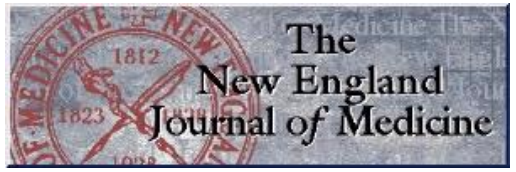
OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.

Ecocardiografia nelle Cardiopatie da accumulo

Sergio Severino,MD,Fesc
UO Cardiologia Cotugno
Dipartimento Cardiologico
AORN Monaldi-Cotugno-CTO (Napoli)



Linee Guida

..quello che linee guida non dicono

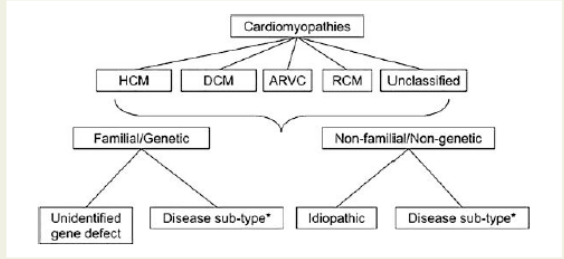
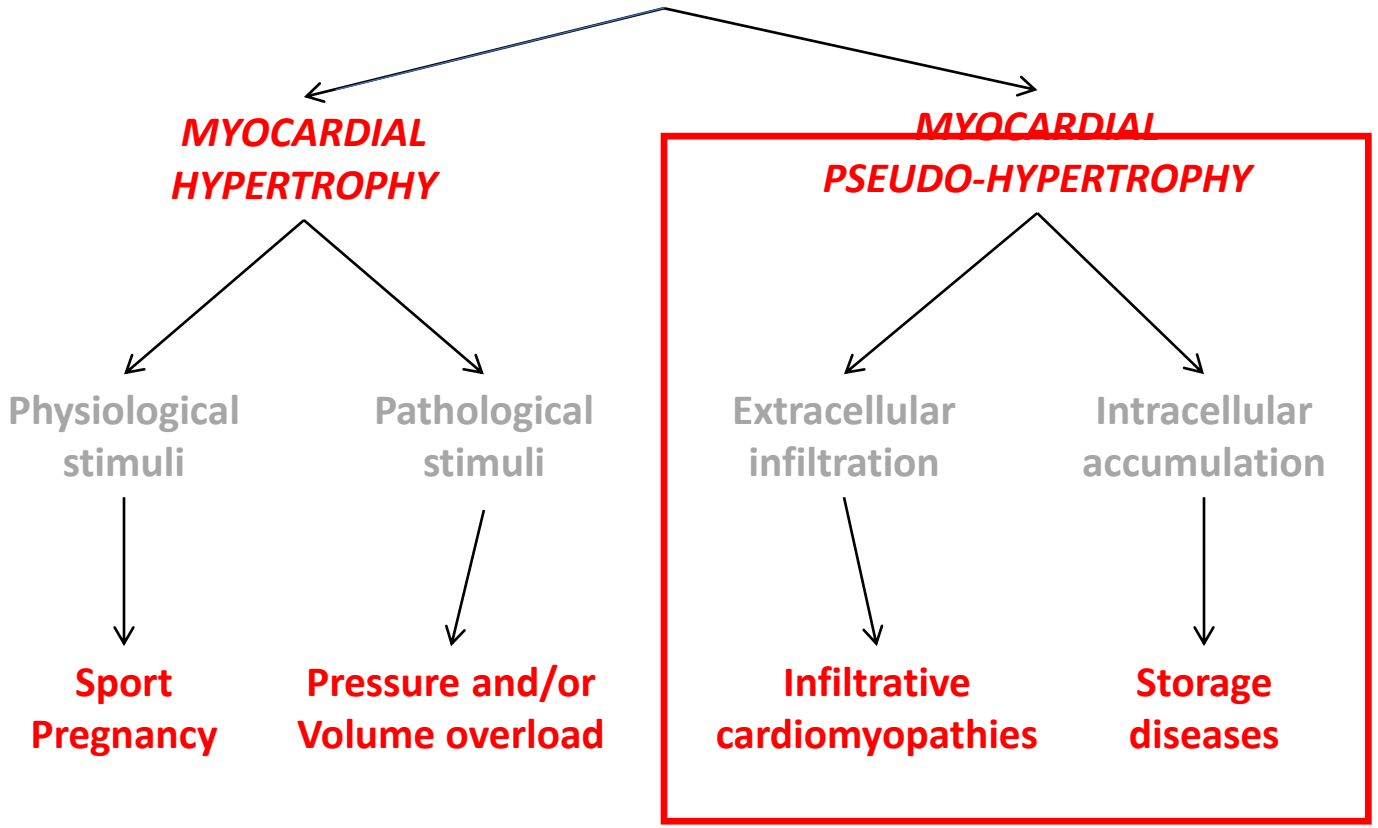


Figure 1 Classification of cardiomyopathies according to the 2008 European Society of Cardiology position statement. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy. Reprinted with permission from: Elliott *et al.*[1]

INCREASED VENTRICULAR WALL THICKNESS

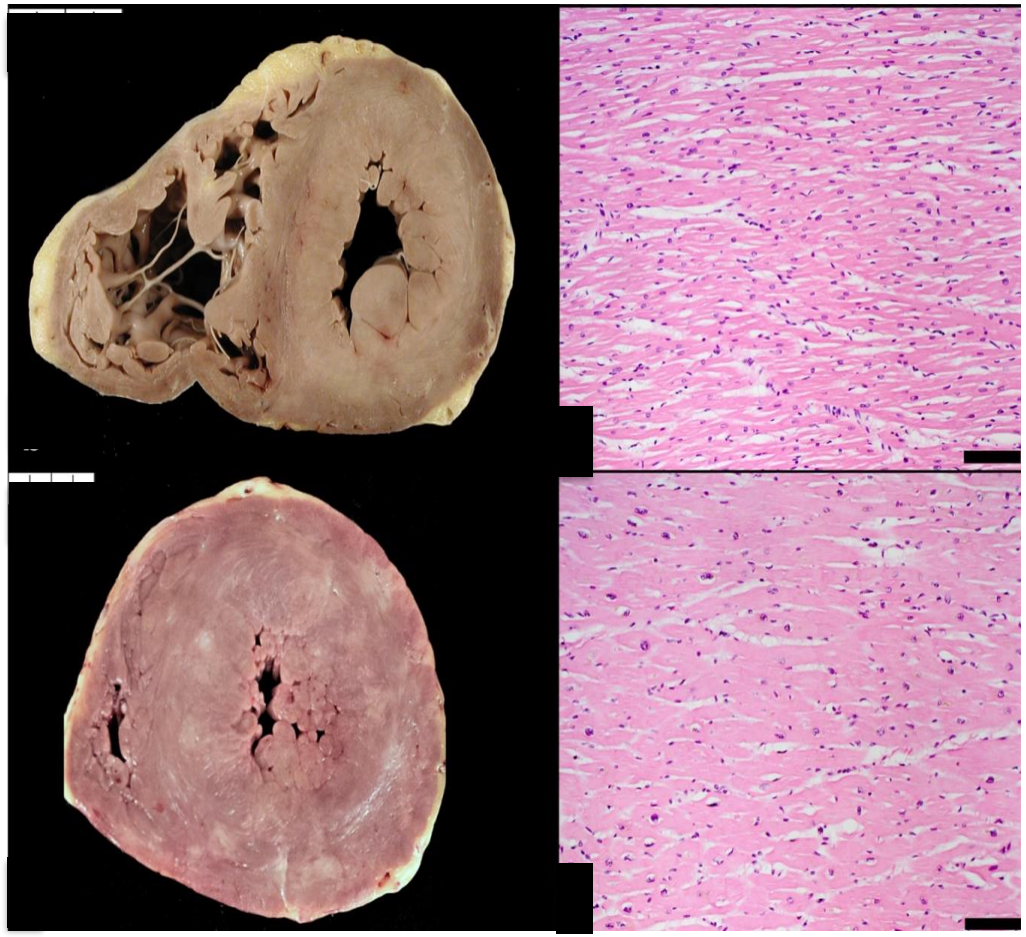


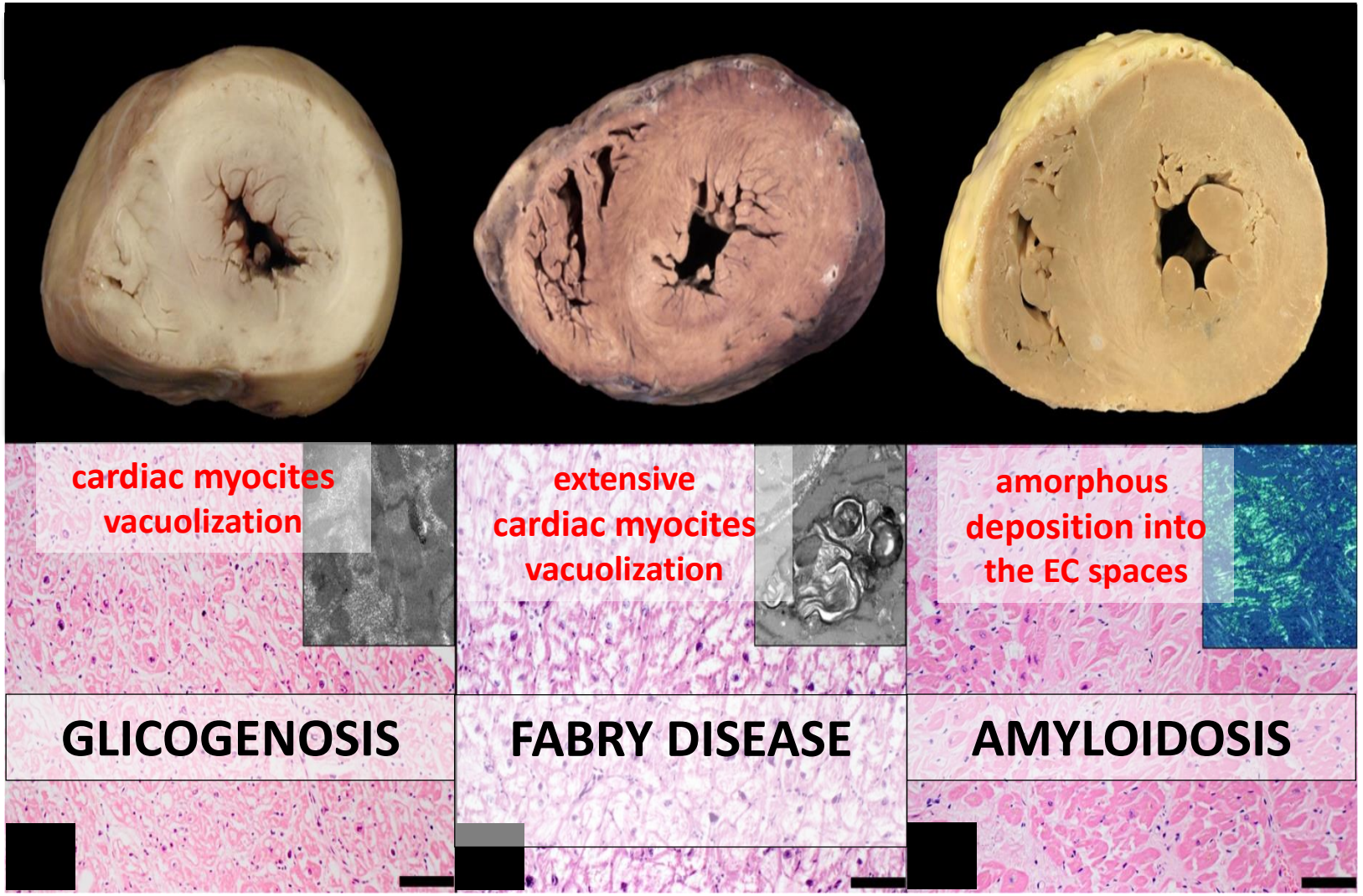
Cardiac hypertrophy at autopsy

Cristina Basso[1] · Katarzyna Michaud[2] · Giulia d'Amati[3] · Jytte Banner[4] · Joaquin Lucena[5] · Kristopher Cunningham[6] · Ornella Leone[7] · Aryan Vink[8] · Allard C. van der Wal[9] · Mary N. Sheppard[10] · on behalf of the Association for European Cardiovascular Pathology

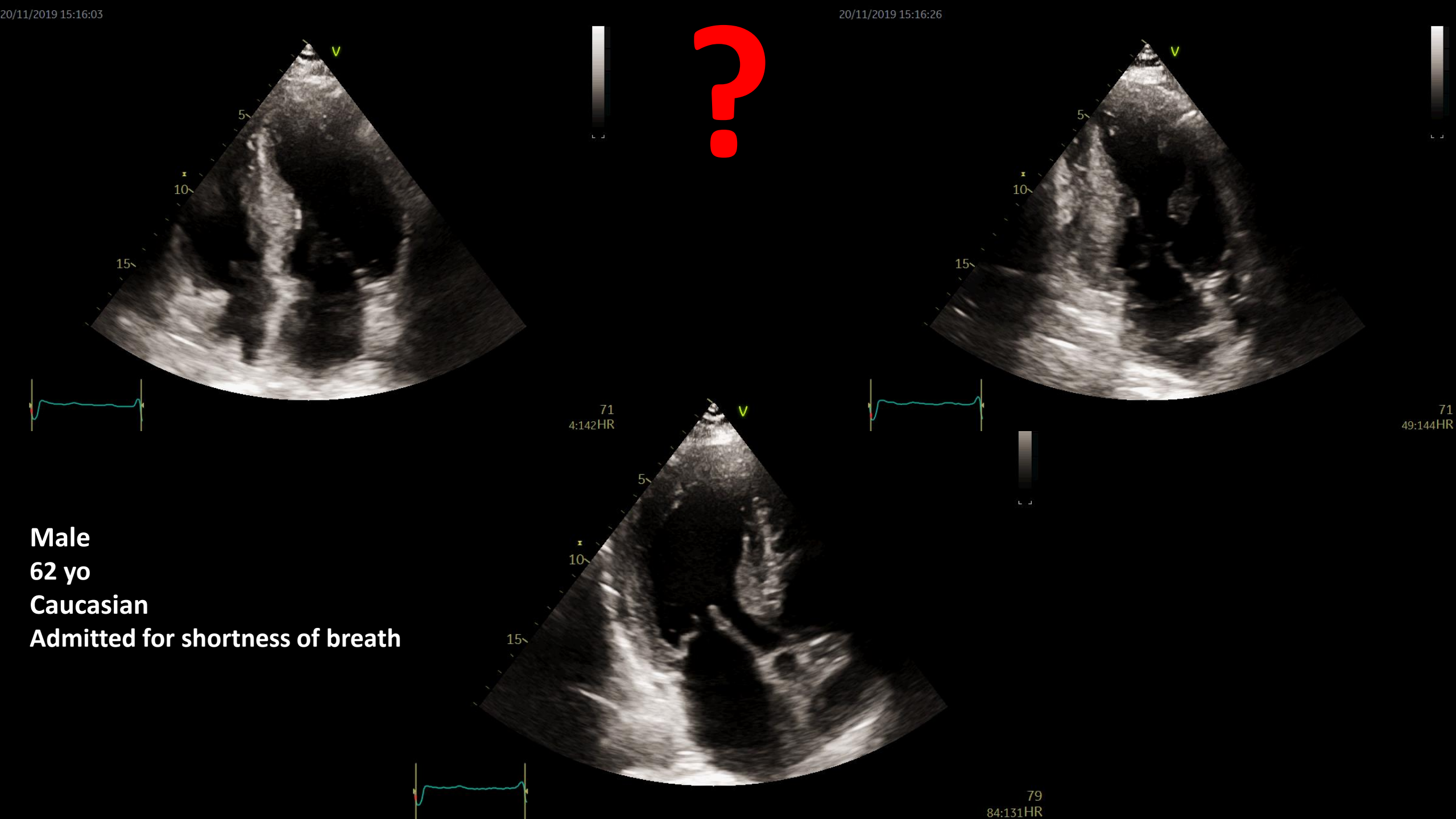
Normal heart

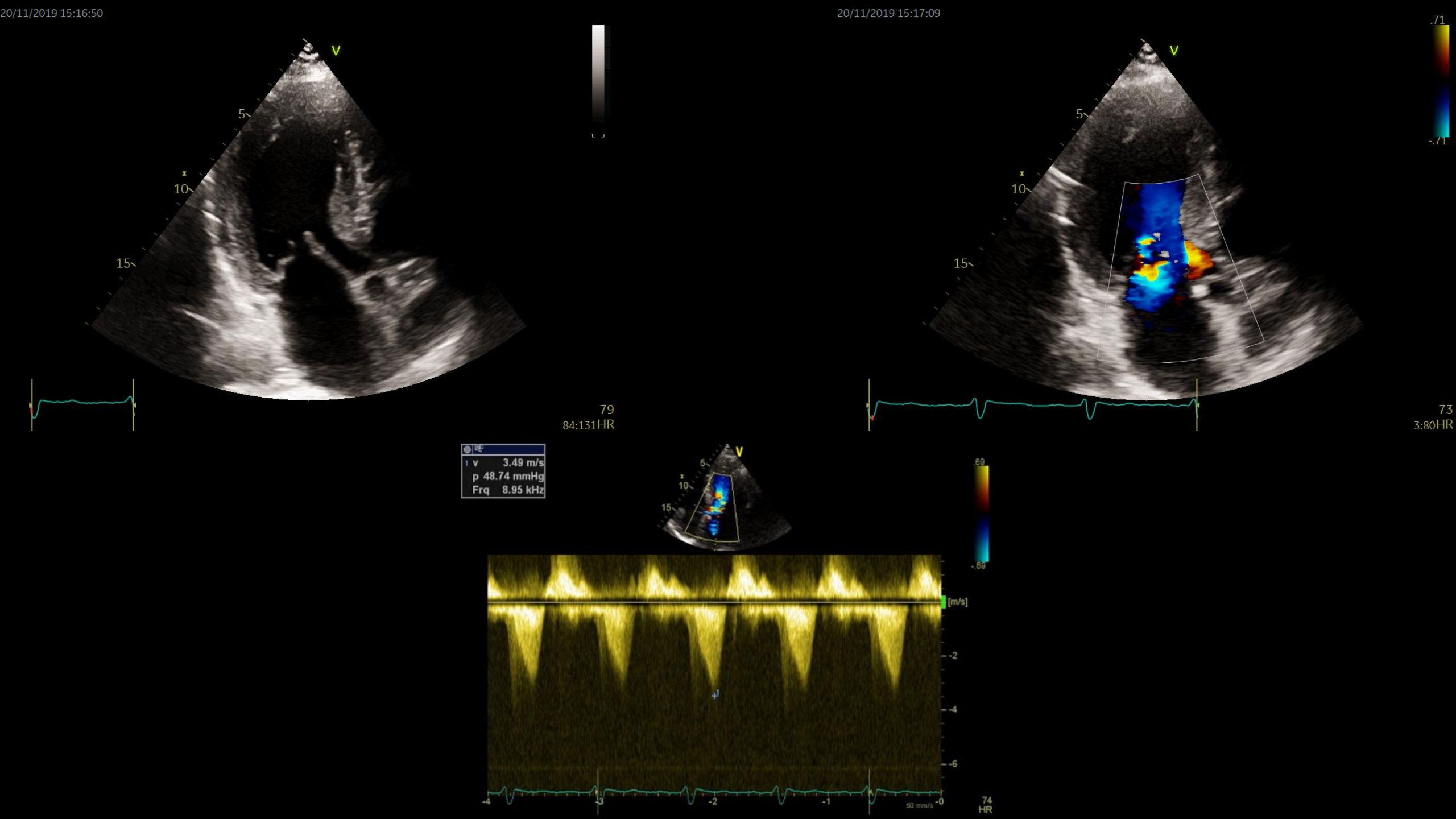
Hypertrophied heart

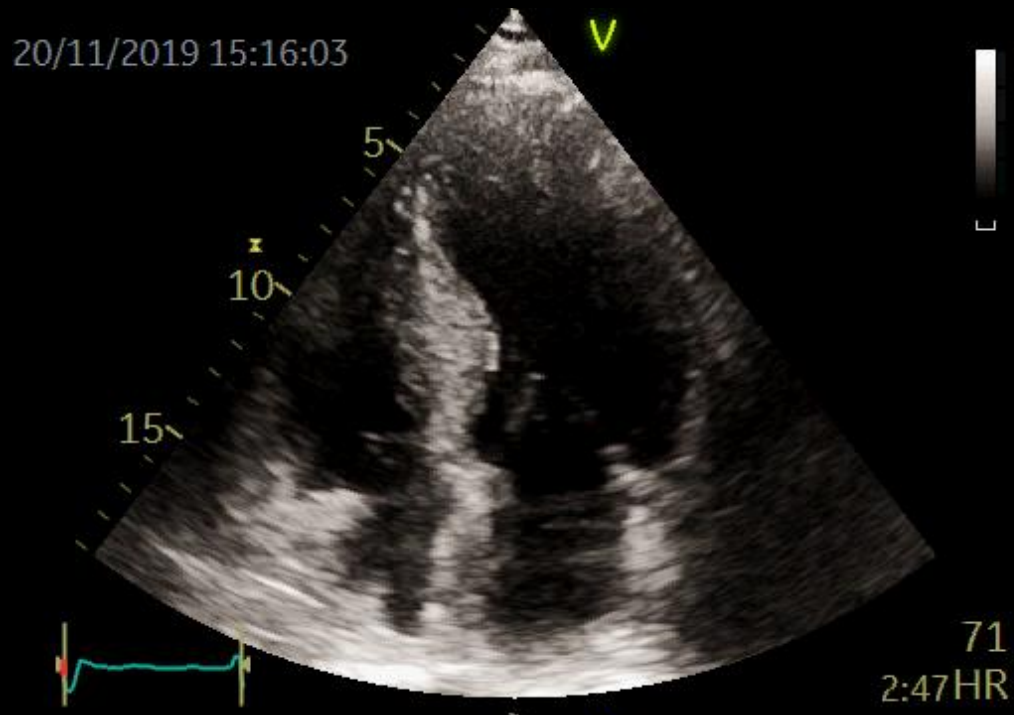



cardiac myocites vacuolization
extensive cardiac myocites vacuolization
amorphous deposition into the EC spaces
GLICOGENOSIS
FABRY DISEASE
AMYLOIDOSIS

