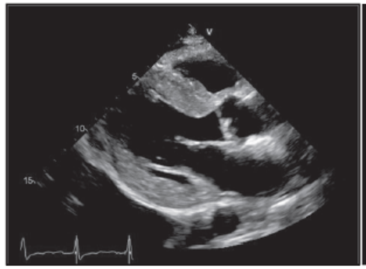
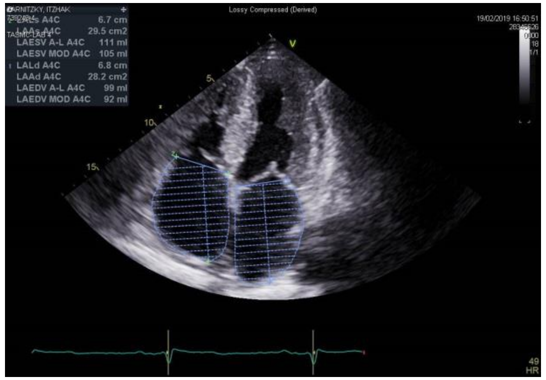
ATTR-CM –
Echocardiography as a screening tool

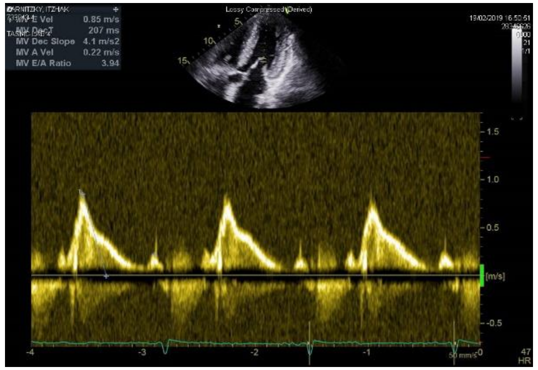
Michal Laufer Perl, MD, MHA
Director of the Cardiovascular Clinics
Director of the Heart Failure Service
Head of the Cardio-Oncology clinic
Tel Aviv Sourasky Medical Center
Secretary of the Cardiomyopathy Section of the Israel Cardiology Association



Increased LV wall thickness without dilated LV on echocardiogram

LVH>12mm





+ ≥1 of the following Red-flags

Category	Red-flags
Demographic	Elderly men over the age of 60 years
Family history	Progressive neuropathy HF at early age
Clinical history	HFpEF in the absence of hypertension

- Right ventricular hypertrophy on Echo
- Biatrial enlargement with normal ventricular chamber size on Echo
- Atrial septal or cardiac valve thickening on Echo
- Pericardial effusion on Echo
- Restrictive filling pattern on Echo

	Apical sparing pattern on Echo CMR with LGE
Alert signs	Intolerance to standard HF medications: ACE-I, ARB, beta-blockade, CCB, digitalis Symptomatic hypotension or resolution of hypertension in previously hypertensive patients

Yamamoto et al. Transthyretin cardiac amyloidosis: an update on diagnosis and treatment. *ESC Heart Failure 2019; 6: 1128-1139*

Clinical Cases

Case N1

- A 80 years male.
- Non smoker
- Medical History – Hypothyroidism
- Medical Therapy – Euthyrox
- 07.2016 – Complaining of **effort dyspnea**, no chest pain, (minimal neuropathy in legs).

Case N2

- A 78 years female.
- Non smoker
- Medical History – HTN, CAF, CKD, Hypothyroidism
- Medical Therapy – Aldactone, Fusid, Eliquis, Euthyrox, Vasodip
- 03.2018 – Complaining of **effort dyspnea** and weight gain. No chest pain. No neuropathy.

