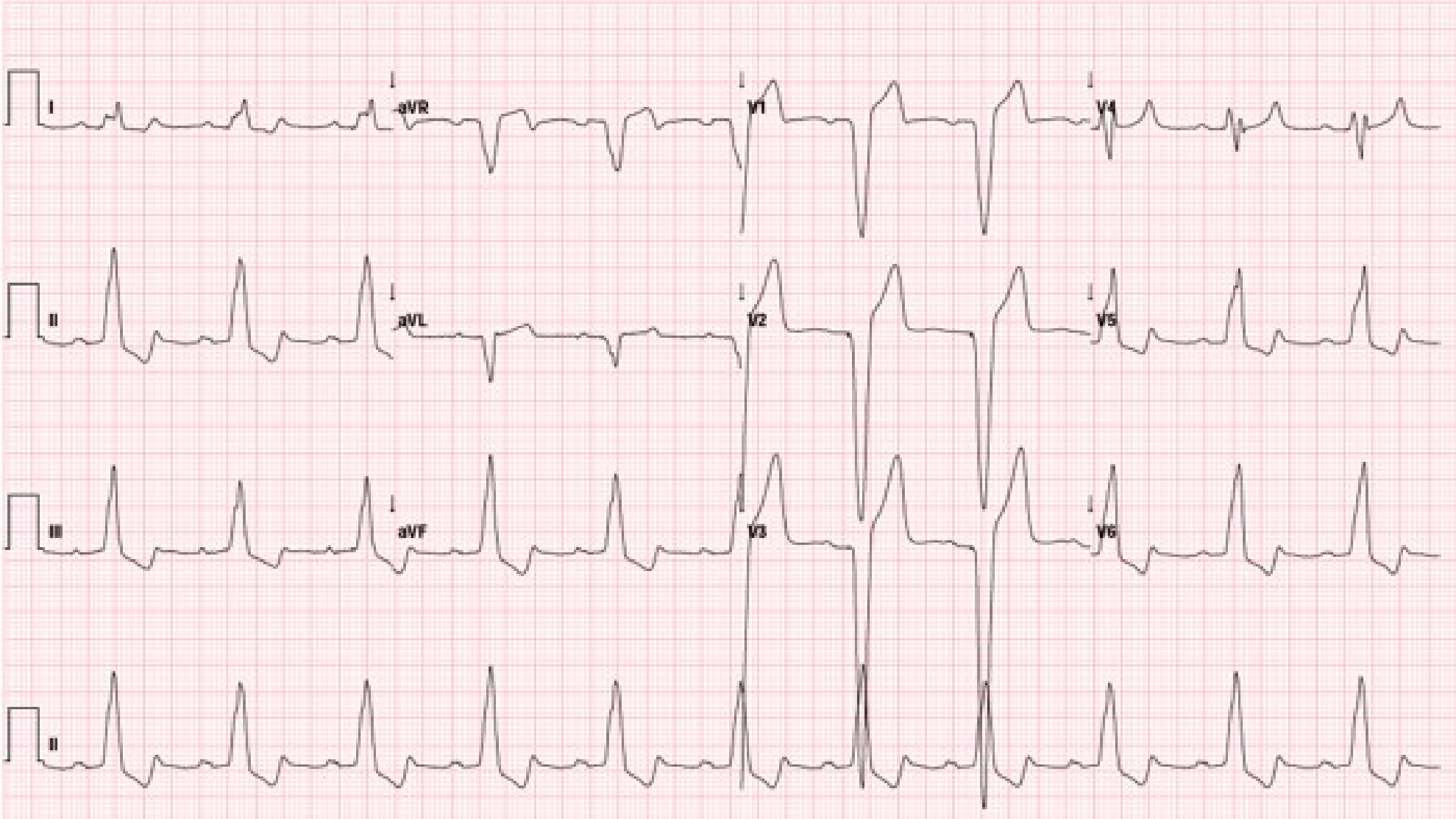
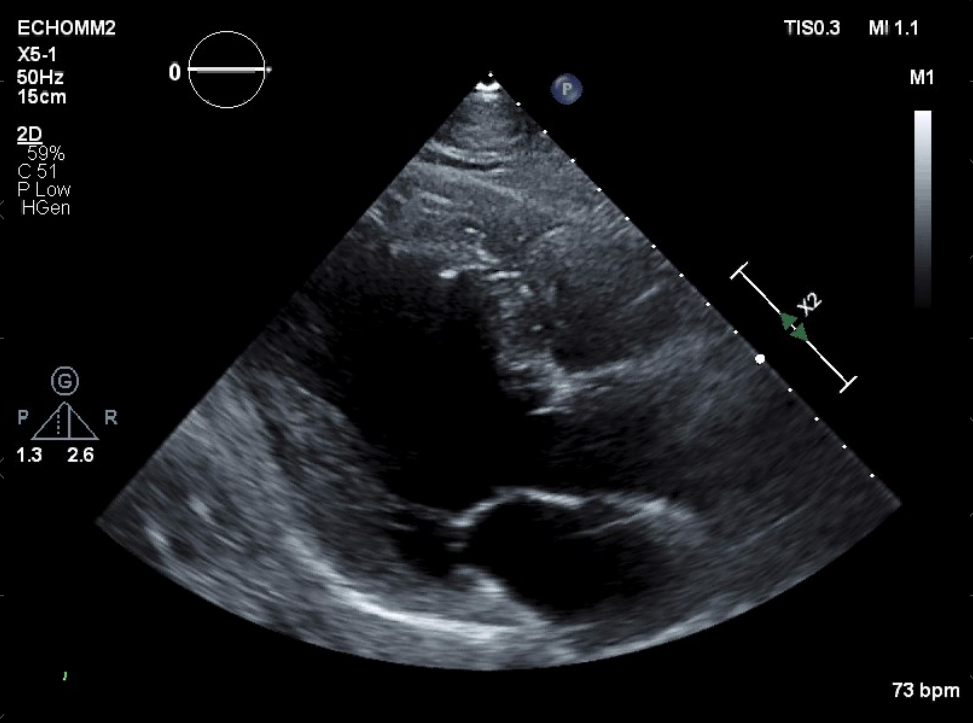
Thickened LV with Dysfunction

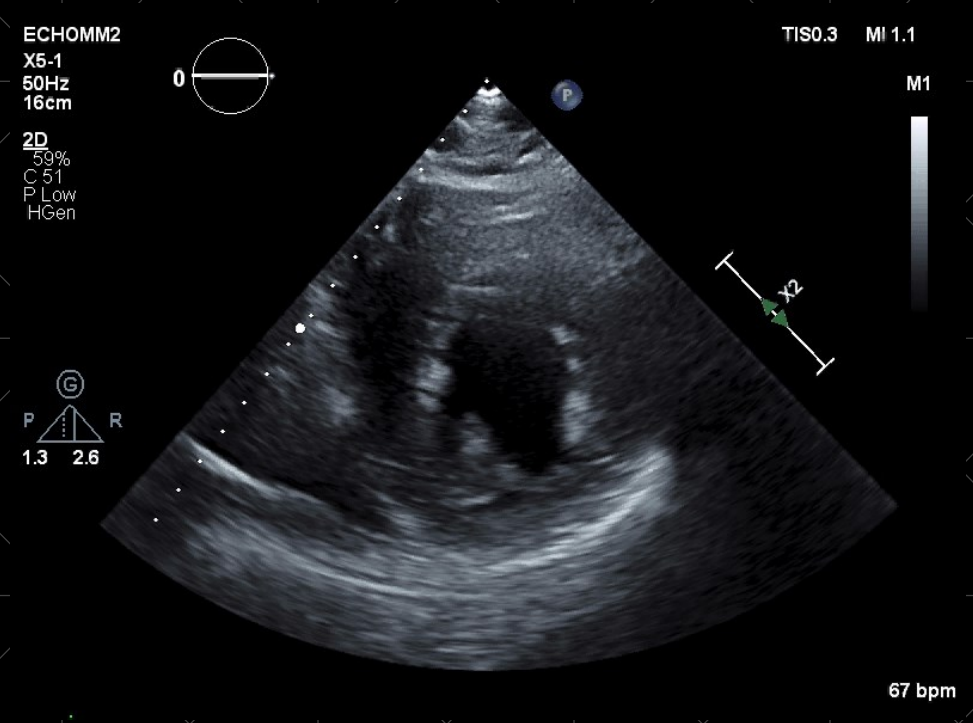
פרופ' רונן בארי
מנהל היחידה לקרדיולוגיה אבחנתית
מערך הלב
ביהח האוניברסיטאי "הדסה" עין כרם

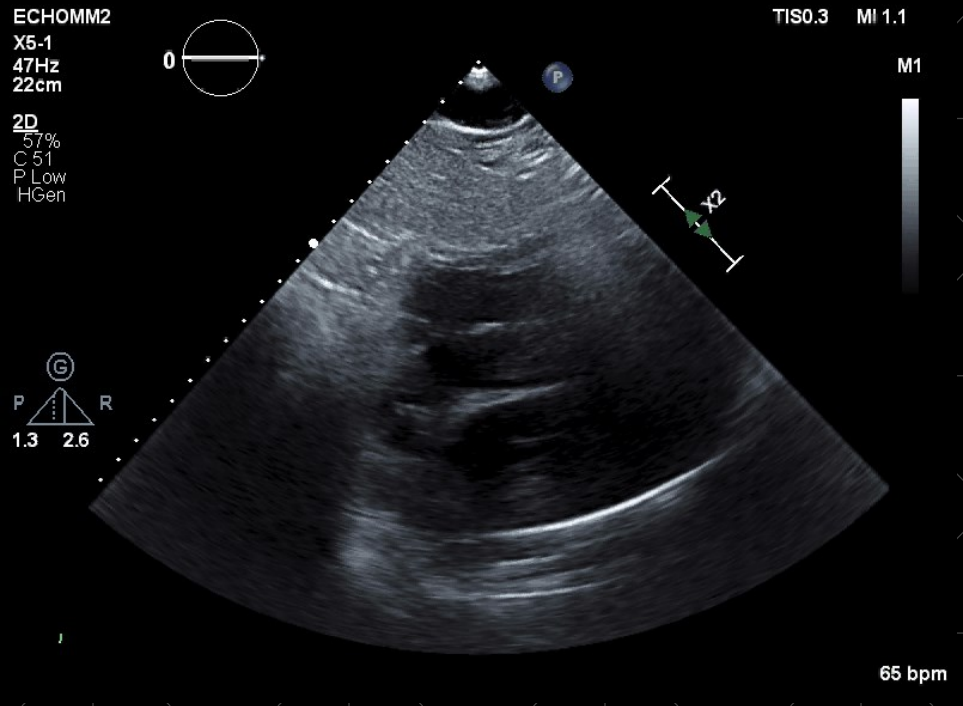
בן 50 עם חסם עלייתי חדרי ואי-ספיקת לב

- בן 50, גמלאי צה"ל. ברקע יתר לחץ דם, PTSD. מטופל בקנביס. מעשן כבד. אין נסיעות לחו"ל לאחרונה.
- משפחה: מוצא תימני. אם- בת כ-70, אס"ק לב עם תפקוד ססטולי ירוד, נוירופתיה פריפרית, פרוטאינוריה. אב- נפטר בגיל 61 עם CRF. שני דודים מצד האם- קרדיומיופתיה עם דפיברליטור. אח- מושתל קוצב.
- מטופל ב RAMIPRIL
- בגיל 47- CAVB עם סינקופה. הושתל קוצב DDD. אקו מדווח כתקין.
- פניות חוזרות לחדר מיון באזור מגוריו עם גודש ראתי. אקו חוזר עם מקטע פליטה של 30%-40% ללא פרטים נוספים. צנתור כלילי תקין. הוסף טיפול באלדקטון.
- NT-PRO BNP =740, No monoclonal light chains,


