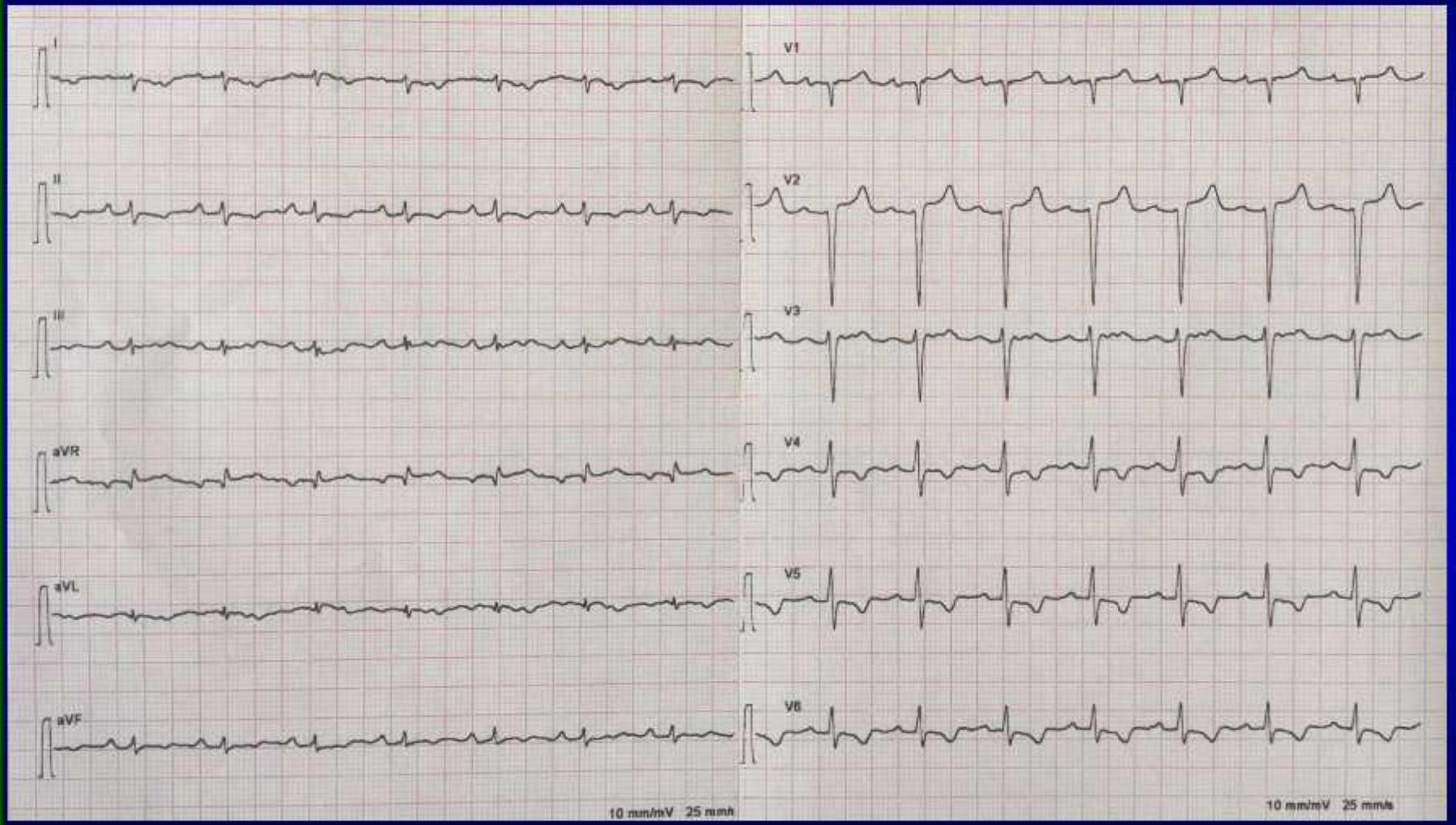
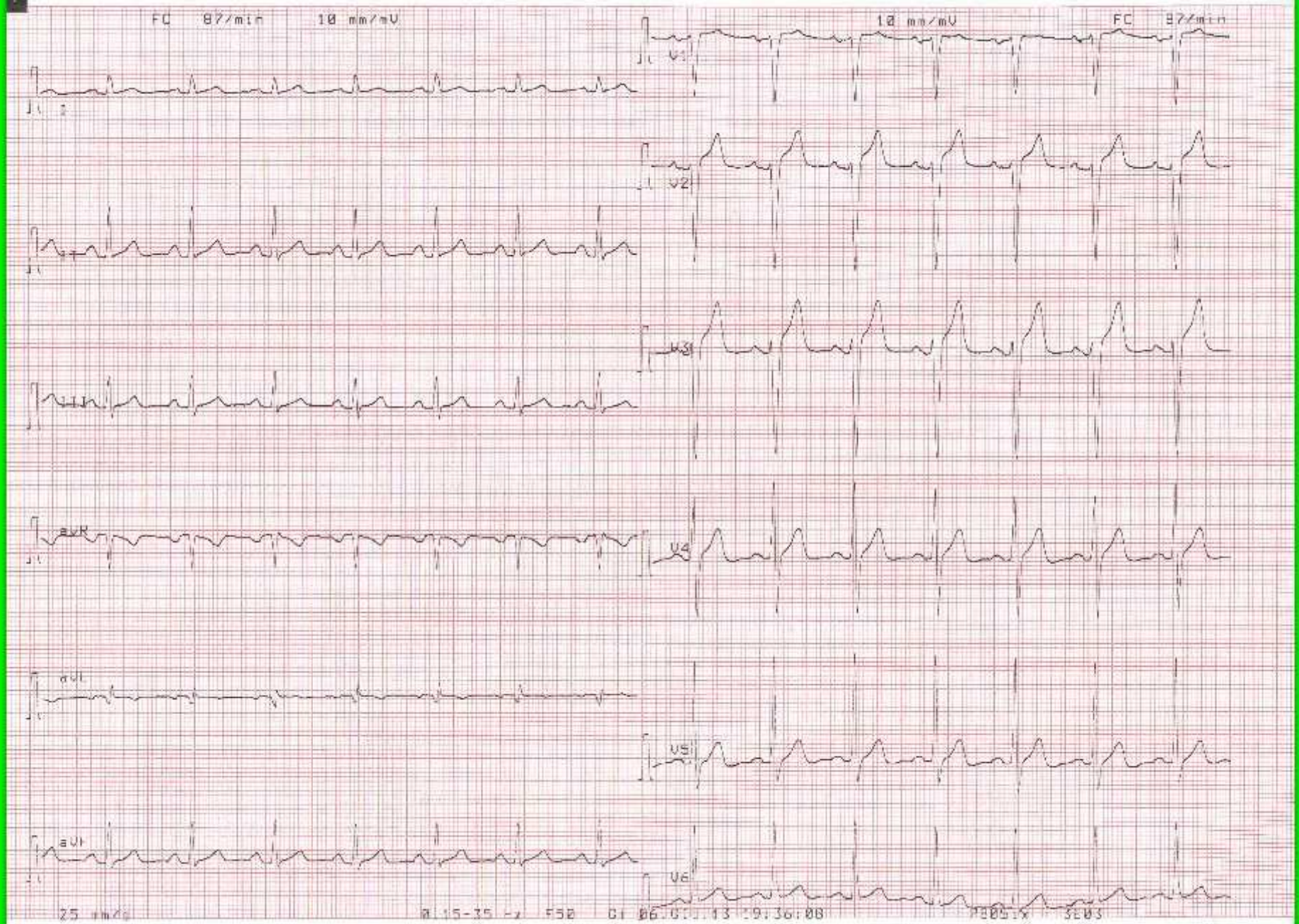
Dott. Walter Grosso Marra

Division of Cardiology
University of Turin
Città della Salute e Della Scienza

COMPLICANZE CARDIOLOGICHE NEL PAZIENTE CON MIELOMA MULTIPLO ed AMILOIDOSI CARDIACA

Elettrocardiogramma

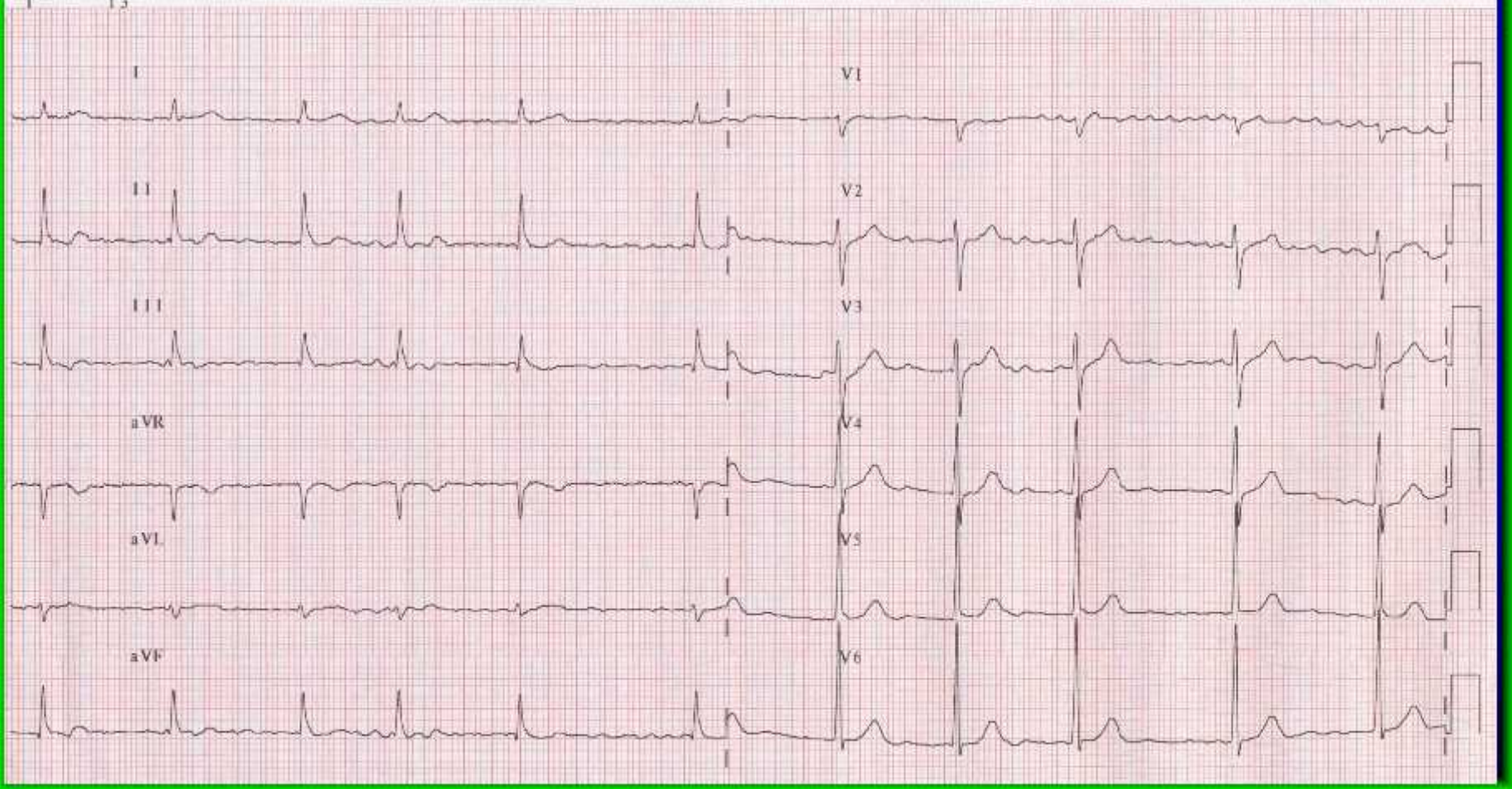



FC 87/min
10 mm/mV
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
25 mm/s
0.15-35 -x F50 CI 06.01.13 09:36:08

LUOTTO EVASIO 06-Giu-2008 10:49:44 INGRESSO PAO130-85 KG73 ALT181 ASL 19 ASTI CARDIOLOGIA
69 Anni

Freq. 65
PR 0
QRSD 85
QT 375
QTc 390

--Asse--
P
QRS 68
T 13



Paziente:

SAVIO ILLUMINATO

.....

Età: ..... M / F

..... cm / ..... kg

24/12/1921

nato

FC 74/min

Intervalli:

RR 811 ms

P 130 ms

PQ 290 ms

QRS 84 ms

QT 390 ms

QTC 433 ms

Asse el.:

P 3 °

QRS -39 °

T 28 °

P (II) 0.07 mV

S (V1) -0.27 mV

R (V5) 0.69 mV

Sokol. 1.21 mV

RITMO SINUSALE

BLOCCO A-V DI 1o GRADO

DEVIAZIONE ASSIALE SINISTRA ANORMALE

ZONA DI TRANSIZIONE R-S SPOSTATA A SINISTRA

BLOCCO DEL FASCICOLO ANTERIORE SINISTRO

5.73

NEUROLOGIA

10 mm/mV

10 mm/mV

I

II

III

aVR

aVL

aVF

V1

V2

V3

V4

V5

V6

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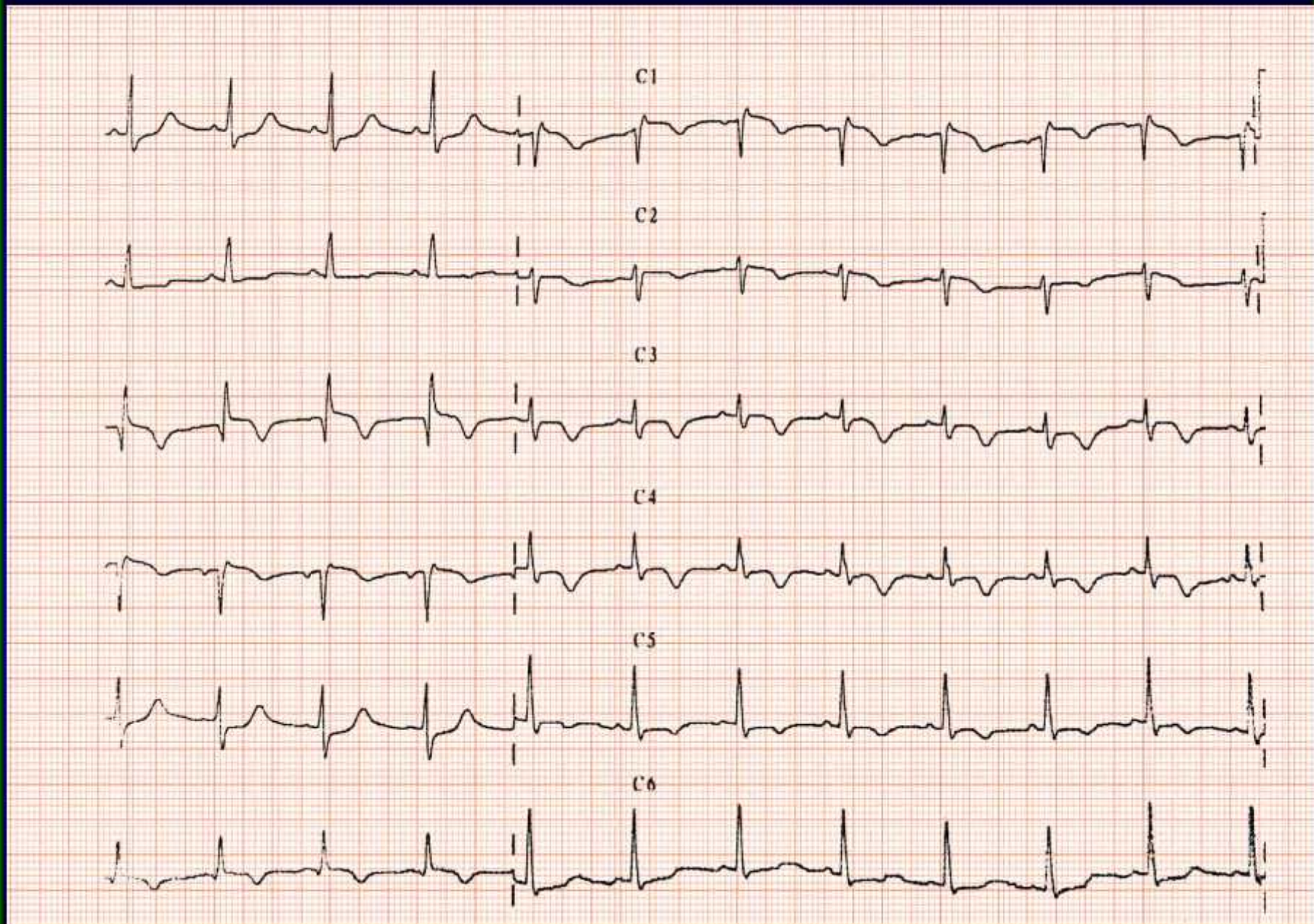
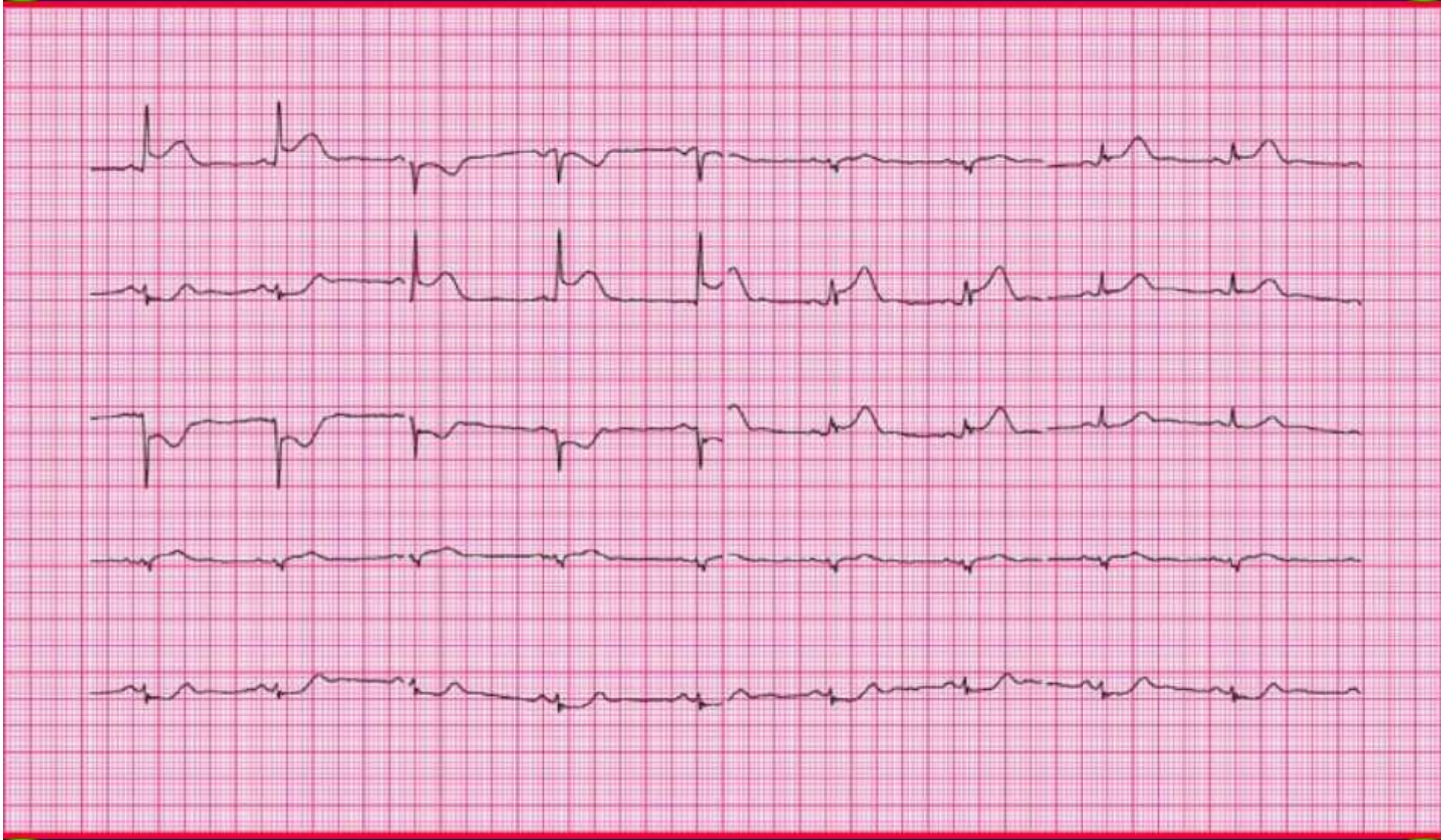
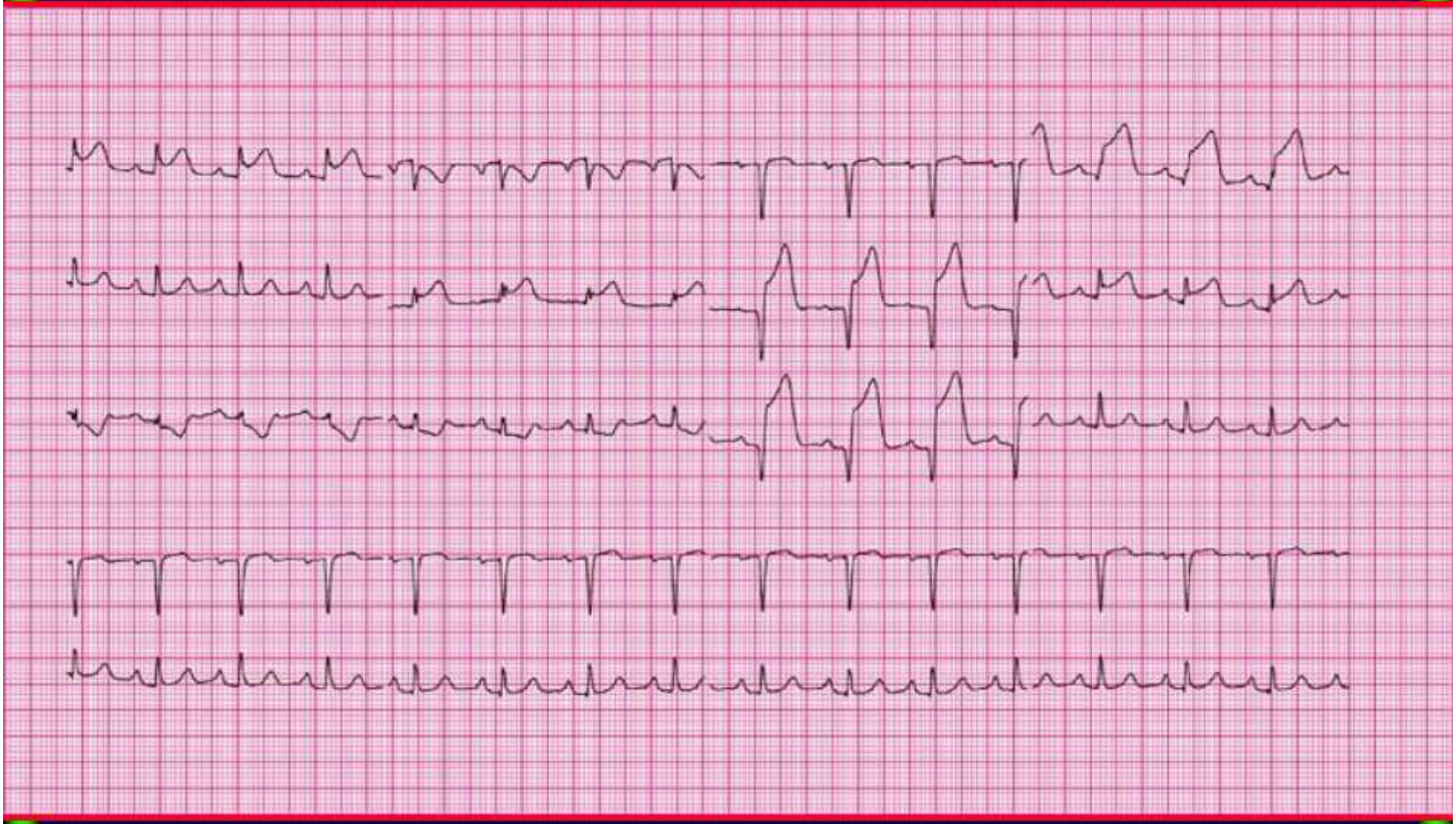
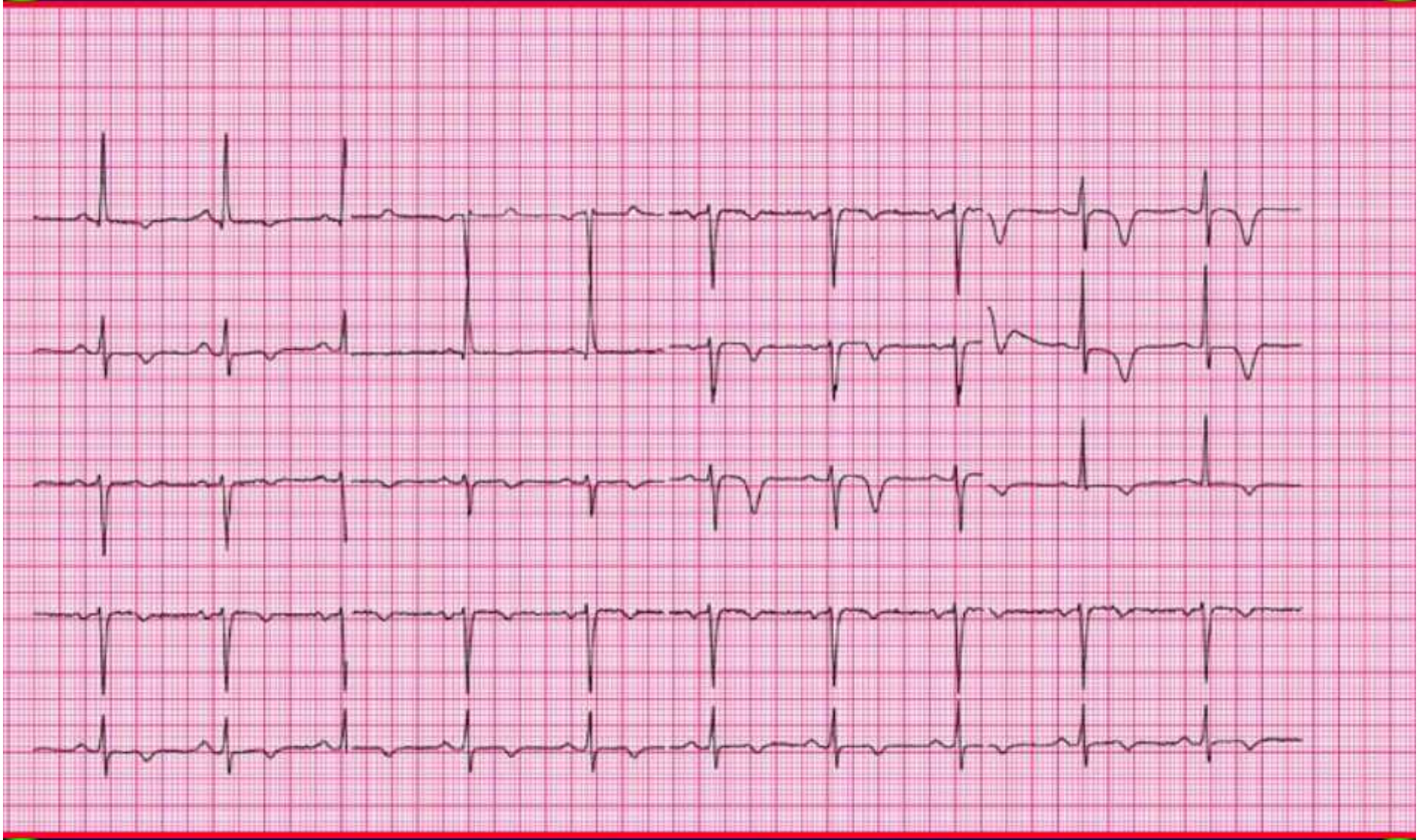
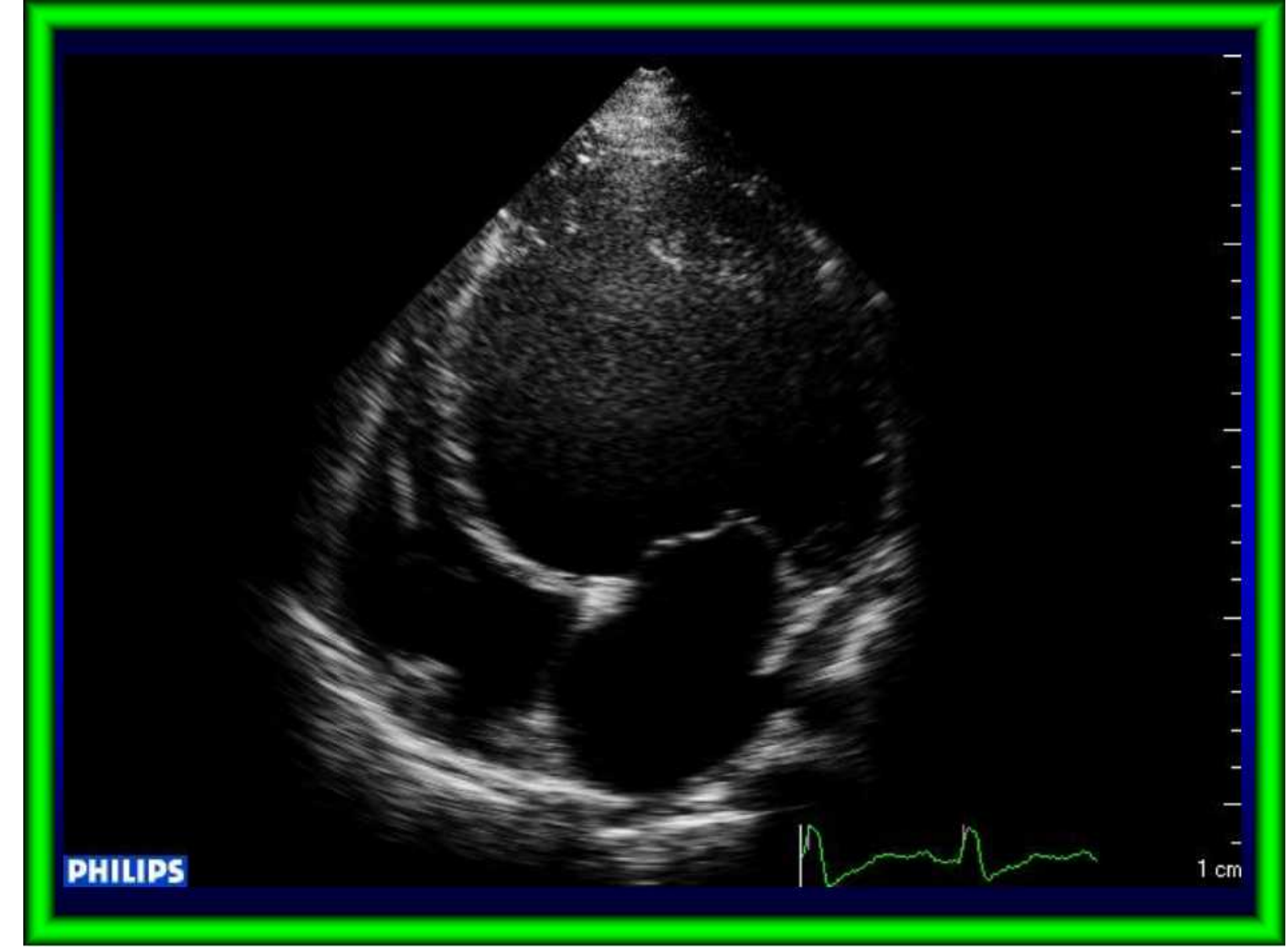

