
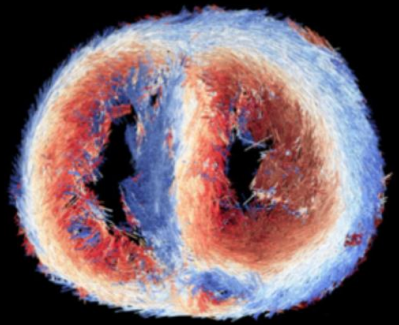
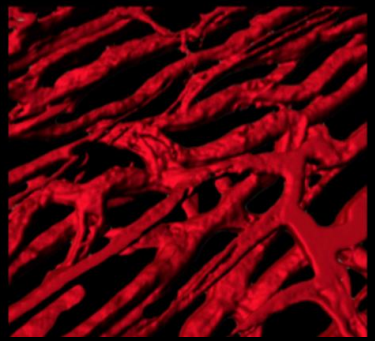
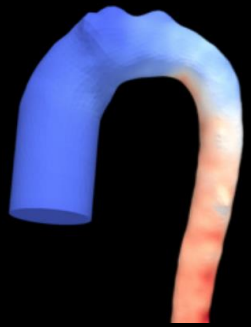
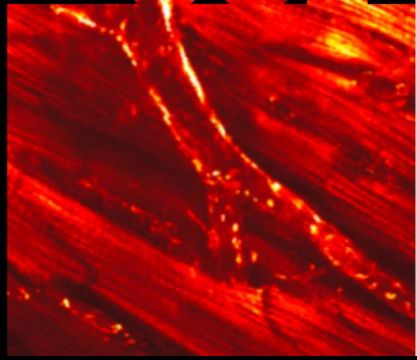

What are the challenges in making the right diagnosis?

Declaration of interest

Consultancies/Ad Board:

- MyoKardia (BMS)
- Pfizer
- Sanofi-Genzyme
- DinaQor
- Astra Zeneca
- Sarepta
- Freeline

2023 ESC Guidelines for the management of cardiomyopathies

Authors/Task Force Members:

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[1]Representing the Association for European Paediatric and Congenital Cardiology (AEPC). [2]Representing the European Society of Human Genetics (ESHG).

Cardiomyopathy: Definition

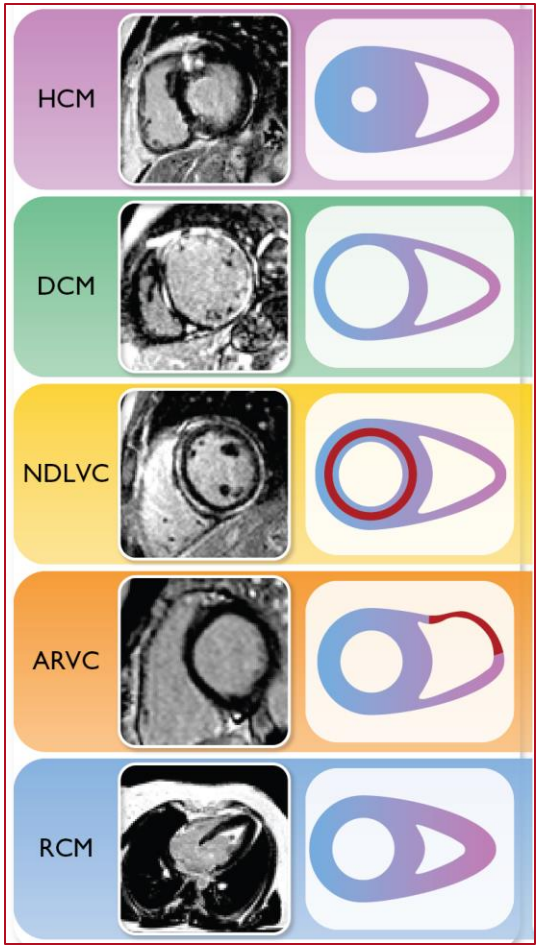
"A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality."

ESC Working Group on Myocardial Pericardial Diseases (Elliott P et al. EHJ 2007)

Phenotypic approach to cardiomyopathies

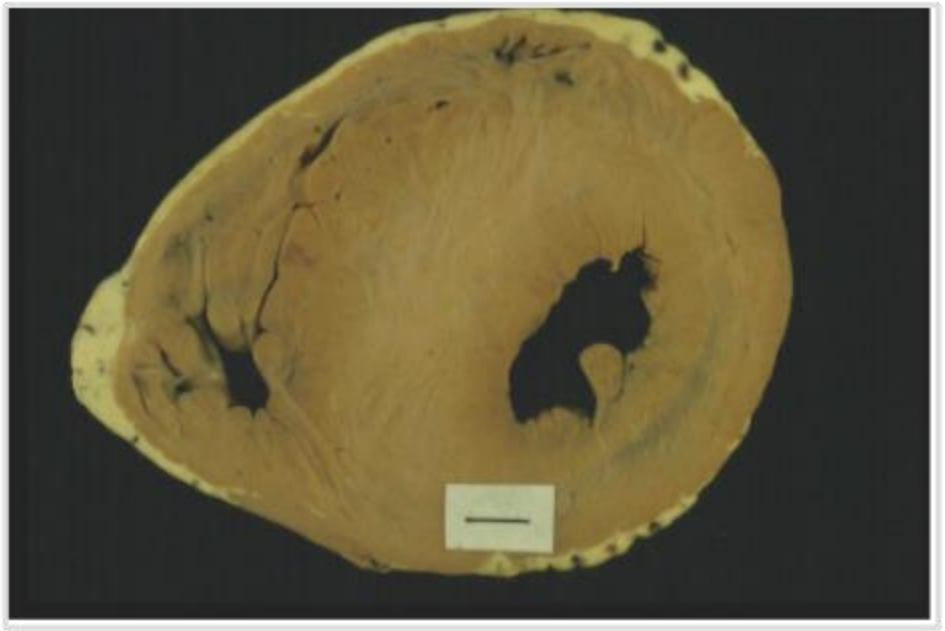
Morphological and functional traits used to describe cardiomyopathy phenotypes

Morphological traits
Ventricular hypertrophy: left and/or right
Ventricular dilatation: left and/or right
Non-ischaemic ventricular scar and other myocardial tissue characterization features on cardiac magnetic resonance
Functional traits
Ventricular systolic dysfunction (global, regional)
Ventricular diastolic dysfunction (restrictive physiology)



2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Hypertrophic Cardiomyopathy



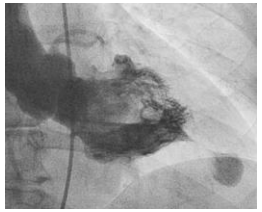
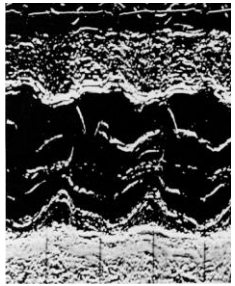
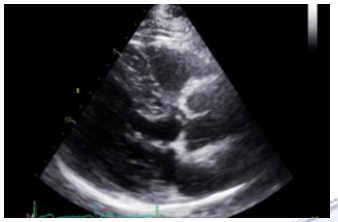
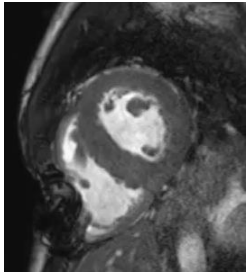
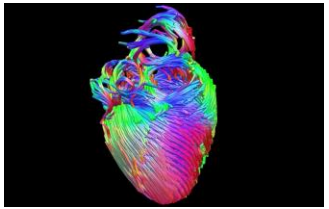
Increased left ventricular wall thickness not solely explained by abnormal loading conditions