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


ECHOMM2
X5-1
50Hz
15cm
2D
59%
C 51
P Low
HGen
TIS0.3 MI 1.1
M1
X2
P R
1.3 2.6
73 bpm


ECHOMM2
X5-1
50Hz
16cm
2D
59%
C 51
P Low
HGen
TIS0.3 MI 1.1
M1
X2
P R
1.3 2.6
67 bpm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X5-1
47Hz
22cm
2D
57%
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P Low
HGen
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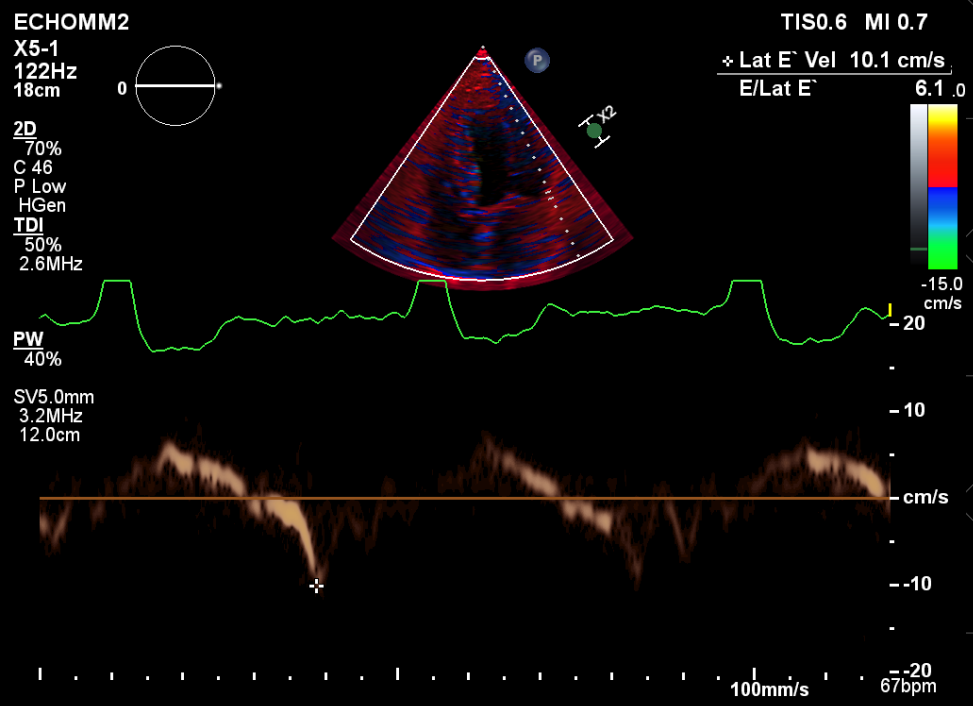
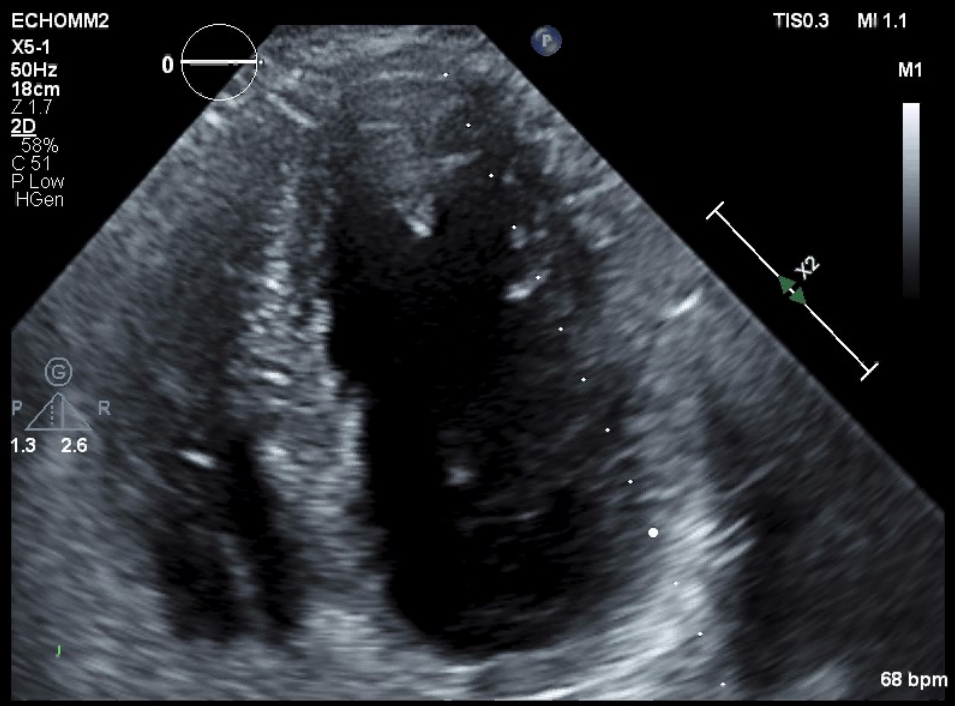
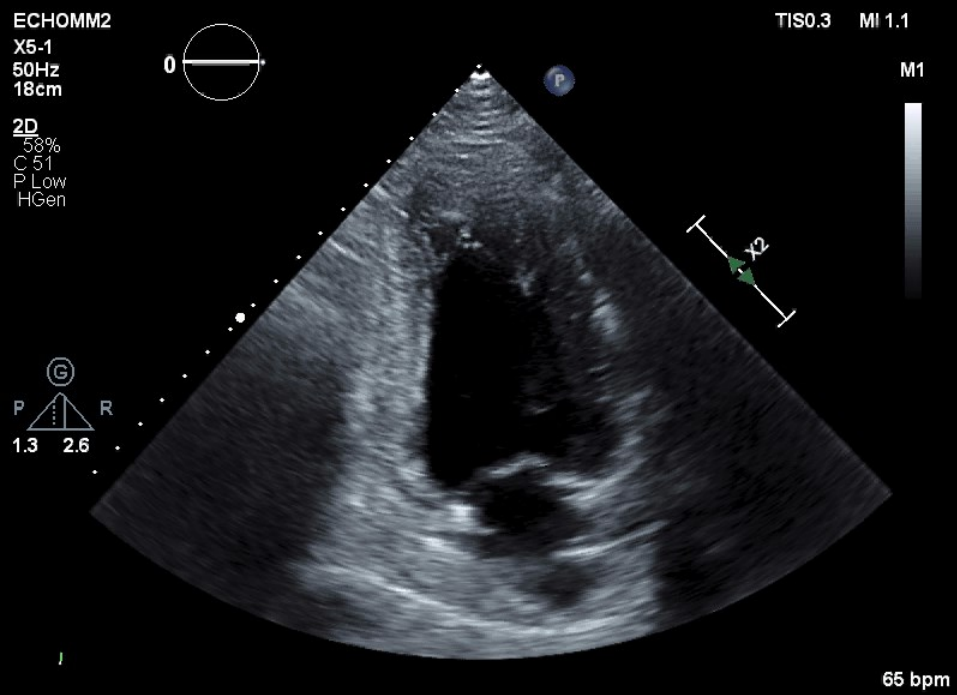
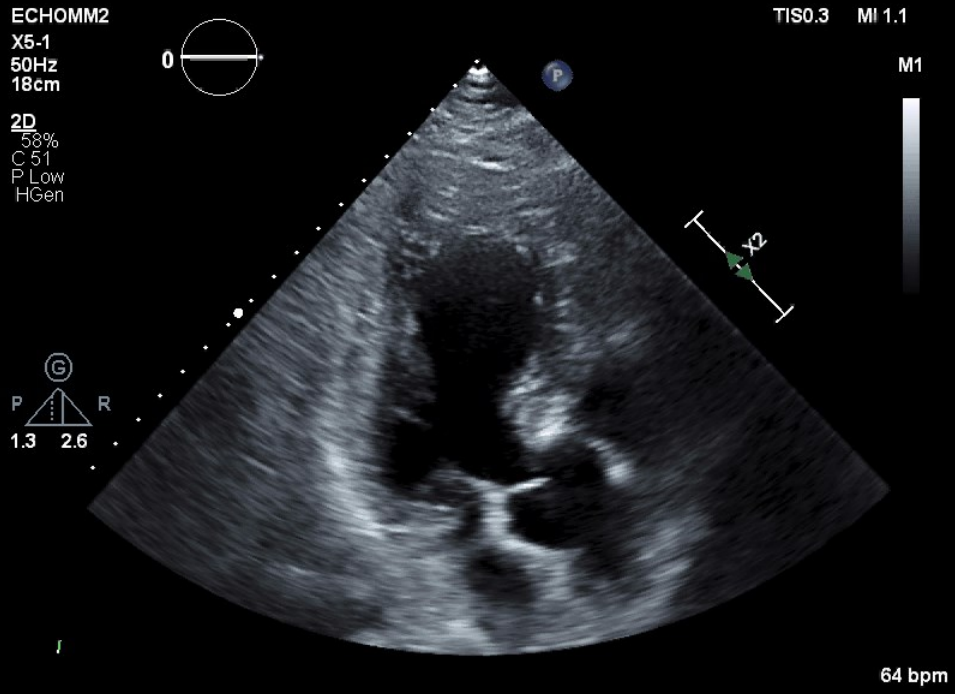
M1
X2
P R
1.3 2.6
65 bpm


ECHOMM2
X5-1
122Hz
18cm
2D
70%
C 46
P Low
HGen
TDI
50%
2.6MHz
PW
40%
SV5.0mm
3.2MHz
12.0cm
TIS0.6 MI 0.7
Lat E` Vel 10.1 cm/s
E/Lat E` 6.1
-15.0
cm/s
20
10
cm/s
-10
-20
100mm/s
67bpm

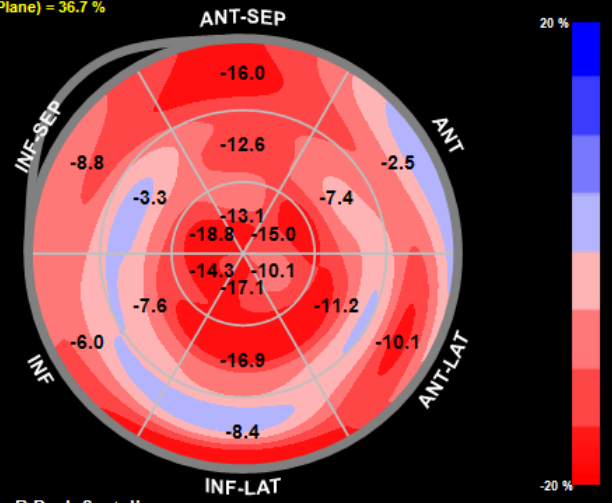






L. Strain
HR (Avg.) = 66 bpm
EDV (LV Bi-Plane) = 211.8 ml
ESV (LV Bi-Plane) = 134.1 ml
EF (LV Bi-Plane) = 36.7 %

* : HR Variation > 10%
Yellow: Accepted
Red: Accept Pending



R.Peak Systolic

LV AP4 Endo Peak L. Strain = -9.5 %
LV AP3 Endo Peak L. Strain = -12.7 %
LV AP2 Endo Peak L. Strain = -7.9 %
LV Global Endo Peak L. Strain = -10.1 %

LV AP4 Endo Peak L. Time SD = 64.8 ms
LV AP3 Endo Peak L. Time SD = 74.1 ms
LV AP2 Endo Peak L. Time SD = 60.3 ms
LV Global Endo Peak L. Time SD = 19.4 ms

Echo Predictors of Diseases in Myocardial Thickening

Summary of best discriminators for differentiation of left ventricular hypertrophy of unknown etiology

	Fabry (%)	HCM (%)	Amyloid (%)	HHD (%)
Hypertension	**0**	19	31	**100**
Orthostasis	0	12	**38**	0
Acroparesthesia or polyneuropathy	**69**	0	31	14
Hypo-/anhydrosis	**62**	0	0	0
Sokolow criteria LVH	**80**	47	**0**	33
Left bundle branch block	0	6	6	**25**
QTc duration prolongation	0	46	47	39
Severe diastolic dysfunction	38	50	56	27
Abnormal papillary muscle	8	**56**	0	0
Pericardial effusion	0	6	**38**	5

HCM = non-obstructive HCM; Amyloid = amyloidosis; HHD = hypertensive heart disease; LVH = left ventricular hypertrophy; QTc = corrected QT time.