Clinical Cases - Physical examination

Case N1

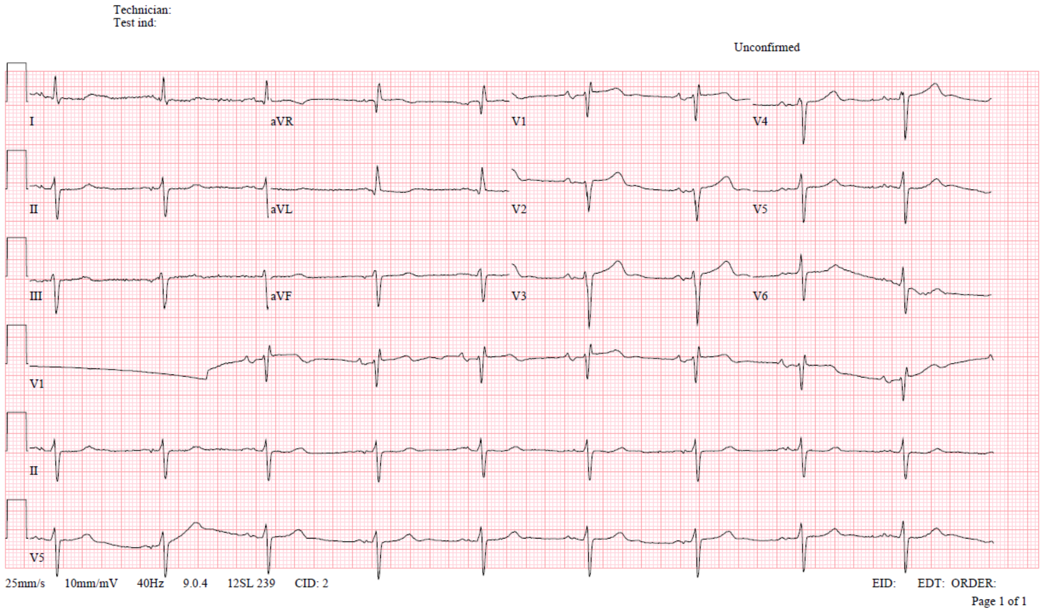
- Blood pressure – 120/80
- Pulse – 52 per min
- No fever
- Clear lungs
- Normal JVP
- Normal heart sounds without murmurs
- Mild **legs edema** (1+ Bilateral)

Case N2

- Blood pressure – 151/70
- Pulse – 67 per min
- No fever
- Clear lungs
- **Elevated JVP**
- Normal heart sounds with systolic murmur
- Mild **legs edema** (1+ Bilateral)

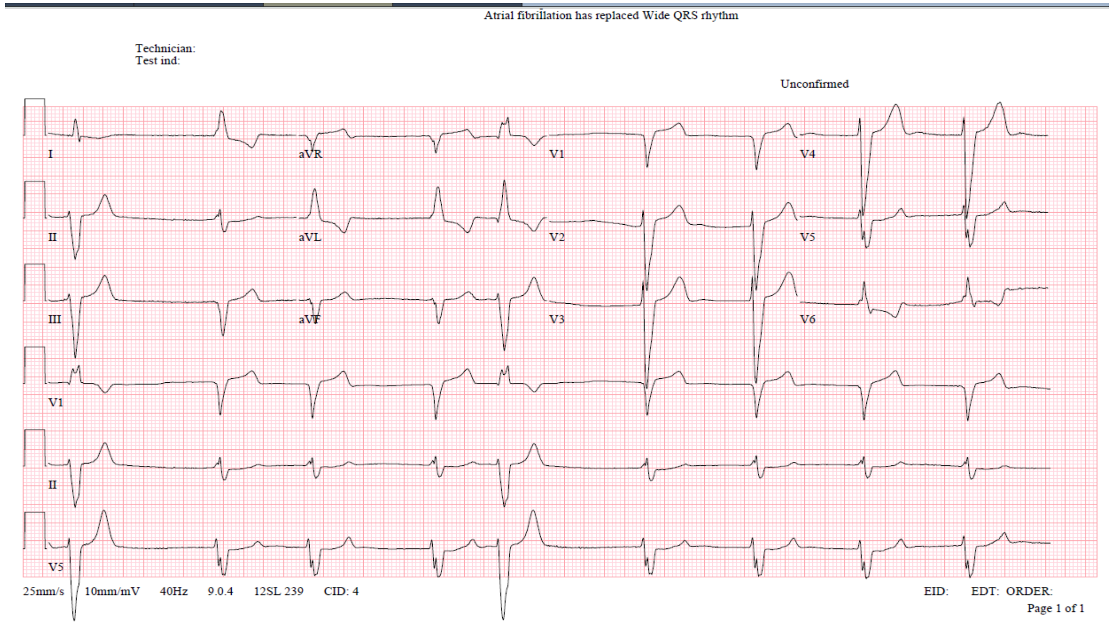
Clinical Case - ECG

Case N1



ECG – Sinus **Bradycardia 55/min**, **LAHB, ICRBBB**, normal voltage, abnormal progression of R waves

