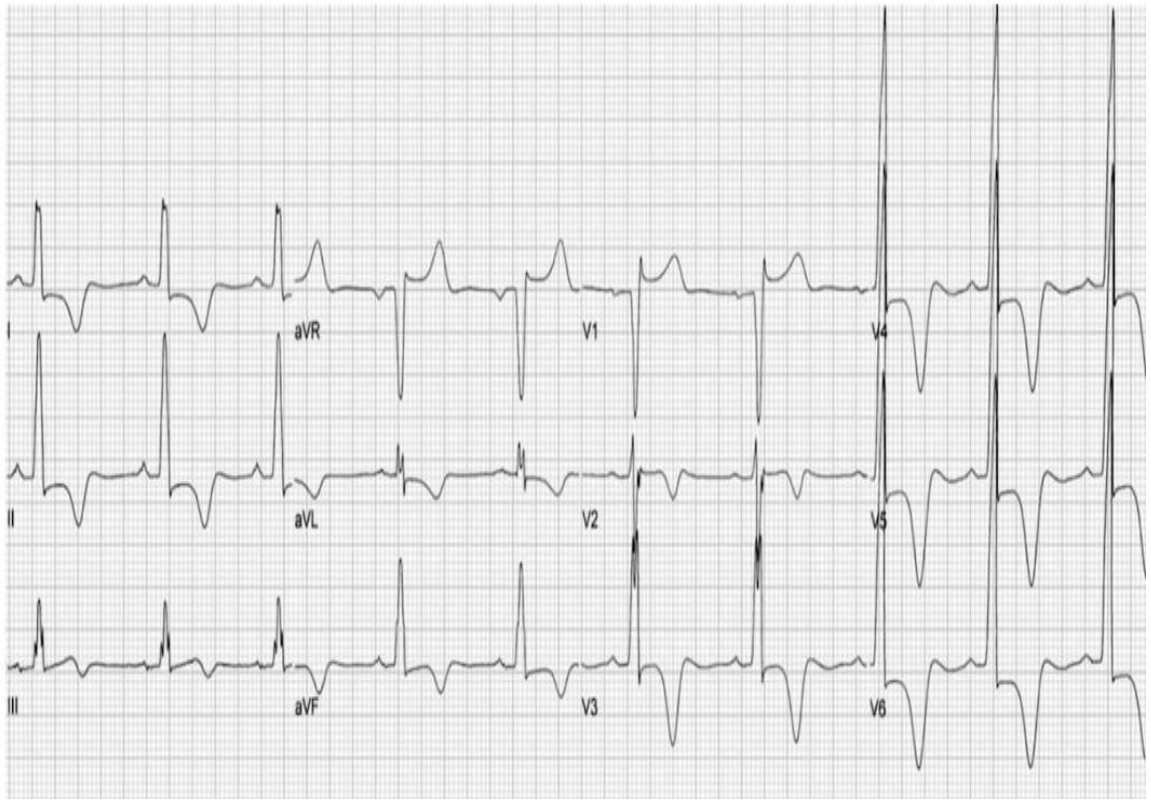
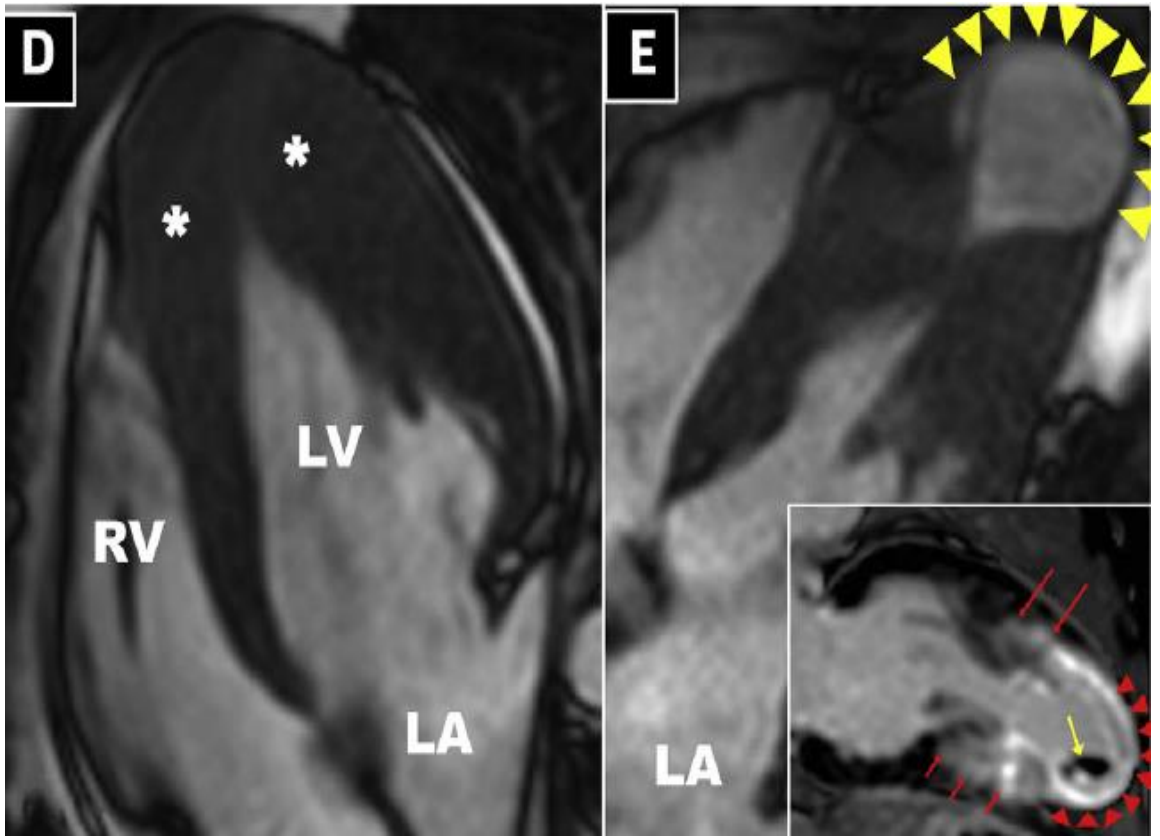
Apical HCM



