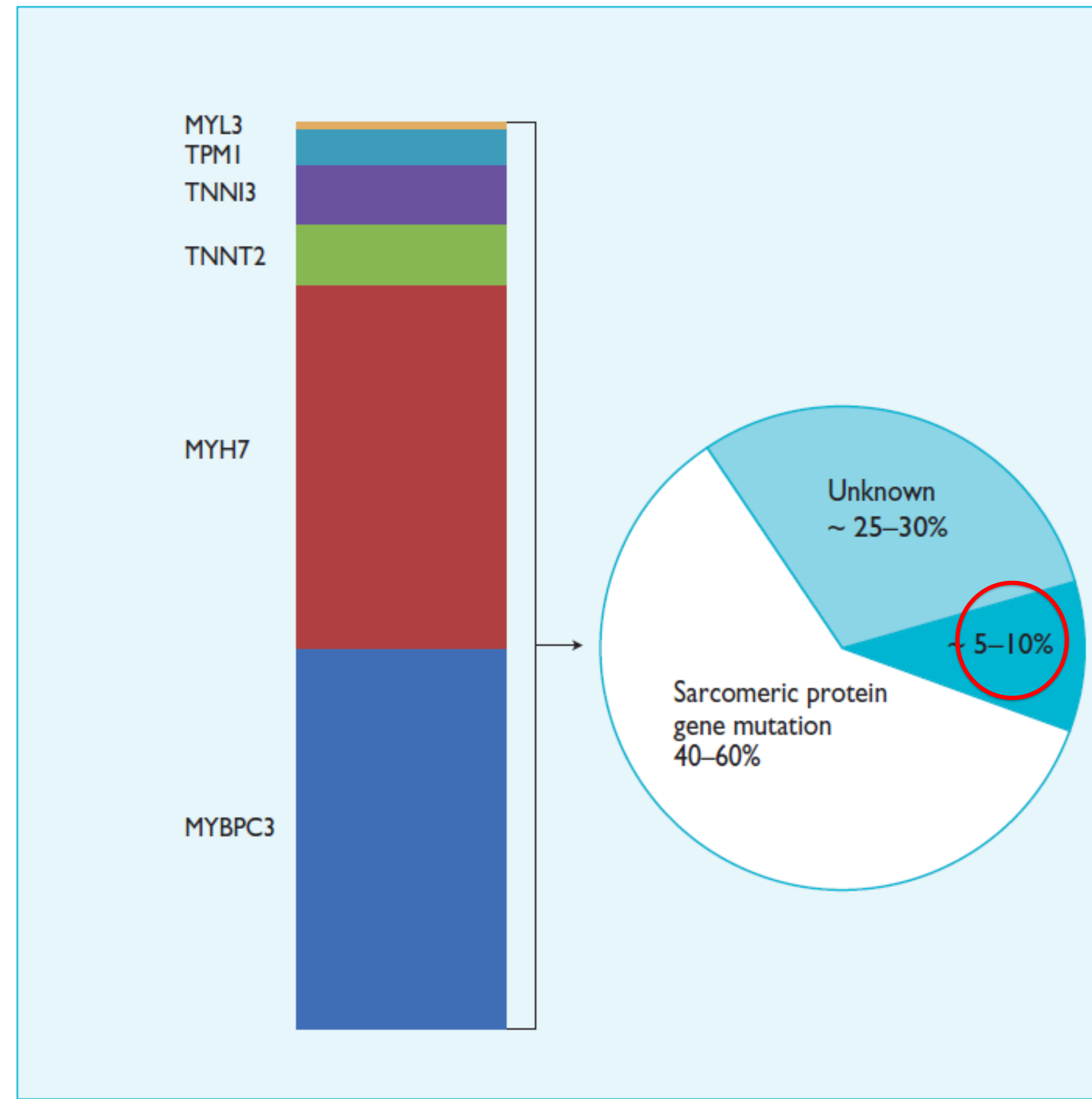


**CARDIOMIOPATIE RARE, CARDIOPATIE NEUROMUSCOLARI
E MALATTIA DI ANDERSON-FABRY**

Red flags per la diagnosi differenziale delle cardiomiopatie a fenotipo ipertrofico non sarcomeriche

Dott.ssa Fabiana Romeo





Other genetic and non-genetic causes

• Inborn errors of metabolism

Glycogen storage diseases:

- Pompe
- Danon

• AMP-Kinase (PRKAG2)

• Carnitine disorders

• Lysosomal storage diseases

- Anderson-Fabry

• Neuromuscular diseases

- Friedreich's ataxia
- FHLI

• Mitochondrial diseases

- MELAS
- MERFF

• Malformation Syndromes

- Noonan
- LEOPARD
- Costello
- CFC

• Amyloidosis

- Familial ATTR
- Wild type TTR (senile)
- AL amyloidosis

• Newborn of diabetic mother

• Drug-induced

- Tacrolimus
- Hydroxychloroquine
- Steroids



Terapie specifiche:

- Terapia enzimatica sostitutiva (ERT): M. Pompe, M. A. Fabry, Mucopolisaccaridosi
- Terapia chaperonica: M. Fabry (migalastat) e M. Pompe (miglustat)
- Terapia genica: M. Danon (studi fase II), M. Pompe (studi fase I)
- Omaveloxolone: Atassia Friedreich
- Silenziatori genici (patisiran, vutrisiran) e stabilizzatori (tafamidis, acoramidis): Amiloidosi da TTR
- Chemioterapia: Amiloidosi AL



Sei qui: [Home](#) ► [Malattie rare](#) ► [Malattia di Pompe](#) ► Malattia di Pompe, miglustat approvato in Europa

Malattia di Pompe: news su terapie, sperimentazioni e qualità della vita

Malattia di Pompe, miglustat approvato in Europa

Autore: Redazione, 02 Agosto 2023



La Commissione Europea ha autorizzato l'impiego del farmaco in combinazione con cipaglicosidasi alfa per gli adulti con malattia di Pompe a esordio tardivo

A fine giugno è stata annunciata l'**approvazione per miglustat (nome commerciale Opfolda) 65 mg capsule, uno stabilizzatore enzimatico della cipaglicosidasi alfa (nome commerciale Pombiliti), una terapia enzimatica sostitutiva (ERT) a lungo termine per gli adulti affetti dalla malattia di Pompe ad esordio tardivo (LOPD).** Ad aprile, miglustat *aveva ricevuto parere* positivo da parte del Comitato per i Medicinali per Uso Umano (CHMP) dell'Agenzia Europea per i Medicinali (EMA), che ne raccomandava l'autorizzazione all'immissione in commercio, mentre cipaglicosidasi alfa è stato approvato dalla Commissione Europea (CE) già a marzo 2023. L'azienda

produttrice, Amicus Therapeutics, prevede di lanciare immediatamente il farmaco in Germania e sta avviando le procedure di rimborso con le autorità sanitarie di altri Paesi europei.



Sei qui: [Home](#) ► [Malattie rare](#) ► [Atassia di Friedreich](#) ► Atassia di Friedreich: approvazione europea per omaveloxolone

Atassia di Friedreich: approvazione europea per omaveloxolone

Autore: Redazione, 20 Febbraio 2024



Negli studi clinici, il farmaco ha dimostrato di migliorare le funzionalità neurologiche dei pazienti rispetto al placebo

Milano – La **Commissione Europea (CE)** ha **autorizzato l'utilizzo di omaveloxolone per il trattamento dell'atassia di Friedreich (FA)** negli adulti e negli adolescenti di età pari o superiore a 16 anni. Omaveloxolone è il primo farmaco approvato nell'Unione europea per questa rara malattia genetica, neurodegenerativa e progressiva.

L'Atassia di Friedreich è la forma più comune di atassia ereditaria. I primi sintomi compaiono generalmente durante l'infanzia e comprendono la progressiva perdita di coordinazione, la debolezza muscolare e l'affaticamento. Con il progredire della malattia, possono insorgere anche problemi alla vista, all'udito, difficoltà nell'articolazione verbale e nella deglutizione, diabete, scoliosi e patologie

cardiache gravi. **Molte persone con FA necessitano di ausili per la deambulazione e spesso sono costrette all'utilizzo di una sedia a rotelle entro 10-20 anni dalla diagnosi.** Purtroppo, le complicazioni legate alla FA contribuiscono a ridurre l'aspettativa di vita media a 37 anni.





European Heart Journal Advance Access published December 4, 2012

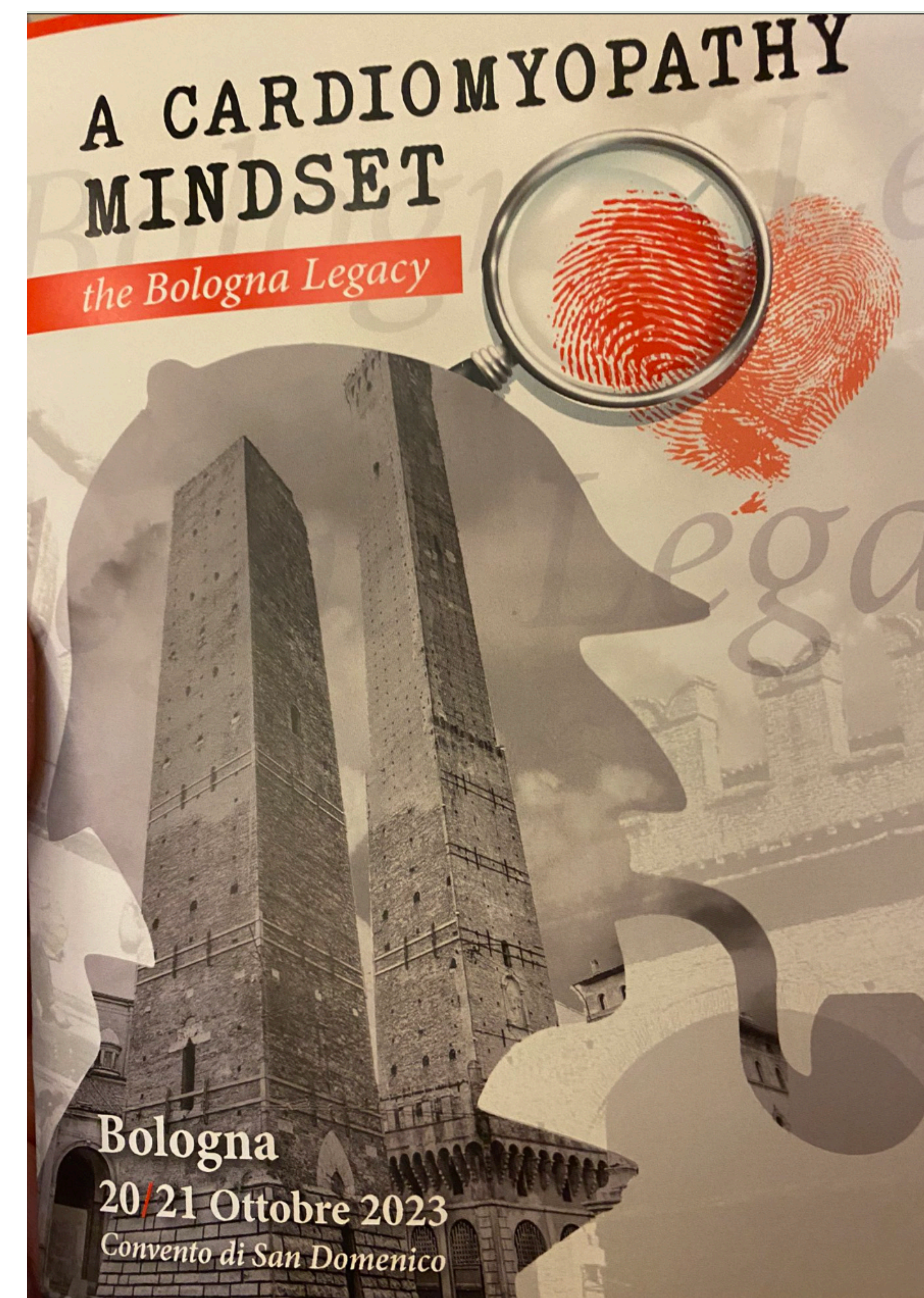


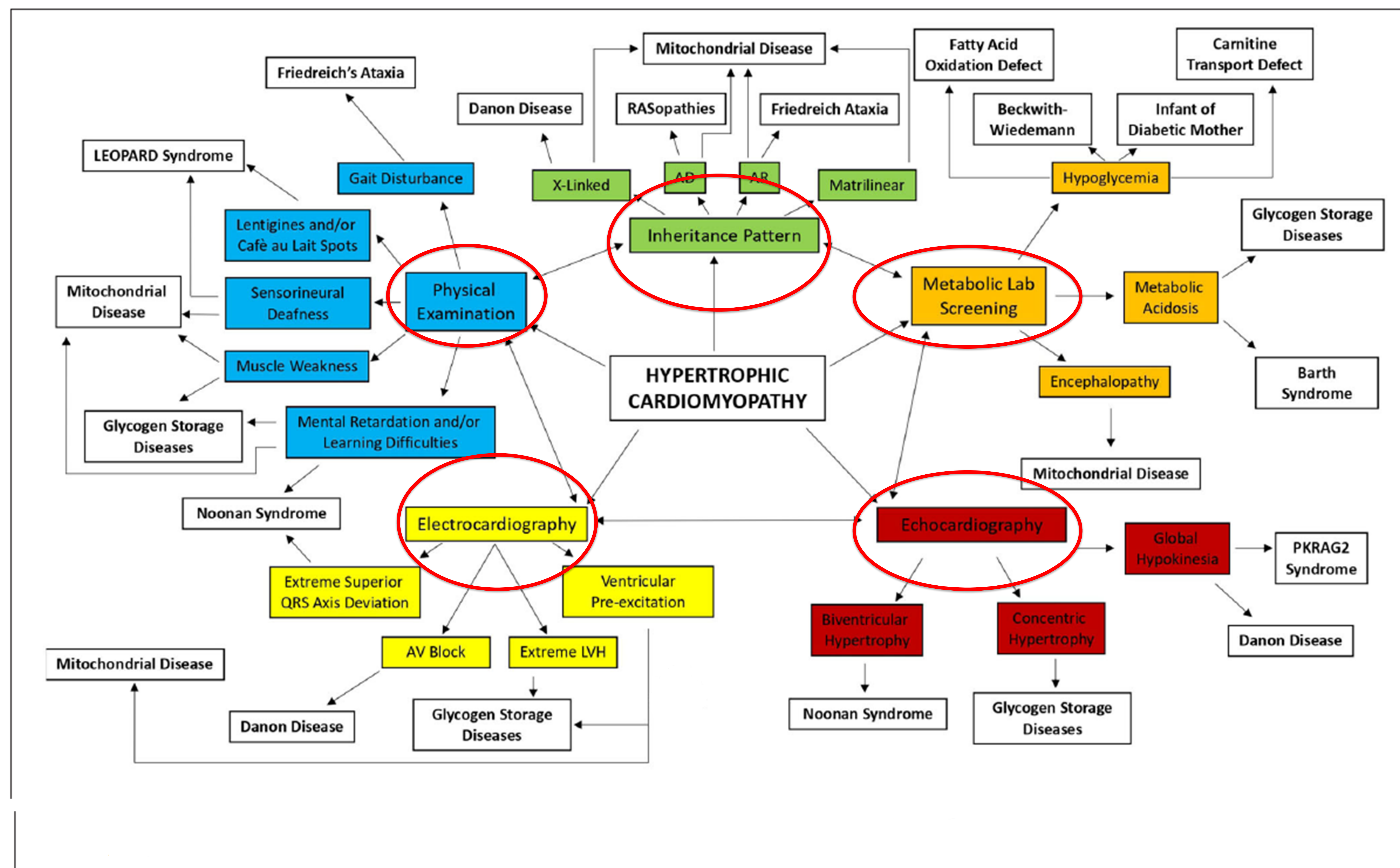
European Heart Journal
doi:10.1093/eurheartj/ehs397

SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*



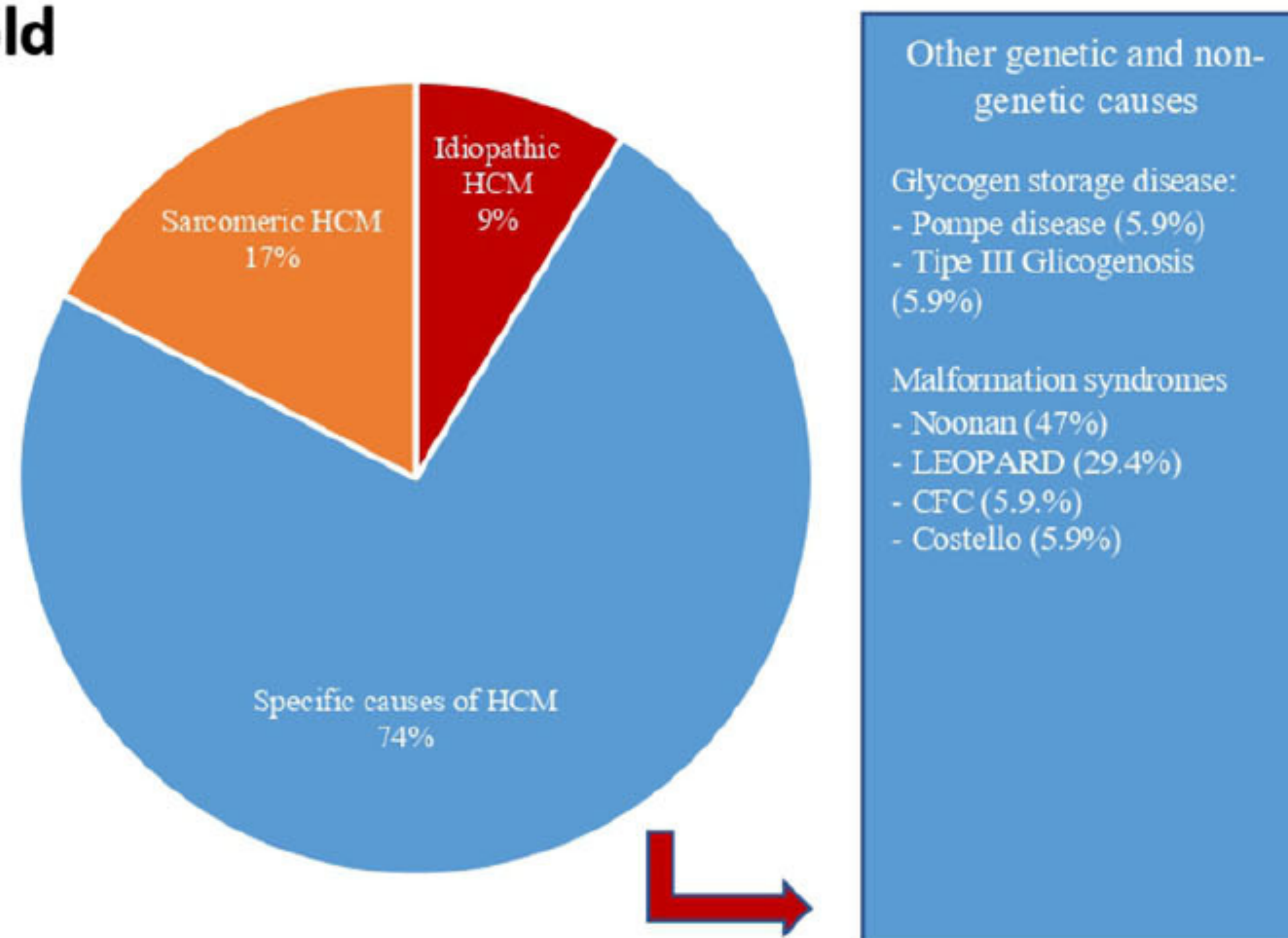


➤ Età di insorgenza

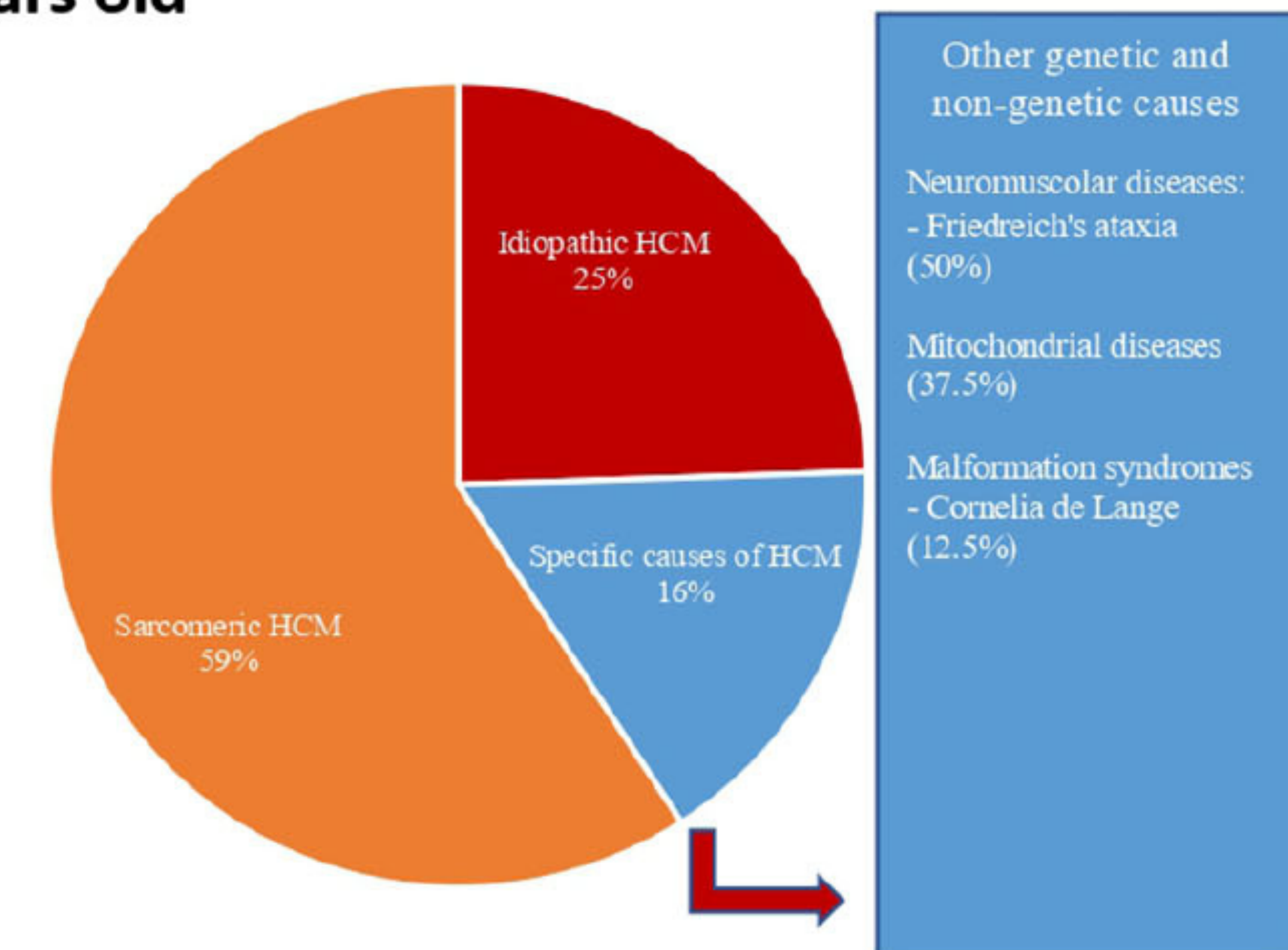
- < 1 aa di vita: sindromi malformative o storage disease
- Età pediatrica/adolescenza: malattie neuromuscolari, mitocondriali, storage disease, PRKAG2
- Età adulta: Amiloidosi cardiaca (dal 7% al 29% delle cardiomiopatie ipertrofiche dell'adulto) e Malattia di Anderson Fabry (1% delle cardiomiopatie ipertrofiche dell'adulto)