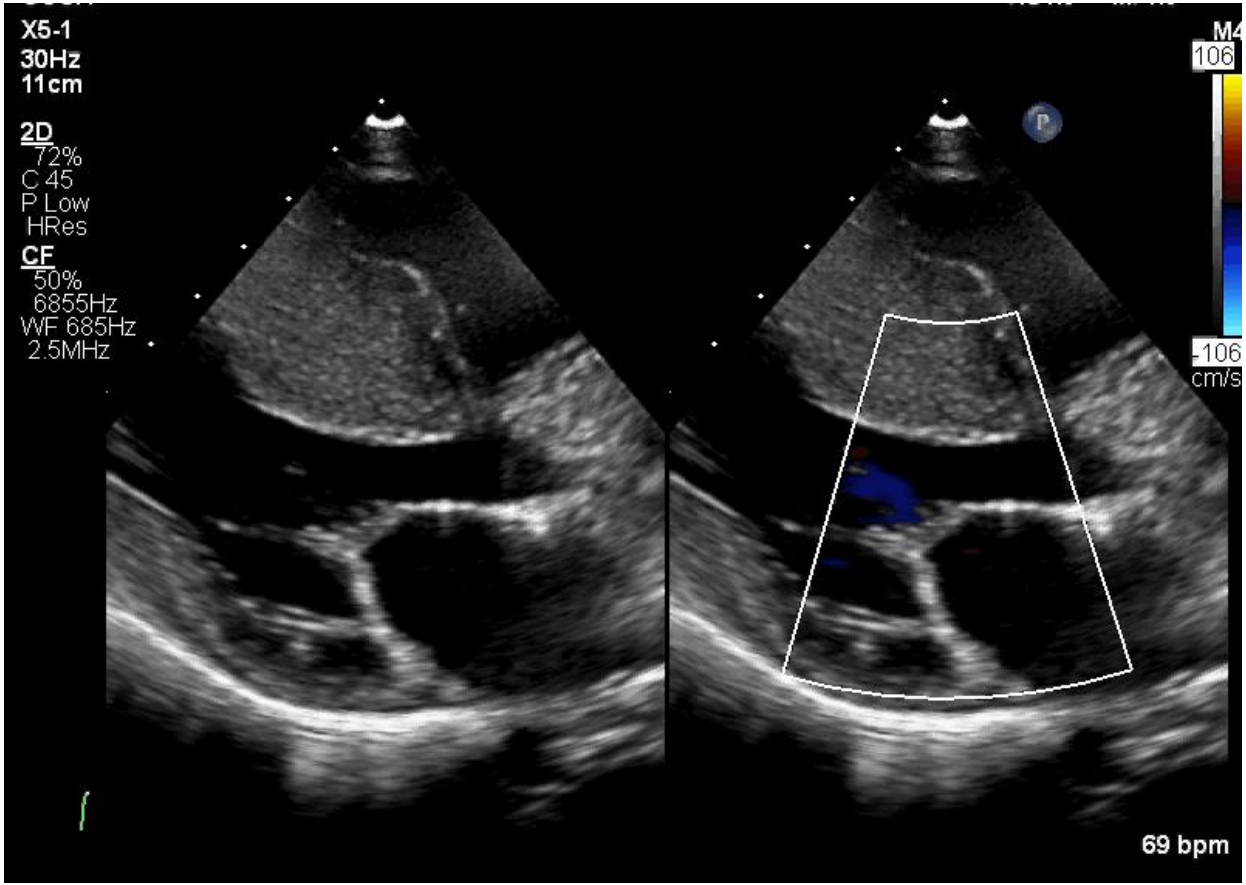
ADULTS:

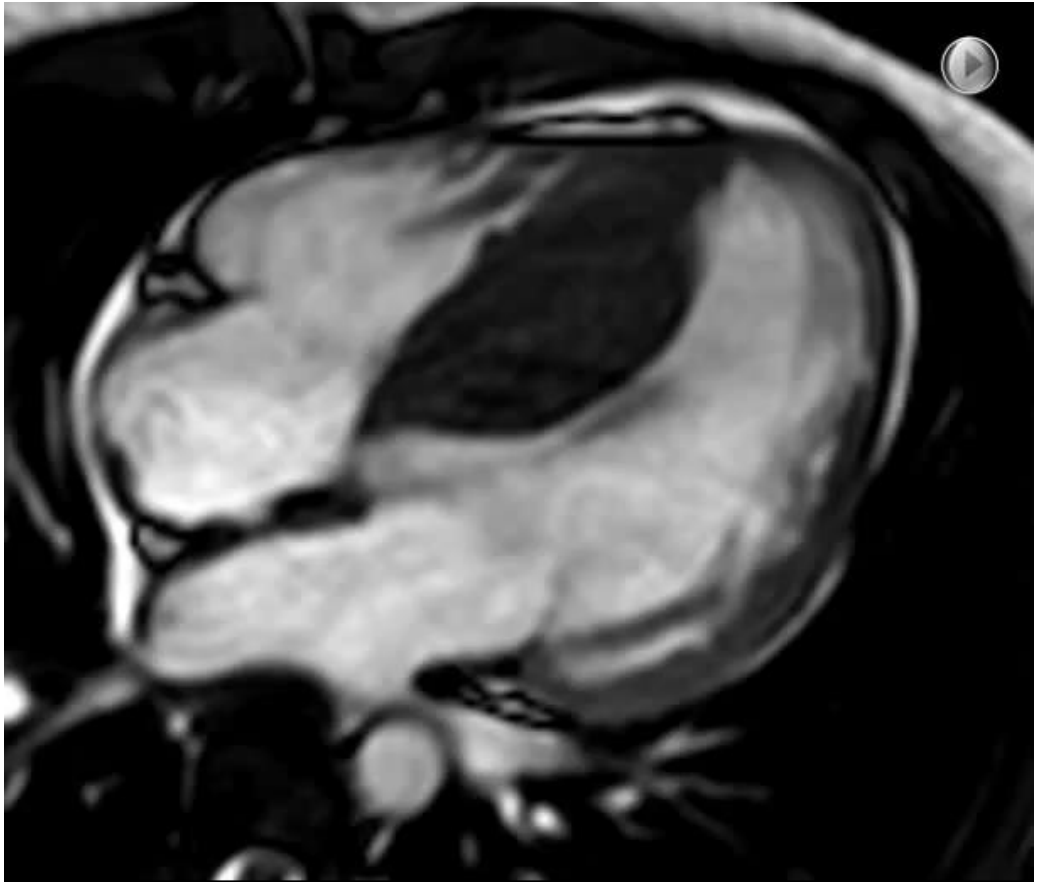
LV wall thickness ≥15 mm in one or more LV myocardial segments measured by any imaging technique

