VALVULAR HEART DISEASE IN RESTRICTIVE AND INFILTRATIVE CARDIOMYOPATHIES

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CARDIOMYOPATHY AND VALVULAR HEART DISEASE: POSSIBILE LINKS

- CMP with secondary VHD >> “functional” or organic
- Advanced organic VHD with secondary LV remodelling/hypertrophy/dysfunction
- CMP and VHD >> incidental association of 2 unrelated diseases

European Heart Journal (2008) **29**, 270–276
doi:10.1093/eurheartj/ehm342

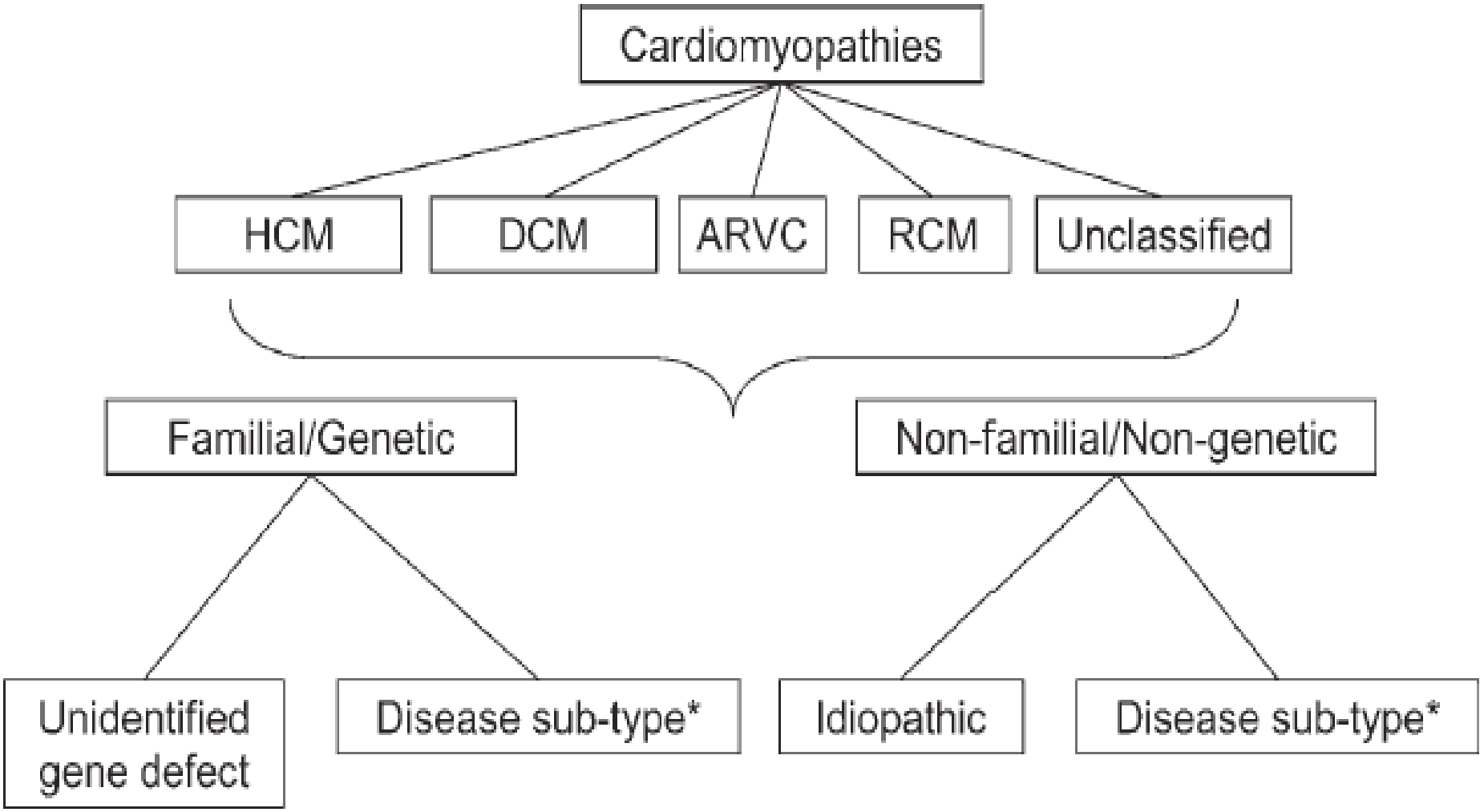
ESC REPORT

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*

Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases

P Elliott et al. Eur Heart J 2008;29:270–276



RESTRICTIVE CARDIOMYOPATHY DEFINITION

- CMP characterized by a “restrictive filling” and by a reduced diastolic volume of one or both ventricles, with preserved systolic function and in absence of significant hypertrophy.
- Myocardial interstitial fibrosis: typical pathological finding
- Idiopathic forms or associated with other diseases (infiltrative CMP, like amiloidosis, endomyocardial fibrosis, hypereosinophilic Loeffler disease)

Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases

P Elliott et al. Eur Heart J 2008;29:270–276

RCM

- Familial, unknown gene
- Sarcomeric protein mutations
  - Troponin I (RCM +/− HCM)
  - Essential light chain of myosin
- Familial amyloidosis
  - Transthyretin (RCM + neuropathy)
  - Apolipoprotein (RCM + nephropathy)
- Desminopathy
- Pseuxanthoma elasticum
- Haemochromatosis
- Anderson–Fabry disease
- Glycogen storage disease
- Amyloid (AL/prealbumin)
- Scleroderma
- Endomyocardial fibrosis
  - Hypereosinophilic syndrome
  - Idiopathic
  - Chromosomal cause
  - Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)
- Carcinoid heart disease
- Metastatic cancers
- Radiation
- Drugs (anthracyclines)

RESTRICTIVE CMP
HAEMODYNAMIC FEATURES

- Major typical haemodynamic feature: ↑ diastolic “stiffness” (↑ steep of diastolic pressure/volume curve) of one or both ventricles, consequence of structural abnormalities of ventricular myocardium (fibrosis)
- “Dip-plateau” morphology of diastolic ventricular pressure curve (“square root sign”)

RESTRICTIVE CMP
ECHO-DOPPLER FEATURES

- No pathognomonic signs (exclusion of other pathologies)
- LV non dilated, non hypertrophic, with preserved systolic function
- Significant dilation of atria and of vena cava
- RESTRICTIVE FILLING PATTERN at transmitral/transtricuspid Doppler curve
- Doppler signs of ↑ filling pressure
- **“Functional” MR, TR**
- Secondary pulmonary hypertension

Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy

Naser M. Ammash, MD; James B. Seward, MD; Kent R. Bailey, PhD; William D. Edwards, MD; A. Jamil Tajik, MD

Background—Idiopathic restrictive cardiomyopathy is a poorly recognized entity of unknown cause characterized by nondilated, nonhypertrophied ventricles with diastolic dysfunction resulting in dilated atria and variable systolic function.

Methods and Results—Between 1979 and 1996, 94 patients (61% women) 10 to 90 years old (mean, 64 years) met strict morphological echocardiographic criteria for idiopathic restrictive cardiomyopathy, mainly dilated atria with nonhypertrophied, nondilated ventricles. None had known infiltrative disease, hypertension of >5 years' duration, or cardiac or systemic conditions associated with restrictive filling. Nineteen percent were in NYHA class I, 53% in class II, and 28% in class III or IV. Atrial fibrillation was noted in 74% of patients and systolic dysfunction in 16%. Follow-up (mean, 68 months) was complete for 93 patients (99%). At follow-up, 47 patients (50%) had died, 32 (68%) of cardiovascular causes. Four had heart transplantation. The death rate compared with actuarial statistics was significantly higher than expected ($P<0.0001$). Kaplan-Meier 5-year survival was 64%, compared with expected survival of 85%. Multivariate analysis using proportional hazards showed that the risk of death approximately doubles with male sex (hazard ratio [HR] =2.1), left atrial dimension >60 mm (HR=2.3), age >70 years (HR=2.0), and each increment of NYHA class (HR=2.0).

Conclusions—Idiopathic restrictive cardiomyopathy or nondilated, nonhypertrophic ventricles with marked biatrial dilatation, as defined morphologically by echocardiography, affects predominantly elderly patients but can occur in any age group. Patients present with systemic and pulmonary venous congestion and atrial fibrillation and have a poor prognosis, particularly men >70 years old with higher NYHA class and left atrial dimension >60 mm. **(*Circulation*. 2000;101:2490-2496.)**

Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy

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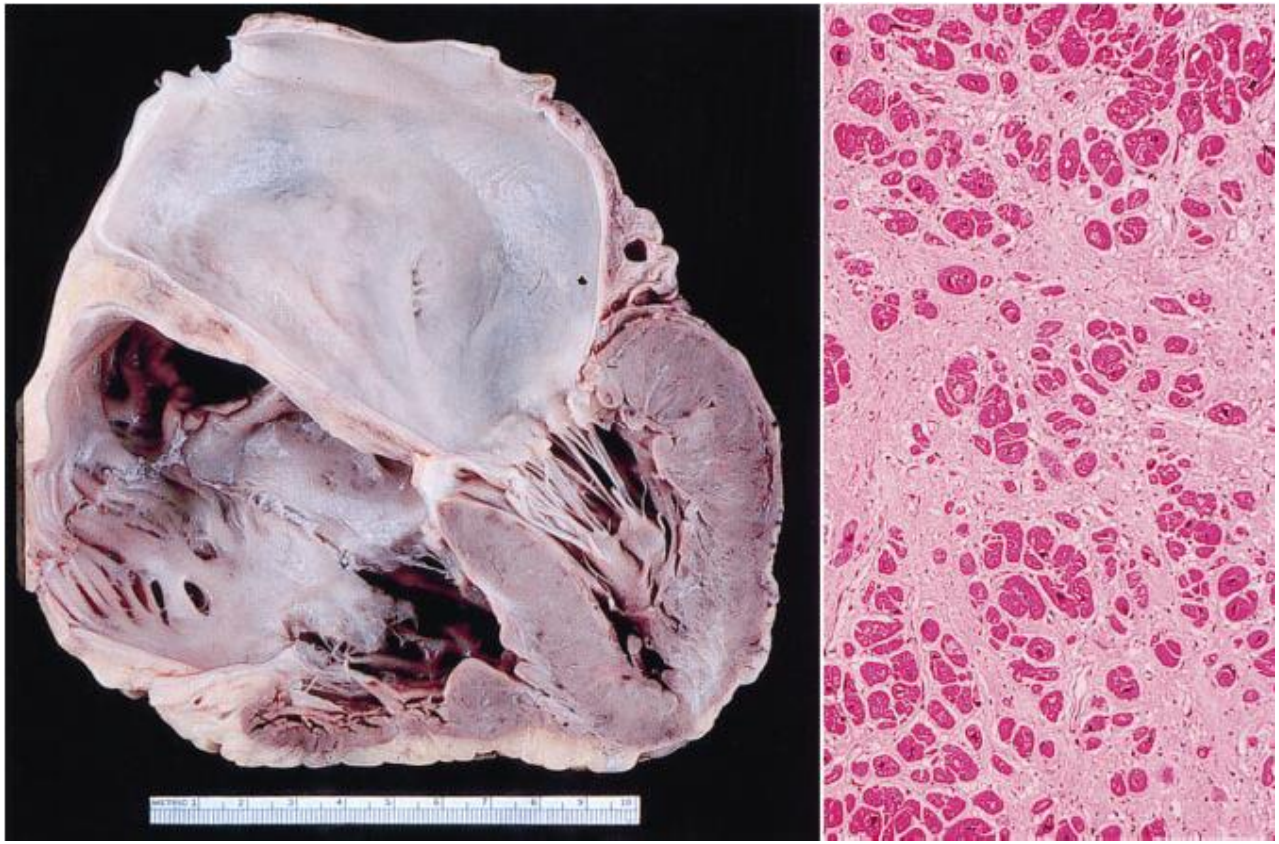


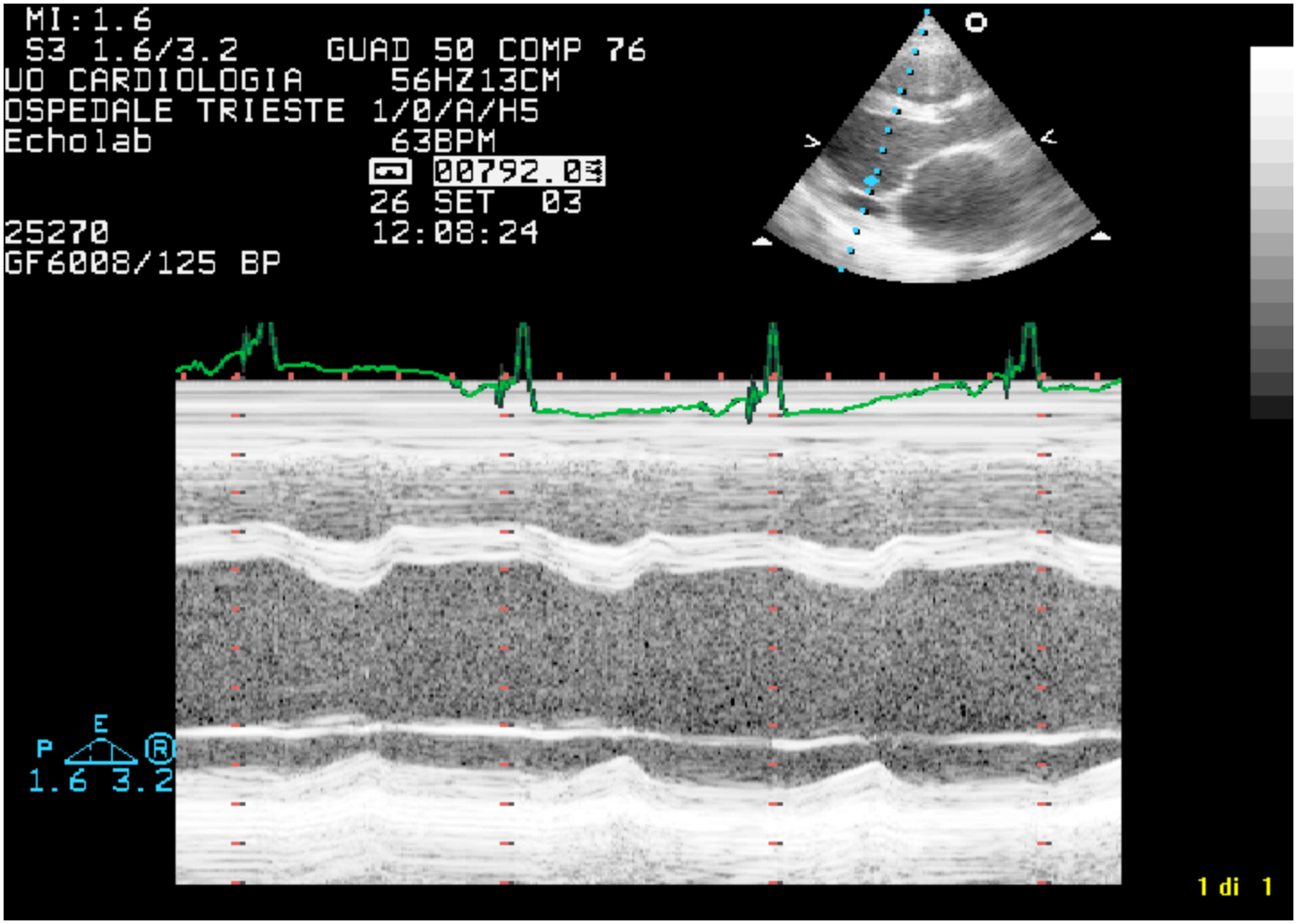
Circulation **May 30, 2000**

Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy

Naser M. Ammash, MD; James B. Seward, MD; Kent R. Bailey, PhD;
William D. Edwards, MD; A. Jamil Tajik, MD