Age <1 years old



Age 1-18 years old

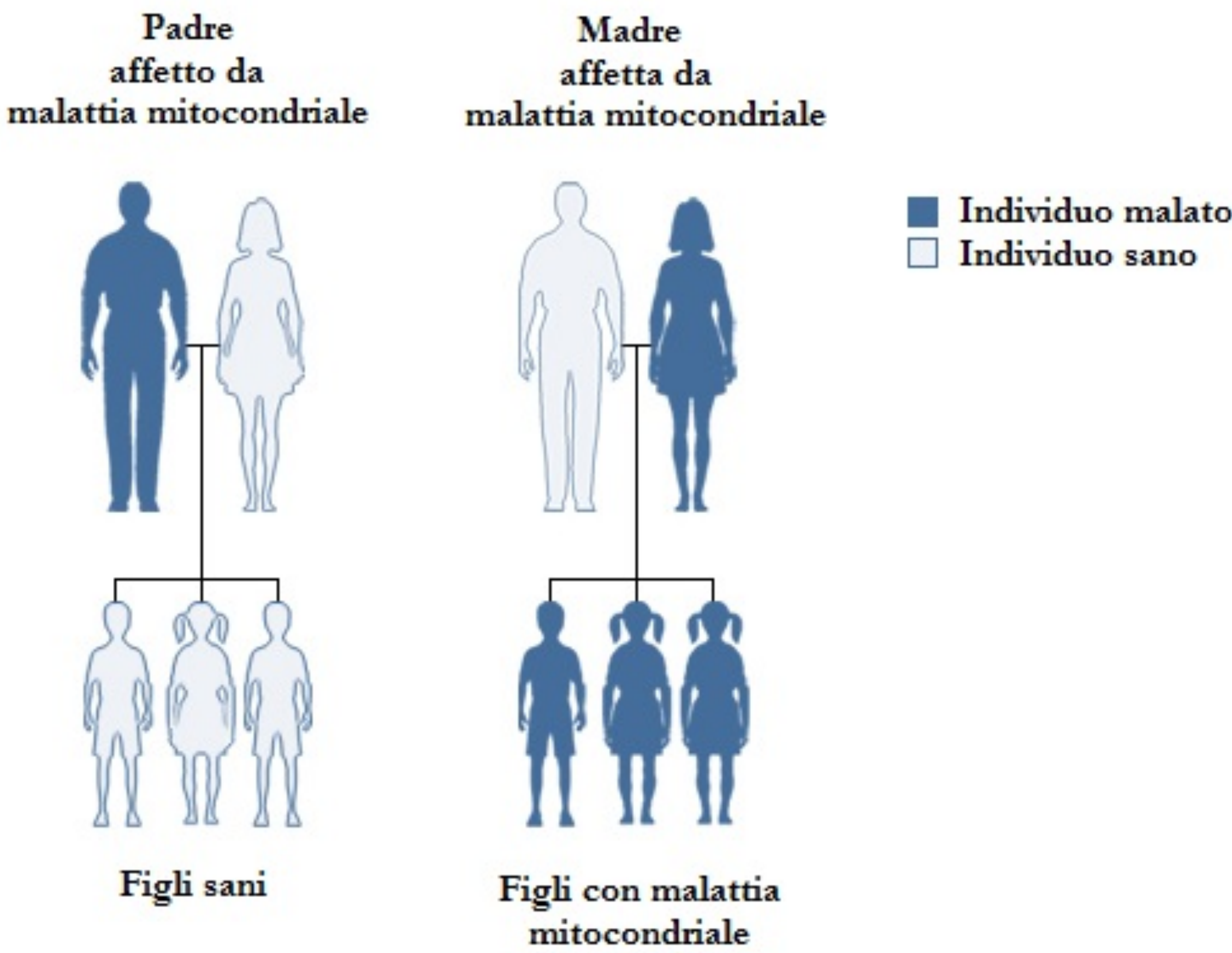
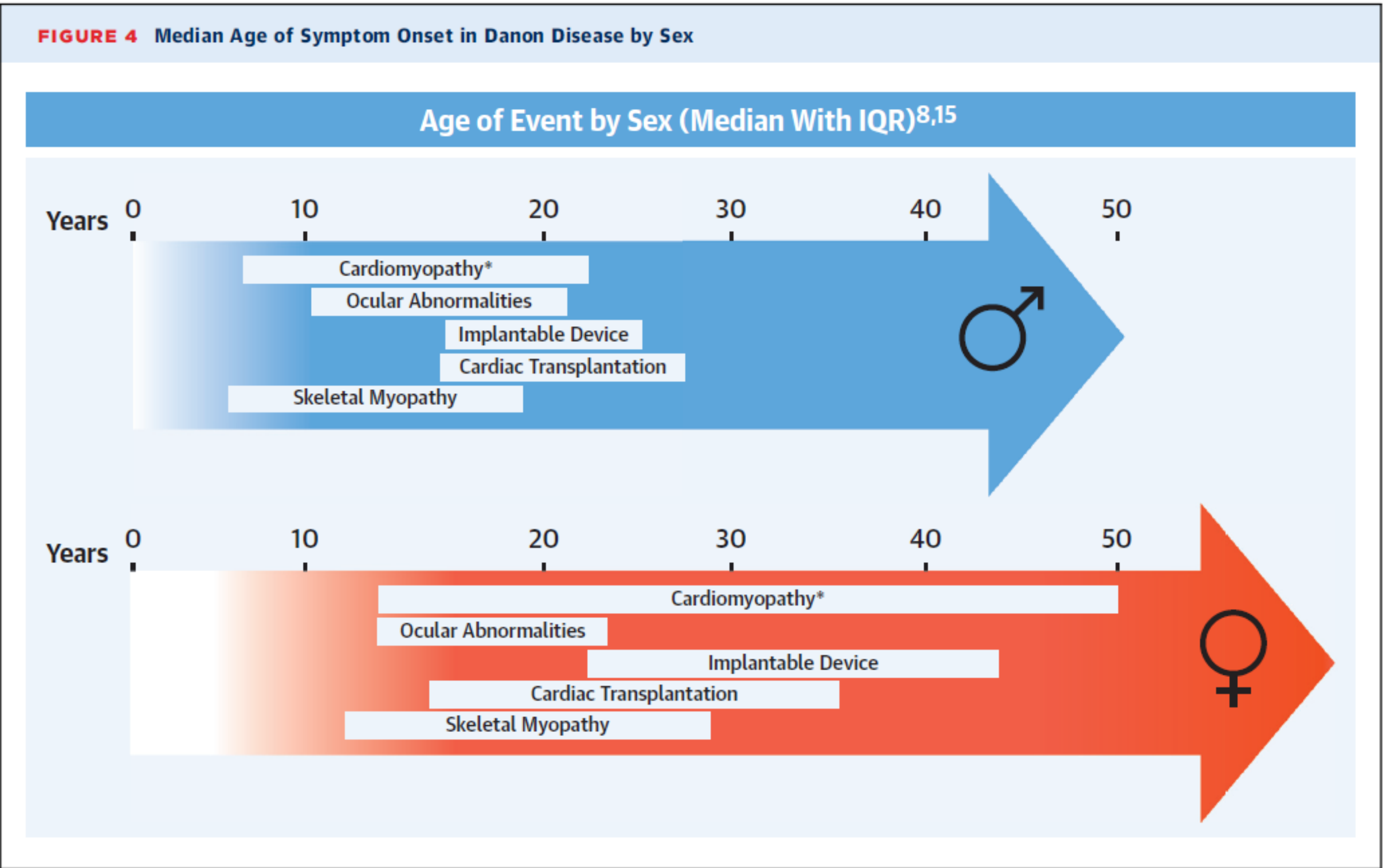
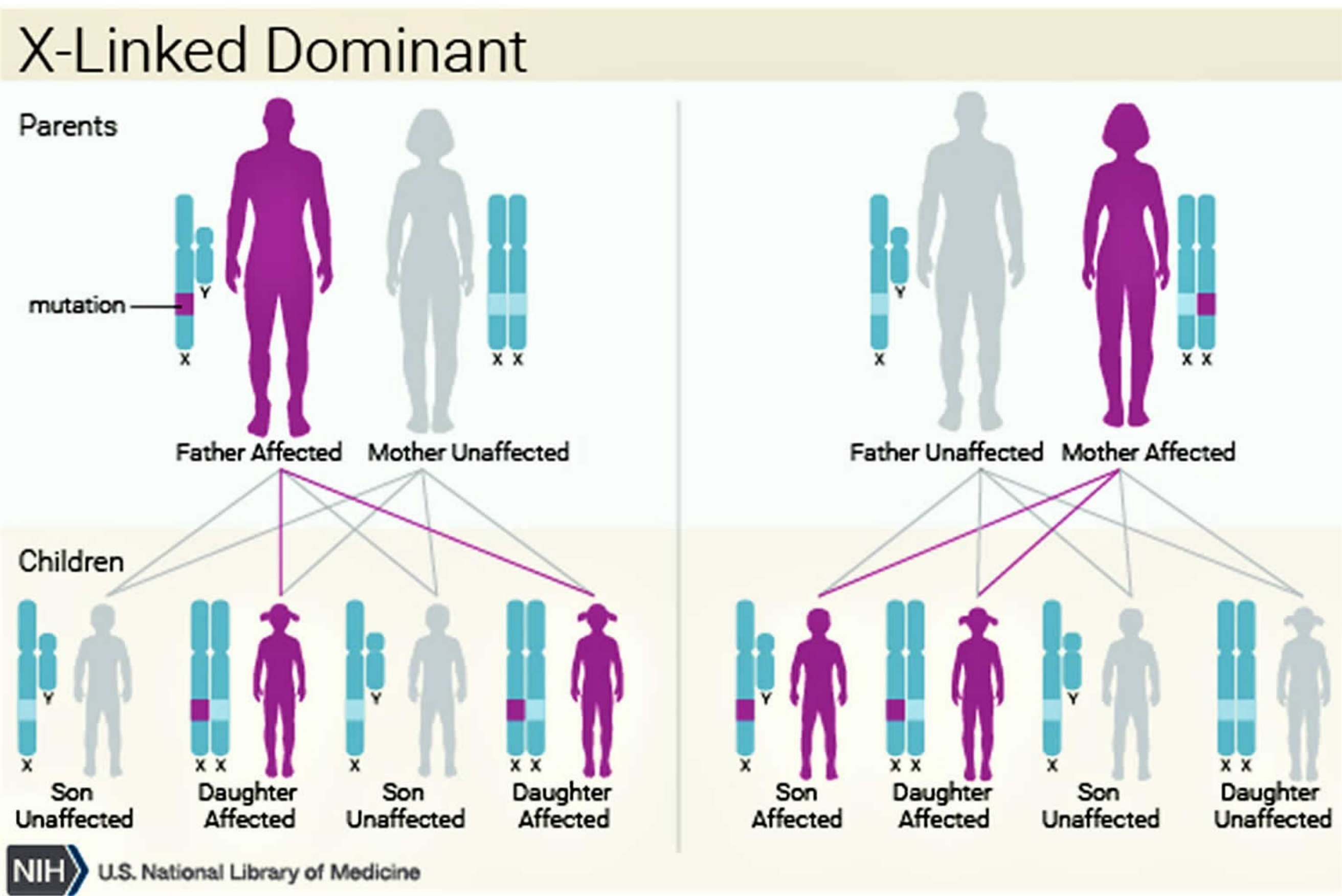


Etiology of hypertrophic cardiomyopathy in infants (age < 1 year) and in a young child (age 1–18 years). Modified from Limongelli et al. Int J Cardiol 2020



➤ **Ereditarietà** -> costruzione albero genealogico a tre/quattro generazioni

Cardiomyopathy phenotype		AD	AR	X-linked	Matrilineal
HCM	Sarcomeric	X			
	Anderson-Fabry			X	
	Danon			X	
	TTR amyloidosis	X			
	RASopathy	X	(X)		
	Friedreich ataxia		X		
	Mitochondrial				
	Mitochondrial DNA				X
	Nuclear DNA	X	X	X	



Examples of signs and symptoms suggestive of specific diagnoses

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 atrophy) • TTR-related amyloidosis (cotton wool type vitreous opacities) • Danon disease (retinitis pigmentosa) • Anderson-Fabry disease (cataracts, corneal opacities)

www.escardio.org/guidelines European Heart Journal (2014);35:2733-2779 - doi:10.1093/eurheartj/ehu284



Examples of signs and symptoms suggestive of specific diagnoses (Cont.)

Symptom/sign	Diagnosis
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

FHL1 = four and a half LIM domains 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and sensorineural deafness; TTR = transthyretin.

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Stroke, TIA

Anderson-Fabry disease, mitochondrial disease



Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants

Finding	Comment
Short PR interval/ pre-excitation	Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.
AV block	Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.
Extreme LVH (Sokolow score ≥ 50)	Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.
Low QRS voltage (or normal voltages despite increased LV wall thickness)	Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.

www.escardio.org/guidelines European Heart Journal (2014);35:2733-2779 - doi:10.1093/eurheartj/ehu284



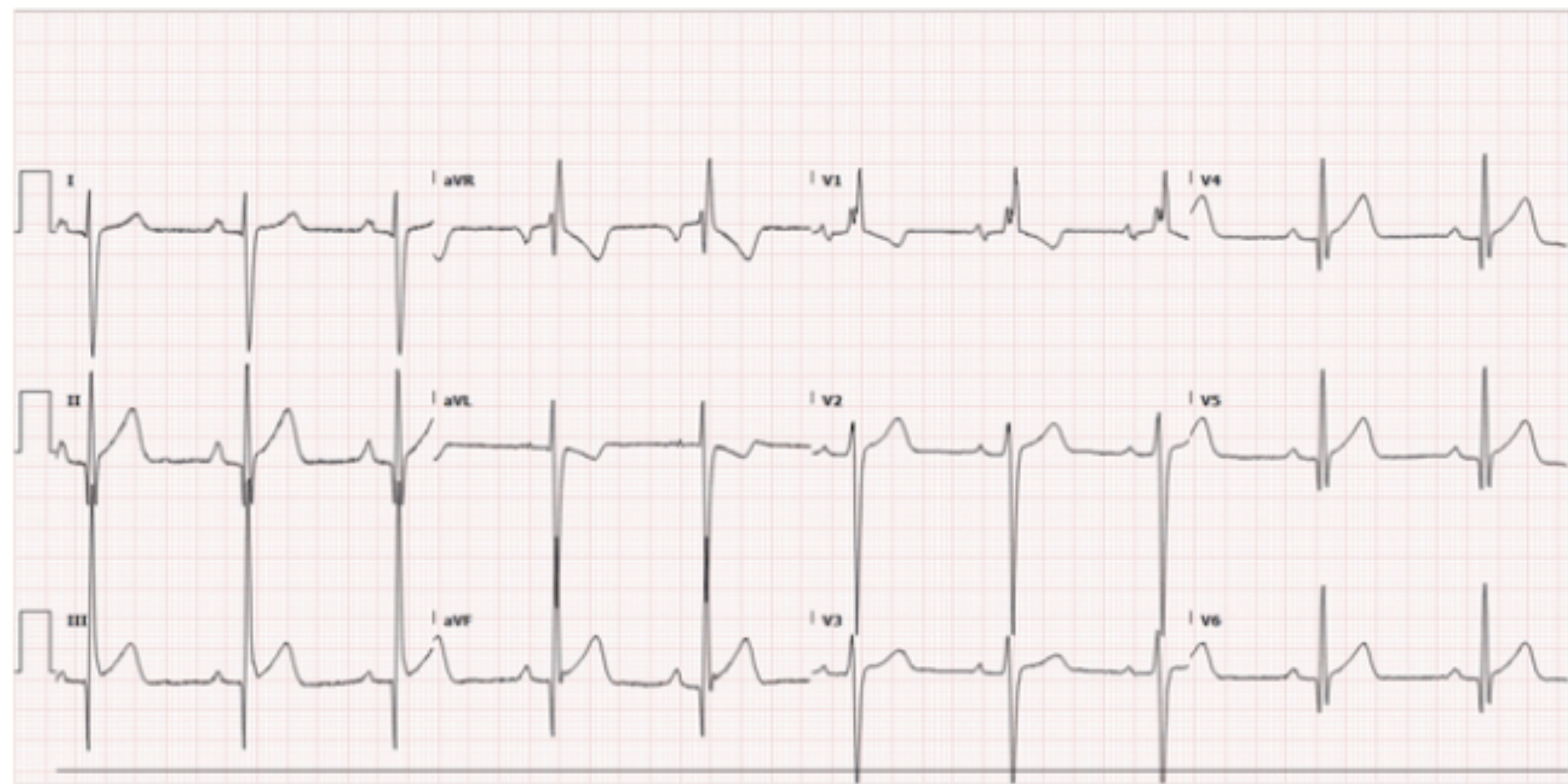
Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants (Cont.)

Finding	Comment
Extreme superior ("North West") QRS axis deviation	Seen in patients with Noonan syndrome who have severe basal hypertrophy extending into the RV outflow tract.
Giant negative T wave inversion (>10 mm)	Giant negative T wave inversion in the precordial and/or inferolateral leads suggests involvement of the LV apex.
Abnormal Q waves ≥ 40 ms in duration and/or $\geq 25\%$ of the R wave in depth and/or ≥ 3 mm in depth in at least two contiguous leads except aVR	Abnormally deep Q waves in the inferolateral leads, usually with a positive T wave, are associated with an asymmetrical distribution of LVH. Q waves of abnormal duration (≥ 40 ms) are associated with areas of replacement fibrosis.
Coved ST-segment elevation in lateral chest leads	Some patients with apical or distal hypertrophy develop small apical aneurysms, sometimes associated with myocardial scarring. These may only be detectable on CMR, ventriculography or contrast echo, and are occasionally associated with ST-segment in the lateral chest leads.

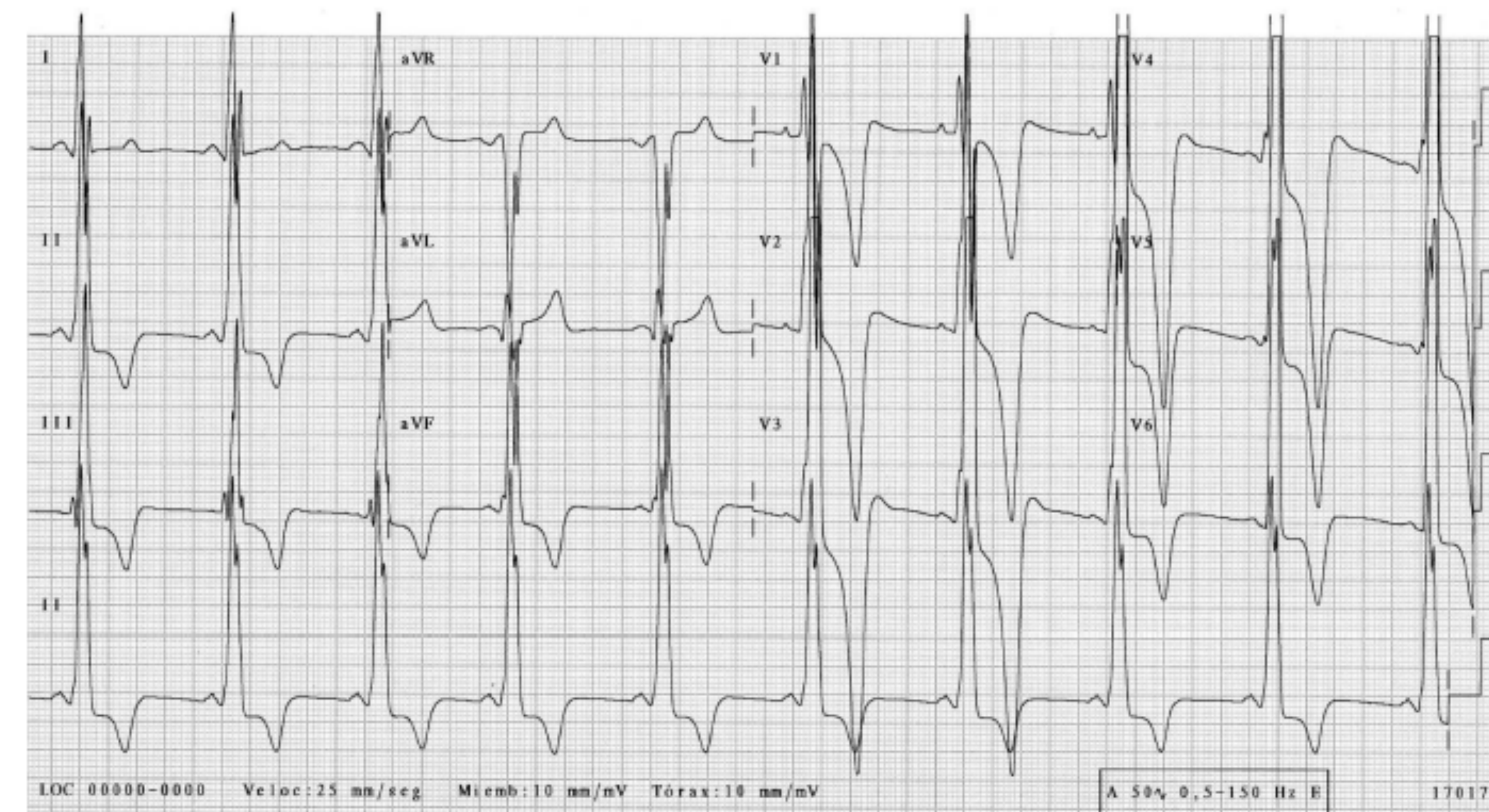
MELAS =mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF =myoclonic epilepsy with ragged red fibres; PRKAG2 = gamma-2 subunit of the adenosine monophosphate-activated protein kinase.

www.escardio.org/guidelines European Heart Journal (2014);35:2733-2779 - doi:10.1093/eurheartj/ehu284