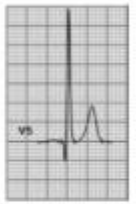
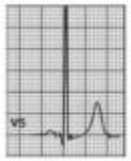
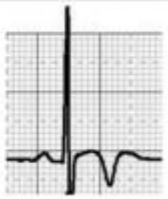
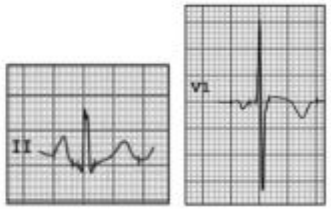
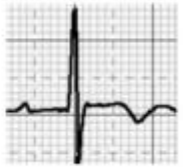


J Am Coll Cardiol 2022;79:372–389

EKG in young Athletes

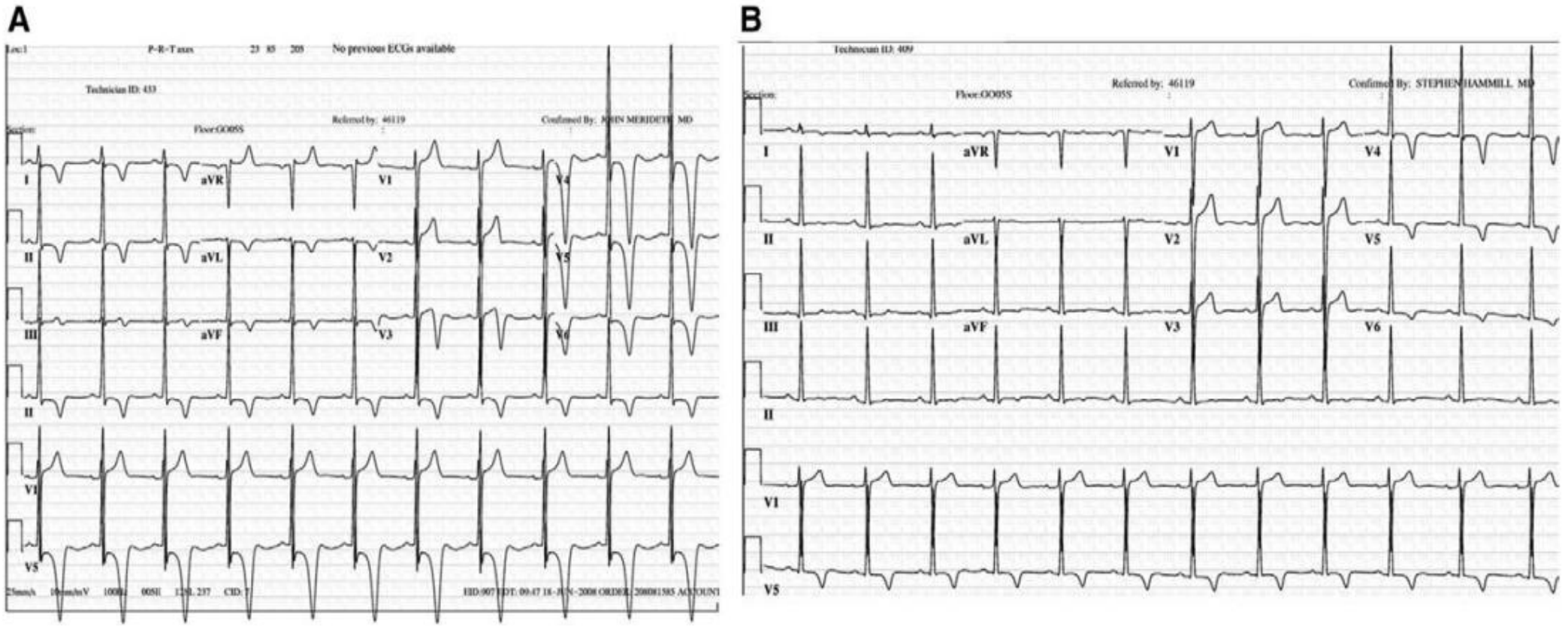
Physiologic

- Increase QRS voltage
- Early repolarization
- Sinus bradycardia
- PR prolongation (not > 300ms)
- Absence of
  - axis < -30, > 115 degree
  - RAE, LAE
  - pathologic Q wave
  - wide QRSd
  - 2^{ry} STT change

ECG Abnormality	Criteria for further evaluation	Example
Q waves	>3 mm in depth or >40 ms duration in any lead except III, aVR, aVL and V1	