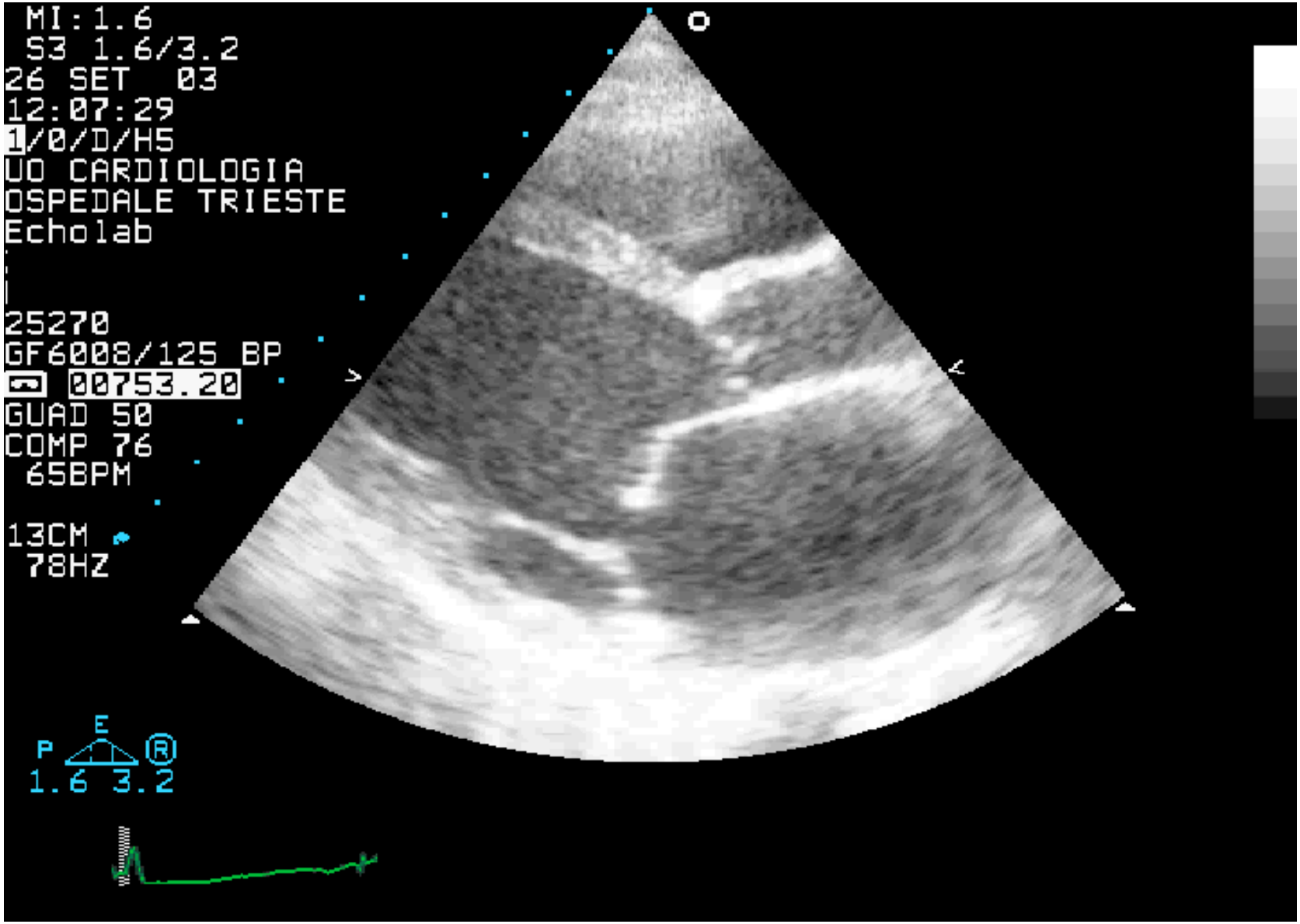
in 23 patients. Color flow Doppler echocardiography in 71 patients demonstrated predominantly mild-to-moderate mitral regurgitation in 84% and mild-to-moderate tricuspid regurgitation in 70%. Transmitral valve Doppler was performed in 51 patients and demonstrated an average mitral valve deceleration time of 144 ms (range, 70 to 250 ms). The latter was >200 ms in only 10% of patients, 150 to 200 ms in 25%, and <150 ms in 65%. The E/A ratio in 20 patients in sinus rhythm was >2 in 17 (85%). Tricuspid valve regurgitant velocity was measured in 50 patients. The Doppler-derived right ventricular systolic pressure was normal (tricuspid regurgitant velocity <2.5 m/s) in only 13% and was markedly elevated in 10% (tricuspid regurgitant velocity >3.5 m/s).

RCM



LVEDD: 58 mm, FS: 28%;IVS: 7 mm, PW: 6 mm

RCM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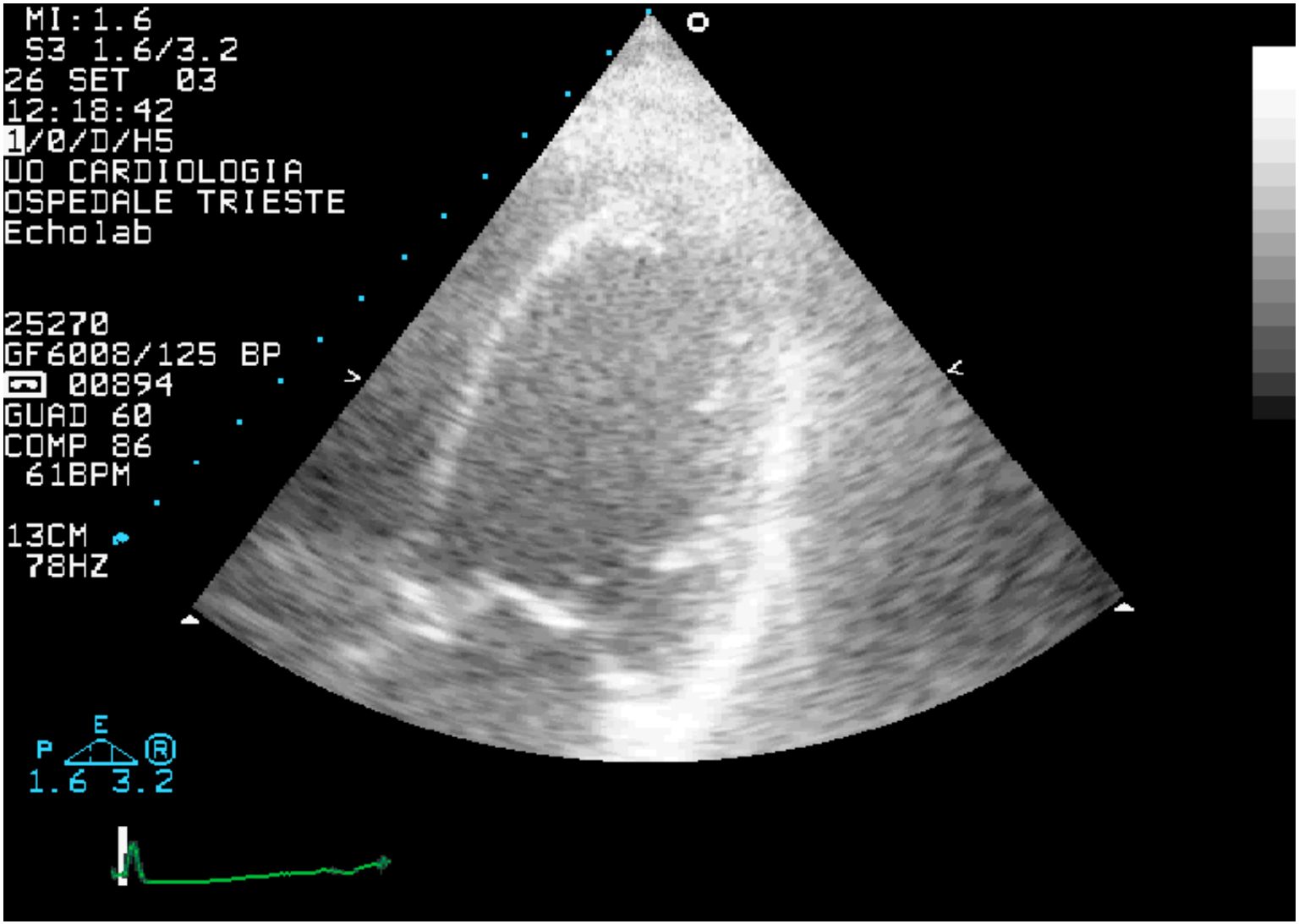
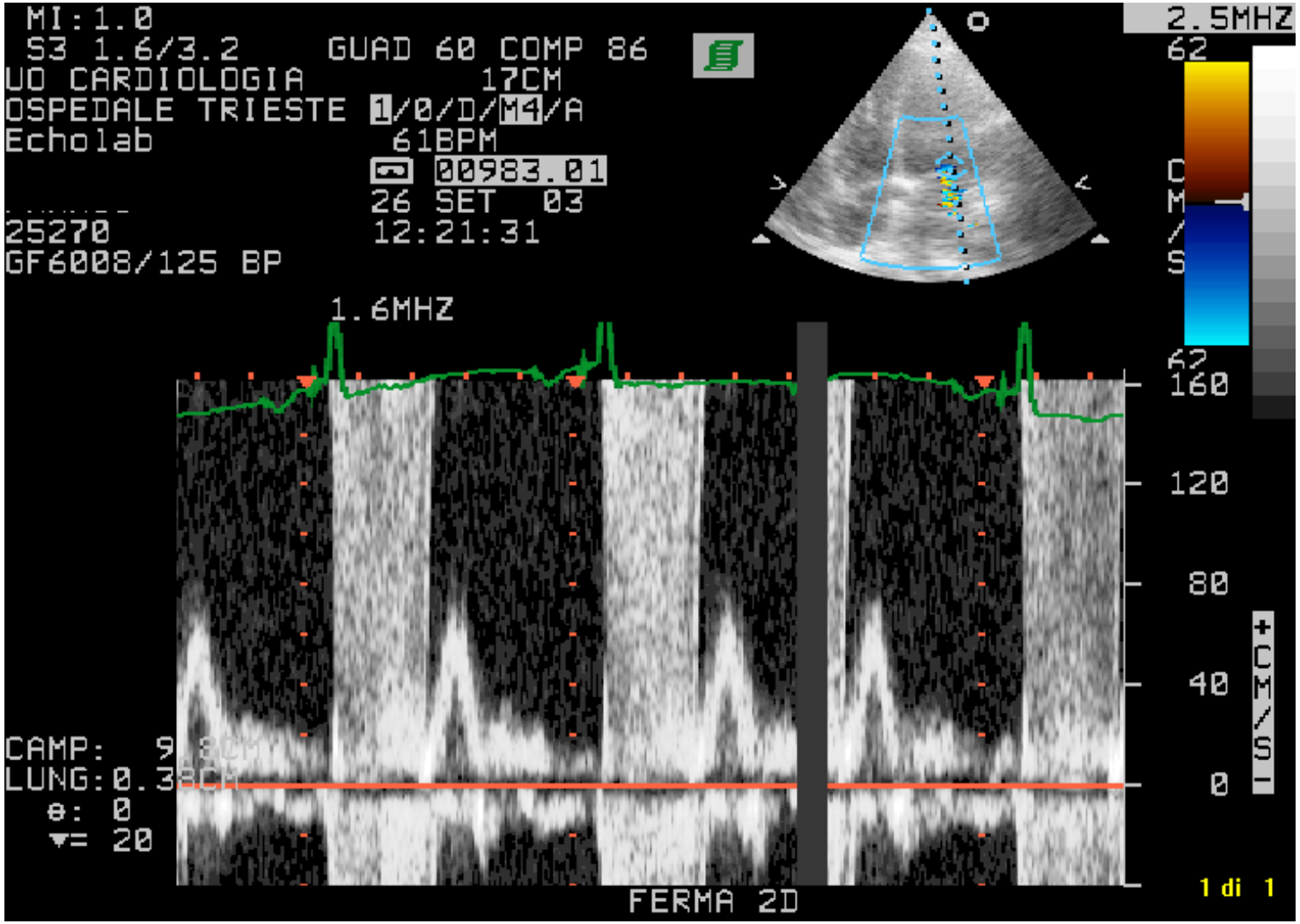
RCM