Hoigné Ph. et al .Int J Cardiol 2006; 111(3): 413-422

Typical Echo Features of Infiltrative Cardiomyopathies

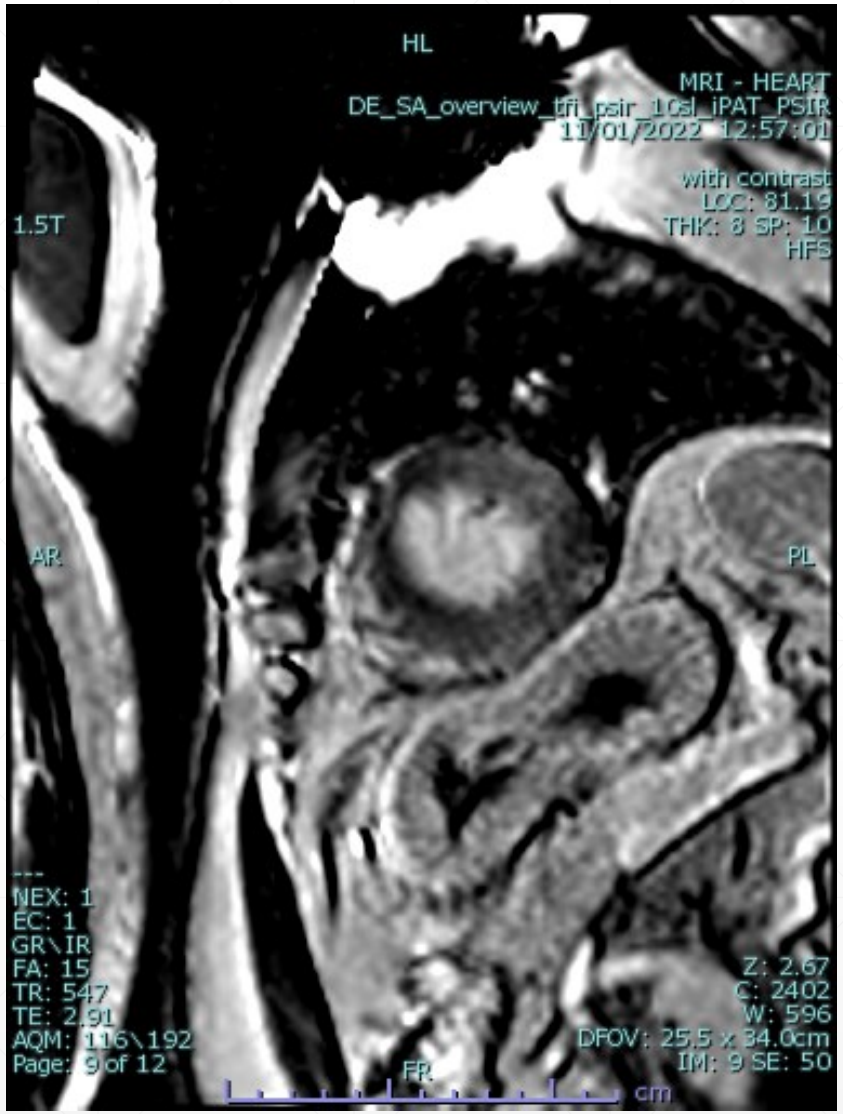
Disease	Maximal wall thickness	Systolic function	Diastolic function	Special feature	Age at onset	Causal treatment
Transthyretin-related amyloidosis (aTTR)	14 mm	Normal	Markedly reduced	Sparkling texture	>60 years	No
Fabry disease	16 mm	Normal	Slightly reduced	Prominent papillary muscle	>25 years	Yes, enzyme replacement therapy
Pompe disease	30 mm	Reduced	Reduced	Extreme biventricular hypertrophy	6 months	Yes, enzyme replacement therapy
Friedreich's ataxia	15 mm	Normal	Normal	Sparkling texture	5–40 years	No

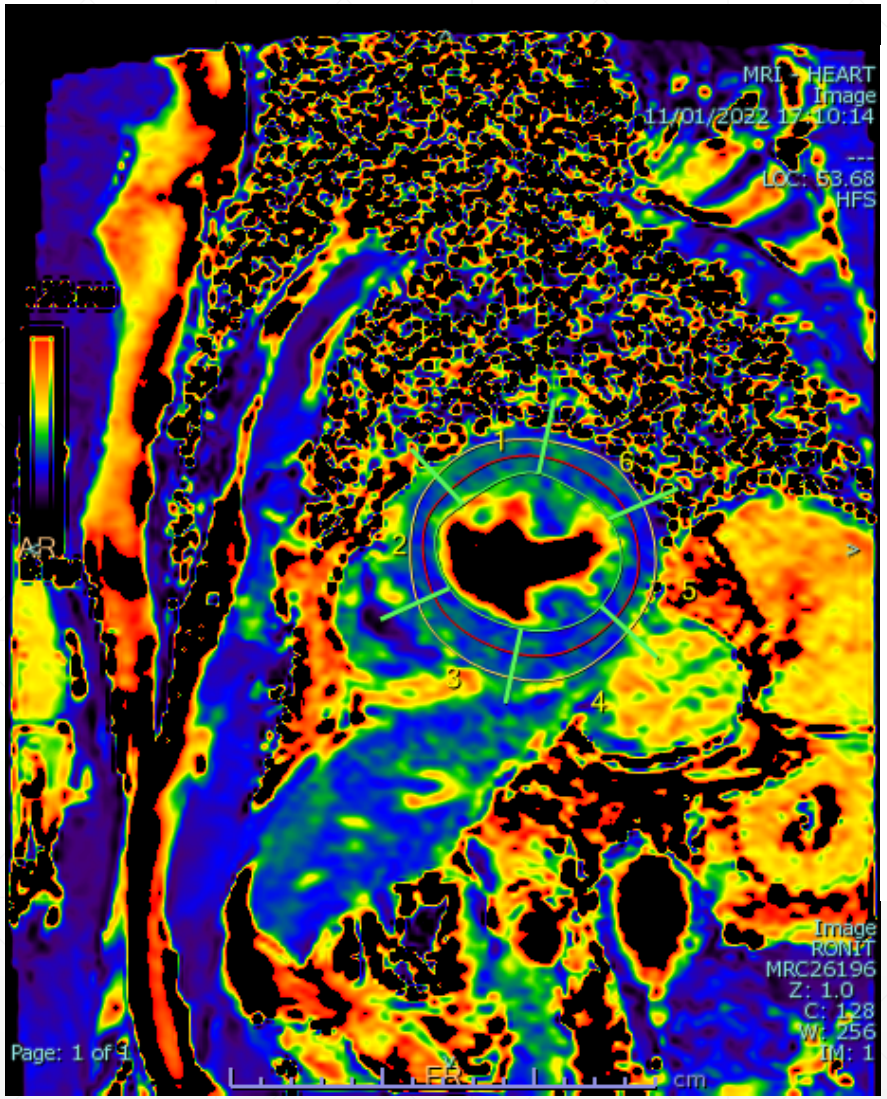
Right heart catheterization

- PCW - 18 mmHg
- EMB - yellowish gross appearance.