Case N2



ECG – Sinus **Bradycardia 54/min**, **LBBB**, normal voltage

Clinical Cases – Blood Tests

Case N1

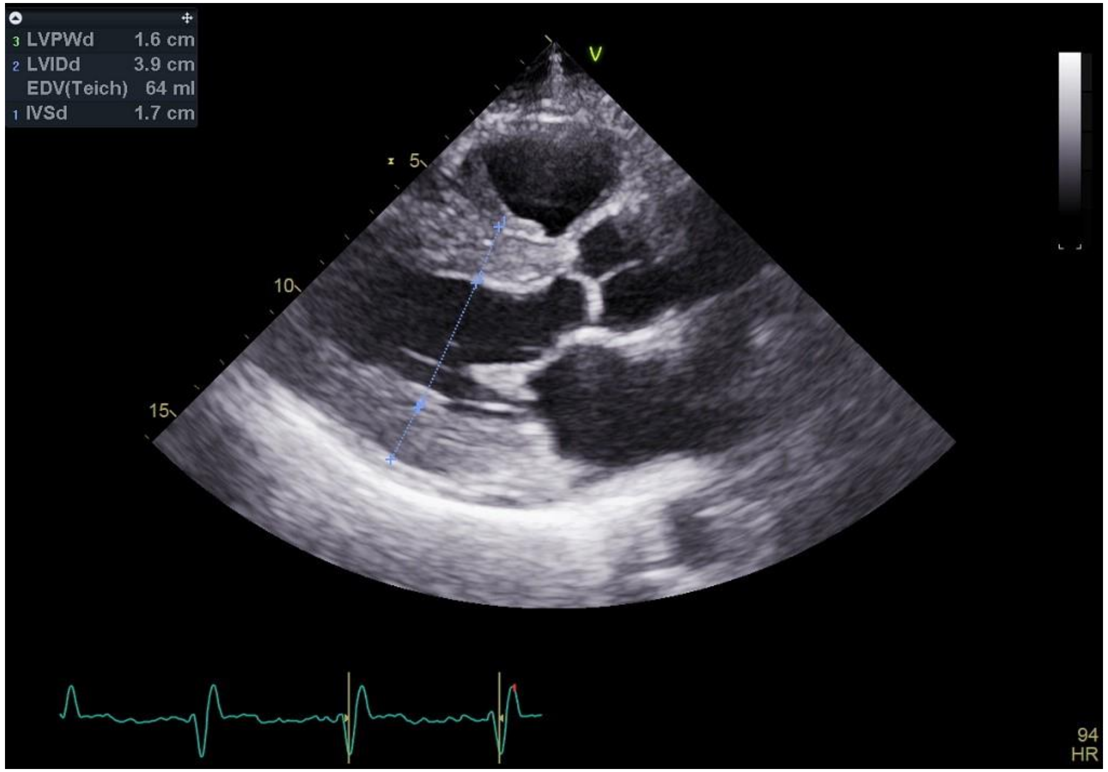
HB g/dL	14.6
WBC 10e3/mcgL	5.9
PLT 10e3/mcgL	176
CR mg/dL	0.95
TROPONIN I ng/ml (0-50)	**229**
NT pro BNP	**1578**

Case N2

HB g/dL	10
WBC 10e3/mcgL	6
PLT 10e3/mcgL	130
CR mg/dL	**1.7**
TROPONIN I ng/ml (0-50)	**70**
BNP	**150**