Danon disease


20/11/2019 15:16:03
20/11/2019 15:16:26
?
71
4:142HR
71
49:144HR
79
84:131HR
Male
62 yo
Caucasian
Admitted for shortness of breath


20/11/2019 15:16:50
20/11/2019 15:17:09
V
5
10
15
.71
-.71
79
84:131HR
73
3:80HR
v 3.49 m/s
p 48.74 mmHg
Frq 8.95 kHz
.69
-.69
[m/s]
-2
-4
-6
-4
-3
-2
-1
-0
50 mm/s
74
HR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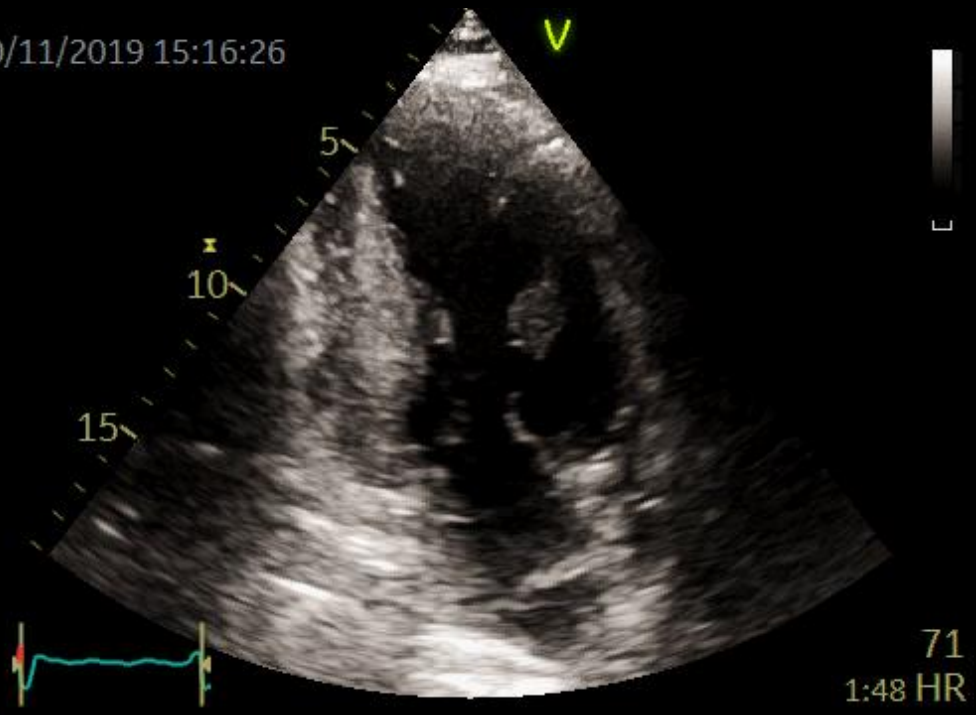
10
15
71
2:47 HR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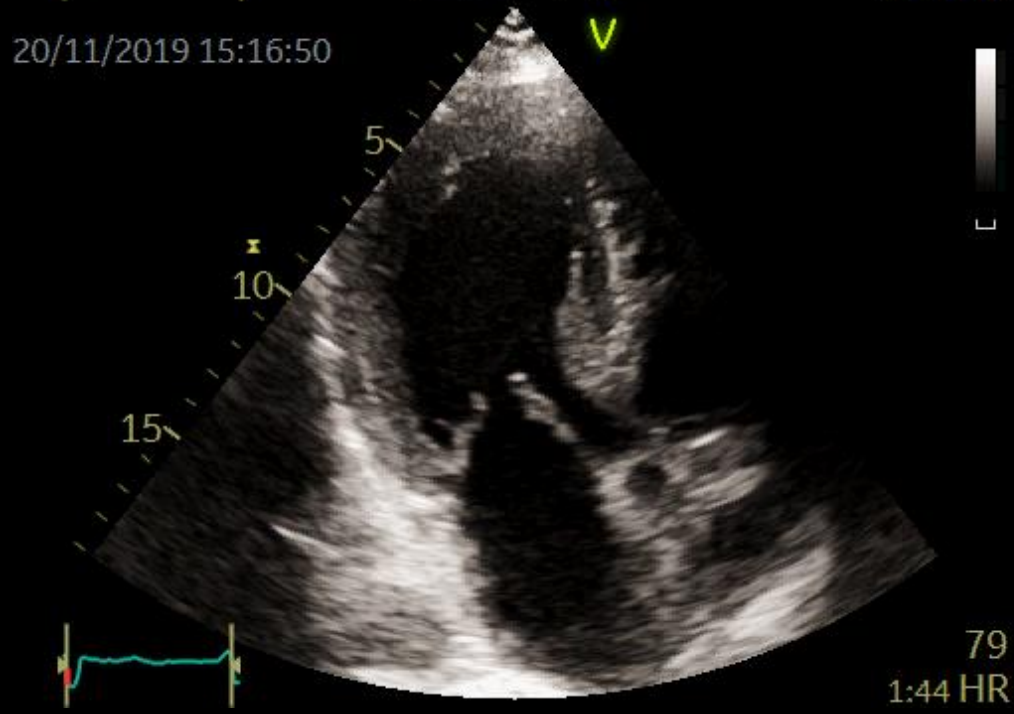
15
71
1:48 HR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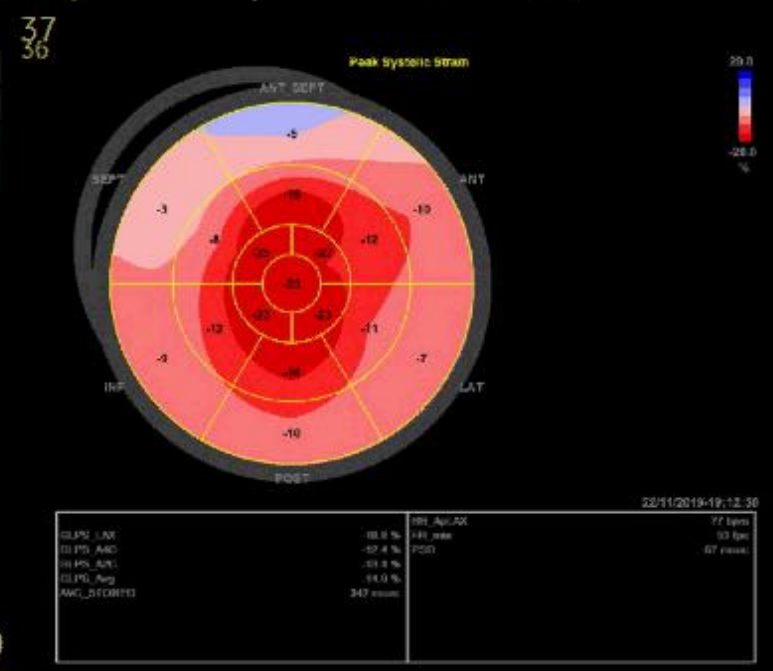
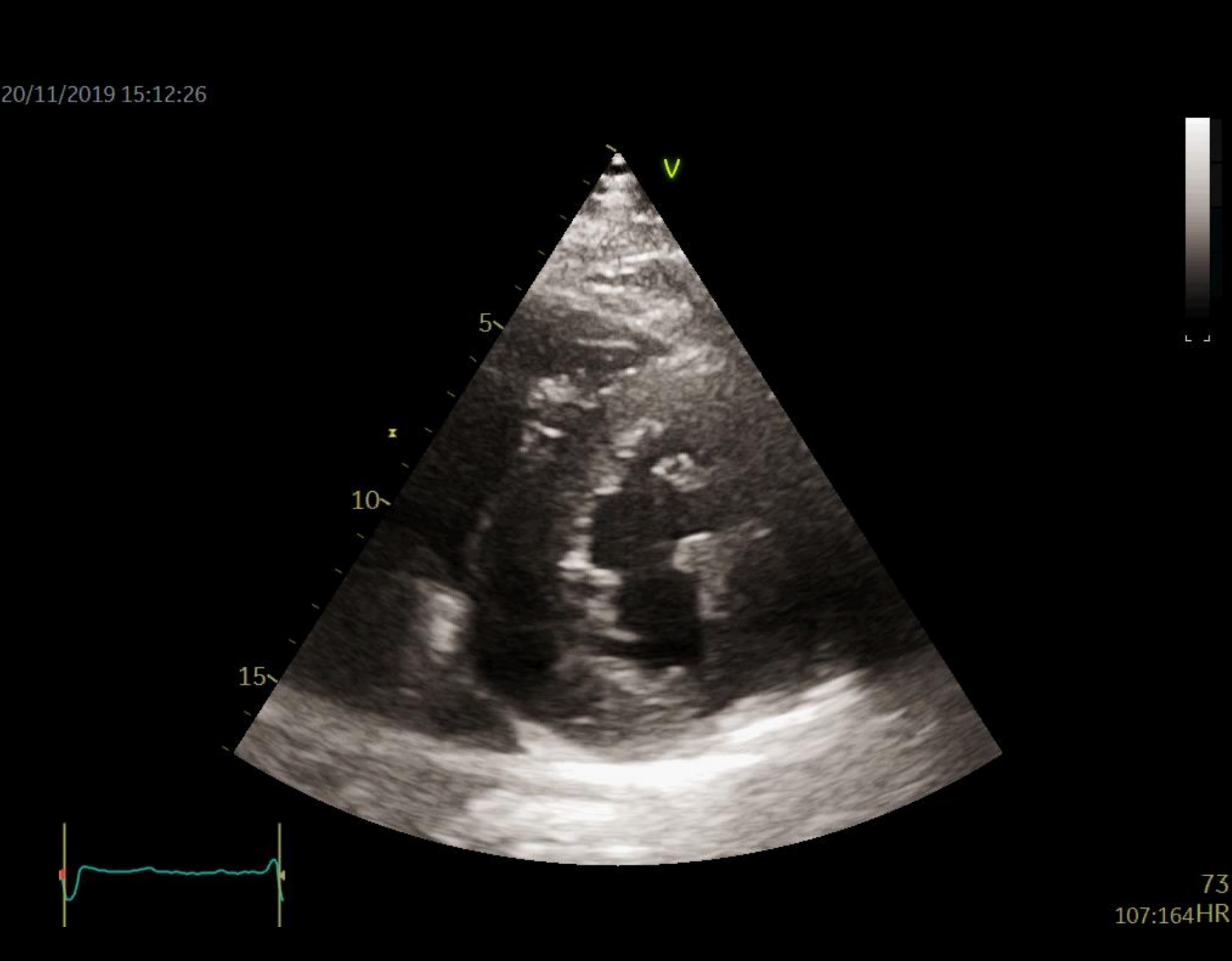
5
10
15
79
1:44 HR


37
36
Peak Systolic Strain
ANT SEPT
SEPT
ANT
INF
LAT
POST

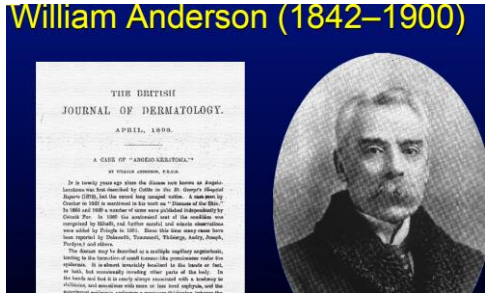


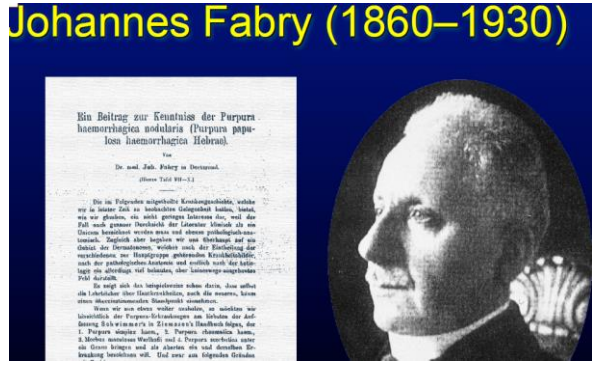
Stroke-like episodes

End-stage CKD

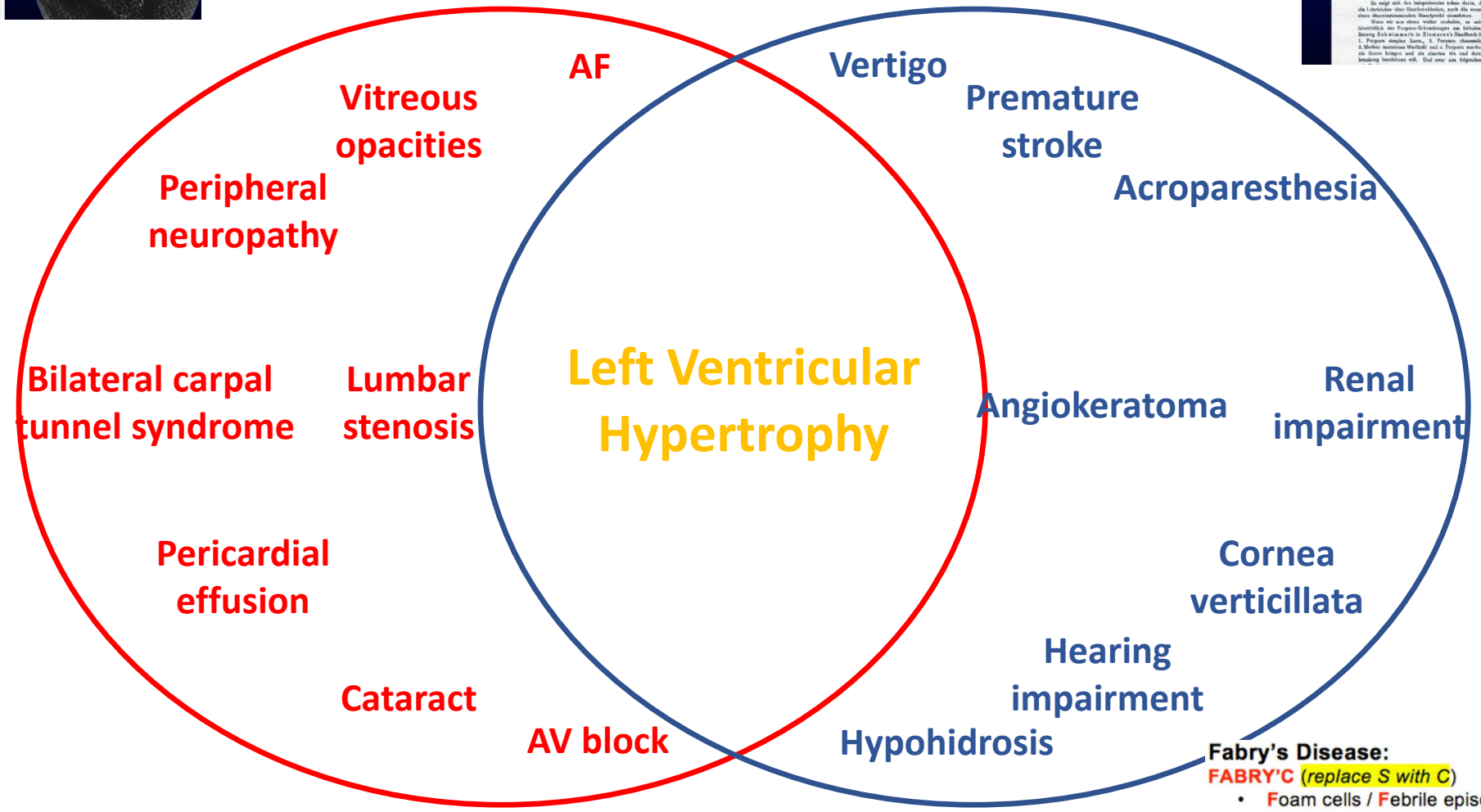
Peripheral Neuropathy

Angiokeratoma





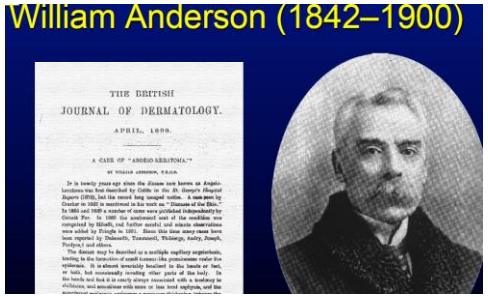
AFD Diagnosis



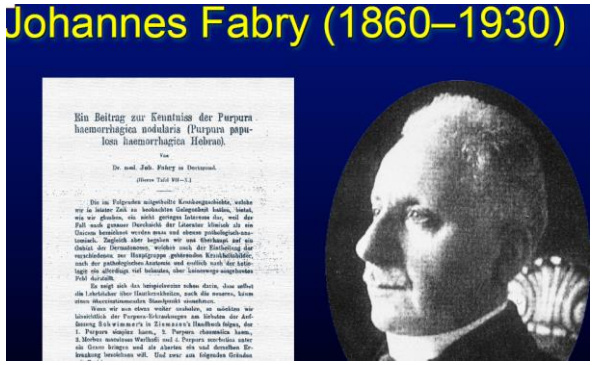
Fabry's Disease:

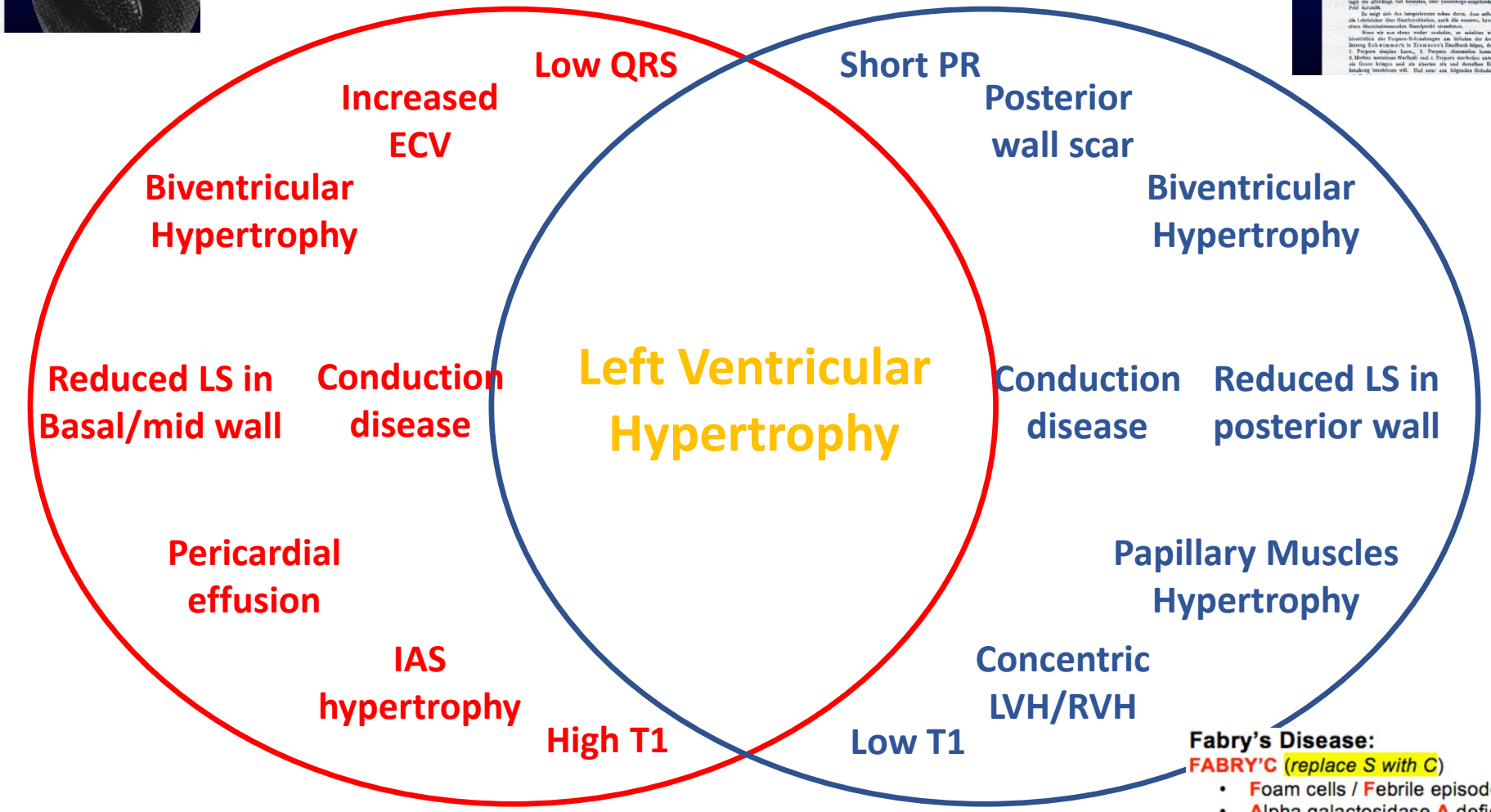
FABRY'C (*replace S with C*)