C1
C2
C3
C4
C5
C6





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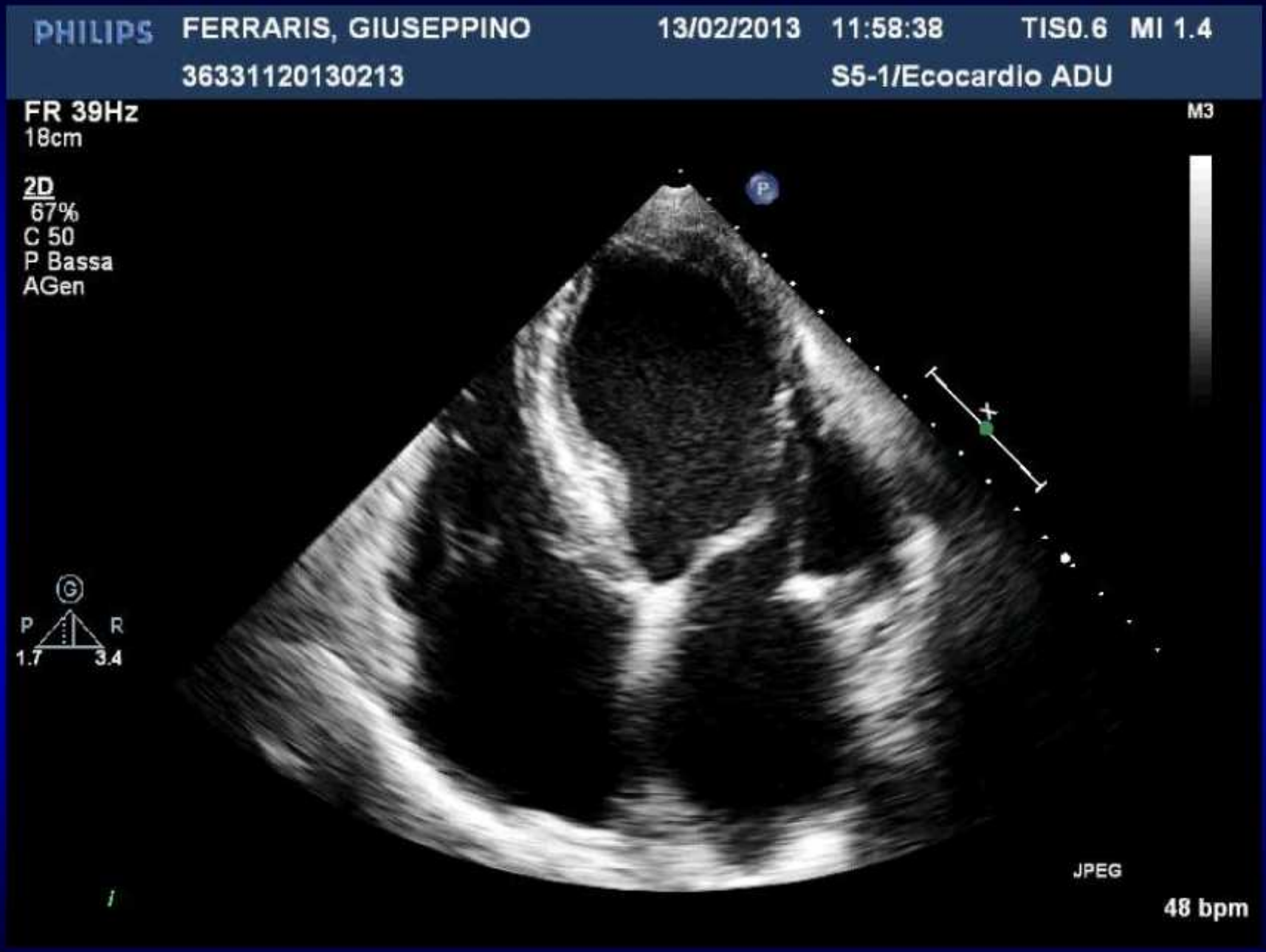
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M3
G
P
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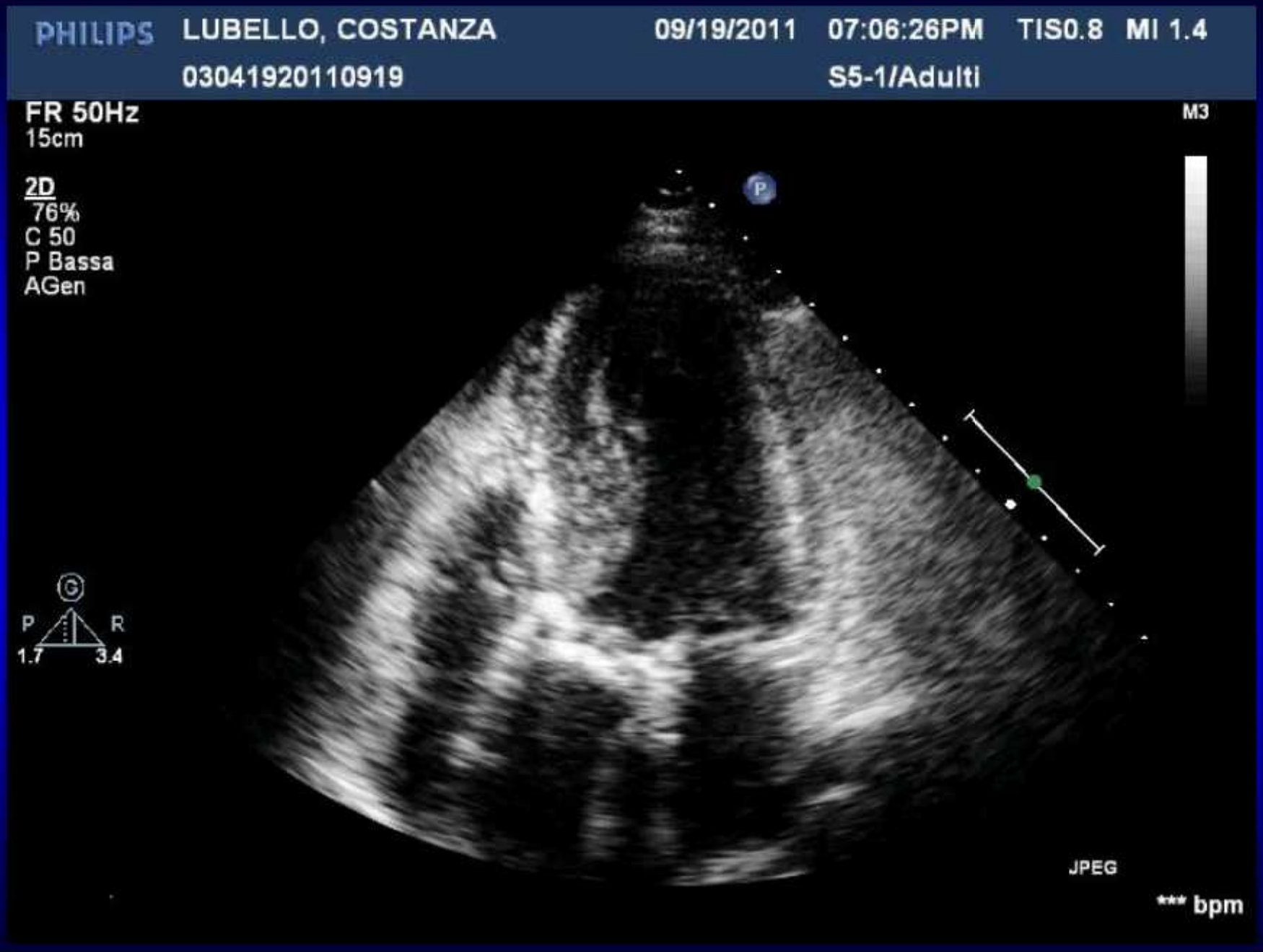
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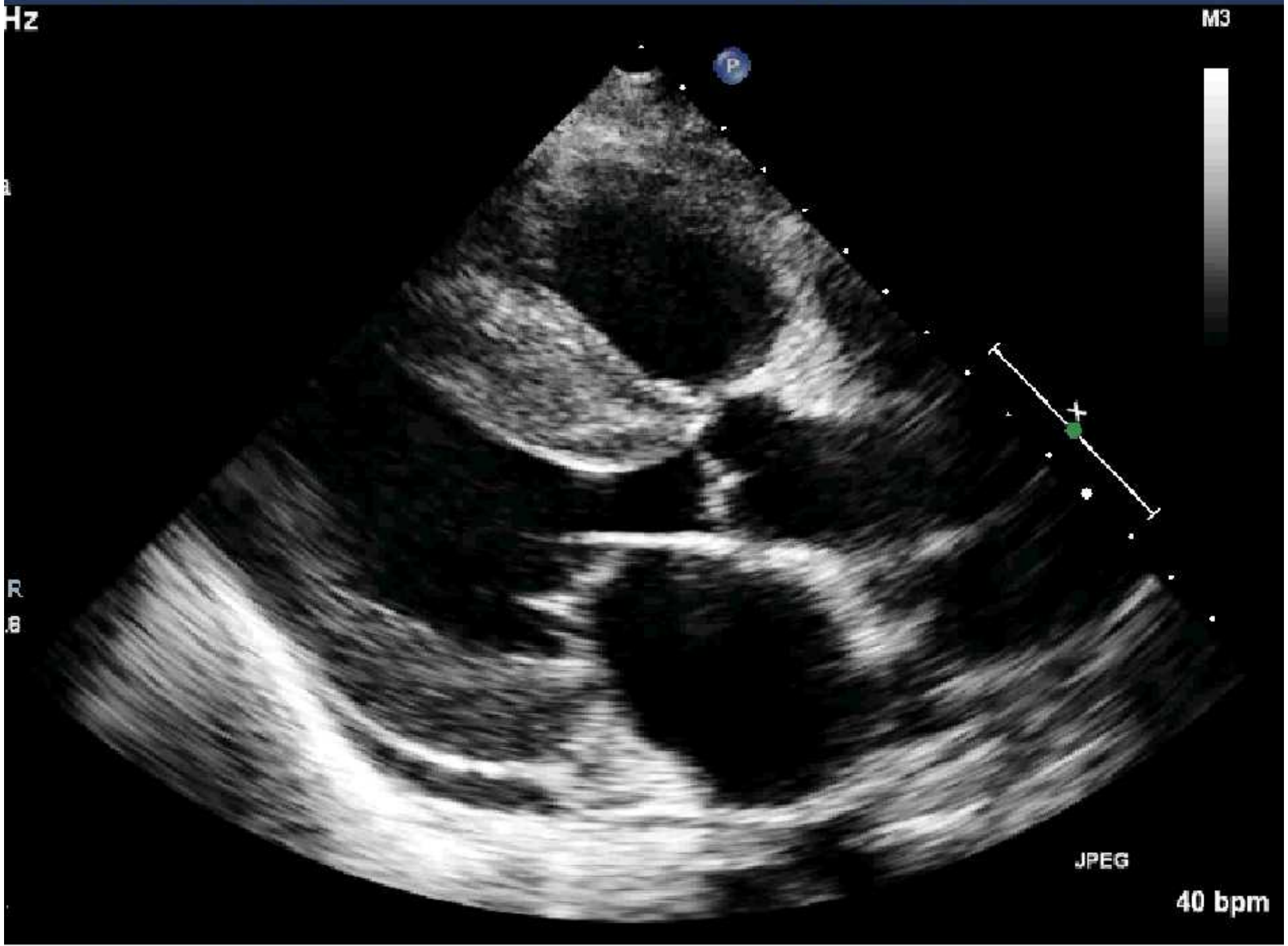
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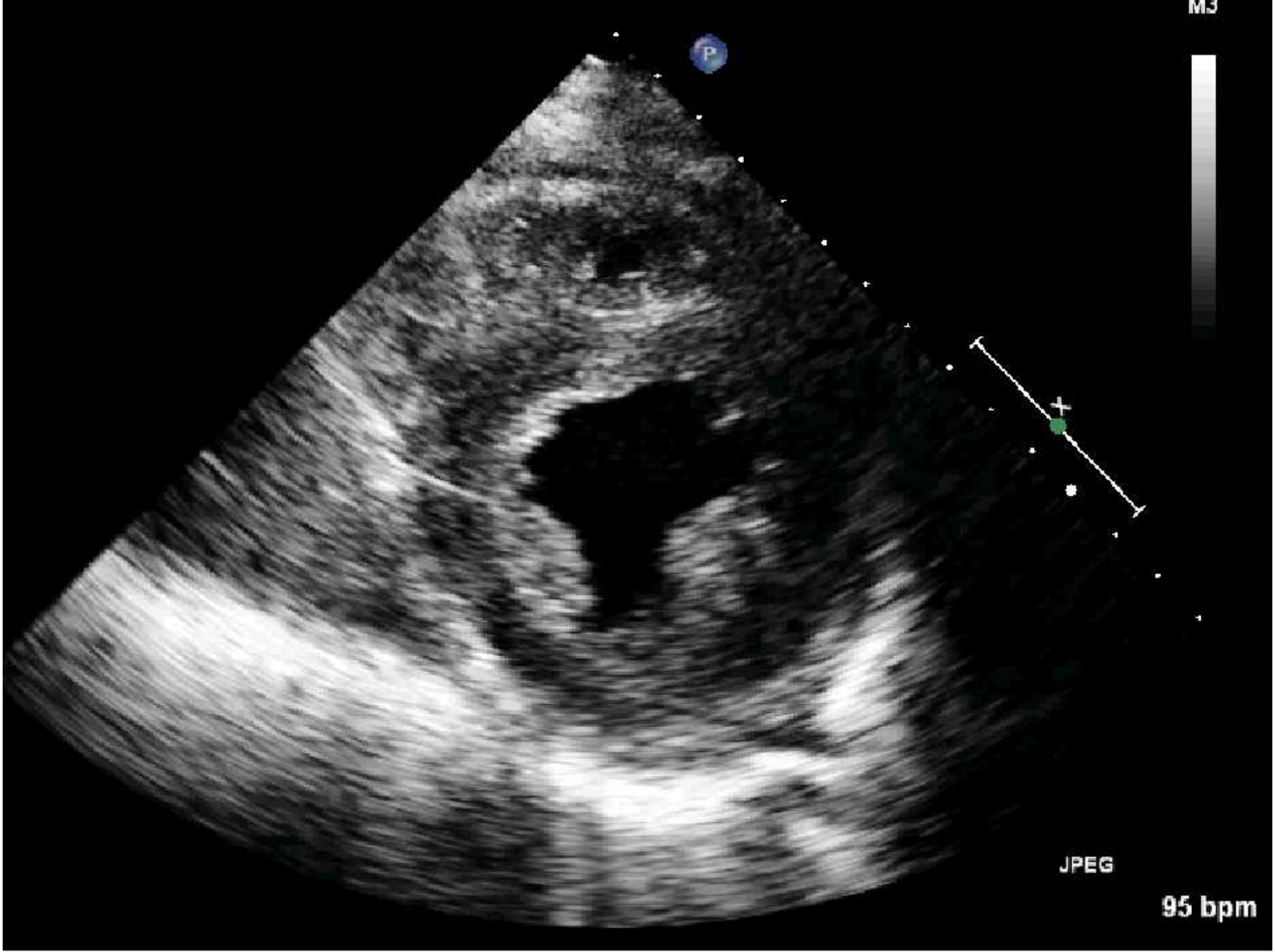
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P
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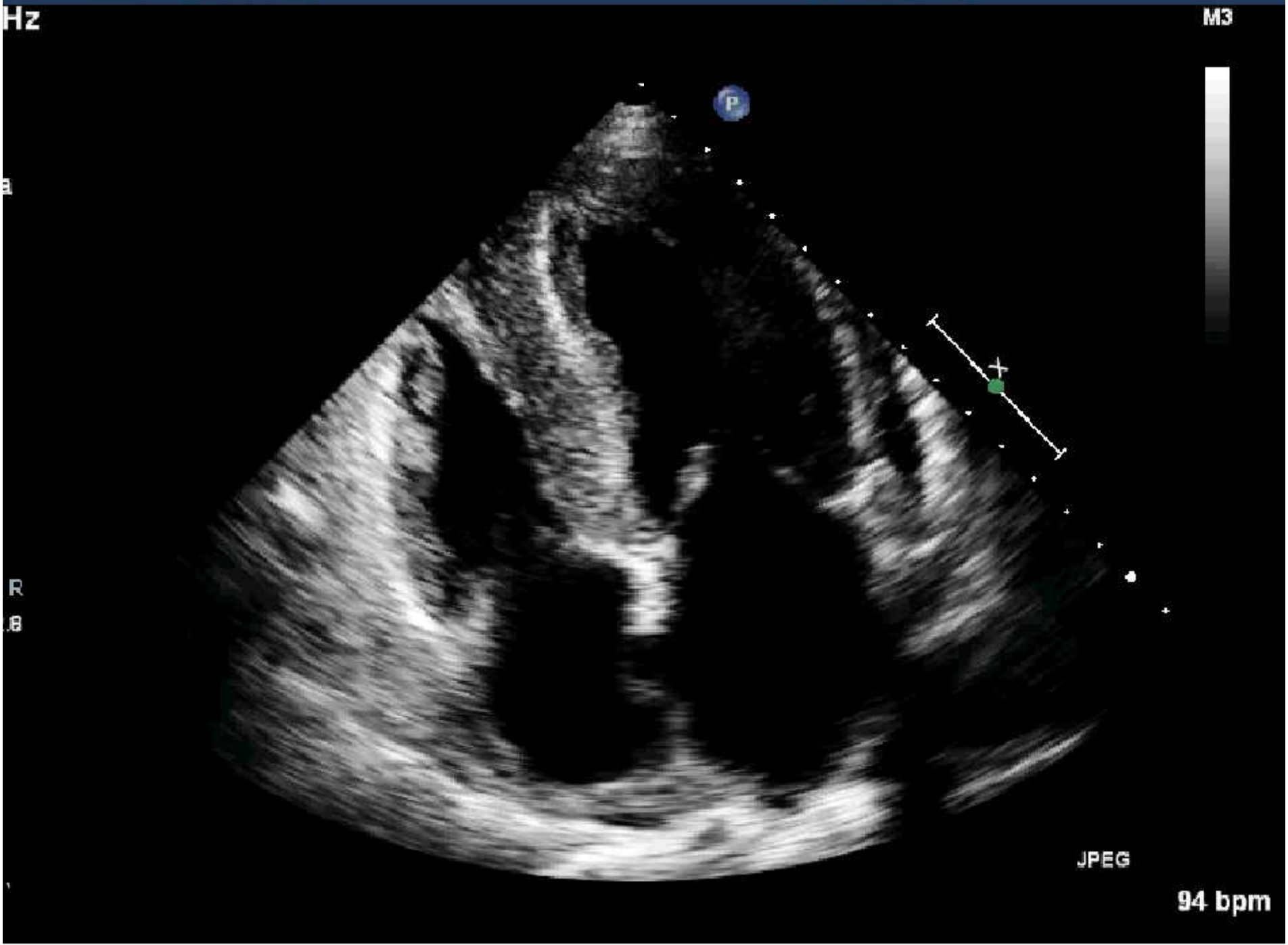
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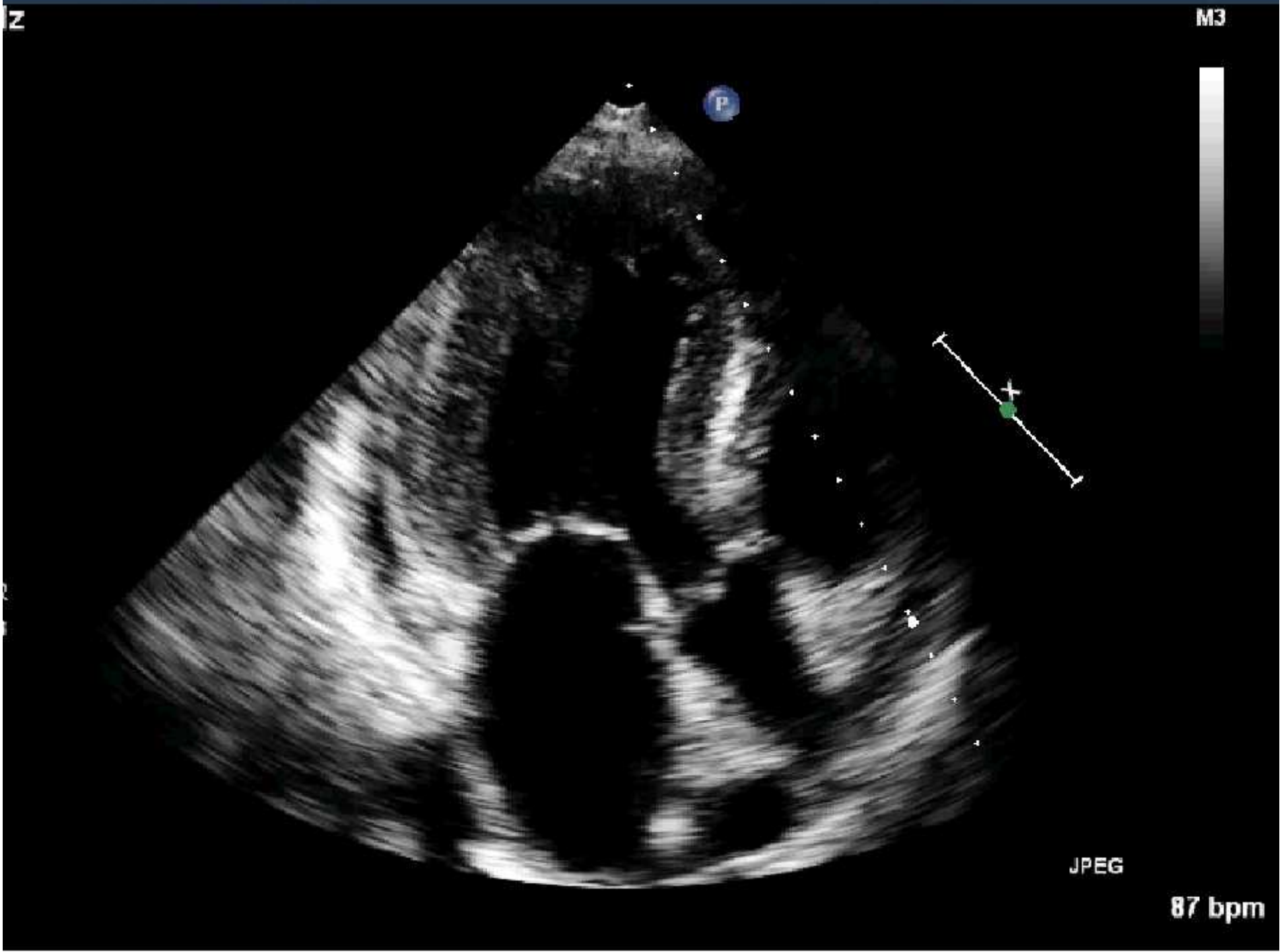
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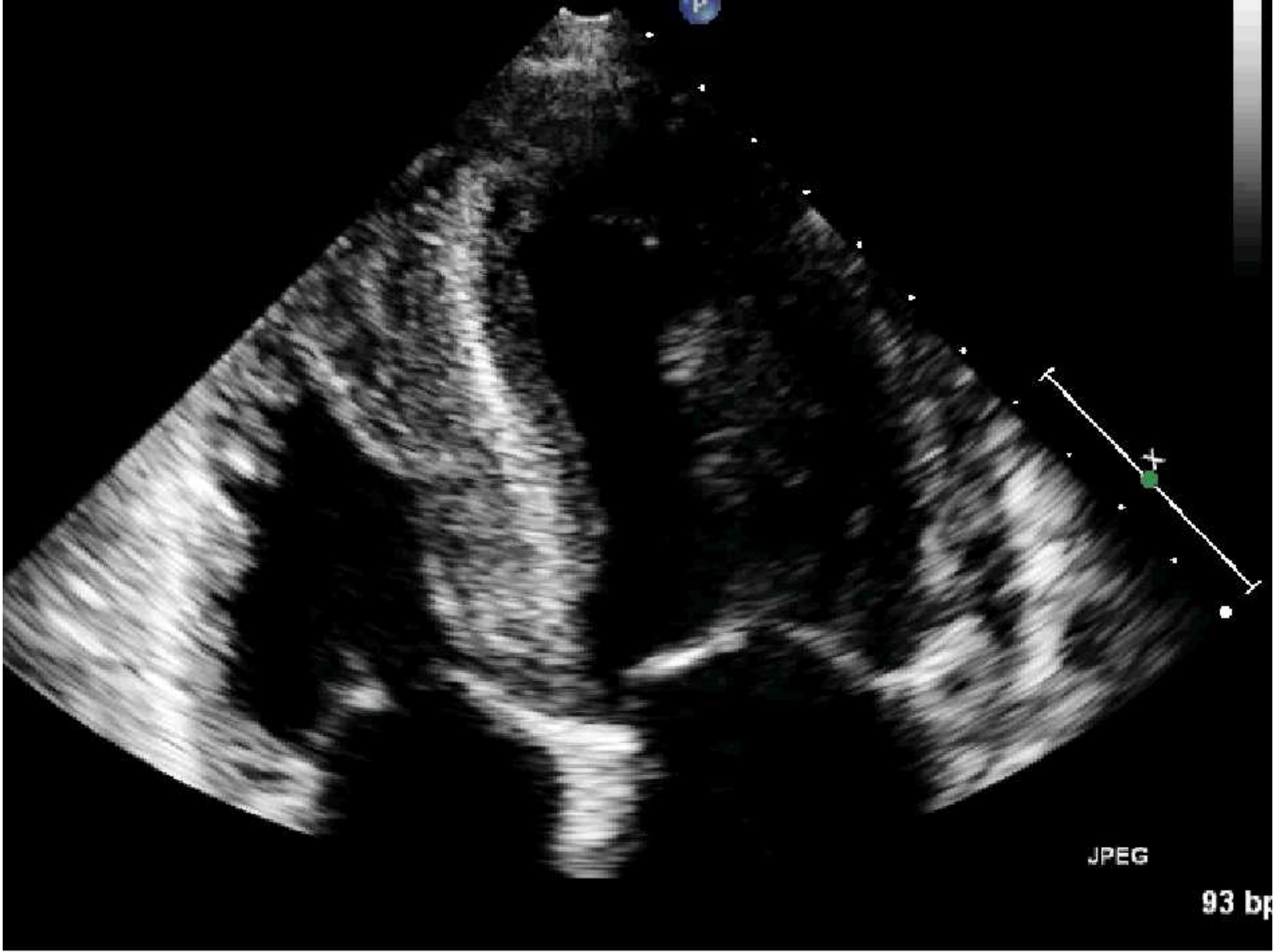
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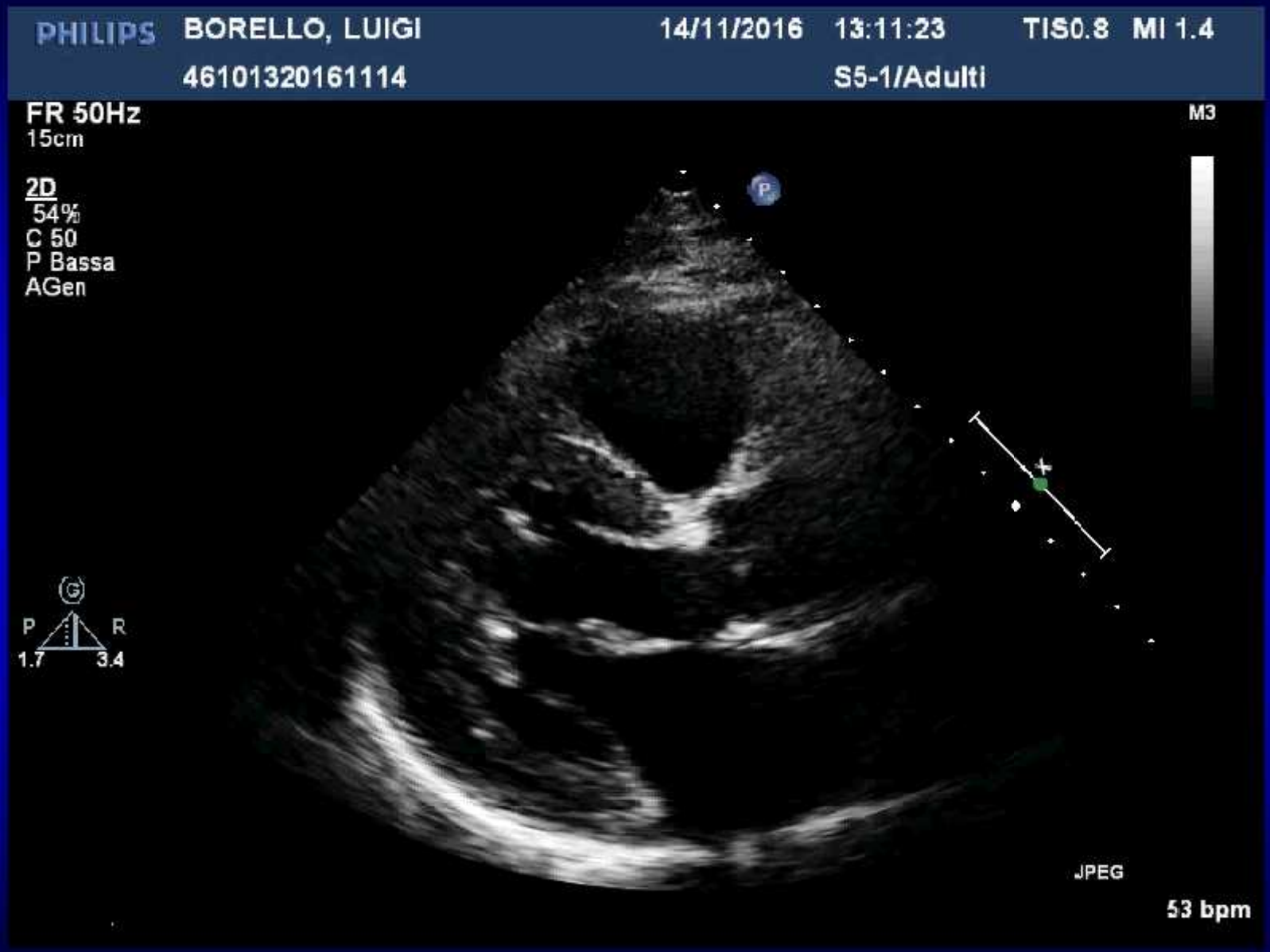
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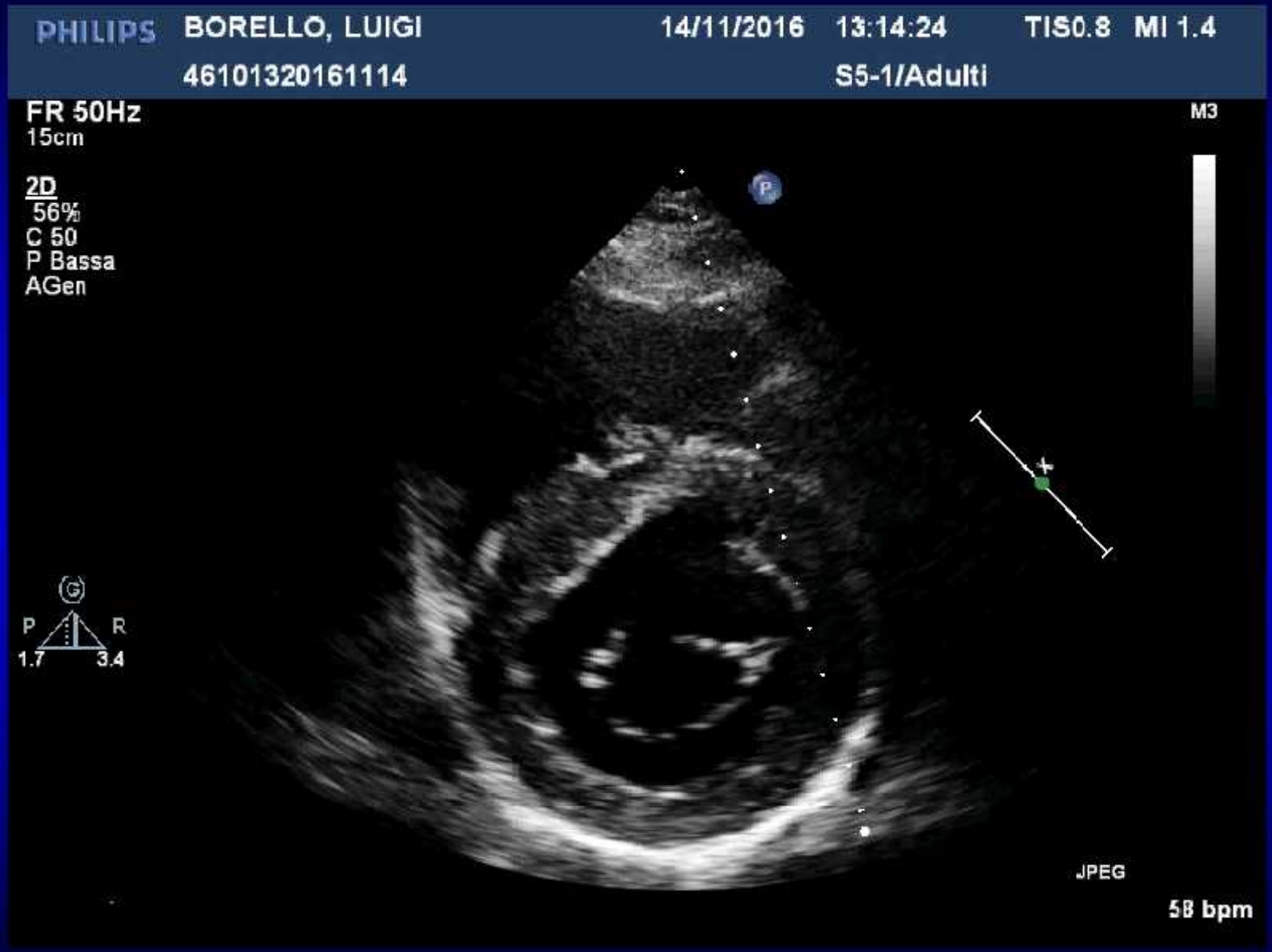
C 50
P Bassa
AGen
P
R
1.7
3.4
JPEG
53 bpm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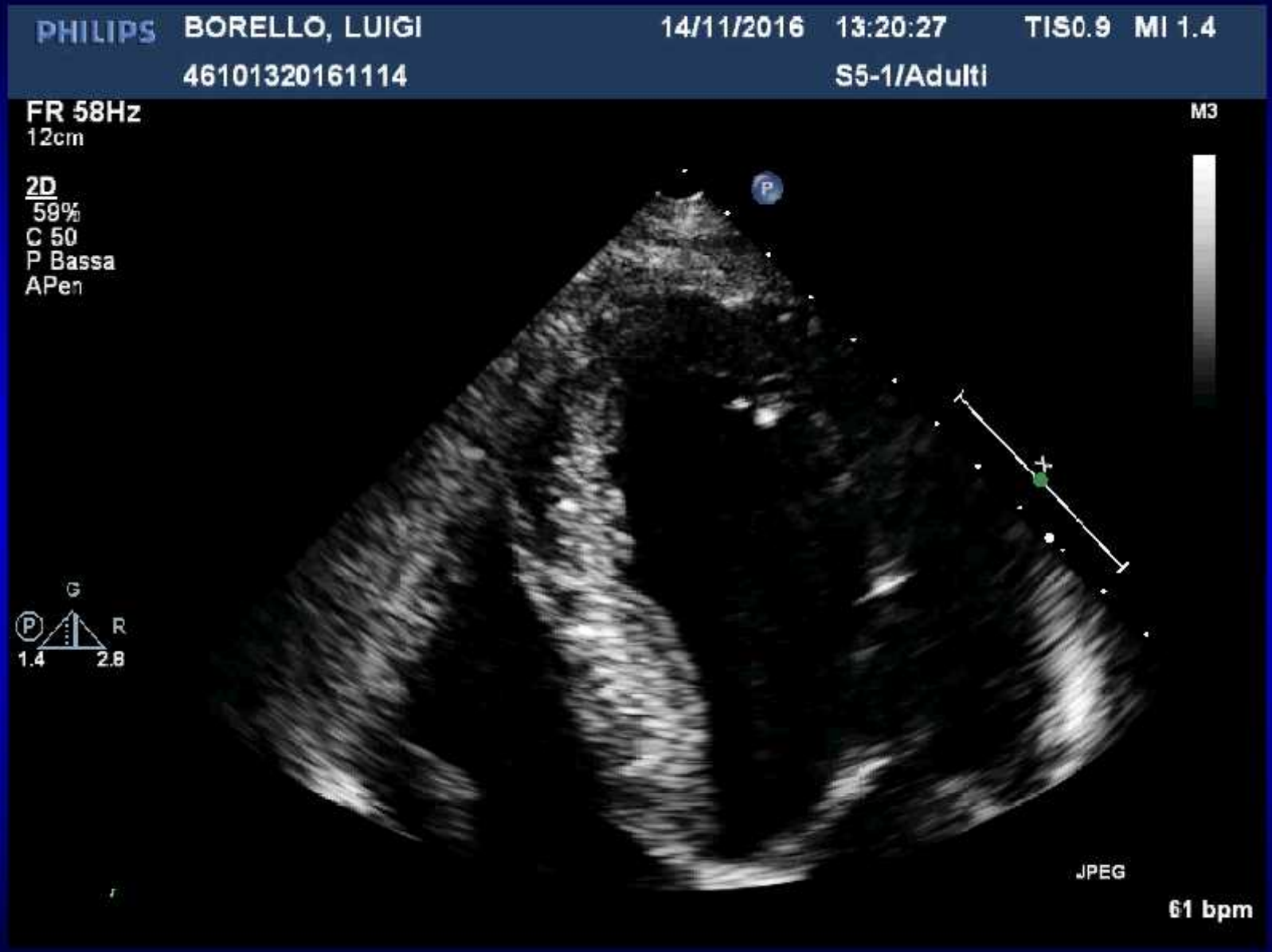
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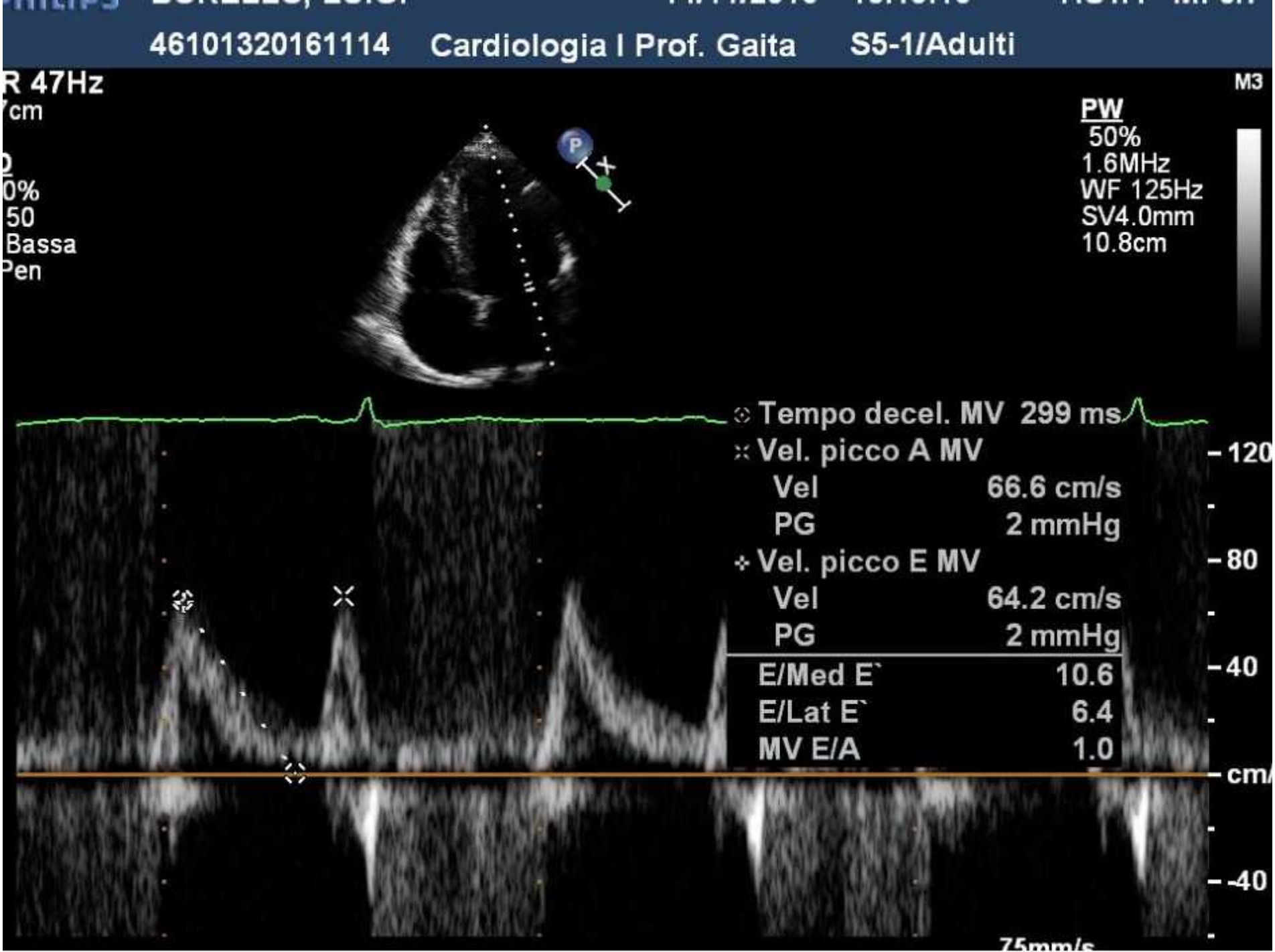
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M3
PW
50%
1.6MHz
WF 125Hz
SV4.0mm
10.8cm
Bassa
Tempo decel. MV 299 ms
Vel. picco A MV
Vel 66.6 cm/s
PG 2 mmHg
Vel. picco E MV
Vel 64.2 cm/s
PG 2 mmHg
E/Med E` 10.6
E/Lat E` 6.4
MV E/A 1.0
120
80
40
cm/
-40
75mm/s