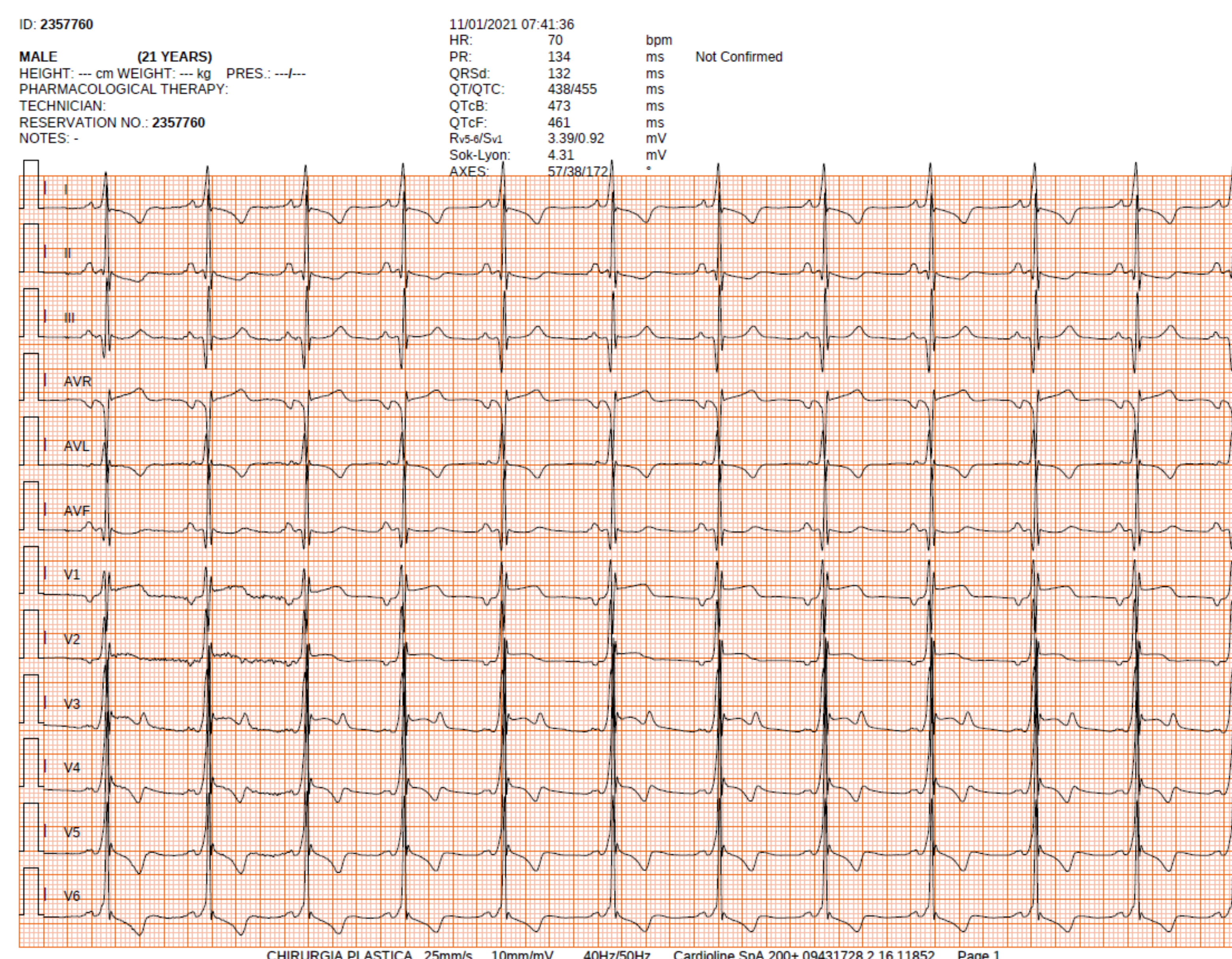




S. di Noonan



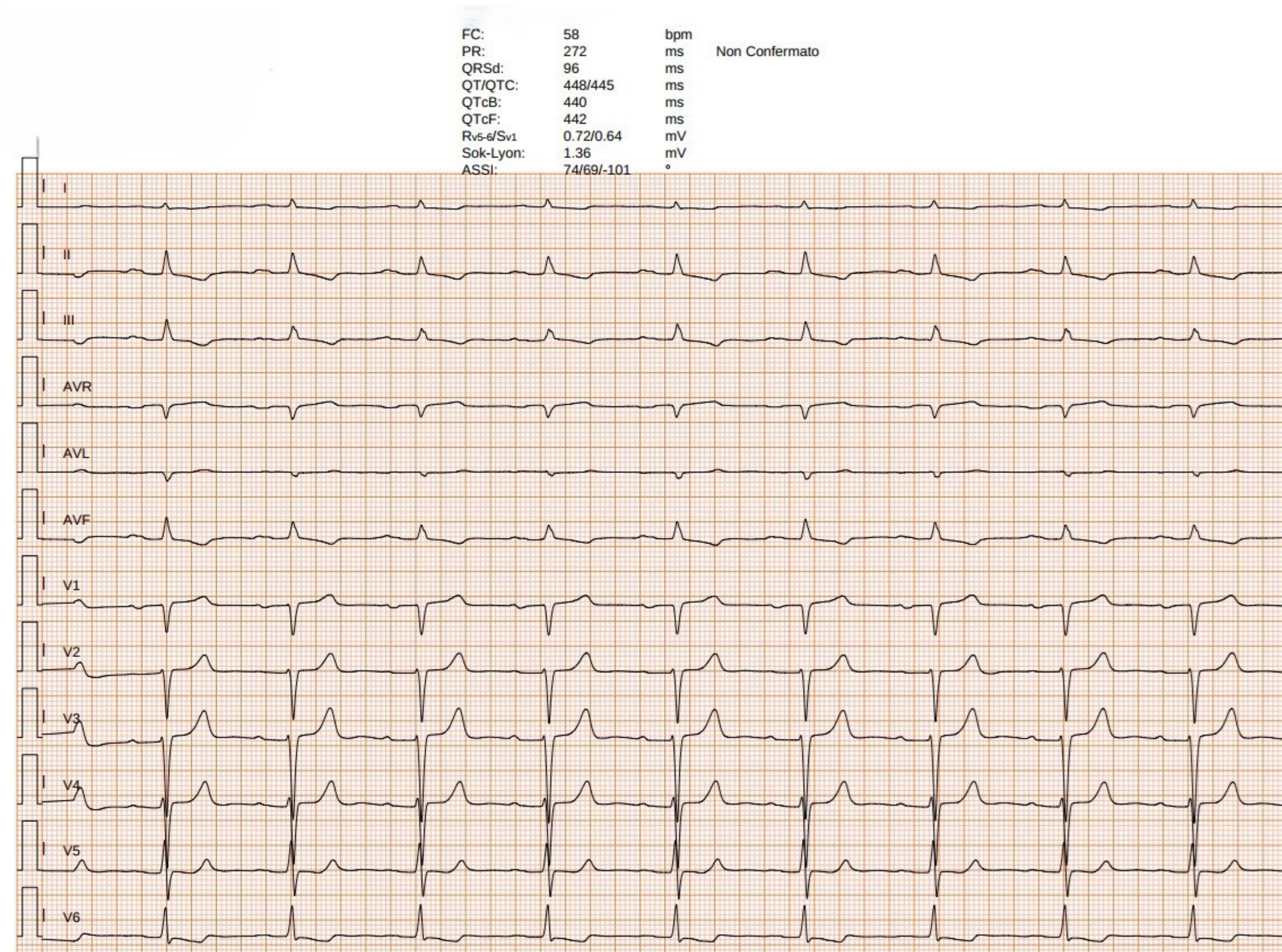
S. di Danon



S. PRKAG2

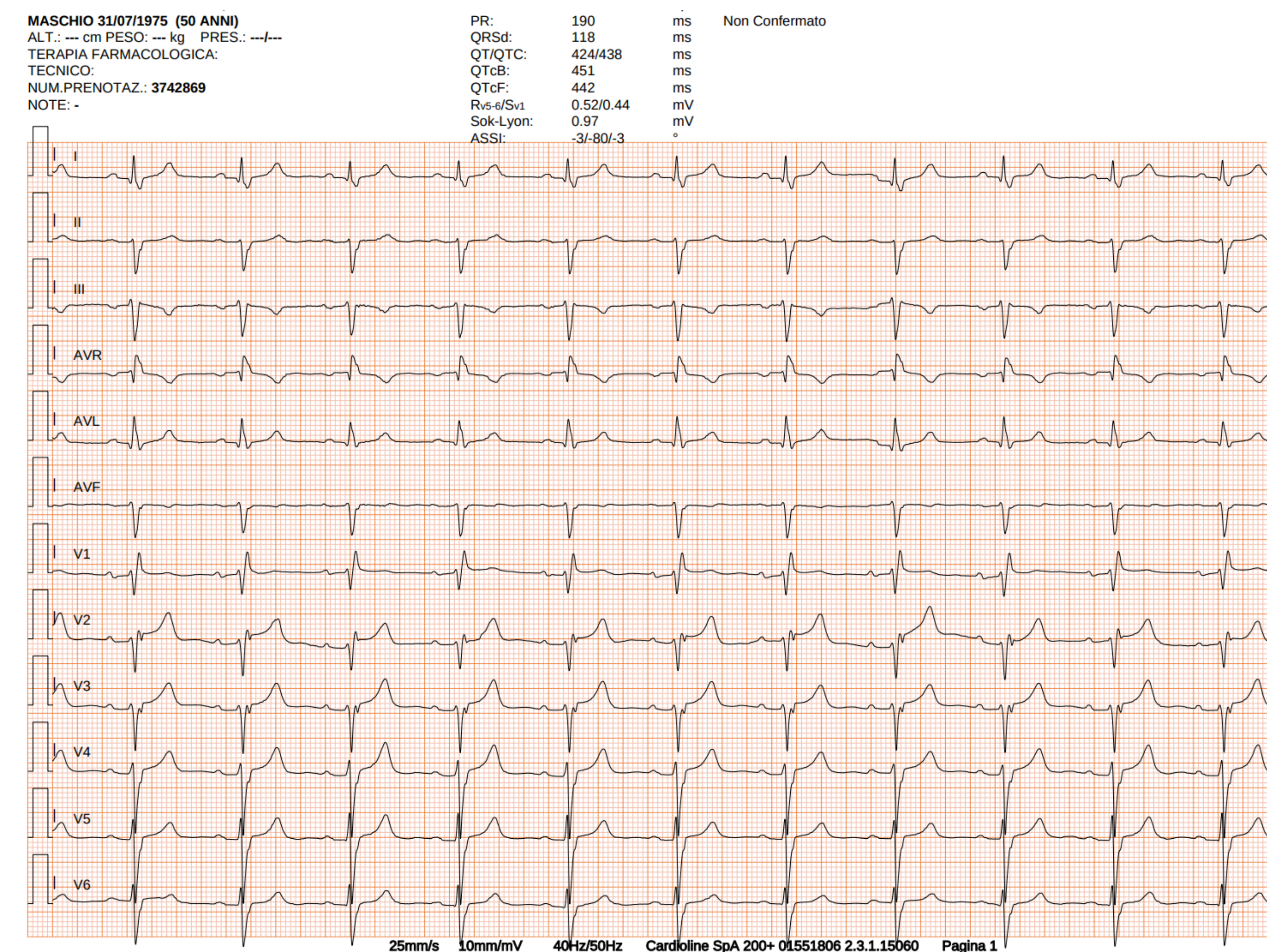


ATTRwt

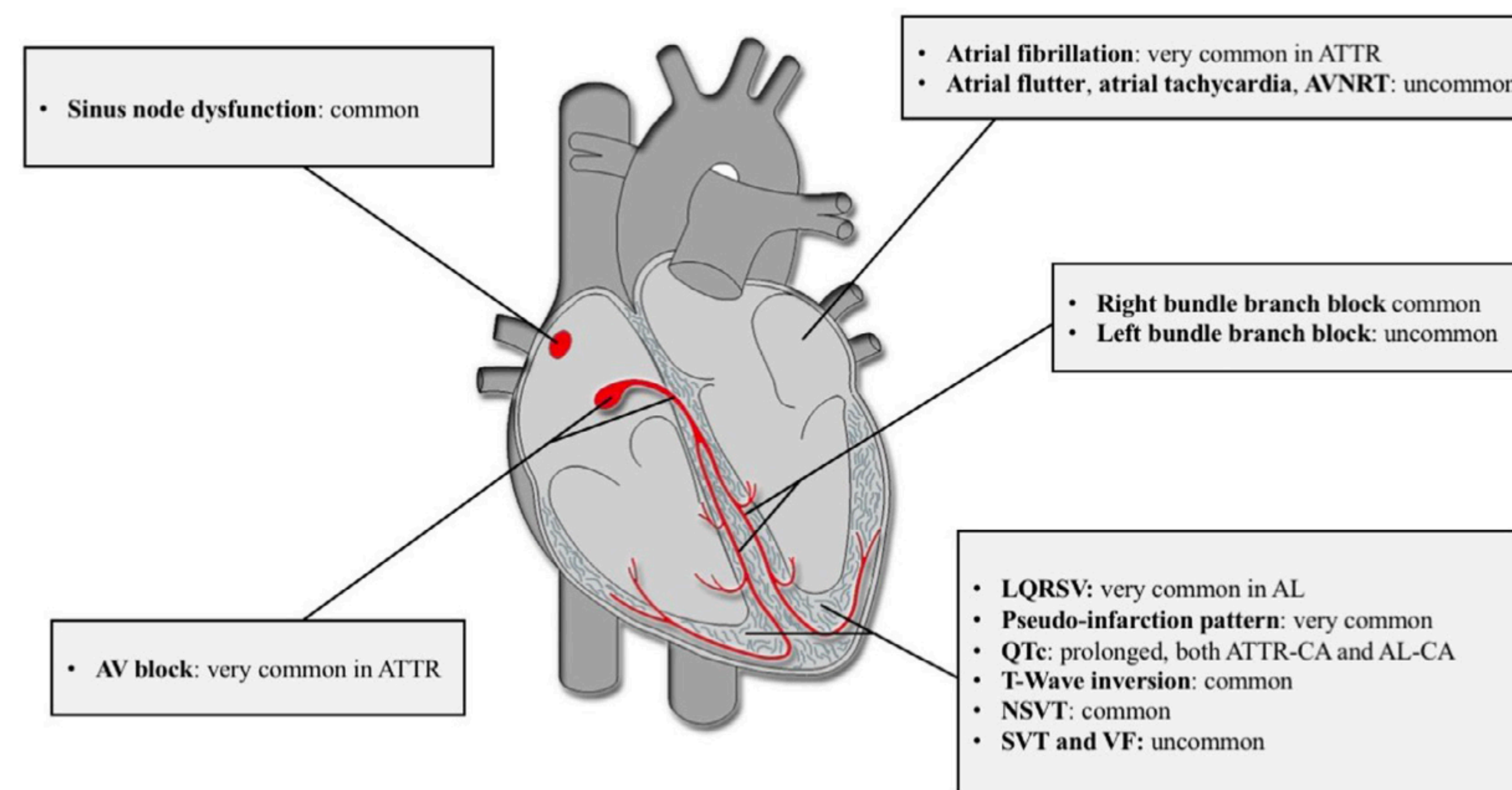


SIV 16 mm, PP 15 mm

ATTRv



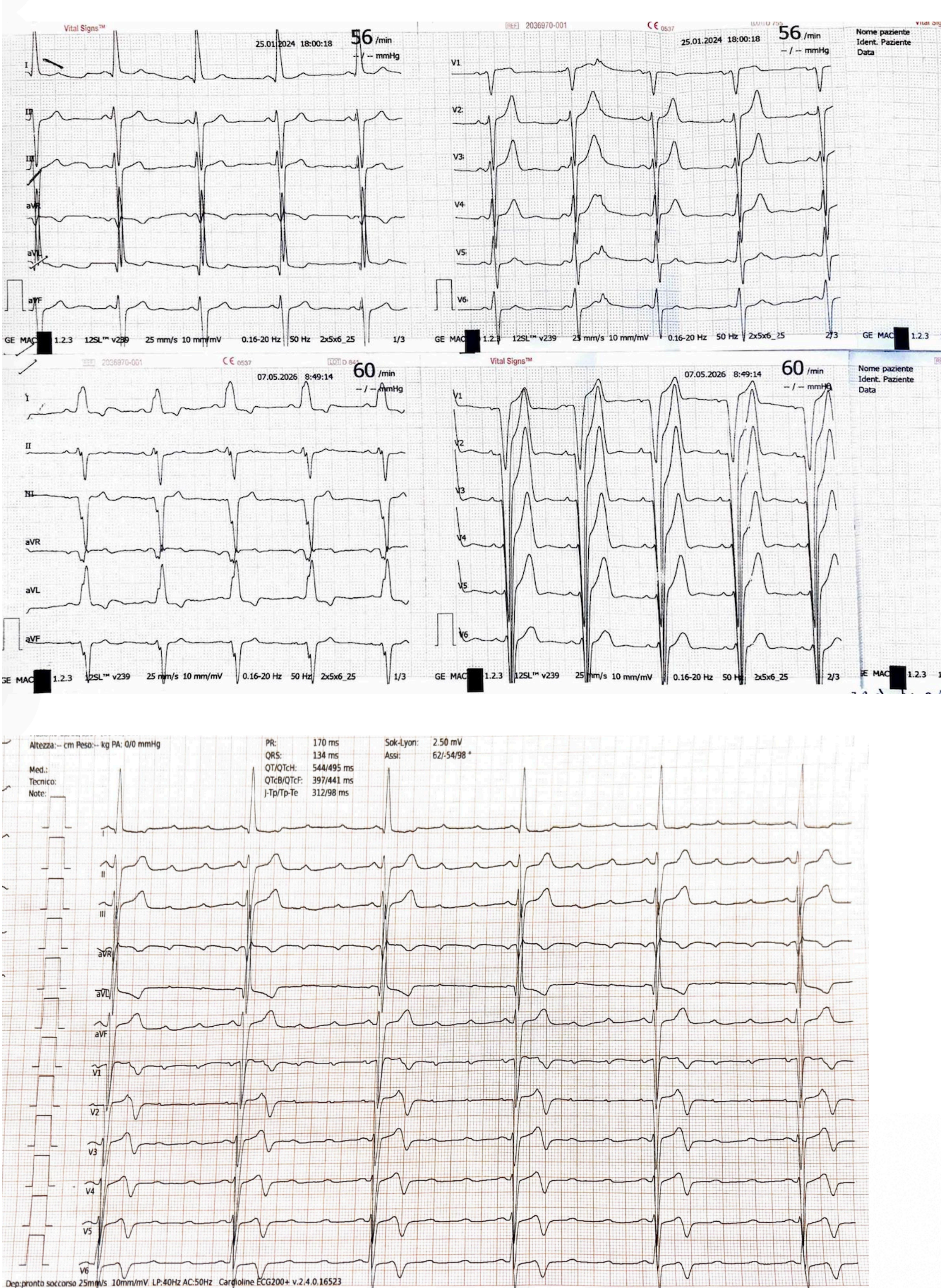
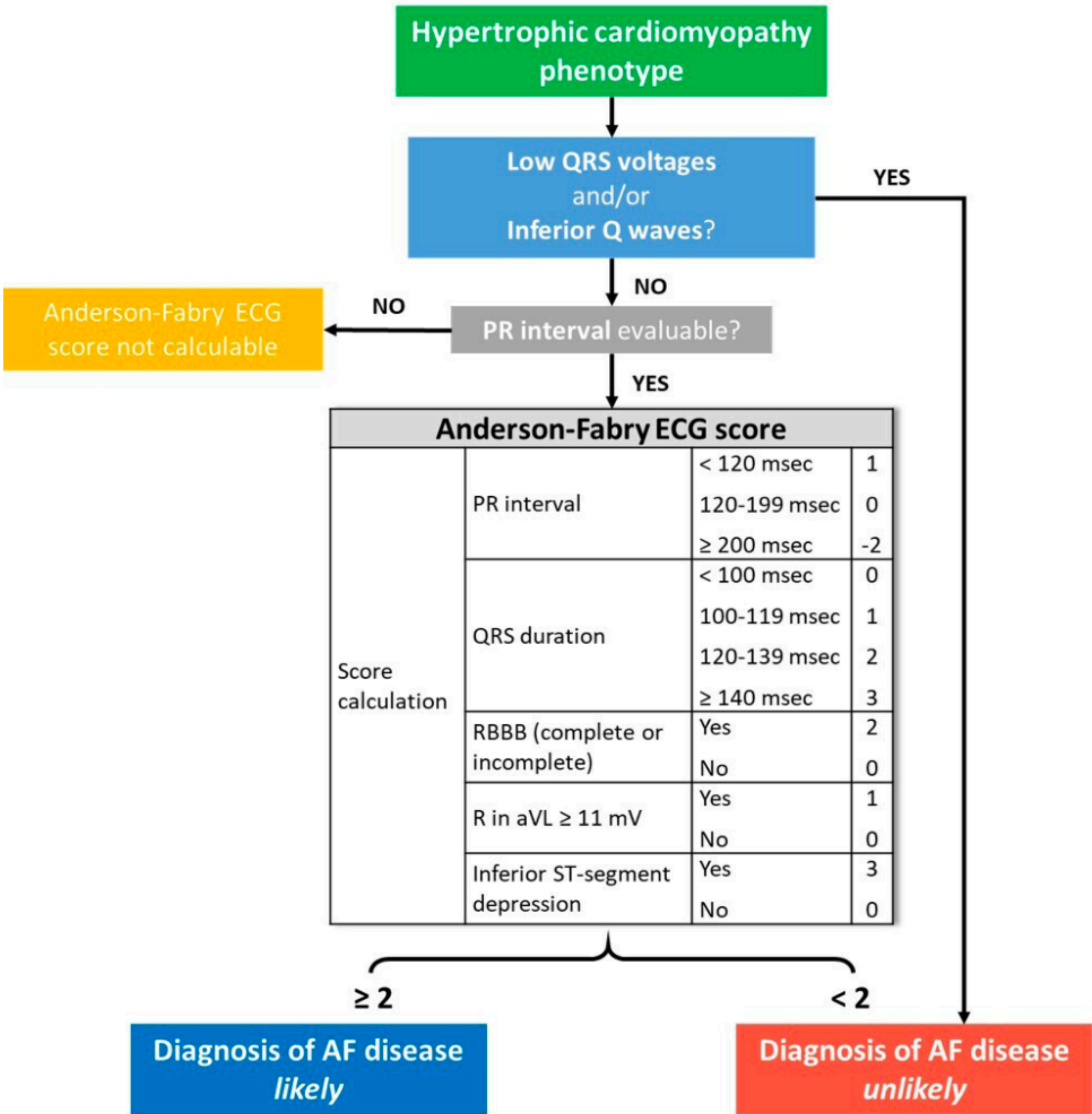
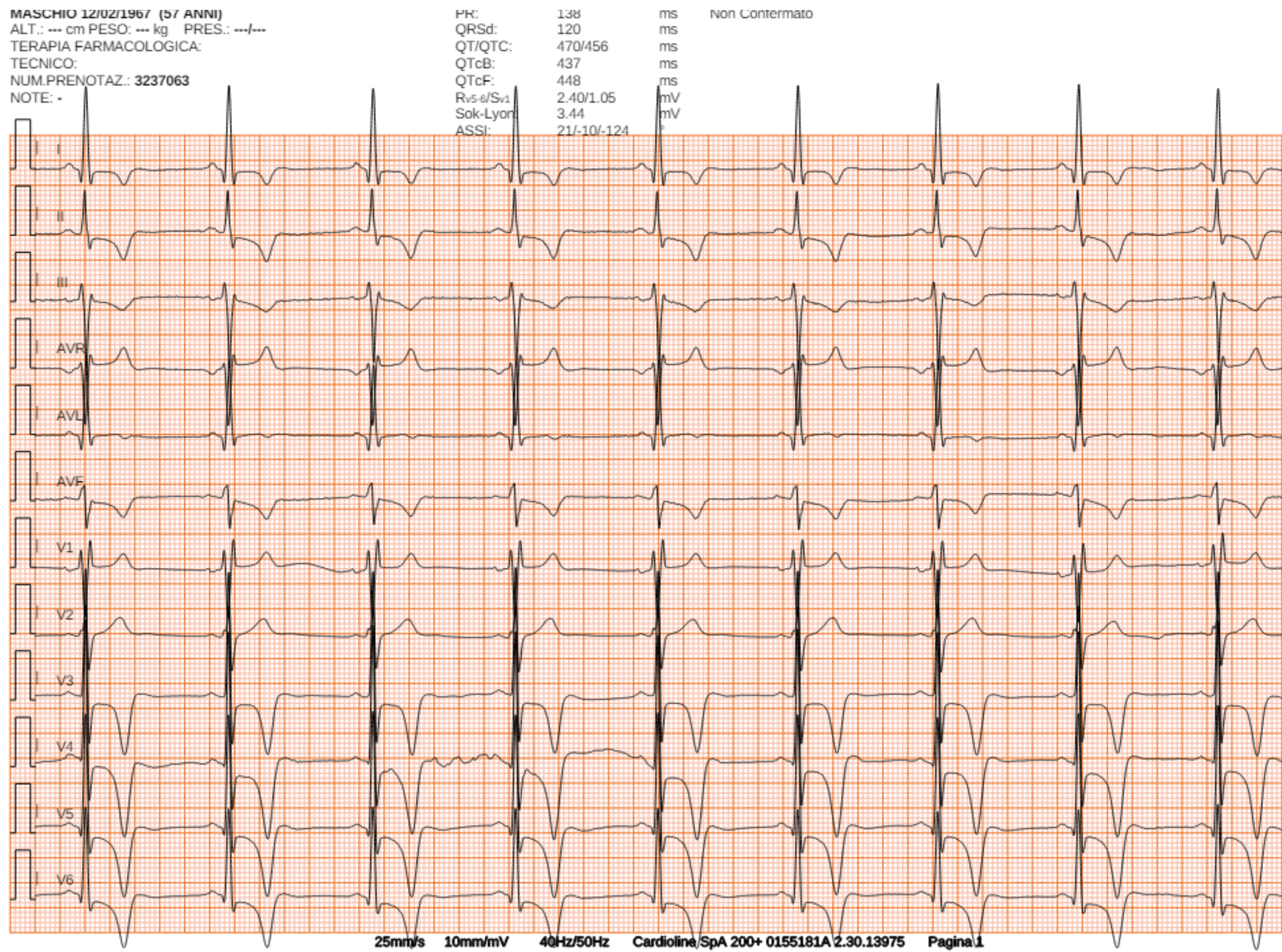
SIV 18 mm, PP 14 mm



Voltage-to-mass ratio, defined as Sokolow/Lyon index divided by the LV cross-sectional area, is generally more pronounced in ATTR- than AL-CA, reflecting the relatively higher LV thickness, mass and QRS voltages of the former



M. A. Fabry



Vitale G. et al Standard ECG for differential diagnosis between Anderson-Fabry disease and hypertrophic cardiomyopathy. Heart. 2022 Jan;108(1):54-60. doi: 10.1136/heartjnl-2020-318271.



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of cardiomyopathies



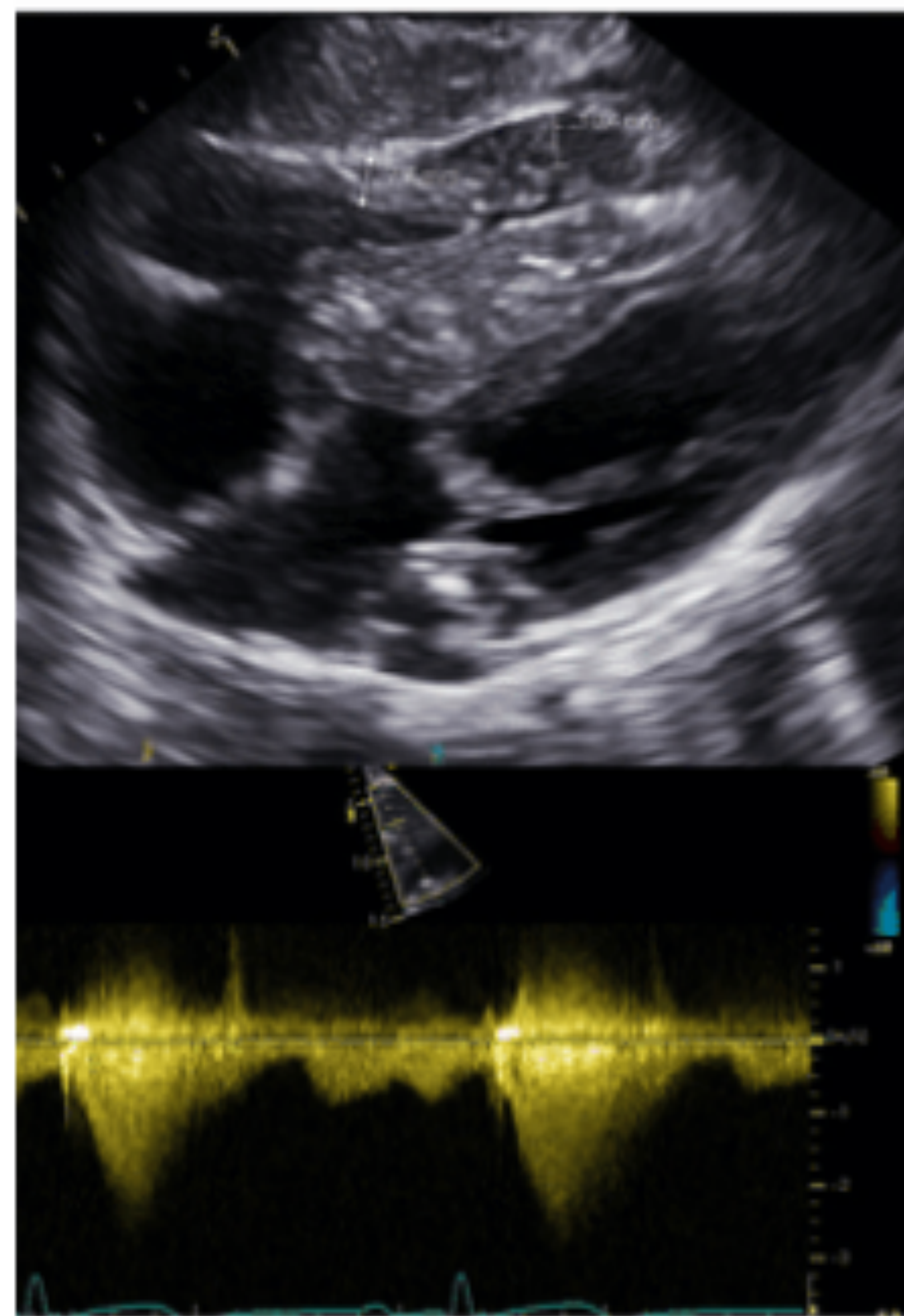
Table 18 Echocardiographic features that suggest specific aetiologies in hypertrophic cardiomyopathy

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/myopericarditis
Ground-glass appearance of ventricular myocardium on 2D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson–Fabry disease, <i>PRKAG2</i> variants, Friedreich ataxia
Extreme concentric LVH (wall thickness ≥ 30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, <i>PRKAG2</i> variants, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson–Fabry disease, Friedreich ataxia
RVOTO	Noonan syndrome and associated disorders
Apical sparing pattern on longitudinal strain imaging	Amyloidosis

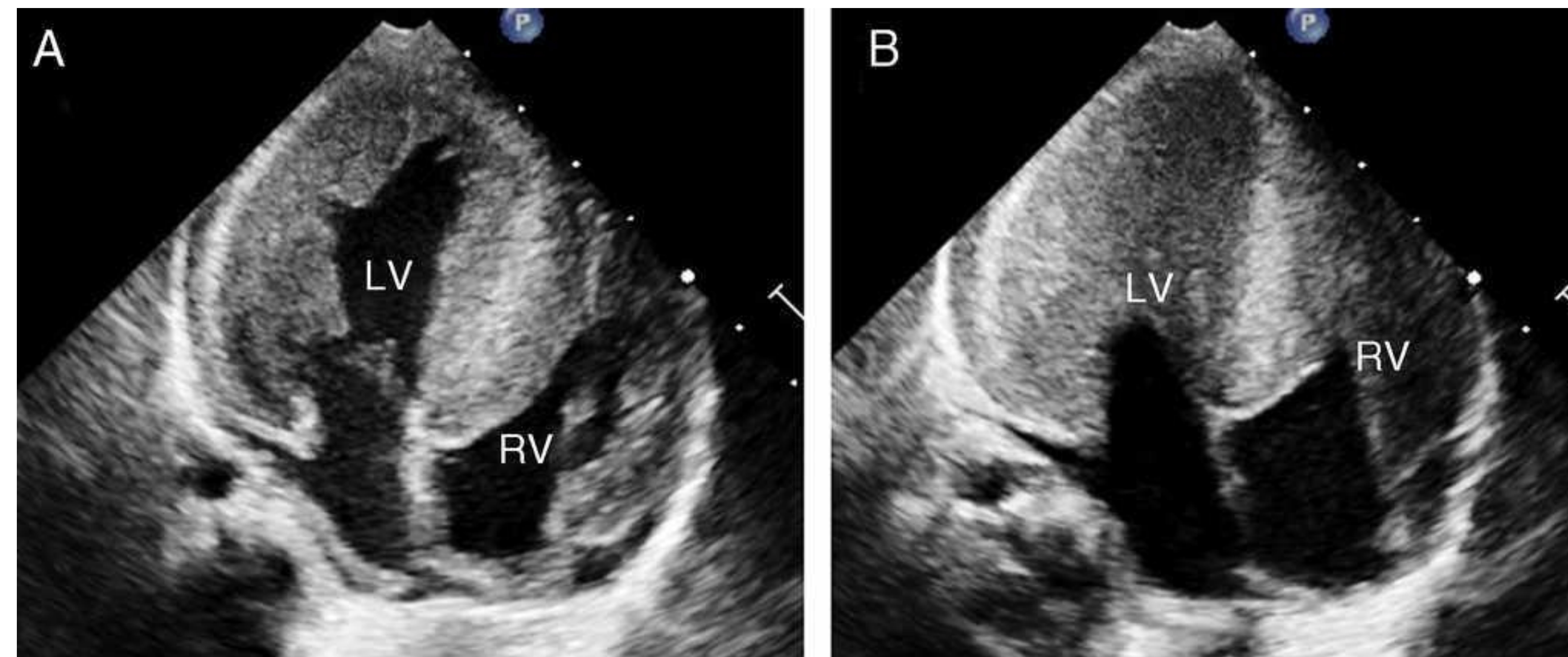
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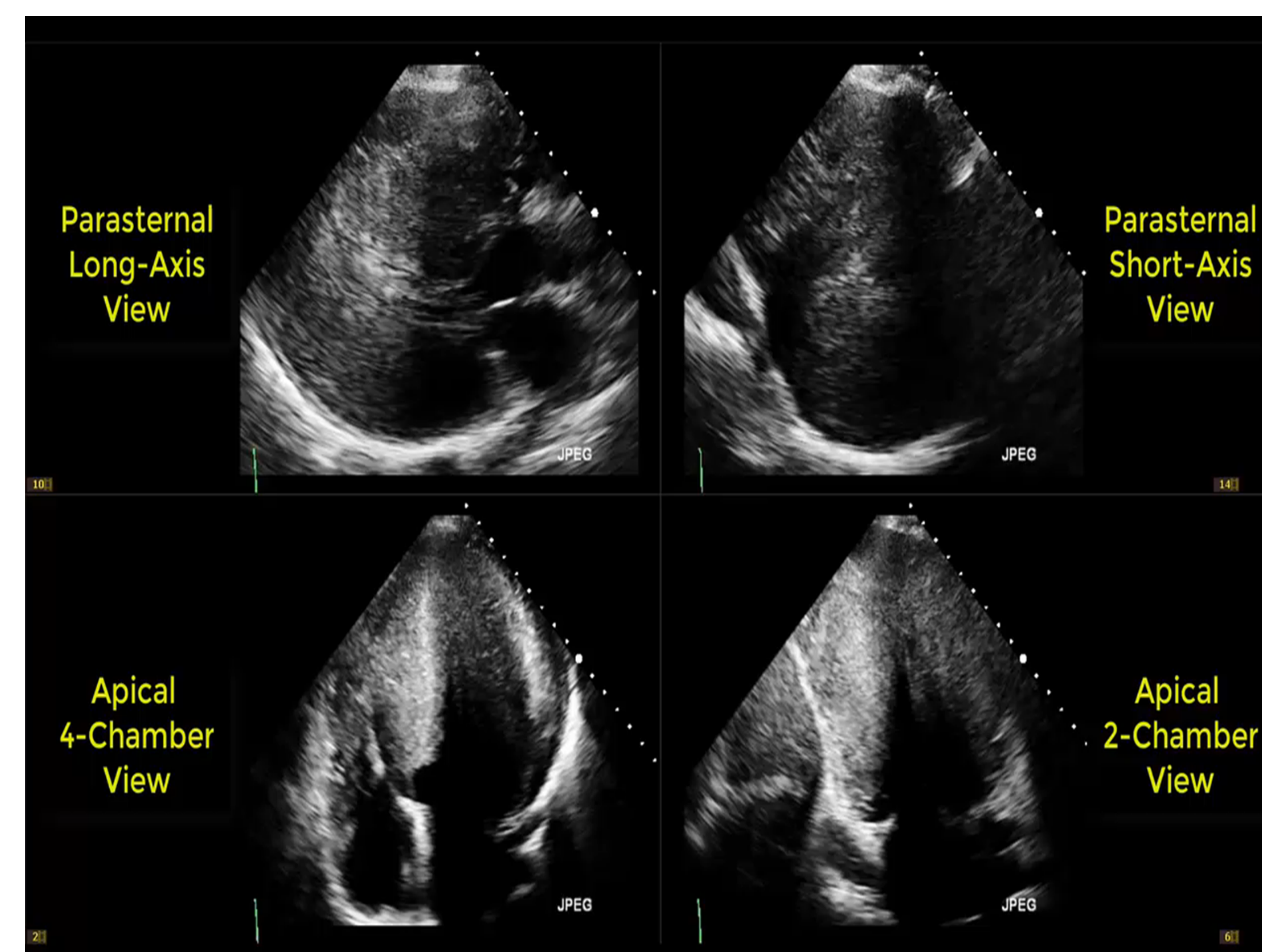
S. di Noonan