- **F**oam cells / **F**ebrile episodes
- Alpha galactosidase **A** deficiency / **A**ngiokeratomas
- **B**urning pain in hands & feet "Peripheral neuropathy" / **B**oys
- **R**enal Failure
- **Y**X genotype (Male, X-linked recessive)
- **C**eramide trihexoside *accumulation* / **C**ardiovascular disease



AFD Diagnosis





Fabry's Disease:

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- **Y**X genotype (Male, X-linked recessive)
- **C**eramide trihexoside *accumulation* / **C**ardiovascular disease

AFD Epidemology

Deficient a-galactosidase A activity that leads to an **accumulation of globotriasylceramide (Gb3)**

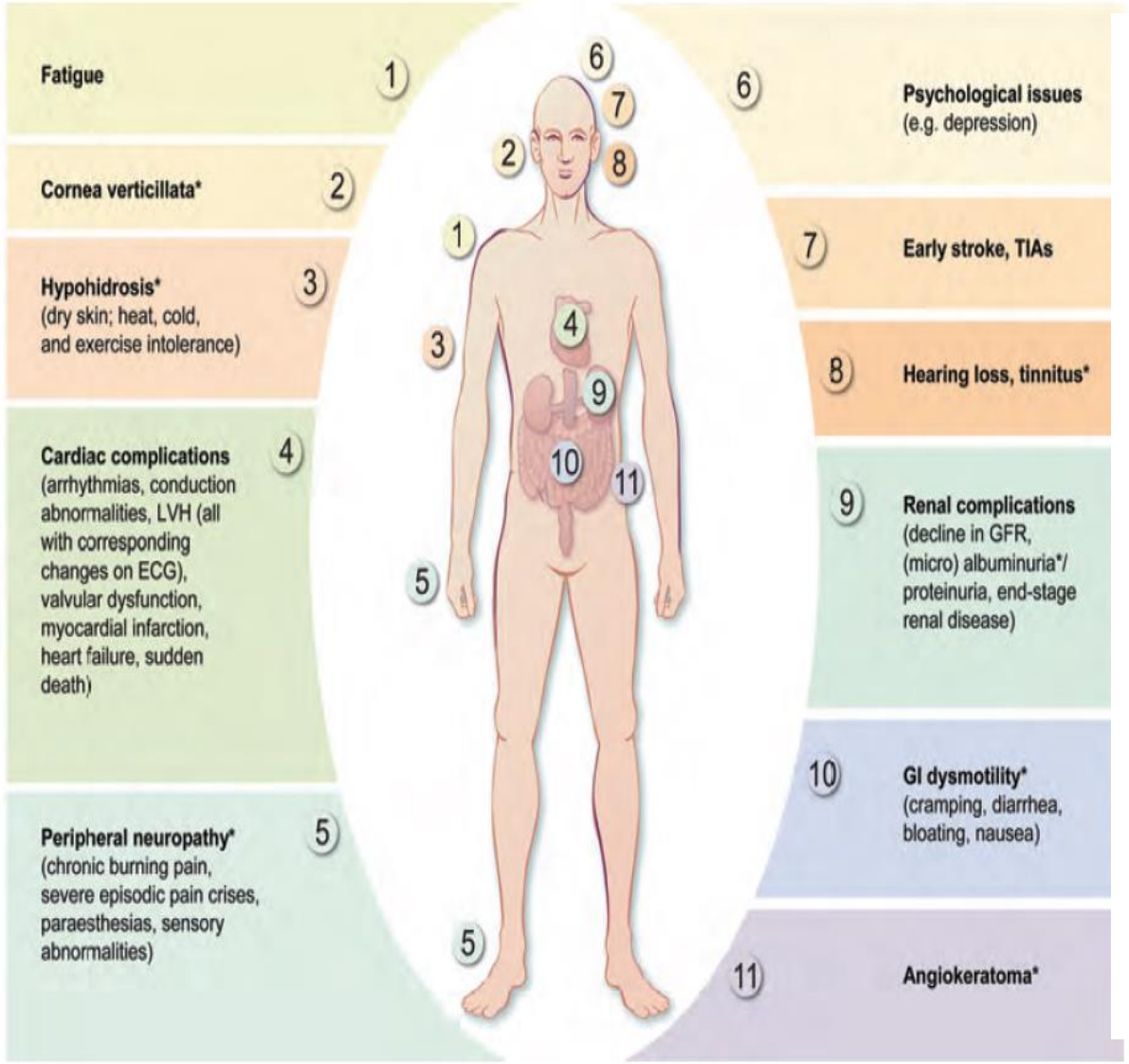
X-linked inheritance

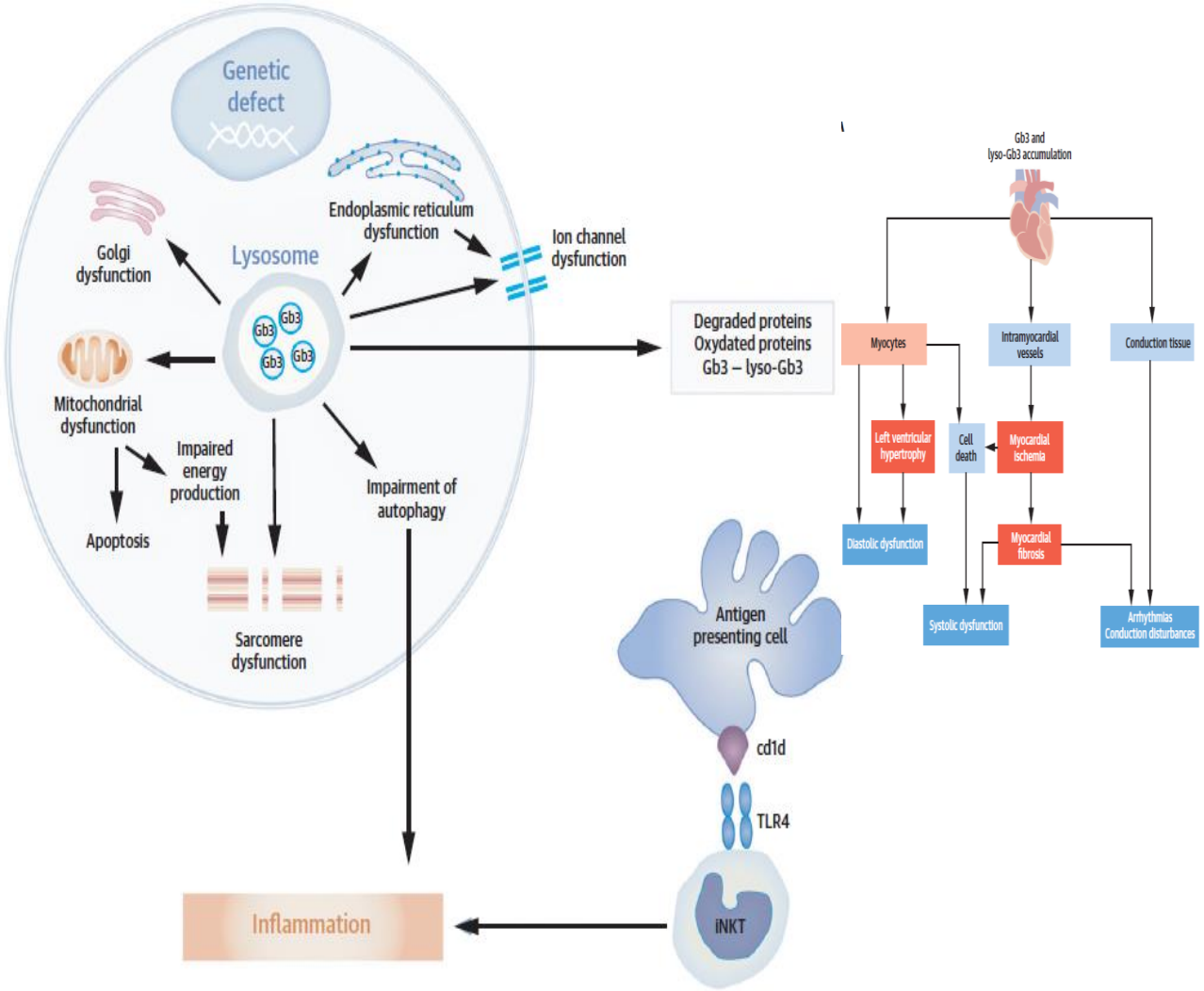
Rare: reported incidence between 1 in 40.000 and 1 in 117.000

Sex differences

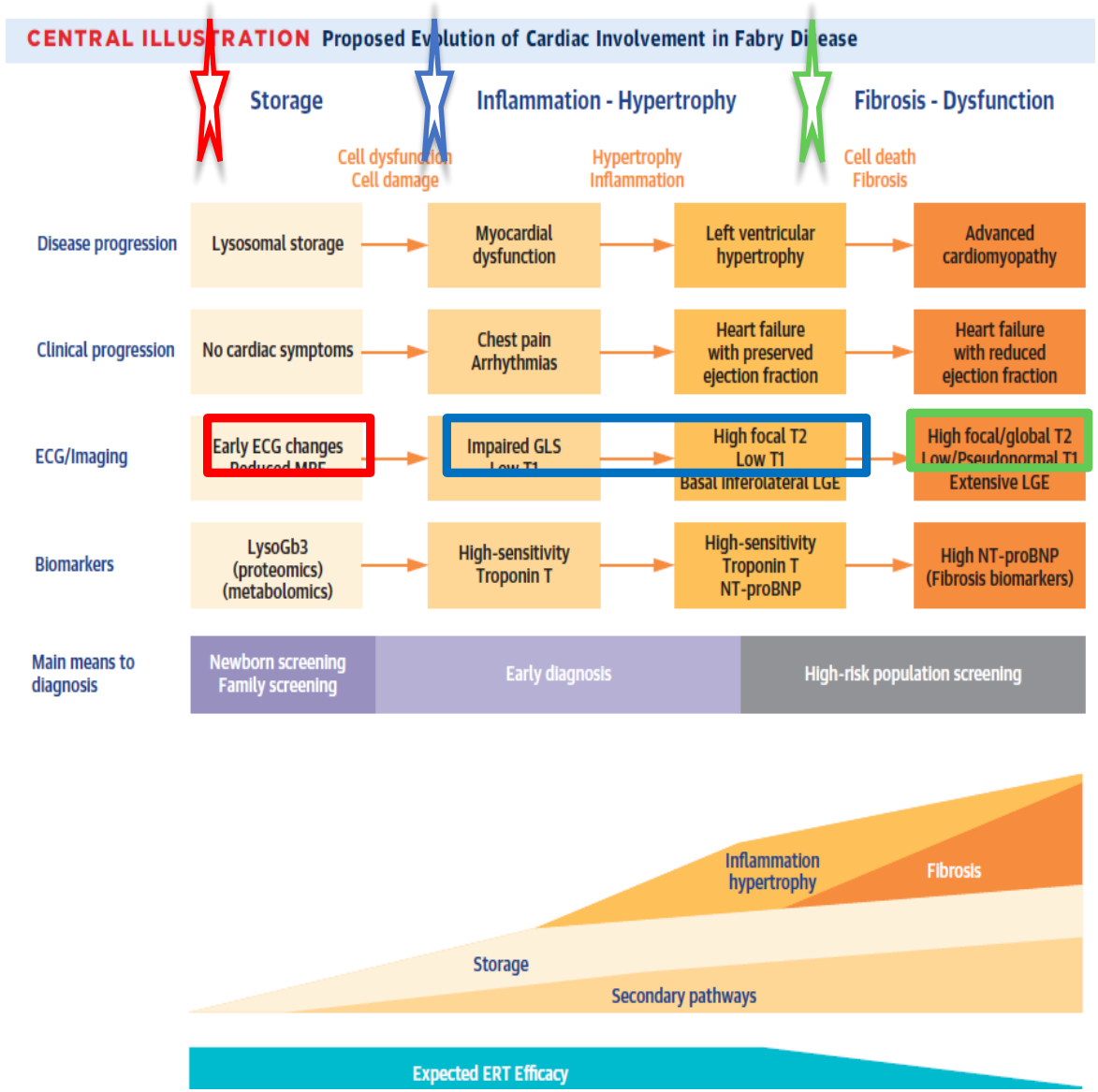
Male	Female
Classic manifestations	***Heterogeneous manifestations*** *(lyonization)* = Asymptomatic/mild phenotype (*late onset*) Severe phenotype (*classic AFD*)
Presymptomatic phase	
Overt disease	
End-stage phase	

AFD Epidemology and pathophisiology

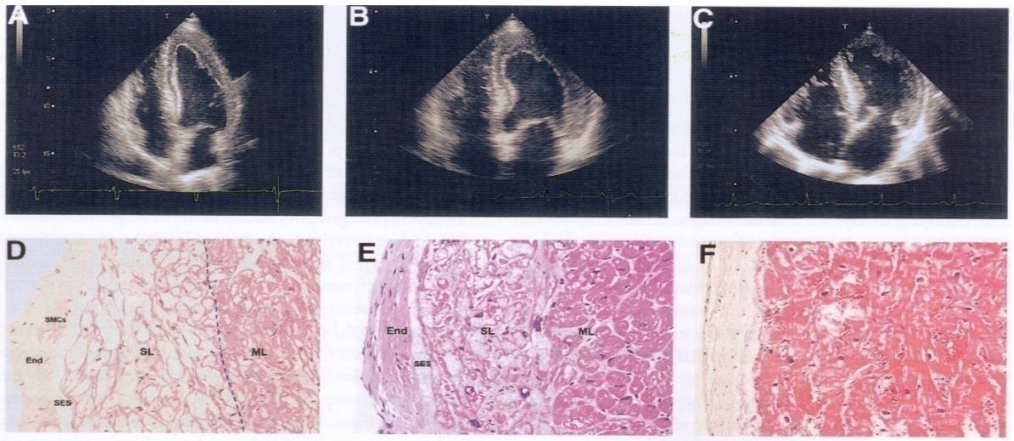




AFD Disease Progression



The "Binary Sign" in Fabry Disease



Sensitivity= 94%

Specificity= 100%

"…the binary appearance to reflect an endomyocardial glycosphingolipids compartmentalization, consisting of thickened glycolipid-rich endocardium, free glycosphingolipid subendocardial storage, and an inner severely affected myocardial layer with a clear subendocardial-midwall layer gradient of disease severity.

Pieroni, JACC 2006

Cardiogenetics 2013; volume 3:e3

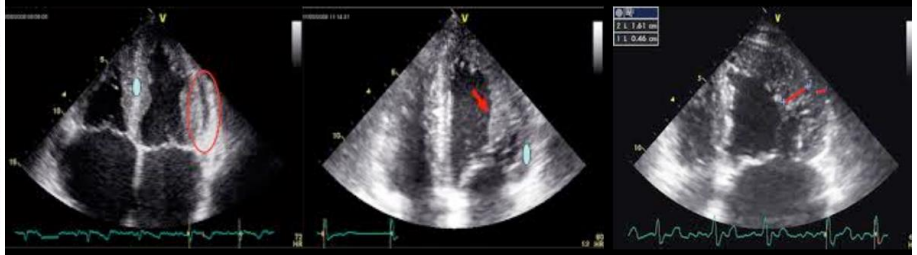
Take home message

Prominent papillary muscles are typical.

pagepress

Echocardiography in Fabry disease

Markus Niemann, Frank Weidemann



"In a recent study it could be shown that the absolute papillary muscle area as well as the ratio of the papillary muscle area and the left ventricular circumference is enlarged in AFD"

Ultrasound Med Biol 2011;37:37-43.

Journal of the American College of Cardiology
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ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.02.046

Cardiac Imaging

The Binary Endocardial Appearance Is a Poor Discriminator of Anderson-Fabry Disease From Familial Hypertrophic Cardiomyopathy

Stavros Kounas, MD,* Camelia Demetrescu, BSc, MD,* Antonios A. Pantazis, MD,*
Andre Keren, MD,† Philip J. Lee, DM, FRCPCH, FRCP,‡
Derralynn Hughes, MA, DPHIL, MRCP, MRCPATH,§ Atul Mehta, MA, MD, FRCP, FRCPATH,§
Perry Mark Elliott, MBBS, MD, FRCP, FACC, FESC*

London, United Kingdom; and Jerusalem, Israel

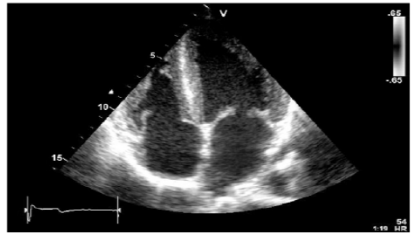


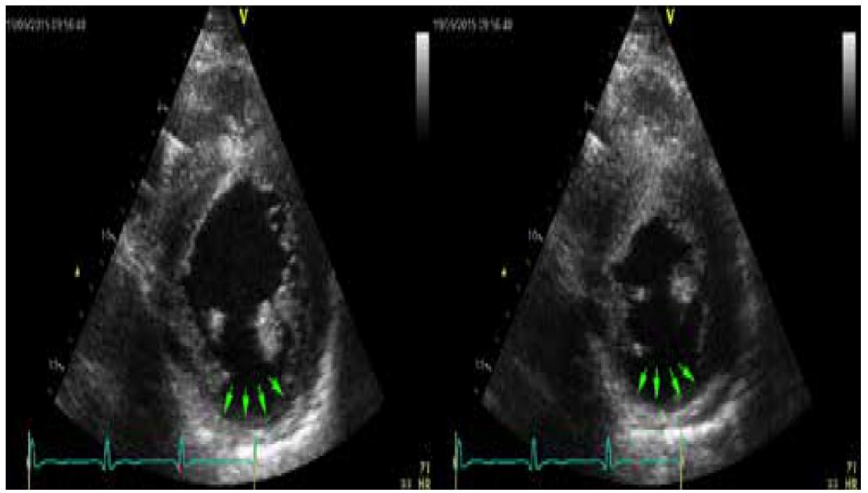
Figure 1 Apical View of a Patient With Anderson-Fabry Disease

Left ventricular hypertrophy is present with no binary endocardial appearance.