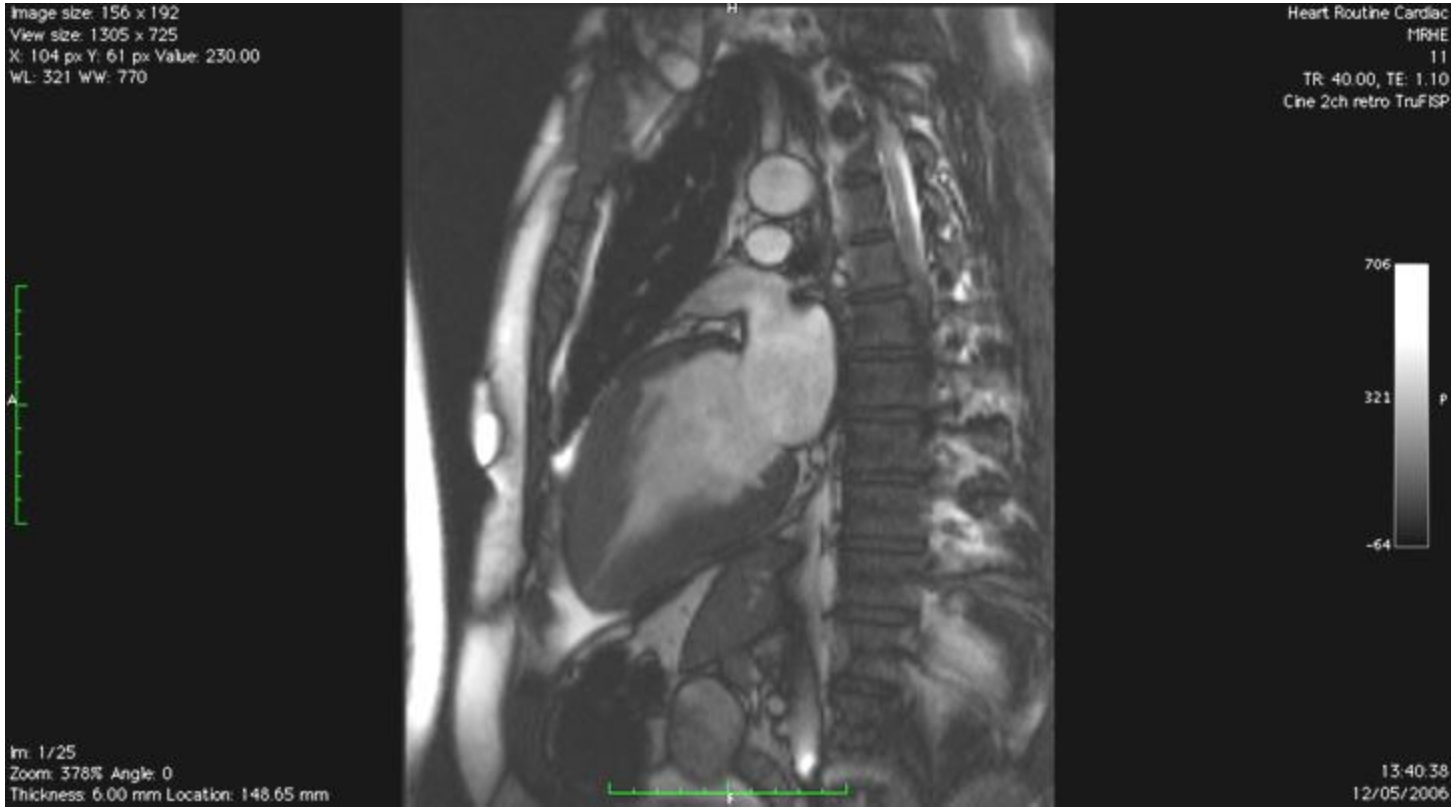
CHILDREN:

LV wall thickness more than two standard deviations above the predicted mean (z-score >2)


X5-1
30Hz
11cm
2D
72%
C 45
P Low
HRes
CF
50%
6855Hz
WF 685Hz
2.5MHz
106
-106
cm/s
69 bpm

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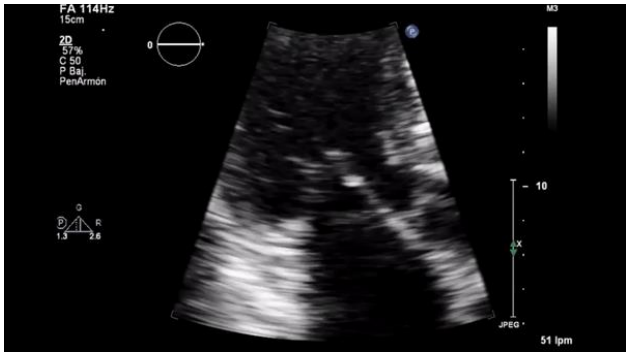
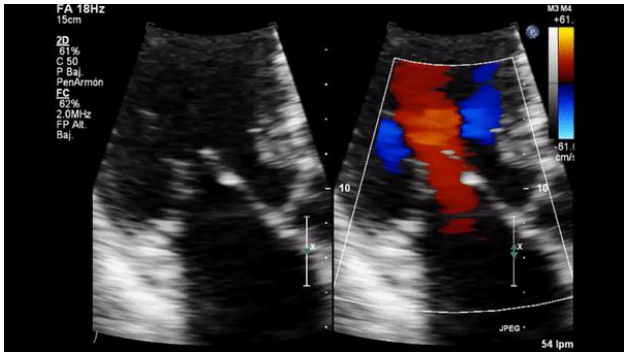
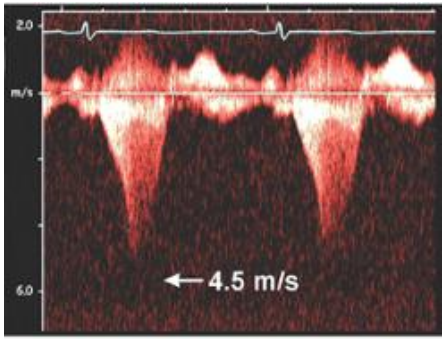
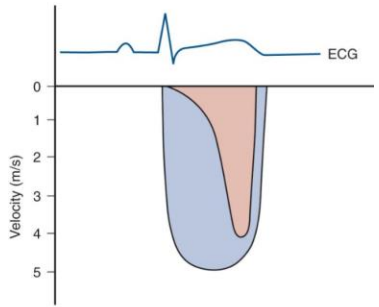
View size: 1305 x 725
X: 104 px Y: 61 px Value: 230.00
WL: 321 WW: 770
H
A
F
Heart Routine Cardiac
MRHE
11
TR: 40.00, TE: 1.10
Cine 2ch retro TruFISP
706
321
P
-64
Im: 1/25
Zoom: 378% Angle: 0
Thickness: 6.00 mm Location: 148.65 mm
13:40:38
12/05/2006