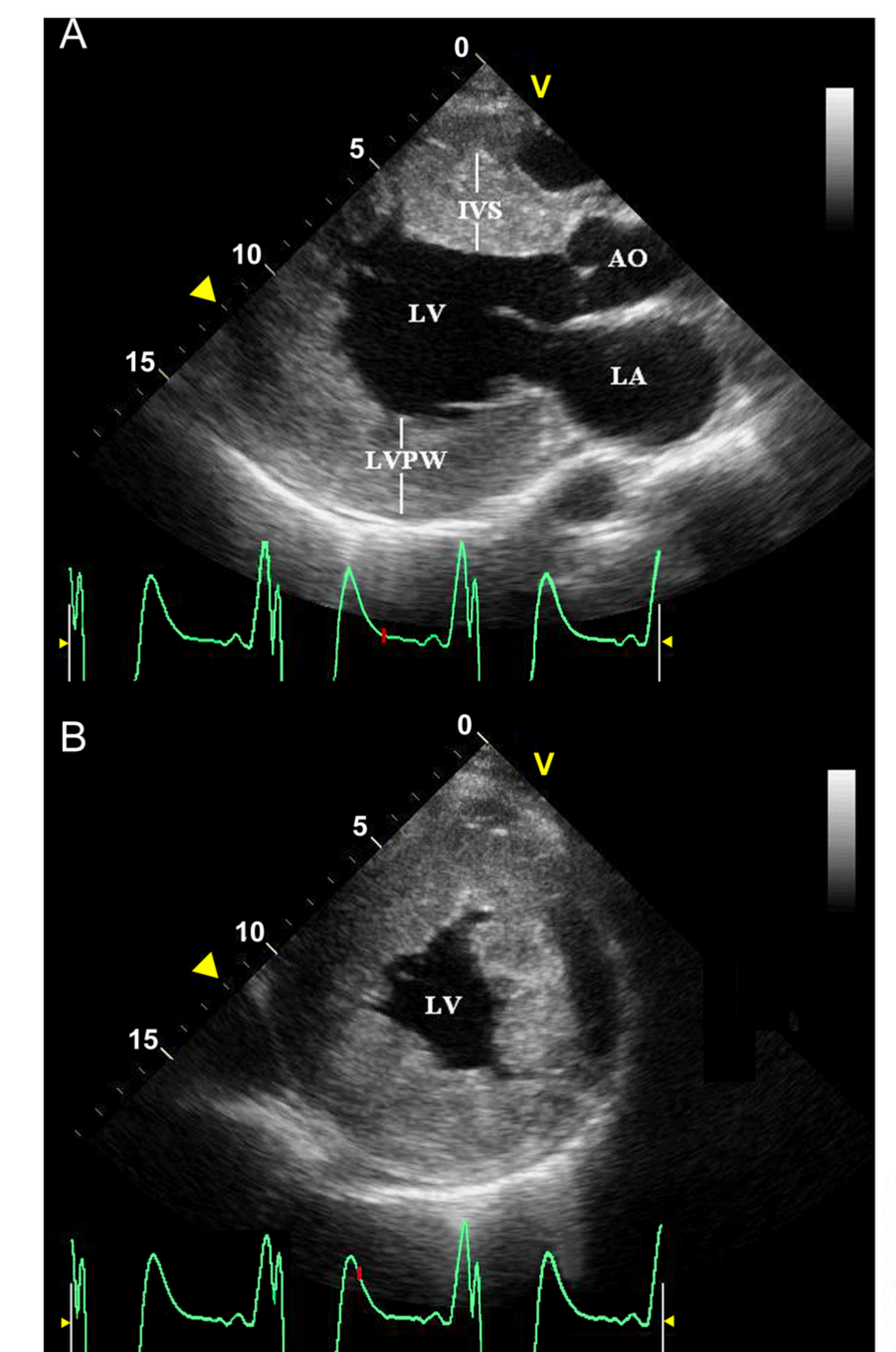
S. di Pompe



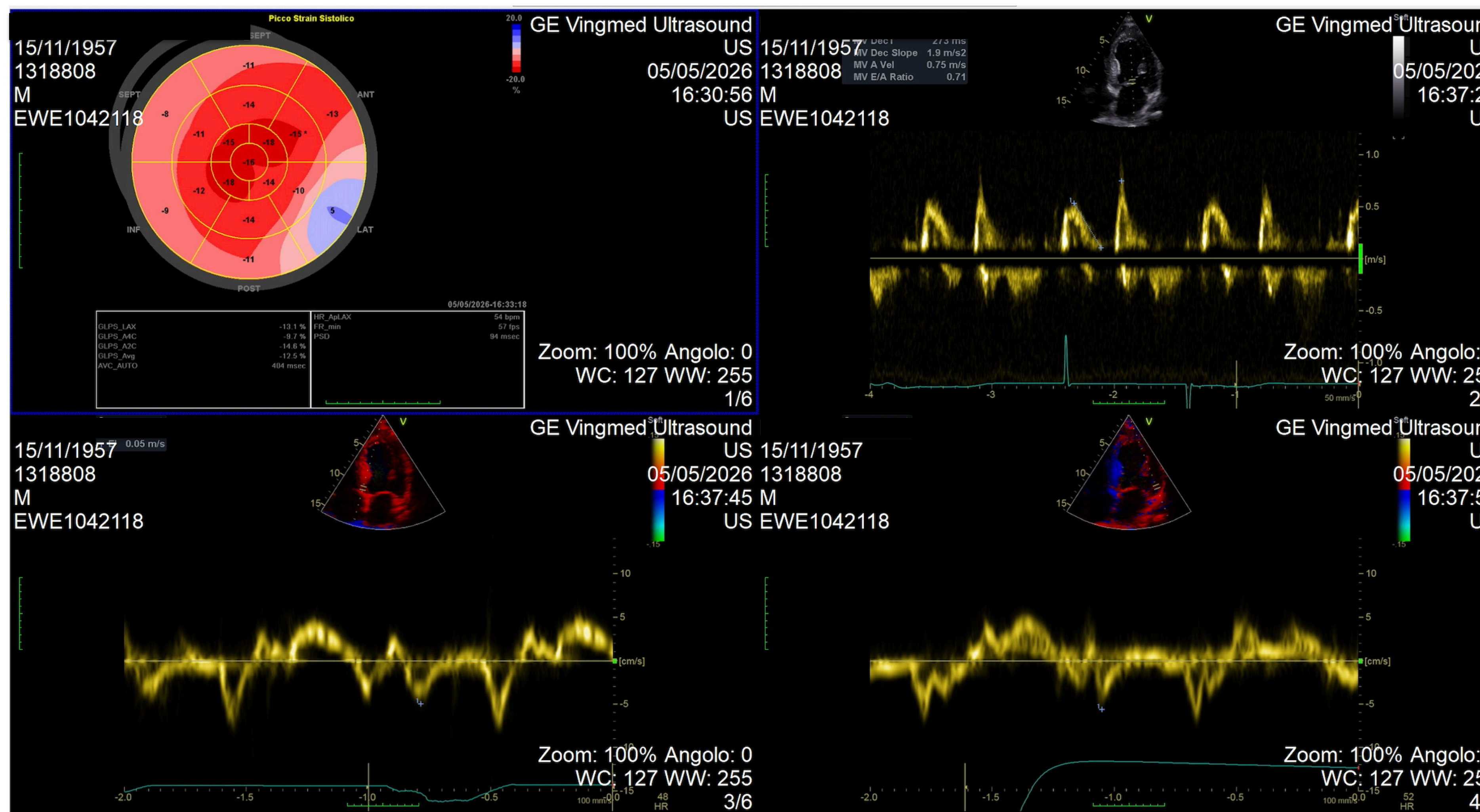
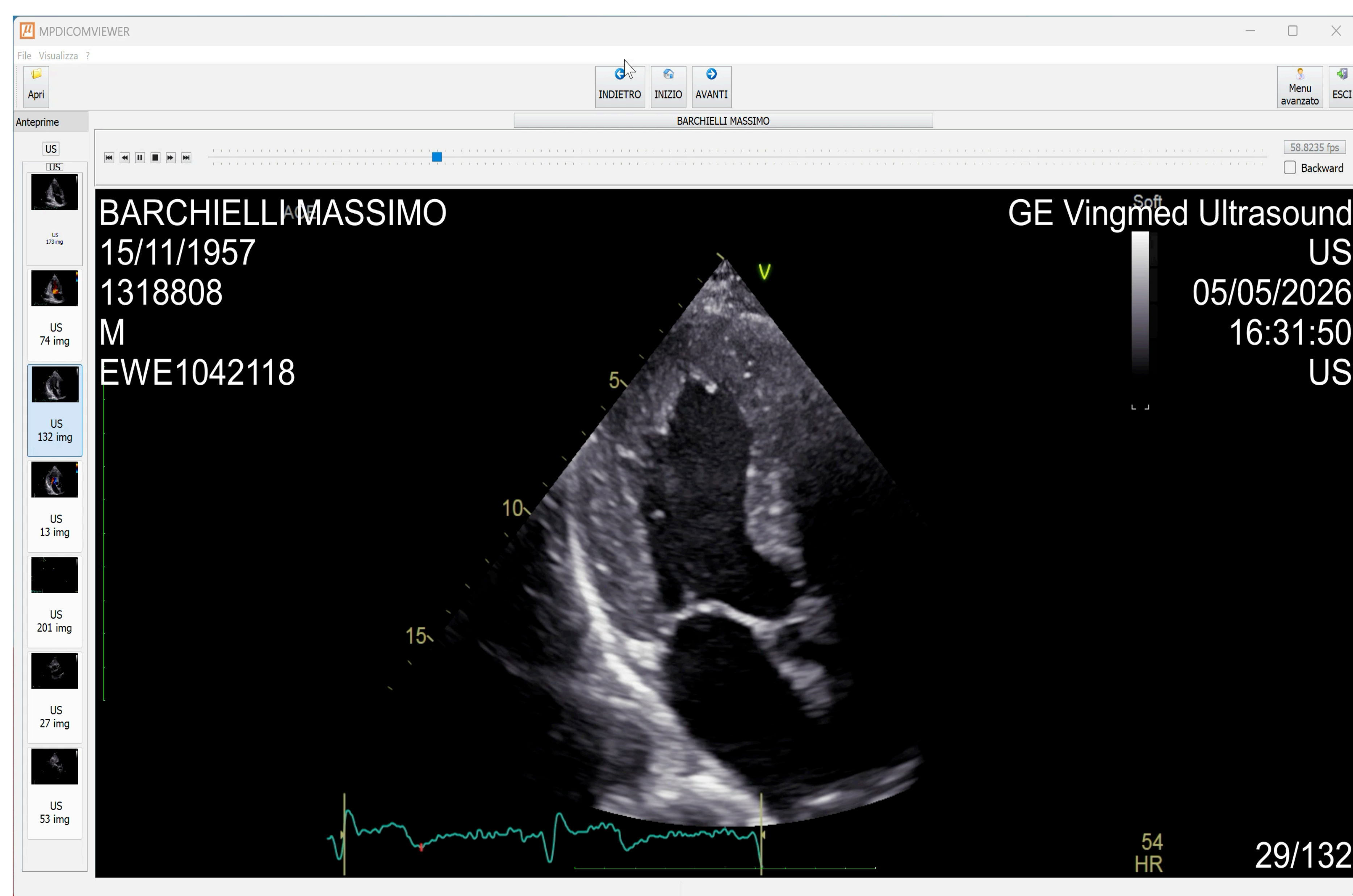
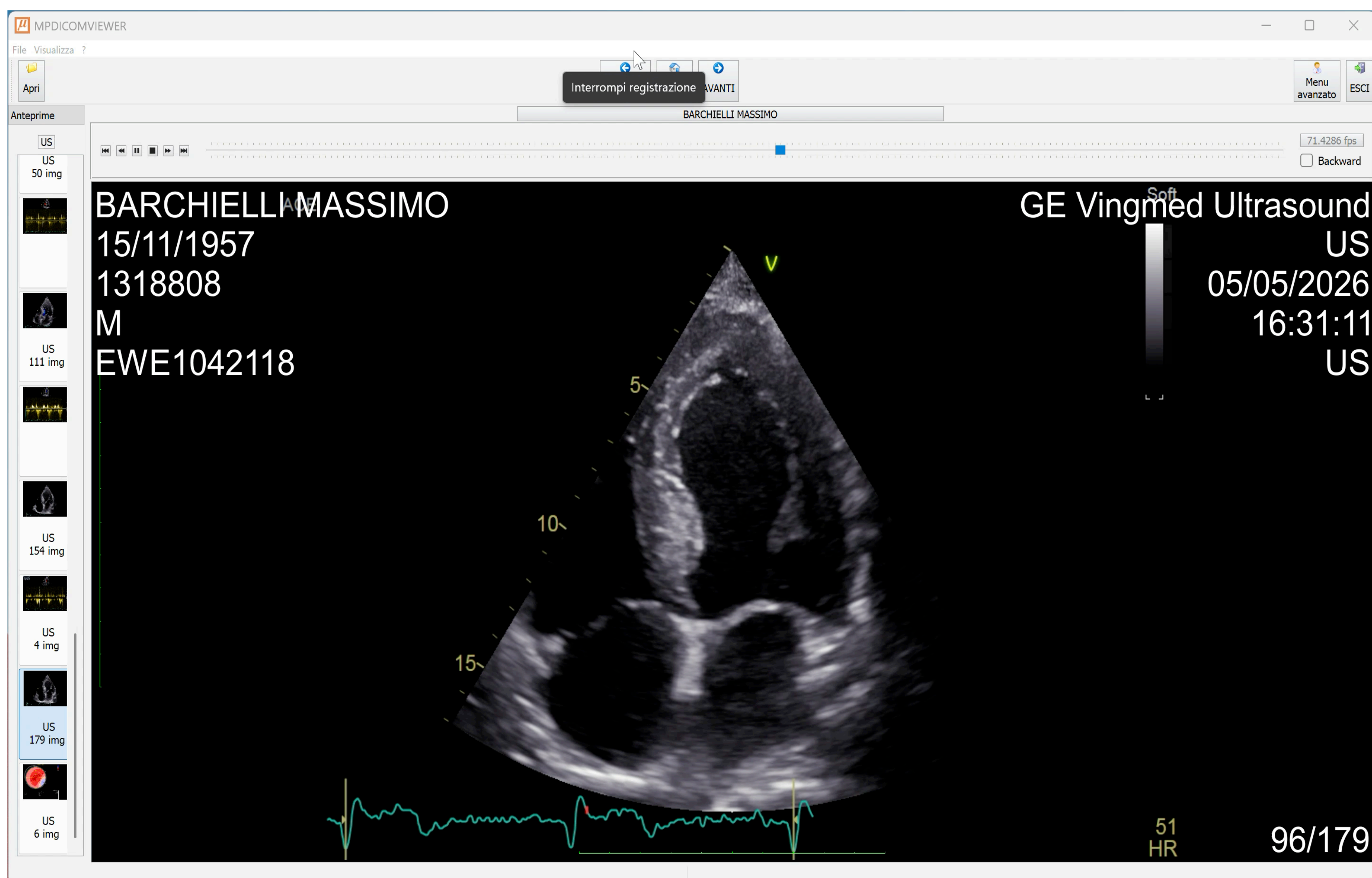
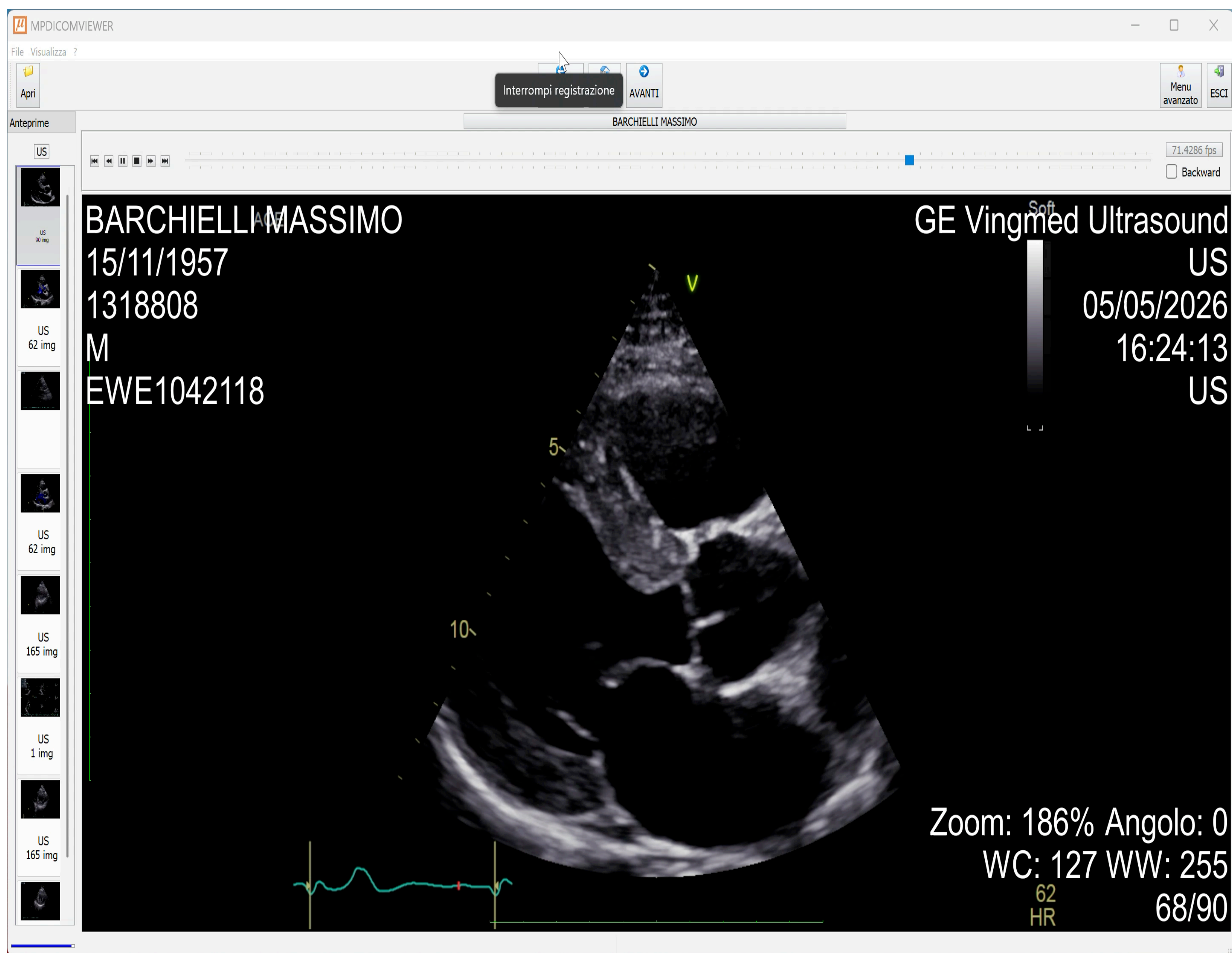
S. di Danon

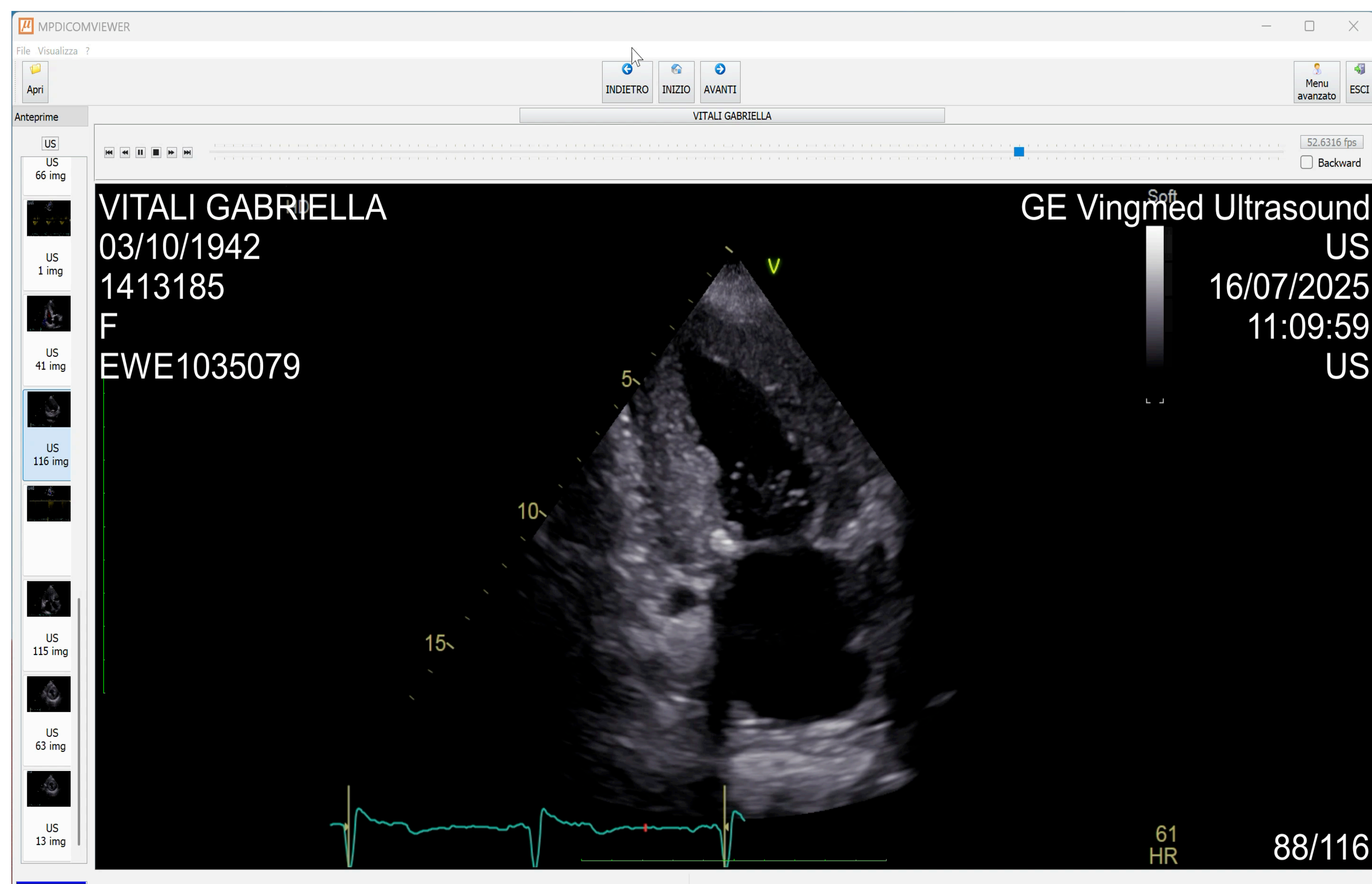
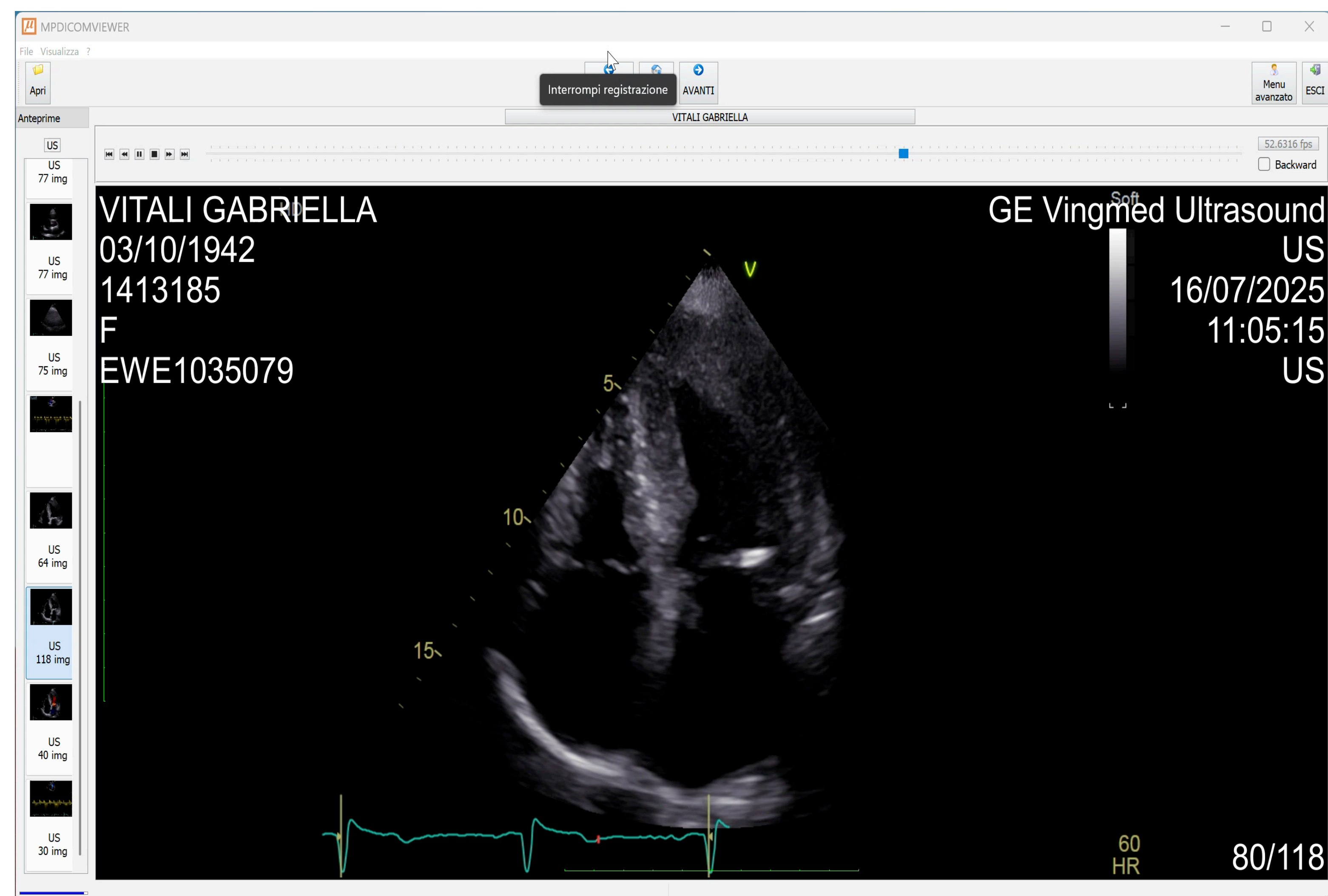
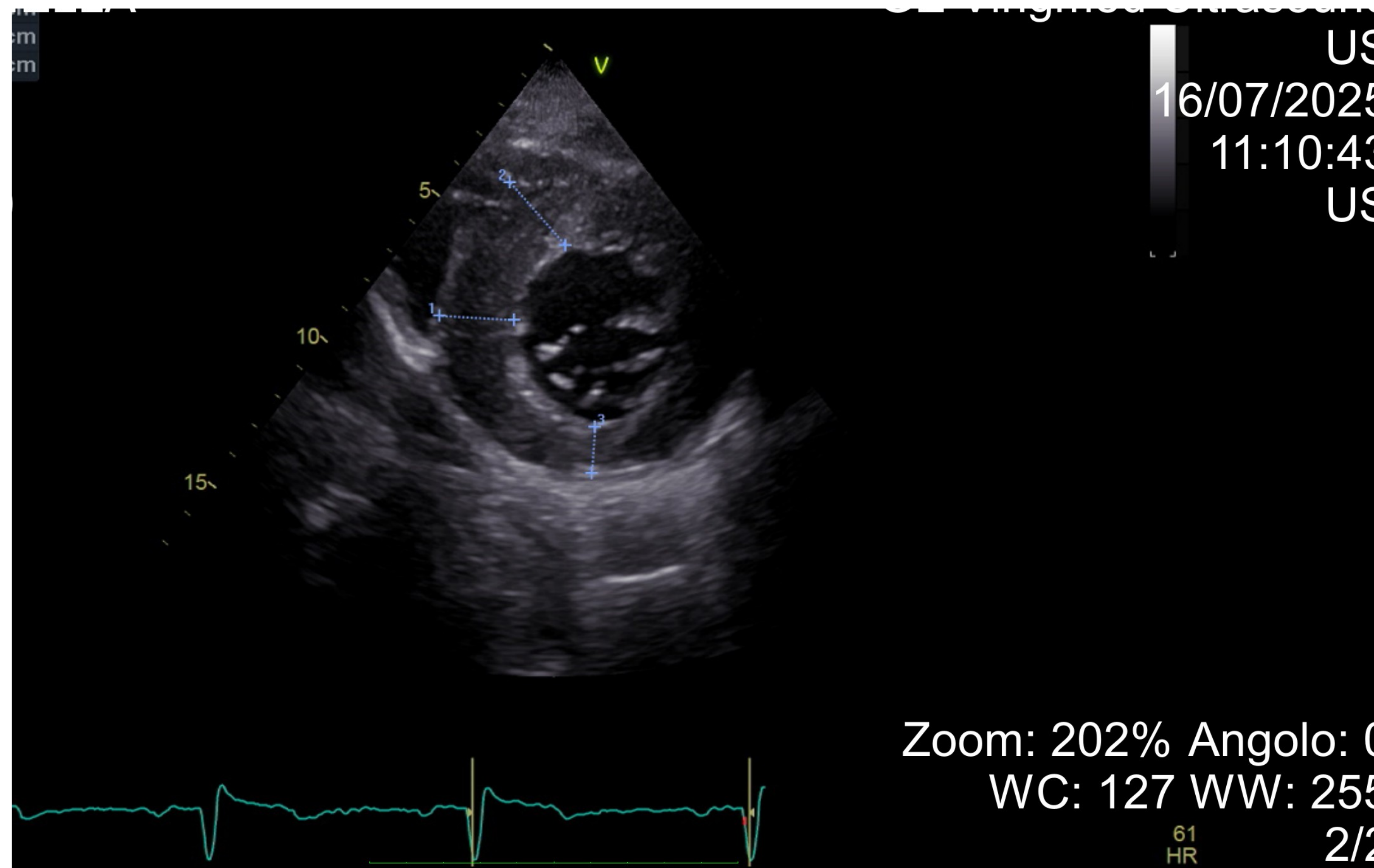
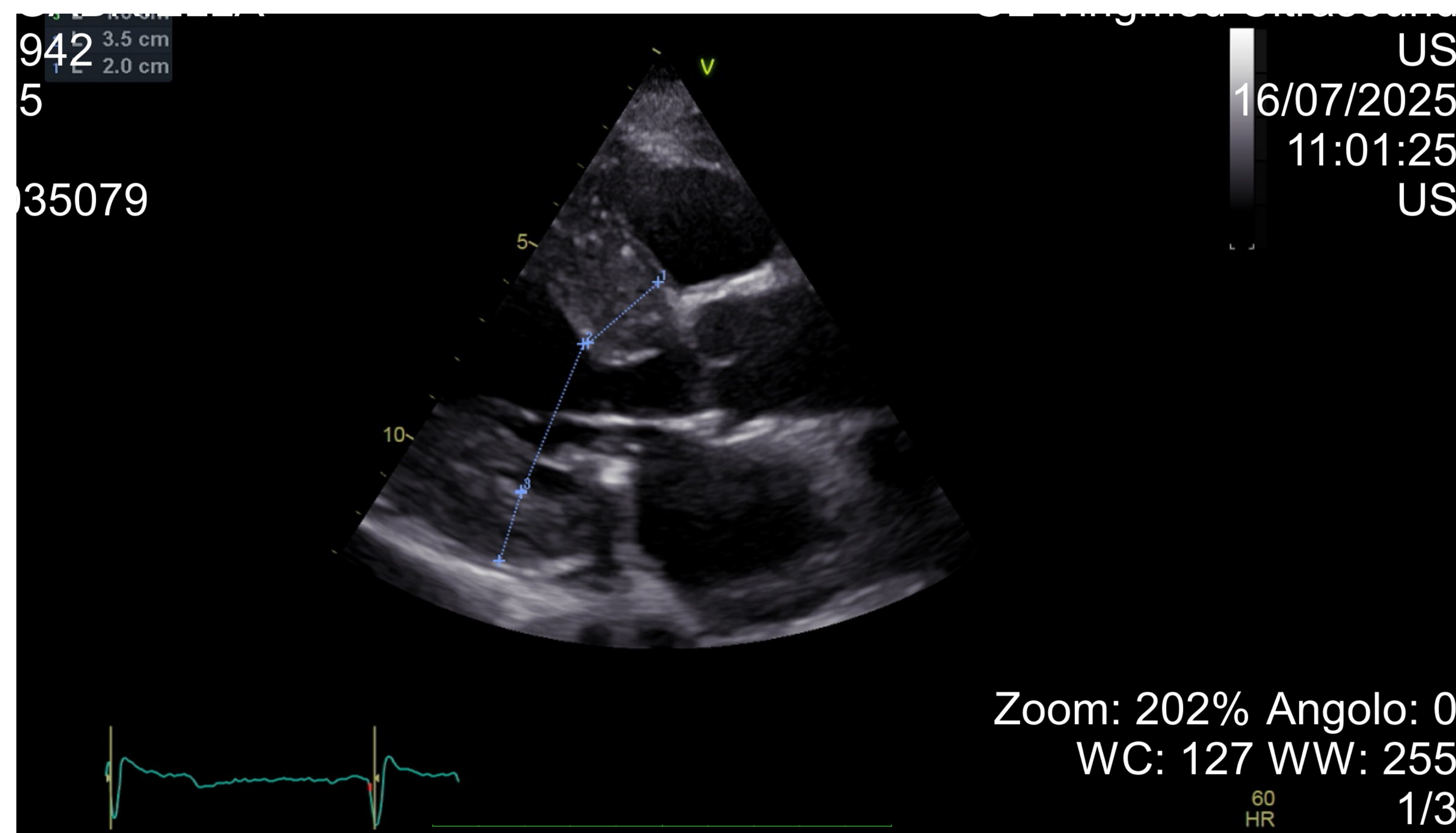