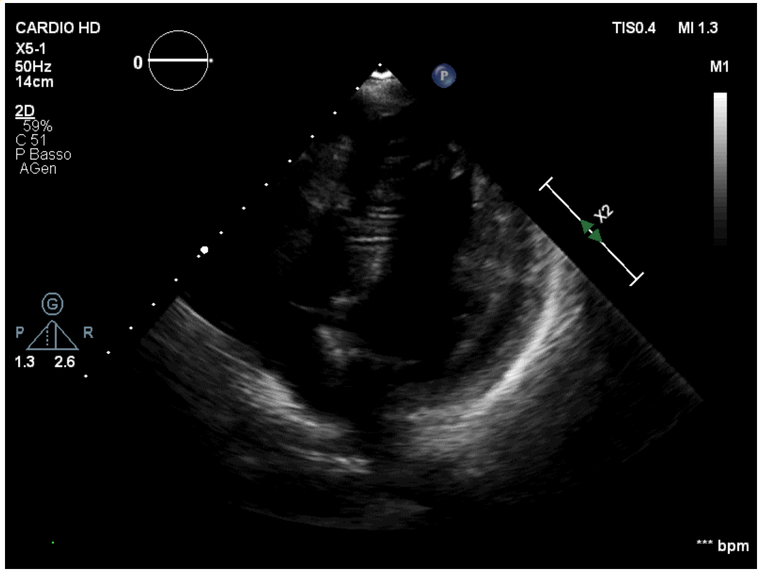
Table 2 Sensitivity and Specificity of the Binary Endocardial Appearance

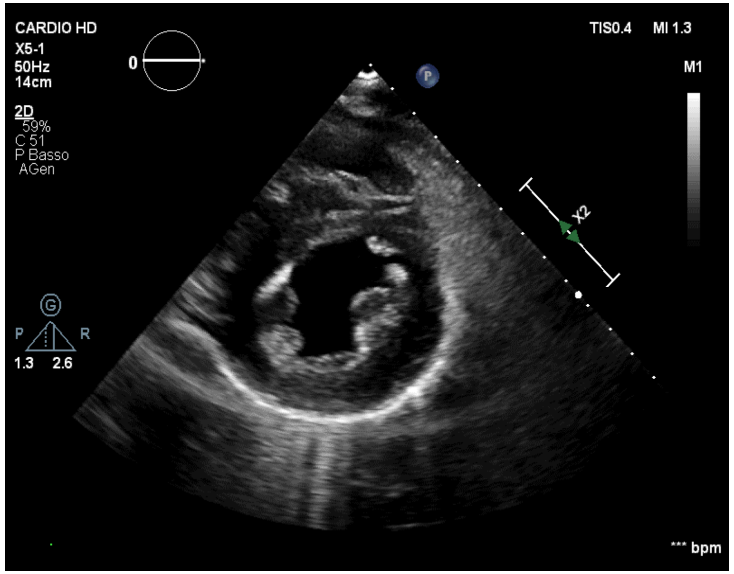
		Maximum LVWT		
		<15 mm	≥15 mm	Overall
AFD	No. of patients	5	9	14
	Binary sign	1	4	5
	Sensitivity	20%	44%	35%
HCM	No. of patients	4	10	14
	Binary sign	0	3	3
	Specificity	100%	70%	79%

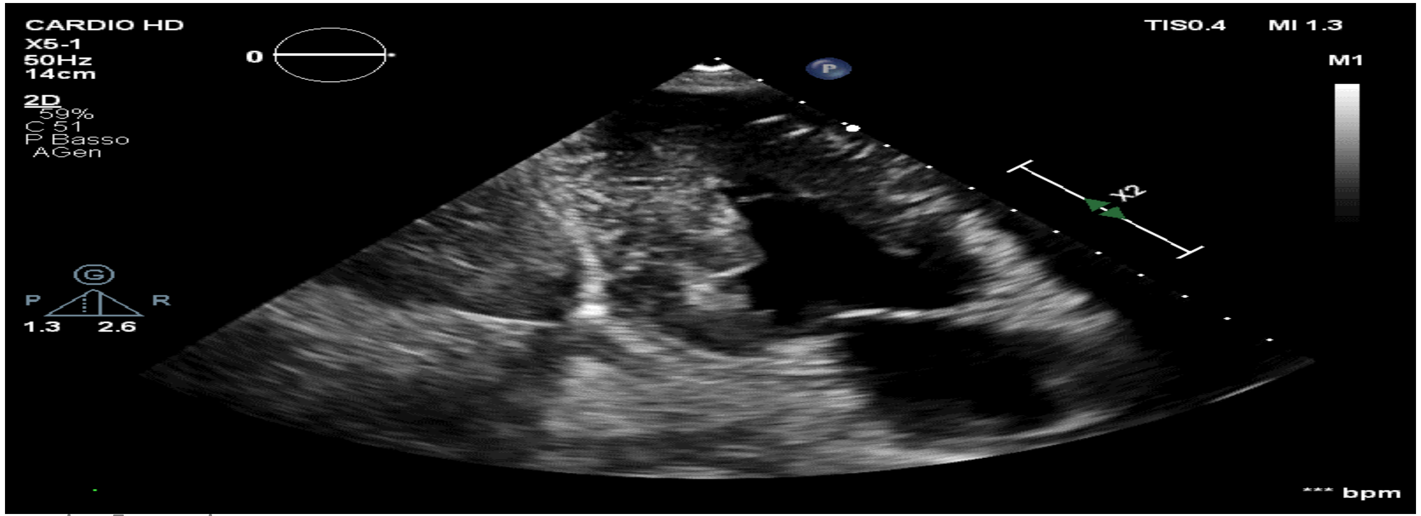
Figure 8 Extensive thinning and aneurysmal bulging of the posterior LV wall in a patient with advanced cardiac phenotype of Anderson Fabry disease.
Courtesy First Faculty of Medicine and General University Hospital, Prague, CZ.



Singh ADF

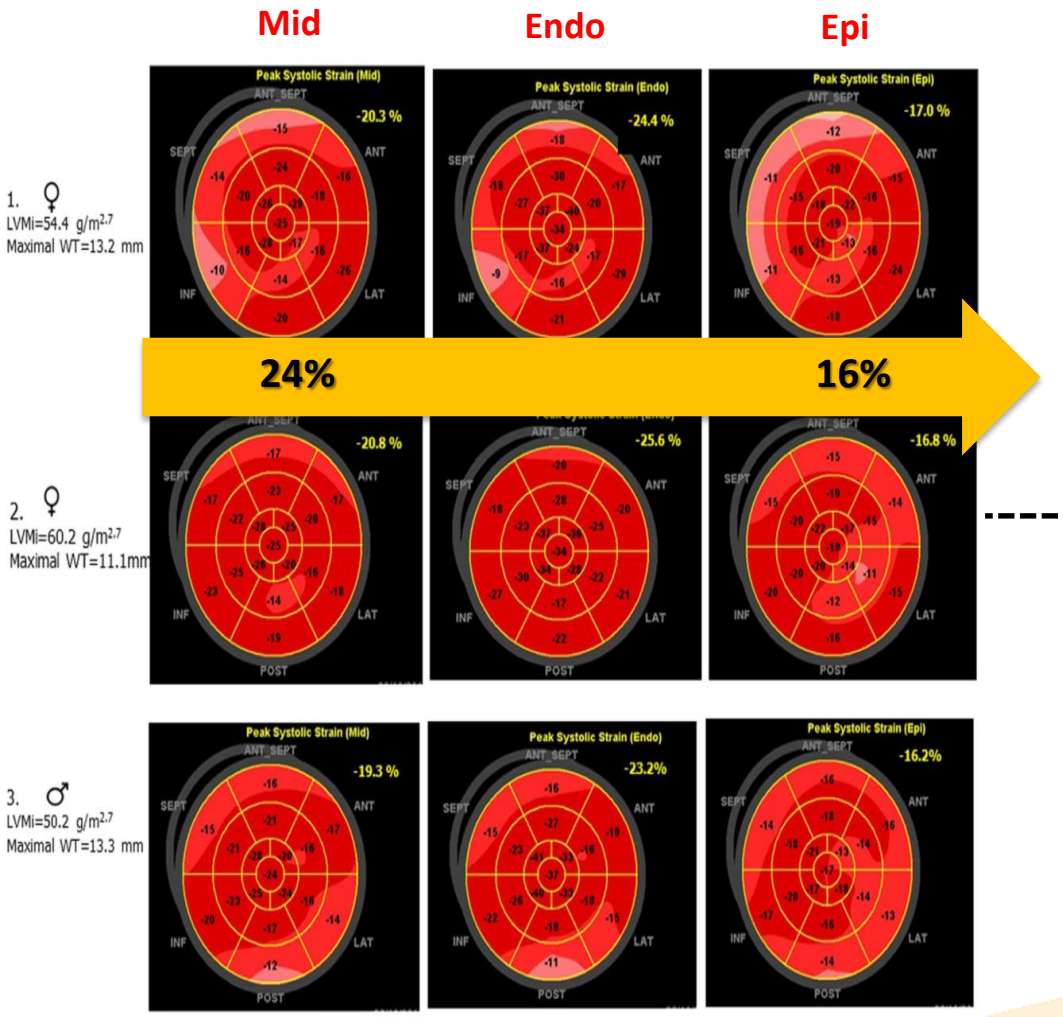






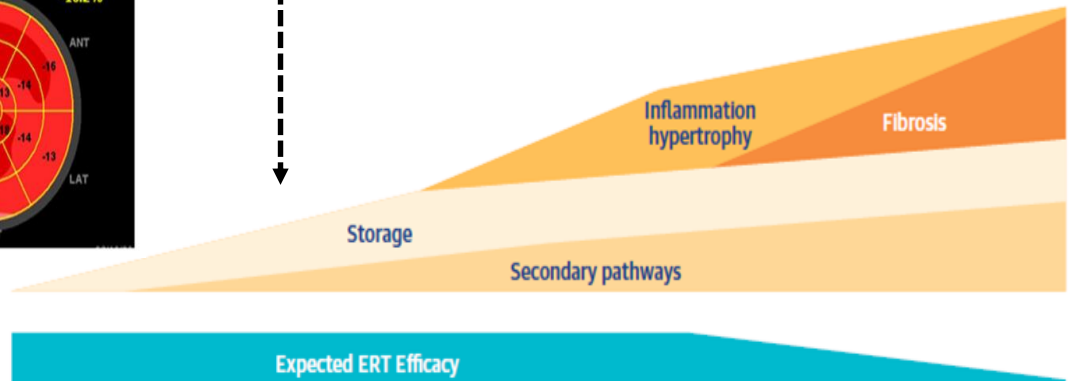
S.H. 44 a
Polmonite Interstiziale
Covid relata
IRC
Parestesie arti inferiori
Sordità
DBS +

AFD Diagnosis



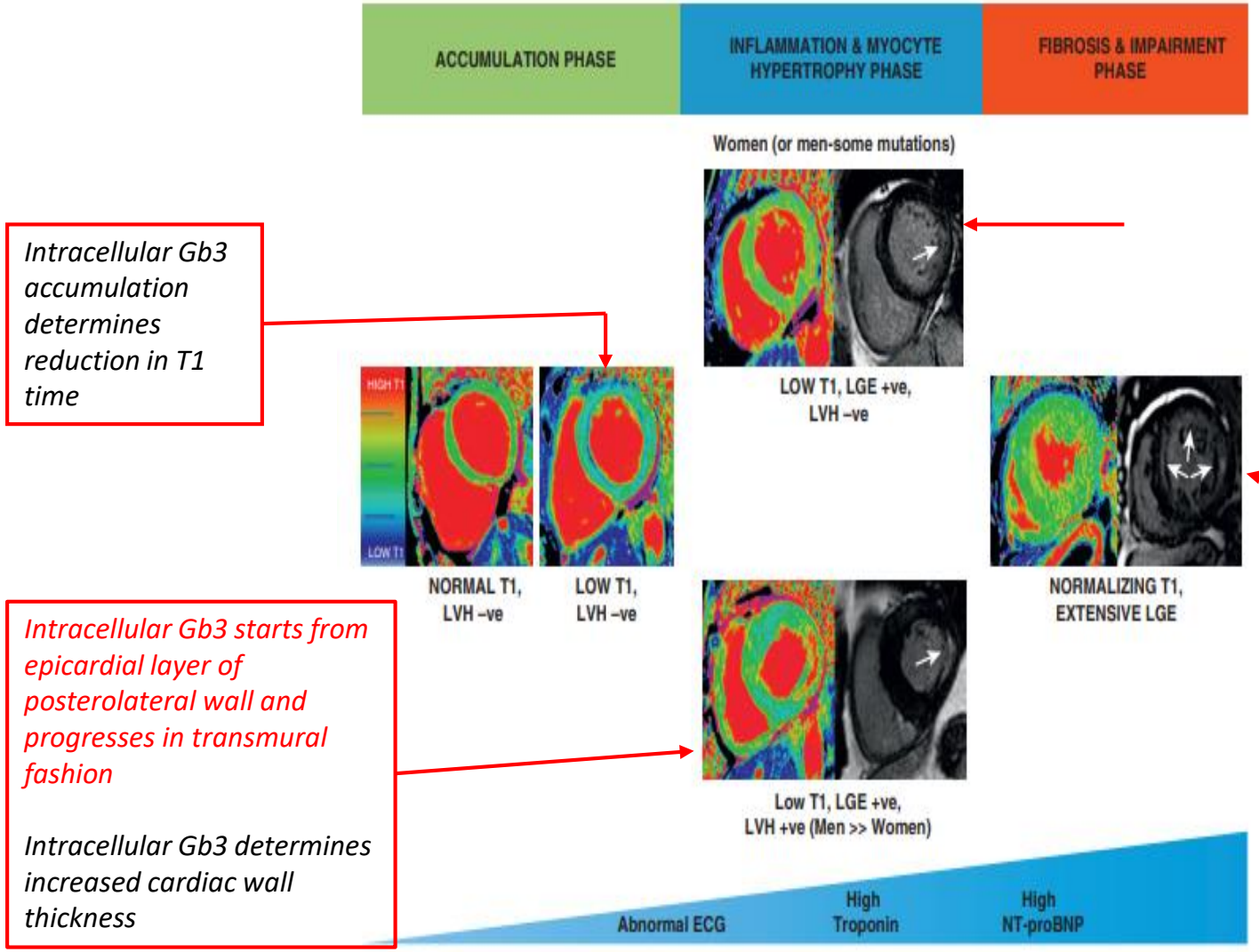
Layer-specific longitudinal strain in Anderson–Fabry disease at diagnosis: A speckle tracking echocardiography analysis

Roberta Esposito MD, PhD[1,2] | Ciro Santoro MD[1] | Regina Sorrentino MD[1] | Eleonora Riccio MD[3] | Rodolfo Citro MD[4] | Agostino Buonauro MD[1] | Teodolinda Di Risi MD[5] | Massimo Imbriaco MD[1] | Bruno Trimarco MD[1] | Antonio Pisani MD[3] | Maurizio Galderisi MD[1] | on behalf of the Anderson-Fabry Federico II Naples, ITalY (AFFINIITY) Group



AFD Diagnosis

Nordin S, et al. JACC Cardiovasc Imaging. 2018 European Heart Journal (2013) 34, 802–808



Intracellular Gb3 accumulation determines reduction in T1 time

Myocardial inflammation determines edema and increases T2 time

Extracellular myocardial fibrosis determines increase in T1 time

Intracellular Gb3 starts from epicardial layer of posterolateral wall and progresses in transmural fashion

Intracellular Gb3 determines increased cardiac wall thickness

AFD Diagnosis

An expert consensus document on the management of cardiovascular manifestations of Fabry disease

Aleš Linhart[1], Dominique P. Germain[2], Iacopo Olivotto[3], Mohammed M. Akhtar[4], Aris Anastasakis[5], Derralynn Hughes[6], Mehdi Namdar[7], Maurizio Pieroni[8], Albert Hagège[9,10,11], Franco Cecchi[3,12], Juan R. Gimeno[13], Giuseppe Limongelli[14], and Perry Elliott[4]*

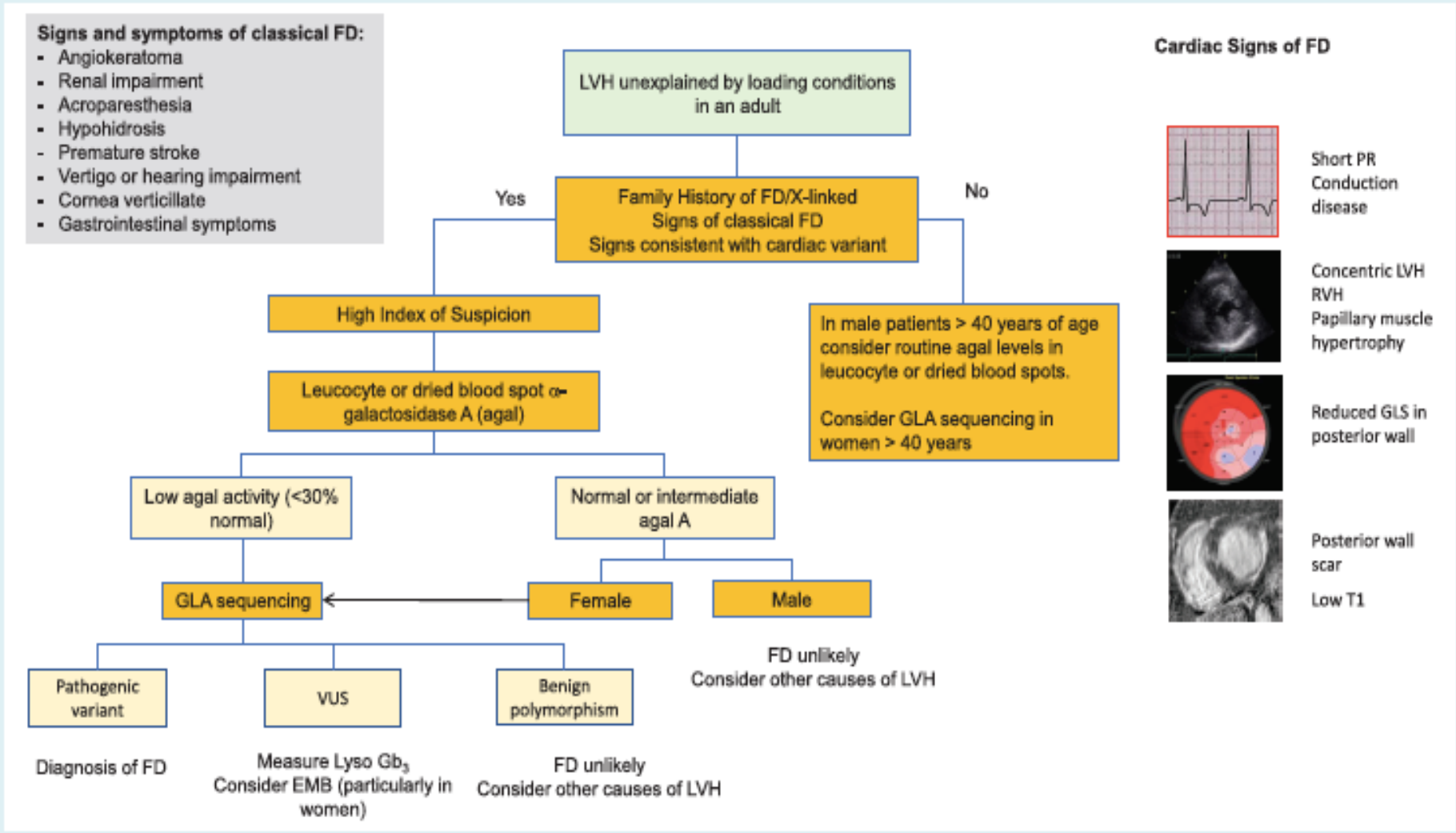


Figure 1 Diagnosis. Flow chart showing a suggested approach to the diagnosis of Fabry disease (FD) in a patient with unexplained left ventricular hypertrophy (LVH). Agal, α-galactosidase A; Gb_3, globotriaosylceramide; GLA, α-galactosidase A gene; GLS, global longitudinal strain; EMB, endomyocardial biopsy; RVH, right ventricular hypertrophy; VUS, variant of unknown significance.

CARDIAC AMYLOIDOSIS (the great pretender)

Underdiagnosed

Challenging

Tricky

Treatable (trendy?)

Table 1 Classification of cardiac amyloid types most frequently encountered in humans

Amyloid protein	Precursor	Main features	Myocardial involvement
AL	Immunoglobulin light chain	Primary/myeloma associated	Frequent
ATTR	Transthyretin	Familial	Variable according to genotype
ATTR	Transthyretin	Wild type	Constant
AApo AI	Apolipoprotein AI	Familial	Occasional but severe
AApo AII	Apolipoprotein AII	Familial	Exceptional
AFib	Fibrinogen α chain	Familial	Exceptional
ALys	Lysozyme	Familial	Exceptional
AA	Serum AA	Secondary, reactive	Exceptional
A β2 M	β2 microglobulin	Hemodyalisis associated	Exceptional
IAA	Atrial natriuretic factor	Atrial fibrillation	Atrial tissue

Modified from Sipe et al. [3]

AL, immunoglobulin light-chain amyloid; ATTR, transthyretin-related amyloid; AApoAI, apolipoprotein A-I amyloid; AApoAII, apolipoprotein A-II amyloid; Afib, fibrinogen alpha chain amyloid; ALys, lysozyme amyloid; AA, amyloid A; A β2M, β2 microglobulin amyloid; IAA, isolated atrial amyloid

Heart Fail Rev (2015) 20:117–124
DOI 10.1007/s10741-015-9480-0

Cardiac amyloidosis: the great pretender

Claudio Rapezzi[1,4] · Massimiliano Lorenzini[1] · Simone Longhi[1] · Agnese Milandri[1] · Christian Gagliardi[1] · Ilaria Bartolomei[2] · Fabrizio Salvi[2] · Mathew S. Maurer[3]

misdiagnosis

Table 2 Factors leading to misdiagnosis

Physician-related factors
Fragmented knowledge among different specialties and subspecialties
Shortage of centres and experts dedicated to specialised disease management
Common misconceptions about diagnosing and typing amyloid
• Low voltage is not sensitive nor specific finding in isolation to exclude the presence of cardiac amyloidosis
• Serum protein electrophoresis is not a sufficient screening test to exclude the presence of a plasma cell disorder than can cause AL amyloid
• A fat pad biopsy has a sensitivity for AL amyloid of 70 % at best and is positive in < 50 % of subjects with ATTR CA
Erroneous belief it is an untreatable disease
Disease-related factors
Rarity
Intrinsic phenotypic heterogeneity
Genotypic heterogeneity in ATTR
Necessity of target organ tissue histological diagnosis in the vast majority of cases

PATHOPHYSIOLOGY

Extracellular deposition of insoluble low molecular weight fibrils in tissues and organs

↓

Cardiac deposition of fibrils
(proteins misfolding caused by excessive production or inherited mutation)

↓

2 types of fibrils for 98% of cases

Light chain Amyloidosis (AL)

Transthyretin Amyloidosis (ATTR)