4.75	CO
2.21	CI
7	TPG
2.74	TPR
21.91	SVR
1.47	PVR
10.18	SVRI
69.	PVRI
1.47	PAR

MRI





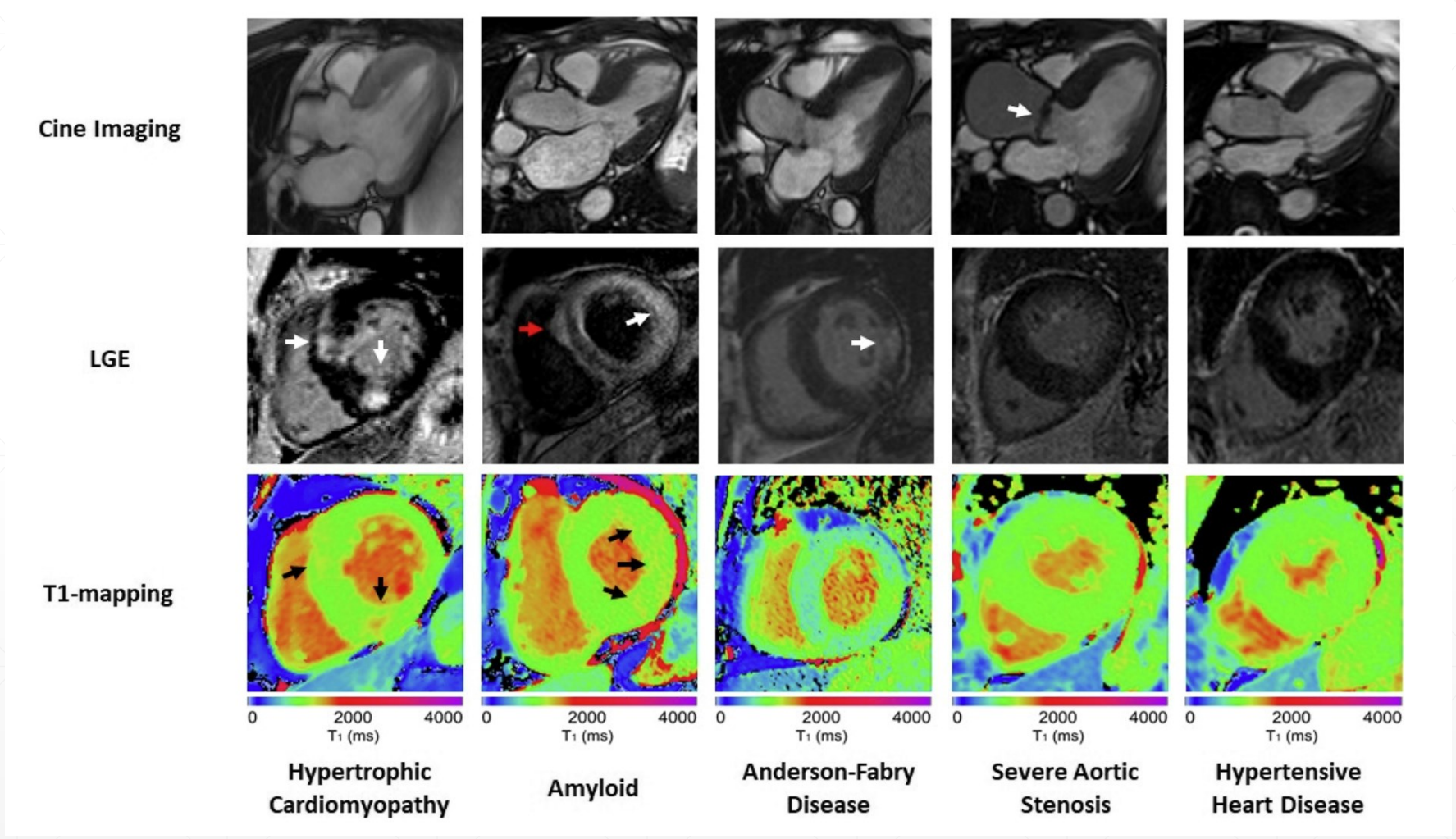
Left ventricle - results summary

% Ejection fraction	24
Stroke volume	36.9 ml
Cardiac output	3.7 L/min
ED volume	151.6 ml
ES volume	114.7 ml
ED volume/BSA	71.6 ml/m²
ES volume/BSA	54.2 ml/m²
ED wall mass	295.7 gr
ED wall mass/BSA	139.6 gr/m²
(BSA	2.12 m² (Mostellar
Heart Rate	100 bpm

Right ventricle - results summary

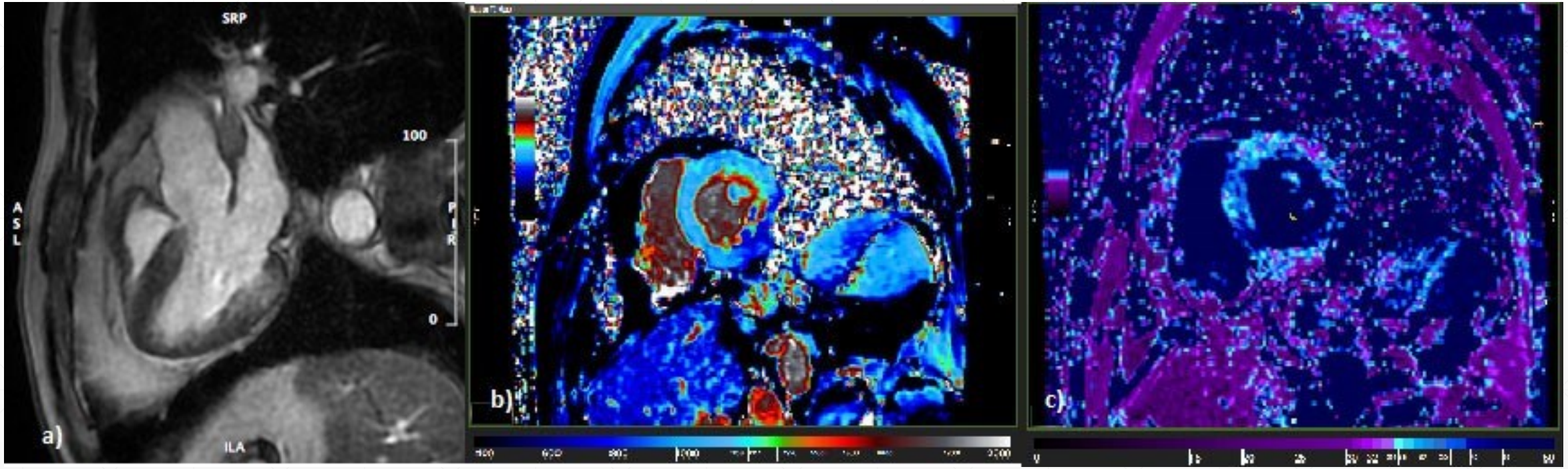
% Ejection fraction	50
Stroke volume	56.7 ml
Cardiac output	5.7 L/min
ED volume	114.5 ml
ES volume	57.8 ml
ED volume/BSA	54.1 ml/m²
ES volume/BSA	27.3 ml/m²
(BSA	2.12 m² (Mostellar

MRI DD of Myocardial Thickening



Burrage MK and Ferreira VM. Current Heart Failure Reports (2020) 17:192–204

CMR in a patient with Fabry disease.



LGE T1 T2

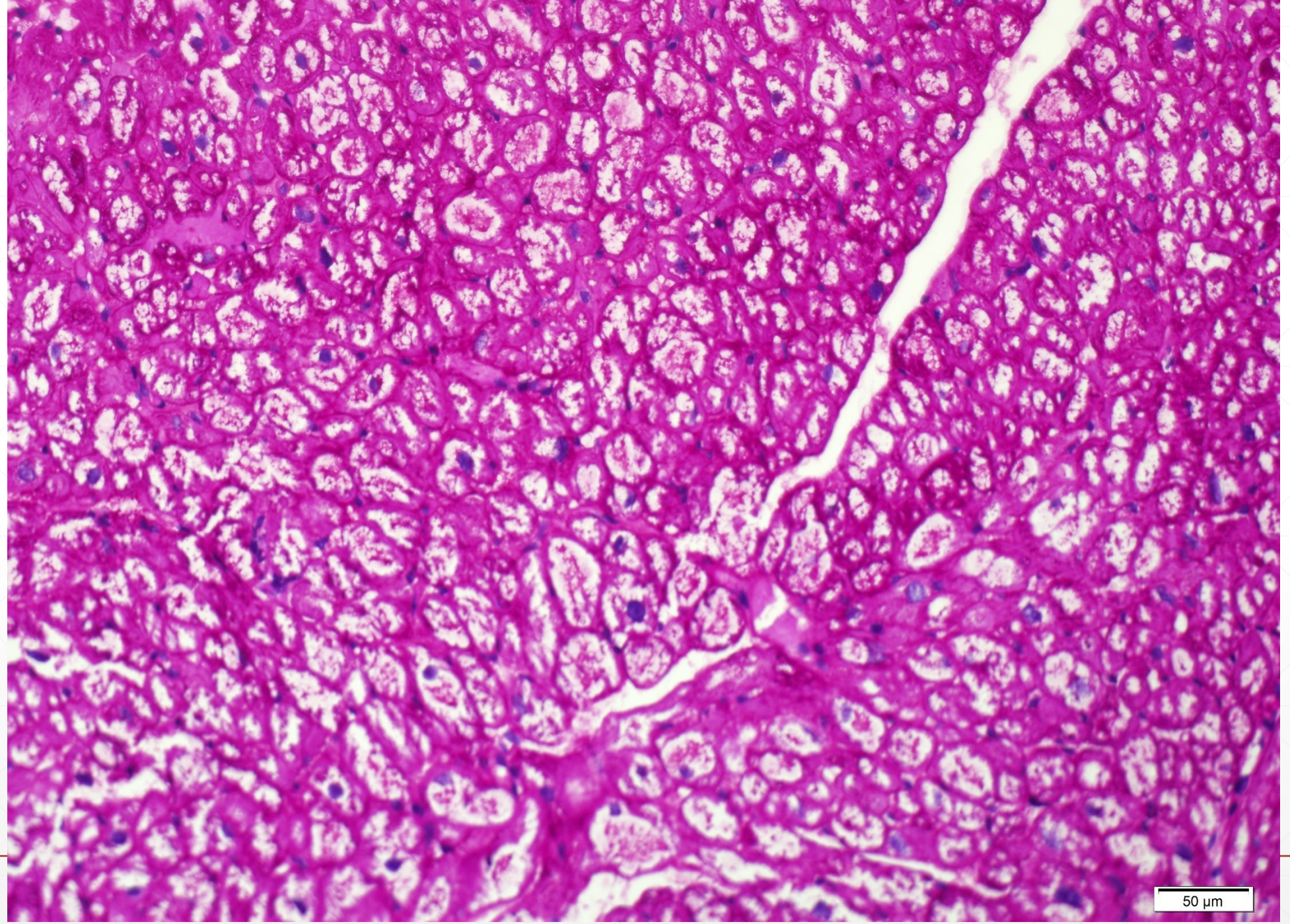
Dudley P, Garg R, Friedrich MG (ed.), in John Camm AJ et al (eds), The ESC Textbook of Cardiovascular Medicine, 3 ed. (Oxford, 2018; online edn, ESC Publications, 1 Oct. 2020), accessed 15 Apr. 2023