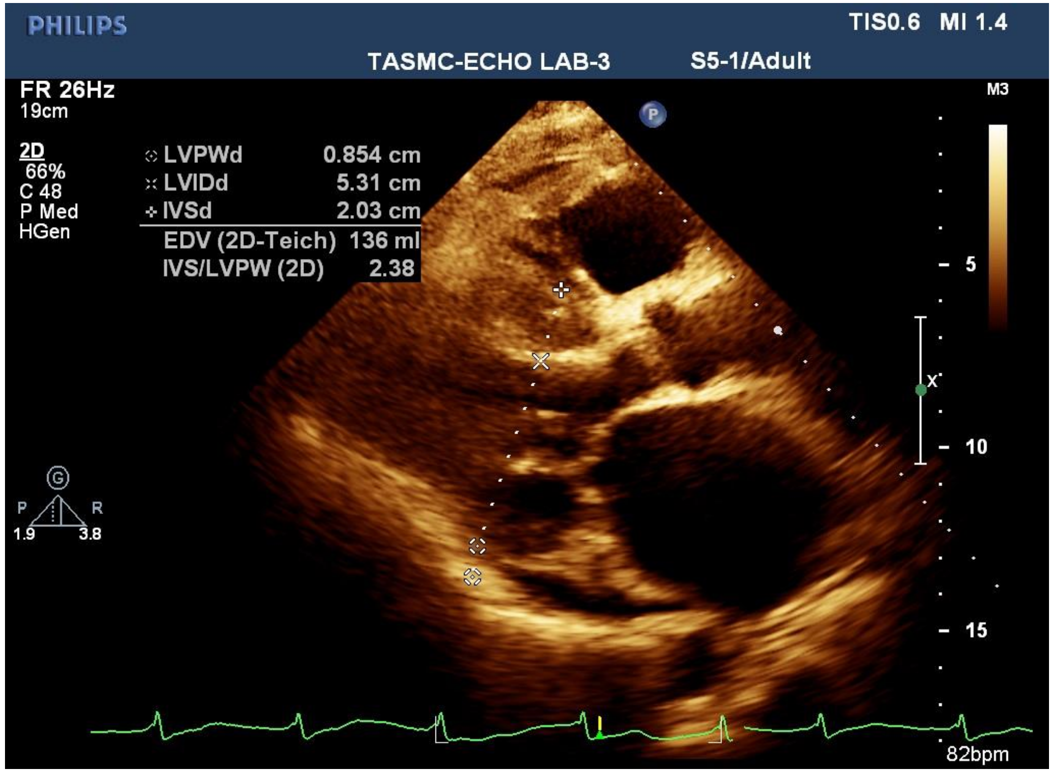
Clinical Cases – LVH

Case N1



- IVS 17mm

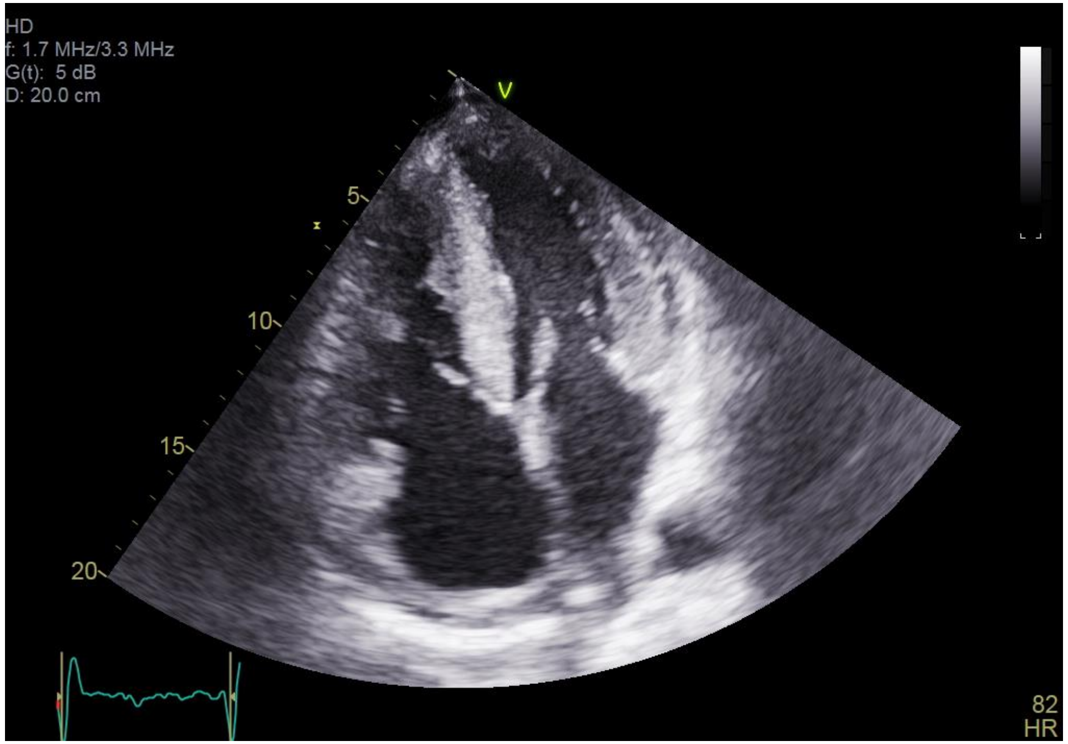
Case N2