- **Mutant**
- **Wild-type**

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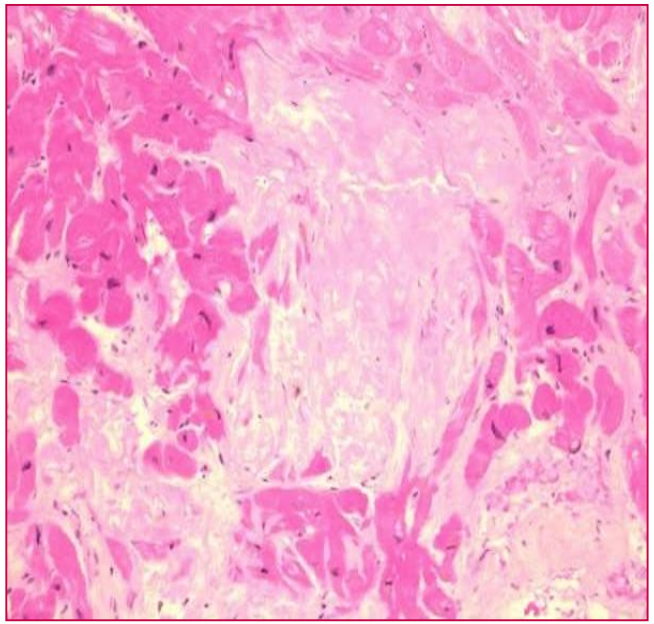
PATHOPHYSIOLOGY

Extracellular deposition of insoluble low molecular weight fibrils in tissues and organs

Cardiac myocytes isolation



Vessels involvement

Ischaemic damage

Architecture disruption

Oxidant stress

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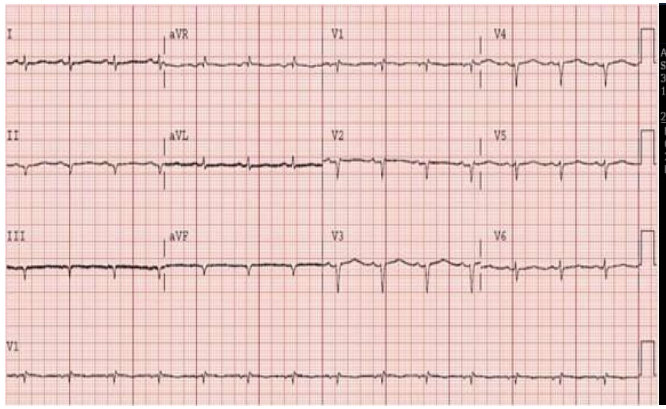
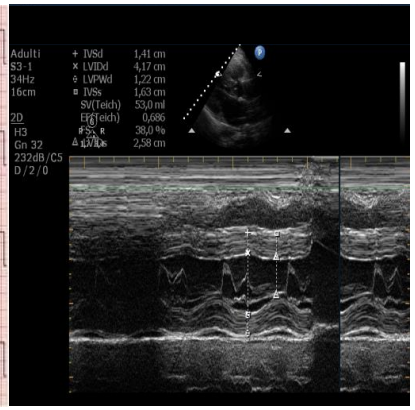
ELECTROCARDIOGRAPHY

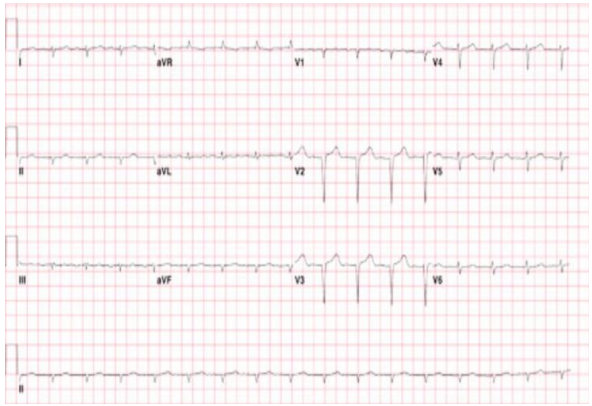
VOLTAGE DISCORDANCE PATTERN

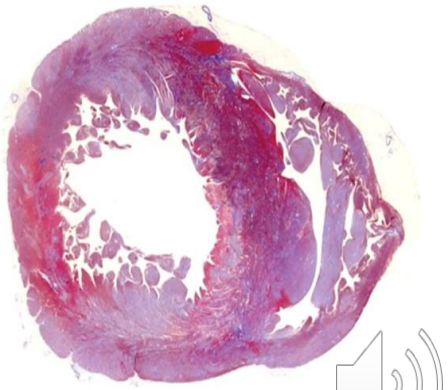




LV wall thickness/QRS voltages ratio

PSEUDOINFARCTION PATTERN





Non Ischaemic Scar

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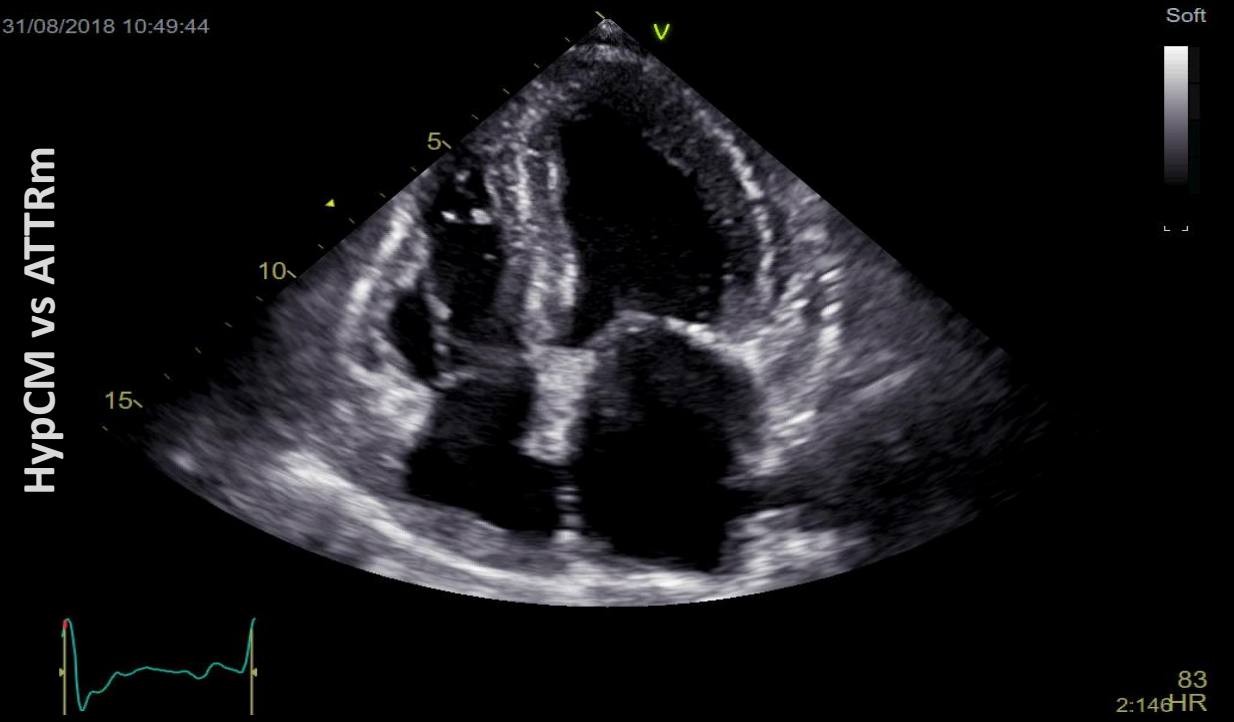
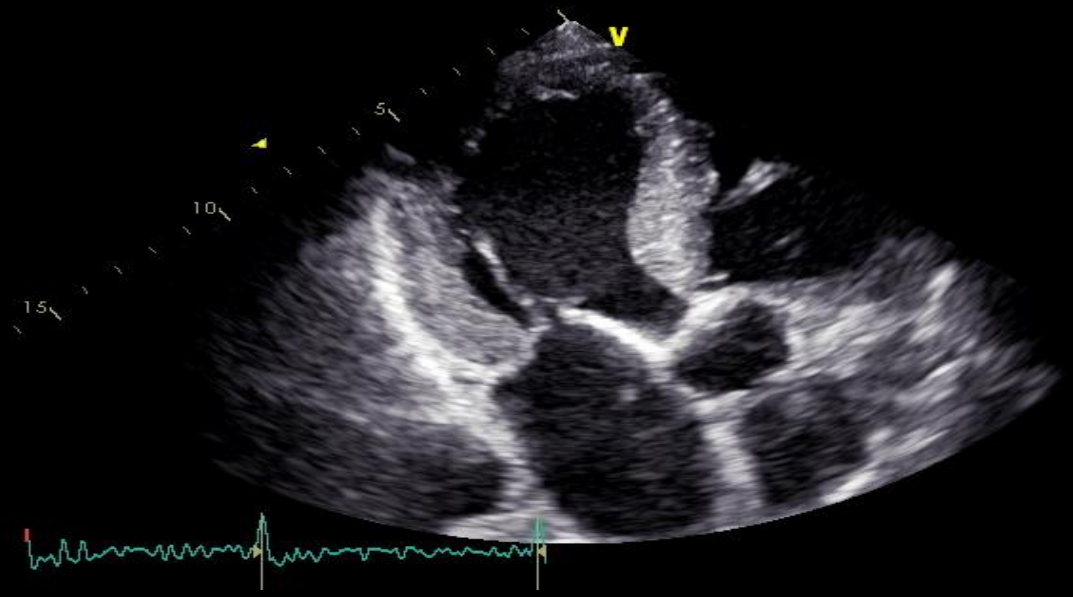
PHENOTYPICAL HETEROGENICITY

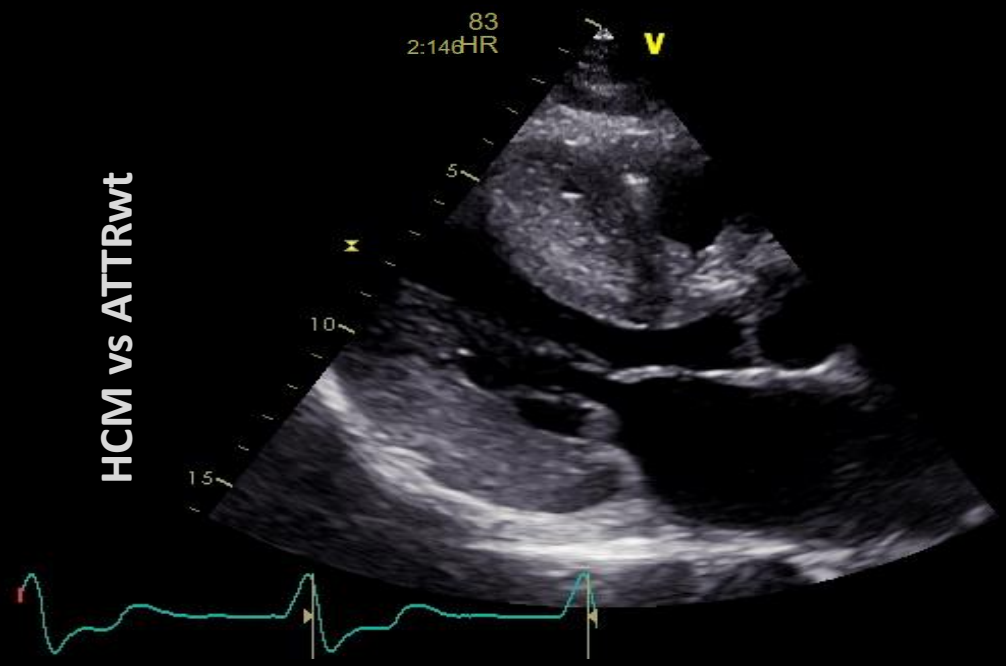
HypCM vs ATTRm



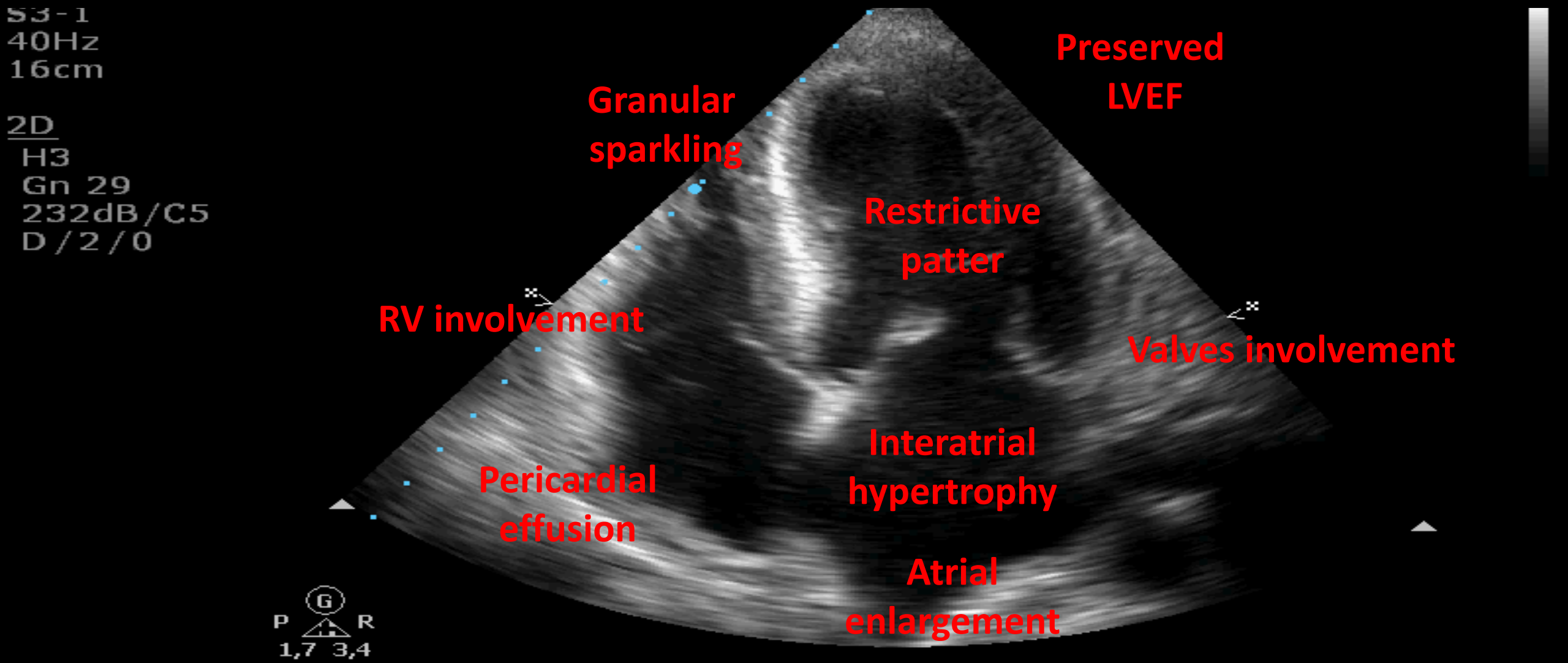
Aortic stenosis vs ATTRwt



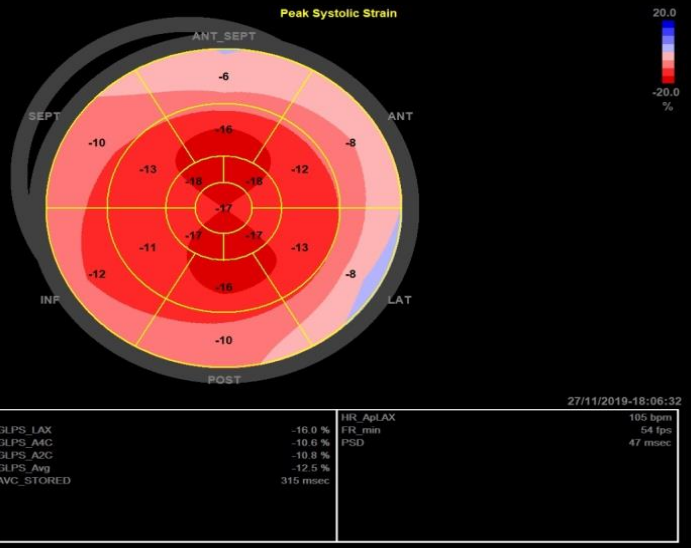
HCM vs ATTRwt

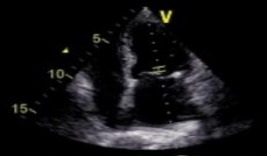


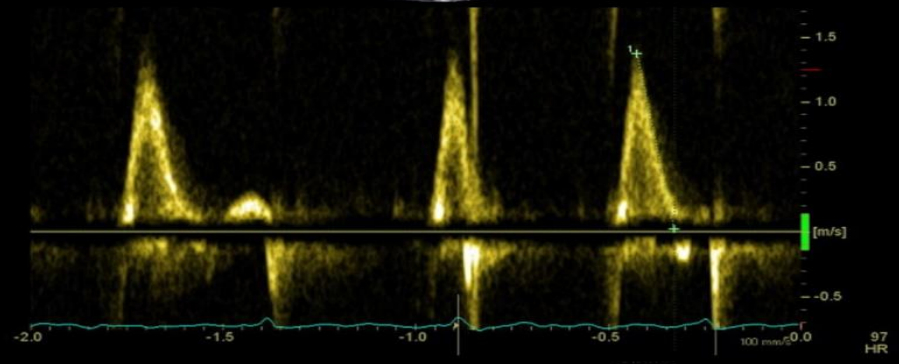
ECHOCARDIOGRAPHY

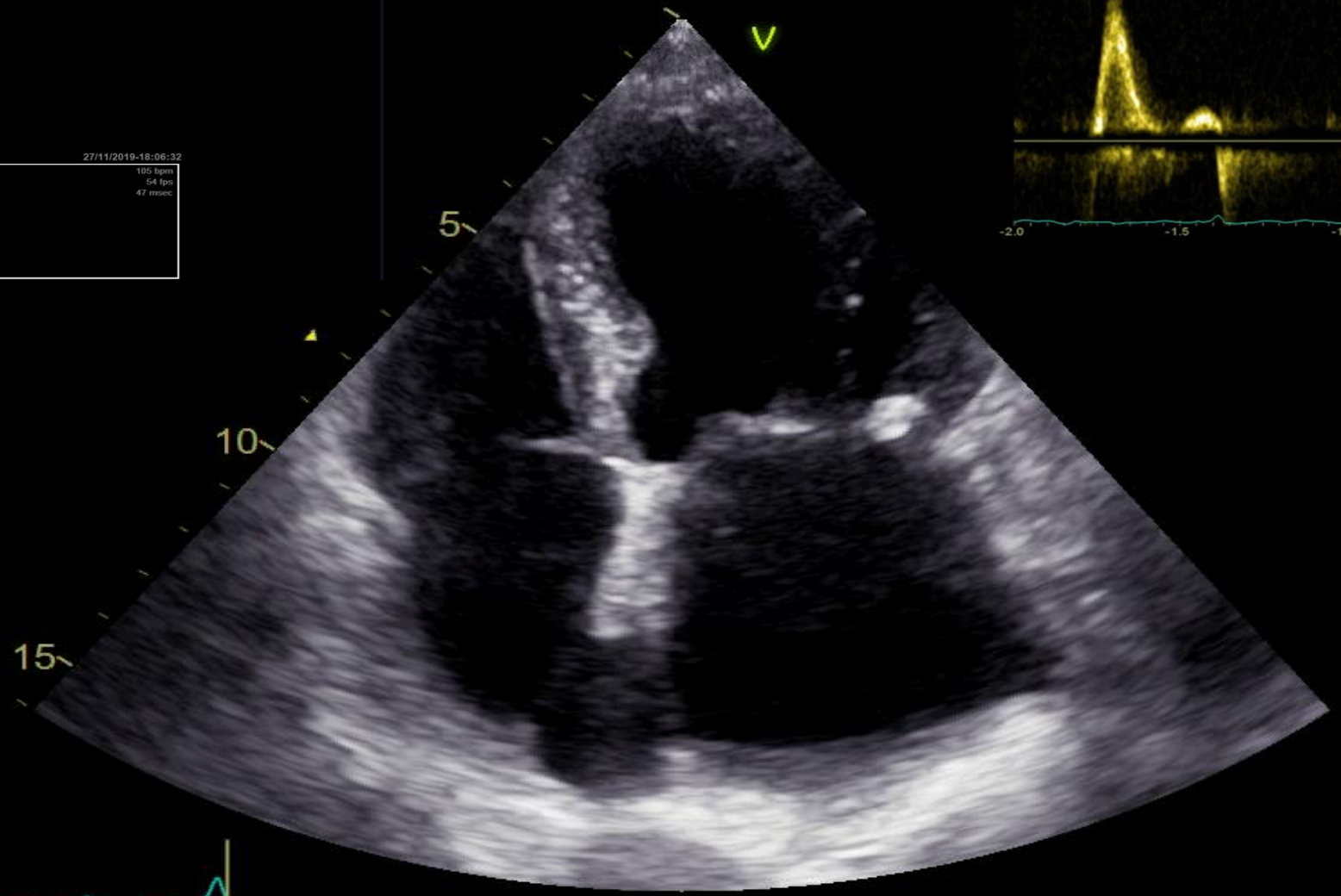


ECHOCARDIOGRAPHY – Restrictive phenotype



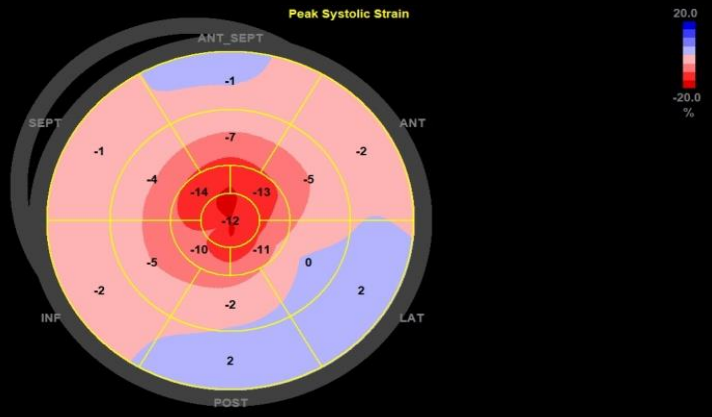






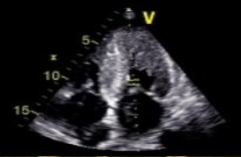
66
166:220 HR

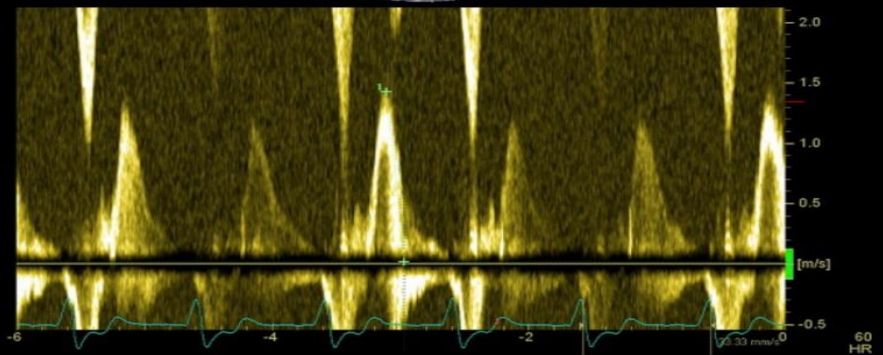
ECHOCARDIOGRAPHY – Hypertrophic phenotype