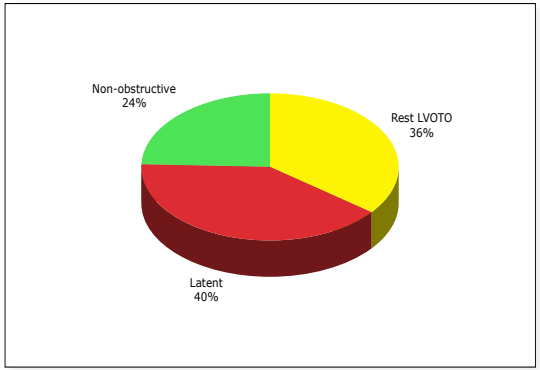
Echo features of HCM



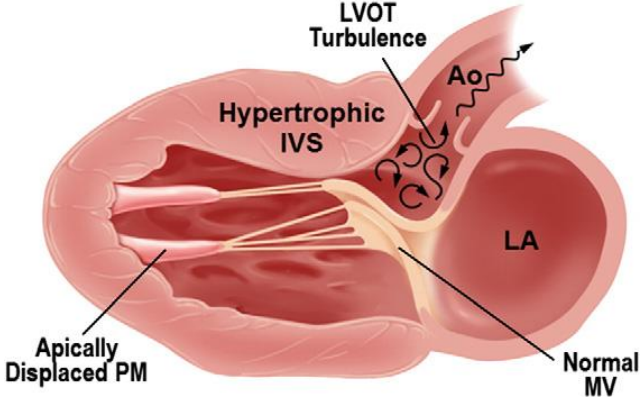


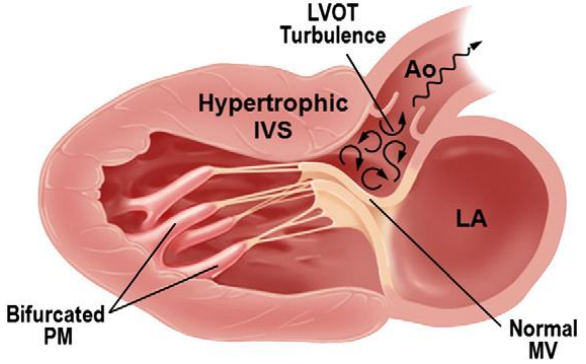


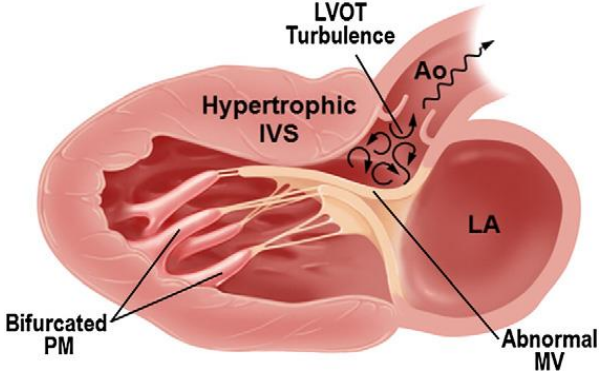




Courtesy K. Savvatis, Barts

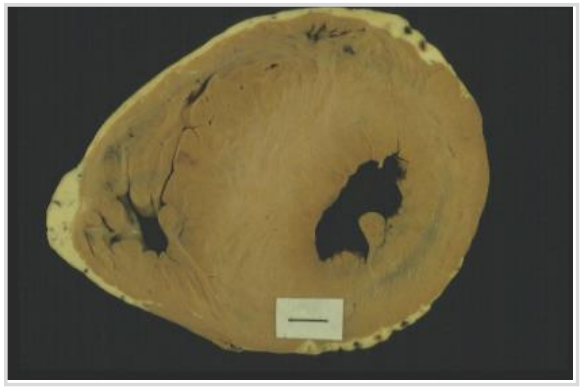


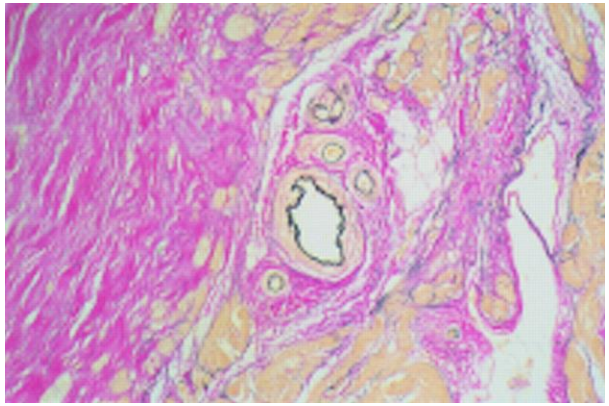


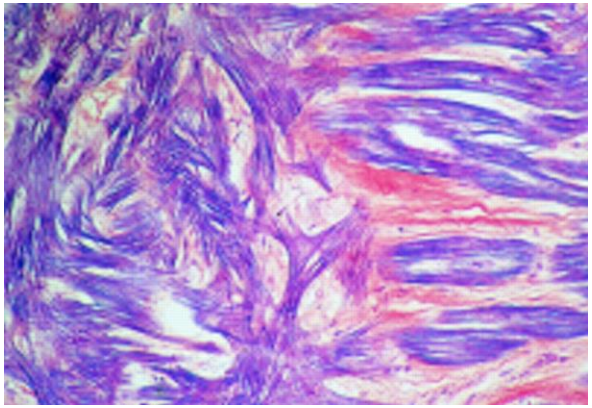


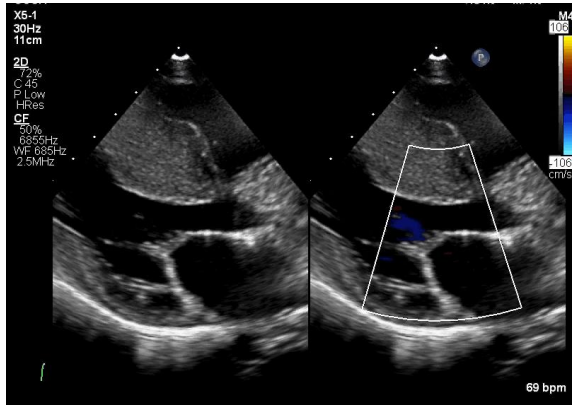
Cavalcante, Prog Cardiovasc Dis 2012;54:517-522

HCM is not a diagnosis!

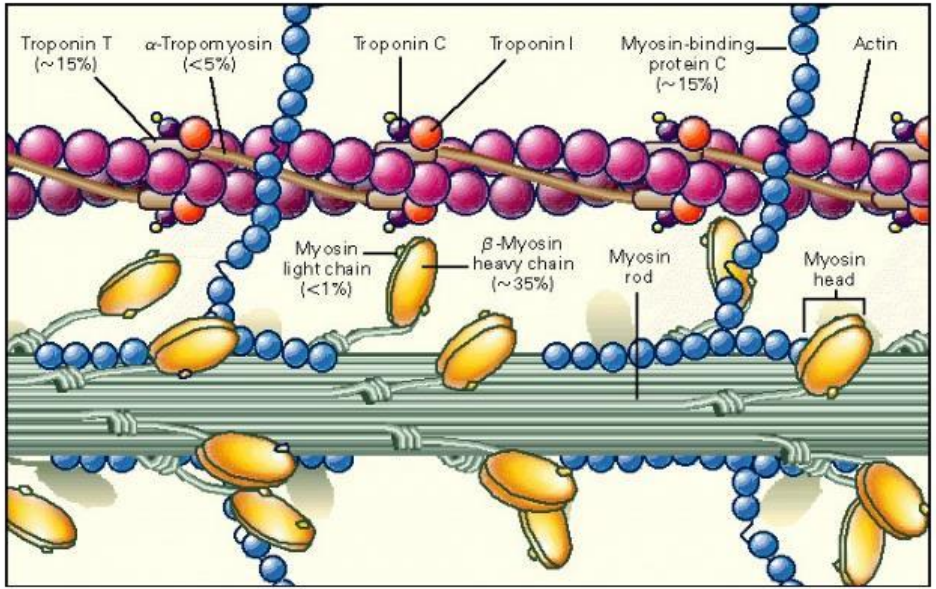







X5-1
30Hz
11cm
2D
72%
C 45
P Low
HRes
CF
50%
6855Hz
WF 685Hz
2.5MHz
106
-106
cm/s
69 bpm

The evolving story of genetics in HCM



Gene	Protein	Frequency (%)
Cardiac myosin-binding protein C	MYBPC3	30–40%
β cardiac myosin heavy chain	MYH7	20–30%
Cardiac troponin T	TNNT2	5–10%
Cardiac troponin I	TNNI3	4–8%
Regulatory myosin light chain	MYL2	2–4%
Essential myosin light chain	MYL3	1–2%
α tropomyosin	TPM1	<1%
α cardiac actin	ACTC1	<1%
Muscle LIM protein	CSRP3	<1%

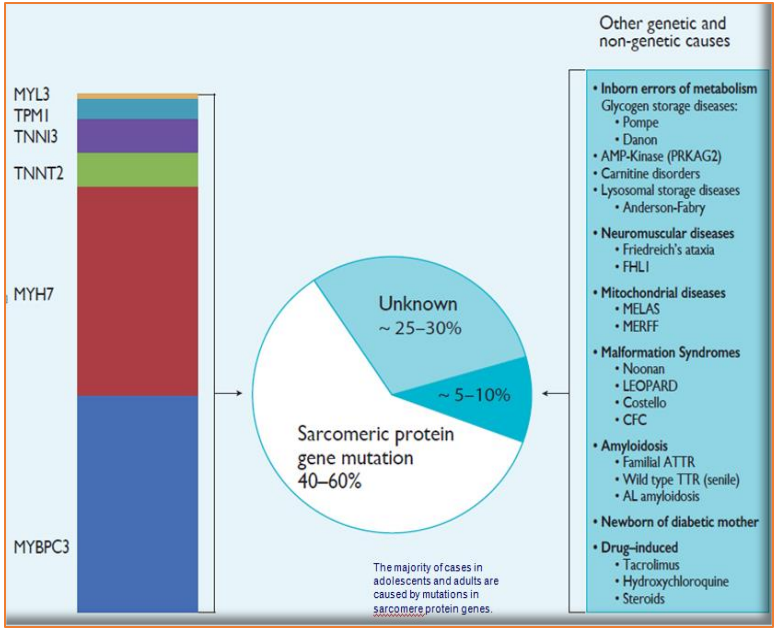
Spirito P, Seidman CE, McKenna WJ, Maron BJ. N Engl J Med. 1997 Mar 13;336(11):775-85.
Liew AC et al. J. Clin. Med. 2017, 6, 118;

Formin Homology 2 Domain Containing 3 *(FHOD3)* Is a Genetic Basis for Hypertrophic Cardiomyopathy

JACC 2018; 72: 2457-2467

Mutations in *TRIM63* cause an autosomal-recessive form of hypertrophic cardiomyopathy

Heart 2020;106:1342–1348.