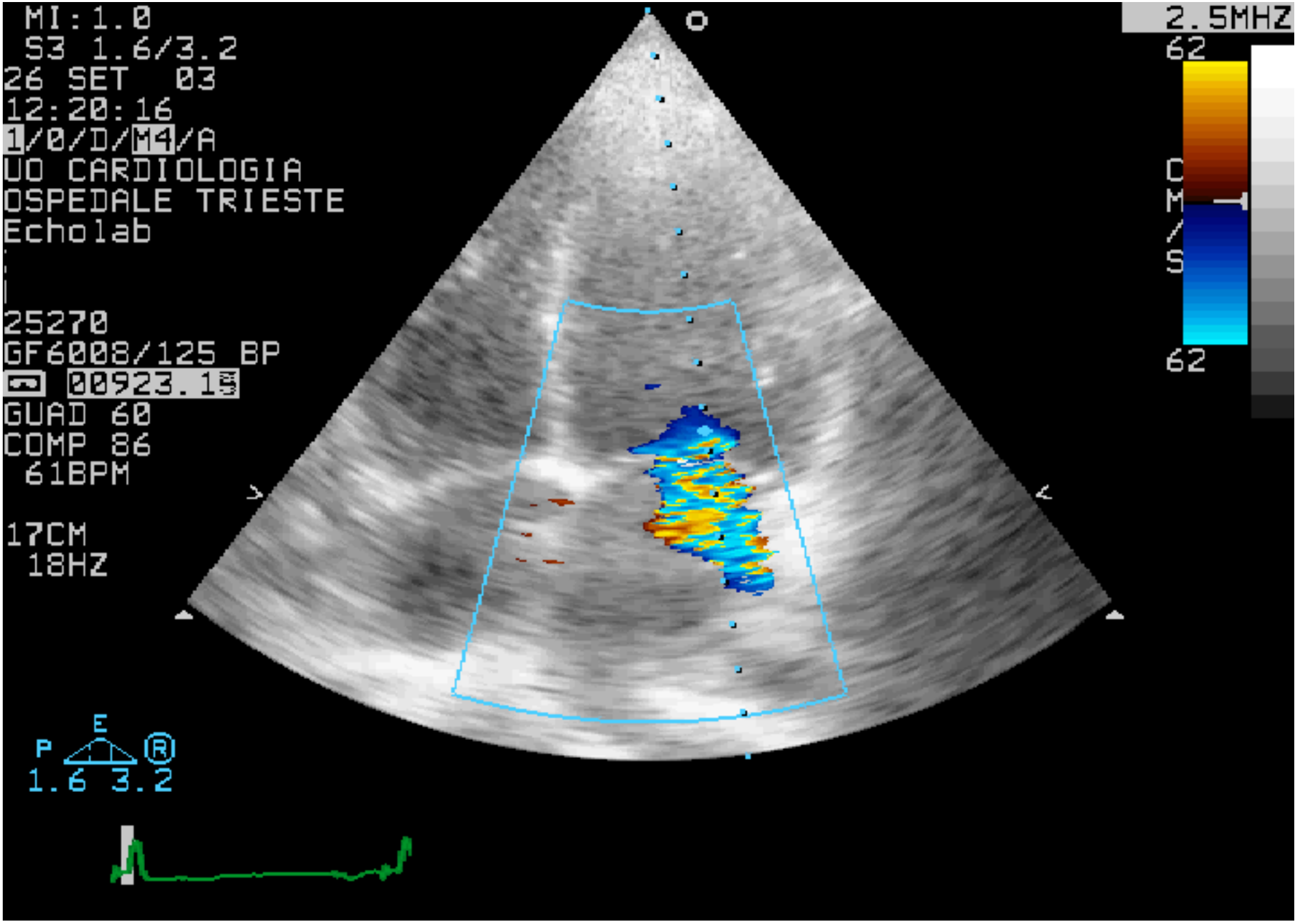


LVEDV: 108 ml; EF: 49%

RCM: LV RFP



E: 0.6 m/s; A: 0.1 m/s; E/A: 6.0; EDT: 90 ms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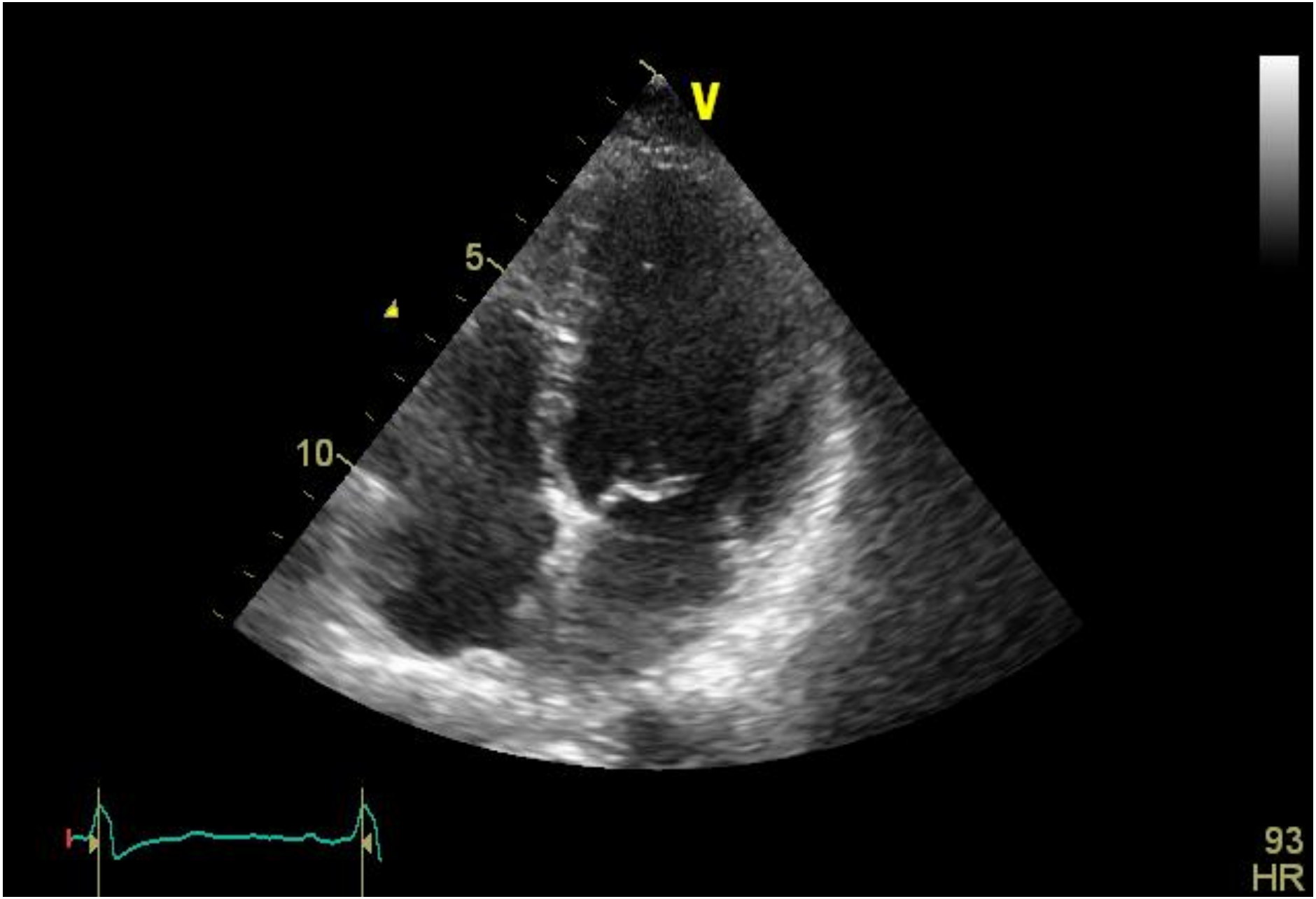
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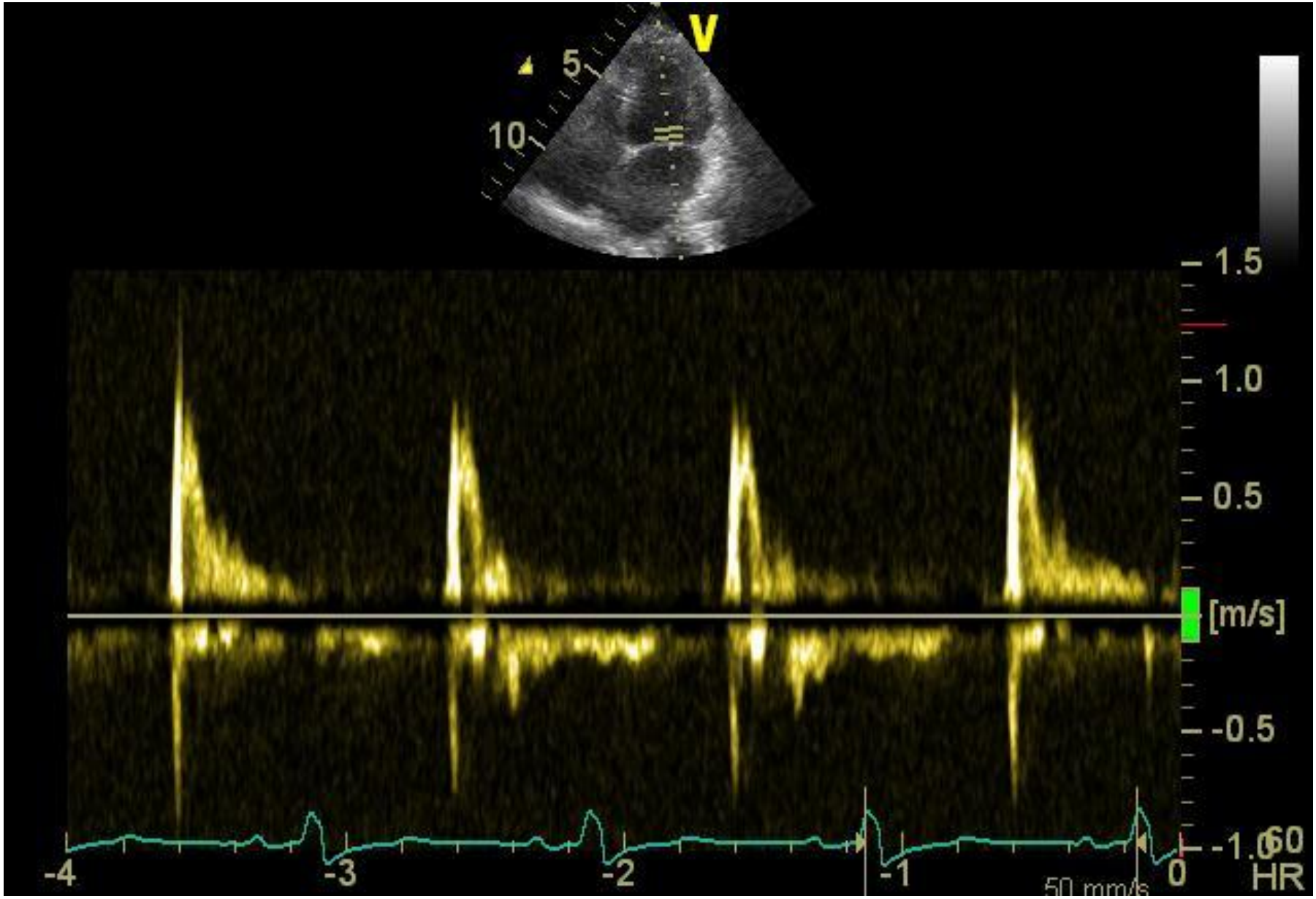
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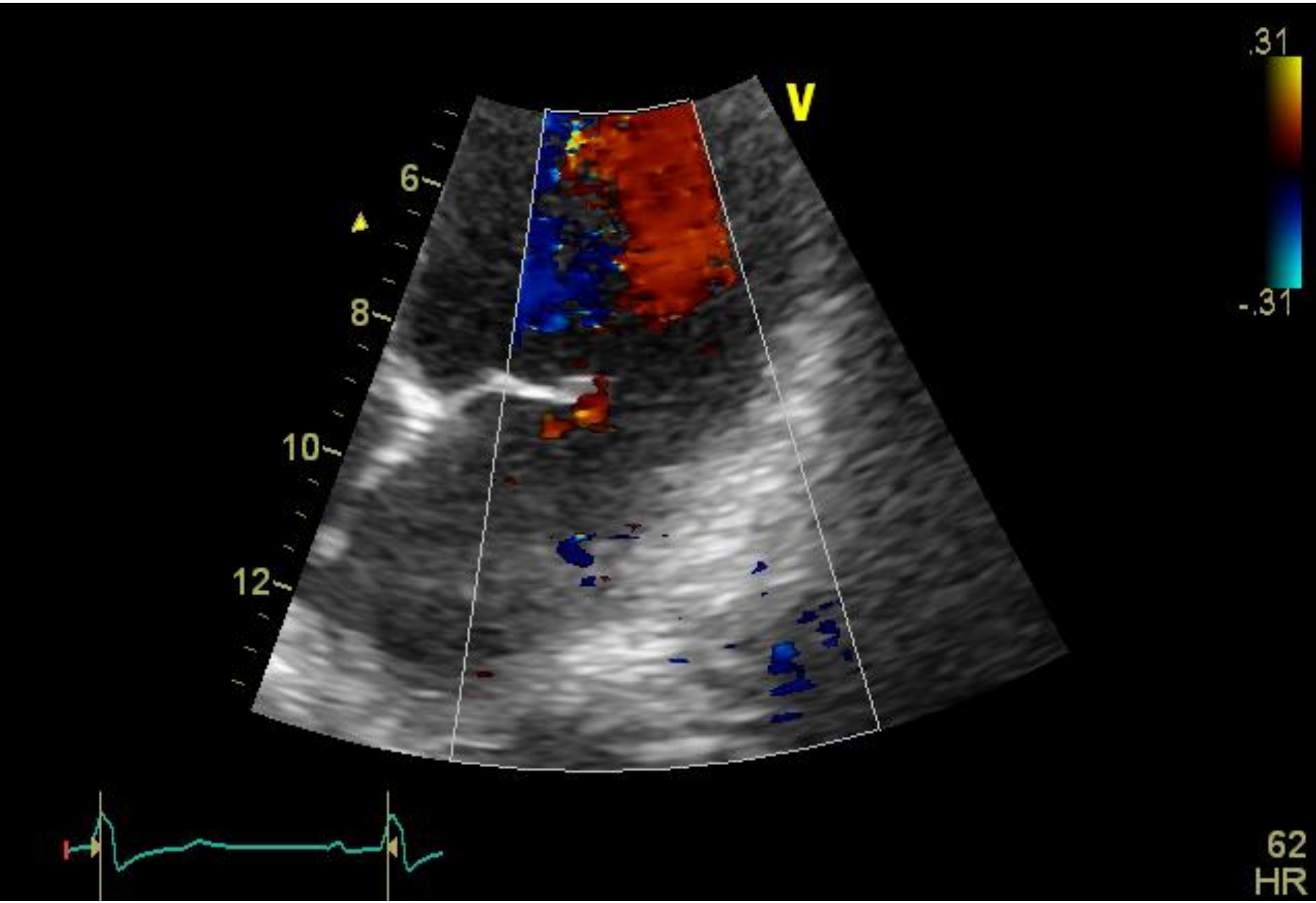
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HR

LOEFFLER HYPEREOSYNOPHILIC CMP– ENDOMYOCARDIAL FIBROSIS: DIAGNOSTIC FEATURES

- Clinical: HF, embolic episodes, SV arrhythmias
- Persistent hypereosinophilia (>1500 eos/mm3 for >6 months) without cause (IHS)
- Early stage: Eosinophilic infiltration of endomyocardium + necrosis, thrombosis (Loeffler disease)
- Late stage (EMF): Fibrotic thickening/obliteration of ventricular apex and basal ventricular endomyocardium (one or both ventricles), **possible involvement of papillary muscles and M/T leaflets, with valvular dysfunction**

Loeffler Endomyocarditis/EMF Stages of disease

- Acute necrotic stage (weeks): eosynophilic endomyocarditis
- Thrombotic stage (months): ventricular thrombi in damaged endocardium (apex or basal portion of one or both VV)
- Fibrotic stage (EMF)(years): RCM with apical obliteration, progressive scarring of endomyocardium, M and/or T valve involvement with MR/TR, often severe

LOEFFLER CMP/EMF
ECHO-DOPPLER FINDINGS

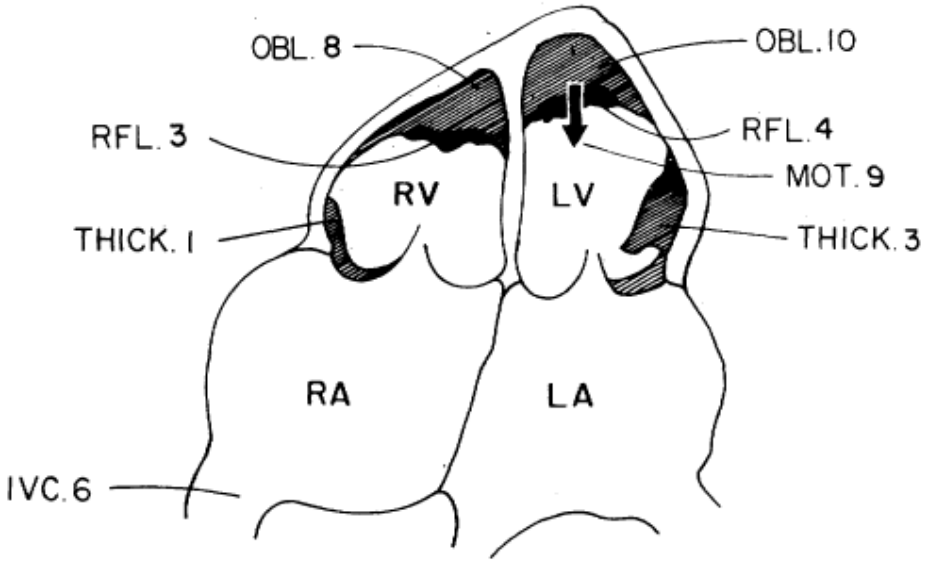
- Thickening and hyperechogenicity of LV/RV apex (obliteration) and/or basal segments
- Apical thrombi of LV/RV
- Preserved EF
- Severe diastolic dysfunction (“restrictive filling pattern”) of LV and/or RV
- **MR and/or TR due to entrapment of chordae tendineae in the fibrotic process and retraction of valve leaflets**

Value of Two-dimensional Echocardiography in Endomyocardial Disease With and Without Eosinophilia

A Clinical and Pathologic Study

Circulation 1983, 67:1219-1226

HARRY ACQUATELLA, M.D., NELSON B. SCHILLER, M.D., JUAN JOSÉ PUIGBÓ, M.D.,
JOSÉ RAMÓN GÓMEZ-MANCEBO, M.D., CLAUDIA SUAREZ, M.D.,
AND GRETA ACQUATELLA, M.D.



Five patterns of cardiac lesions:
Type 1: only apical obliteration
Type 2: lesion extending form apex to AV valve
Type 3: AV Valvular lesions only
Type 4: Separate lesions in apex and AV valvular tissue
Type 5: patches in areas other than Apex and AV valves

Clinical and Echocardiographic Features of Hypereosinophilic Syndromes

Steve R. Ommen, MD, James B. Seward, MD, and A. Jamil Tajik, MD

The American Journal of Cardiology Vol. 86 July 1, 2000

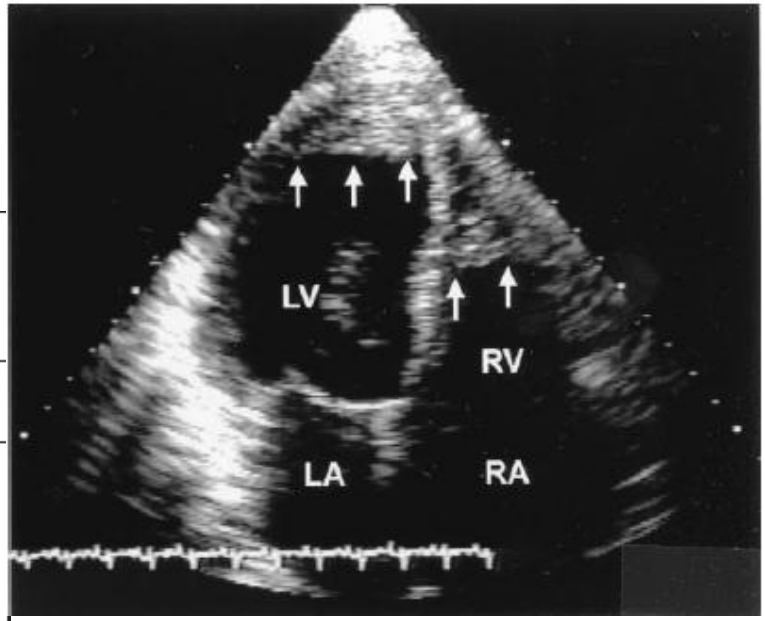
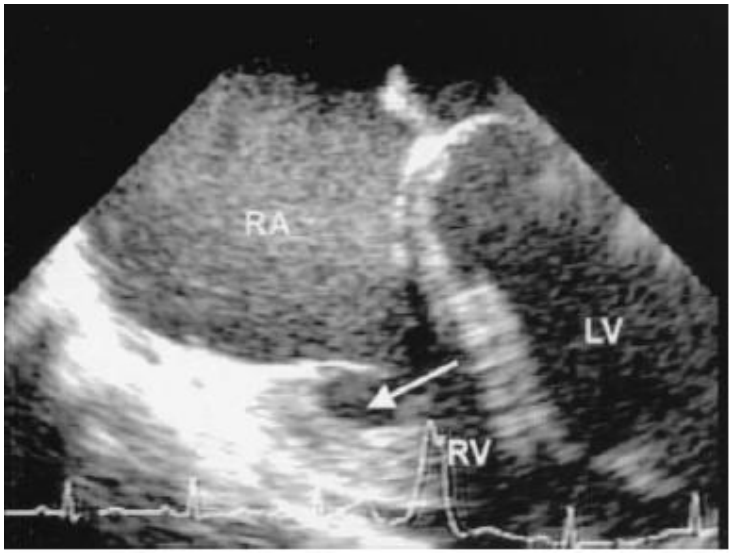


TABLE I Comparison of Baseline Characteristics and Echocardiographic Findings in Patients With Hypereosinophilic Syndrome (group 1) and in Those With Other Eosinophilia (group 2)

Findings	Group 1 (n = 51)	Group 2 (n = 43)	p Value
Mean age (yrs)	45 ± 17	43 ± 20	NS
Mean duration of symptoms (mo)	21 ± 33	40 ± 54	0.04
Mean eosinophilic count, × 10⁹/L	18.6 ± 29.7	9.2 ± 9.1	0.05
	No. of Patients (%)	No. of Patients (%)	
Men	40 (78)	22 (51)	0.009
Deaths	17 (33)	5 (12)	0.02
Embolic events	8 (16)	3 (7)	NS
Heart failure	9 (18)	3 (7)	NS
Echocardiography	(n = 49)	(n = 36)	
Classic findings	24 (49)	5 (14)	0.002
Endocardial thickening*	6 (12)	1 (3)	
LV apical thrombus*	12 (24)	3 (8)	
RV apical thrombus*	10 (20)	1 (3)	
PML involvement*	10 (20)	3 (8)	
Tricuspid involvement	5 (10)	0	
Hyperdynamic left ventricle	8 (16)	4 (11)	
LV hypertrophy	5 (10)	3 (8)	
Dilated left ventricle	7 (14)	4 (11)	
Pericardial effusion	9 (18)	3 (8)	

*Classic findings in hypereosinophilic syndrome.
LV = left ventricular; PML = posterior mitral leaflet; RV = right ventricular.