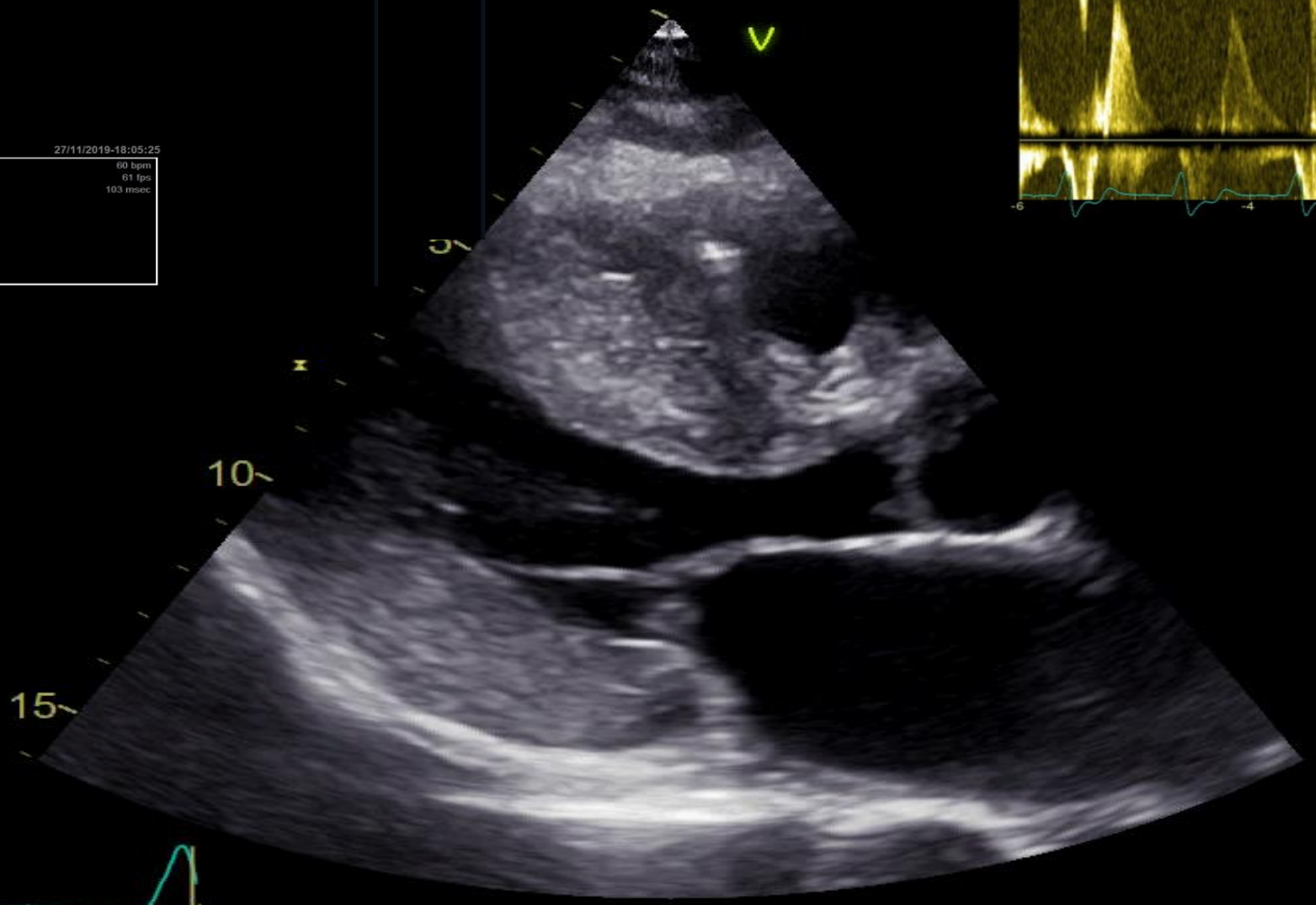


27/11/2019-18:05:25

GLPS_LAX	-7.2 %	HR_ApLAX	60 bpm
GLPS_A4C	-5.4 %	FR_min	61 fps
GLPS_A2C	-6.0 %	PSD	103 msec
GLPS_Avg	-6.2 %		
AVC_AUTO	230 msec		

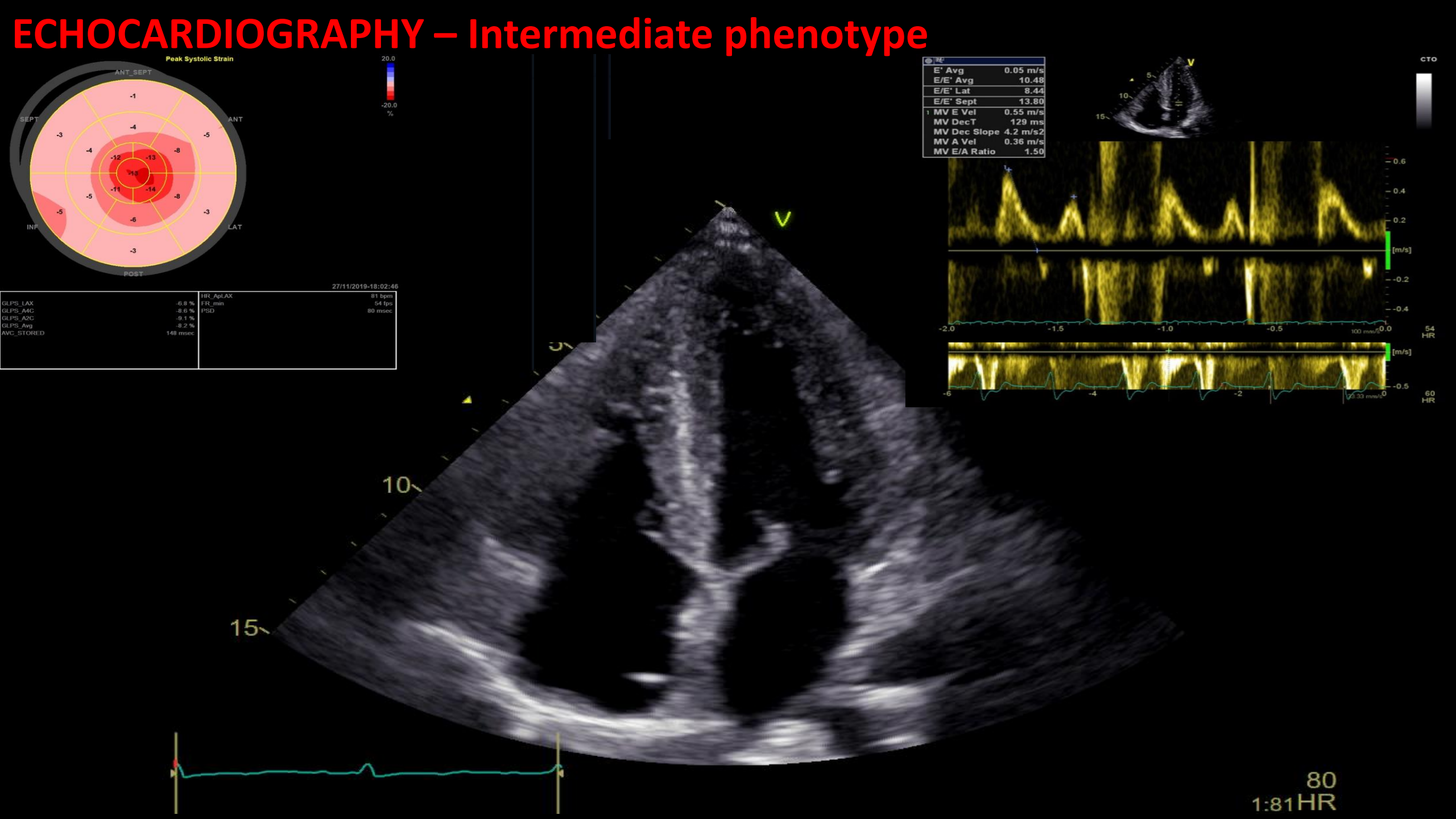


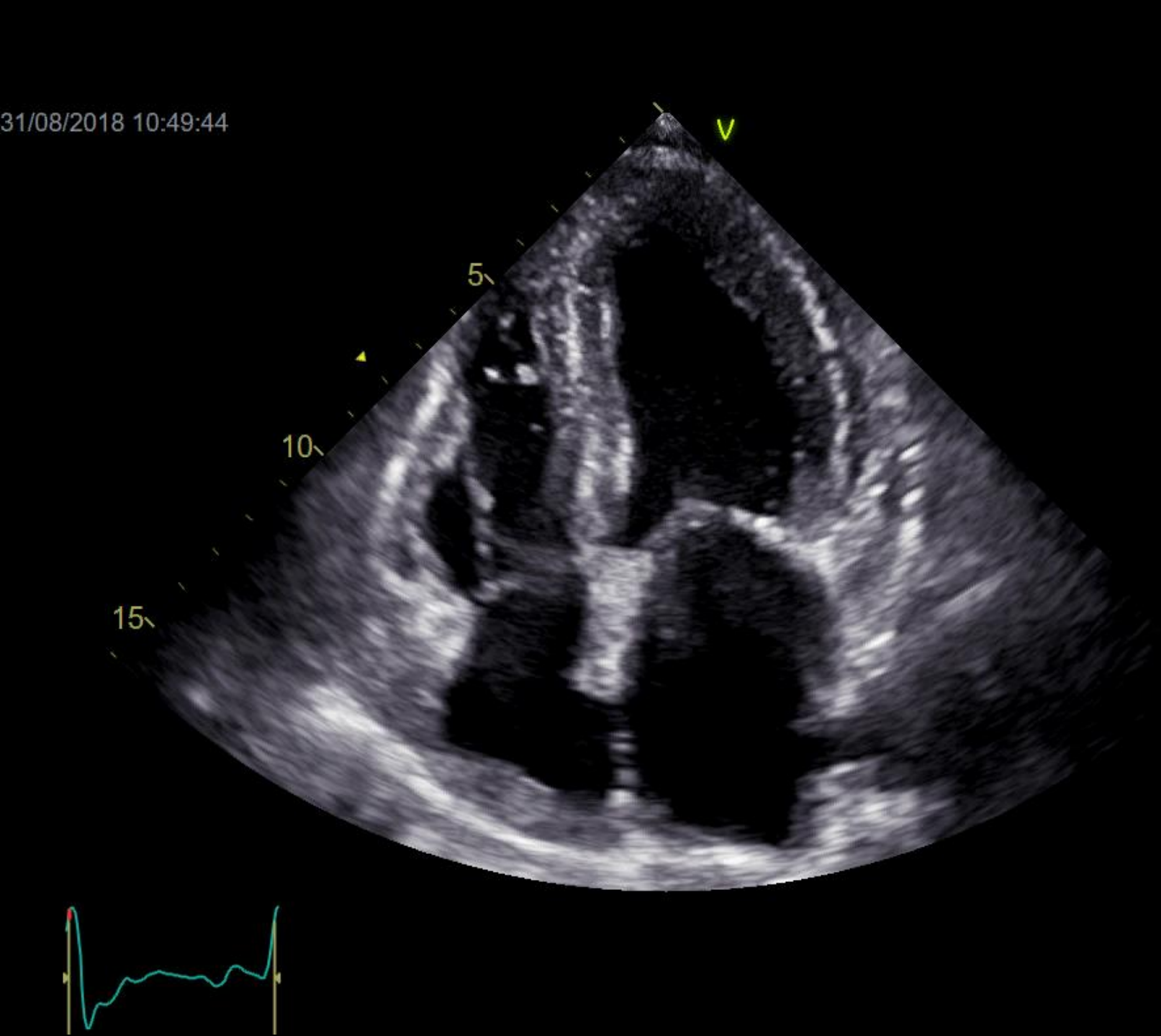




60
65:126 HR

ECHOCARDIOGRAPHY – Intermediate phenotype





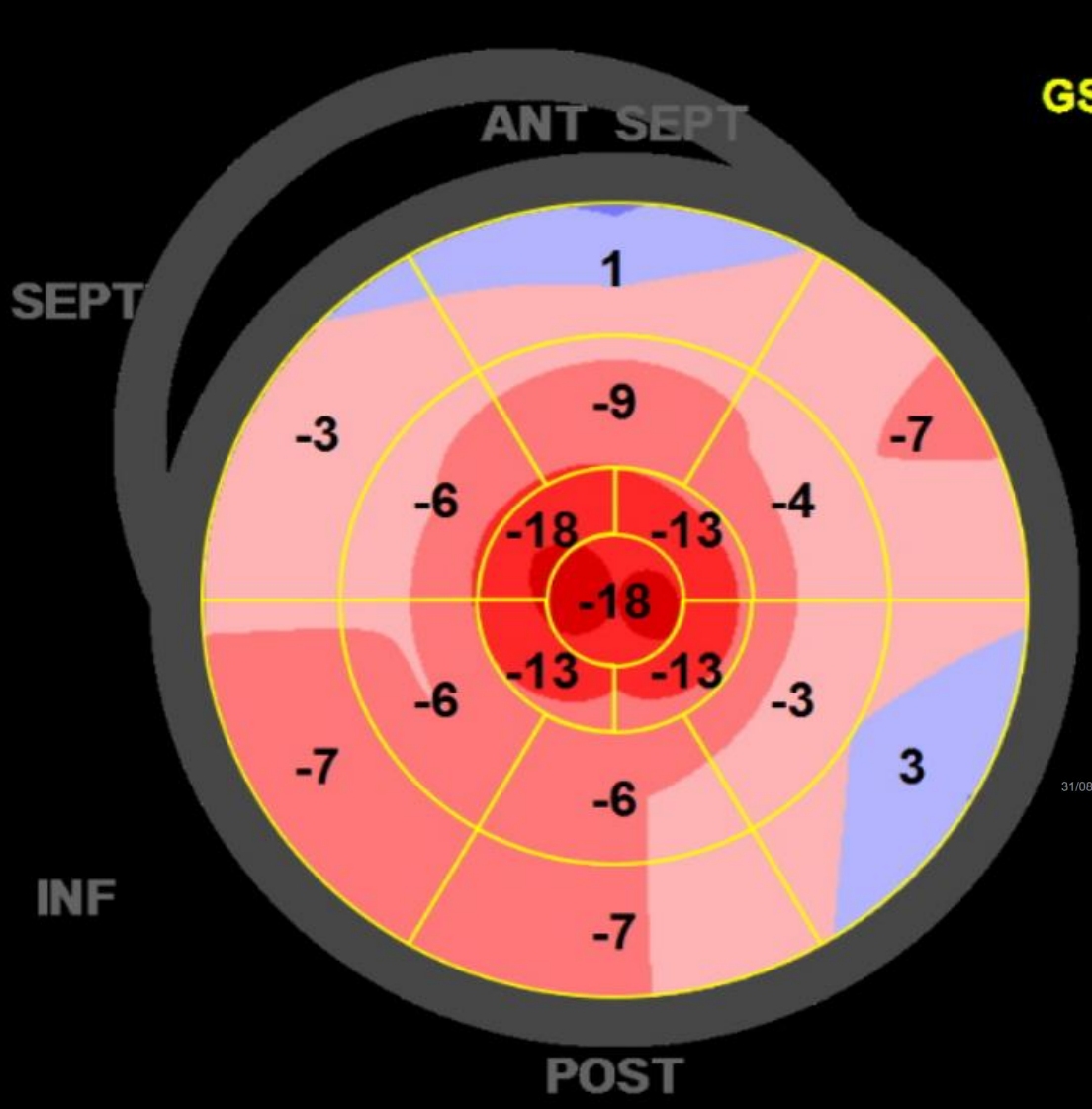
First-level evaluation

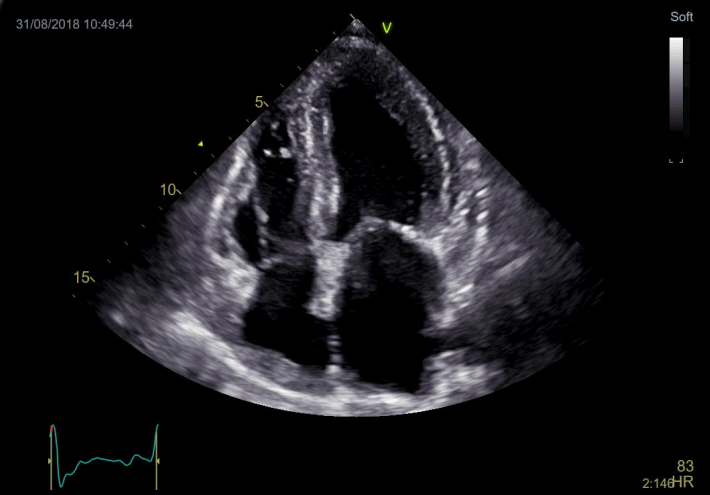
Imaging first

Symmetrical LVH

Preserved LVEF

(until the latest stages of disease progression)





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Imaging first

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Preserved LVEF

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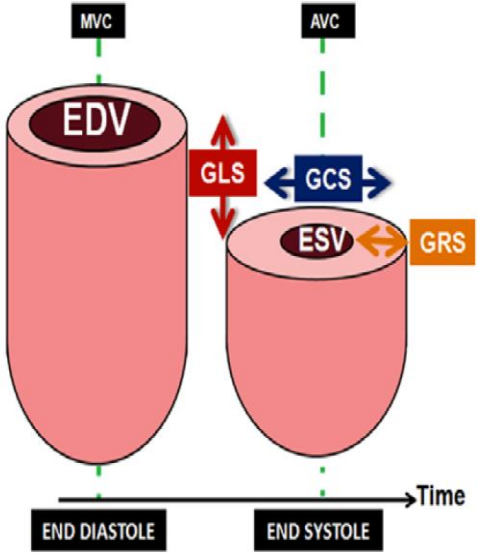
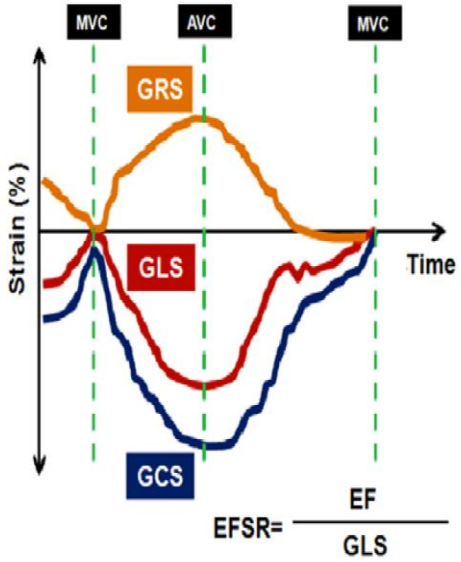
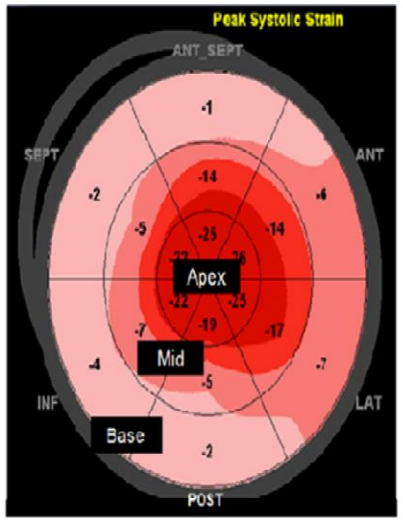
Early reduction LS in basal regions with basal-apex gradient

(Apical sparing pattern)