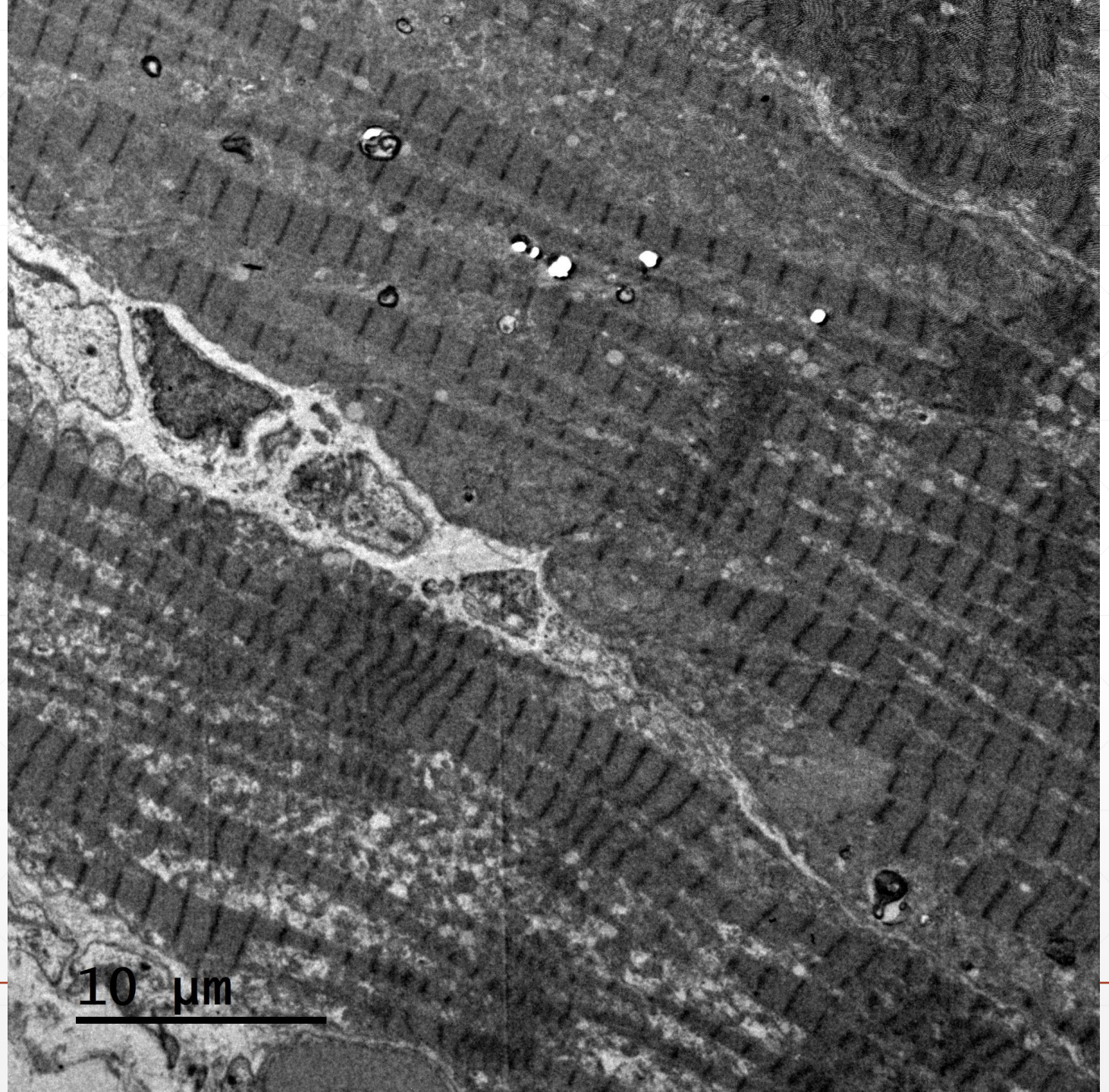
פתולוגיה

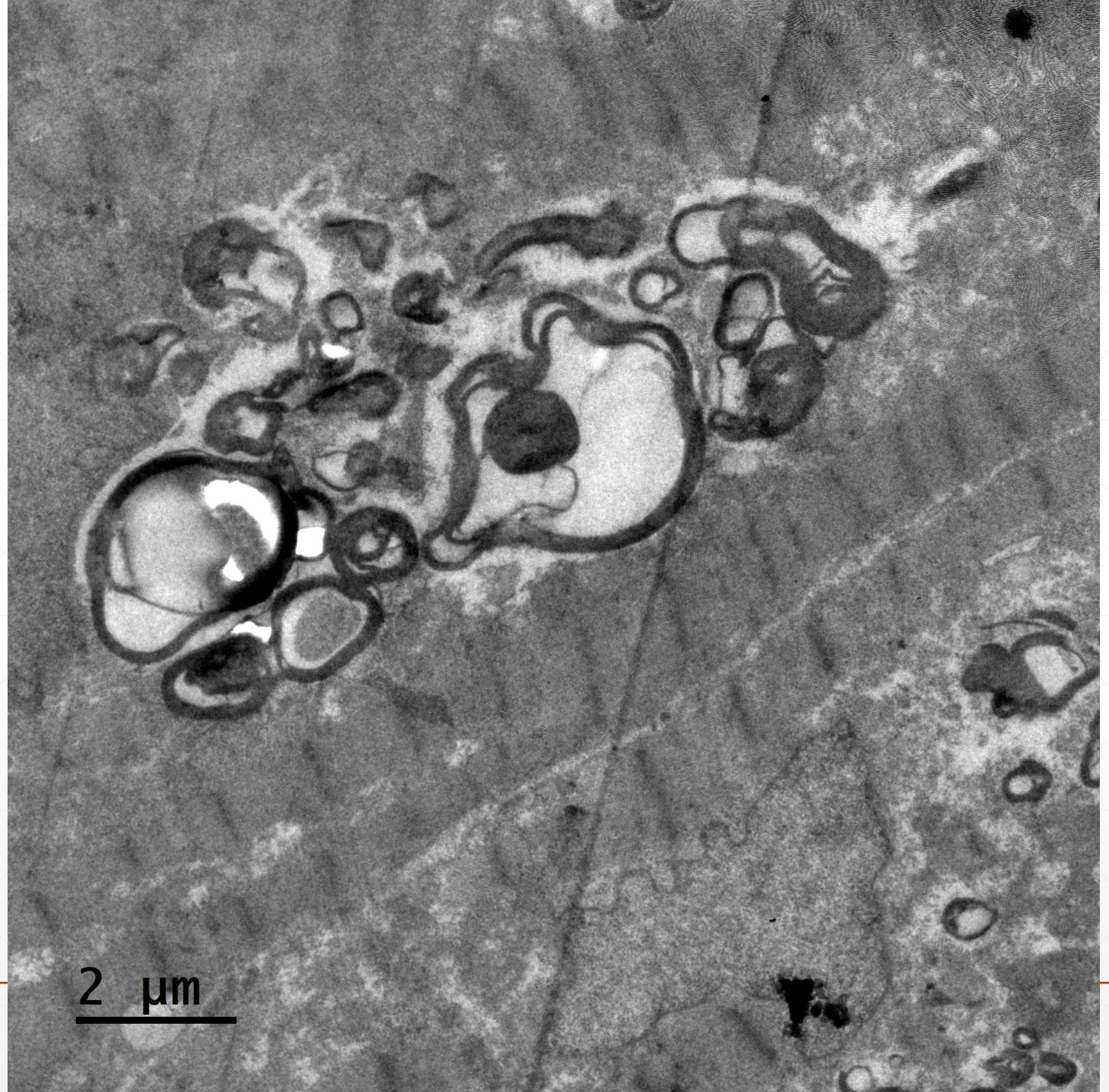
ממצא מיקרוסקופי

Three fragments of cardiac muscle with diffuse vacuolation of myocytes.
PAS stain shows cytoplasmic granular content (possibly artefactual; fixed material), some of which is present on diastase-pretreatment. CD68 immunostain shows only scattered interstitial macrophages.
Trichrome stain does not demonstrate interstitial fibrosis.
No significant inflammation.
Congo red stain does not demonstrate amyloid deposition.

The findings are consistent with the clinical impression of storage disease, possibly Fabry disease.


50 µm


10 µm


2 µm

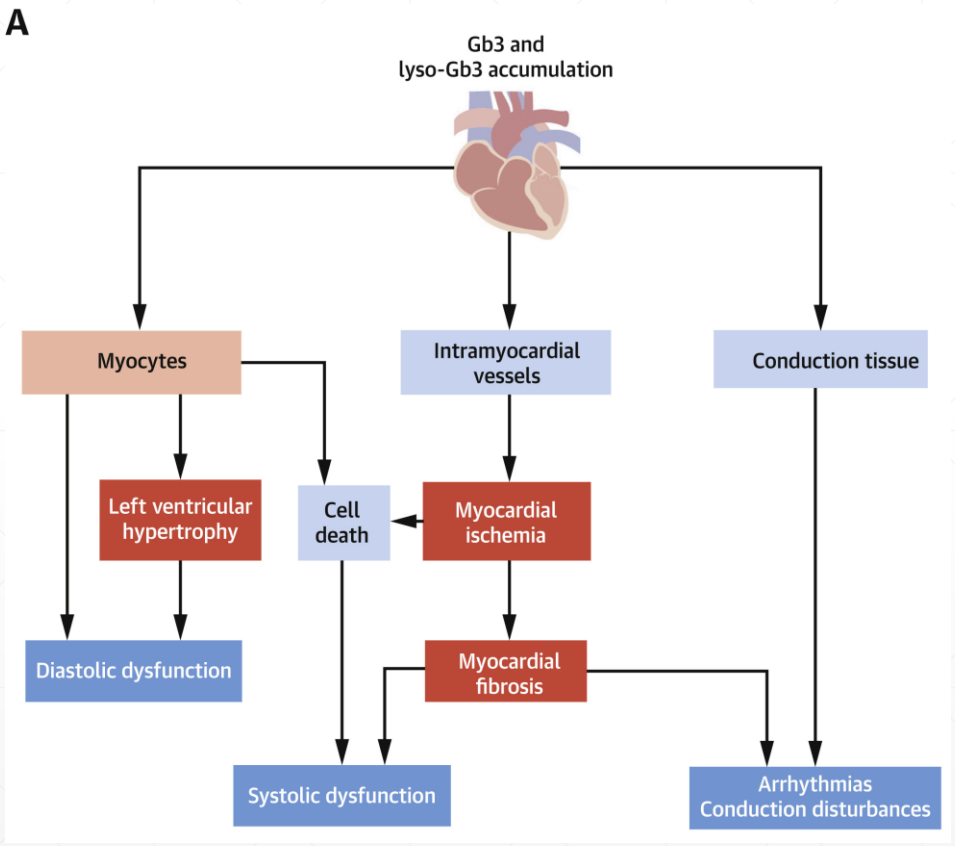
תשובה גנטית

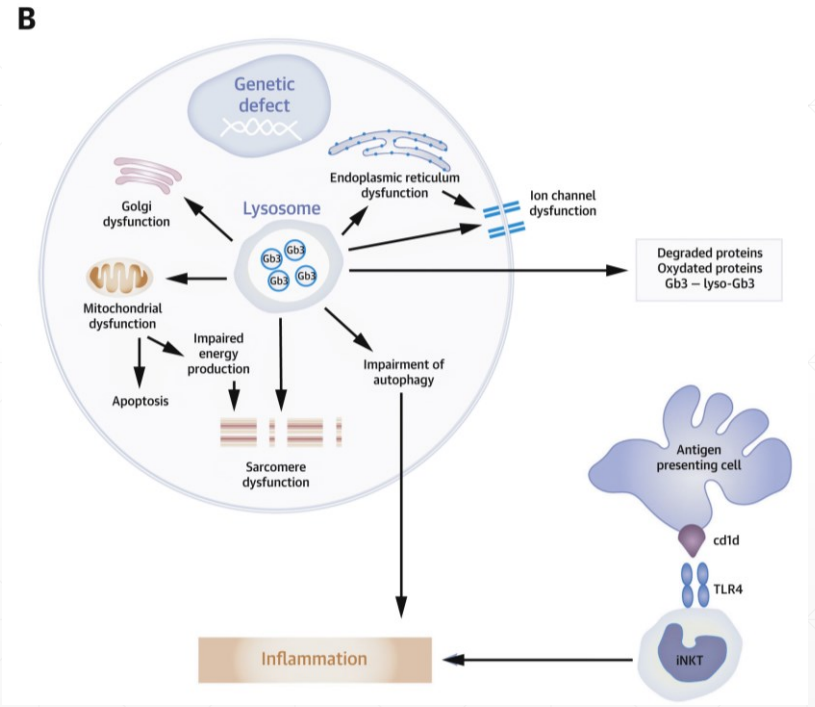
- אובחנה מוטציה בגן GLA
- ALPHA GALACTOSIDASE DEFICIENCY
- FABRY

Anderson Fabry's Disease

- Second most common glycosphingolipid storage disorder (after Gaucher disease) with birth frequency of 1 in 100 000
- Deficiency of X linked α-galactosidase (GLA), with accumulation of uncleaved glycosphingolipids in the lysosomes, predominantly globotriosylceramide (Gb3) causing engorgement of cells, tissue hypertrophy, and eventually cell death and organ failure
- Deposits are prominent in the endothelium and the media of small vessels, renal tubules and glomeruli, cardiac muscle and conducting fibers, autonomic ganglia, and in specific cortical and brain stem structures.
- Most significant symptoms are renal failure, cardiomyopathy, and multiple cerebrovascular accidents (CVAs)