ST depression	>0.5 mm below PR isoelectric line between J-junction and beginning of T waves in V4, V5, V6, I, aVL >1 mm in any lead	
T wave inversion	>1 mm in leads other than III, aVR and V1 (except V2 and V3 in women <25 years)	
Atrial abnormalities	Right: P wave amplitude >2.5 mm Left: i) Negative portion of P wave in V1, V2 of >40 ms duration and 1 mm in depth; or ii) total P wave duration >120 ms	
Right ventricular hypertrophy	>30 years: i) R wave >7 mm in V1; or ii) R/S ratio >1 in V1; or iii) sum of R wave in V1 and S wave in V5 or V6 >10.5 mm <30 years: above plus right atrial enlargement, T wave inversion in V2, V3, or right axis deviation >115°	

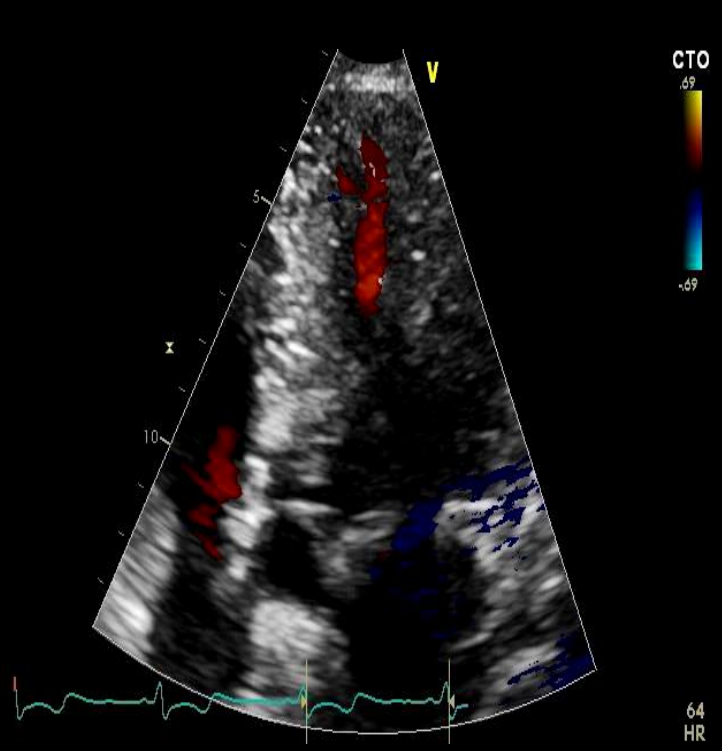
Uberoi et al. Electrocardiogram in Young Athletes *Circulation* August 9, 2011