S. PRKAG2

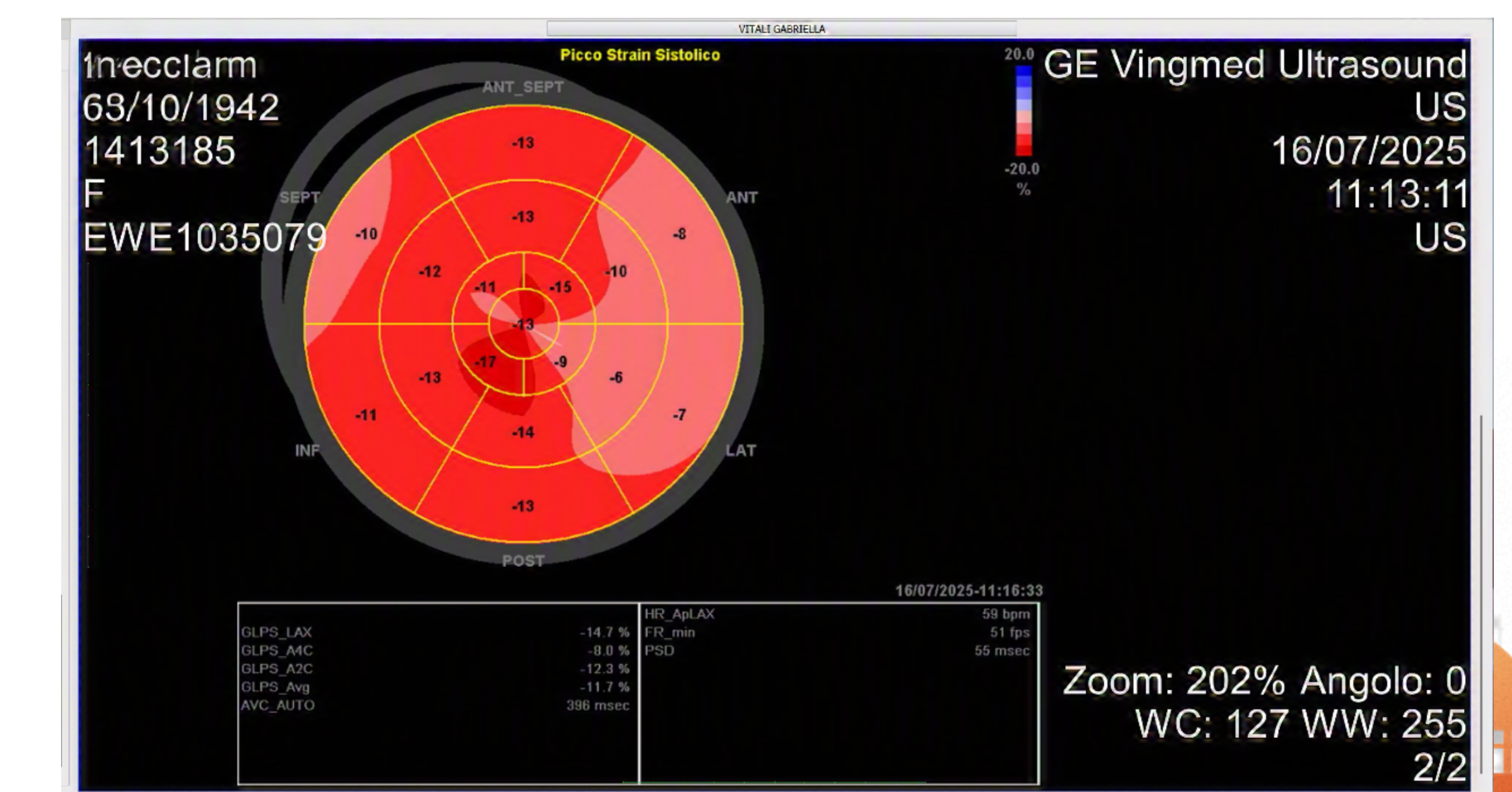
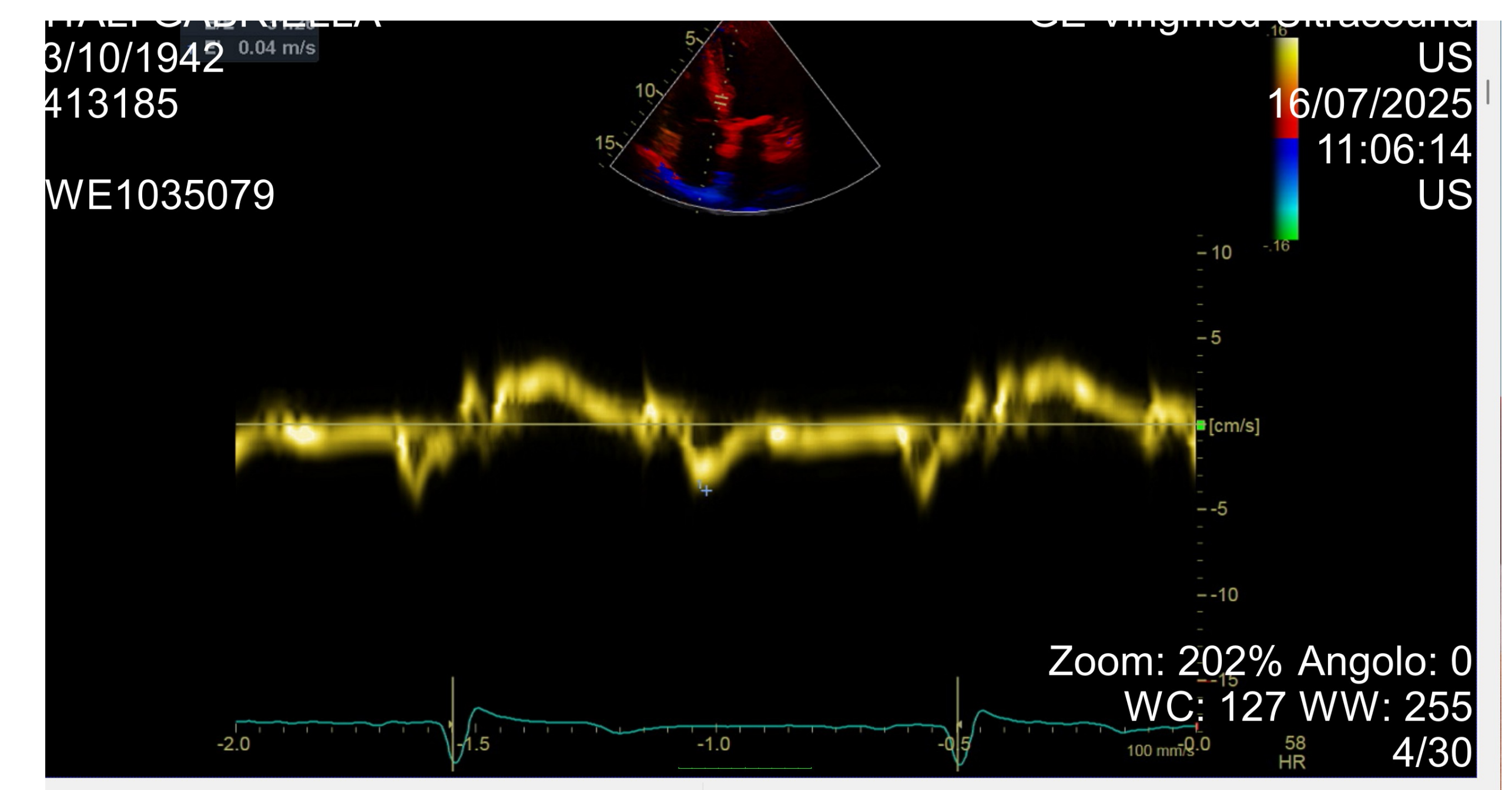
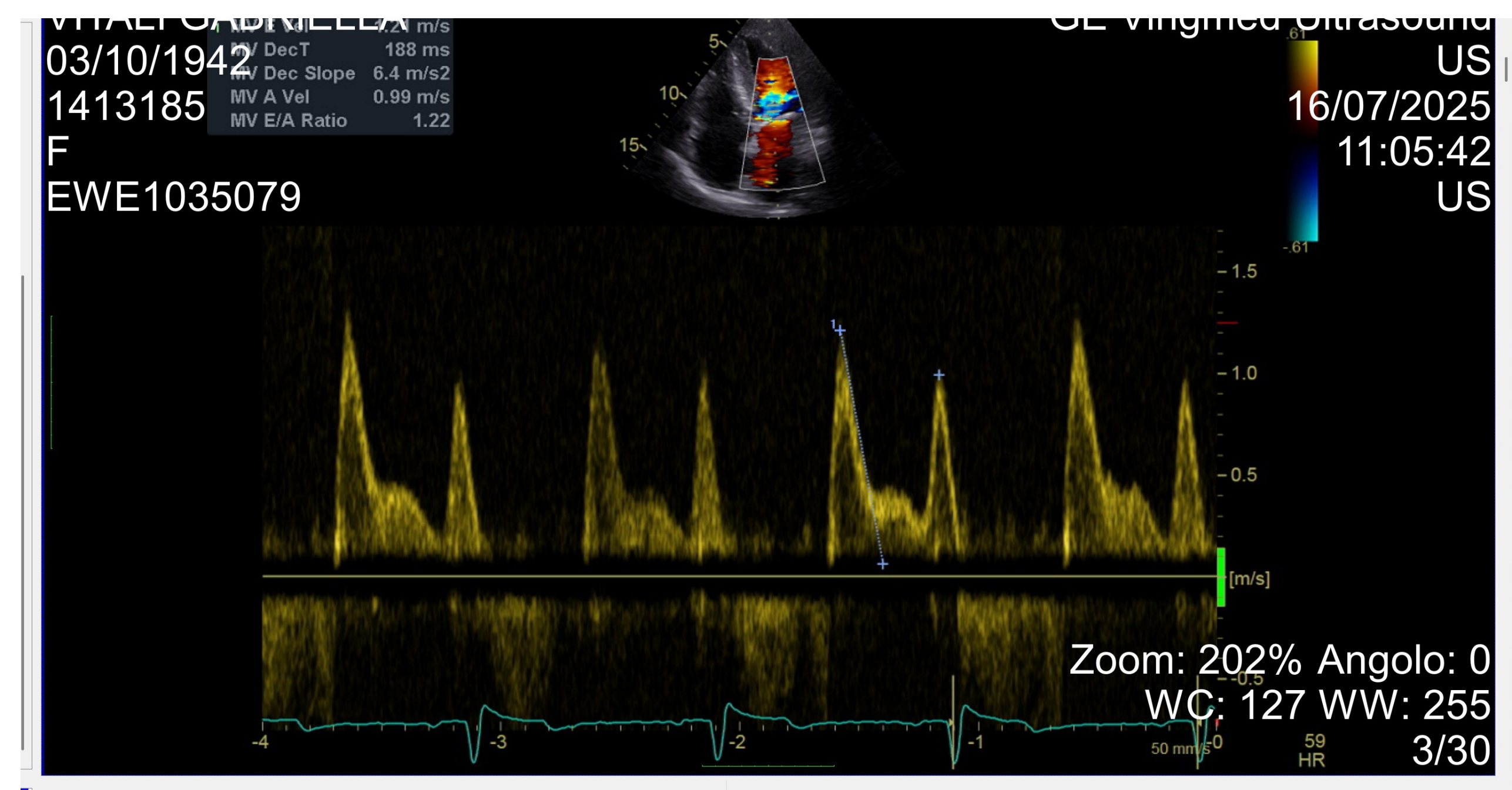


M. A. Fabry





Amiloidosi cardiaca





Laboratory tests in adult patients with hypertrophic cardiomyopathy (HCM)

Test	Comment
Haemoglobin	Anaemia exacerbates chest pain and dyspnoea and should be excluded whenever there is a change in symptoms.
Renal function	- Renal function may be impaired in patients with severe left ventricular impairment. - Impaired GFR and proteinuria may be seen in amyloidosis, Anderson-Fabry disease and mitochondrial DNA disorders.
Liver transaminases	Liver tests may be abnormal in mitochondrial disorders, Danon disease and β-oxidation defects.
Creatine phosphokinase	Serum creatine phosphokinase is raised in metabolic disorders such as Danon and mitochondrial disease.

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Laboratory tests in adult patients with HCM (Cont.)

Test	Comment
Plasma/leucocyte alpha galactosidase A (in men aged >30 years)	- Low (<10% normal values) or undetectable plasma and leucocyte alpha galactosidase A is present in male patients with Anderson-Fabry disease^a. - Plasma and leucocyte enzyme levels are often within the normal range in affected females and so genetic testing may be considered if clinically suspected.
Serum immunoglobulin free light chain assay, serum and urine immunofixation, and urine electrophoresis	Should be considered if amyloidosis is suspected from history and non-invasive tests. Confirmation of the diagnosis usually requires histological analysis.
Fasting glucose	May be elevated in some mitochondrial DNA disorders and low in fatty acid and carnitine disorders.
Brain natriuretic peptide and troponin T	Elevated plasma levels of BNP, NT-proBNP and troponin T are associated with higher risk of cardiovascular events, heart failure and death.
Thyroid function tests	Should be measured at diagnosis and monitored every 6 months in patients treated with amiodarone.
Plasma Lactate	Elevated in some patients with mitochondrial disorders.

^aPseudo-deficiency may be seen in some genetic variants such as D313Y

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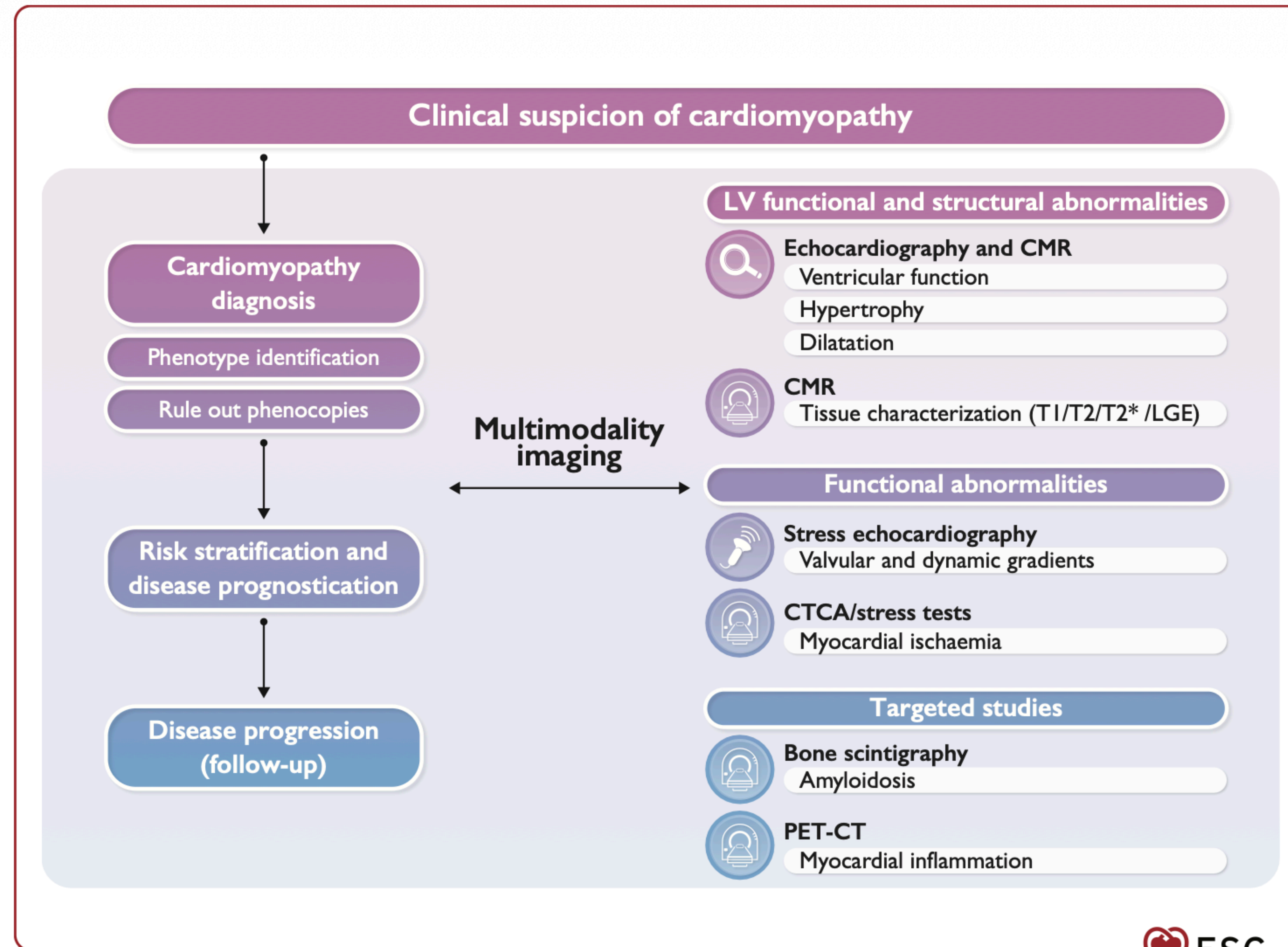
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Level	HCM
First	• CK • Liver function • NT-proBNP^a • Proteinuria • Renal function • Troponin



Second	• Alpha-galactosidase A levels (males) and lyso-Gb3 • Carnitine profile • Free fatty acids • Immunofixation and free light chains • Lactic acid • Myoglobinuria • Pyruvate • PTH • Urine and plasma protein • Urine organic acids and plasma amino acids
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Cardiomyopathy phenotype

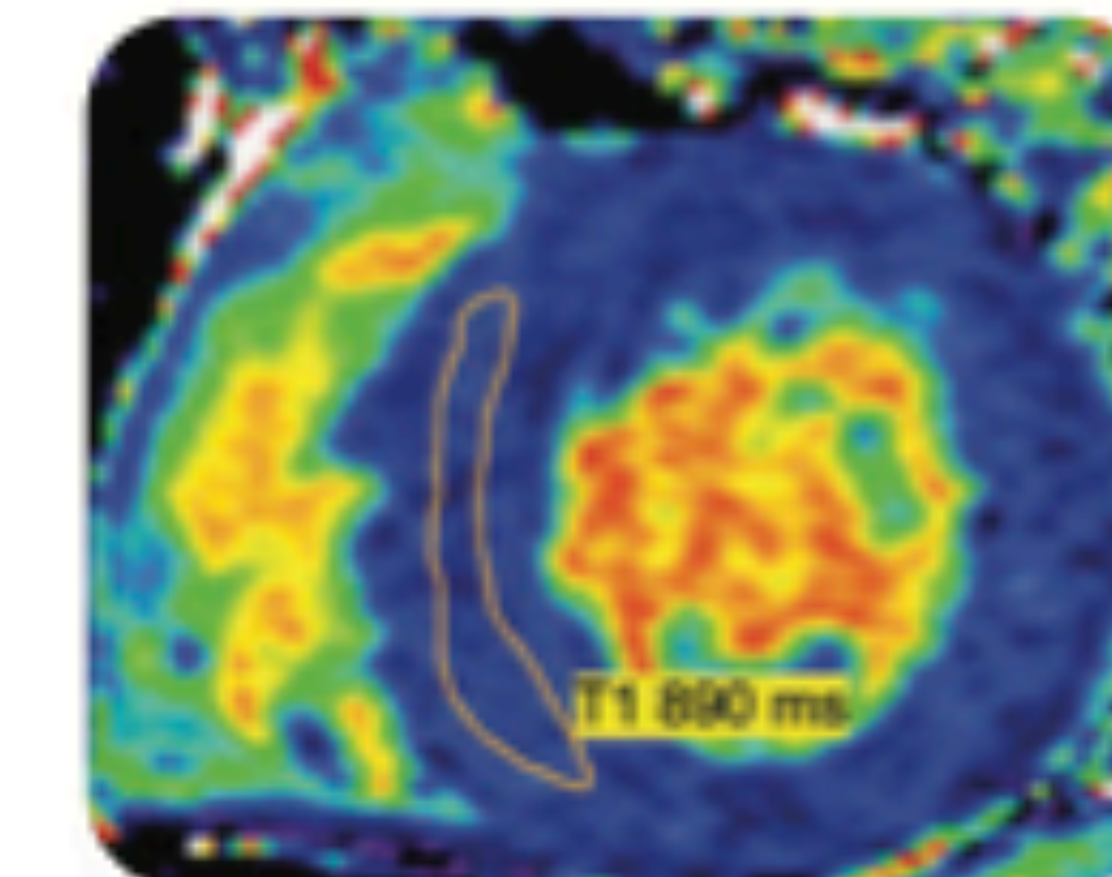
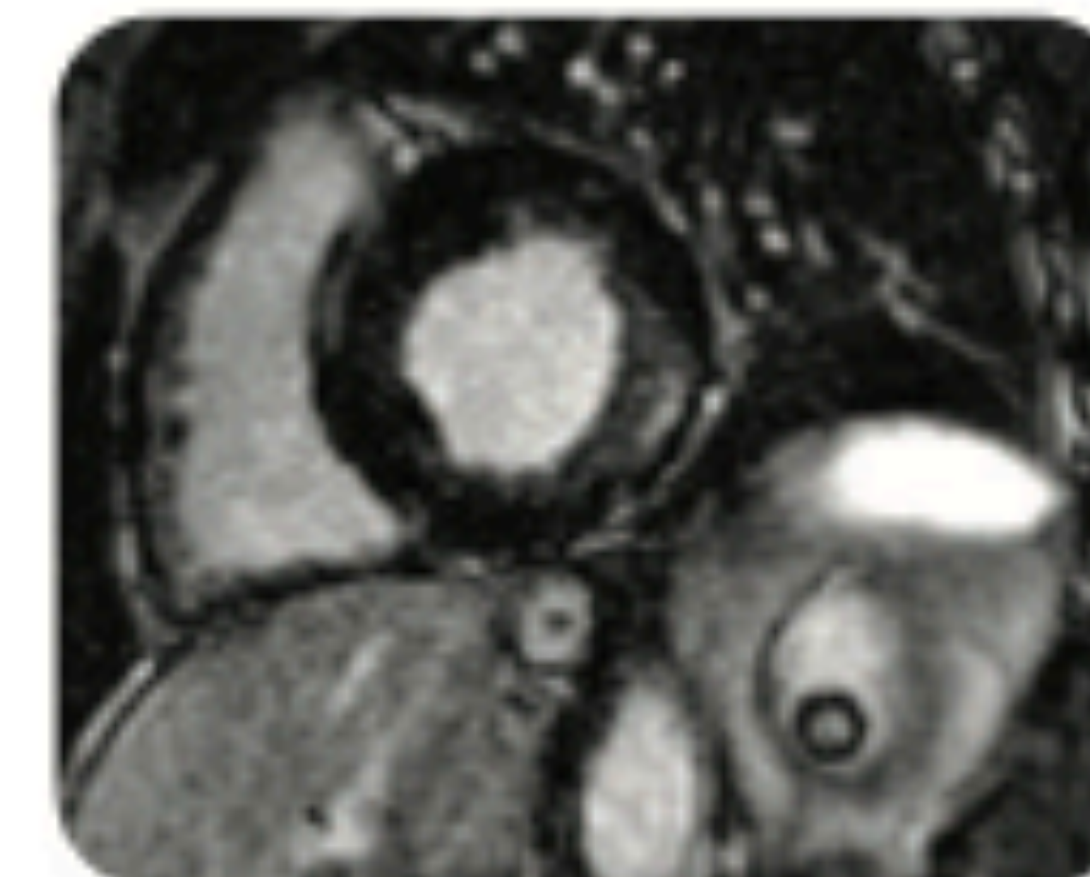
Finding