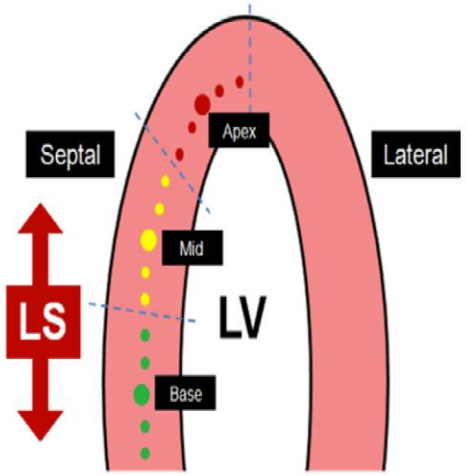
ECHOCARDIOGRAPHY







RELAPS= Average Apical LS / Sum of the average Basal and Mid LS



SAB= Apical septal LS / Basal septal LS

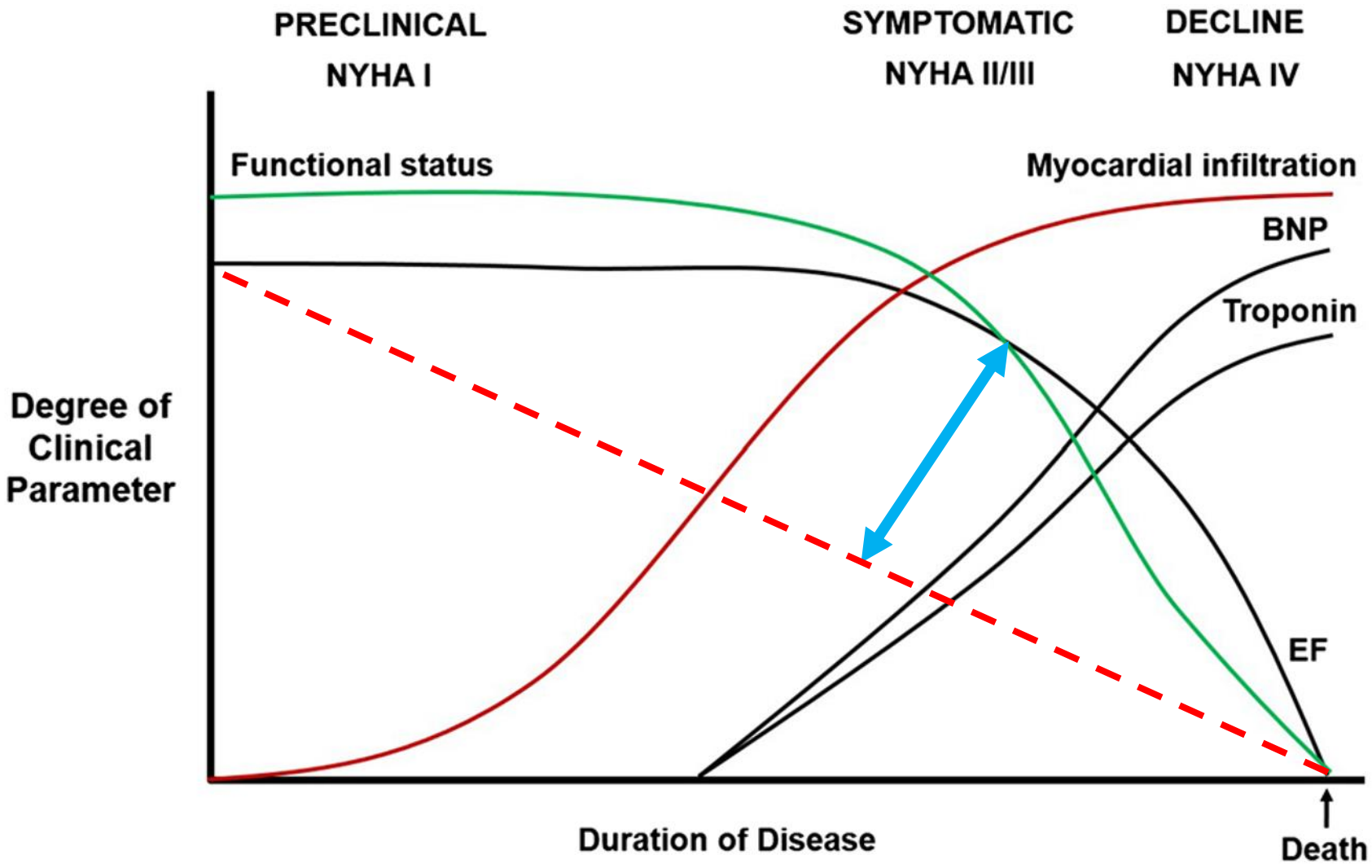
Traditional deformation parameters

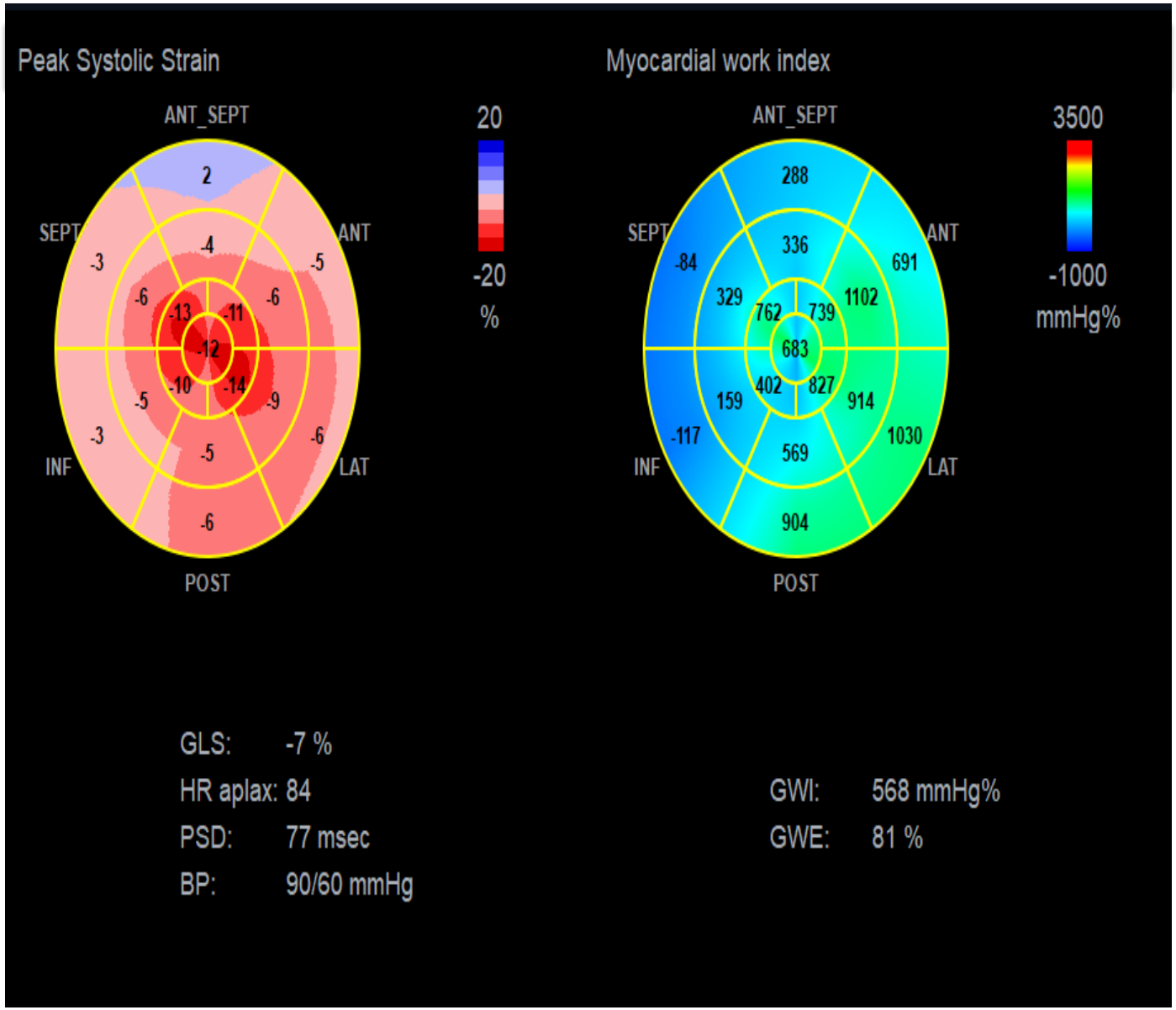
GLS, Global Longitudinal Strain
GCS, Global Circumferential Strain
GRS, Global Radial Strain
Torsion

Novel deformation parameters

EFSR, EF/Strain ratio
RELAPS, Relative Apical Sparing
SAB, Septal Apical-to-Basal ratio

Amyloidosis diagnosis





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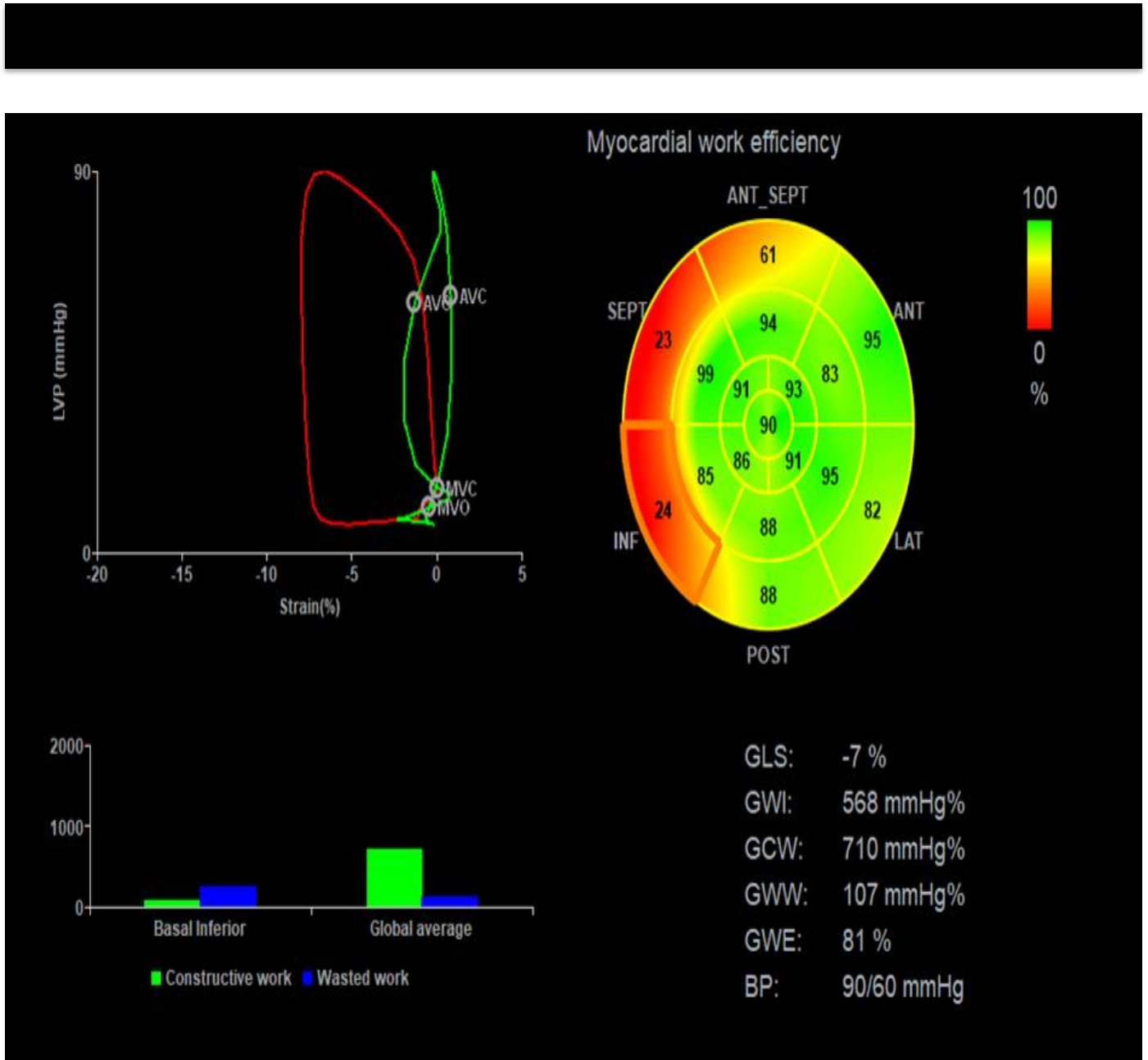
(until the latest stages of disease progression)

Early reduction LS in basal regions with basal-apex gradient

(Apical sparing pattern)

Reduced MW in regions of maximal infiltration

(mid-basal segments)



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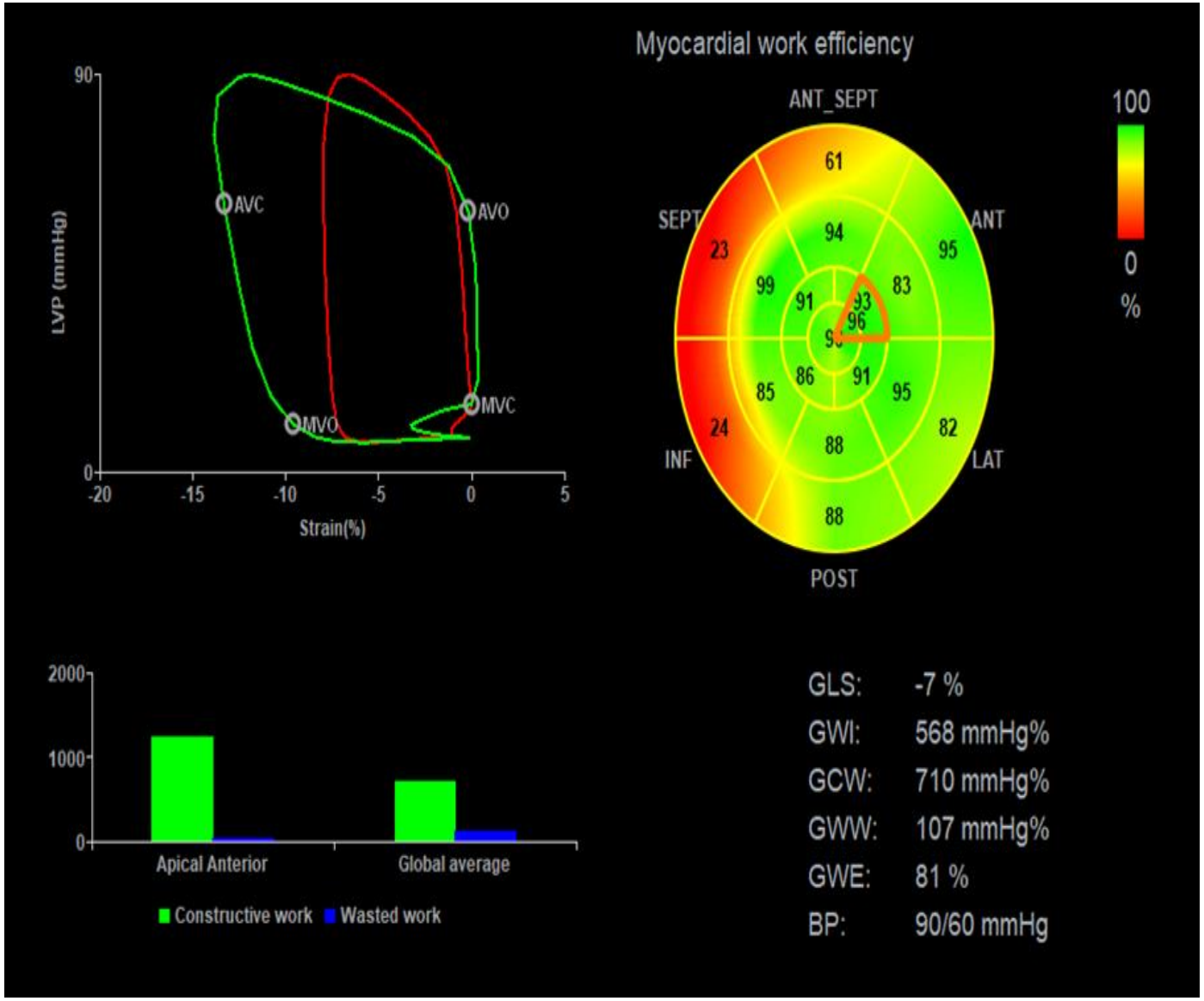

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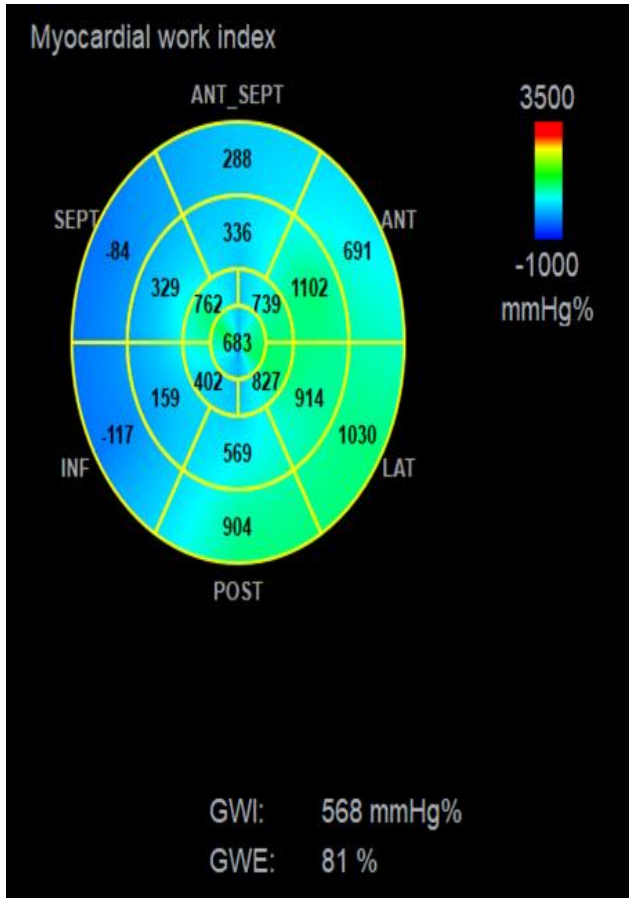
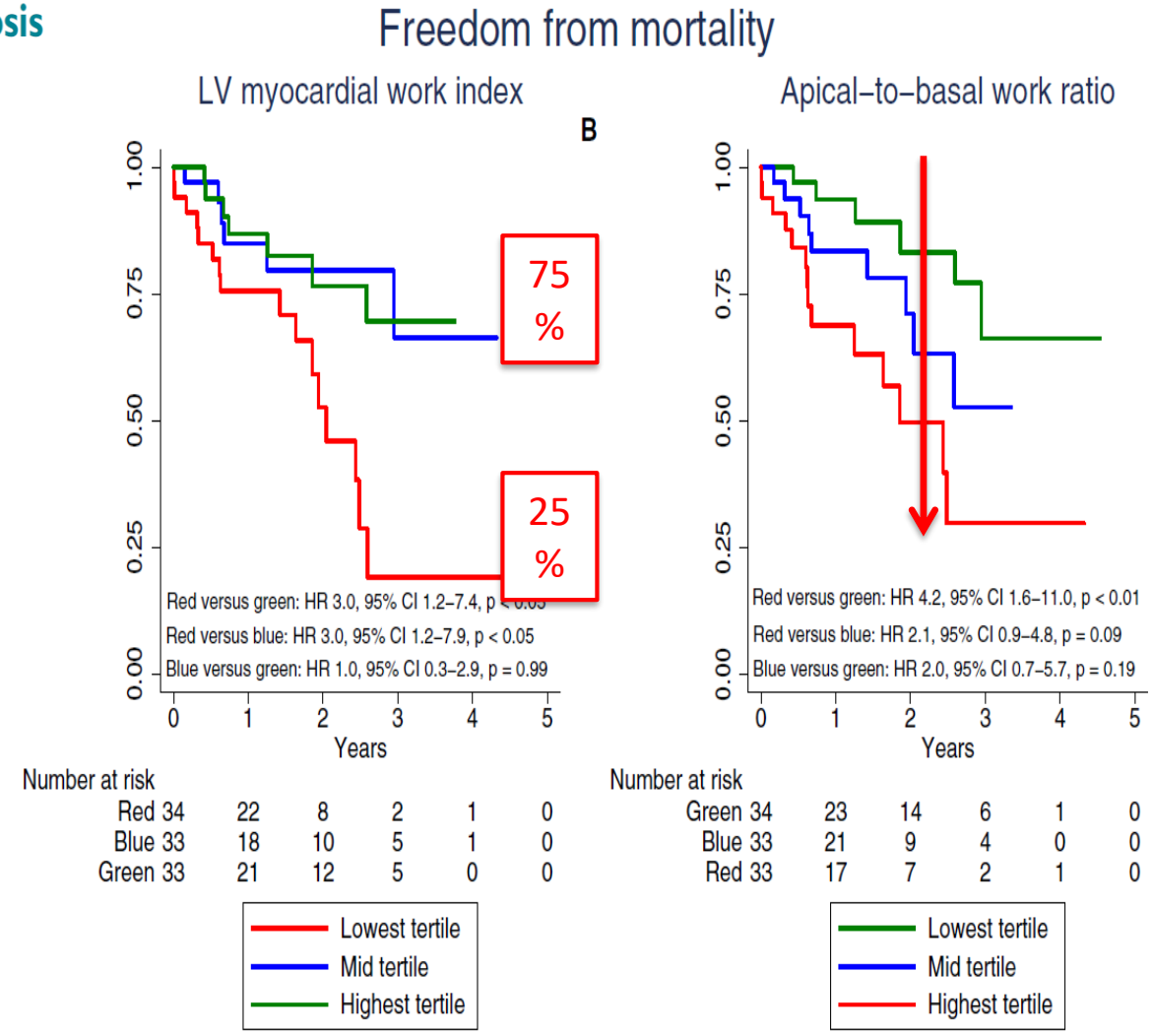
(mid-basal segments)