- IVS 20mm

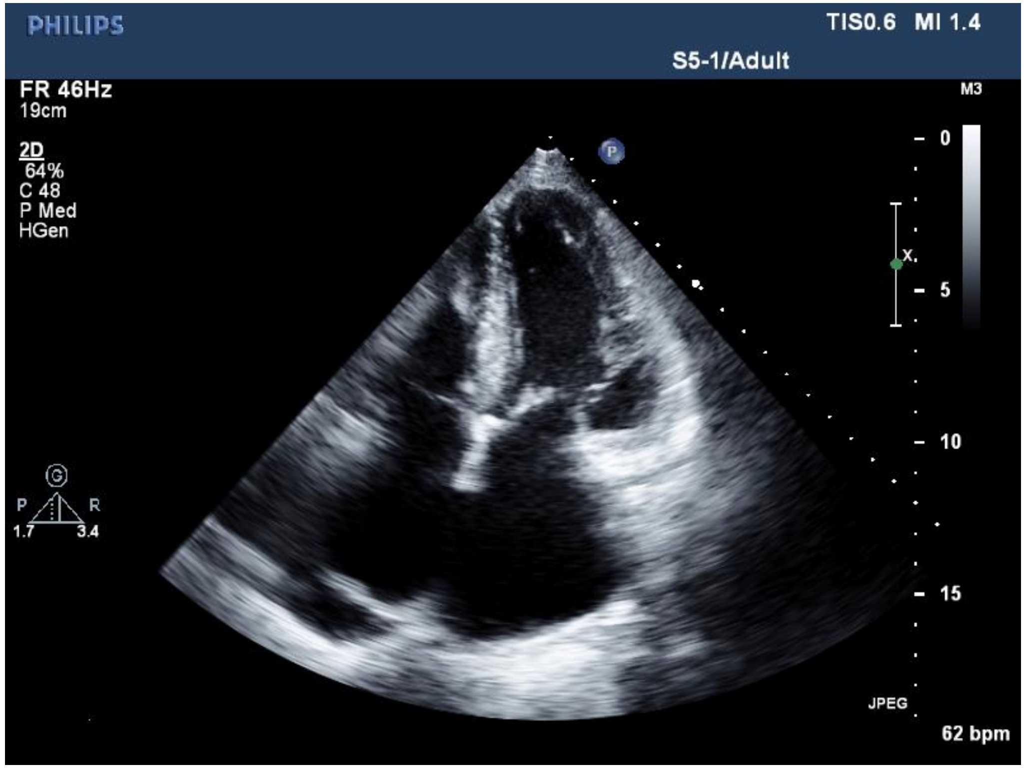
Clinical Cases - Echocardiography

Case N1



- Echogenic
- Biatrial enlargement (LAVI 50ml/m2)