Cardiac CMR examples

Specific diseases to be considered

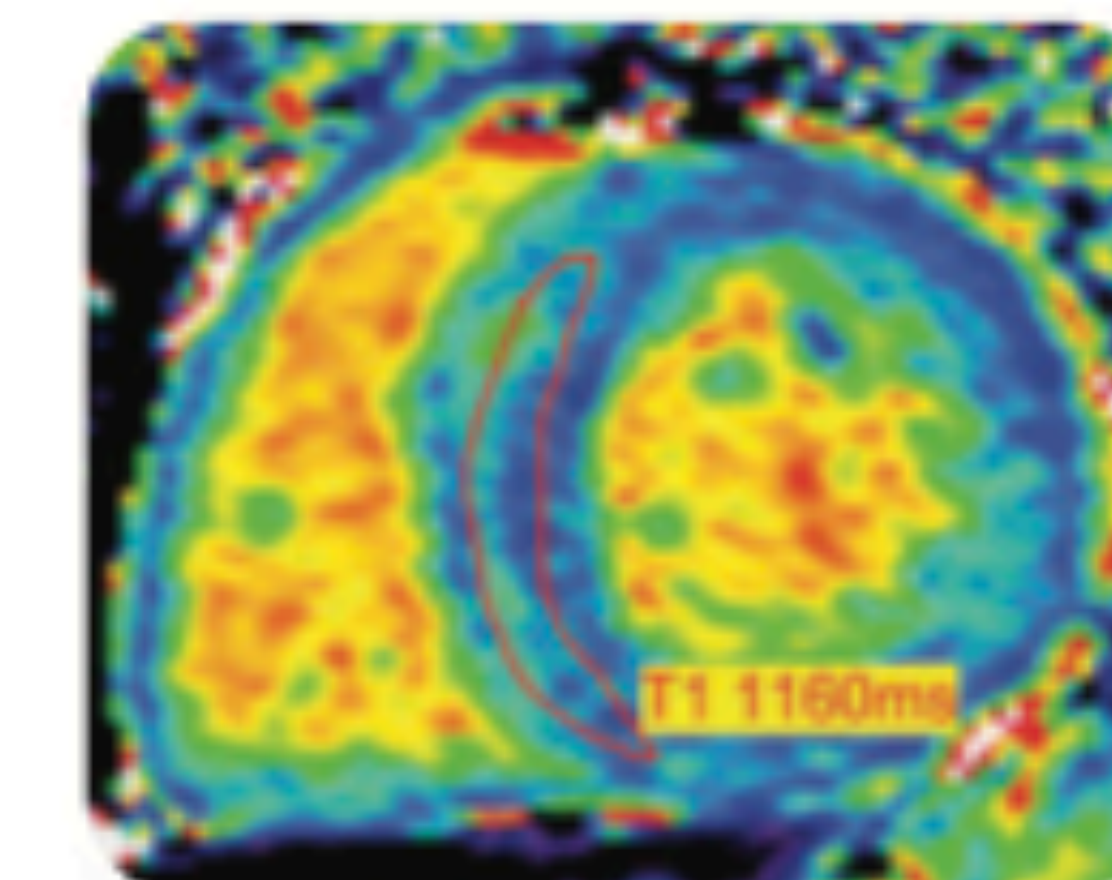
HCM

Posterolateral LGE and concentric LVH
 Low native T1



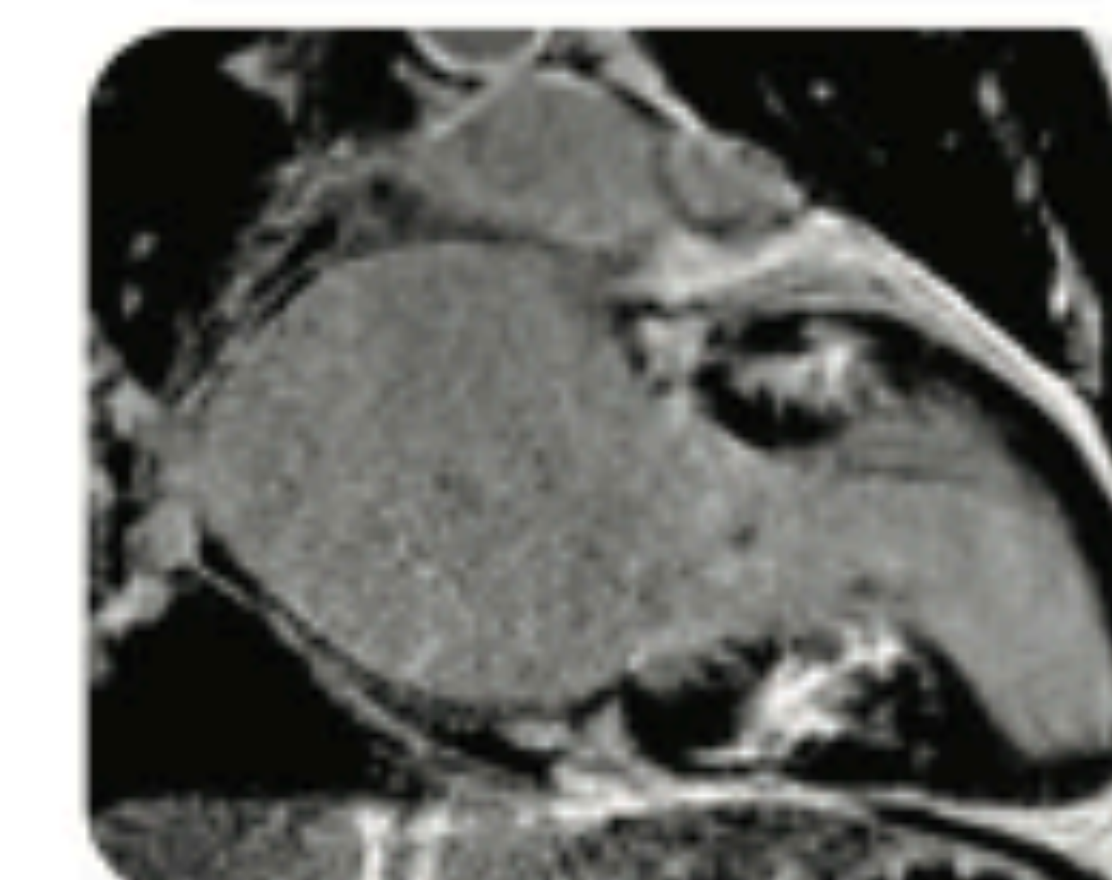
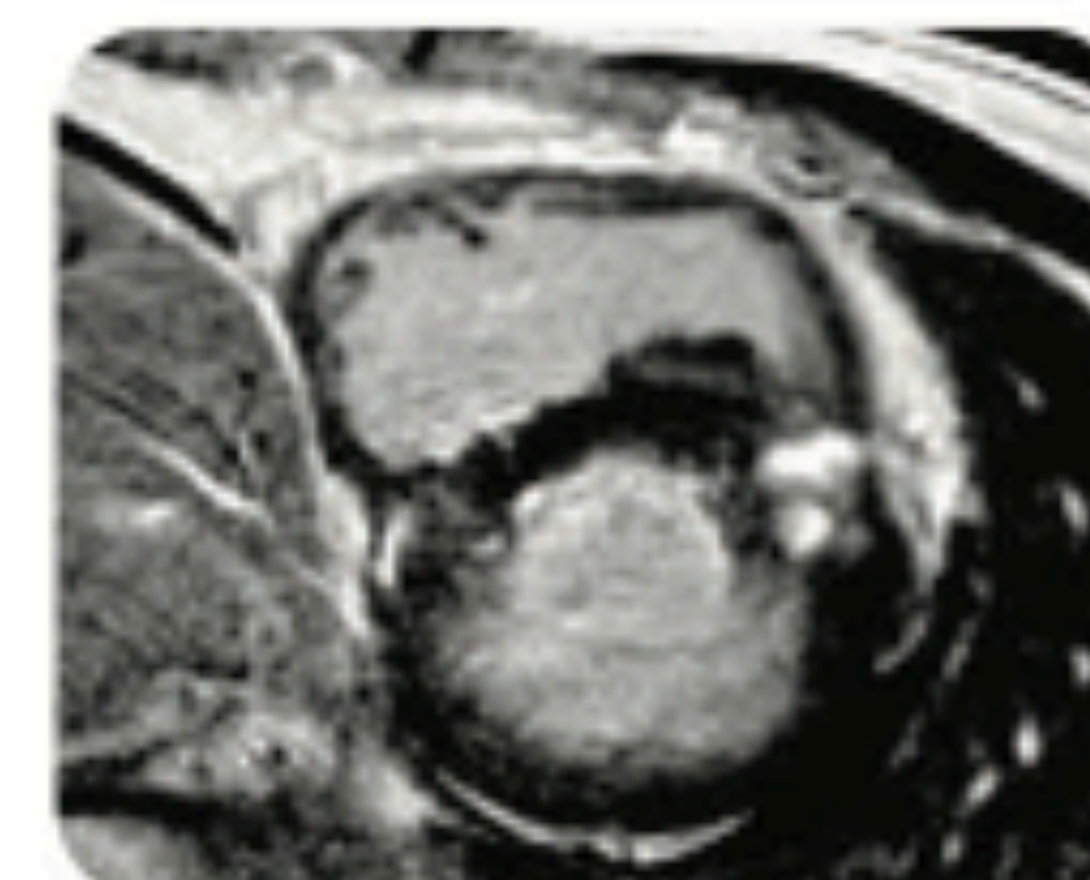
Anderson–Fabry disease

Diffuse subendocardial LGE,
 high native T1



Amyloidosis

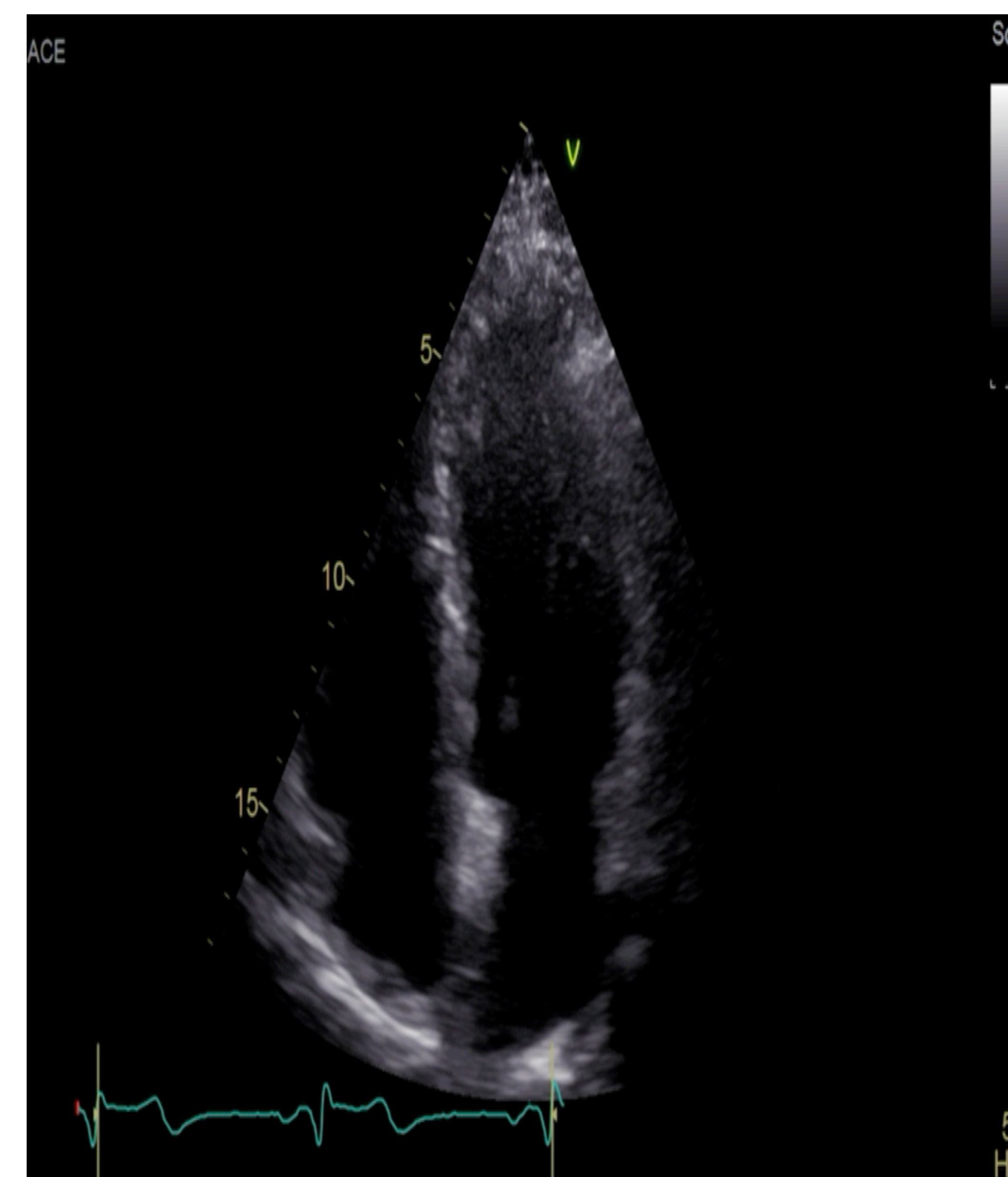
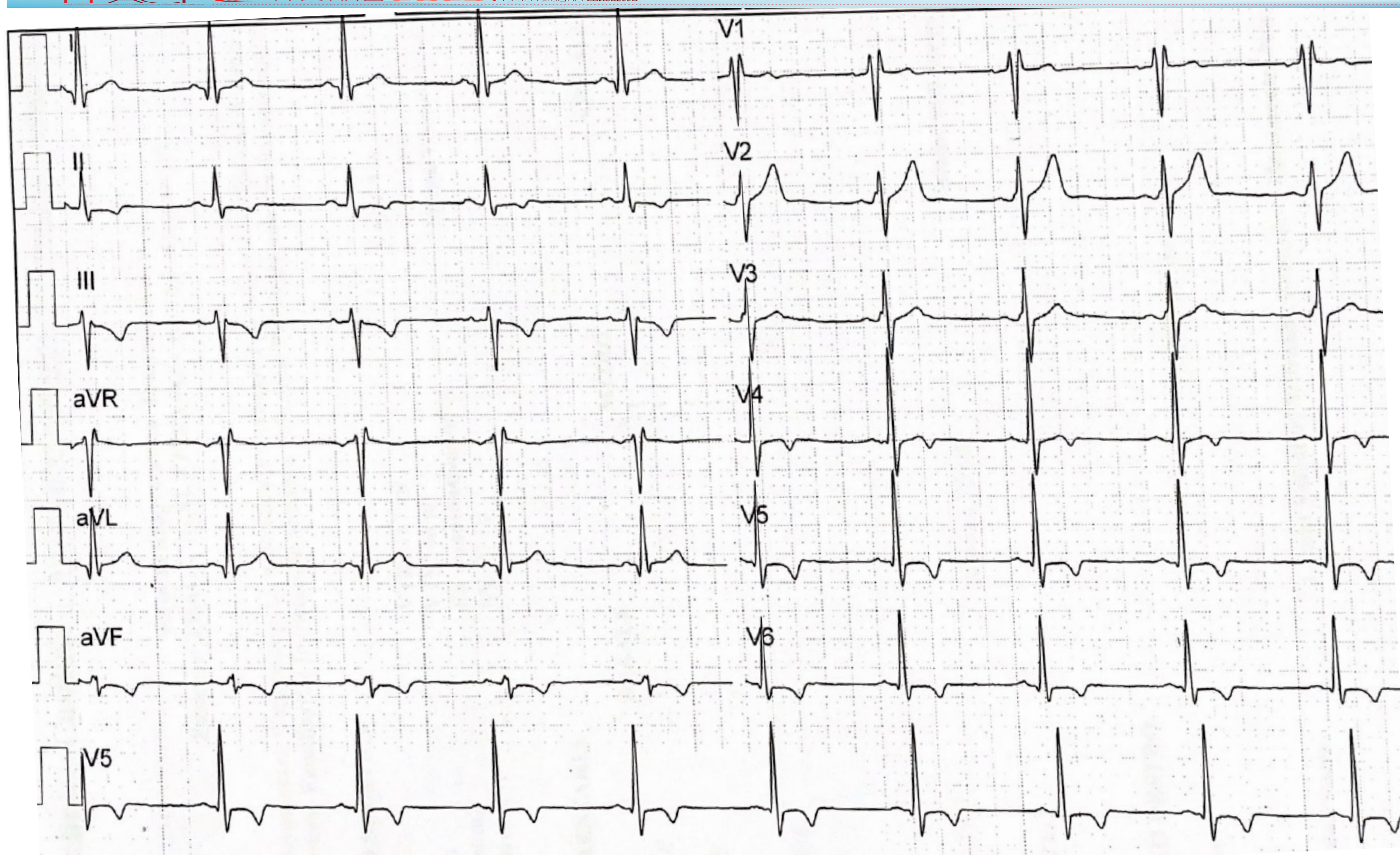
Patchy mid-wall in hypertrophied areas

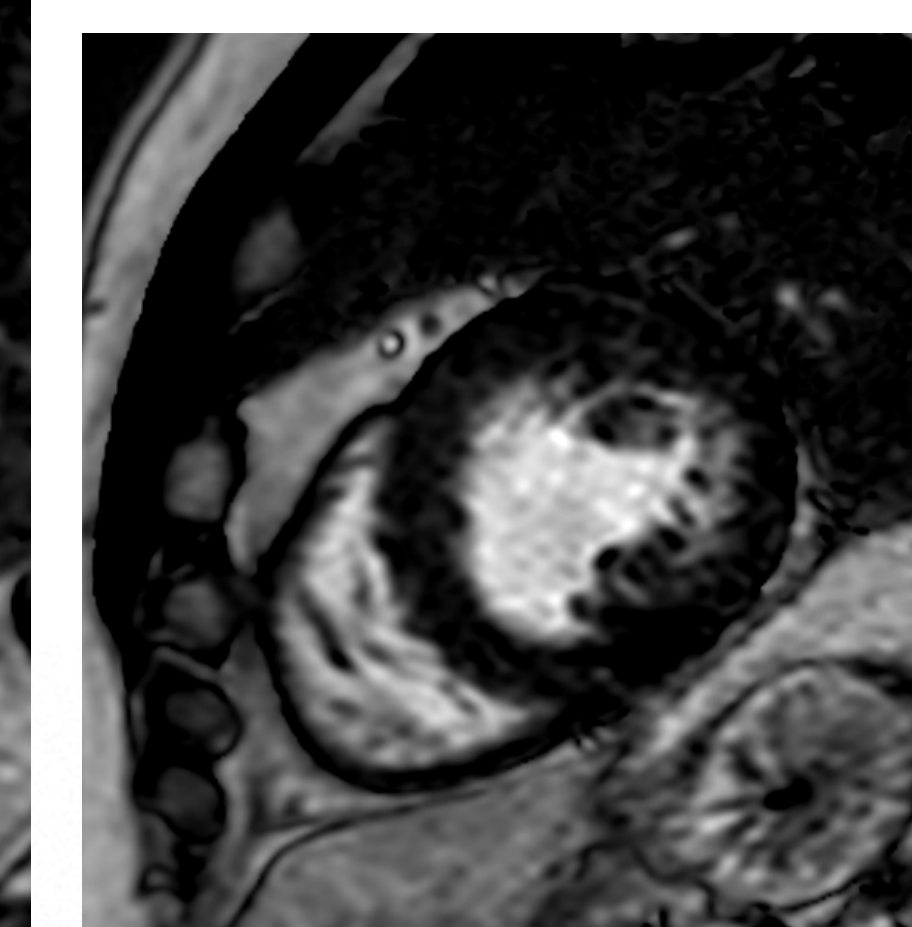
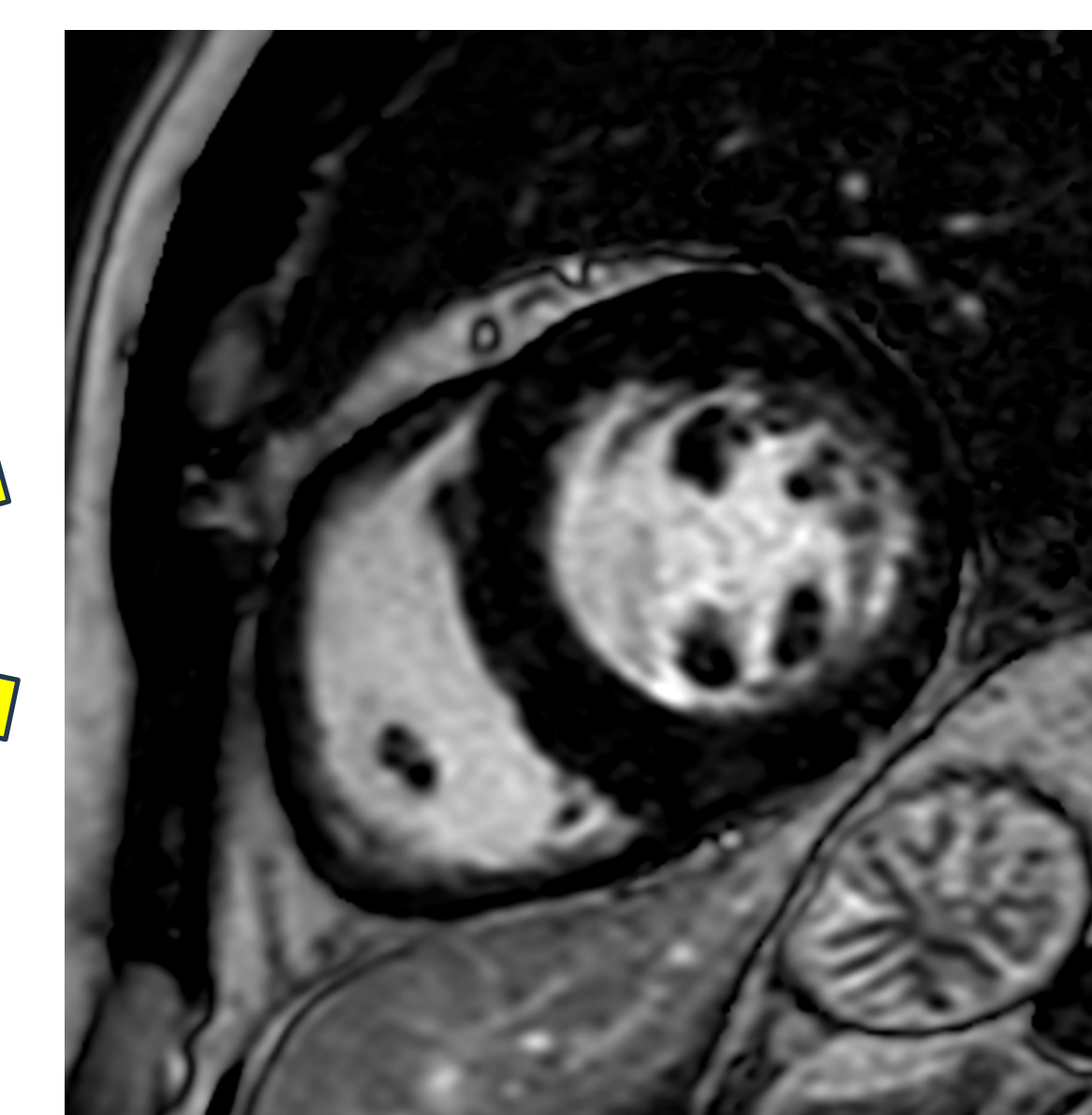
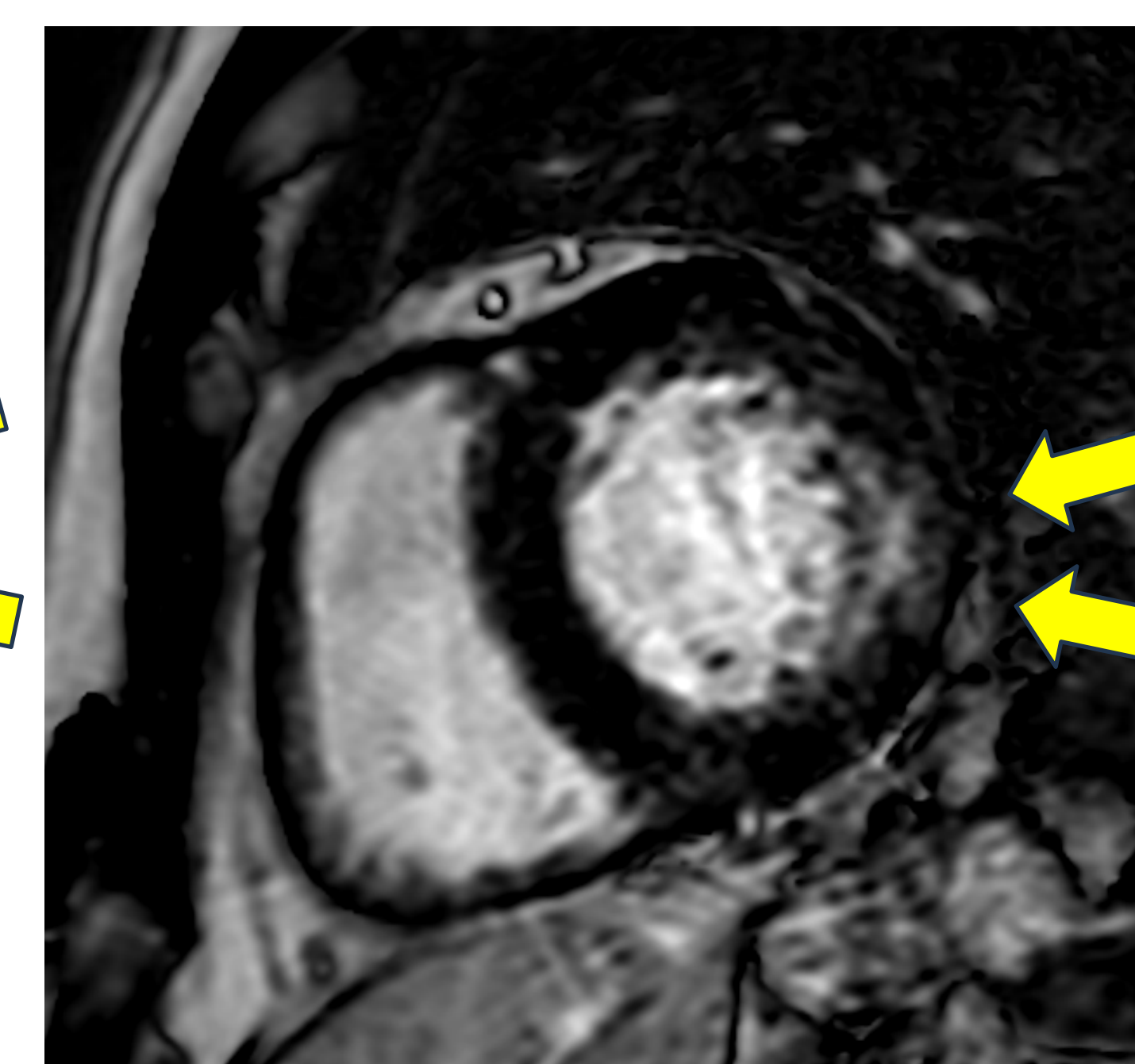
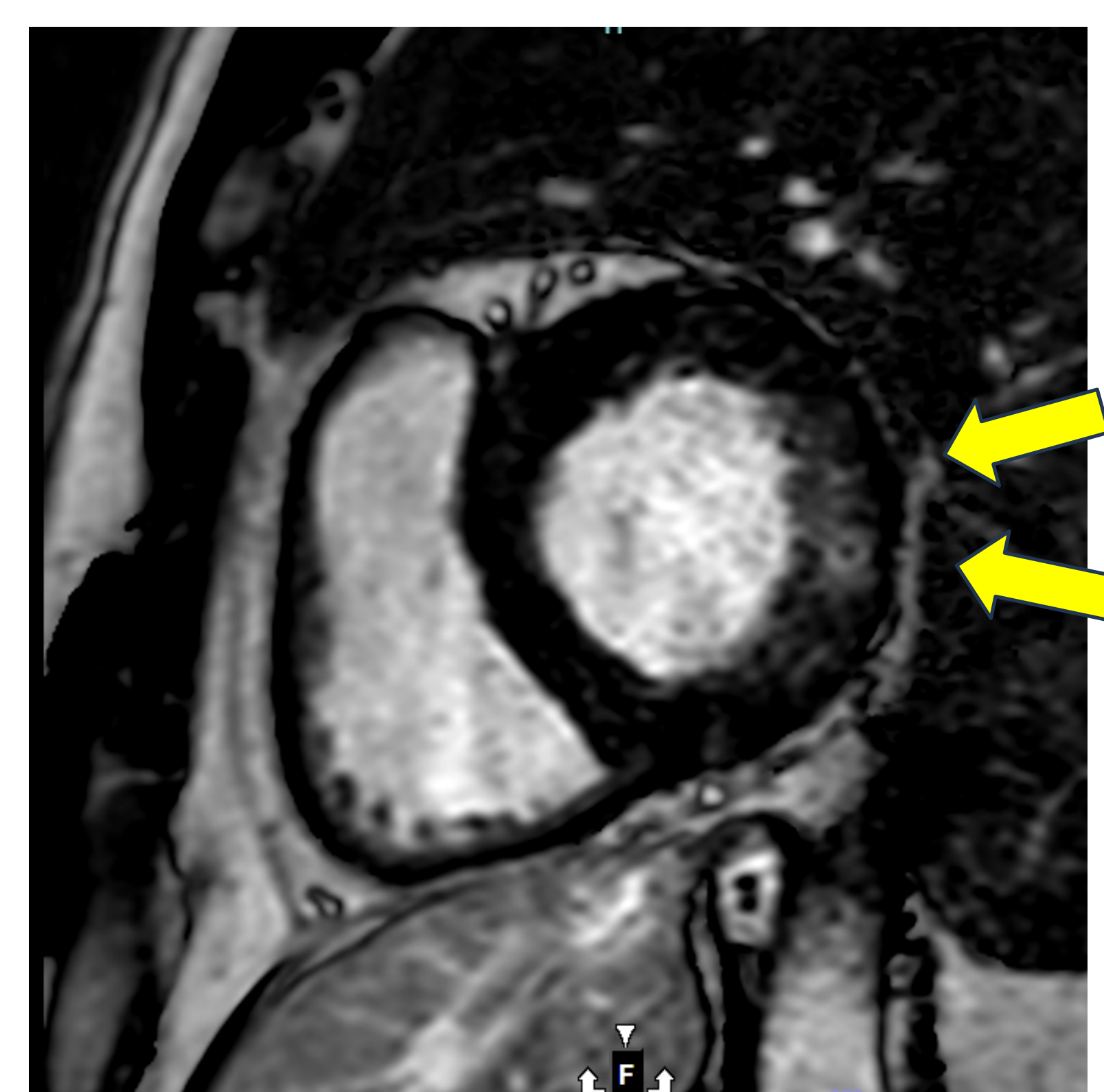
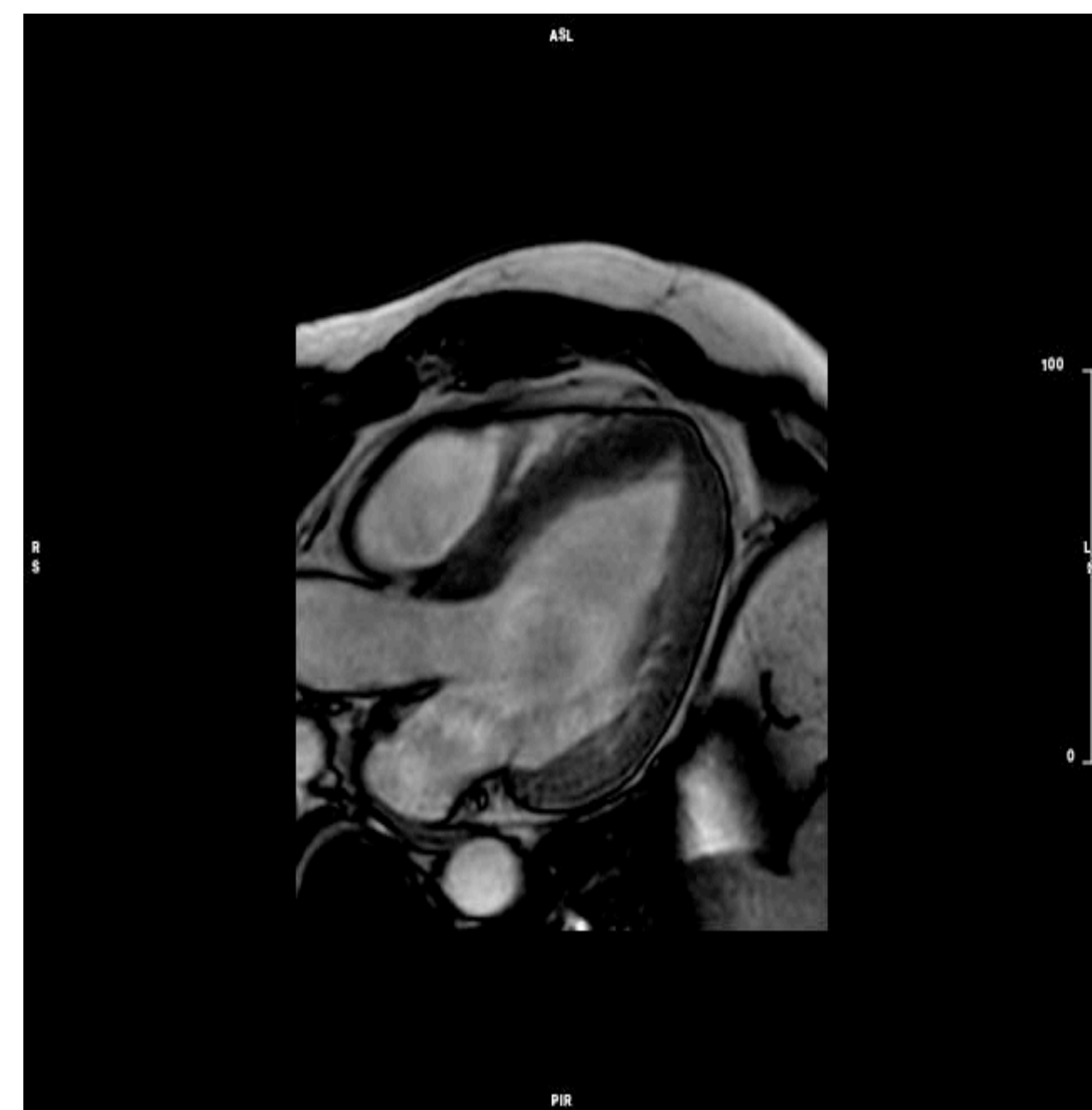
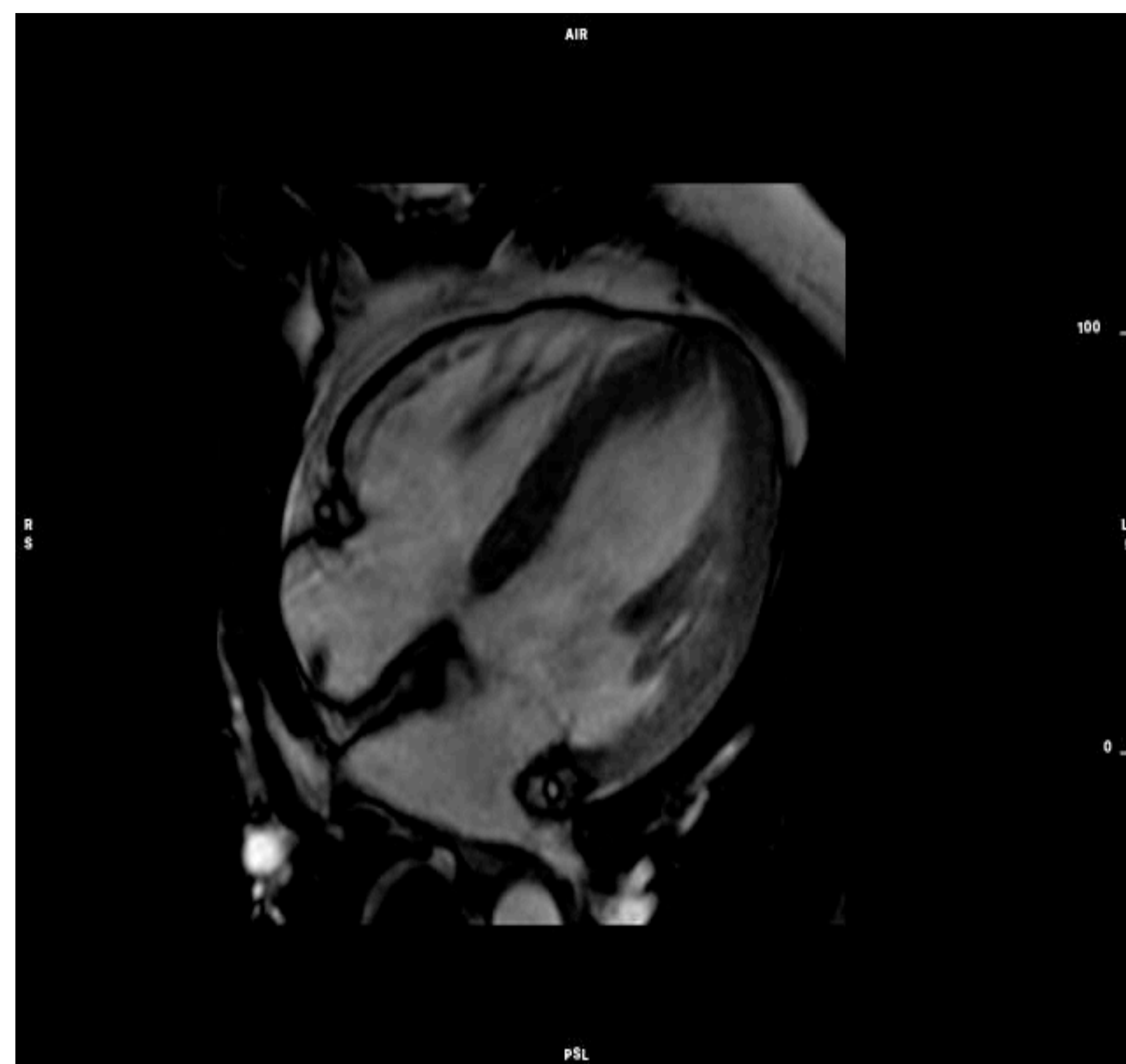