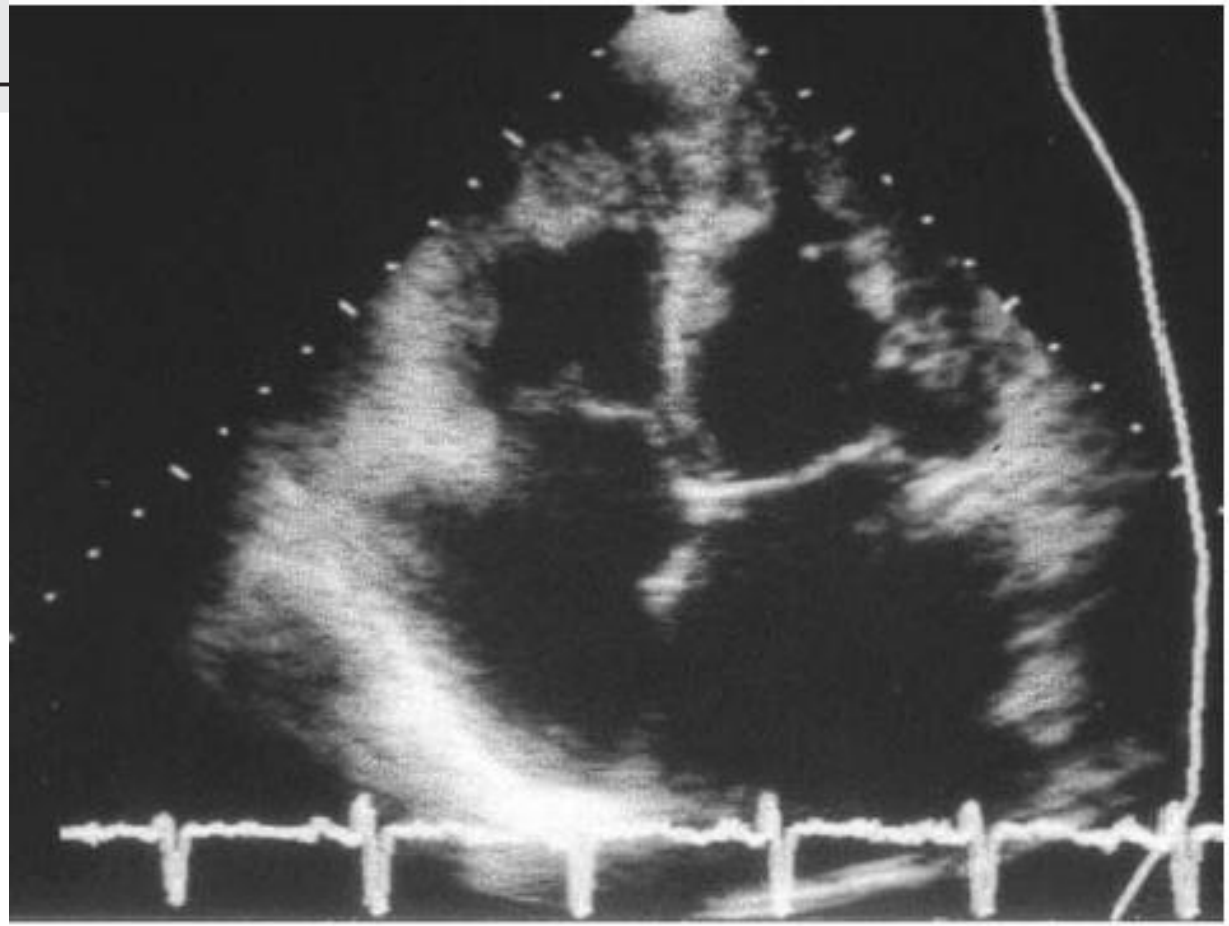
Restrictive cardiomyopathies

European Journal of Echocardiography (2009) **10**, iii23–iii33
doi:10.1093/ejechocard/jep156

Petros Nihoyannopoulos[1]* and David Dawson[2]

Table 4 Echocardiographic features of endomyocardial fibrosis

LV thrombus at the apex
Good LV function (including the apex)
RV thrombus
Endocardial thickening of the LV
Restriction to mitral and tricuspid valve mobility
Mitral and tricuspid regurgitation (often severe)
E/*A* ratio >1



Restrictive cardiomyopathies

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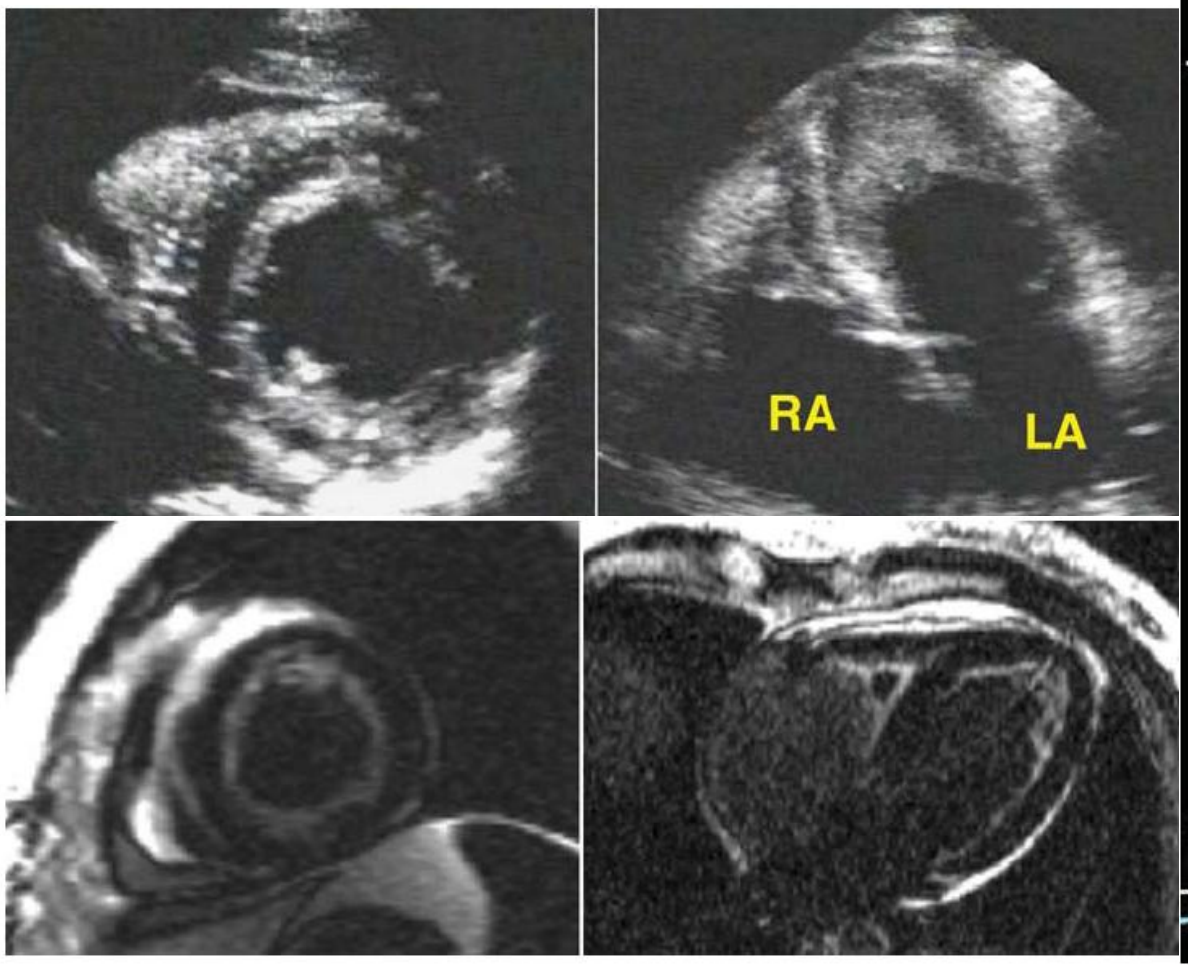
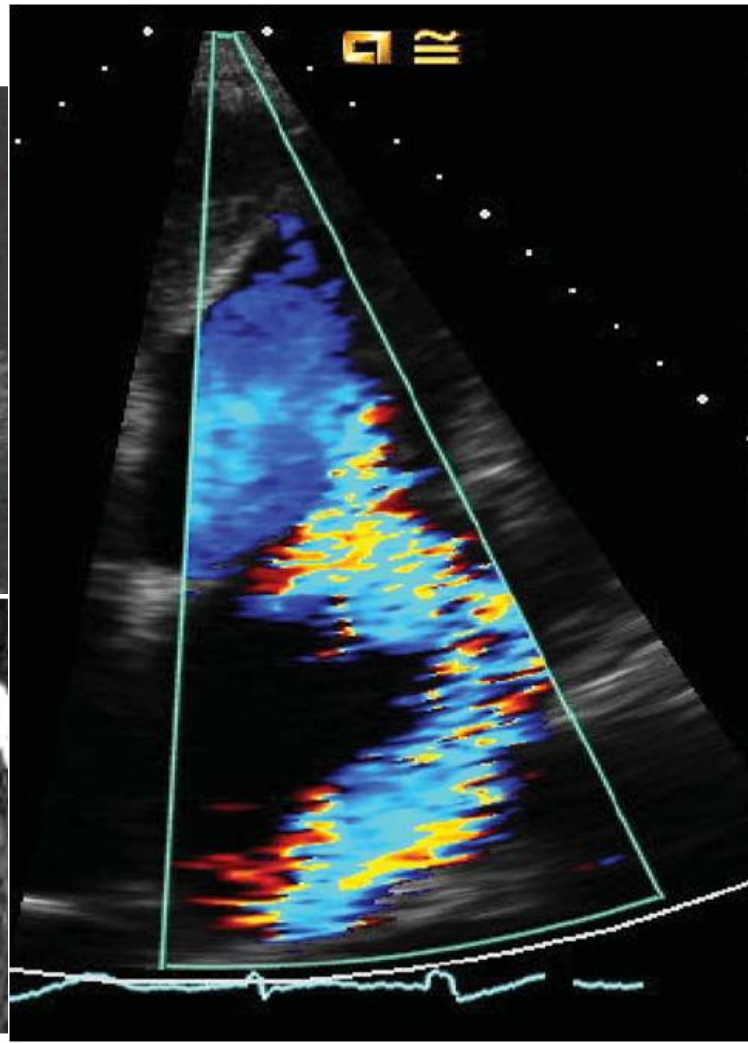
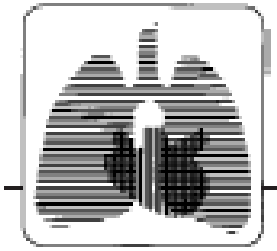
Petros Nihoyannopoulos[1]* and David Dawson[2]

Significant MR in EMF

Examples of EMF CMP: Echo & MRI







special reports

Pitfalls in Diagnosis and Clinical, Echocardiographic, and Hemodynamic Findings in Endomyocardial Fibrosis*

A 25-Year Experience

Walid M. Hassan, MD, FCCP; Mohamed E. Fawzy, MD; Sumaya Al Helaly, MD; Hesham Hegazy, MD; and Shahid Malik, MD

Endomyocardial fibrosis (EMF) is a fascinating disease entity of unknown etiology. It is prevalent in the tropical zone. Its essential features are the formation of fibrous tissue on the endocardium and to a lesser extent in the myocardium of the inflow tract and apex of one or both ventricles. It results in endocardial rigidity, atrioventricular valve incompetence secondary to papillary muscle involvement, and progressive reduction of the cavity of the involved ventricle leading to restriction in filling and atrial enlargement. This article will present 21 patients with EMF who were initially referred to our hospital from 1979 to 2004 with different diagnoses: rheumatic heart disease with mitral and or tricuspid regurgitation (n = 9), constrictive pericarditis (n = 6), restrictive cardiomyopathy (n = 1), hypertrophic cardiomyopathy apical type (n = 2), dilated cardiomyopathy (n = 2), and Ebstein malfunction of the tricuspid valve (n = 1). The clinical, echocardiographic, hemodynamic, and angiographic findings in these 21 patients are presented; echocardiographic findings lead to the right diagnosis. The presence of a small ventricle with obliteration of the apex and large atrium shown on two-dimensional echocardiography is highly suggestive of EMF. *(CHEST 2005; 128:3985–3992)*

Pitfalls in Diagnosis and Clinical, Echocardiographic, and Hemodynamic Findings in Endomyocardial Fibrosis* : A 25-Year Experience

Walid M. Hassan, Mohamed E. Fawzy, Sumaya Al Helaly, Hesham Hegazy and Shahid Malik

Chest 2005;128;3985-3992

Table 1—*Symptoms and Physical Signs in 21 Patients With EMF

Case No.	Age/Sex	Dyspnea NYHA Class	Edema	Distended Neck Veins	Pulse	Ascites	Hepatomegaly	S3 Gallop	MR	TR
Left ventricular										
1	20/female	III	No	No	SR	No	No	Yes	2+	No
2	40/male	III	No	No	SR	No	No	Yes	4+	No
3	41/male	III	No	No	SR	No	No	Yes	No	1+
4	43/male	II	No	No	SR	No	No	No	3–4+	1+
Right ventricular										
5	30/male	IV	Yes	Yes	SR	Yes	Yes	Yes	No	No
6	32/female	III	Yes	Yes	SR	Yes	Yes	Yes	No	No
7	15/male	IV	Yes	Yes	AF	Yes	Yes	Yes	No	4+
8	44/male	IV	Yes	Yes	AF	Yes	Yes	Yes	No	2+
9	25/female	IV	Yes	Yes	SR	Yes	Yes	No	No	4+
10	60/male	III	Yes	Yes	SR	Yes	Yes	No	No	No
11	76/male	III	Yes	Yes	SR	Yes	Yes	No	No	3+
Biventricular EMF										
12	32/male	IV	Yes	Yes	SR	Yes	Yes	Yes	2+	2+
13	40/male	III	Yes	Yes	AF	No	No	Yes	2+	1+
14	52/male	II	Yes	Yes	AF	No	Yes	Yes	No	1+
15	60/female	III	Yes	Yes	AF	Yes	Yes	Yes	No	1+
16	24/female	II	No	No	SR	No	Yes	Yes	4+	1+
17	59/male	III	Yes	Yes	CHB	Yes	Yes	Yes	4+	4+
18	24/female	III	Yes	Yes	AF	No	No	Yes	4+	1+
19	25/female	III	No	Yes	SR	No	No	Yes	2+	1+
20	18/male	III	Yes	Yes	SR	Yes	Yes	Yes	2+	No
21	28/ male	III	Yes	Yes	SR	No	Yes	Yes	4+	4+

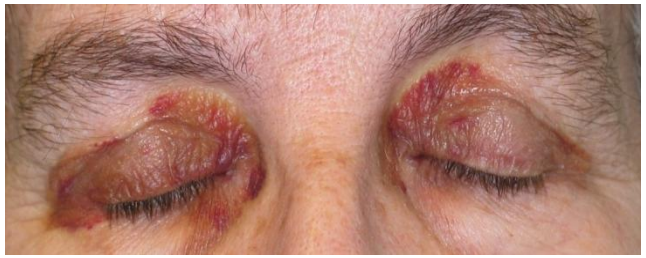
*CHB = complete heart block; SR = sinus rhythm; AF = atrial fibrillation.