Amyloidosis diagnosis

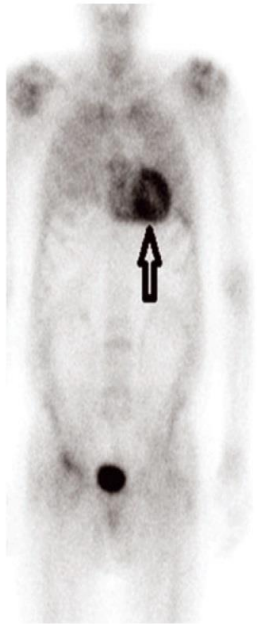
Prognostic implications of left ventricular myocardial work indices in cardiac amyloidosis

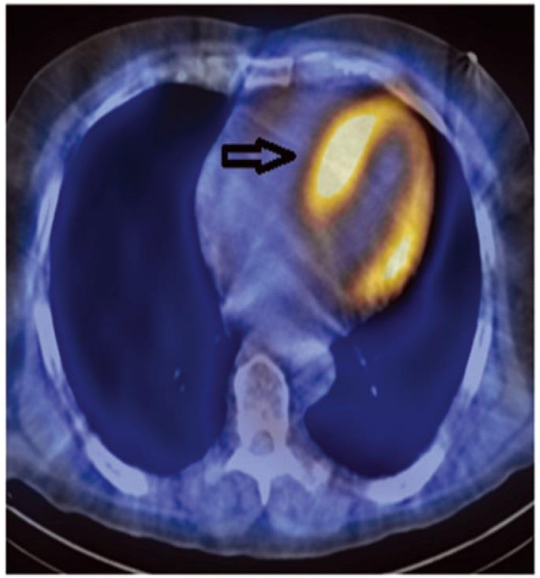
Tor Skibsted Clemmensen [1]*, Hans Eiskjær[1], Bertil Ladefoged[1], Fabian Mikkelsen[1], Jens Sørensen[2,3], Sven-Olof Granstam[4], Sara Rosengren[4], Frank A. Flachskampf [4,5], and Steen Hvitfeldt Poulsen [1],





Nuclear Scintigraphy





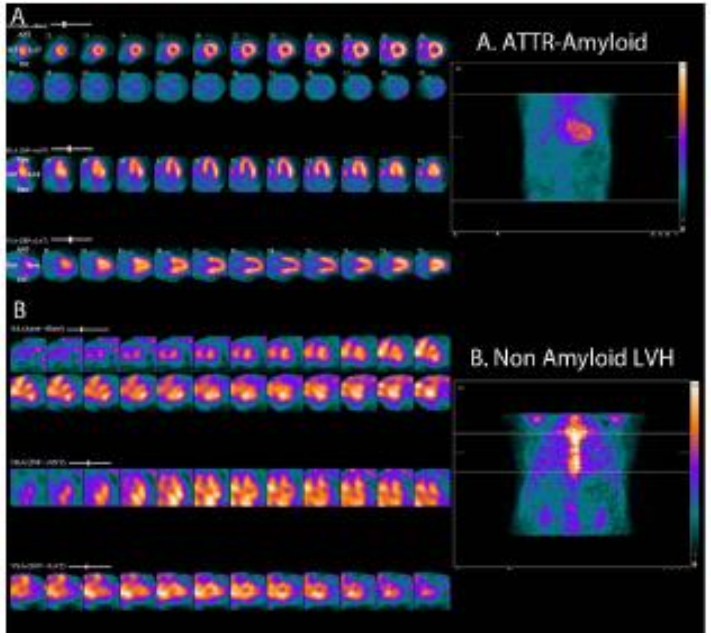


Table 3. Sensitivity and Specificity of Radionuclide 'Bone' Scintigraphy Compared With EMB Histology

Positive Radionuclide Scan vs Cardiac Amyloid Deposits (n=374)			
	Positive Scan (Grade 1, 2, or 3), n	Negative Scan (Grade 0), n	Sensitivity and Specificity (CI), %
Cardiac amyloid deposits	289	38	88 (84–92) sensitive*
No cardiac amyloid deposits	6	41	87 (73–95) specific
	Positive Scan (Grade 1, 2, or 3), n	Negative Scan (Grade 0), n	
Cardiac ATTR amyloid deposits	259	2	>99 (97–100) sensitive
No cardiac ATTR amyloid deposits	36	77	68 (59–77) specific
	Grade 2/3 Scan, n	Grade 0/1 Scan, n	
Cardiac ATTR amyloid deposits	238	23	91 (87–94) sensitive
No cardiac ATTR amyloid deposits	15	98	87 (79–92) specific

CI indicates confidence interval; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; EMB, endomyocardial biopsy; HDMP, hydroxymethylene diphosphonate; and PYP, pyrophosphate.

*The sensitivity of a positive radionuclide scan for detecting cardiac amyloid deposits of any type is likely to be falsely high owing to the high proportion of patients with ATTR amyloid in the sample.

Cappelli, F. et al J Nucl Cardiol. 2017

Cardiac MRI

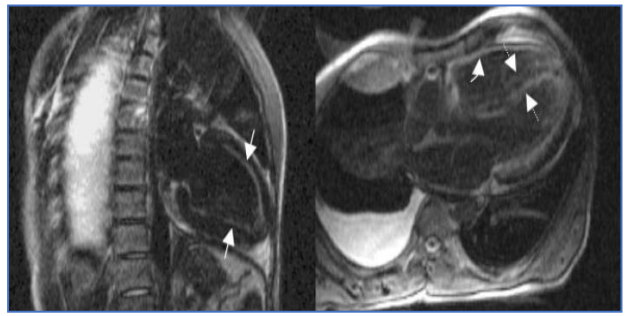
Standard CMR sequences for Cardiac Amyloidosis

Cine images in short and long axis view

LV FUNCTION, RWT, MASS

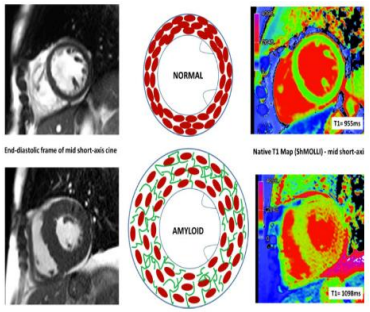
Late Gadolinium Enhancement imaging in short and log-axis view

LGE PATTERN



Optimal myocardial inversion time assessed 4 min after injection of gadolinium

MYOCARDIAL NULLING PATTERN



T1 Mapping native (precontrast) and post-gadolinium injection to calculate ECV

T1 TIME & ECV

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.

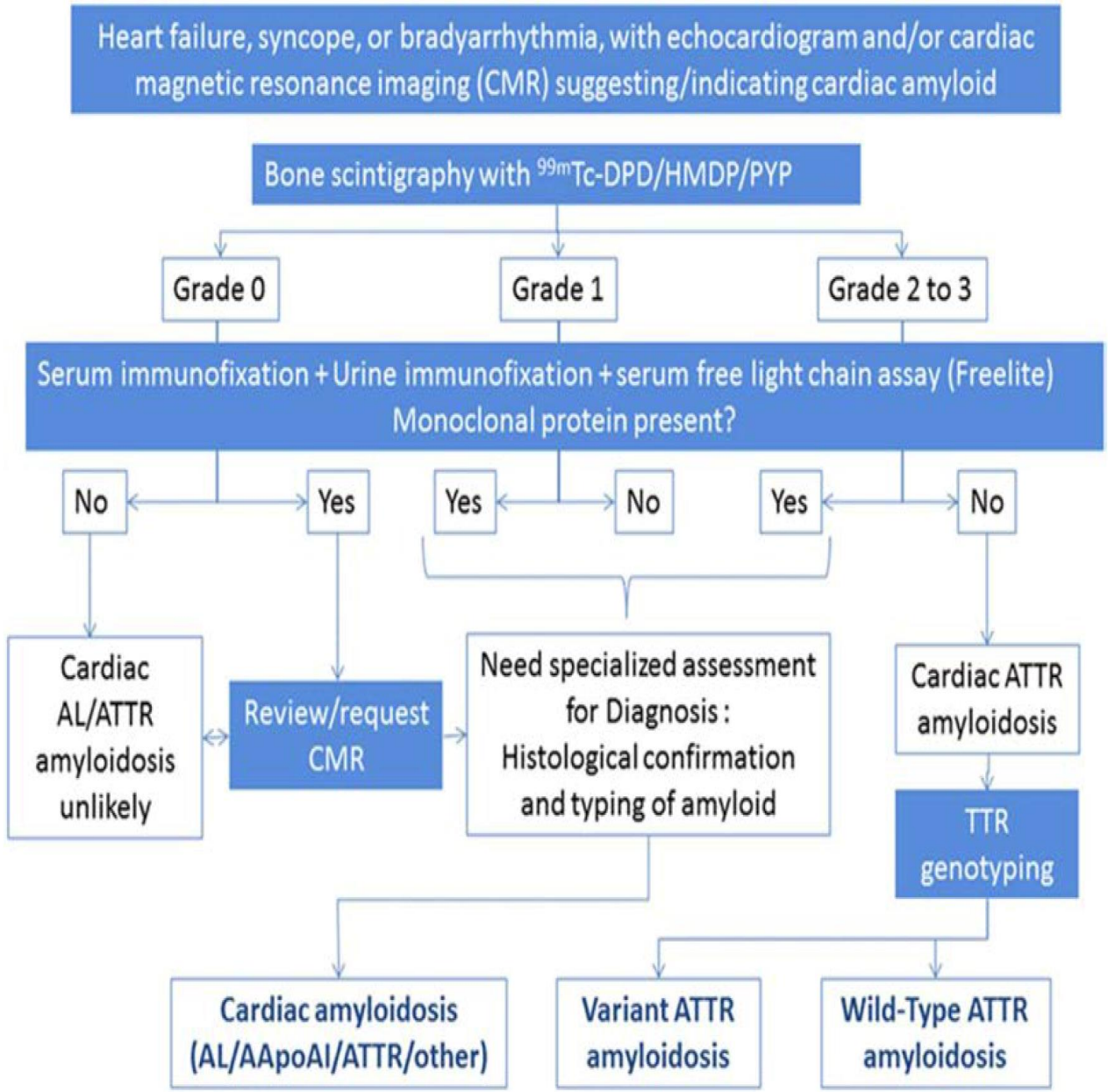
MRI pattern of CA

Table 2

Typical cardiac magnetic resonance (CMR) imaging features of cardiac amyloidosis

Parameters	Comments
Characteristic morphological features of cardiac amyloidosis/restrictive cardiomyopathy as listed in Table 1	Better resolution images than echocardiography No limitation of difficult echo windows
Left ventricular LGE	Diffuse and subendocardial LGE of the LV myocardium is more common than patchy focal delayed enhancement May be an early feature of cardiac involvement compared to increased wall thickness
Atrial LGE and function	A characteristic feature of cardiac amyloidosis Atrial function can be studied well with CMR
T1 mapping	Subendocardial T1 relaxation time may be shortened in cardiac amyloidosis This is an early feature of cardiac amyloid involvement
Extracellular volume estimation based on T1 mapping and hematocrit measures	Extracellular volume expansion may permit an early diagnosis of cardiac amyloid even before overt left ventricular LGE

Diagnostic Work-Up



OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.

Usefulness of main tests

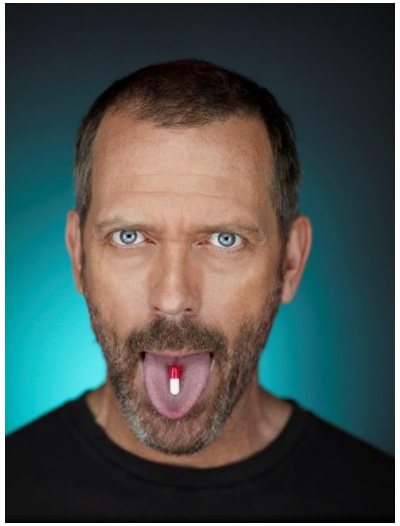
Table 4 Usefulness of main tests in diagnosis and management of cardiac amyloidosis

Work-up stage	Echocardiogram	Magnetic resonance	Bone tracer scintigraphy	NT-proBNP and troponins
Suspicion	+++	++	+ (ATTR)	+
Definite diagnosis	+	++	+++ (ATTR)	–
Aetiological diagnosis	–	+?	+++	–
Early diagnosis	+	?	++ (ATTR)	+?
Functional evaluation	+++	++	+ (MIBG)	–
Prognostic stratification	++	+	+	+++
Amyloidotic burden	–	++ ?	+?	–
Response to therapy	±	?	?	+++ (AL)

MIBG metaiodobenzylguanidine

Therapy (HFpEF)

1. No ACE i(ARB,ARNI)
2. No BB (low CO)
3. No CC (tox dir)
4. No digitale(tox,iperacc)
5. Ni diuretici (loop,thiaz,ma)
6. Warfarin/NAO
7. AICD/PMK (GL)
8. Midodrine (for OI)
9. Gabapentin,oppioides (periph.neuropathy)



10. Transplant (liver/heart)

CA as confounder in HFpEF trials

JACC: HEART FAILURE

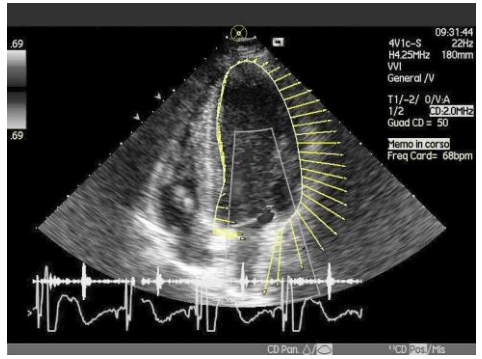
PUBLISHED BY ELSEVIER

Letters

TO THE EDITOR

Cardiac Amyloidosis as a Potential Confounder in Heart Failure With Preserved Ejection Fraction Trials

diagnosed. Therefore, we postulate that inadvertent inclusion of cardiac amyloidosis in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) (4) and I-PRESERVE trials represents an alternative explanation of the lack of apparent therapeutic response in HFpEF patients with higher natriuretic



Marked patient and pathophysiological heterogeneity present unique problems to clinical HFpEF trials. Recruitment criteria for HFpEF trials should be careful to exclude patients with cardiac amyloidosis, and other confounding causes of "HFpEF" that would never respond to the therapy under evaluation.

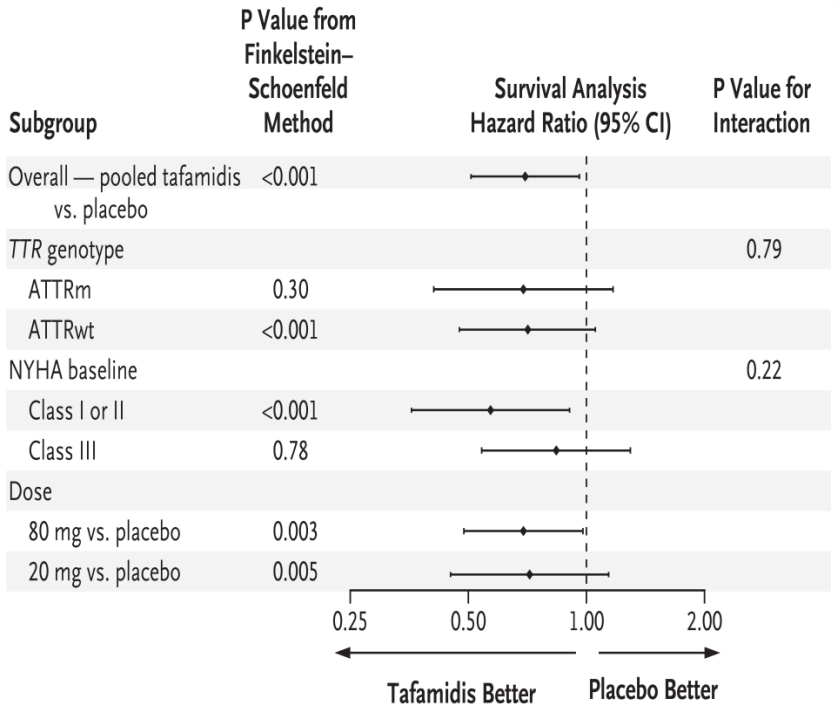
THERAPY

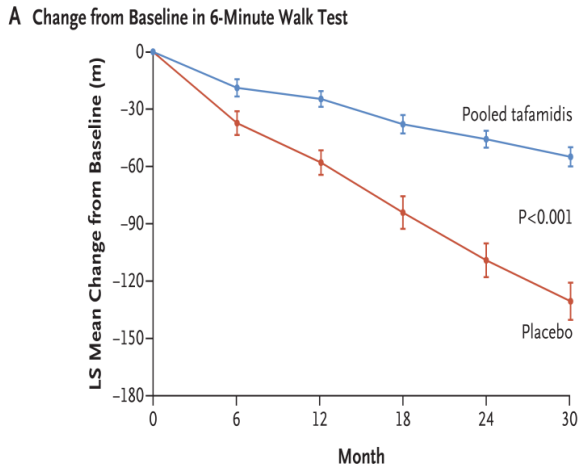
The NEW ENGLAND JOURNAL of MEDICINE

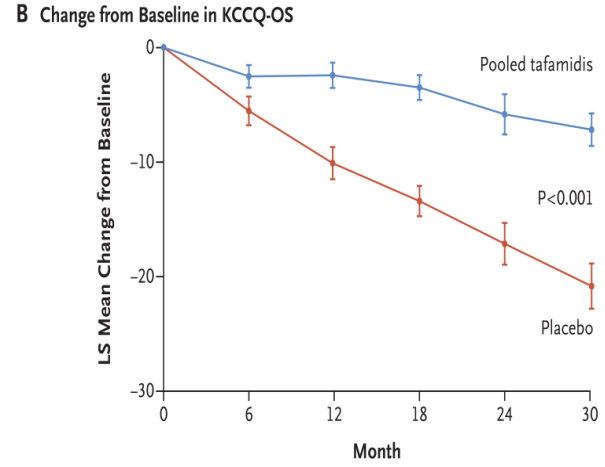
ORIGINAL ARTICLE

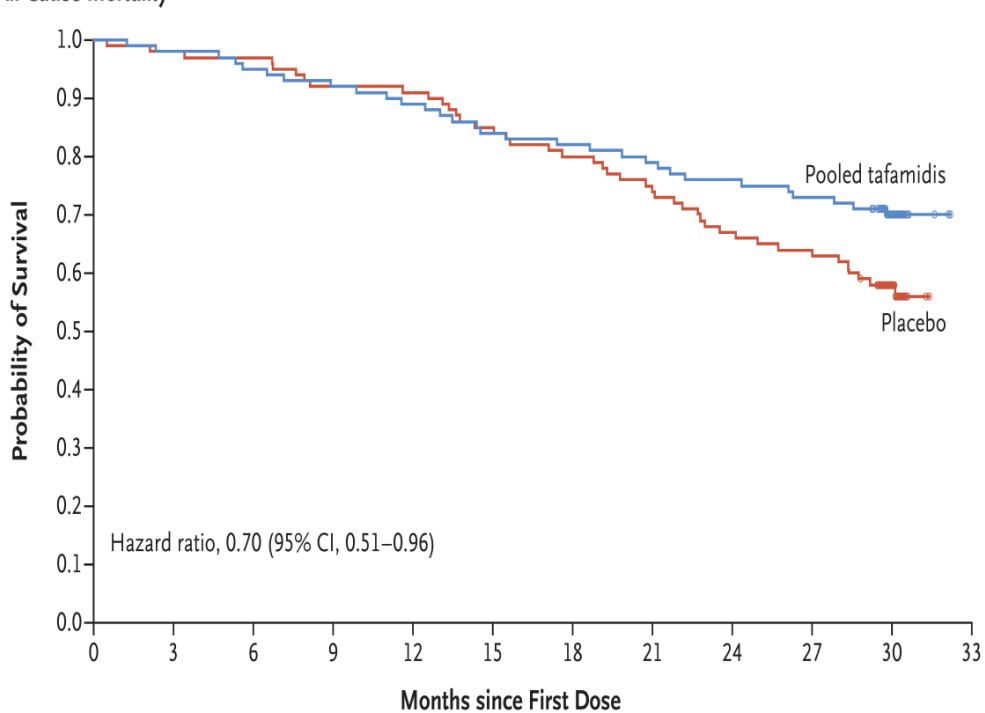
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D.,
Balarama Gundapaneni, M.S., Perry M. Elliott, M.D.,









Take Home Message

Rare things are rare
if you don't look for them
(P. Elliott)
If you don't think of it you won't diagnose it
(C.Rapezzi)

Echo in myocardiopathies should be as complete as possible
(S.Severino)