PHILIPS
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76%
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AGen
TDI
89%
3.4MHz
PW
60%
3.6MHz
SV5.0mm
9.4cm
M3 M6
+15.0
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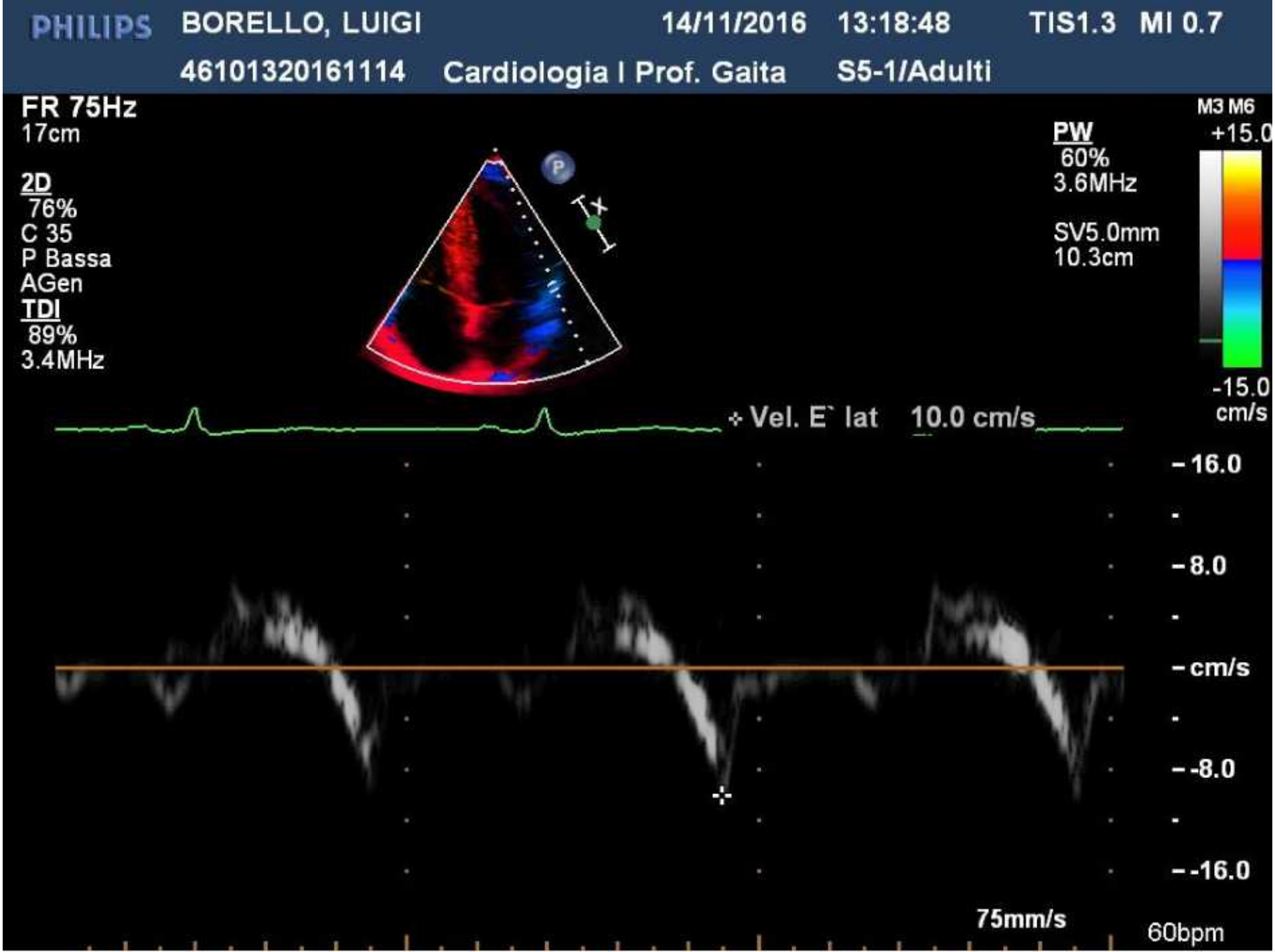
cm/s
-8.0
-16.0
75mm/s
57bpm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PW
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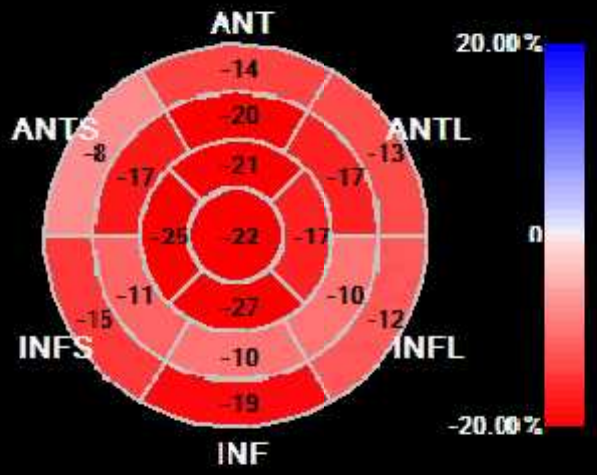
+15.0
-15.0
cm/s
Vel. E` lat 10.0 cm/s
16.0
8.0
cm/s
-8.0
-16.0
75mm/s
60bpm