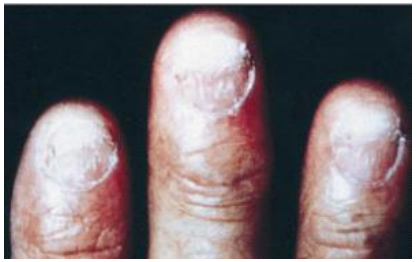
Echocardiography: Obliteration of the apex of the involved ventricle is the hallmark of the disease, along with a grossly dilated atrium with a normal-sized (or mildly dilated) ventricle and thickening of the posterior left ventricular wall or anterior interventricular septum in patients with left-sided or right-sided involvement, respectively.[18–20] One condition that mimics right-sided EMF is Behçet disease, in which obliteration of the right ventricular apex by clot without TR may occur.[21] Other conditions that may well mimic EMF are apical thrombus and the apical type of HCM, in which obliteration of the apex occurs in systole only. In the setting of clinically severe MR or TR, EMF can be suspected if there is echocardiographic evidence of a small or normal-size ventricle with a grossly dilated corresponding atrium. This finding is in contrast to rheumatic valve regurgitation, in which the involved ventricle tends to be dilated. The hugely dilated atria also help in differentiating the disease from CP and Behçet disease in which the atria tends to be of normal size. Also, the presence of normal-size ventricles on echocardiography in patients with gross cardiomegaly on CXR helps to differentiate EMF from DCM.

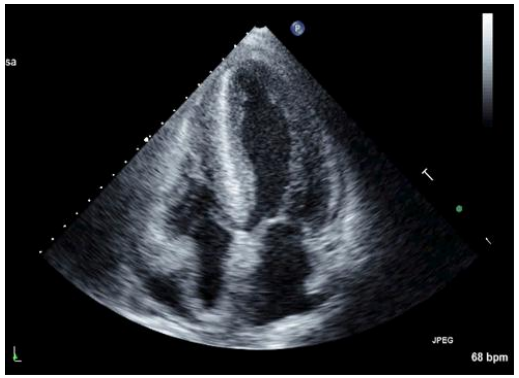
INFILTRATIVE/STORAGE CMP

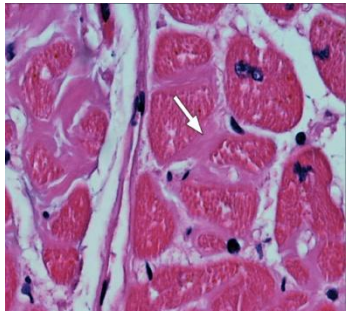
- Infiltrative CMP >> intercellular infiltration of myocardium by abnormal substances (ex. Amyloidosis)
- Storage CMP >> intracellular accumulation within myocardial cells by various substances
- Genetically inherited and acquired sporadic forms

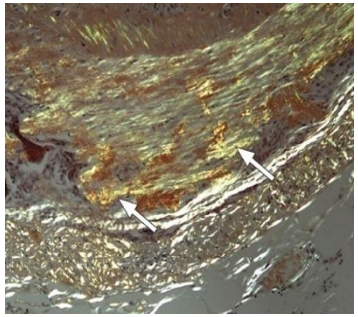
Systemic Amyloidosis – Clinical and Lab features

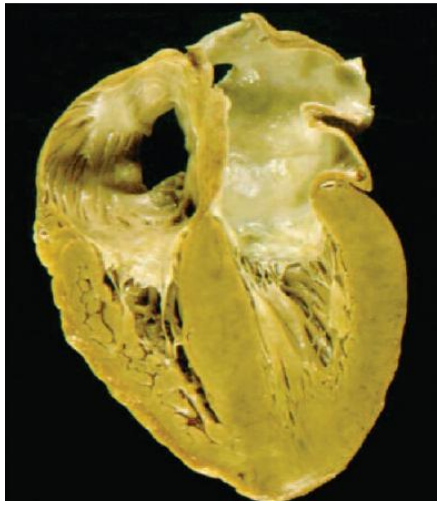


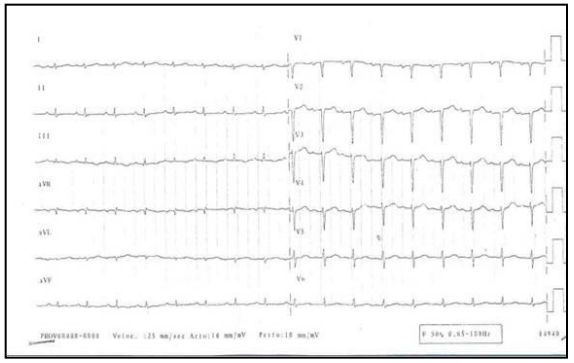


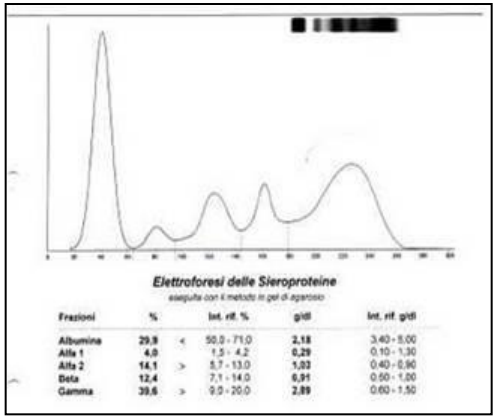


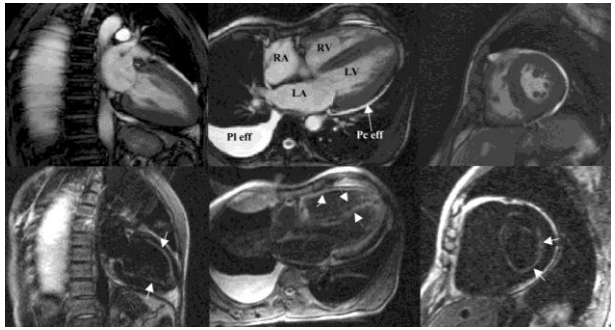












Restrictive cardiomyopathies

Petros Nihoyannopoulos[1]* and David Dawson[2]

European Journal of Echocardiography (2009) **10**, iii23–iii33
doi:10.1093/ejechocard/jep156

Table 2 Amyloid heart disease

Primary amyloidosis (AL)
Cardiac involvement common
Secondary amyloidosis (amyloid A)
Cardiac involvement rare
Hereditary amyloidosis (TTR)
Usually autosomal dominant
Age-related amyloidosis
Senile in 25% aged >80 years (TTR)
Atrial in 90% aged >90 years (ANP)

Table 2 Cardiac clinical manifestations of amyloidosis

Clinical characteristics of cardiac amyloid involvement
Dilated cardiomyopathy (cardiomegaly, predominant systolic dysfunction)
Restrictive cardiomyopathy (slight cardiomegaly, predominant diastolic dysfunction, stiff heart syndrome)
Congestive heart failure
Electrocardiographic disorders (rhythm abnormalities, low voltage QRS complex, sick sinus syndrome, pseudoinfarct pattern, atrioventricular and ventricular conduction abnormalities)
Coronary insufficiency (myocardial infarction, angina pectoris)
Valvular dysfunction
Pericardial tamponade
Enhanced sensitivity to digitalis glycosides
Atrial thrombosis—embolisation

Restrictive cardiomyopathies

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Table 3 Echocardiographic features of amyloid infiltration of the heart

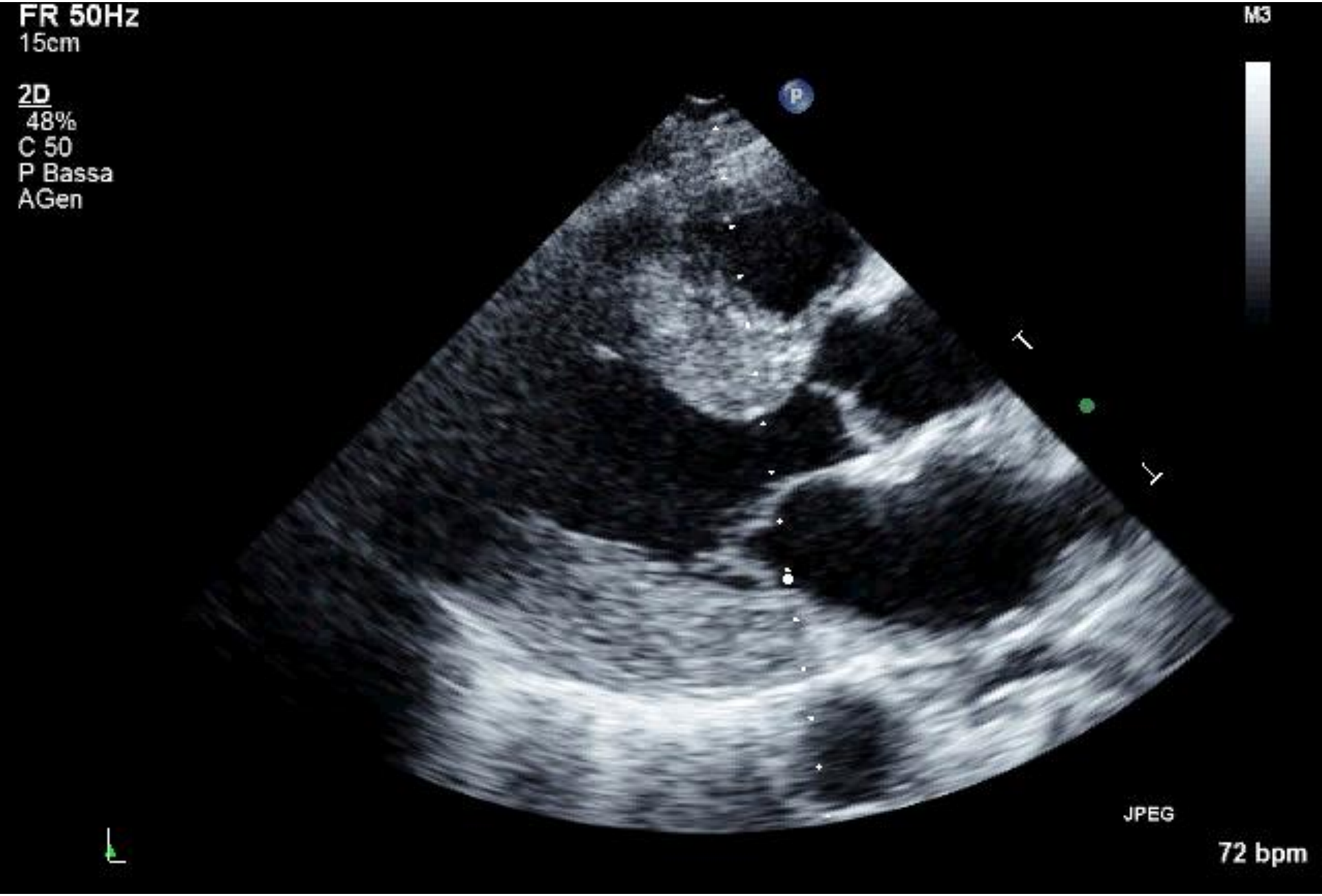
Increased LV wall thickness
Increased RV wall thickness
Small, well, or poorly contracting LV
Enlarged LA
Valve thickening (all valves)
Mitral regurgitation (usually mild)
Thickened atrial septum
E/*A* ratio >1
Pericardial effusion (advanced disease)

Cardiac amyloidosis
Trieste Heart Muscle Disease Registry

Echocardiographic and Doppler data

	Total (48)	Group 1 (AL) (29)	Group 2 (secondary) (7)	Group 3 (unknown: ?ATTR) (12)	p
Left atrium area (cm2)	28±8	27±9	28±7	28±9	NS
Right atrium area (cm2)	23±7	24±8	21±5,8	26±10	NS
LVEDD (mm)	45±9	46±10	43±7	45±10	NS
LVESD (mm)	30±9	30±10	25±5	31±9	NS
IVS thickness (mm)	17±4	18±4	15±2	16±3	NS
PW thickness (mm)	15±3	15±4	13±1	15±3	NS
IVS thick >15 mm (%;n)	54(26)	59(17)	43(3)	50(6)	NS
LVEDV (ml)	74±37	73±36	75±30	76±43	NS
LVESV (ml)	35±23	36±25	34±15	34±23	NS
LVEF (%)	55±13	55±15	56±8	56±11	NS
LVEF < 50% (%;n)	19(9)	24(7)	14(1)	8(1)	NS
MV EDT <150 msec (%;n)	**37(17)**	**24(7)**	**43(3)**	**64(7)**	**0,05**
E/A wave ratio>2 on 34 pts (%;n)	38(13)	36(8)	40(2)	43(3)	NS
LV restrictive filling pattern (%;n)	25(12)	17(5)	33(2)	42(5)	NS
Mod-Sev MR (%;n)	**10(5)**	14(4)	0(0)	8(1)	NS
Pericardial effusion (%;n)	40(19)	38(11)	29(2)	50(6)	NS
Right ventricular hypertrophy (%;n)	33(16)	38(11)	14(1)	33(4)	NS