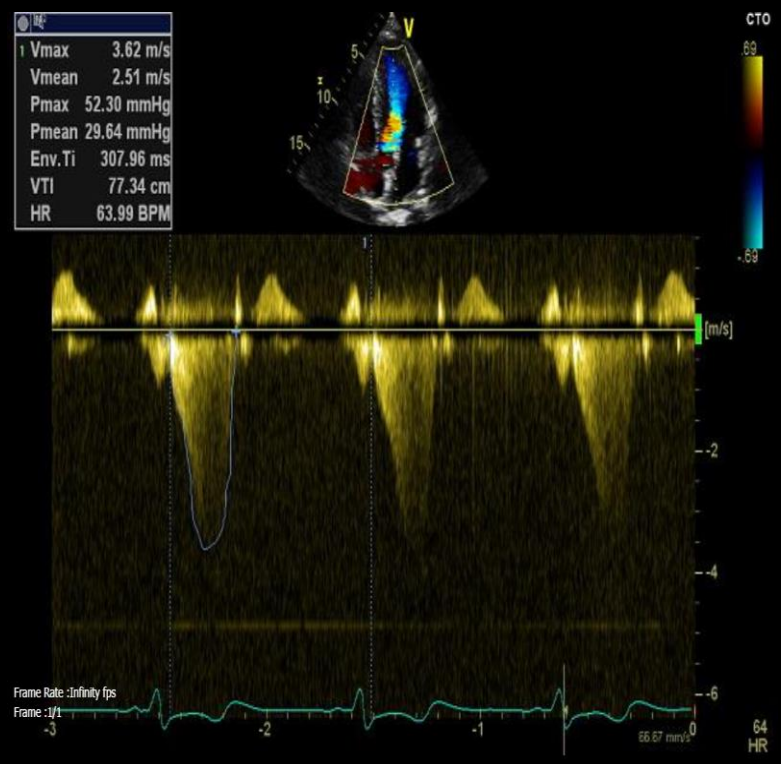
EKG of athlete pre vs post detraining



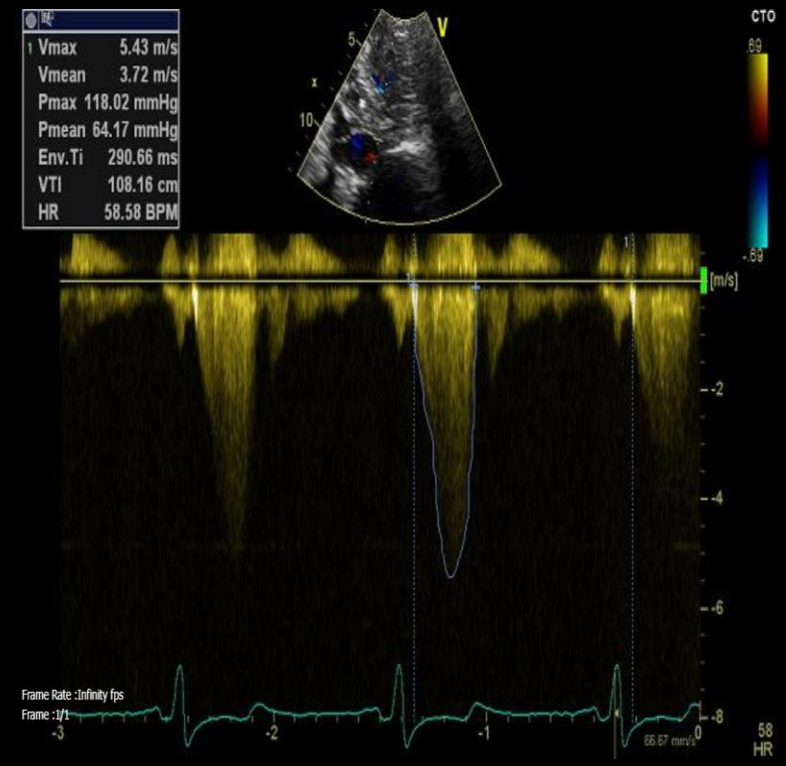
Circ Cardiovasc Imaging. 2015;8

Exercise Stress Echocardiography



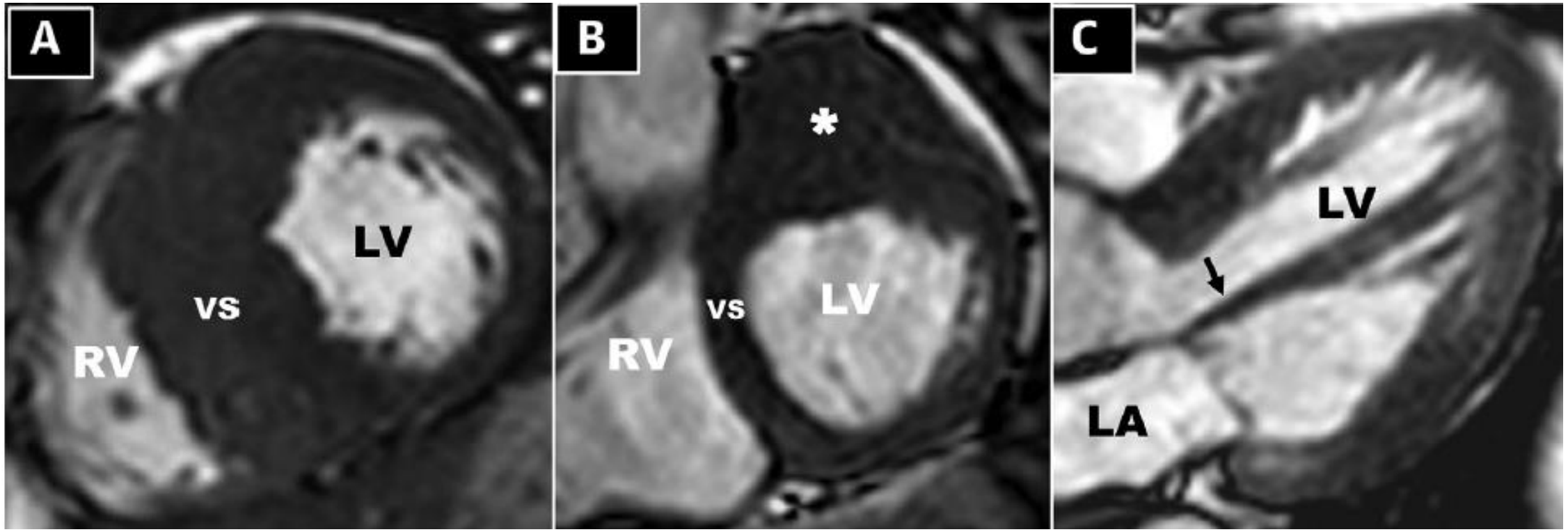


Pre-exercise



Peak-exercise

Cardiac MRI



DDx Thick Heart

- Athlete heart
- HT heart disease
- Fixed obstruction: Supravalve/subvalve aortic stenosis
- Infiltrative disease: metabolic, or systemic conditions associated with LVH that clinically mimic HCM
  - Lysosomal storage diseases such as LAMP-2(Danon)
  - Fabry disease
  - Noonan syndrome
  - Cardiac amyloidosis
  - Sarcoidosis

PHENOCOPY CONDITIONS FOR HCM

Phenotype	Gene	Protein	Phenotypic Clue
AMPK-mediated glycogen storage	*PRKAG2*	Protein kinase A, γ subunit	Normal or reduced left ventricular systolic function, pre-excitation pattern
Pompe disease	*GAA*	α-1,4-glucosidase (acid maltase)	Autosomal recessive, multiorgan disease, pre-excitation pattern
Anderson–Fabry disease	*GLA*	α-galactosidase A	X-linked, multisystem also involving skin, kidney, and peripheral nerves