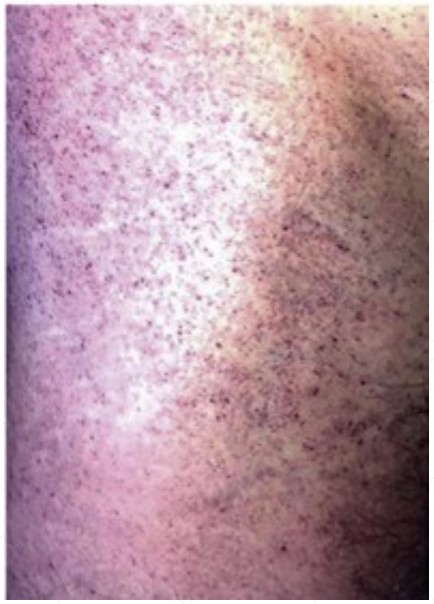
Pathophysiology of Fabry's Disease





Pieroni et al. J Am Coll Cardiol (2021);77(7):921-8

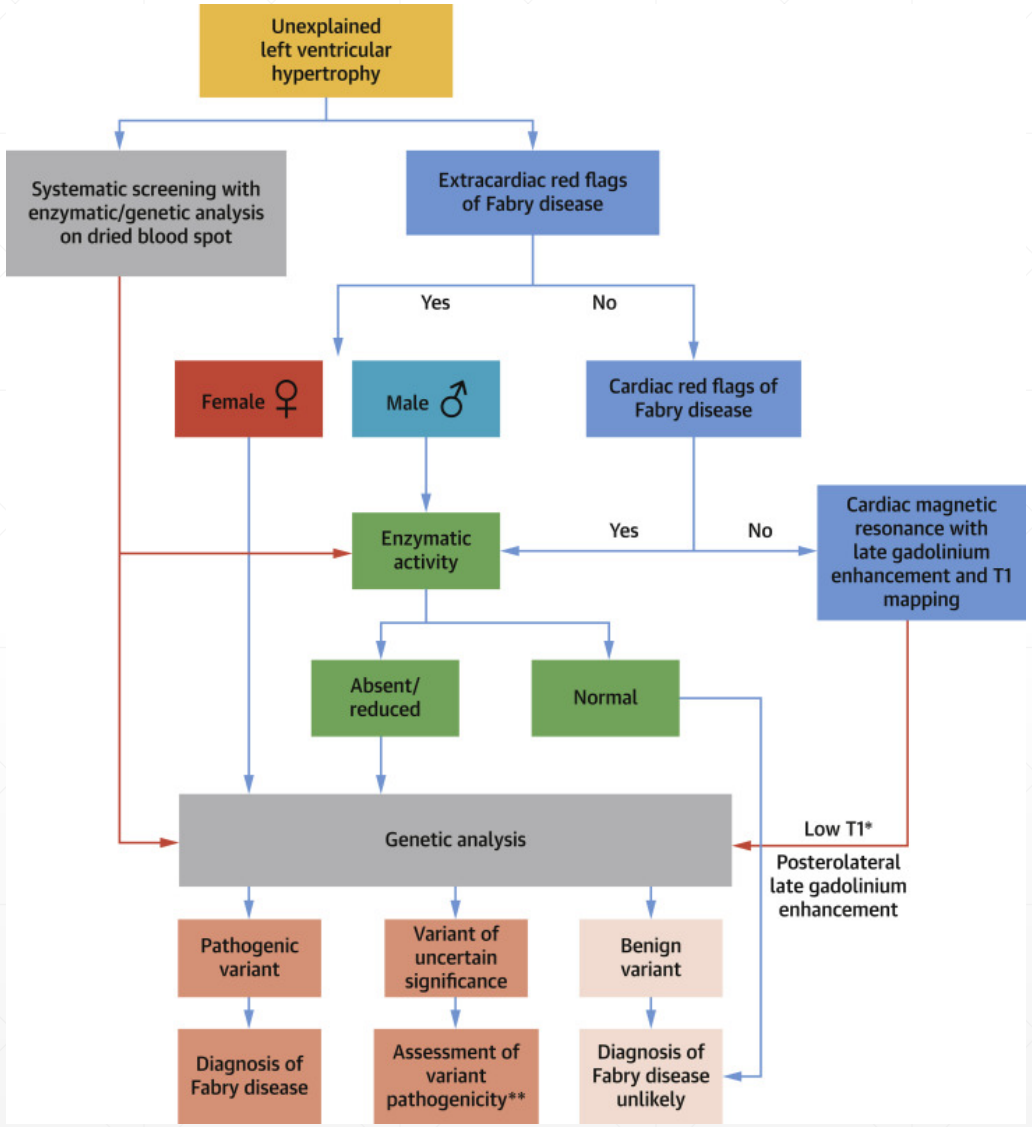
Red Flags in Fabry's Disease



Extra-Cardiac Red Flags			Cardiac Red Flags		
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval†	Electrocardiography	
	1–2	Angiokeratomas	Bradycardia		
	1–2	Cornea verticillata*	Chronotropic incompetence		
	1–2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks†		
	1–2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3–4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3–4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3–4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3–4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3–4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3–4	Lymphedema	Low native T1		

Pieroni et al. J Am Coll Cardiol (2021);77(7):921-8

Diagnosis of Fabry's Disease



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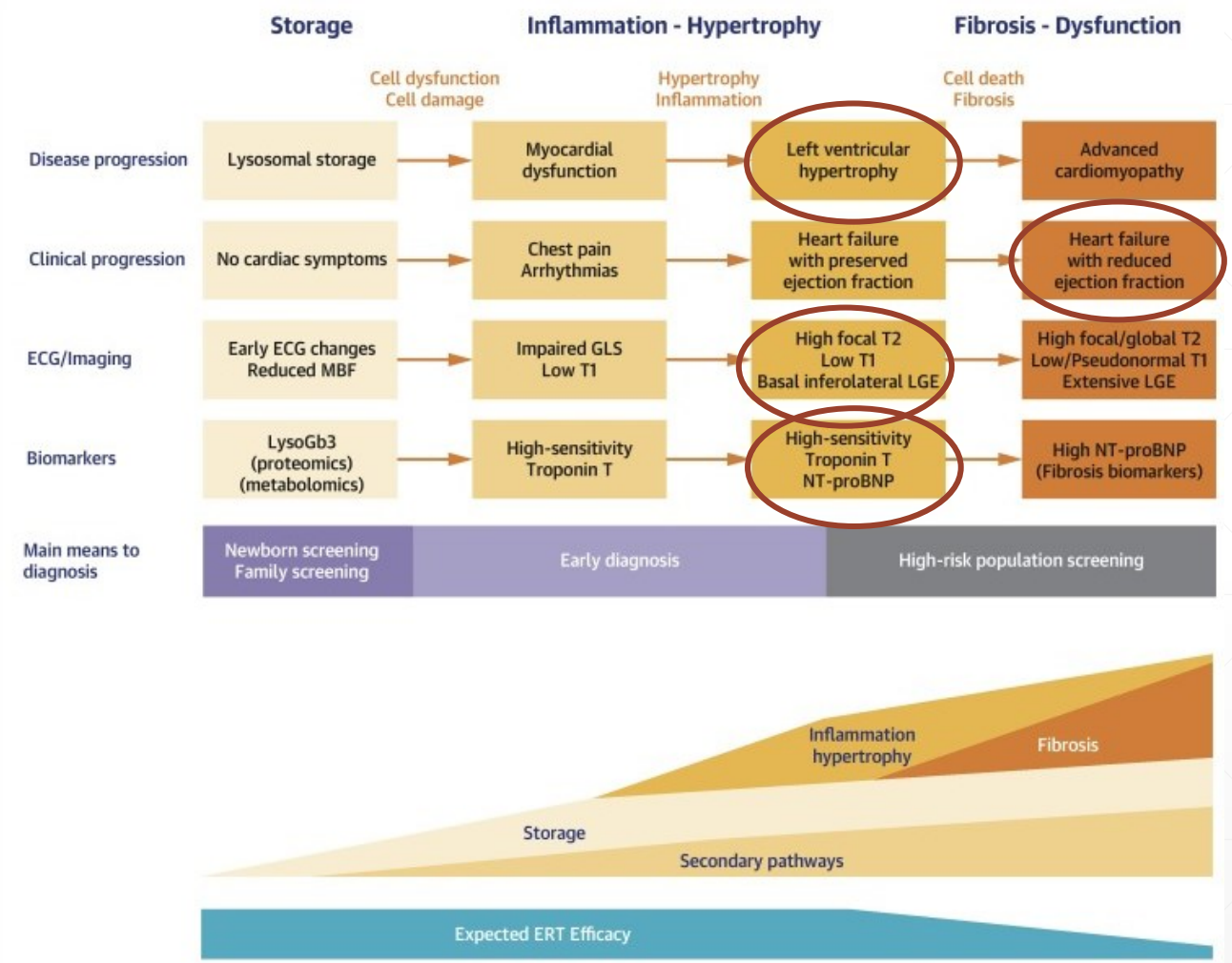
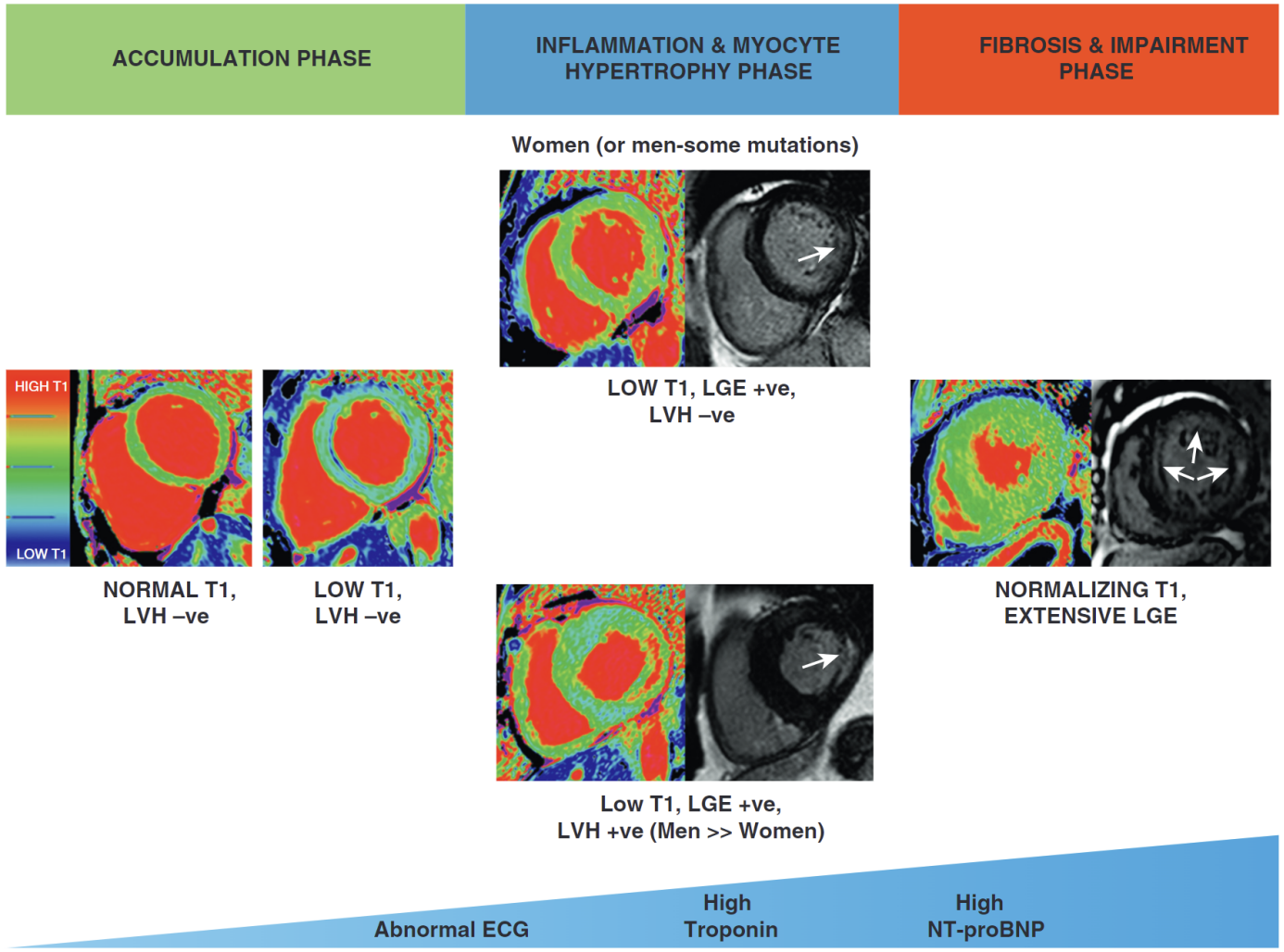
Evolution of Cardiac Involvement in Fabry's Disease