Ospedali Riuniti di Trieste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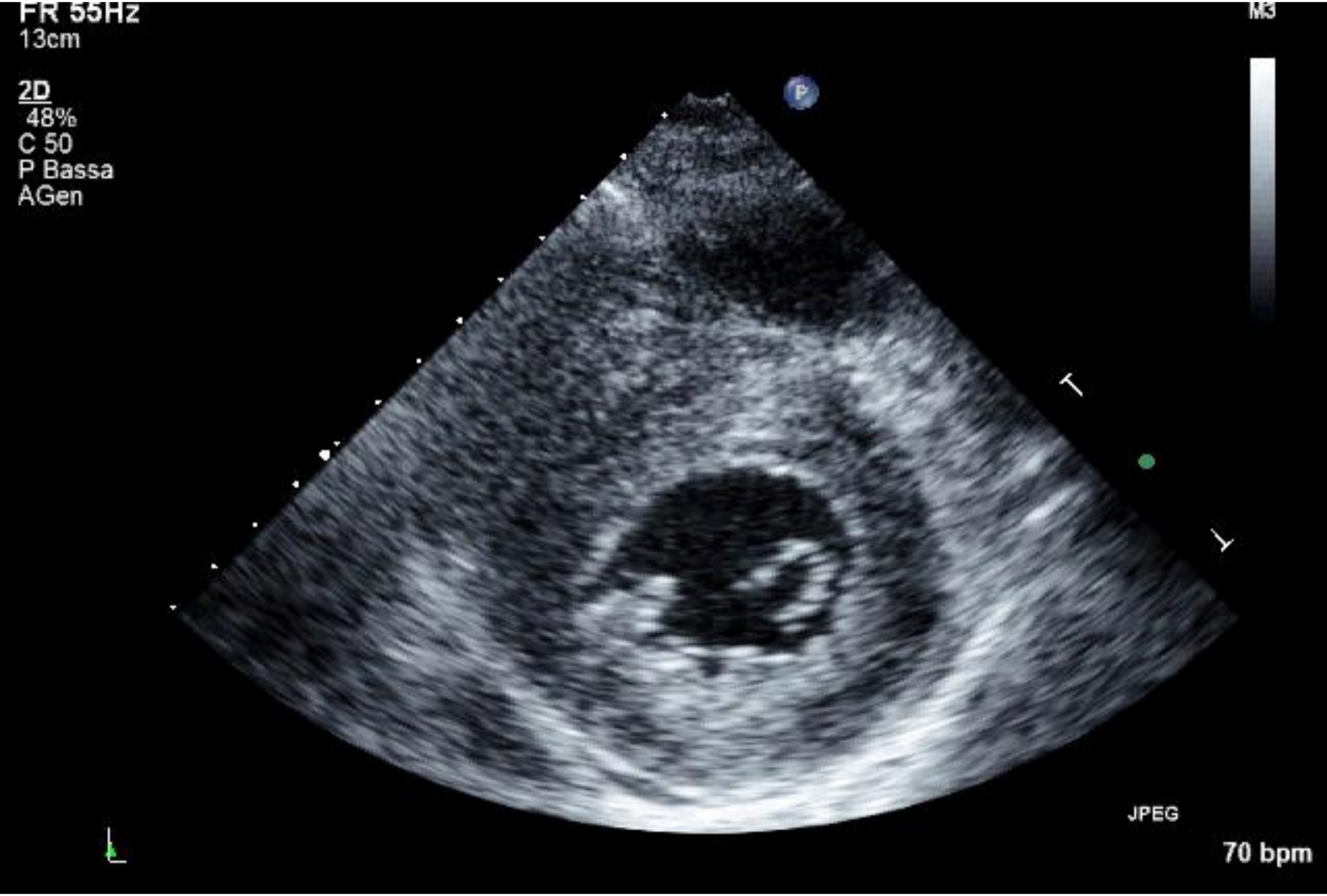
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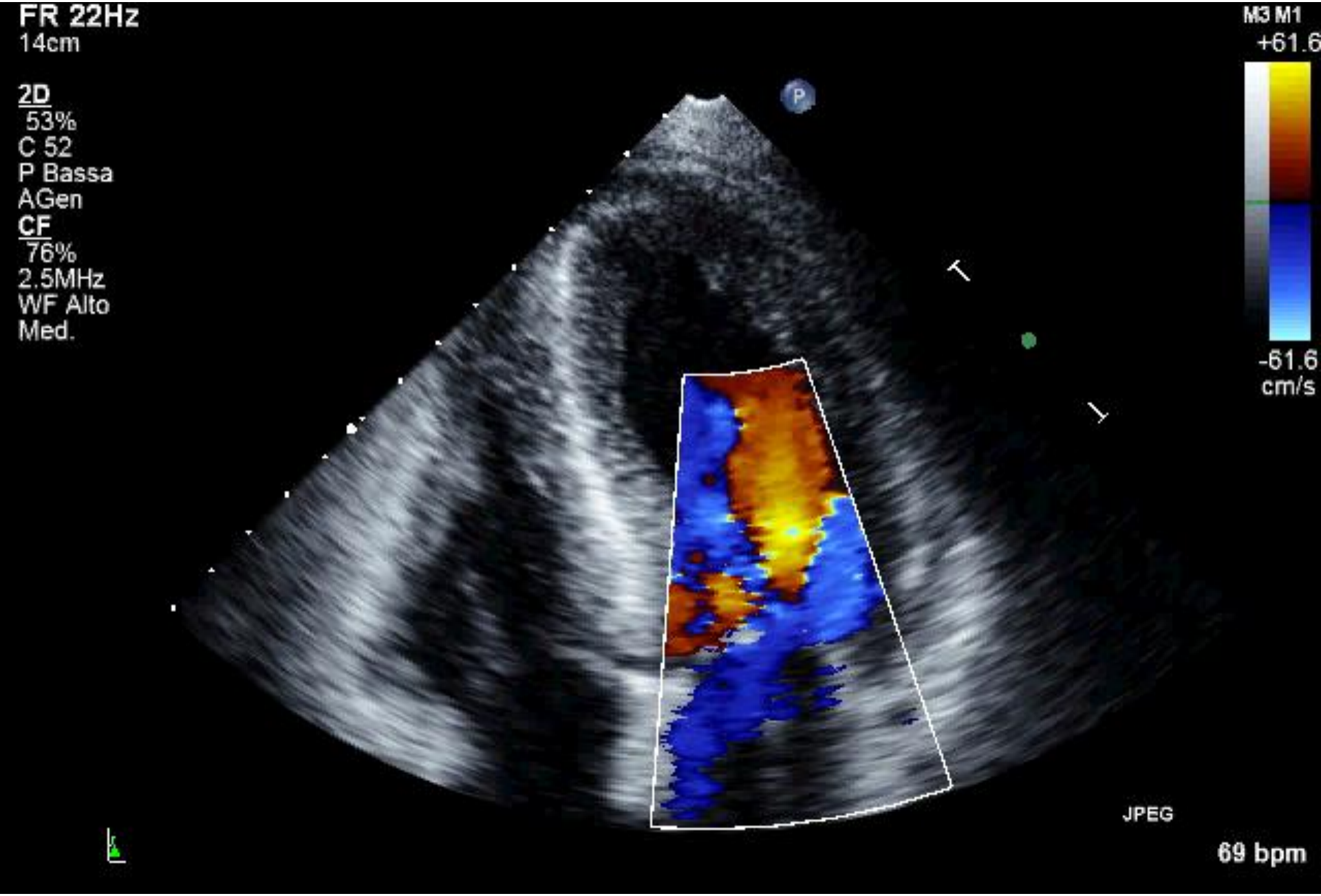
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JPEG
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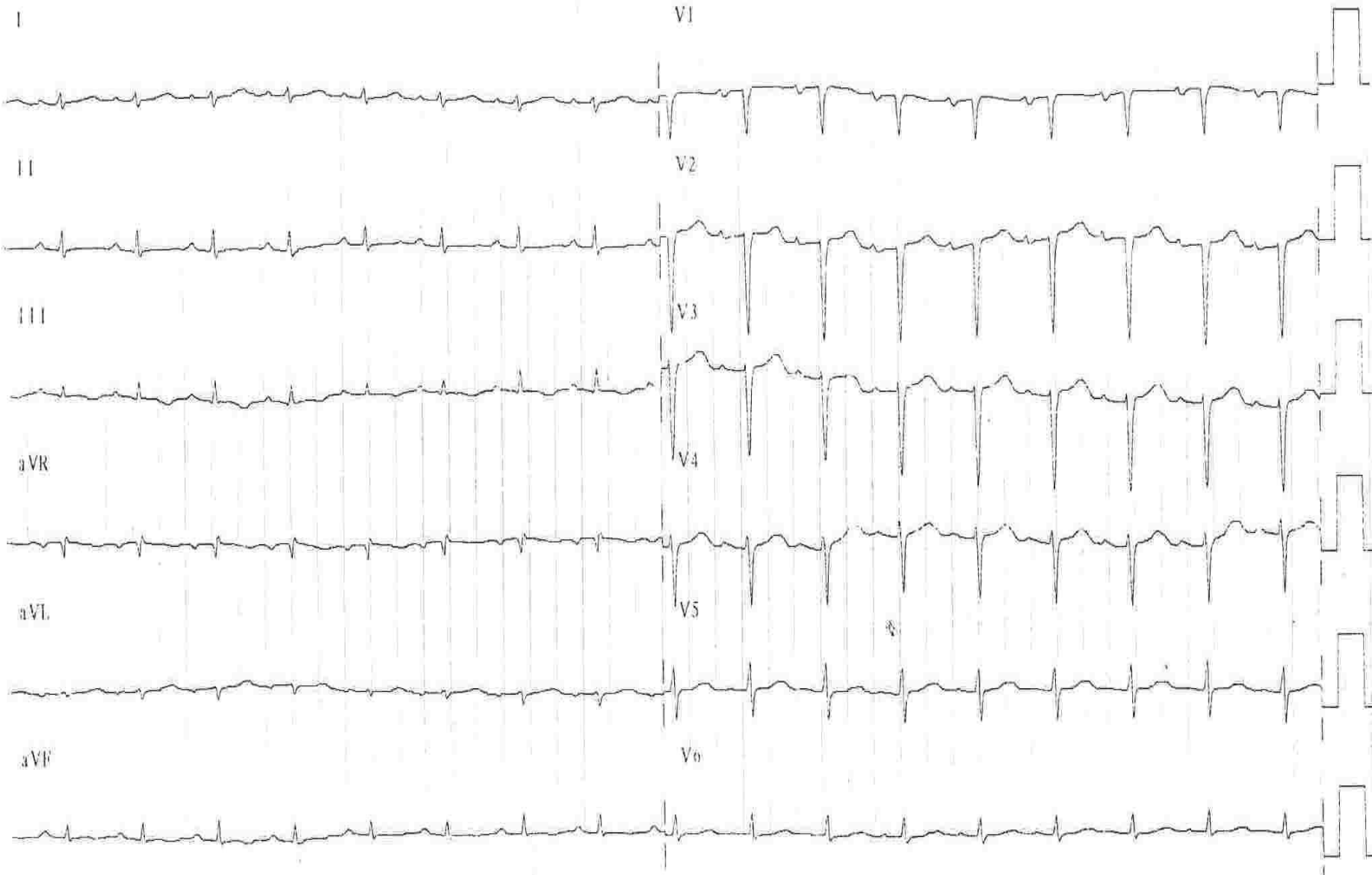
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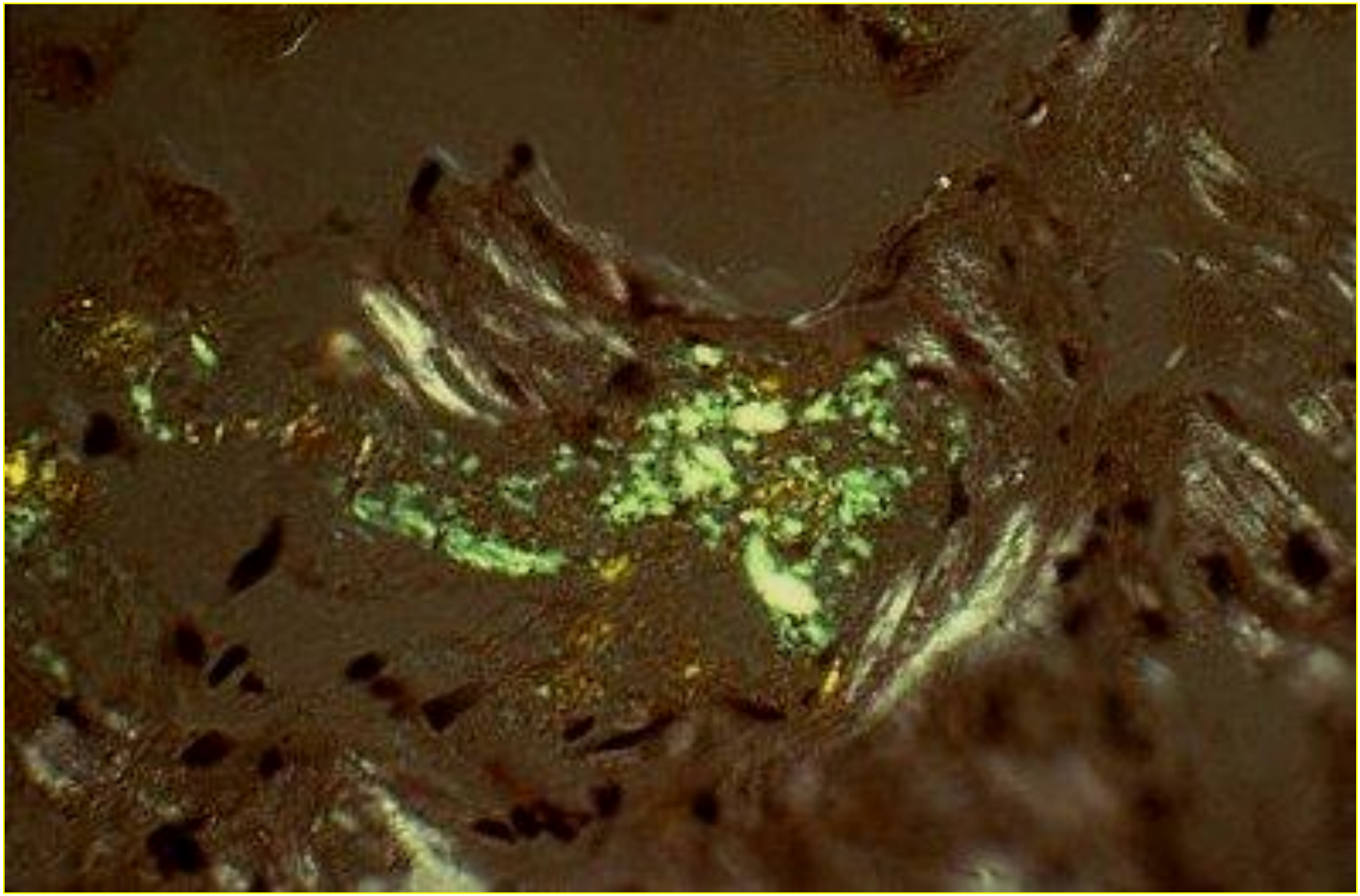

THE HEART IN ANDERSON-FABRY DISEASE AND OTHER LYSOSOMAL STORAGE DISORDERS

Aleš Linhart, Perry M Elliott

Heart 2007;**93**:528–535. doi: 10.1136/hrt.2005.063818

Lysosomal storage disorders (LSD) comprise a group of more than 40 diseases caused by a deficiency of lysosomal enzymes, membrane transporters or other proteins involved in lysosomal biology. The predominant inheritance pattern is autosomal recessive except for Anderson-Fabry disease, glycogen storage disease (GSD) type IIb (Danon disease) and mucopolysaccharidosis (MPS) type II (Hunter disease). While the metabolic defects affect all cells, clinical organ involvement usually occurs only in the presence of substrate excess or metabolic pathway activation. Cardiac disease is particularly important in lysosomal glycogen storage diseases (Pompe and Danon disease), mucopolysaccharidoses and in glycosphingolipidoses (Anderson-Fabry disease). Various disease manifestations may be observed including hypertrophic and dilated cardiomyopathy, coronary artery disease and valvular disease (table 1).

Cardiomyopathy

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Table 1 Lysosomal storage disease causing cardiac disease

Disease group and subtypes	General manifestations	Cardiac manifestations
Glycogen storage diseases (lysosomal)		
	Autosomal recessive	Massive LVH and RVH, cardiac failure (only in the infantile form)
	Myopathy, hypotonia, hepatomegaly, macroglossia cardiopulmonary failure,	Short PR, broad QRS; endomyocardial fibrosis
Type IIb (Danon disease, LAMP-2 deficiency)	*X-linked*	Hypertrophic cardiomyopathy, isolated cardiac variants, short PR, progressive conduction system disease
	Myopathy, mental retardation	
Mucopolysaccharidoses		
IH (Hurler)	*Autosomal recessive*	Valvular involvement (thickening, regurgitation, stenosis); endomyocardial infiltration; interstitial infiltration—fibrosis; hypertrophy; systolic dysfunction—dilated cardiomyopathy (less frequent); coronary artery infiltration—stenosis; aortic stenosis (abdominal); arterial hypertension
IS (Scheie)	*X-linked – MPS II (Hunter)*	
II (Hunter)	Dysmorphic features, organomegaly, decreased joint mobility, bone deformities, loss of motor skills, mental retardation, corneal clouding, recurrent otitis or pneumonia, hearing loss	
III (Sanfilippo)		
IV (Morquio)		
VI (Maroteaux-Lamy)		
VII (Sly)		
IX (Natowicz)		
Sphingolipidoses		
Gaucher disease (β-glucocerebrodiase)	*Autosomal recessive*	Pulmonary hypertension, cor pulmonale; pericardial effusion (rare); valvular involvement (rare)
Chronic non-neuronopathic (type I)	Gaucher cells—lipid laden macrophages	
Acute (type II)	Hepatosplenomegaly, anaemia, thrombocytopenia, bone involvement	
Chronic neuronopathic (type III)	Neurodegeneration (neuronopathic forms)	
Niemann Pick disease (acid sphingomyelinase)	*Autosomal recessive*	Endomyocardial fibrosis (very rare)
Type A	Early onset, neurological involvement, hypotonia, psychomotor retardation (type A), hepatosplenomegaly, pancytopenia, pulmonary involvement	
Type B		
Anderson-Fabry disease (α-galactosidase A)	*X-linked*	Cardiac hypertrophy; short PR, progressive conduction system dysfunction, arrhythmias; valvular involvement; coronary involvement (decreased coronary reserve)
	Multiorgan involvement	

LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

ANDERSON FABRY DISEASE

- Systemic disease with multiorgan involvement due to genetic (recessive x linked) lysosomal enzyme deficiency (alpha galactosidase) > intracellular storage of glicosphyngolipids.
- Heart involvement: LV “pseudohypertrophy”, valvular involvement
- Systemic manifestations: skin angiocheratoma, diffuse pain, renal failure, ocular abnormalities, cerebral TIA/stroke

Fabry's disease

Yuri A Zarate, Robert J Hopkin

Panel 1: Cardiac manifestations in Fabry's disease

- Valvular disease: valves are thickened and distorted, with mild-to-moderate regurgitation. Changes are most frequently found on left heart valves (mitral insufficiency)
- Left ventricular hypertrophy (LVH): concentric remodelling in early stages, which progresses later to concentric hypertrophy, septal and posterior wall thickness
- Right ventricular hypertrophy: does not seem to have major functional or clinical consequences
- Ischaemia: vasospastic or stenotic coronary artery disease leads to myocardial infarction, angina, and chest pain, particularly in patients with LVH
- Electrocardiogram abnormalities: voltage criteria for LVH and repolarisation changes. Short PR interval, bundle branch block, atrioventricular conduction delay, and progressive sinus node dysfunction
- Arrhythmias: bradycardia, supraventricular tachycardias, atrial fibrillation, atrial flutter, and cardiac sudden death

Lancet 2008; 372: 1427–35

New insights in cardiac structural changes in patients with Fabry's disease

Aleš Linhart, MD, PhD,[a] Tomáš Paleček, MD,[a] Jan Bultas, MD, PhD,[a] James J. Ferguson, MD, PhD,[b] Jana Hrudová, MD,[a] Debora Karetová MD,[a] Jiři Zeman MD, PhD,[c] Jana Ledvinová, MD,[d] Helena Poupětová, MD,[d] Milan Elleder, MD, PhD,[d] and Michael Aschermann, MD, PhD[a] *Prague, Czech Republic, and Houston, Tex*

Background Fabry's disease is an X-linked recessive genetic deficiency of the enzyme α-galactosidase leading to the pathologic intracellular deposition of neutral glycosphingolipids. Although cardiac involvement is frequent, there is controversy regarding the character of the associated left ventricular (LV) changes and the severity of valvular involvement.

Methods Clinical evaluation (disease severity scaling, laboratory tests, and echocardiography) was performed in 13 hemizygous men (mean age 39 ± 10 years) and 17 heterozygous women (mean age 35 ± 19 years).