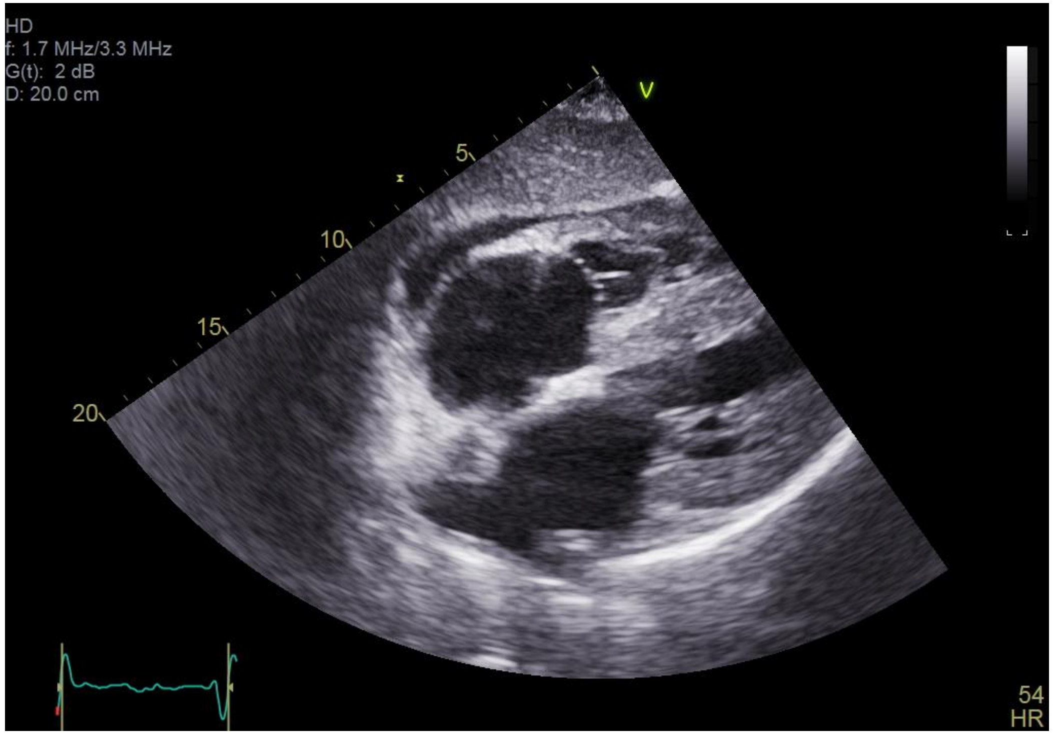
Case N2



- Echogenic
- Biatrial enlargement (LAVI 83ml/m2)