Regionale

Deform. sistolica di picco Tempo picco



HR = 60 bpm

AP2 Deform. long. = -17 %

AP4 Deform. long. = -16 %

AP3 Deform. long. = -14 %

Deform. G.L. (Med.) = -16 %

Deform. sistolica di picco

Diagnosi Differenziale

Infiltrative Cardiovascular Diseases

Cardiomyopathies That Look Alike

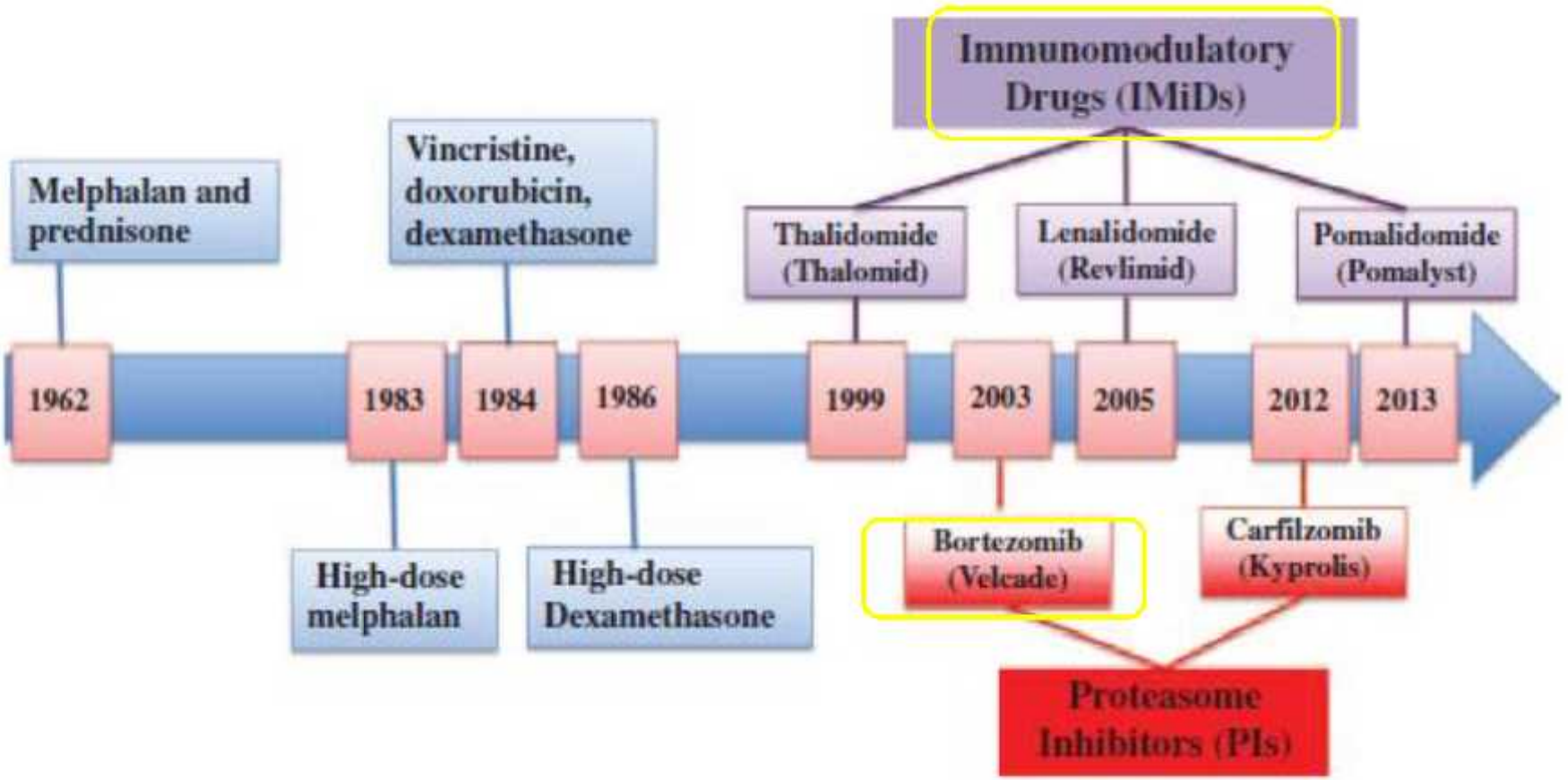
James B. Seward, MD,* Grace Casaclang-Verzosa, MD†

Condition	Age at Presentation	History and Clinical Presentation	Echocardiography	ECG Profile	CMR LGE	Biopsy
Cardiac amyloid	>30 yrs	Heart failure symptoms, nephrotic syndrome, idiopathic peripheral neuropathy, unexplained hepatomegaly	Symmetrical increase in LV and RV wall thickness, dilated LA and RA, granular appearance of myocardium, pericardial effusion, decrease EF in advanced cases	Decreased or normal QRS complex voltage, pseudoinfarction in inferolateral leads	Global, diffuse, pronounced in subendocardium: RV and LV walls	Myocyte atrophy, amyloid replaces normal cardiac tissue
Fabry disease	Male: 11 + 7 yrs	Neuropathic pain, impaired	Symmetrical increase in LV and	Increased or normal QRS complex	Focal, midwall, inferolateral	Enlarged myocytes with

Table 2 Conditions With Dilated LV and Infarct Pattern

Condition	Age at Presentation	History	Echocardiography	ECG	CMR LGE	Cardiac Biopsy
Sarcoidosis	Young adults	Congestive heart failure	Variable wall thickness, focal or global hypokinesis, LV aneurysm	Infrahisian block, atypical infarction pattern	Patchy, basal and lateral LV walls	Noncaseating, multinucleated giant cell granuloma surrounded by band of dense collagen fibers
Wegener disease	Young adults	Chronic upper and lower respiratory tract infections	Regional hypokinesis, pericardial effusion, mild MR, LV systolic dysfunction	Atrial fibrillation, atrioventricular block, atypical infarction pattern	Diffuse, midwall	Vasculitis with necrotizing granulomatous inflammation
Hemochromatosis	Hereditary hemochromatosis: >30 yrs in men, older in women; secondary hemochromatosis: any age	Hereditary hemochromatosis: liver function abnormalities, weakness and lethargy, skin hyperpigmentation, diabetes mellitus, arthralgia, impotence in men; secondary hemochromatosis: hemolytic anemia, multiple blood transfusions	Dilated LV with global systolic dysfunction	Supraventricular arrhythmia, ventricular conduction abnormality is rare		Iron deposits within the myocyte
		mental development, skeletal deformities, corneal clouding, hepatosplenomegaly	aortic valve stenosis or insufficiency, normal EF	arrhythmia		accumulation of mucopolysaccharides within lysosomes
Differential diagnosis						
Hypertrophic cardiomyopathy	17–18 yrs	Maybe asymptomatic, dyspnea, angina, syncope, sudden death	Asymmetrical hypertrophy, small LV cavity, LVOT obstruction, normal EF	Increased QRS complex voltage, pseudo-delta wave, giant T-wave inversion	Patchy, midwall, junctions of the ventricular septum and RV	Myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis
Hypertensive heart disease	Adults	History of hypertension	Symmetrical increase in LV wall thickness, mild LV dilation, normal EF	Increased QRS complex, nonspecific ST-T-wave changes	No pattern, predominantly subendocardial	Enlarged myocytes with enlarged or replicated nuclei

MILESTONES IN MULTIPLE MYELOMA TREATMENT



Circulation. 2016;133:908-912

CARDIOVASCULAR COMPLICATIONS

THROMBOSIS

Venous thromboembolic events (VTEs)

Arterial thromboembolic events (ATEs)

VTEs

- Cancer is associated with increased risk of VTEs

Circulation. 2013;128:2614–2618

- Hematologic malignancies have the highest reported risk of VTEs among patients with cancer

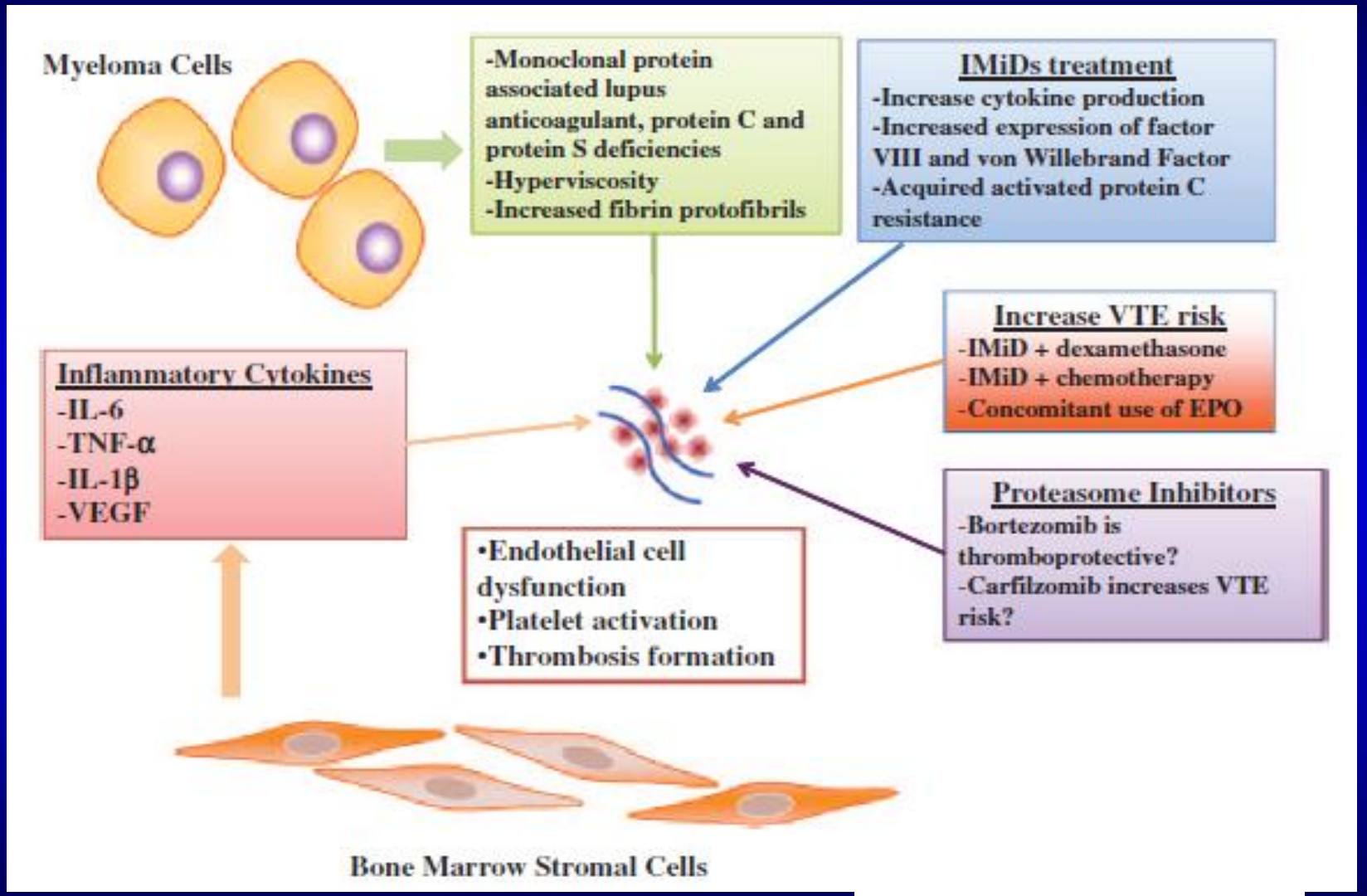
JAMA. 2005;293:715–722.

- Multiple myeloma is an independent risk factor for VTEs

Br Med J. 1970;3:438–439.

Clin Appl Thromb Hemost. 2013;19:469–475

MECHANISMS OF INCREASED VTEs IN MULTIPLE MYELOMA



Circulation. 2016;133:908-912

VTEs and IMiDs

Table. VTE Incidences in IMiDs Trials[17,25]

Treatment Regimen	VTE Incidence Without Thromboprophylaxis, %	VTE Incidence With Thromboprophylaxis, %*
Thalidomide		
Alone	2–10	NA
Plus dexamethasone	2–26	8–25
Plus chemotherapy†	3–58	3–31
Lenalidomide		
Alone	0–33	NA
Plus dexamethasone	8–75	3–14
Plus chemotherapy†	14	5–9
Pomalidomide		
Alone	NA	2
Plus dexamethasone	NA	2–5

IMiD indicates immunomodulatory agents; and VTE, venous thromboembolic events.

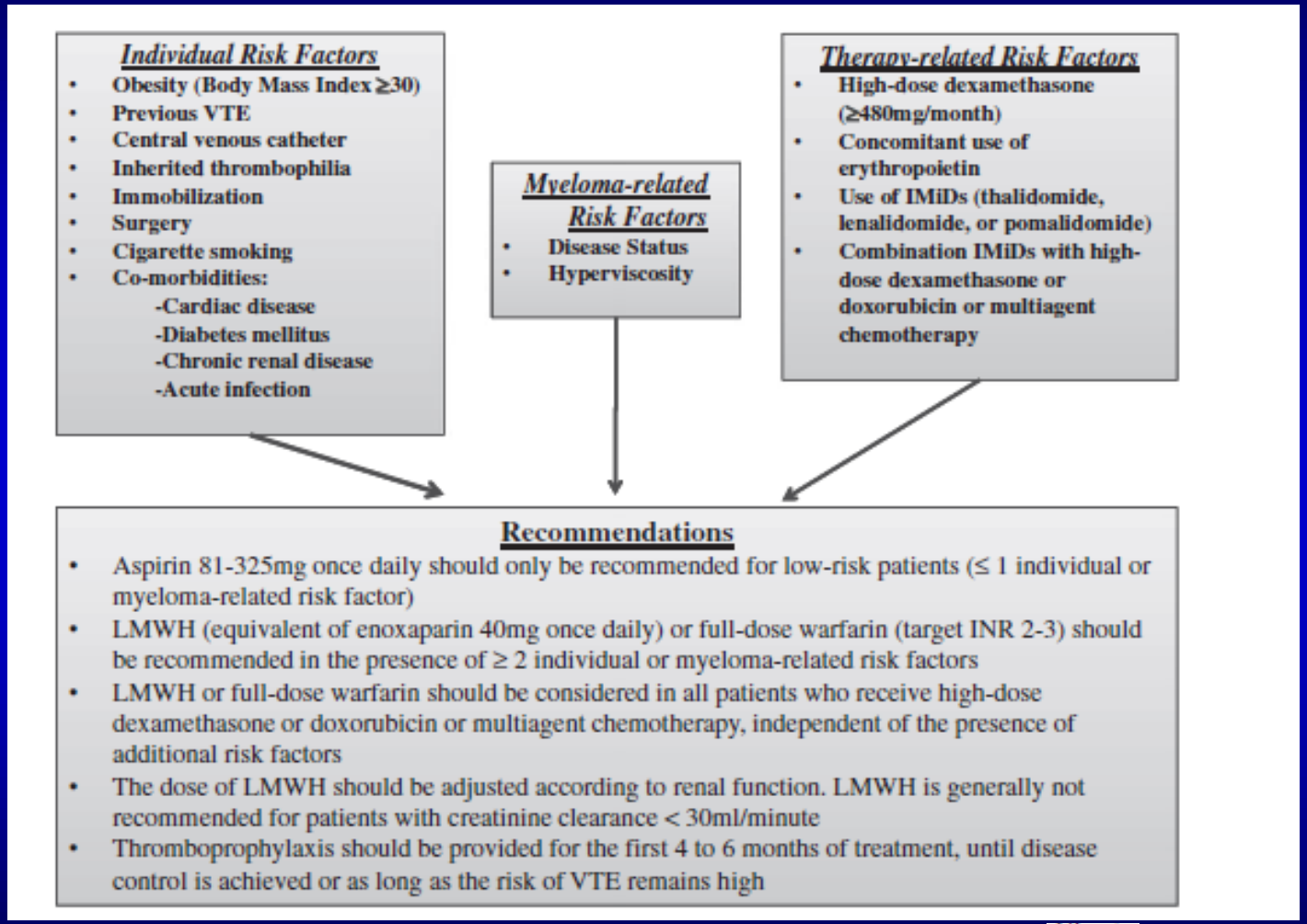
*Aspirin (81–325 mg daily), low-molecular-weight heparin, fixed low-dose warfarin (1–1.25 mg daily), and full-dose warfarin (target international normalized ratio, 2–3) have all been used for prophylaxis. Choice of thromboprophylaxis was based largely on physicians' discretion.

†Thalidomide and lenalidomide were used in combination with other therapeutic agents, including melphalan, doxorubicin, and cyclophosphamide.

Circulation. 2016;133:908-912

VTEs and thromboprophylaxis: reccomendations

American College of Chest Physicians



Chest. 2012;141(suppl):e419S–e494S.

ATEs

The importance of cardiovascular risk factors…

Table 3. The influence of factor VIII:C, hypertension, and smoking on the risk of arterial thrombosis in 195 multiple myeloma patients

Risk factor	Univariate analysis, HR (95% CI)	Multivariate analysis,* HR (95% CI)
Factor VIII:C†	1.92 (1.17-3.14)	1.85 (0.99-3.47)
Hypertension	3.70 (1.13-12.2)	11.7 (2.23-61.2)
Smoking	6.25 (1.61-24.2)	15.2 (1.78-130)

BLOOD, 8 JULY 2010 • VOLUME 116, NUMBER 1

ATEs and IMiDs

	Lenalidomide and dexamethasone	Dexamethasone alone (controls)
Myocardial infarction	1.98%	0.57%
Cerebral vascular events	3.4%	1.7%
Deep venousthrombosis	9.1%	4.3%
Pulmonary embolism	4.0%	0.9%

https://www.gov.uk/drug-safety-update/lenalidomide-risk-of-thrombosis-and-thromboembolism.

ATEs and IMiDs: lenalidomide

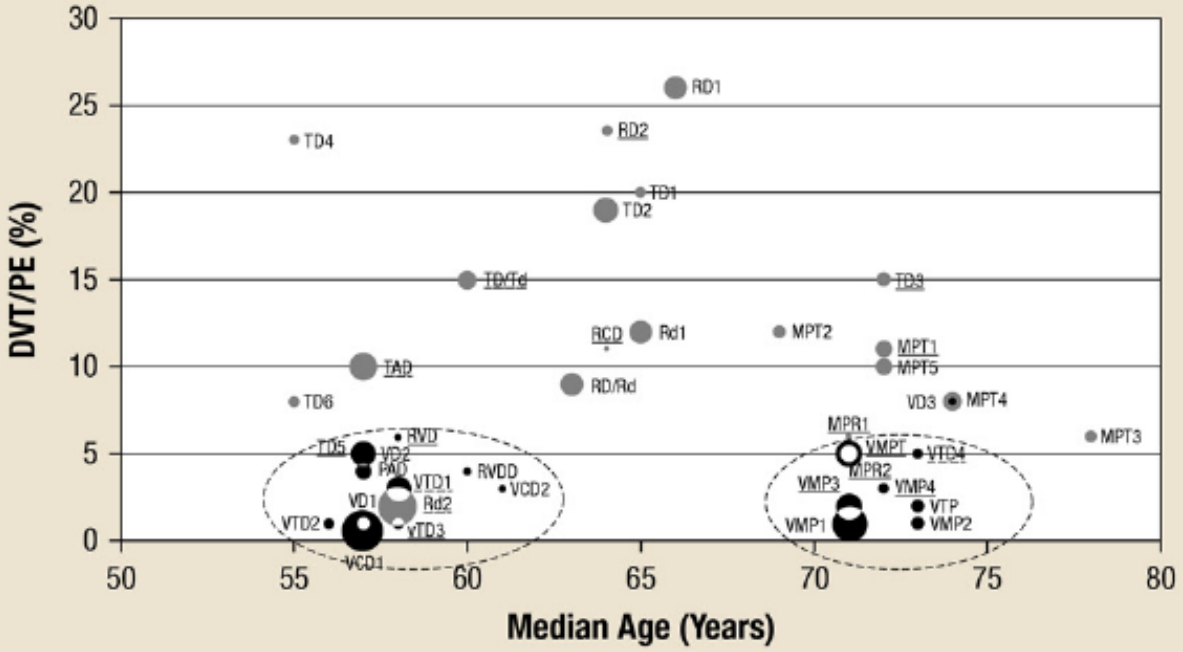
REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism.

Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

http://www.revlimid.com/?gclid=CjwKEAjw8e2sBRCYte6U3suRjFESJAB4gn_gZPF3Dz-5R5nSIxcDNG-tDYtv5r1Dwlz7iPdLnWGH-PJxoCzqTw_wcB.