Results LV hypertrophy (LVH) was frequent in subjects older than 30 years, more often in men (61%) than in women (18%, $P < .001$). The degree of LVH was independently associated with age and the logarithm of α-galactosidase activity ($r^2 = 0.70$, $P < .001$). The predominant LV geometric patterns were concentric LVH and remodeling, both present in 11 subjects (36%). Three patients had an asymmetric septal hypertrophy mimicking hypertrophic cardiomyopathy. In most subjects with LVH, the systolic function was normal and severe diastolic dysfunction (restrictive pattern) was not noted. Minor structural abnormalities of the mitral valve were found in 17 subjects (57%). The aortic valve was affected in 14 patients (47%). Valvular abnormalities were frequently accompanied by regurgitation of minor to mild degree. The presence of LVH or valvular changes was associated with increased disease severity.

Conclusions Echocardiographically detectable cardiac involvement is frequent with Fabry's disease, particularly in older subjects, and more pronounced in affected hemizygous men than in heterozygous women. LVH is frequently observed but usually not associated with significant systolic or restrictive diastolic dysfunction. Concentric LVH and remodeling appear to be the major manifestations of LV structural alteration. The frequently noted valvular abnormalities were not associated with a significant degree of regurgitation. Valvular and especially LV structural changes may serve as a useful marker of disease severity. (Am Heart J 2000;139:1101-8.)

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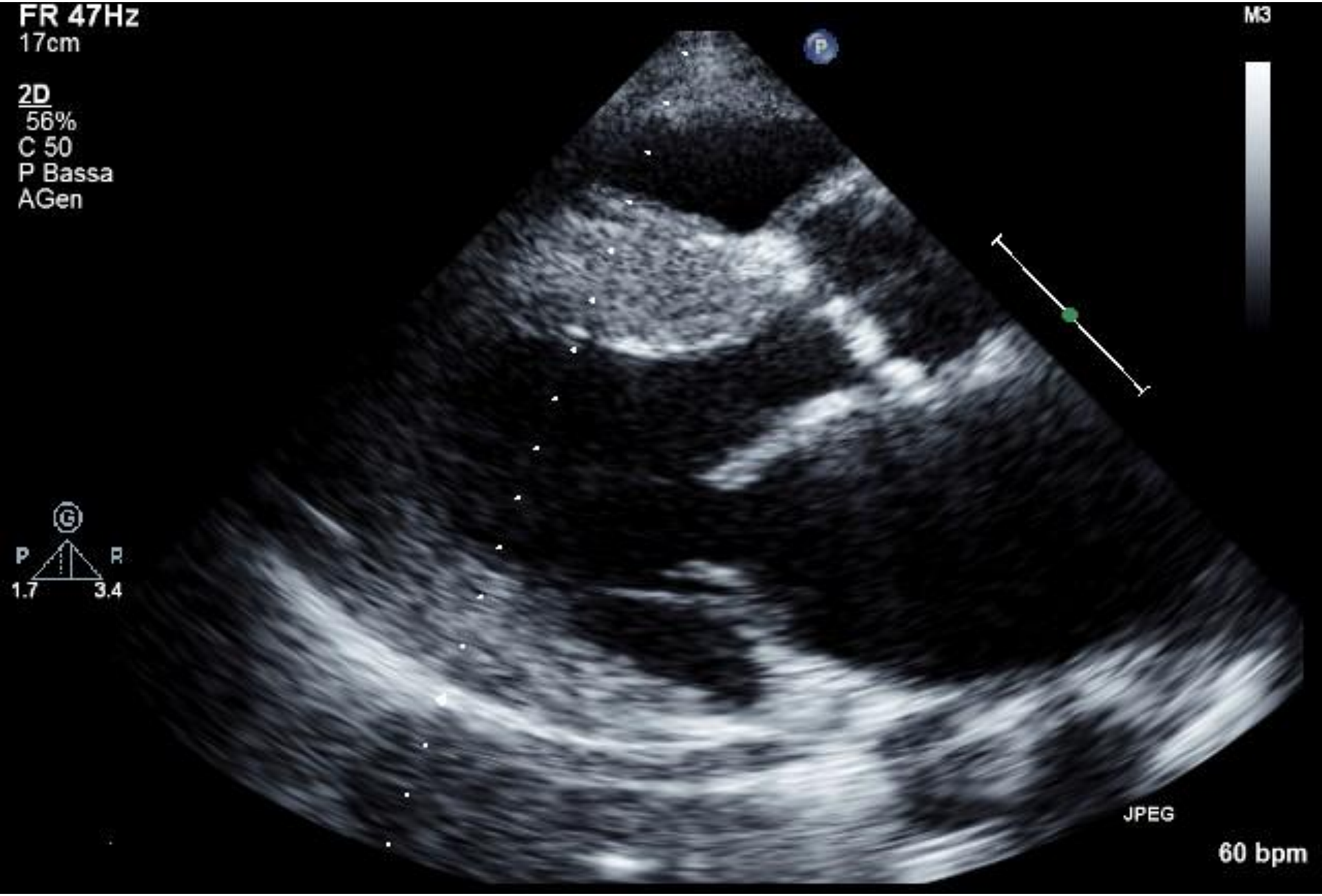
Valve disease