Elliott PM **et al.** Eur Heart J. 2014 Oct 14;35(39):2733-79

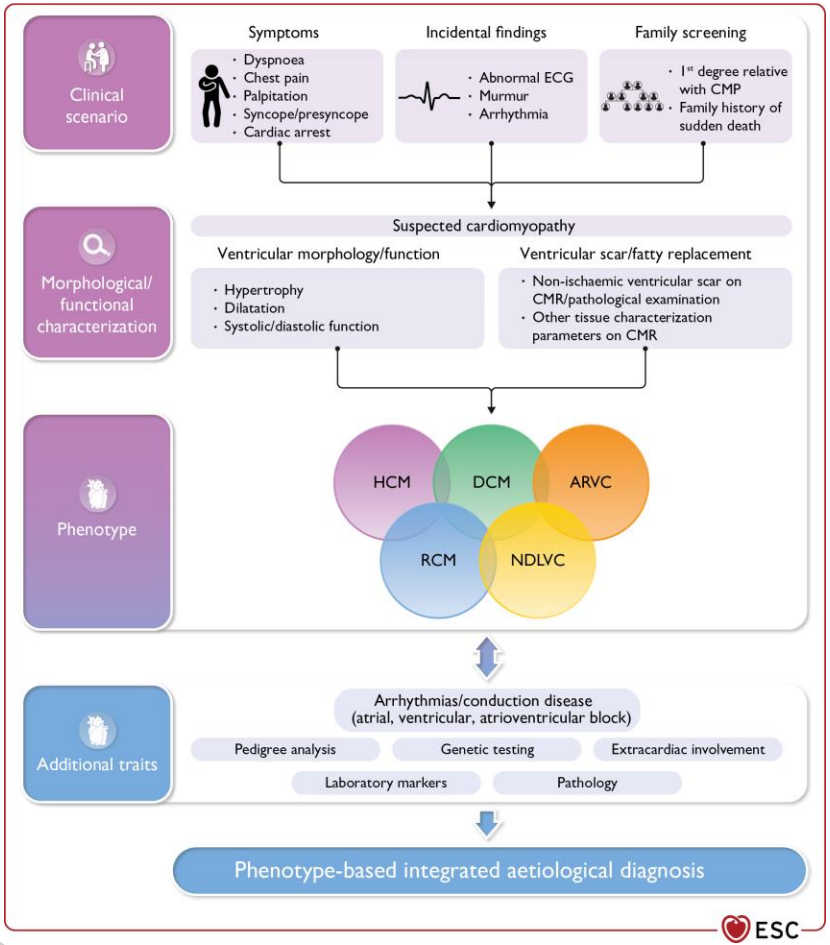
Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

Circulation. 2002;105:1407-1411

Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness

European Heart Journal 2016;37:1826-1834

Clinical diagnostic workflow of cardiomyopathy



'Cardiomyopathy mindset'

Recommendations	Class	Level
It is recommended that all patients with suspected or established cardiomyopathy undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging.	I	C
It is recommended that all patients with suspected cardiomyopathy undergo evaluation of family history and that a three- to four-generation family tree is created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance pattern, and identify at-risk relatives.	I	C

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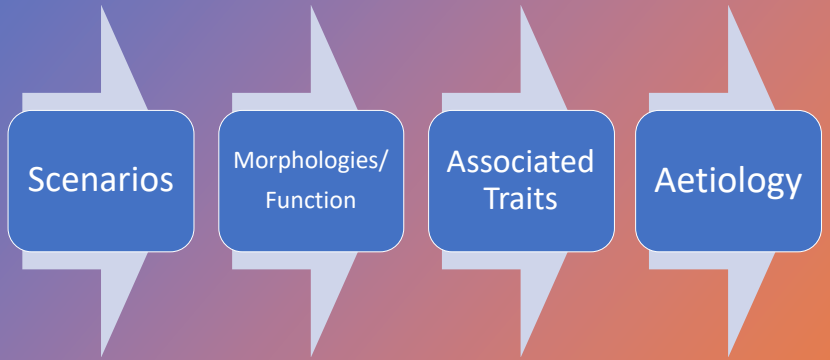
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)



Scenarios

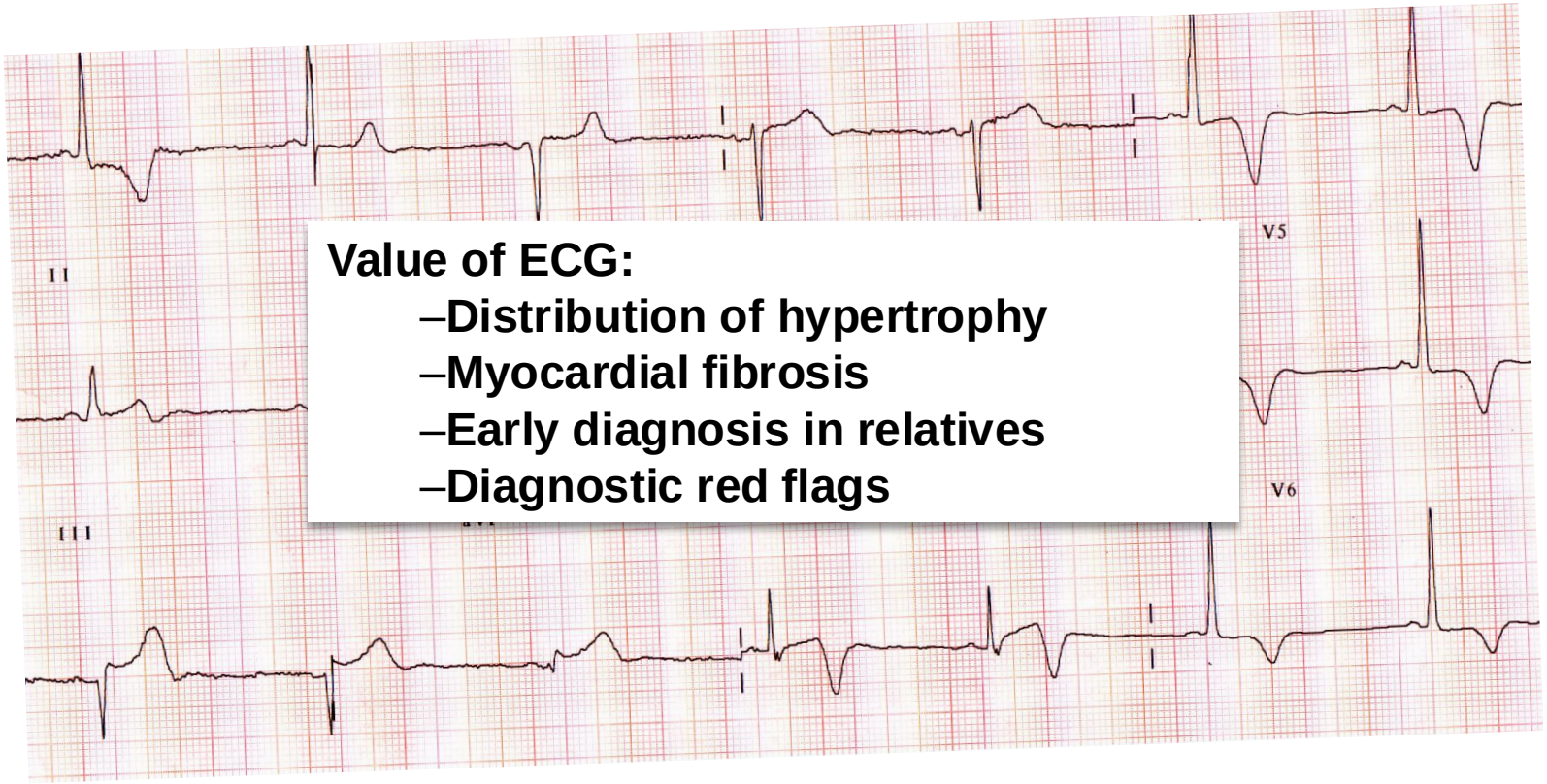
- Symptomatic
- Arrhythmia
- Family Screening
- Incidental