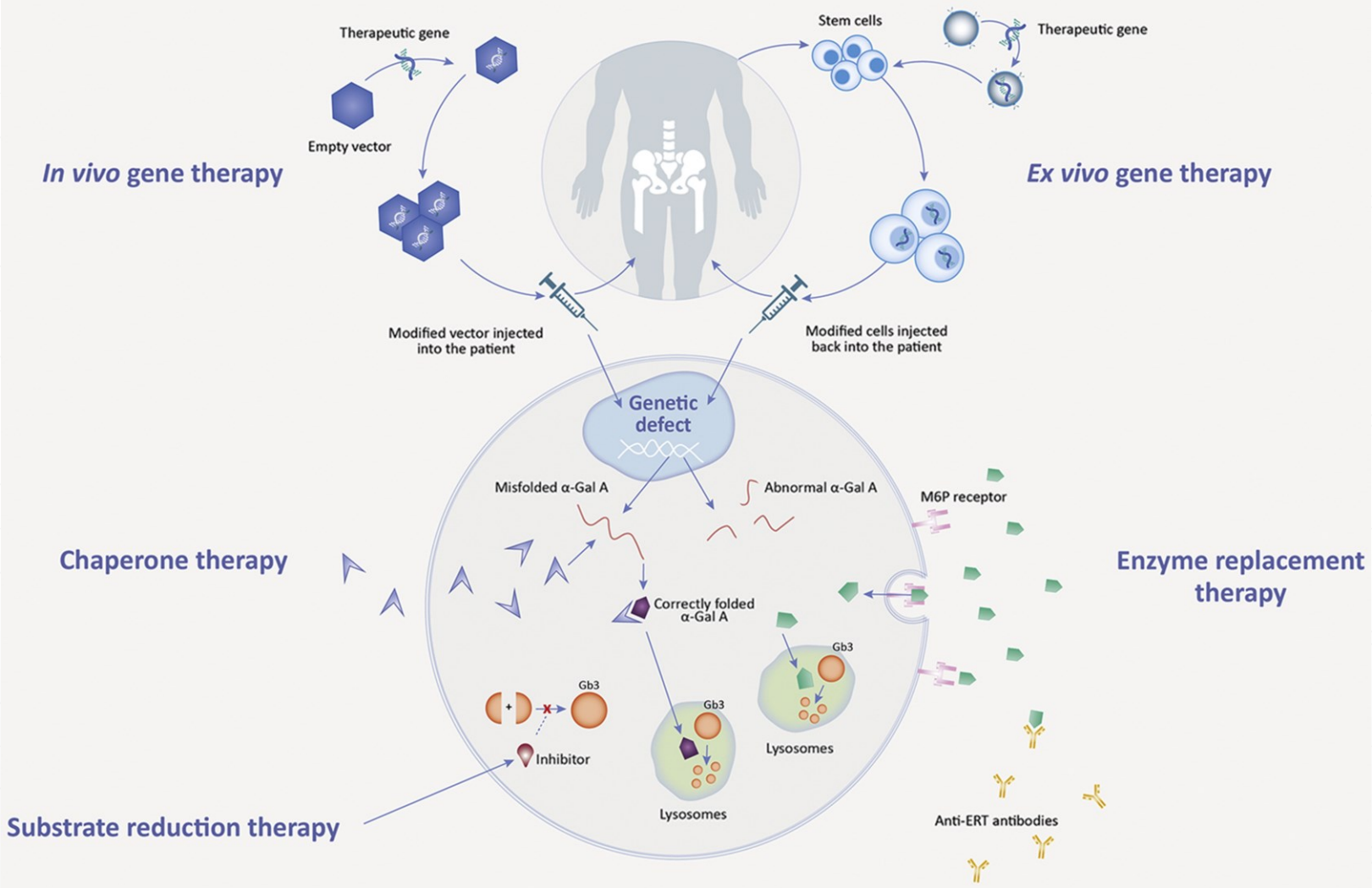
Pieroni, M. et al. J Am Coll Cardiol. 2021;77(7):922-36.

MRI Evolution of Fabry's Disease



Nordin S et al. Am Coll Cardiol Img 2019;12:1673–83

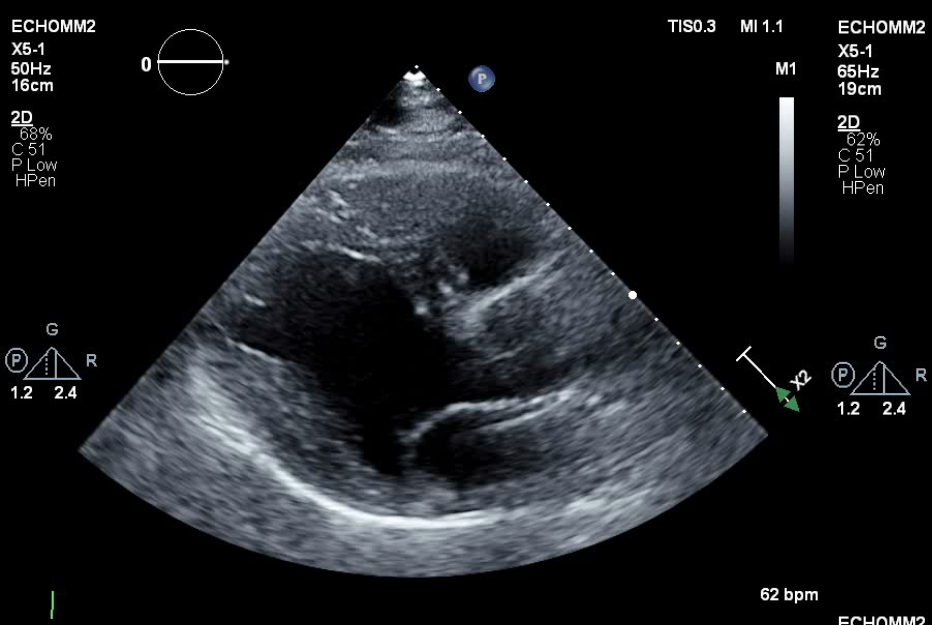
Therapies for Fabry's disease

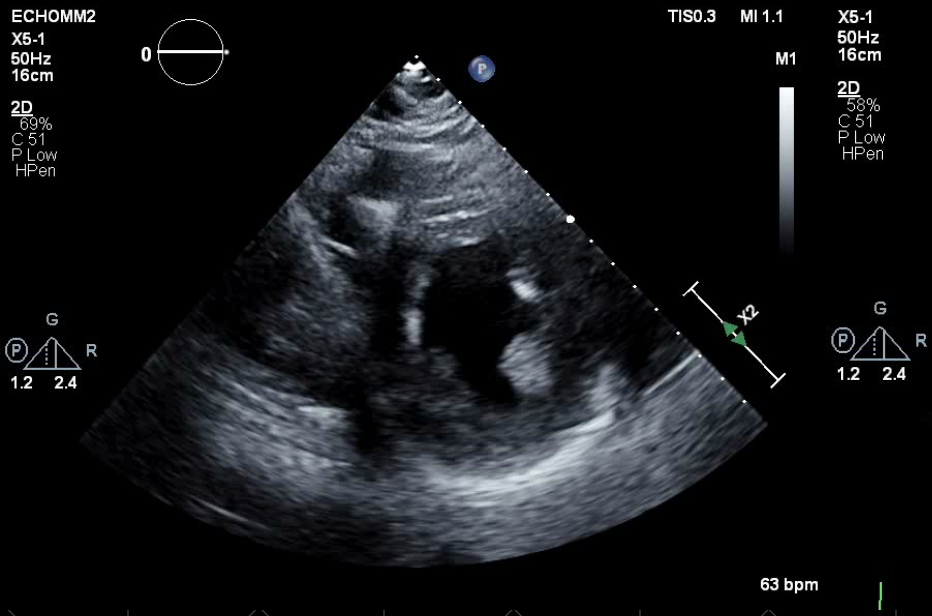


Pieroni et al. J Am Coll Cardiol (2021);77(7):921-8

מהלך

- הוחל טיפול באנטרסטו, MRA, מעכבי SGLT2. שודרג ל-CRTD
- החל טיפול ב Fabrazyme
- ללא תלונות של אי-ספיקת לב ,חזר לעבודה מלאה


ECHOMM2
X5-1
50Hz
16cm
2D
68%
C 51
P Low
HPen
TIS0.3 MI 1.1
M1
G
R
1.2 2.4
62 bpm