Valve disease in AFD is caused by infiltrative changes within valvular fibroblasts (figs 3 and 4). Although pulmonary valve involvement is reported, clinically significant changes are most frequently found on left heart valves, probably due to higher haemodynamic stress. In early reports, mitral valve prolapse was said to be common, but recent studies using two-dimensional imaging suggests that it is relatively rare.[6] Typically, valves are thickened and distorted, resulting in mild-to-moderate regurgitation; severe valve disease requiring surgical correction is infrequent. Aortic root dilatation is a feature in some patients and may contribute to aortic valve insufficiency.[6]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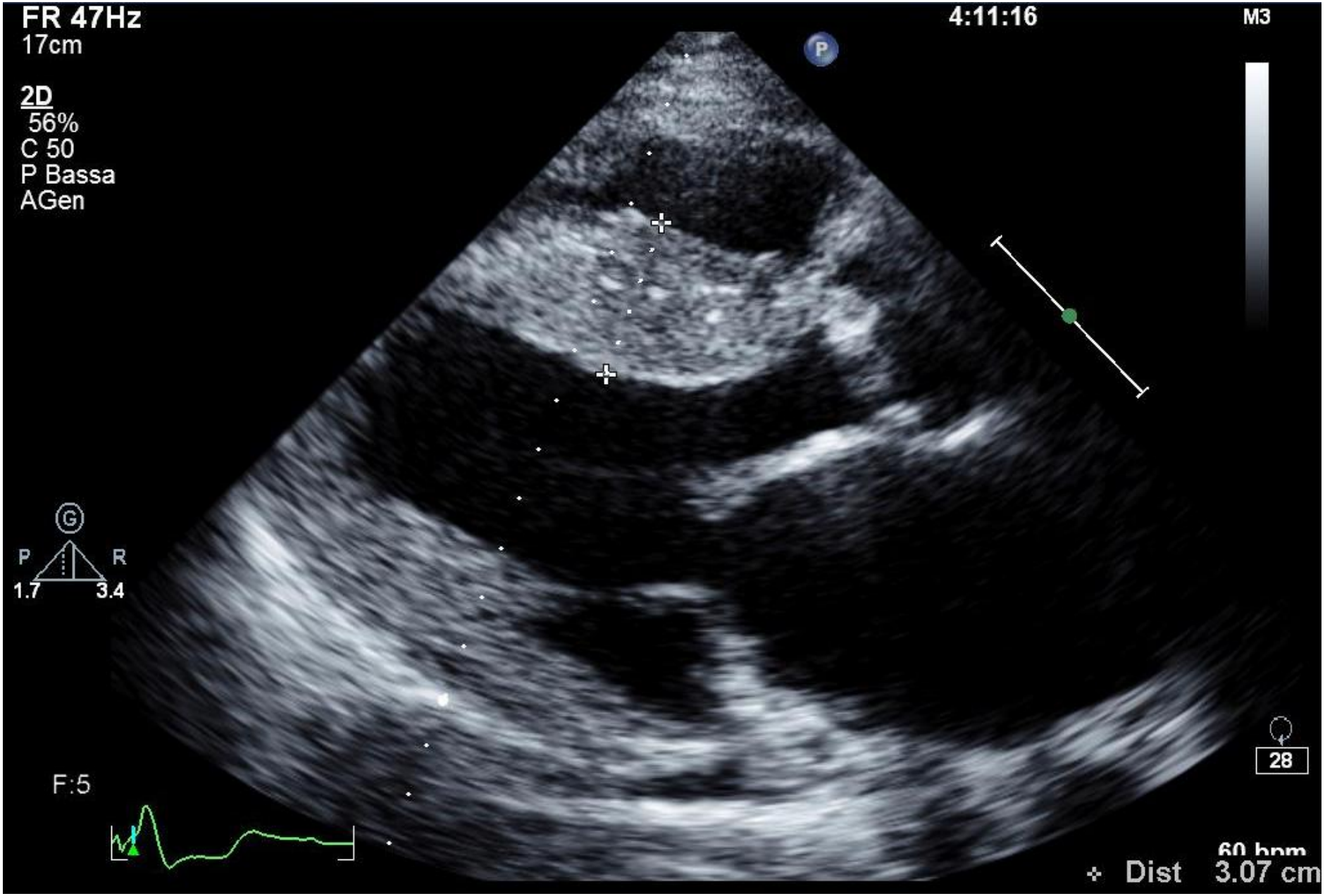
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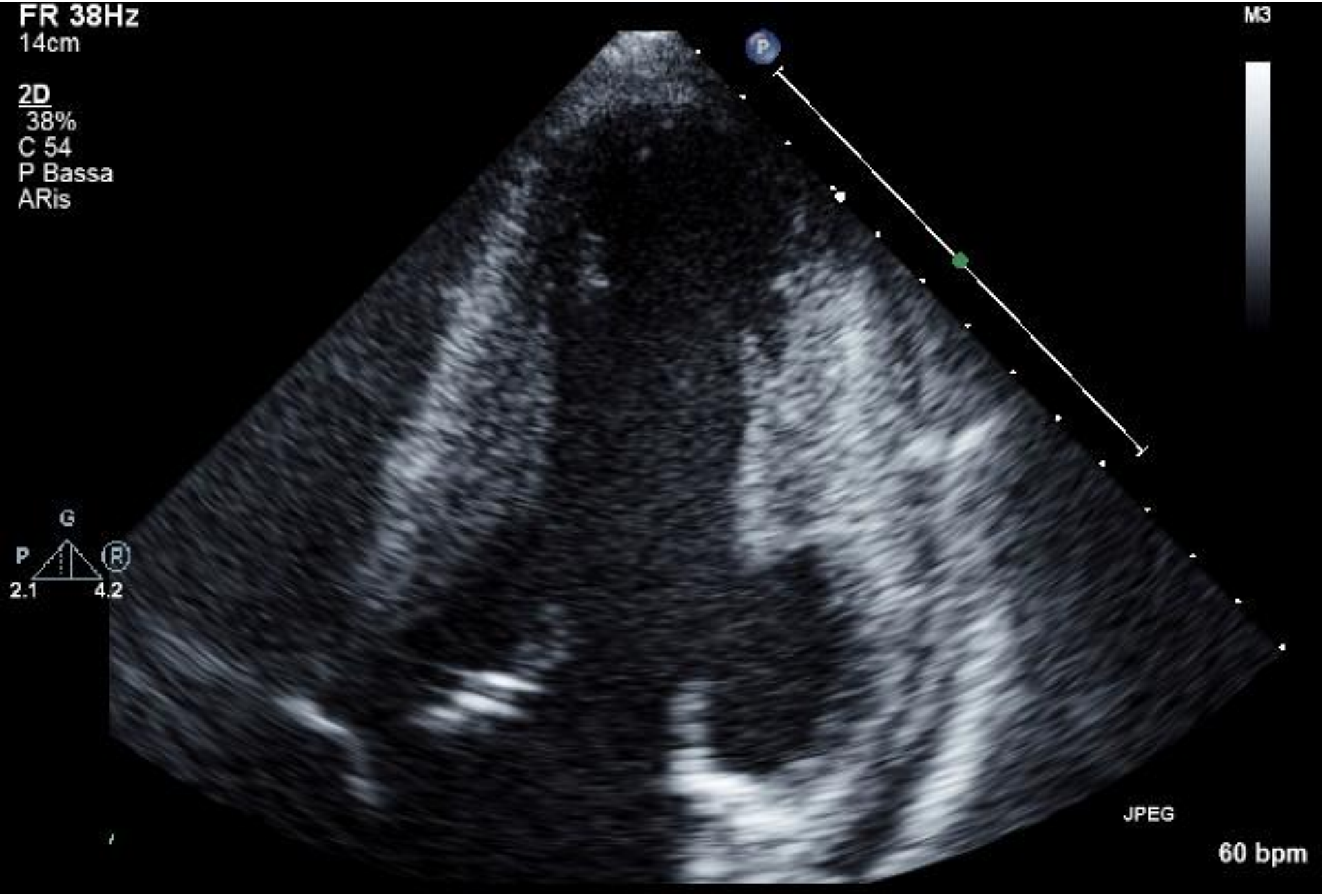
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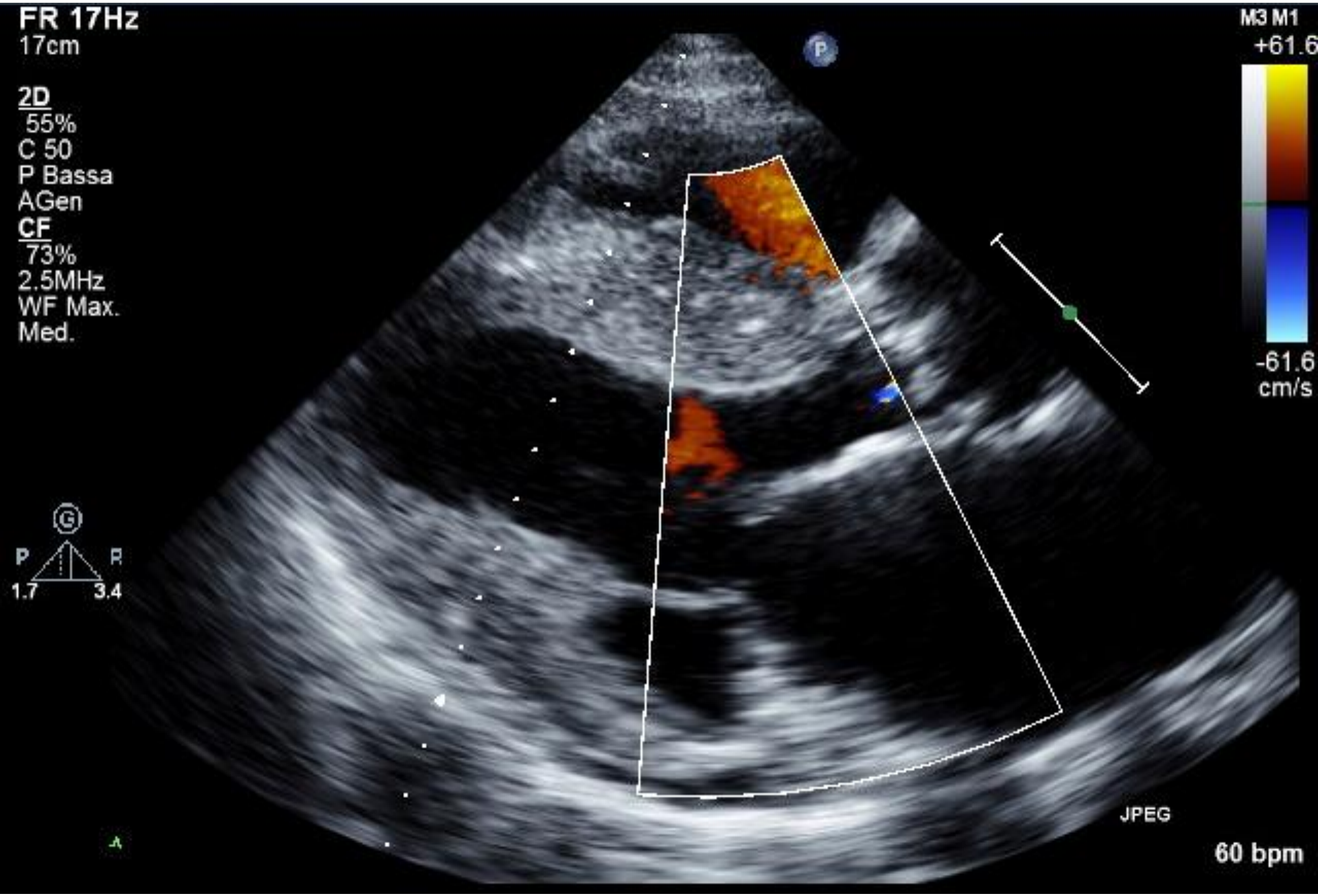
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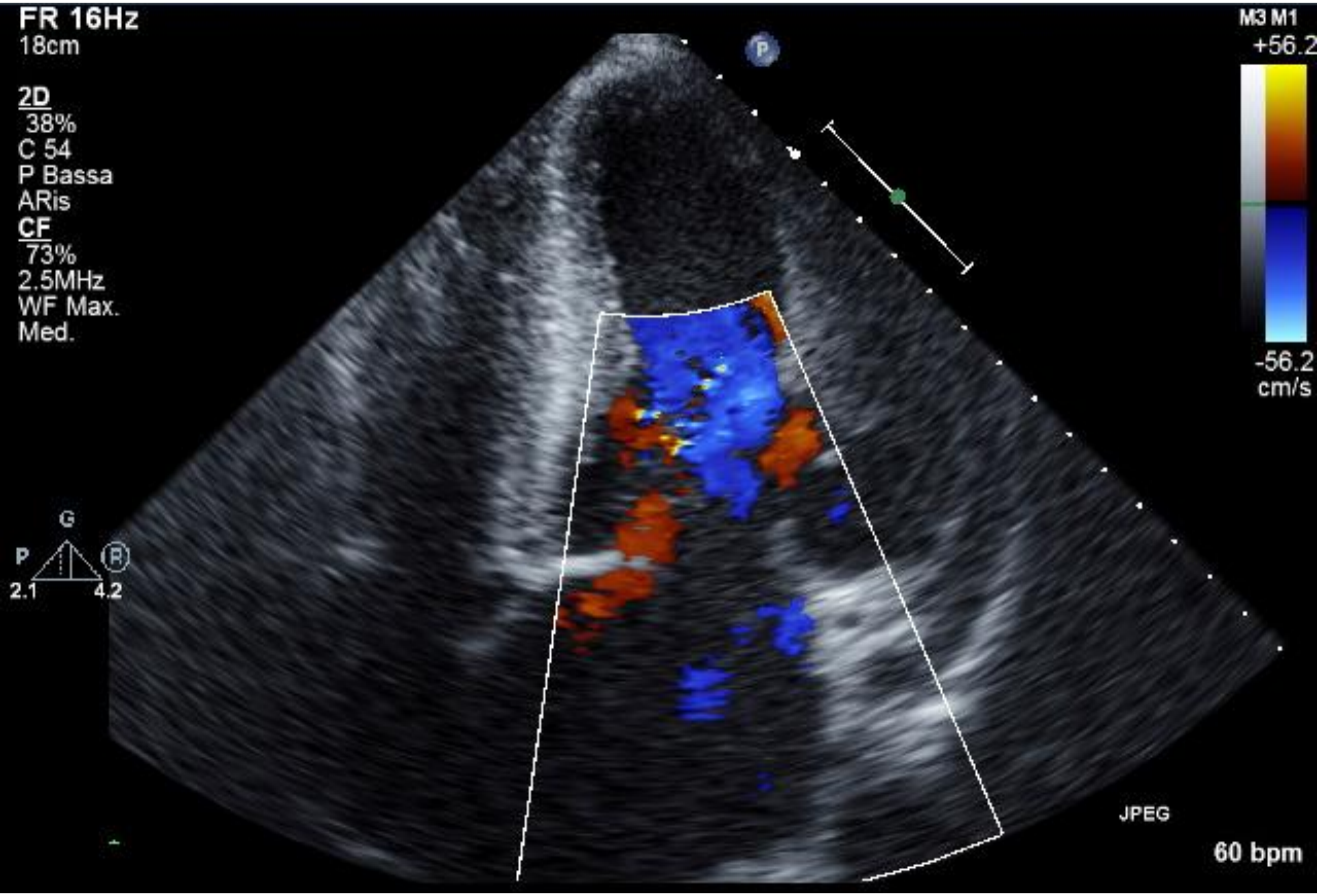
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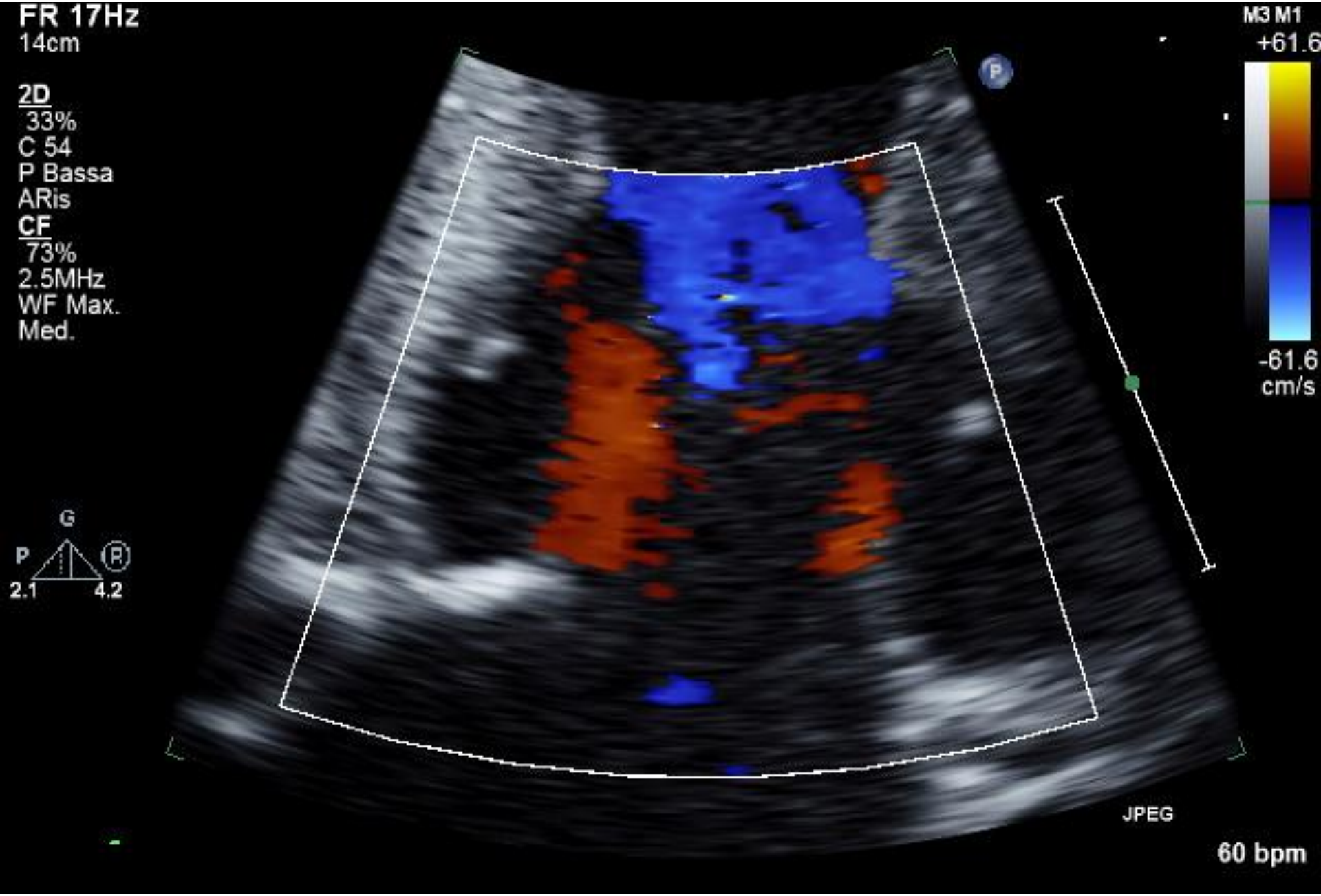
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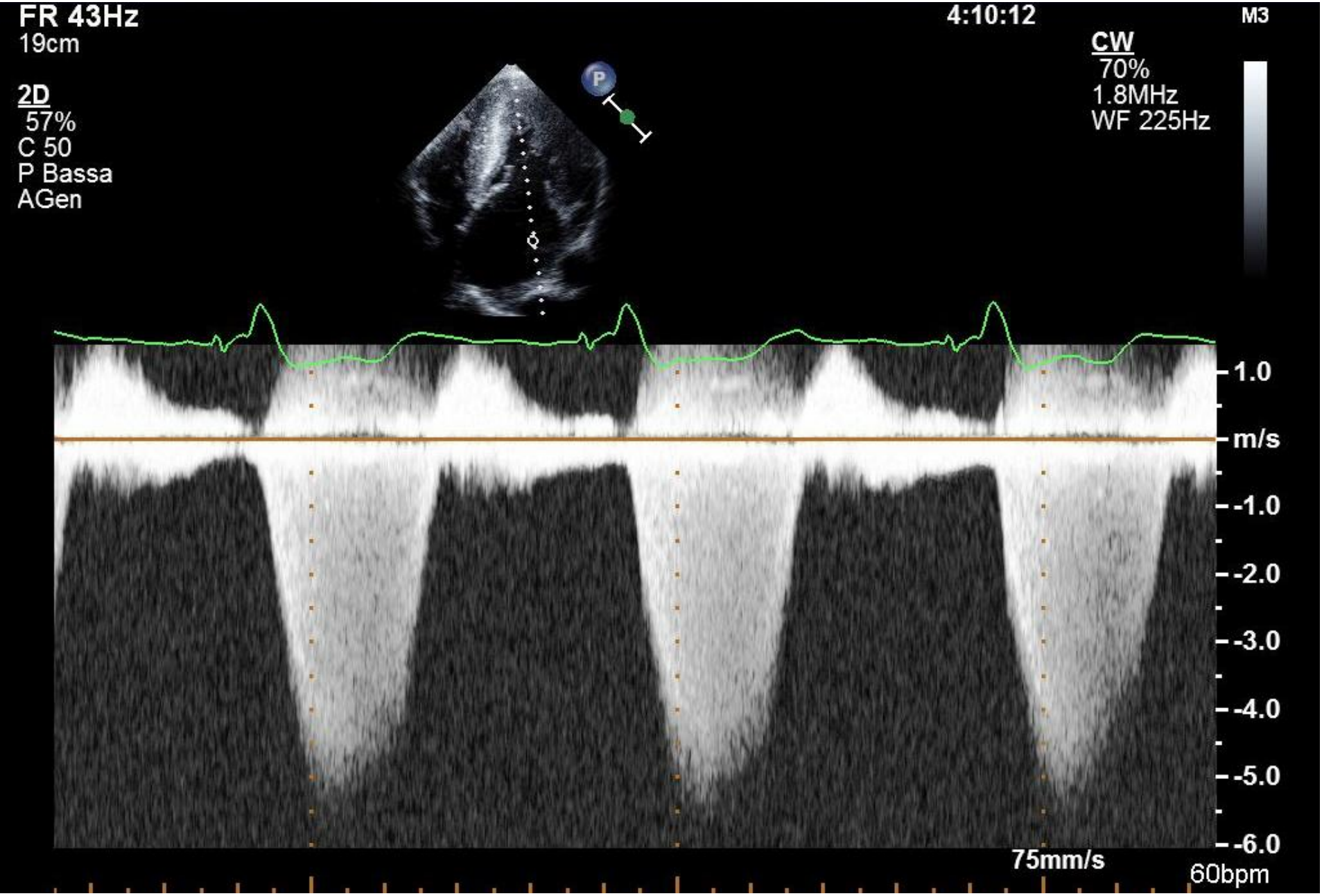
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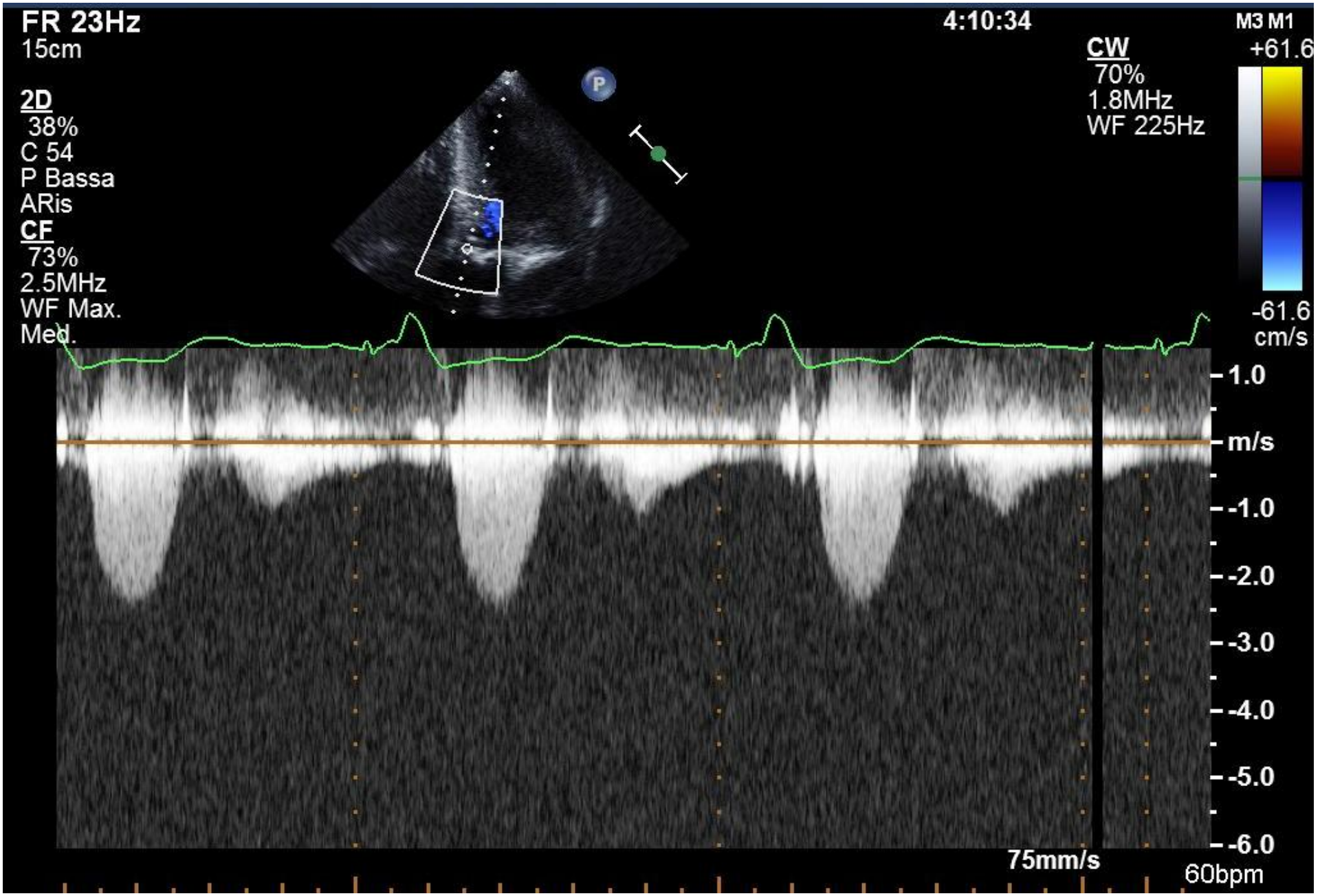
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cm/s
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m/s
-1.0
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-3.0
-4.0
-5.0
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75mm/s
60bpm

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Heart 2007;**93**:528–535. doi: 10.1136/hrt.2005.063818

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a large group of storage diseases caused by a defect of intralysosomal degradation of acid mucopolysaccharides (glycosaminglycans). Seven main forms and several subtypes can be distinguished. Cardiac involvement is detectable in more than two thirds of affected children. The most common abnormalities occur in the valves with mitral and aortic valve thickening resulting in regurgitation and stenosis. The overall prevalence of valve abnormalities ranges from 27–90% depending on disease subtype (highest frequency in MPS I, II and VI, lowest in type IV and III). As in most lysosomal diseases, the involvement is progressive with age.[19] Coronary involvement with intimal infiltration by storage cells is reported in more than 40% of patients, although rarely results in clinical or electrocardiographic evidence of myocardial ischaemia. The aorta may also be affected.[19]

Myocardial changes in MPS include interstitial infiltration and fibrosis. LVH, dilated cardiomyopathy and endomyocardial fibroelastosis are described. Cases of conduction system dysfunction are also reported and sudden cardiac deaths are relatively frequent. Enzyme replacement therapy is available for MPS type I, II and VI.

VHD in RCMP and Infiltrative CMP CONCLUSIONS (I)

- RCMP and infiltrative/storage CMP are a rare heterogeneous group of heart muscle diseases with distinctive clinical and cardiac imaging features
- VHD, particularly of M and T valves, is possible, with different mechanisms (functional or sometimes organic), according to the disease subtype

VHD in RCMP and Infiltrative CMP CONCLUSIONS (II)

- Systematic accurate imaging evaluation of affected valves is needed in order to correctly assess the mechanism and severity of valvular dysfunction
- TT Echo-Doppler evaluation is usually the standard imaging approach. TEE, and/or CMR are useful in selected patients

VHD in RCMP and Infiltrative CMP CONCLUSIONS (III)

- Multidisciplinary diagnostic and therapeutic approach is important for patient management considering the frequent systemic multiorgan pathology
- Considering the rarity and the peculiarity of these cardiac diseases, an international multicentric registry could be advisable to improve their knowledge and management