History & physical examination

Table 3 Examples of signs and symptoms suggestive of specific diagnoses (modified from Rapezzi et al.[67])

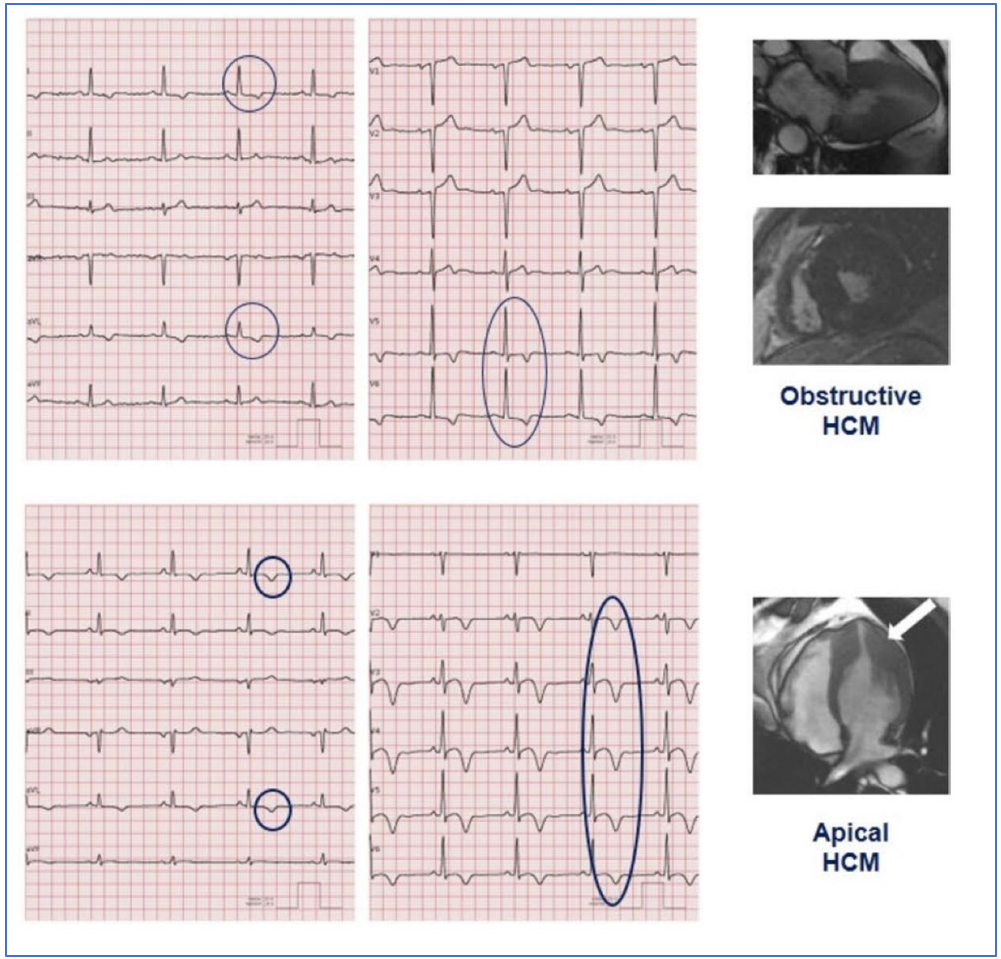
Symptom/sign	Diagnosis
Learning difficulties, mental retardation	• Mitochondrial diseases • Noonan/LEOPARD/Costello syndrome • Danon disease
Sensorineural deafness	• Mitochondrial diseases (particularly with diabetes) • Anderson-Fabry disease • LEOPARD syndrome
Visual impairment	• Mitochondrial diseases (retinal disease, optic nerve) • TTR-related amyloidosis (cotton wool type vitreous opacities) • Danon disease (retinitis pigmentosa) • Anderson-Fabry disease (cataracts, corneal opacities)
Gait disturbance	• Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	• Amyloidosis • Anderson-Fabry disease
Carpal tunnel syndrome	• TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	• Mitochondrial diseases • Glycogen storage disorders • FHL1 mutations • Friedreich's ataxia
Palpebral ptosis	• Mitochondrial diseases • Noonan/LEOPARD syndrome • Myotonic dystrophy
Lentigines/café au lait spots	• LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	• Anderson-Fabry disease

- How old is the patient?
- Family history?
- Non-cardiac symptoms & signs

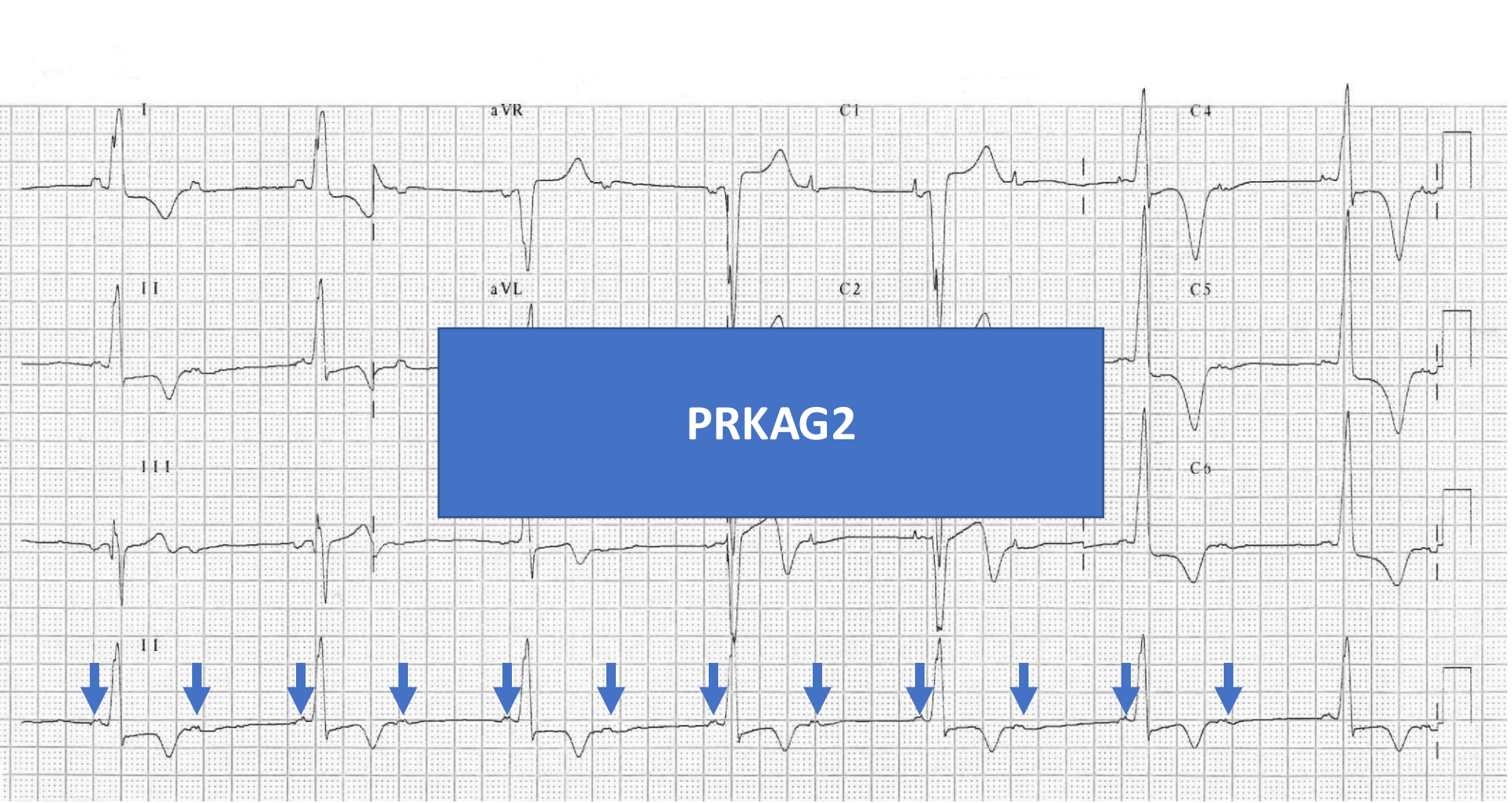


Value of ECG:

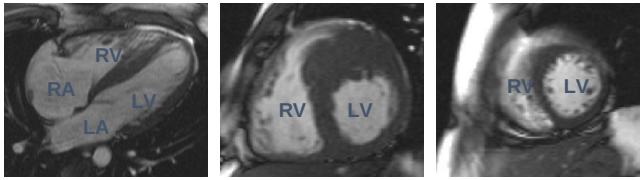
- –Distribution of hypertrophy
- –Myocardial fibrosis
- –Early diagnosis in relatives
- –Diagnostic red flags



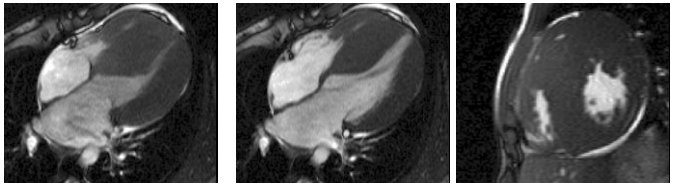
Heart Failure Reviews (2024) 29:151–164


I
aVR
C1
C4
II
aVL
C2
C5
III
C6
II
PRKAG2

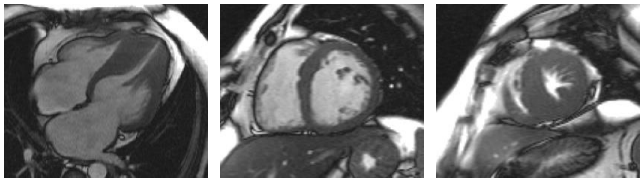
Asymmetrical septal hypertrophy



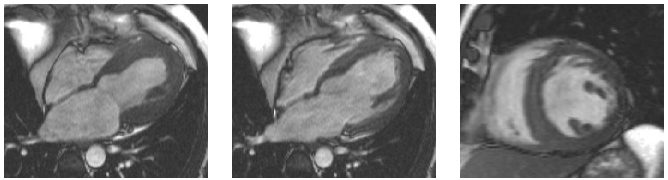
Bi-ventricular hypertrophy



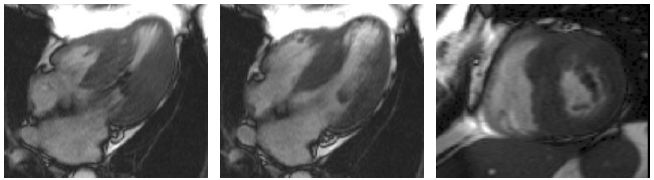
Apical hypertrophy



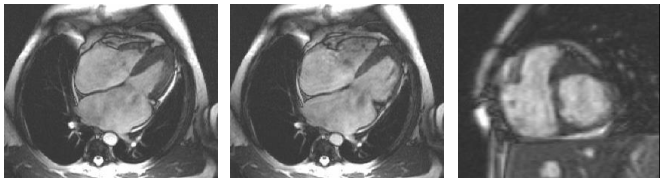
“End-stage” dilatation

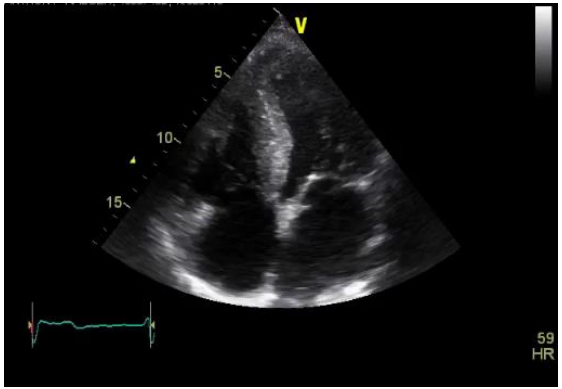


Mid-cavity obstruction

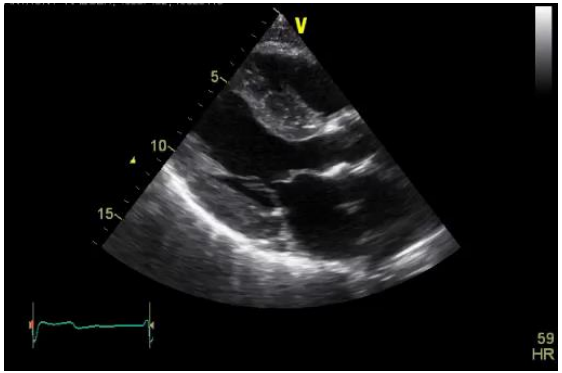


Restrictive cardiomyopathy



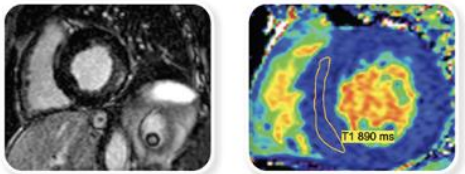
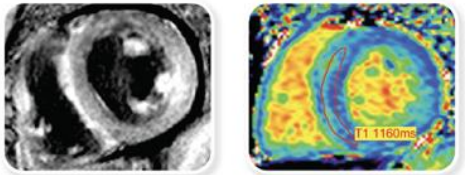
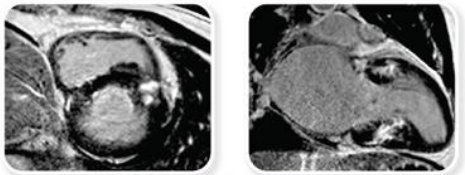


Echocardiographic features that suggest specific aetiologies[a]	
Finding	**Specific diseases to be considered**
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2-D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

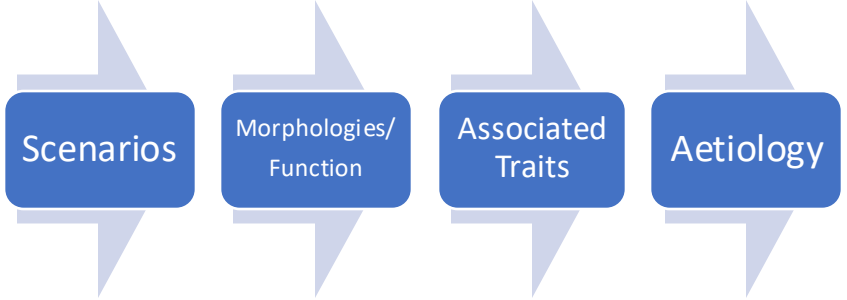


Rapezzi C et al. Eur Heart J. 2013 May;34(19):1448-58

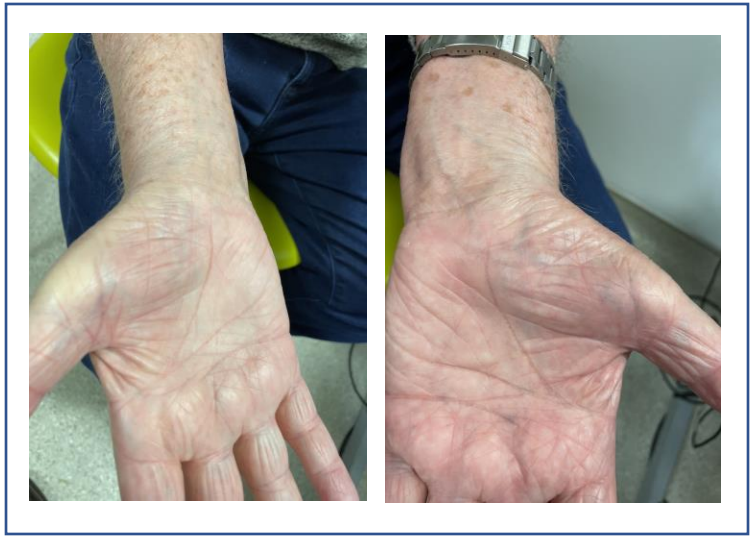
Examples of CMR tissue characterization features that should raise the suspicion of specific aetiologies