VTEs and PIs: BORTEZOMIB

Figure 1 Rates of Deep Vein Thrombosis (DVT) and pulmonary embolism (PE) (DVT/PE) by Median Age, According to Regimen (studies with n > 50). As Shown by the Ringed Areas, Regimens That Contain Bortezomib (black circles) Are Generally Associated With Rates of DVT/PE of ≤5%. Underlined Regimen Names Represent Studies in Which Venous Thromboembolism (VTE) Prophylaxis was Recommended or Reported To Be Used. The Figure Does Not Account for Other Baseline Risk Factors for VTE



Clinical Lymphoma, Myeloma & Leukemia, Vol. 11, No. 2, 228-36

VTEs and PIs: BORTEZOMIB

Thromboprotective effect of bortezomib

THROMBOSIS AND HEMOSTASIS

The thromboprotective effect of bortezomib is dependent on the transcription factor Kruppel-like factor 2 (*KLF2*)

Lalitha Nayak,[1,2] Hong Shi,[2] G. Brandon Atkins,[2] Zhiyong Lin,[2] Alvin H. Schmaier,[1] and Mukesh K. Jain[2]

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Proteasome Inhibitors Enhance Endothelial Thrombomodulin Expression via Induction of Krüppel-Like Transcription Factors

Toyoko Hiroi, Clayton B. Deming, Haige Zhao, Baranda S. Hansen, Elisabeth K. Arkenbout, Thomas J. Myers, Michael A. McDevitt and Jeffrey J. Rade

PIs: CARFILZOMIB

- Selective proteasome inhibitor

- Approved in 2012 in the US for treatment of relapsed and refractory multiple myeloma

PIs: CARFILZOMIB

Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies

David Siegel,[1] Thomas Martin,[2] Ajay Nooka,[3] R. Donald Harvey,[3] Ravi Vij,[4] Ruben Niesvizky,[5] Ashraf Z. Badros,[6] Sundar Jagannath,[7] Leanne McCulloch,[8] Kanya Rajangam,[8] and Sagar Lonial[3]

- 73.6% of patients had a past medical history of cardiovascular events
- 70% had baseline cardiac risk factors (use of at least one cardiovascular or anti-diabetic medication prior to study entry)

PIs: CARFILZOMIB

Table 5. Special analysis of grouped-term organ system adverse events.

Grouped adverse event, n, (%)	Any AE	≥Grade3	SAE
Any cardiac	116 (22.1)	50 (9.5)	41 (7.8)
Cardiac arrhythmia	70 (13.3)	12 (2.3)	11(2.1)
Cardiac failure	38 (7.2)	30 (5.7)	26 (4.9)
Ischemic heart disease	18 (3.4)	7 (1.3)	5 (1.0)
Cardiomyopathy	9 (1.7)	3 (0.6)	2 (0.4)
Any respiratory	363 (69.0)	54 (10.3)	34 (6.5)
Dyspnea	222 (42.2)	26 (4.9)	11 (2.1)
Cough	137 (26.0)	1 (0.2)	1 (0.2)
Pneumonia	67 (12.7)	55 (10.5)	52 (9.9)
Any grouped renal impairment	174 (33.1)	38 (7.2)	32 (6.1)
Increased serum Creatinine	127 (24.1)	14 (2.7)	7 (1.3)
Acute renal failure	28 (5.3)	23 (4.4)	22 (4.2)
Renal failure	20 (3.8)	6 (1.1)	7 (1.3)

« The extent to which the cardiac events reported here were due to patients' baseline comorbidities, toxicity from prior treatments, effects of MM, carfilzomib itself, or a combination of these factors, cannot be determined in these single-arm trials. »

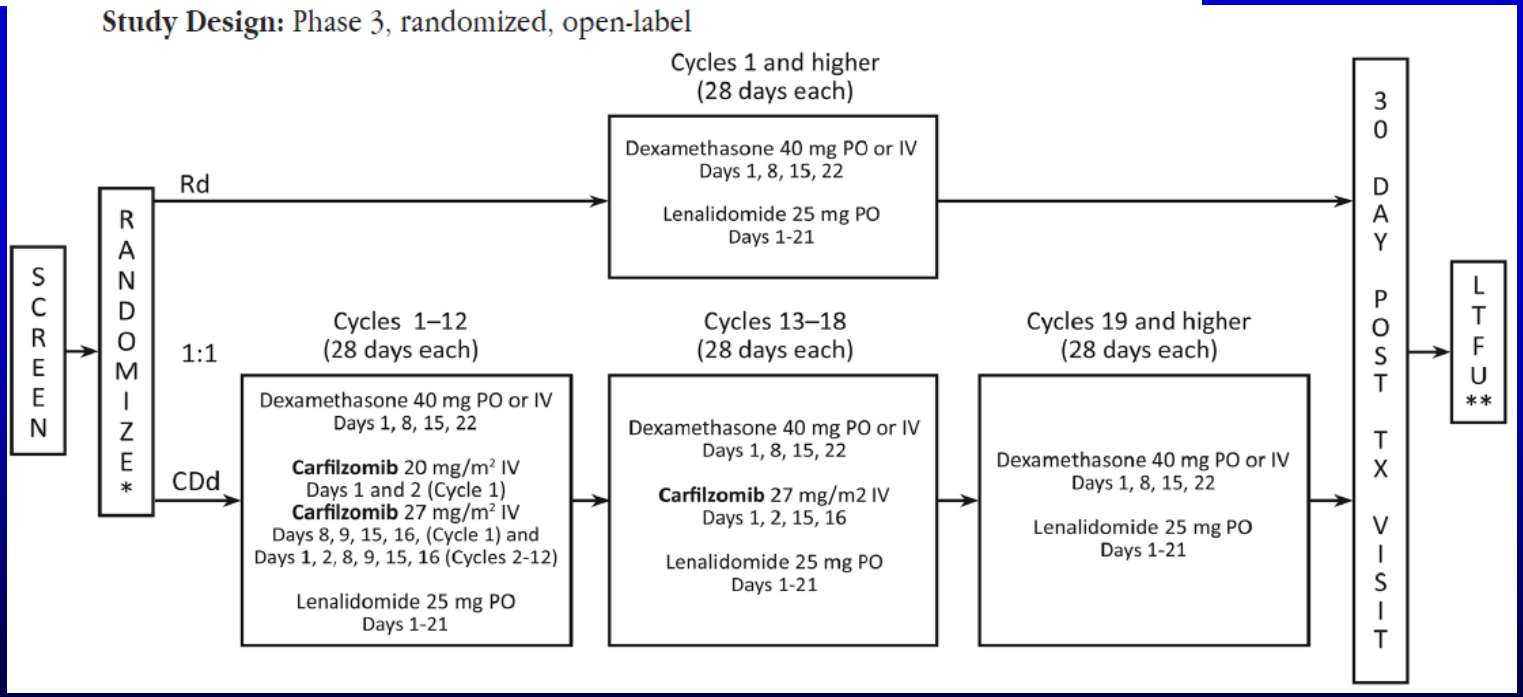
PIs: CARFILZOMIB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

Study Design: Phase 3, randomized, open-label



PIs: CARFILZOMIB

Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

PIs: CARFILZOMIB

the results of ASPIRE pointed to a concerning thrombotic risk when carfilzomib is combined with lenalidomide. Cardiologists need to be aware of these toxicities and work closely with patients and their oncology teams to provide optimal cardiovascular care during MM treatment.

Circulation. 2016;133:908-912

PIs: CARFILZOMIB

Table 3 Recommended monitoring and management of possible carfilzomib-associated cardiac and vascular-related events

(A) Prevention of cardiac and vascular-related events	• Monitor cardiopulmonary symptoms • Monitor cardiopulmonary signs (vitals, weight, physical exam) • Administer carfilzomib over 30 min • Check baseline transthoracic echocardiogram, and repeat echocardiogram every two to three cycles[a] Note, if baseline ejection fraction is below normal, consider utilizing prophylactically strategies listed in (B) Monitor BNP[a] • Close follow-up by cardiologist or cardio-oncologist[a]
(B) Management of treatment-emergent possibly cardiac and vascular-related complications	• Rule out alternative causes (e.g., pulmonary embolus, pneumonia, anemia)\ • Hold carfilzomib until toxicity resolves to grade <2. • If the decision is made to rechallenge: – Implement all preventative/monitoring strategies listed in (A) – Consider dose reduction – Decrease or eliminate hydration, especially if the patient has completed ≥1 cycle of 27 mg/m^2 carfilzomib while retaining stable renal function and without experiencing tumor lysis – Minimize corticosteroids and concomitant fluid retention – Cautious use of diuretics – Use of anti-hypertensives as indicated

Chari and Hajje *BMC Cancer* 2014, **14**:915

PIs: CARFILZOMIB - key points -

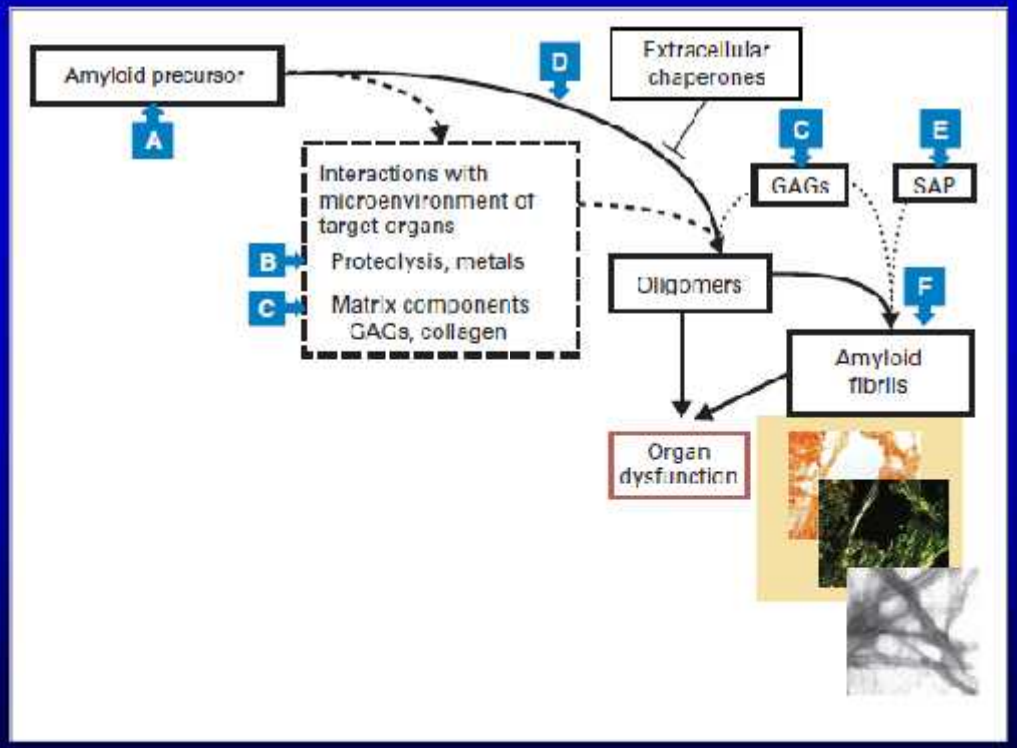
- Patients with multiple myeloma should be closely monitored for cardiac symptoms

- A patient with cardiac risk factors should be assessed by a cardiologist before commencing carfilzomib treatment and should be evaluated during treatment

Oncology (Williston Park) 2013 Dec;27 Suppl 3:24-30.
Overview and management of cardiac and pulmonary adverse events in patients with relapsed and/or refractory multiple myeloma treated with single-agent carfilzomib.
Wang M, Cheng J

AMILOIDOSI

Gruppo eterogeneo di patologie caratterizzate dalla deposizione a livello extracellulare di proteine che hanno assunto una conformazione strutturale aberrante a *β-foglietto*



TIPI DI AMILOIDE

Table I. Amyloid fibril proteins and their precursors in humans.*

Amyloid protein	Precursor	Systemic (S) or localized, organ restricted (L)	Syndrome or involved tissues
AL	Immunoglobulin light chain	S, L	Primary Myeloma-associated
AH	Immunoglobulin heavy chain	S, L	Primary Myeloma-associated
$A\beta_2M$	β_2-microglobulin	S	Hemodialysis-associated
		L?	Joints
ATTR	Transthyretin	S	Familial Senile systemic
		L?	Tenosynovium
AA	(Apo)serum AA	S	Secondary, reactive
AApoAI	Apolipoprotein AI	S	Familial
		L	Aorta, meniscus
AApoAII	Apolipoprotein AII	S	Familial
AApoAIV	Apolipoprotein AIV	S	Sporadic, associated with aging
AGel	Gelsolin	S	Familial (Finnish)
ALys	Lysozyme	S	Familial
AFib	Fibrinogen a-chain	S	Familial
ACys	Cystatin C	S	Familial
ABri	ABriPP	S	Familial dementia, British
ALect2	Leukocyte chemotactic factor 2	S	Mainly kidney
ADan†	ADanPP	L	Familial dementia, Danish
$A\beta$	$A\beta$ protein precursor (A_βPP)	L	Alzheimer's disease, aging
APrP	Prion protein	L	Spongiform encephalopathies
ACal	(Pro)calcitonin	L	Cell thyroid tumors
AIAPP	Islet amyloid polypeptide**	L	Islets of Langerhans Insulinomas
AANF	Atrial natriuretic factor	L	Cardiac atria
APro	Prolactin	L	Aging pituitary Prolactinomas
AIns	Insulin	L	Iatrogenic
AMed	Lactadherin	L	Senile aortic media
AKer	Kerato-epithelin	L	Cornea, familial
ALac	Lactoferrin	L	Cornea
AOaap	Odontogenic ameloblast-associated protein	L	Odontogenic tumors
ASemI	Semenogelin I	L	Vesicula seminalis

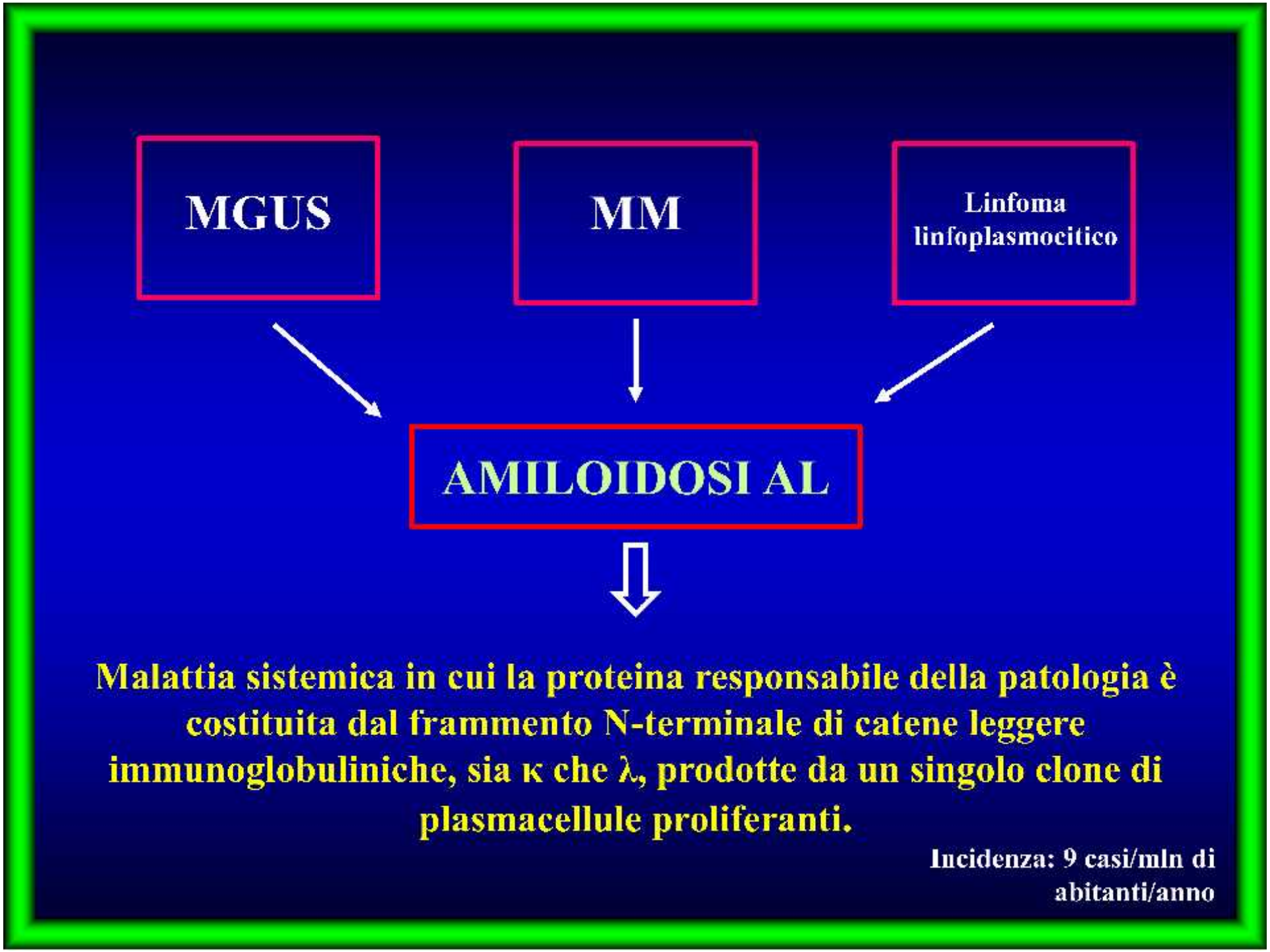
*Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
†ADan comes from the same gene as ABri.
‡Also called 'amylin'.

TIPI PIÚ COMUNI DI AMILOIDOSI

Type	Abbreviation	Precursor	Site of Synthesis	Syndrome and Organs Involved
Immunoglobulin light chain amyloidosis	AL	Monoclonal light chain	Bone marrow plasma cells	Primary, can occur in 10%–15% of patients with multiple myeloma Involvement of heart, kidneys, liver, GI tract, peripheral nerves, autonomic nerves, soft tissues
Reactive amyloidosis	AA	Serum amyloid A	Liver	Secondary to chronic inflammation, infection, or certain neoplasia Involvement of kidneys, GI tract, spleen, liver, autonomic nerves
Senile systemic amyloidosis	SSA	Transthyretin wild type	Liver > 90%	Age-related, usually males (age > 65 years) Primarily cardiac involvement
Transthyretin amyloidosis	ATTR	Variant transthyretin, > 100 amyloidogenic mutations	Liver > 90%	Hereditary Involvement of peripheral nerves, autonomic nerves, heart, eye, leptomeninges, rarely kidneys
Fibrinogen amyloidosis	AFib	Variant fibrinogen A chain	Liver	Hereditary Involvement of kidneys
Apolipoprotein A-I amyloidosis	AApoAI	Variant apolipoprotein AI	Liver, intestine	Hereditary Involvement of heart, liver, kidneys, skin, larynx, testes

	Acquired or hereditary	Patients seen at UK NAC (%, n=5100)	Underlying disorder	Precursor protein	Organ involvement					Treatment	Treatment target
					Heart	Kidneys	Liver	PN (AN)	Other		
AL	Acquired	4067 (68%)	Plasma cell dyscrasia	Monoclonal immunoglobulin light chain	+++	+++	++	+(+)	Soft tissue gastrointestinal	Chemotherapy or ASCT	dFLC <40 mg/L
AA	Acquired	633 (12%)	Inflammatory disorders (RA, JIA, IVDU, FPS)	SAA	−/− (late)	+++	+(late)	−	Gastrointestinal (late)	Suppression of inflammation	SAA <4 mg/L
ATTR	Acquired	168 (3·2%)	..	Wild-type TTR	+++	−	−	−	Carpal tunnel syndrome	Supportive	Optimum control of heart failure
	Hereditary	339 (6·6%)	Mutations in TTR gene	Abnormal TTR	++	−	−	+++ (+++)	−	Liver transplant (younger patients with V30M-related ATTR), diflunisal, (doxycycline/ TUDCA) Supportive	Optimum control of congestive heart failure and symptoms of PN/AN
ATib	Hereditary	87 (1·7%)	Mutations in fibrinogen α-chain gene	Abnormal fibrinogen	−	+++	−/+	−	−	Supportive, organ transplant	Preserve renal function
ALect2	Acquired	16 (0·3%)	Uncertain	Lect2	−	+++	++	−	−	Supportive	Preserve renal function
AApoA1	Hereditary	40 (0·8%)	Mutations in apolipoprotein A1 gene	Abnormal ApoA1	+	++	++	+/−(+)	Testis	Supportive, organ transplant	Preserve renal function
ALys	Hereditary	17 (0·3%)	Mutations in lysozyme gene	Abnormal lysozyme	−	+	++	−	Gastrointestinal or skin	Supportive	..
AGel	Hereditary	4 (0·1%)	Mutations in gelsolin gene	Abnormal gelsolin	−	−/+	−	++(−) cranial	−	Supportive	..
Aβ2M	Acquired or hereditary	93 (1·8%)	Long term dialysis	Aβ2M				(+*)	Carpal tunnel syndrome, arthropathy	Supportive, renal transplant	..