ECHOMM2
X5-1
50Hz
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69%
C 51
P Low
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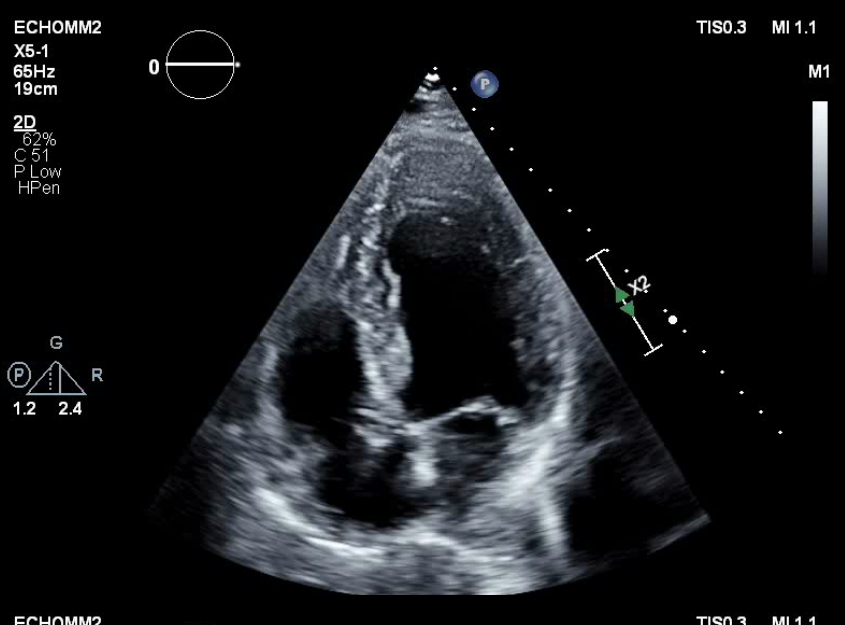
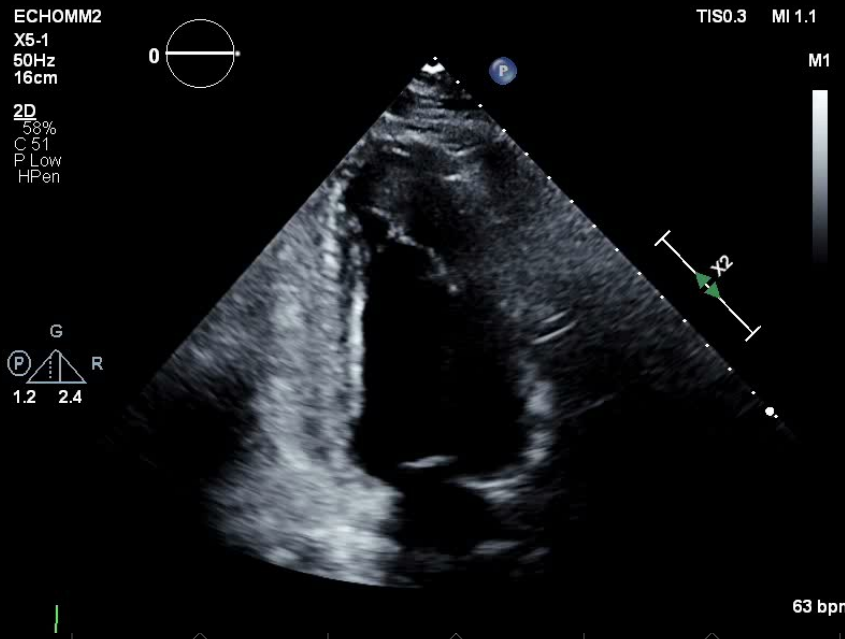
TIS0.3 MI 1.1
M1
G
R
1.2 2.4
63 bpm


ECHOMM2
X5-1
65Hz
19cm
2D
62%
C 51
P Low
HPen
TIS0.3 MI 1.1
M1
G
R
1.2 2.4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X5-1
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16cm
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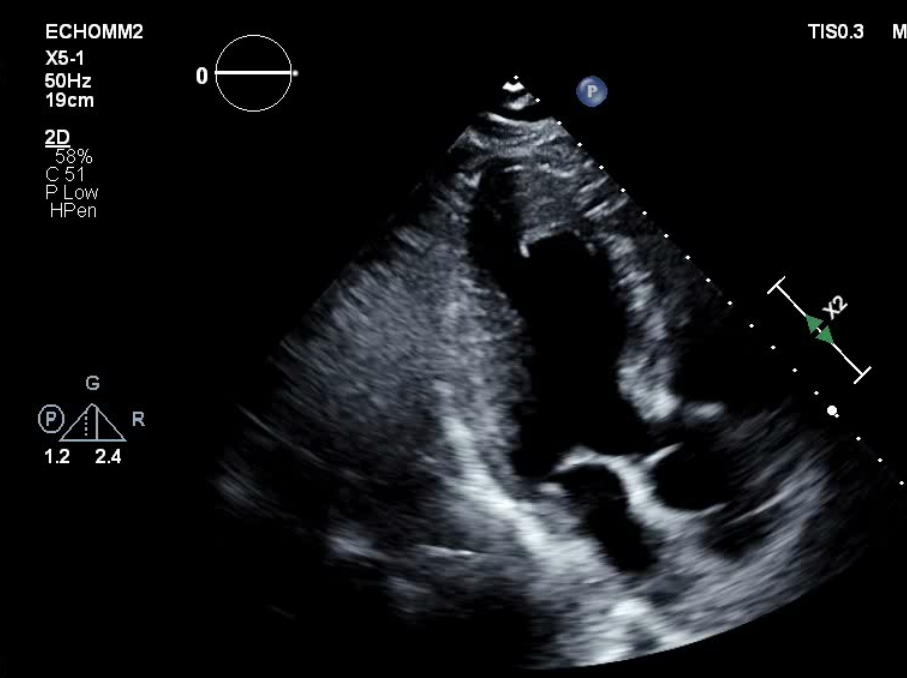
58%
C 51
P Low
HPen
TIS0.3 MI 1.1
M1
G
R
1.2 2.4
63 bpm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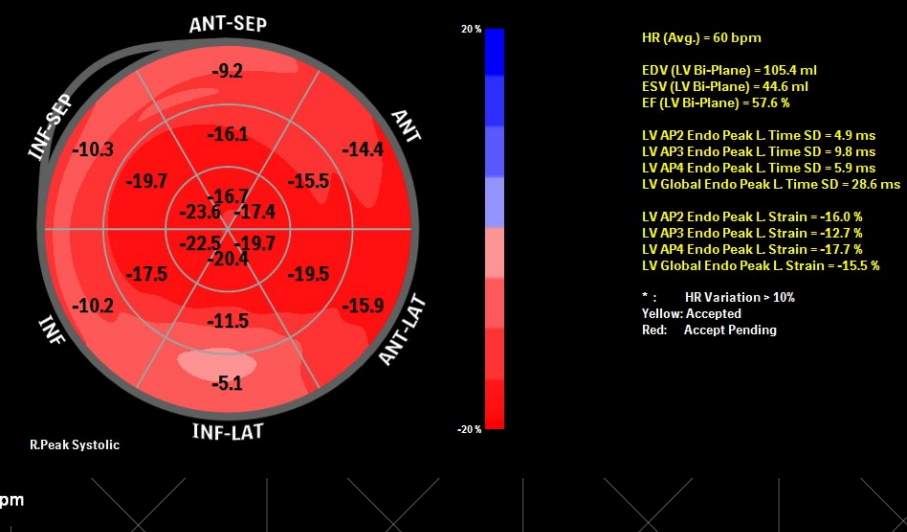
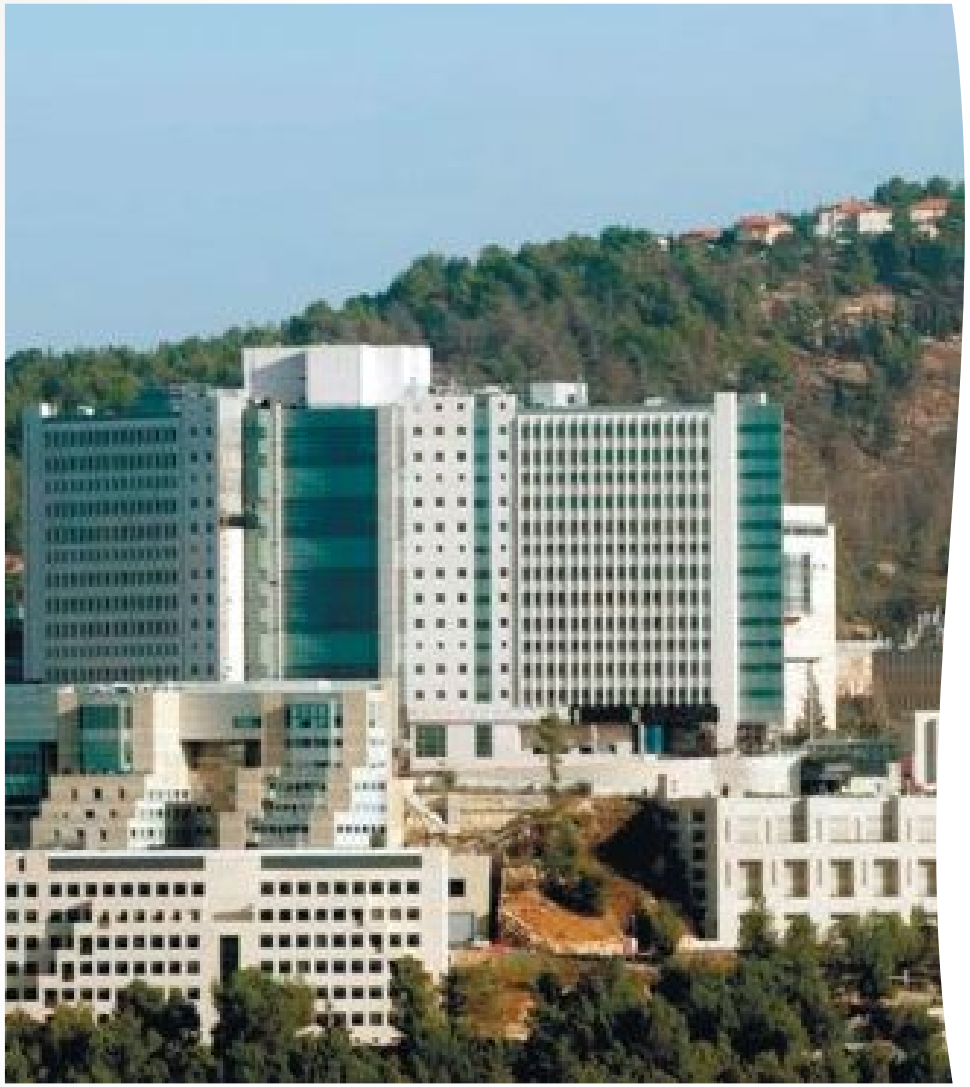
X5-1
50Hz
19cm
2D
58%
C 51
P Low
HPen
TIS0.3 M
G
R
1.2 2.4


ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-9.2
-16.1
-14.4
-10.3
-19.7
-15.5
-16.7
-23.6
-17.4
-22.5
-19.7
-20.4
-17.5
-19.5
-10.2
-11.5
-15.9
-5.1
20%
-20%
R.Peak Systolic
HR (Avg.) = 60 bpm
EDV (LV Bi-Plane) = 105.4 ml
ESV (LV Bi-Plane) = 44.6 ml
EF (LV Bi-Plane) = 57.6 %
LV AP2 Endo Peak L. Time SD = 4.9 ms
LV AP3 Endo Peak L. Time SD = 9.8 ms
LV AP4 Endo Peak L. Time SD = 5.9 ms
LV Global Endo Peak L. Time SD = 28.6 ms
LV AP2 Endo Peak L. Strain = -16.0 %
LV AP3 Endo Peak L. Strain = -12.7 %
LV AP4 Endo Peak L. Strain = -17.7 %
LV Global Endo Peak L. Strain = -15.5 %
* : HR Variation > 10%
Yellow: Accepted
Red: Accept Pending

סיכום

- מחלת FABRY היא מחלת אגירה – בתאחיזה לכרומוזום X- שאינה נדירה. יכולה להתבטא בגברים, אך גם בנשים (בתלות באינקטיבציה של כרומוזום X) ויכולה להיות מבוטאת במערכות רבות בגוף
- בלב יכולה להתבטא כהיפרטרופיה של החדרים, הפרעות קצב והולכה, ובהמשך HFrEF
- סימנים עדינים באקו הם רמז, אבל הסימנים החד משמעיים הם ב-MRI, ואנליזה גנטית היא הכרחית
- למחלה יש טיפול ולכן חשוב האבחון המוקדם, והסקירה המשפחתית במקרים רלוונטים



Thank You!