Cardiomyopathy phenotype	Finding	Cardiac CMR examples	Specific diseases to be considered
HCM	Posterolateral LGE and concentric LVH Low native T1		Anderson–Fabry disease
	Diffuse subendocardial LGE, high native T1		Amyloidosis
	Patchy mid-wall in hypertrophied areas		Sarcomeric HCM

2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

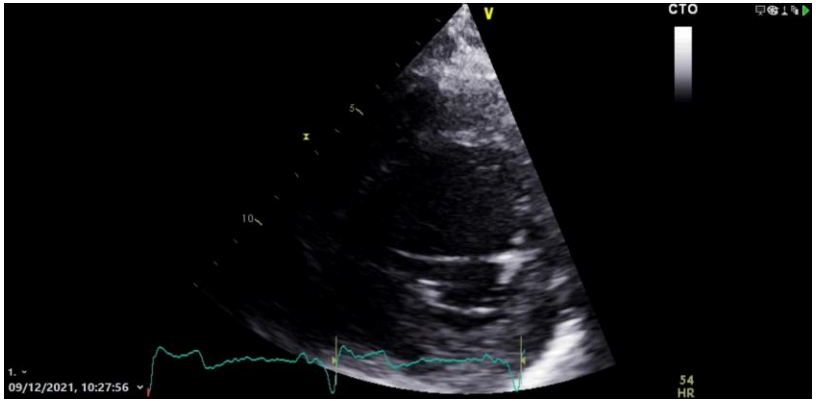


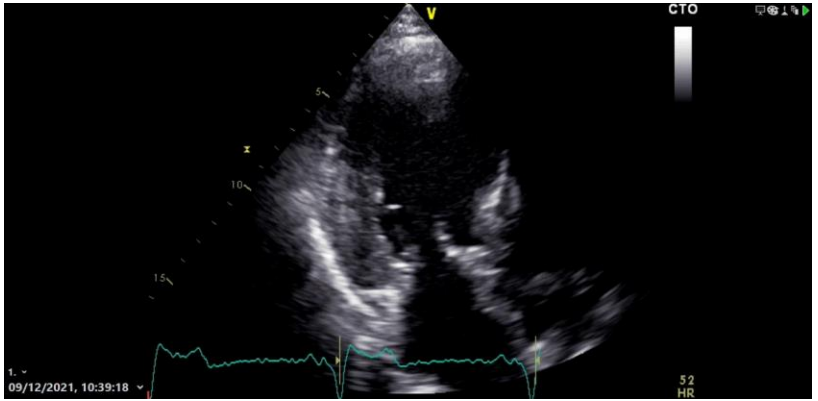
- 79-year-old male
- 1990 myocardial infarction , 2 vessel disease
- 2021 presentation with heart failure, impaired LVEF
- Coronary angiogram-ventricular standstill
- Trifasicular block
- CRT-D

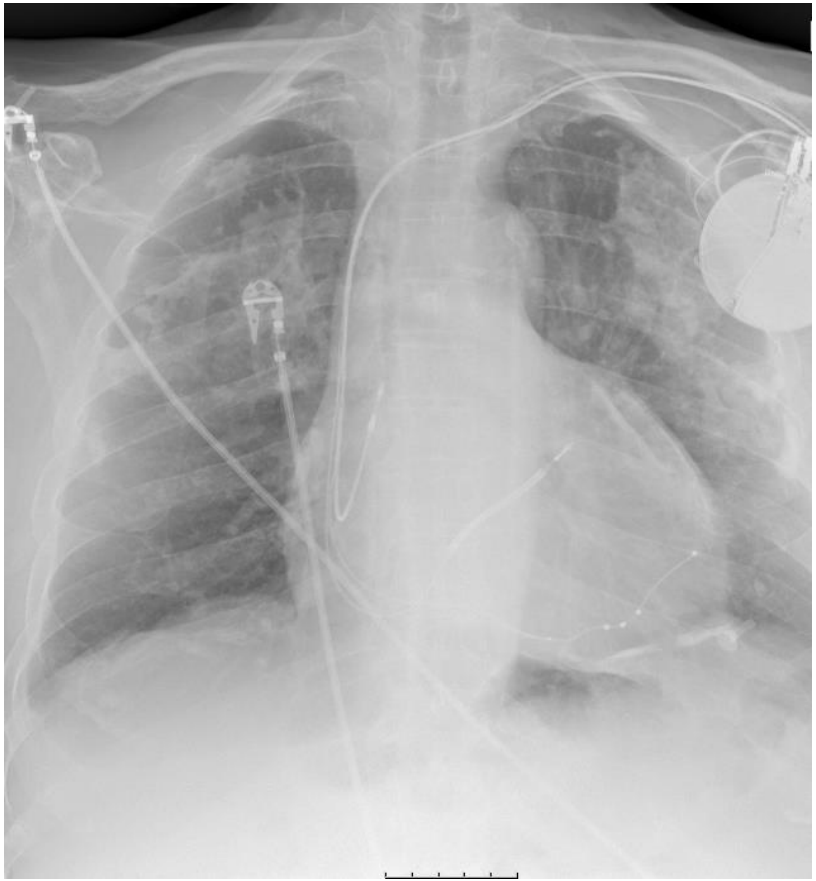


Lumbar stenosis

Scenarios → Morphologies/ Function → Associated Traits → Aetiology





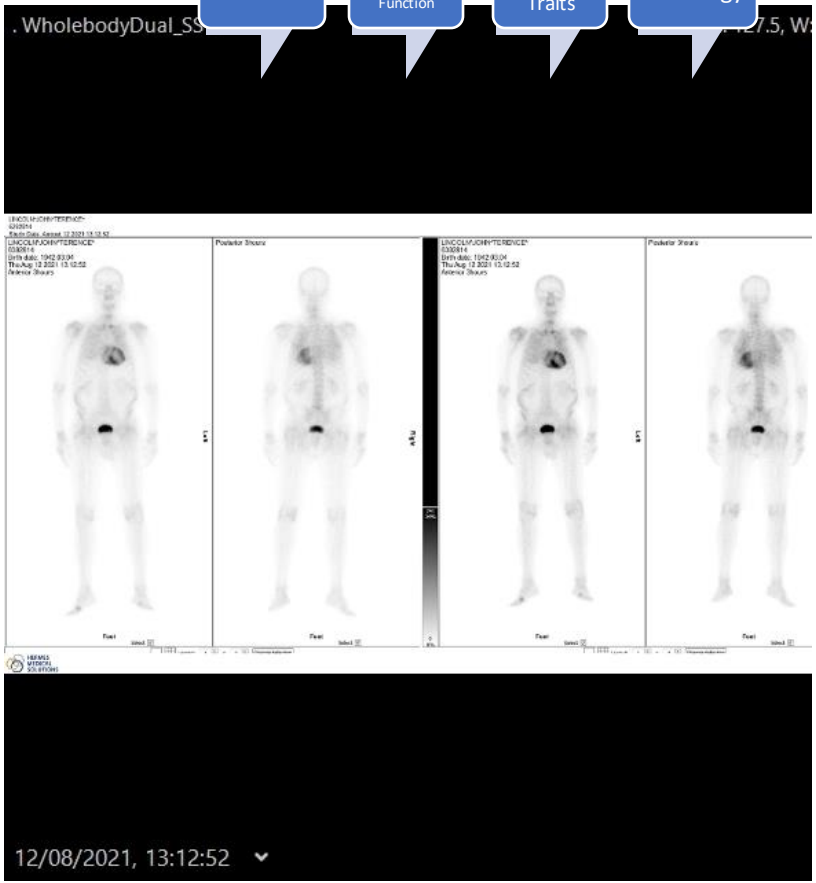


Scenarios

Morphologies/ Function

Associated Traits

Aetiology



SUMMARY

- The term HCM describes a family disorders
- Majority are genetic in origin
- Rare phenocopies should be considered in patients with ‘diagnostic red flags’