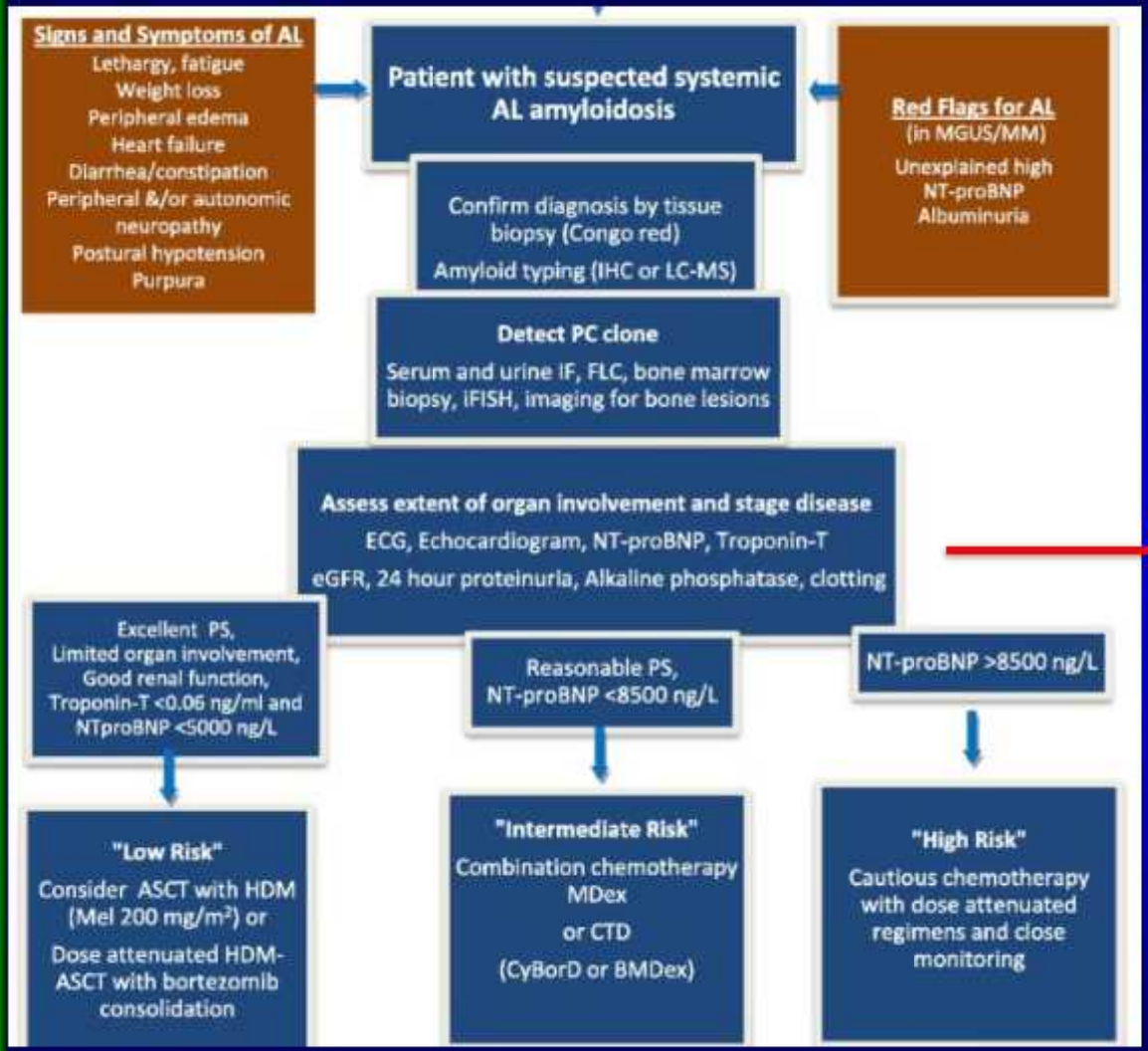
Aβ2M=β2-microglobulin-related. AHb=fibrinogen Aα-chain. AGel=gelsolin amyloid. AL=amyloid light chain. ALect2=leucocyte cell-derived chemotaxin 2. ALys=lysozyme amyloid. AN=autonomic neuropathy. ASCT=autologous stem cell transplant. ATTR=hereditary transthyretin. dFLC=difference between involved and uninvolved free light chain. FPS=familial periodic fever syndromes. IVDU=intravenous drug abuse. JIA=juvenile inflammatory arthritis. PN=peripheral neuropathy. RA=rheumatoid arthritis. SAA=serum amyloid A. TTR=transthyretin. TUDCA=tauro-ursodeoxycholic acid. UK-NAC=UK National Amyloidosis Centre. *AN only in familial Aβ2M amyloidosis.† + indicates relative frequency: +++ very common; ++ common; + less common; −/+ rare; − not applicable or does not occur in this condition. (drug)=undergoing clinical trials. AA=amyloid A. AApoA1= apolipoprotein A1 amyloid.



Malattia sistemica in cui la proteina responsabile della patologia è costituita dal frammento N-terminale di catene leggere immunoglobuliniche, sia κ che λ, prodotte da un singolo clone di plasmacellule proliferanti.

Incidenza: 9 casi/mln di abitanti/anno

Diagnosi e Valutazione del Coinvolgimento d'Organo



MRI indicata se ipertrofia/aumento della massa inspiegabili → Late-enhancement subendocardico diffuso

Cardiac
NT-proBNP (or BNP), cTnT (or hs-cTnT, or cTnI)
Echocardiography (plus strain imaging)
ECG (plus Holter ECG)
Cardiac MRI (if indicated)
^{99m}Tc-DPD scan (if indicated)

Renal
24 h urinary protein
Serum creatinine (and eGFR)

Liver
Liver function tests
Liver US / CT scan

Nerves
Nerve conduction studies (if indicated)
Autonomic testing

Whole body amyloid load
^{123}I labeled SAP scintigraphy (if available)

Merlini, Blood 2013; 121:5124-5130

Mahmood. Haematologica 2014 (99)2

QUADRO CLINICO

L'amiloidosi AL può colpire qualsiasi organo ad eccezione del SNC

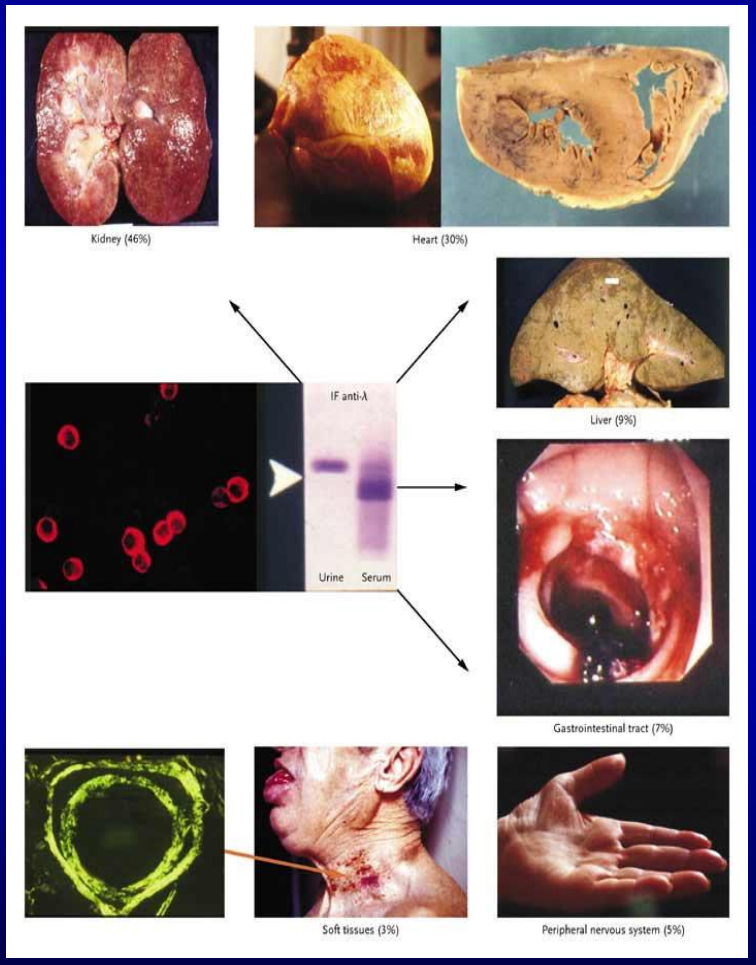


Table 1 Updated definition of organ involvement in AL amyloidosis

Involved organ or tissue	Criteria
Kidney	24-hr urine protein >= 0.5 g/day, predominantly albumin
Heart	NT-proBNP > 332 ng/l (in the absence of renal failure or atrial fibrillation) or mean wall thickness in diastole by echography > 12 mm, no other cardiac cause
Liver	Total liver span > 15 cm in the absence of heart failure, or alkaline phosphatase > 1.5 times institutional upper limit of normal
Nerve	Peripheral: Symmetric lower extremity sensorimotor peripheral neuropathy
	Autonomic: gastric-emptying disorder, pseudo-obstruction,voiding dysfunction not related to direct organ infiltration.
Gastro-intestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms
	Interstitial radiographic pattern
Soft tissues	Tongue enlargement, arthropathy, claudication (presumed vascular amyloid), skin lesions, myopathy (by biopsy or pseudohypertrophy), lymph node (may be localized), carpal tunnel syndrome

Il coinvolgimento cardiaco rappresenta il principale fattore prognostico negativo ed è responsabile del 75% dei decessi per questa patologia.

DIAGNOSI PRECOCE!!!

AMILOIDOSI CARDIACA

- **Distorsione dei cardiomiociti e la loro separazione**
- **Irrigidimento del tessuto**
- **Disfunzione d'organo**

La resistenza intrinseca alla proteolisi della sostanza amiloide ne permette l'accumulo nel tessuto e la progressiva perdita della funzione meccanica ed elettrica del cuore.

DIAGNOSI

1. Visita clinica ed esame obiettivo

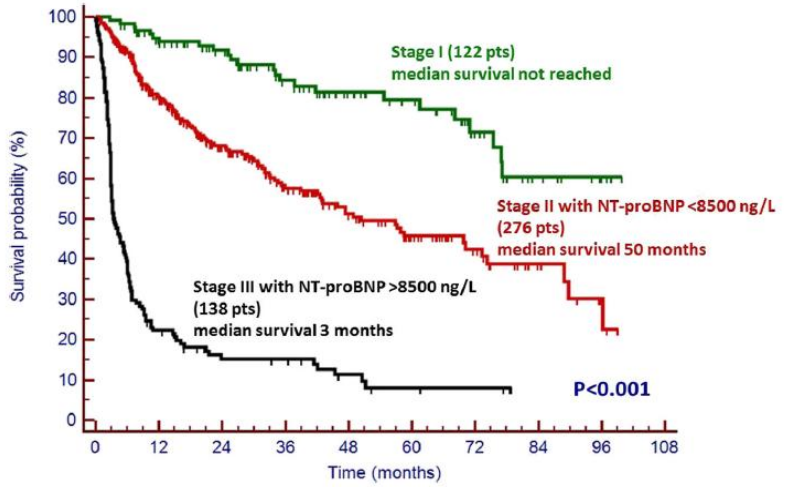
- dispnea progressiva
- segni tipici di scompenso cardiaco destro (epatomegalia, turgore giugulare, edemi declivi)
- perdita di peso
- dolore toracico atipico
- dolore anginoso tipico per coinvolgimento microvascolare
- sincopi dovute a una disfunzione del sistema nervoso autonomo o di origine cardiogena

2. Esami di laboratorio

- **Esami del sangue standard**
  - **cTnT**
  - **NT-proBNP**

WARNING!!

Fig. 1 Survival of patients with AL amyloidosis, without cardiac involvement (stage I), with cardiac involvement with either NT-proBNP or cardiac troponin increased (stage II) and with both NT-proBNP and cardiac troponin increased (stage III) and NT-proBNP >8,500 ng/L. The cardiac staging is modified from Dispenzieri et al. [11]



L'NT-proBNP mostra, inoltre, una stretta dipendenza dalla funzionalità renale che risulta alterata in un gran numero di pazienti affetti da amiloidosi

→ Parametro fondamentale nella valutazione complessiva di questi pazienti, seppur con la necessità di essere inserito nel quadro clinico complessivo.

Nuovi Marker → COPEPTINA

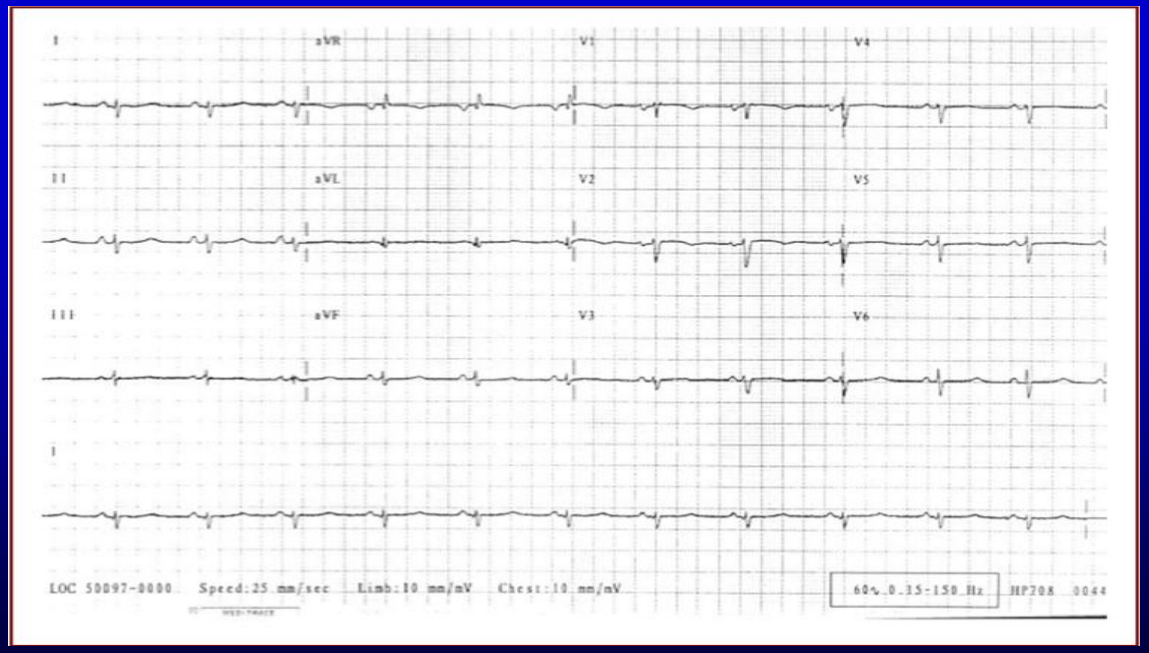
- Appartiene al sistema arginina-vasopressina
- Valore prognostico nei pazienti con HFPEF

3. Elettrocardiogramma

Un recente studio retrospettivo del 2016 ha analizzato 389 pazienti consecutivi:

- **Bassi voltaggi nelle derivazioni periferiche in ca. il 68% dei casi**

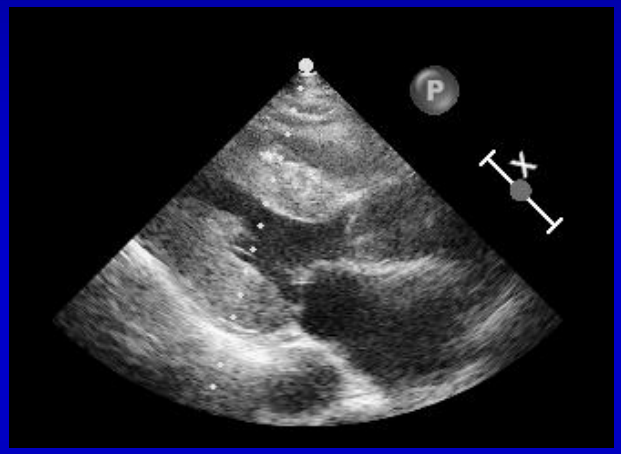
- **Indice di Sokolow < 15 mm nelle derivazioni precordiali, considerando la somma dall'ampiezza dell'onda S nella derivazione D1 e dell'onda R in D5 o D6 in ca. il 72% dei casi**



- **pattern pseudoinfartuale,** **cioè una scarsa progressione dell'onda R nelle derivazioni precordiali**
- **disturbi della conduzione atrio-ventricolare:** **blocco atrio-ventricolare (BAV) I grado in ca. il 20% dei casi, BAV II-III grado in ca. il 3% dei casi**
- **disturbi della conduzione intra-ventricolare** **in ca. il 16% dei casi**
- **aritmie atriali (fibrillazione/flutter atriale)** **in ca. il 20% dei casi**
- **aritmie ventricolari (tachicardia ventricolare)** **in ca. il 5% dei casi**

4. Ecocardiogramma

RUOLO FONDAMENTALE NELLA DIAGNOSI DI AMILOIDOSI CARDIACA!!

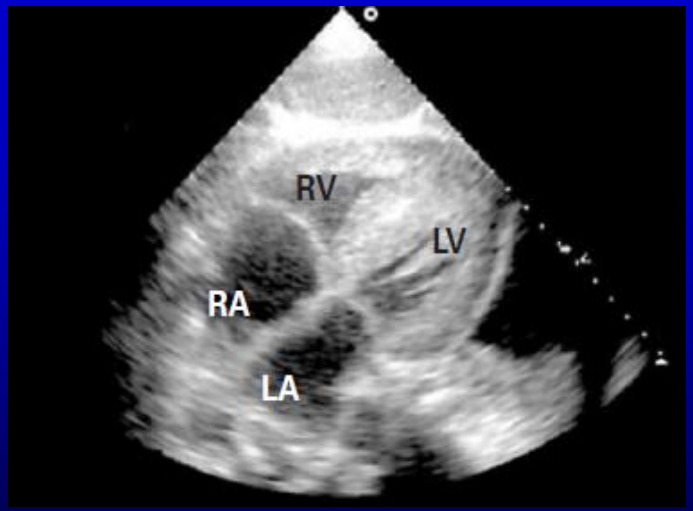


- diffusa
- disponibile
- poco costosa
- scevra da rischi
- studio morfologico e funzionale del cuore

OPERATORE DIPENDENTE!!

REPERTI PIÚ FREQUENTI:

- ✓ **ipertrofia parietale concentrica** (in assenza di altre cause che possano giustificarla)
- ✓ **funzione sistolica ventricolare sinistra** normale o solo lievemente compromessa
- ✓ **disfunzione diastolica** di grado avanzato
- ✓ **dilatazione bi-atriale**
- ✓ **versamento pericardico**
- ✓ **ispessimento valvolare**
- ✓ **ispessimento del setto inter-atriale**



WARNING!!

Queste alterazioni sono proprie delle fasi avanzate della malattia e possono non essere così marcate negli stadi iniziali…

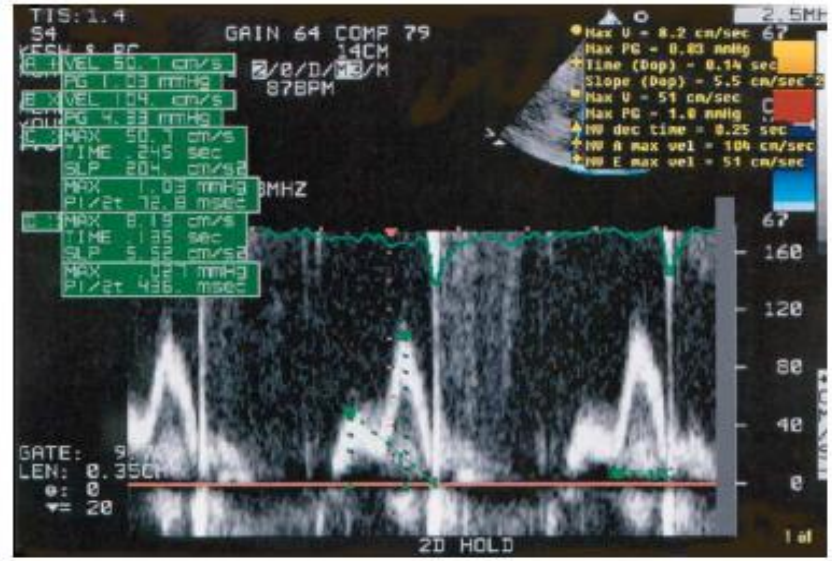


Fig. 3 *Doppler echocardiographic study of a patient in an early stage of cardiac amyloidosis reveals an impaired relaxation pattern with reversal of E/A ratio.*

…Solamente l'alterazione della funzione diastolica può essere evidenziata anche prima della comparsa di sintomi.