Sarcomeric HCM

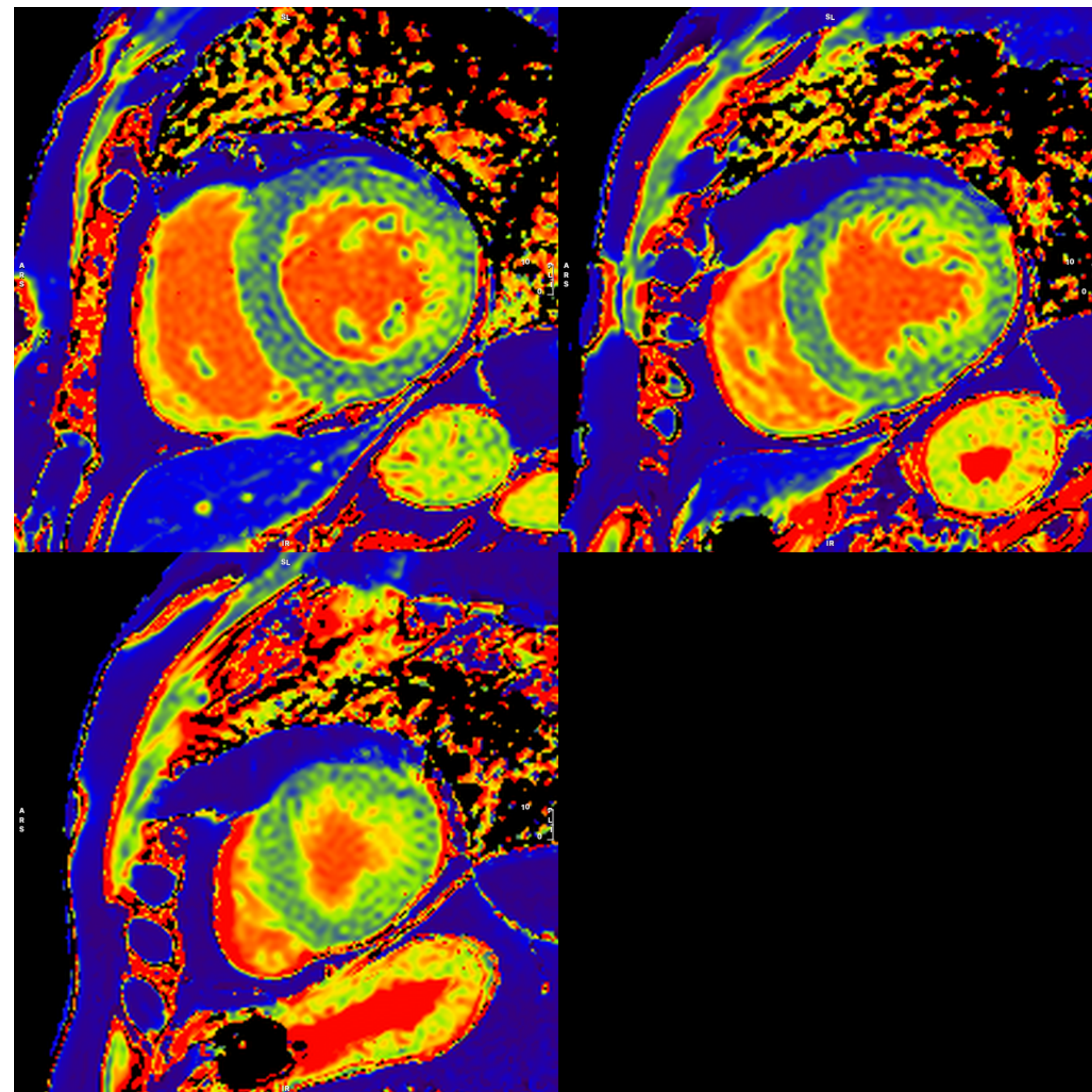


S.F., M, 57 ANNI
Diagnosi di cardiomiopatia ipertrofica apicale





T1 mapping



T1 RIDOTTO

ECV
NORMALE

Malattia di Anderson-Fabry: studio delle alterazioni enzimatiche e genetiche		
Analisi	Valore attività enzimatica dell'alpha-galattosidase A	Valori di Riferimento (nmoli/ml/h)
Enzimatica: Metodo fluorimetrico su DBS	1.2 nmoli/ml/h	Uomini < 1 soggetto Fabry ≤ 3 sospetta inefficienza enzimatica > 3 sano
		Donne Nelle donne i valori dell'attività enzimatica non sono indicativi e presuppongono comunque l'indagine genetica
Lyso Gb3: Spettrometria di Massa	Valore accumulo del Lyso Gb3 6.49 nmol/l	Valori di Riferimento (range normale) < 2.3 nmol/l
Genetica: Ricerca mutazioni nel gene GLA mediante sequenziamento Sanger	Nell'esone 5 del gene GLA è stata riscontrata la mutazione c.644 A>G che determina la sostituzione aminoacidica p.N215S ⁽¹⁾ .	

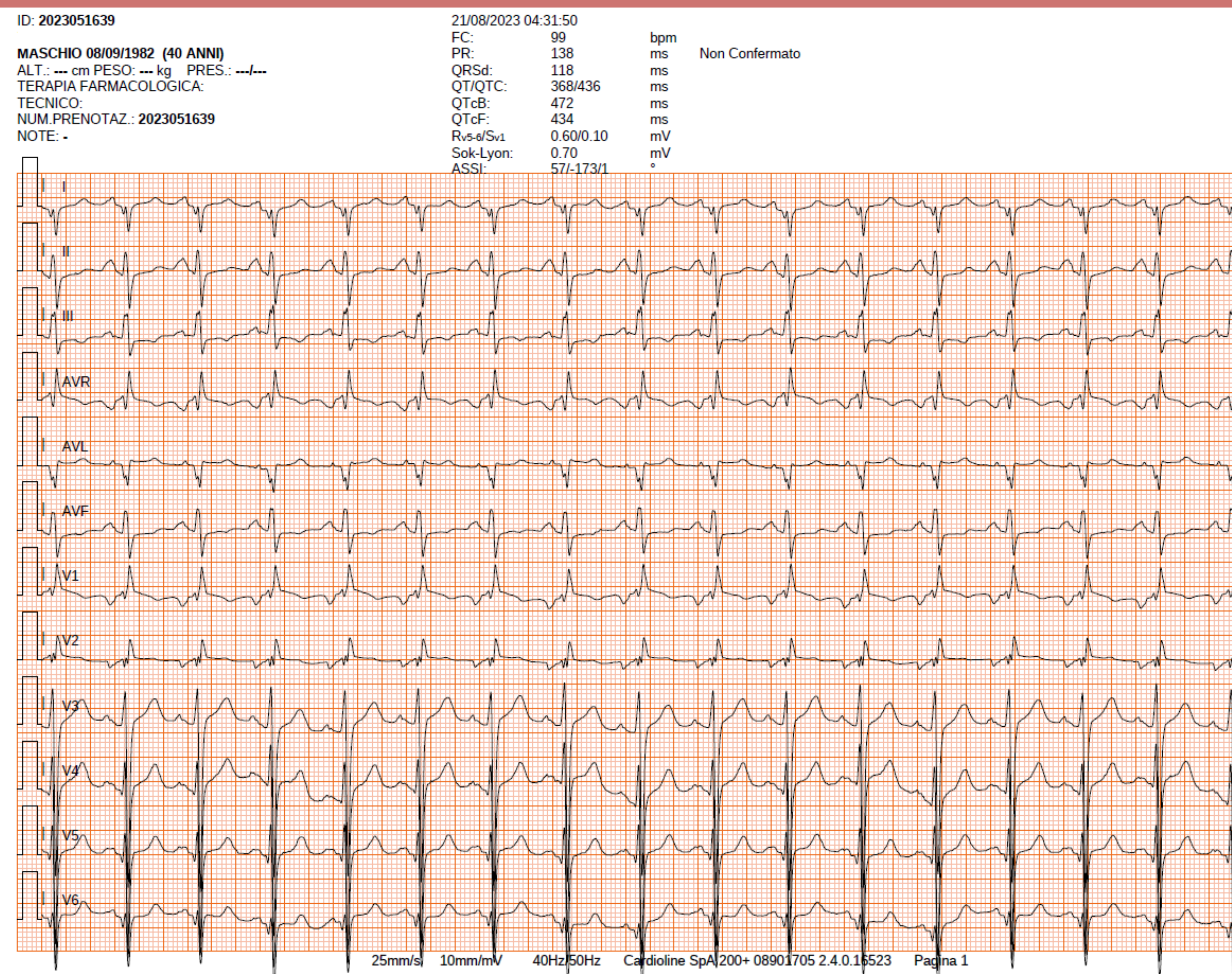
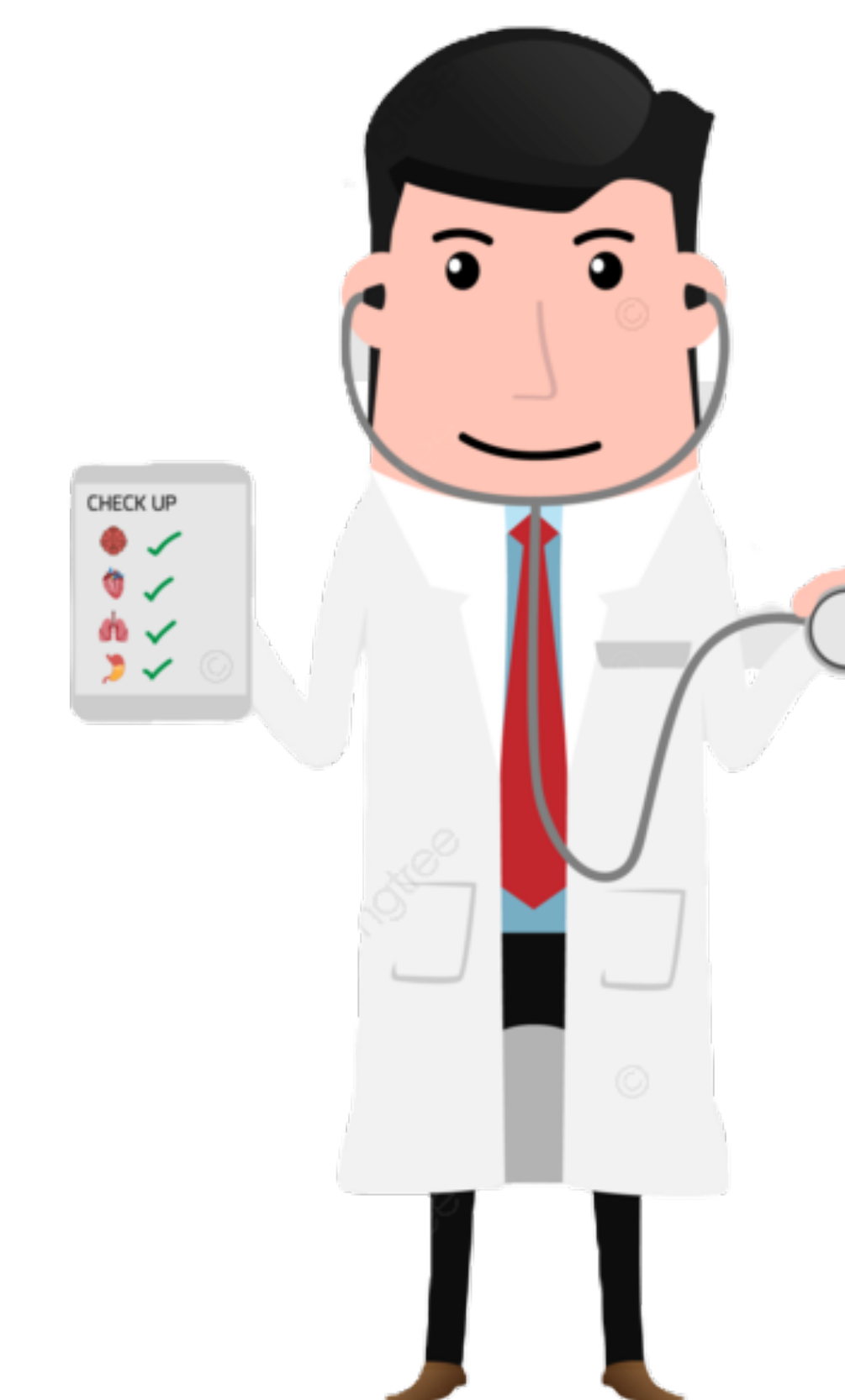


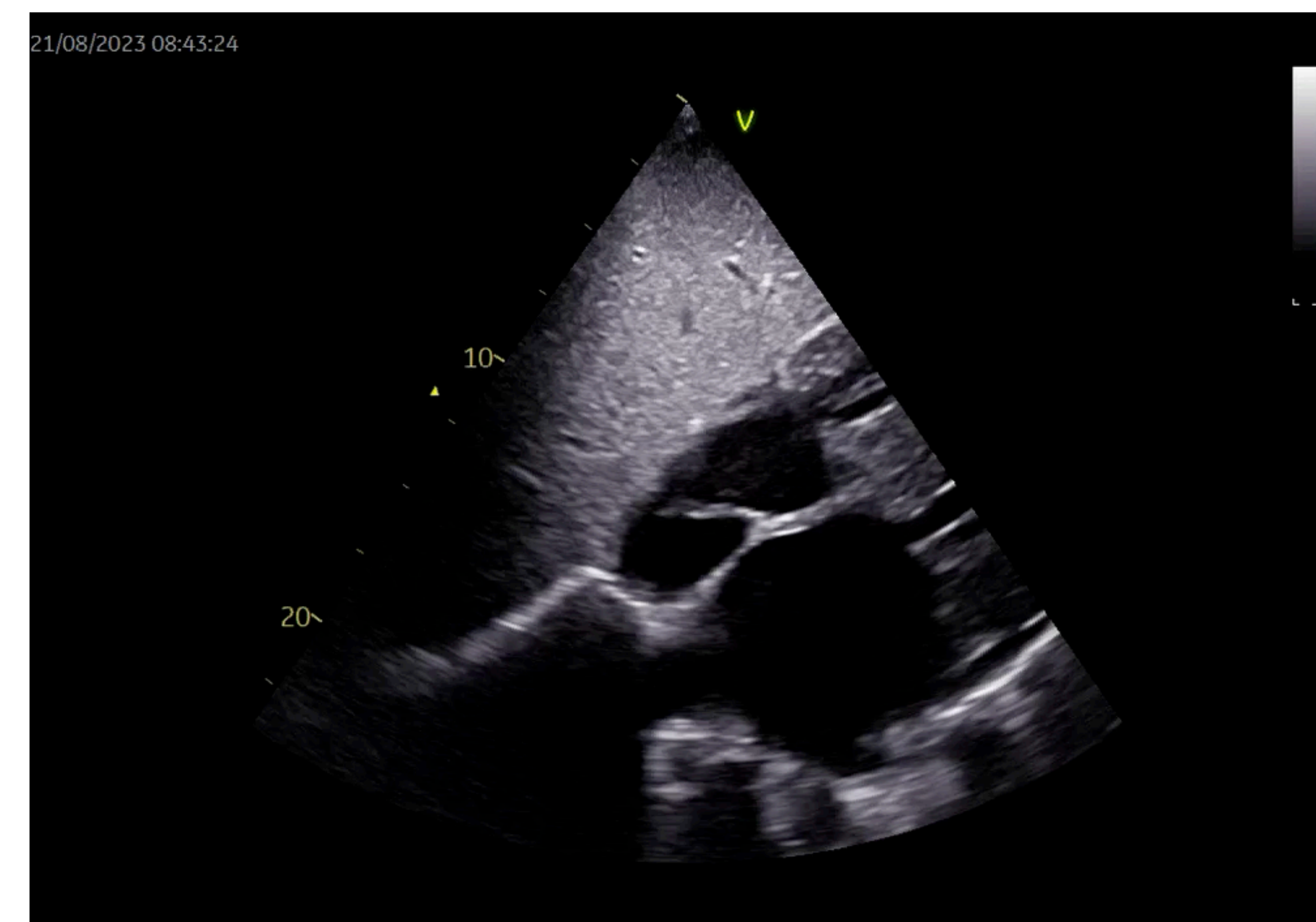
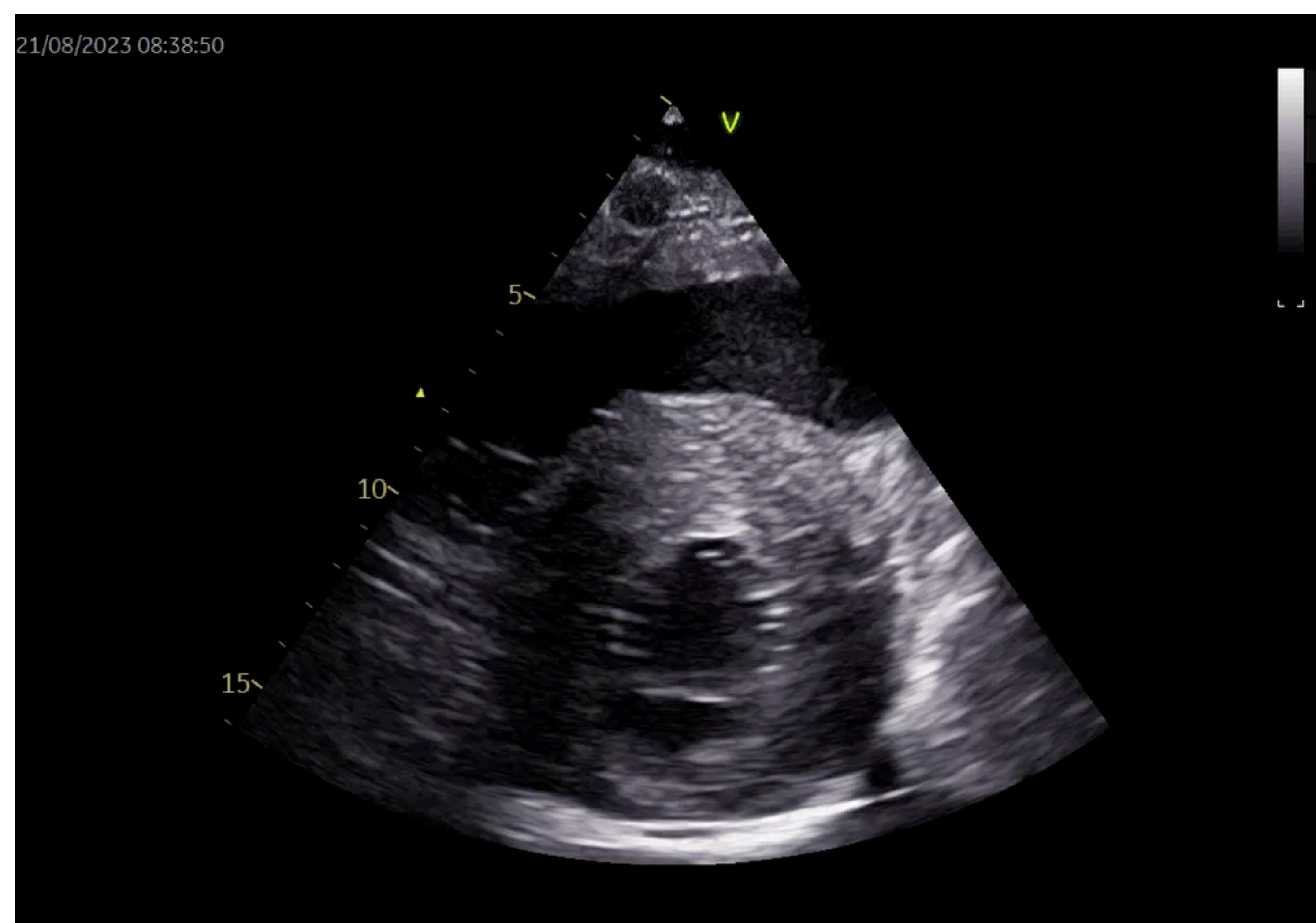
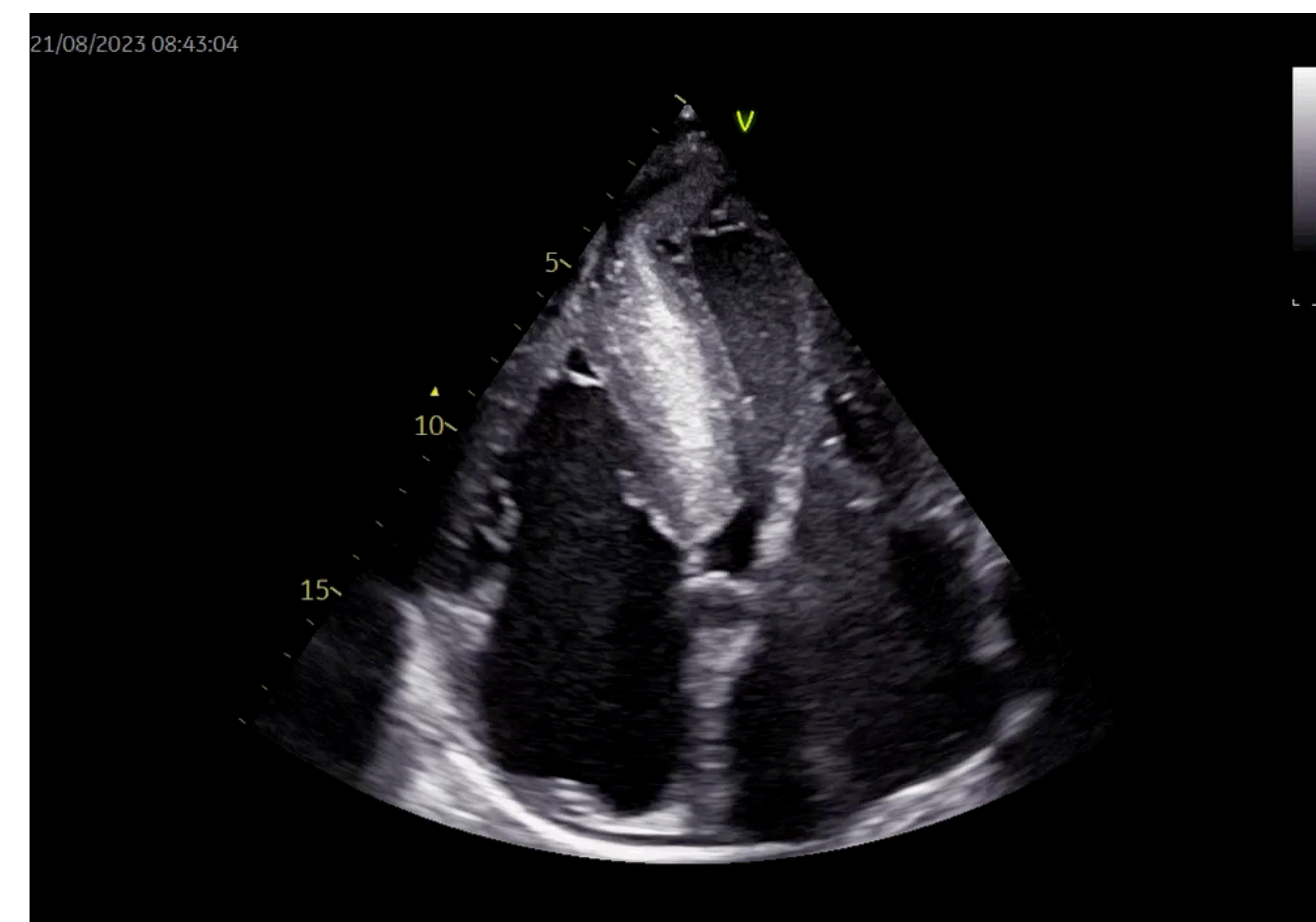
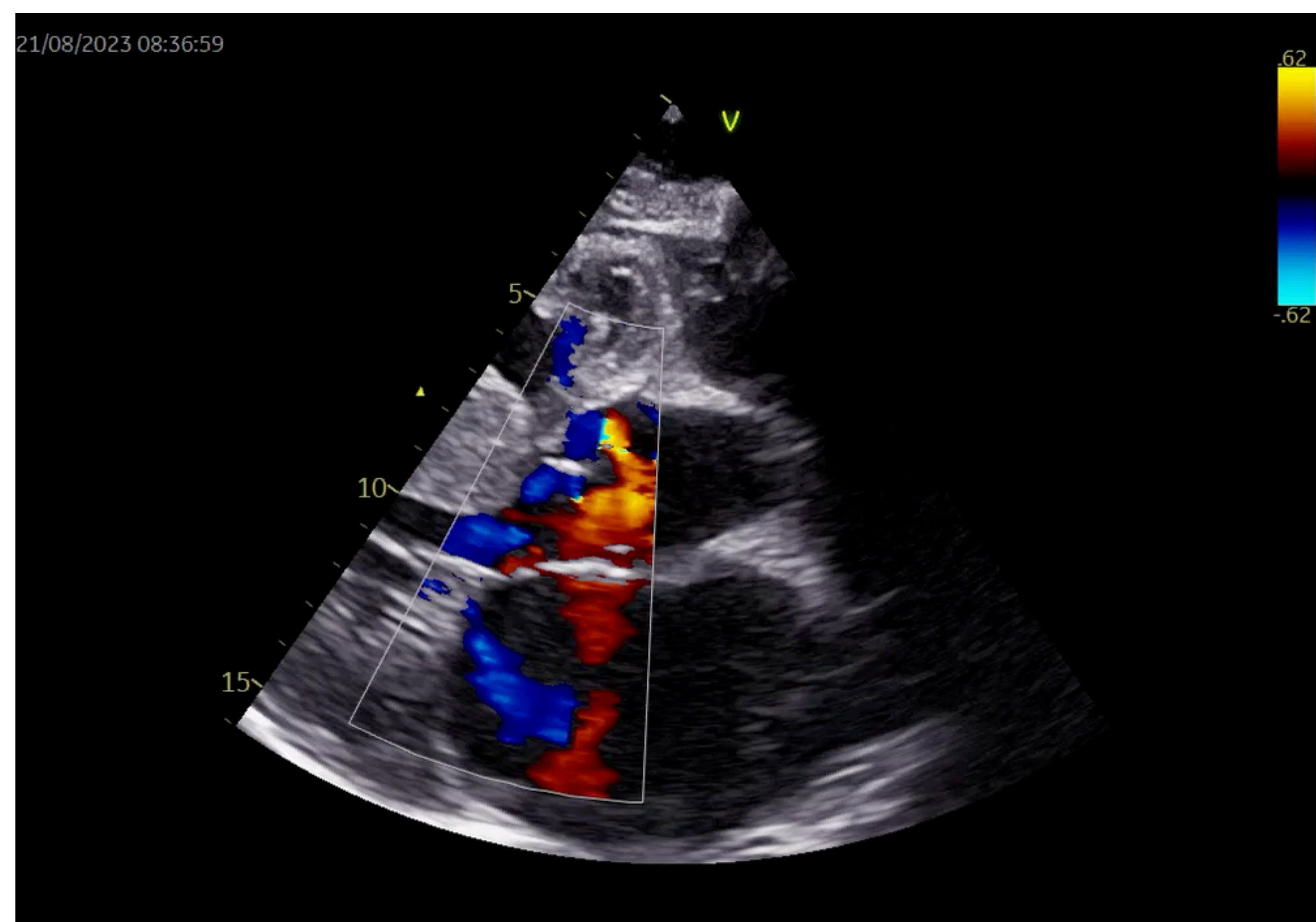
Maschio, 41 aa

Non familiarità per cardiomiopatie o MCI.