Danon disease	*LAMP2*	Lysosome-associated membrane protein 2	X-linked dominant, proximal muscle weakness, intellectual disability, short PR on ECG, elevated CK levels
Amyloidosis	*TTR*	Transthyretin	Low QRS voltage, other organ involvement, subendothelial LGE
Kearns–Sayre syndrome	*mtDNA*	Mitochondrial protein	Multisystem disease
Friedreich ataxia	*FRDA*	Frataxin	Autosomal recessive, neurodegeneration
Myotonic dystrophy	*DMPK*	Myotonin protein kinase	Myotonia, muscular dystrophy, cataract, and frontal baldness
	ZNF9	Zinc finger factor 9	
Noonan/LEOPARD syndromes (rasopathies)	*PTPN11*	Protein tyrosine phosphatase, nonreceptor type 11	Congenital heart defects, lentigines, Café-au-lait spots
	SOS1 and *SOS2*	Son of sevenless	
	RAF1	Murine leukemia viral oncogene homolog 1	
	KRAS	Kirsten rat sarcoma virus homolog	
	Others (*A2ML1*, *BRAF*, *CBL*, *MAP2K1*, *MAP2K2*, *NRAS*, *RIT1*, *RRAS*, and *SHOC2*)		
Neimann–Pick disease	*NPC1*	Neimann–Pick	Autosomal recessive neurodegenerative disease

Subvalvular Aortic Stenosis