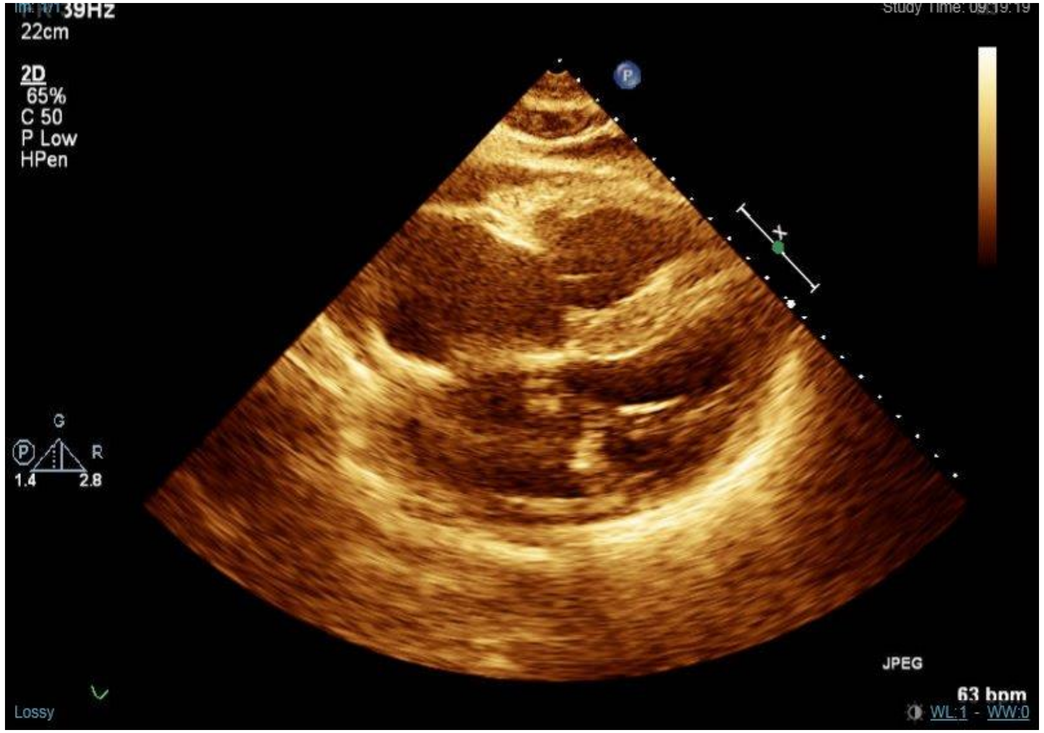
Clinical Cases - Echocardiography

Case N1



- Mild Pericardial Effusion

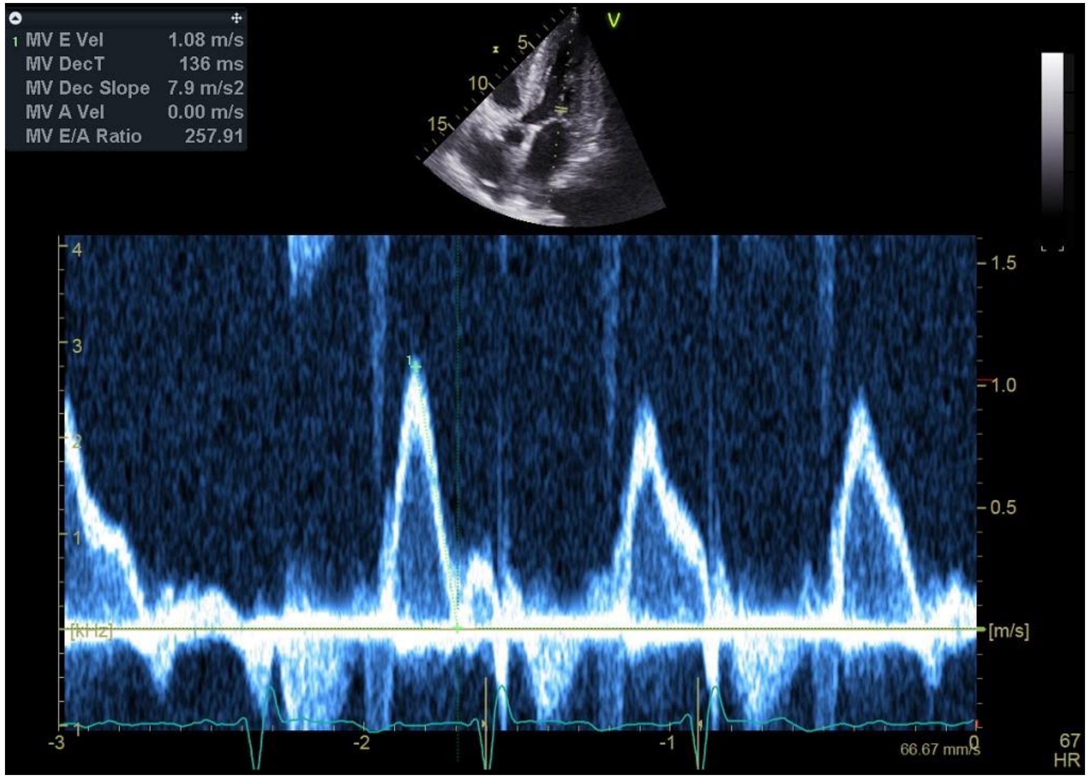
Case N2



- Mild Pericardial Effusion