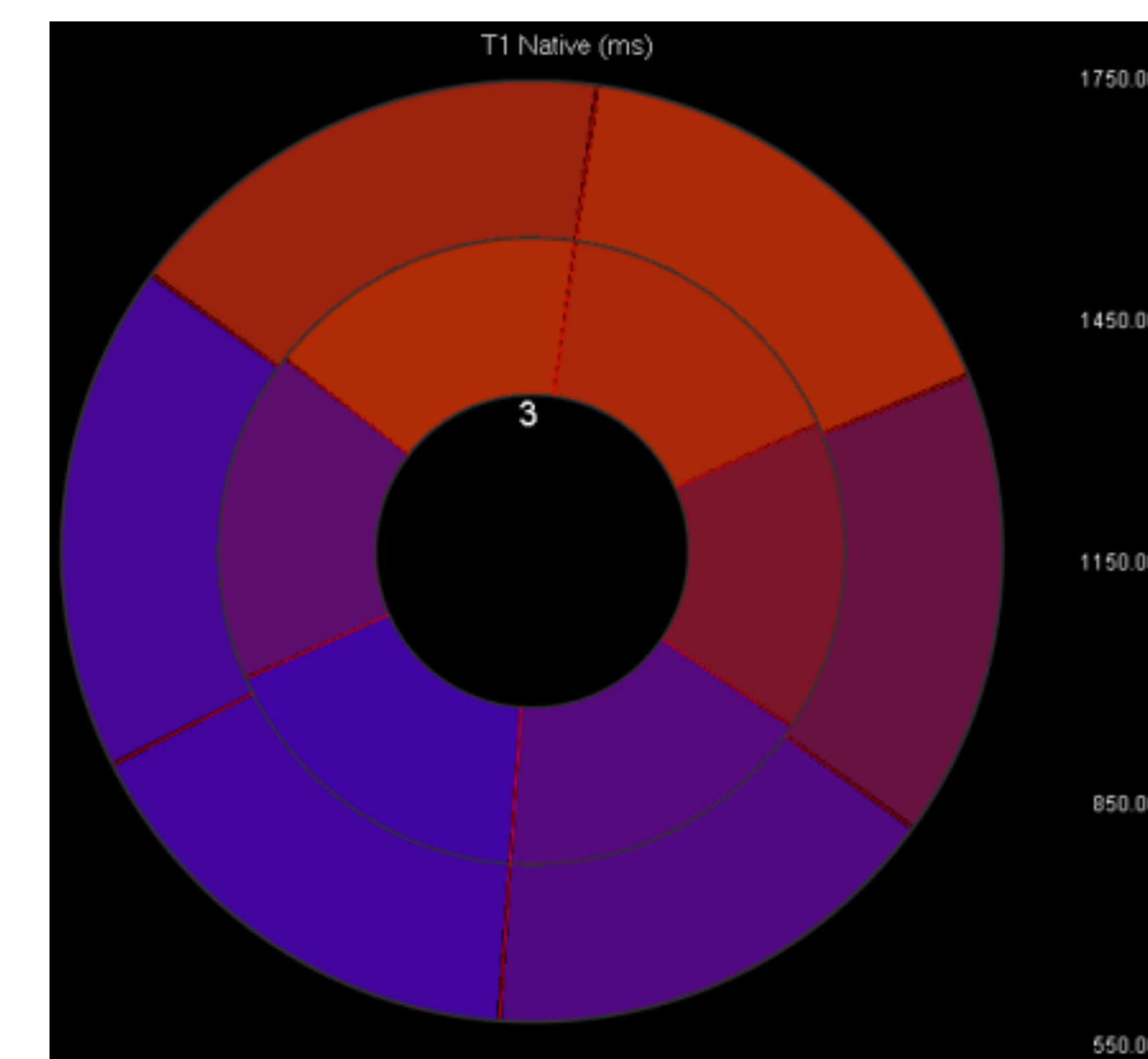
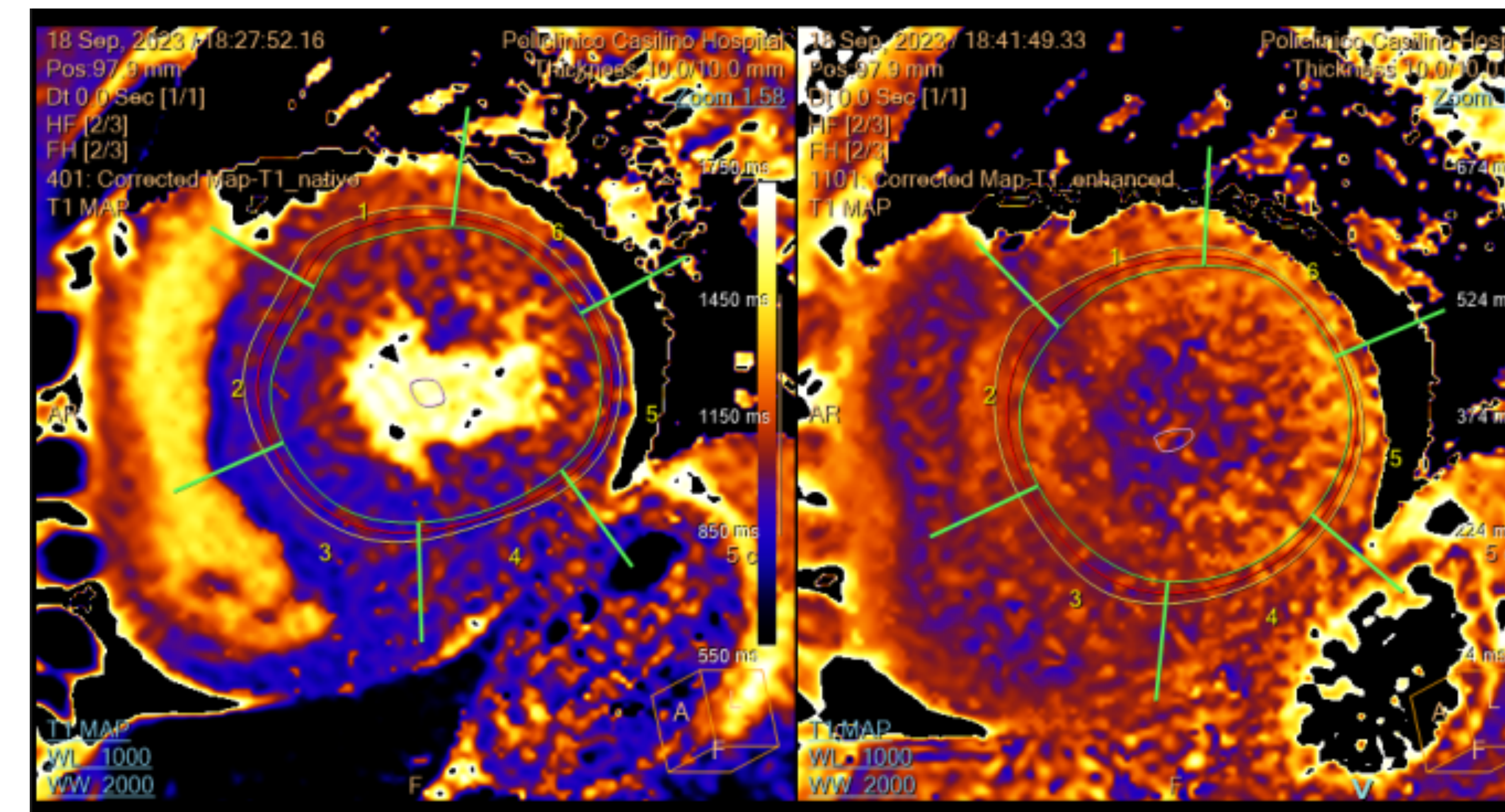
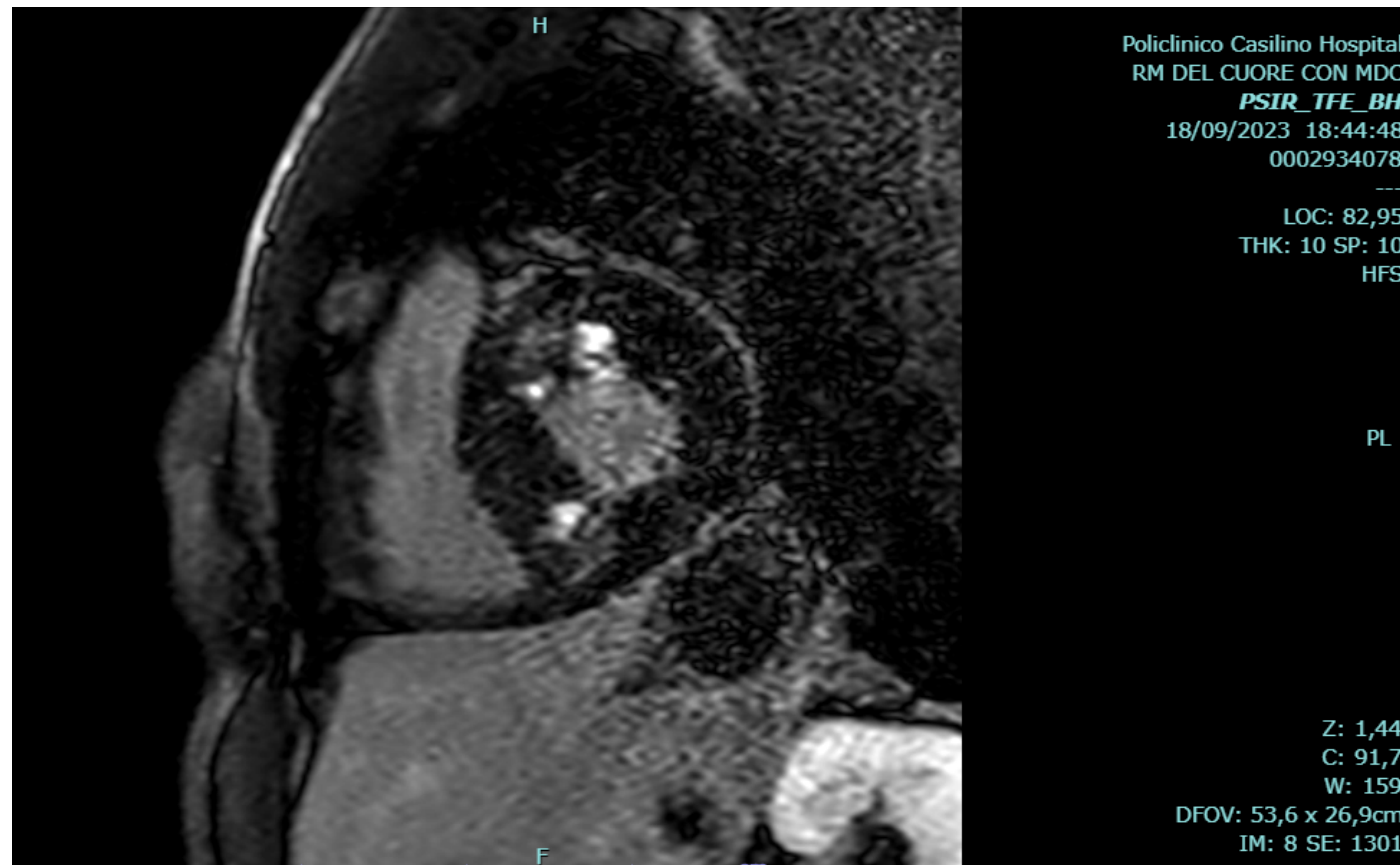
Giunto in PS per dispnea e dolore toracico. PA 160/90 mmHg.

Agli EE: Hb 11 g/dl, PTL 518mila, creatinina 0,99 mg/dl, glicemia 173 mg/dl, GOT 75 U/L, CPK 423 U/L, CK MB 5,71->5,3 ng/ml, TpHs 34->33 ng/ml, BNP 623 pg/ml.





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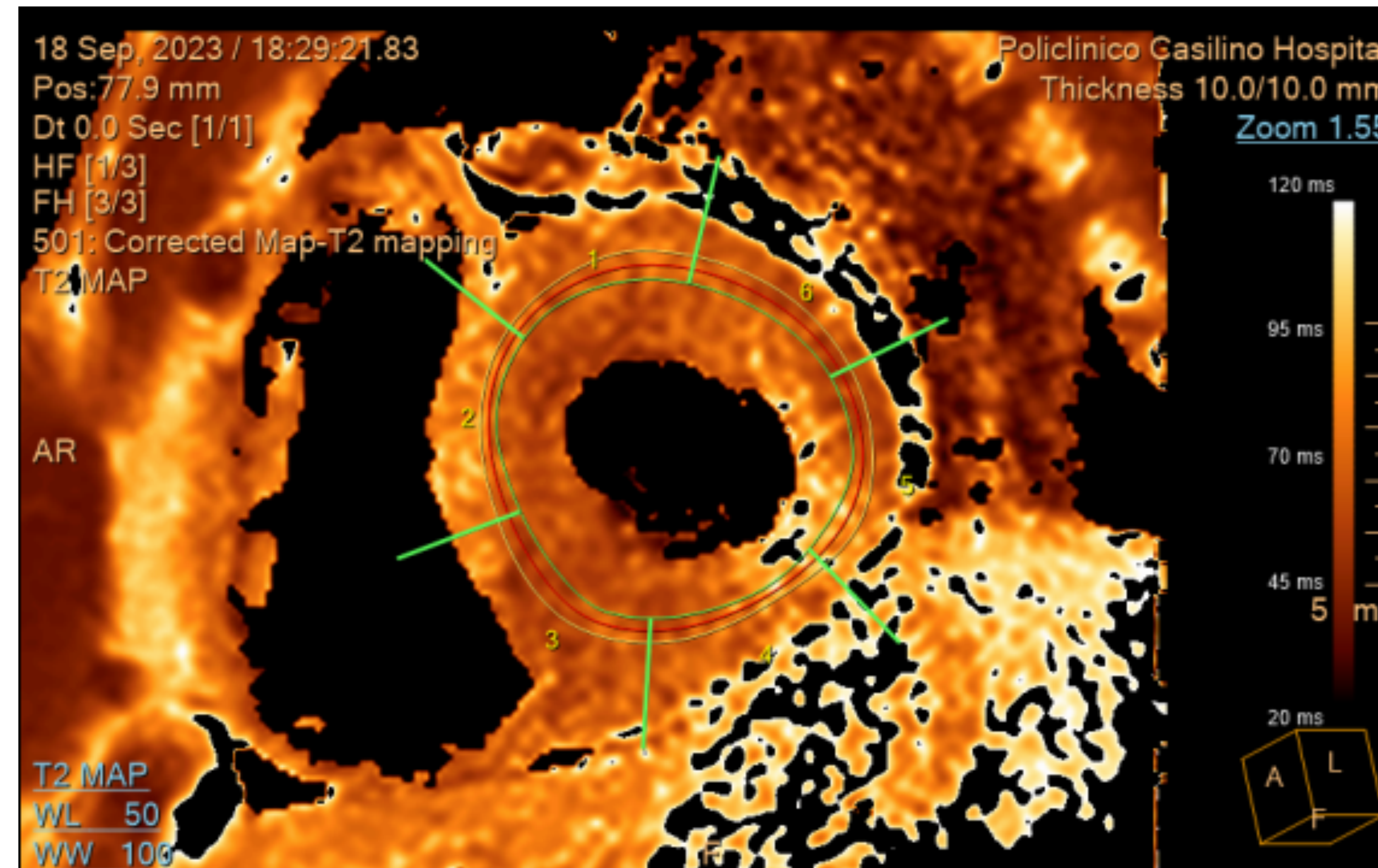


T1 Native: Regional Result-401, Slice No.: 2							
	Segment 1	Segment 2	Segment 3	Segment 4	Segment 5	Segment 6	Summary
T1 Native	1096±58...	978±52.6...	928±57.8...	965±77.6...	1022±78...	1076±71...	1009±86...
R1 Native	0.92±0.05...	1.03±0.05...	1.08±0.07...	1.04±0.08...	0.98±0.08...	0.93±0.06...	1.00±0.09...
T1 Enhanced	352±40.1...	338±23.7...	319±24.6...	357±42.8...	410±46.8...	415±35.7...	365±47.4...
R1 Enhanced	2.88±0.32...	2.97±0.21...	3.15±0.23...	2.84±0.32...	2.47±0.30...	2.43±0.21...	2.86±0.36...
ε	53.3 %	53.6 %	57.0 %	49.0 %	40.5 %	41.1 %	50.5 %
ROI Area Native	183 mm²	215 mm²	164 mm²	99.6 mm²	148 mm²	123 mm²	934 mm²
ROI Area Enhanced	186 mm²	229 mm²	196 mm²	142 mm²	111 mm²	90.9 mm²	954 mm²
Hematocrit	32.0 %	32.0 %	32.0 %	32.0 %	32.0 %	32.0 %	32.0 %
Field Strength	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T

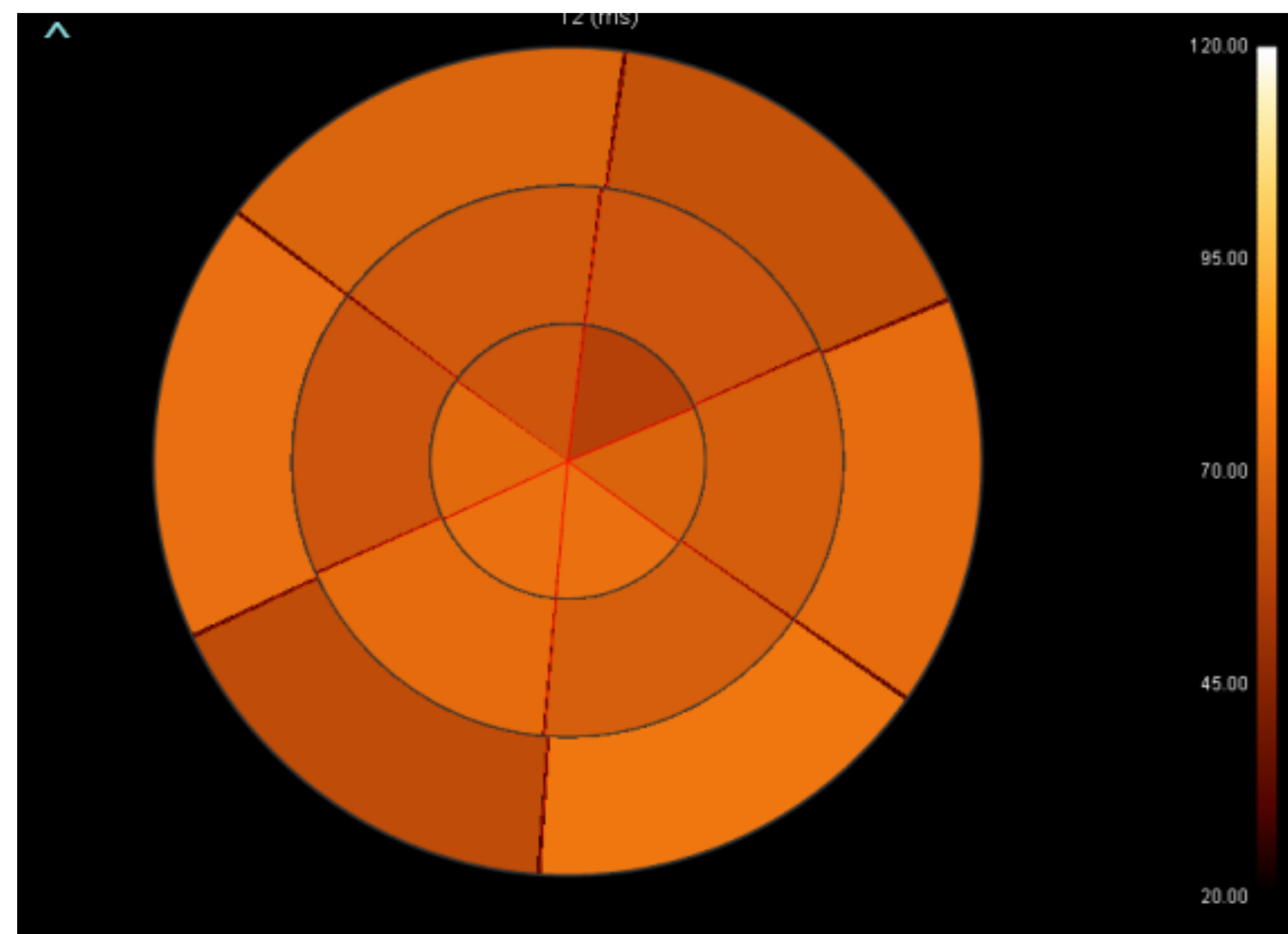
Severo incremento dell'ECV
(50-57%)



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Diffuso incremento dei tempi T2 del miocardio ventricolare come per diffusa condizione di edema interstiziale



	T2 Mapping: Regional Result-501, Slice No.: 1						
	Segment 1	Segment 2	Segment 3	Segment 4	Segment 5	Segment 6	Summary
T2	69.8±6.65 ms	73.8±7.97 ms	60.4±6.88 ms	76.3±16.2 ms	72.5±15.9 ms	62.3±7.30 ms	68.5±12.3 ms
R2	14.5±1.41 Hz	13.7±1.51 Hz	16.8±1.85 Hz	13.7±2.71 Hz	14.4±2.98 Hz	16.3±1.91 Hz	15.0±2.45 Hz
ROI Area	177 mm²	128 mm²	187 mm²	137 mm²	168 mm²	178 mm²	974 mm²
Field Strength	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T



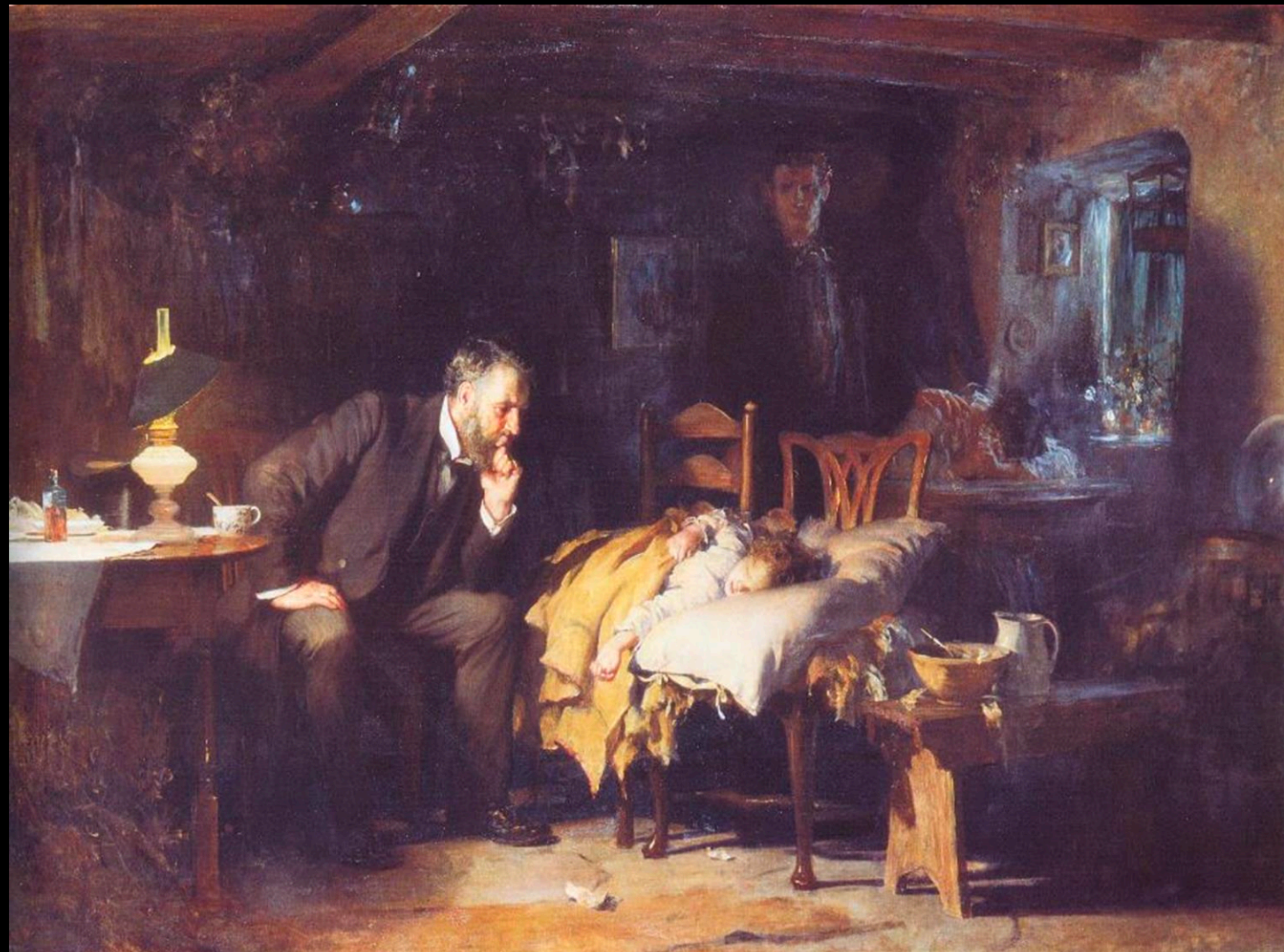


Uso di steroidi anabolizzanti
insulina e GH da anni



Shared characteristics of ideal detectives and clinicians

- Ability in observation
- Ability in “deduction”
- Culture (Knowledge)
- Ability to spot inconsistencies



Courtesy of prof. Sinagra



«WE SEE ONLY WHAT WE KNOW»

GOETHE

ME IGNORING ALL
OF YOUR RED FLAGS



GRAZIE