Diagnosi differenziale con altri tipi di cardiopatie (es. cardiopatia ipertrofica o su base ipertensiva)

⇒ **Nuove tecniche di STRAIN e STRAIN RATE**

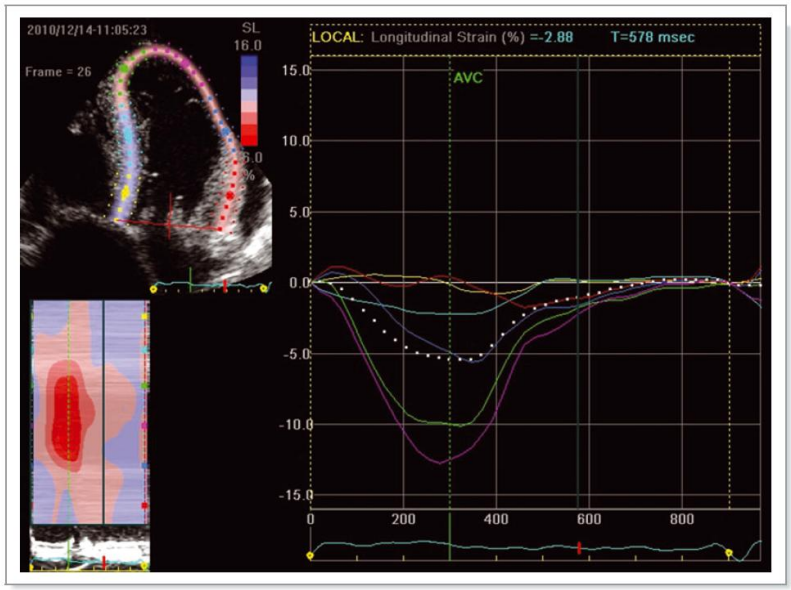


Figure 2. Transthoracic echocardiogram with speckle tracking. The red and yellow lines represent longitudinal motion in the basal segments, whereas the purple and green lines represent apical motion. This shows loss of longitudinal ventricular contraction at the base compared to apex.

↘

caratteristico delle forme di amiloidosi cardiaca un particolare pattern caratterizzato da ridotti valori di strain longitudinale a carico dei segmenti ventricolari medio-basali con relativo risparmio di quelli apicali

5. RMN

Estremamente utile in quei pazienti in cui sono presenti altre cause di ipertrofia, permettendoci di fare diagnosi differenziale tra l'ipertrofia da ipertensione e quella causata da amiloidosi

⇩

- **Non invasiva**
- **Eccellente risoluzione spaziale → precisa caratterizzazione del tessuto anche in caso di spessori ventricolari non aumentati**
- **Misura in maniera più precisa gli spessori e i volumi delle cavità ventricolari, la dilatazione bi-atriale, lo spessore del setto interatriale, la presenza di versamento pericardico e la fase di riempimento ventricolare**
- **Vantaggio maggiore: attraverso l'utilizzo di un bolo di gadolinio nel distretto venoso come mezzo di contrasto, caratterizzazione deil tessuto attraverso la valutazione della modalità di distribuzione**

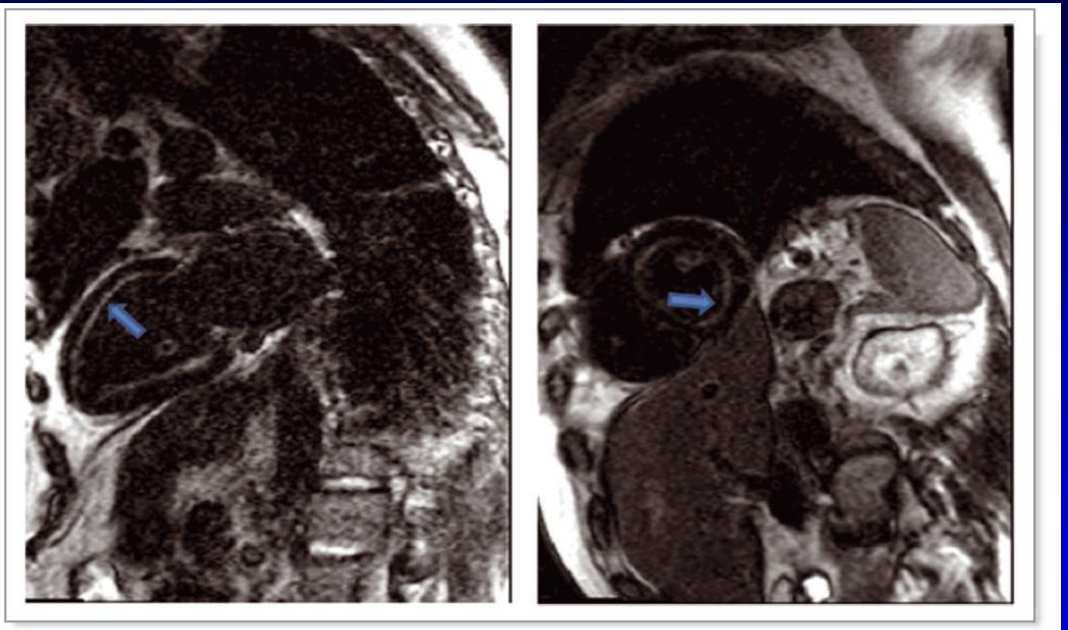


Figure 3. CMR with the classic amyloid global, subendocardial late gadolinium enhancement pattern in the left ventricle with blood and mid-/epimyocardium nulling together.

Amiloidosi cardiaca

↓

pattern di “late enhancement” a livello globale subendocardico

INDICAZIONE

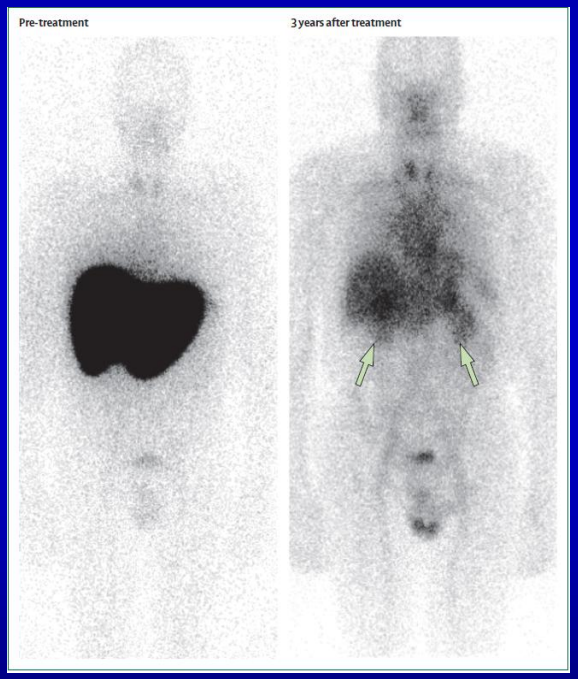
pazienti in cui sono presenti altre cause di ipertrofia, permettendoci di fare diagnosi differenziale tra l'ipertrofia da ipertensione, da cardiomiopatia ipertrofica e quella causata da amiloidosi

ATTENZIONE A

- **ARITMIE**
- **PATTER ATIPICI**

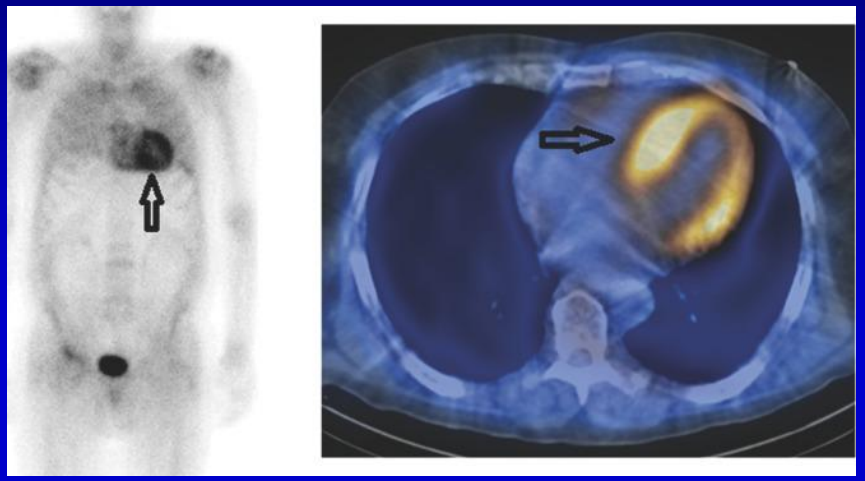
6. SCINTIGRAFIA

Attraverso l'uso dello ^{123}I è in grado di identificare i depositi di sostanza amiloide negli organi viscerali, inclusi fegato, reni, surreni, milza e ossa, attraverso indagini quantitative specifiche..



..ma non è in grado di ottenere delle immagini efficaci e precise del cuore in movimento.

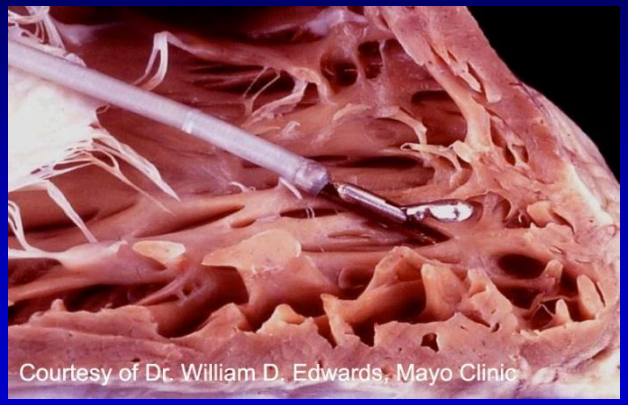
Numerosi case report negli ultimi 30 anni hanno dimostrato che il coinvolgimento cardiaco può essere evidenziato con maggior efficacia attraverso l'utilizzo dei ^{99}Tc-DPD.



La sensibilità di questa tecnica risulta essere molto alta nei pazienti affetti da amiloidosi ATTR, mentre è in grado di localizzare la sostanza amiloidotica a livello cardiaco solo in 1/3 dei pazienti affetti da amiloidosi AL.

→ La ^{99m}Tc-DPD-SPECT-CT aiuta a distinguere le due forme

7. BIOPSIA ENDOMIOCARDICA



E' considerata il gold standard per la dimostrazione della presenza di depositi di sostanza amiloide a livello cardiaco

MA

Il coinvolgimento cardiaco può essere ragionevolmente dedotto sulla base del quadro clinico, elettrocardiografico, ecocardiografico e dei biomarkers nel caso in cui la diagnosi di amiloidosi sistemica sia già sicura.

Quando??

→ **Sospetto di amiloidosi cardiaca ISOLATA**

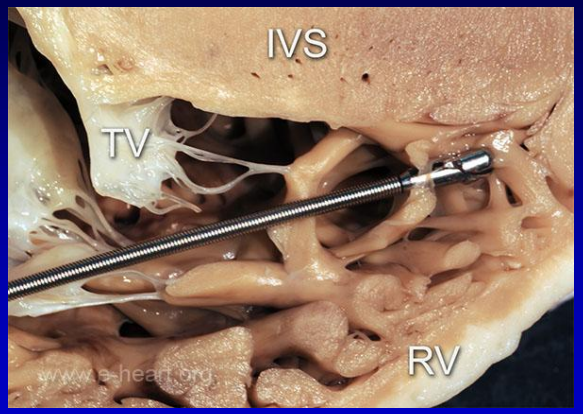
→ **Impossibilità di TIPIZZARE in altro modo le fibrille di amiloide depositate a livello cardiaco**

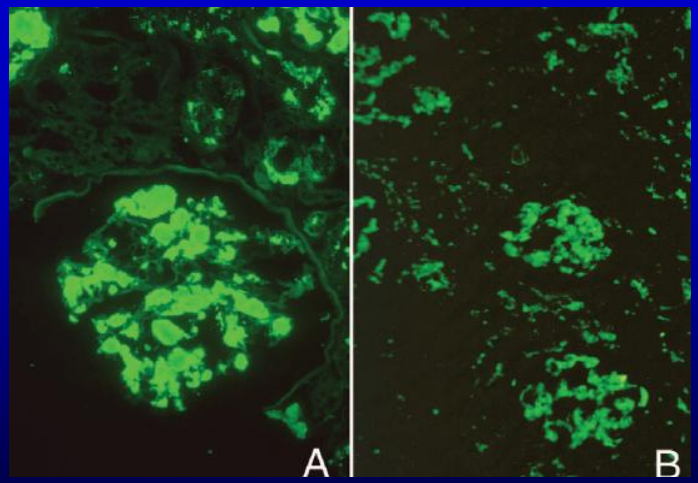
⇩

Sostanzialmente la biopsia endomiocardica serve a differenziare, tra i pazienti di età avanzata, quelli affetti da amiloidosi AL da quelli affetti da amiloidosi ATTR. In questo gruppo di pazienti, infatti, il 5% è affetto da una gammopatia monoclonale di significato incerto.

La biopsia endomiocardica deve inoltre essere presa in considerazione nel caso di paziente con aumentati spessori del ventricolo sinistro all'ecocardiografia in presenza di ipertensione, valvulopatia o storia familiare di CMPI.

Rischio di perforazione





Conferma mediante Rosso Congo e tipizzazione

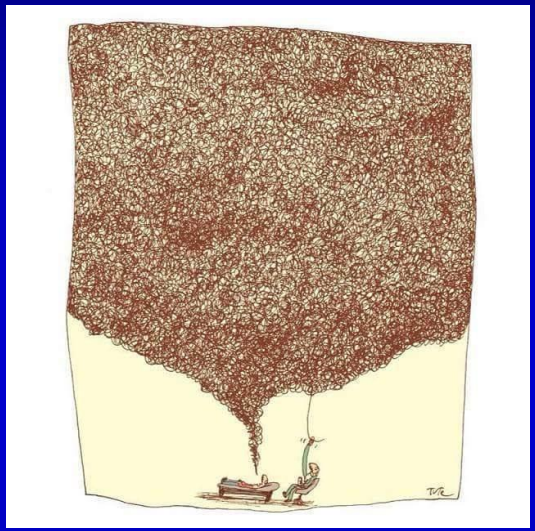
TERAPIA

1. **Terapia ematologica mirata alla soppressione della proteina precursore della sostanza amiloide**

2. **Terapia cardiologica di supporto mirata al compenso emodinamico**

3. **Trapianto cardiaco: solo in casi accuratamente selezionati**

AMILOIDOSI CARDIACA → HFPEF



Molti farmaci comunemente utilizzati nella terapia dello scompenso cardiaco sono controindicati nei pazienti con amiloidosi.

La cura di questi pazienti rappresenta una vera e propria sfida e richiede uno stretto monitoraggio.

A. TERAPIA DIURETICA

L'utilizzo di farmaci DIURETICI DELL'ANSA ad alto dosaggio è un punto centrale della terapia dell'amiloidosi cardiaca.

- **I pazienti devono essere pesati quotidianamente, al fine di poter apportare le opportune modifiche al dosaggio dei farmaci diuretici o dell'introito di liquidi**

- **Restrizione idrica e sodica**

L'utilizzo combinato di DIVERSE CLASSI DI DIURETICI, come l'associazione di diuretici dell'ansa e tiazidici, può risultare utile nei casi resistenti; l'utilizzo di farmaci ANTAGONISTI DELL'ALDOSTERONE può invece aiutare il mantenimento dell'omeostasi del potassio.

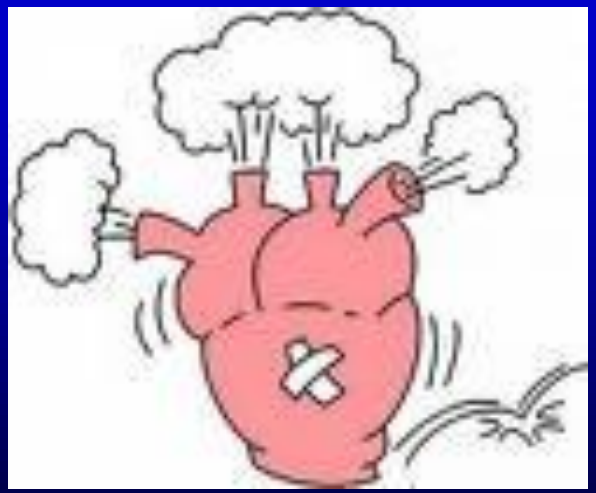
WARNING: IPOTENSIONE ORTOSTATICA!!

B. α-AGONISTI

Al contrario del trattamento del normale scompenso cardiaco, il mantenimento di buoni valori della pressione arteriosa attraverso l'tilizzo di α AGONISTI, come la midodrina, permette l'ottimizzazione del dosaggio della terapia diuretica, con un beneficio clinico per i pazienti.

WARNING!!

L'utilizzo di BETA BLOCCANTI è controindicato a causa dell'effetto ipotensivo che comportano ma soprattutto per il loro effetto inotropo negativo, che causerebbe una riduzione della frazione di eiezione, così come i CALCIO ANTAGONISTI, e per il loro effetto cronotropo negativo, che è l'unico meccanismo attraverso cui i pazienti affetti da amiloidosi cardiaca riescono a mantenere un buon valore di output cardiaco.



Anche l'utilizzo della DIGOSSINA è controindicato in questi casi, dal momento che si è visto che una significativa quantità di questo farmaco va a legarsi alle singole fibrille di amiloide che sono localizzate a livello extracellulare, luogo in cui sono anche presenti i recettori del farmaco.

⇩

TOSSICA

A differenza di quanto concerne lo scompenso cardiaco sistolico, non vi sono evidenze di alcun beneficio apportato dall'utilizzo di ACE inibitori o di inibitori del recettore dell'angiotensina II.

Il warfin o un altro ANTICOAGULANTE deve essere utilizzato in caso di fibrillazione atriale per prevenire la formazione di trombi atriali, a meno che non siano presenti delle controindicazioni maggiori.

L'AMIODARONE deve essere considerato come terapia di prima linea per le aritmie.

L'impianto di PACEMAKER o DEFIBRILLATORI può migliorare i sintomi, ma spesso non è comunque in grado di influire sulla prognosi prevenendo la morte cardiaca improvvisa dal momento che questa è molto spesso dovuta ad una dissociazione elettromeccanica

FOLLOW-UP

In letteratura non ci sono evidenze scientifiche al riguardo, ma…

1 000 000 persons annually.[3,4] Systemic amyloidosis is characterized by the accumulation of abnormal, misfolded protein (amyloid) in various tissue and organs that produce patient-specific clinical manifestations depending on the organ impacted. Progressive amyloid deposition and proteotoxic effects of amyloid proteins lead to organ failure, which is especially catastrophic when the heart is affected, and is the primary cause of death.[1,5] As many as 70% of patients with AL amyloidosis have predominantly cardiac amyloid deposition.[2,5] The prevalence of all types of cardiac amyloidosis is assumed to be underestimated because of missed diagnoses, given that the symptoms of cardiac amyloidosis often mimic those of other far more common conditions.[6–8]

Merlini et al., Leukemia (2016) 30, 1979-1986

DIAGNOSI PRECOCE!!!

Un **approccio di tipo multi-parametrico** permette di diagnosticare con un buon grado di affidabilità e precisione quali pazienti, tra quelli affetti da mieloma multiplo, hanno sviluppato amiloidosi cardiaca.

Diagnosticare precocemente e talvolta addirittura in fase pre-clinica questa malattia permette un intervento terapeutico tempestivo e mirato e, di conseguenza, un maggiore controllo della malattia, con un vantaggio in termini di sopravvivenza e qualità della vita per questa categoria di pazienti. Per poter ottenere dei risultati validi è quindi necessario uno screening sistematico dei pazienti con nuova diagnosi di mieloma multiplo, con un follow-up stretto e periodico.

Indispensabile è la creazione di gruppi di lavoro multidisciplinari al fine di poter effettuare una valutazione a 360° di questi pazienti affetti da una patologia multi-organo.

GRAZIE PER L'ATTENZIONE

GRAZIE PER L'ATTENZIONE