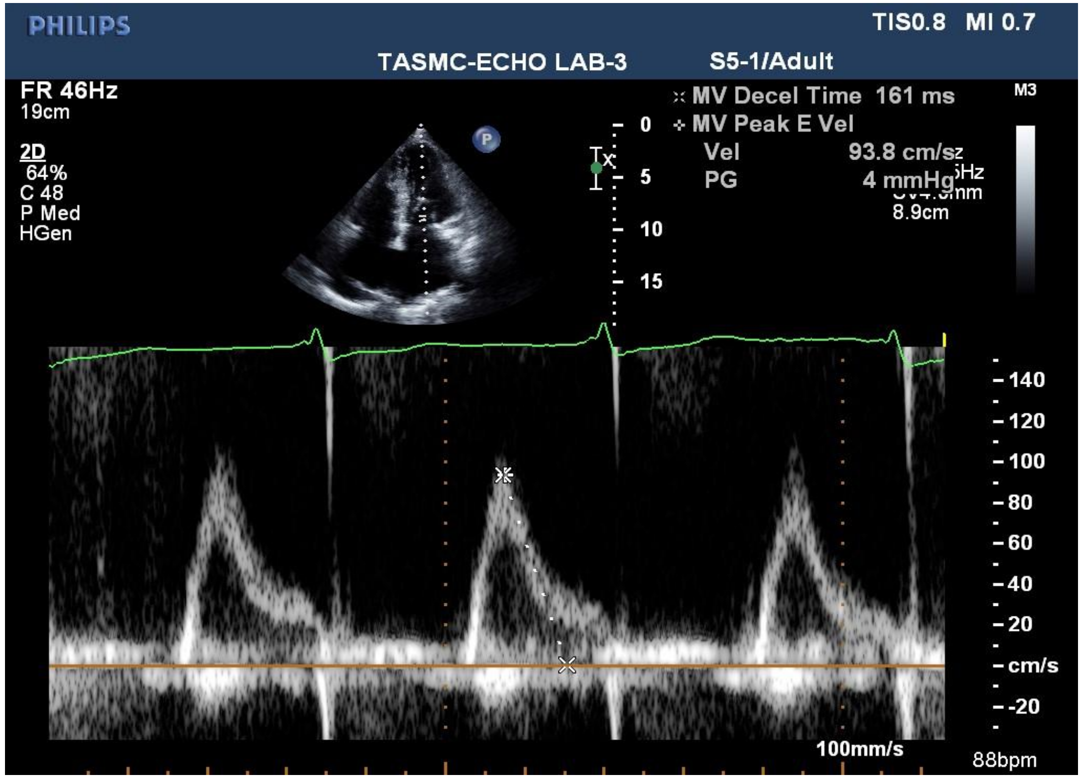
Clinical Cases – Restrictive pattern

Case N1



- Short DT (136) and Elevated E/A (2.5)

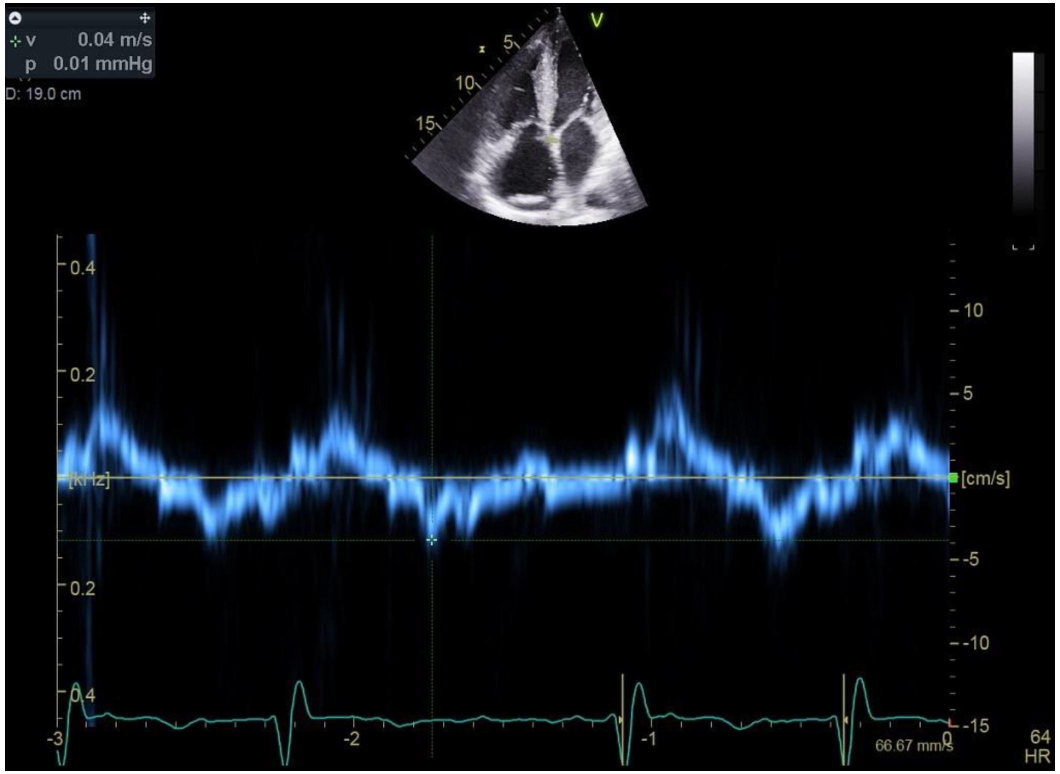
Case N2



- Short DT (161)

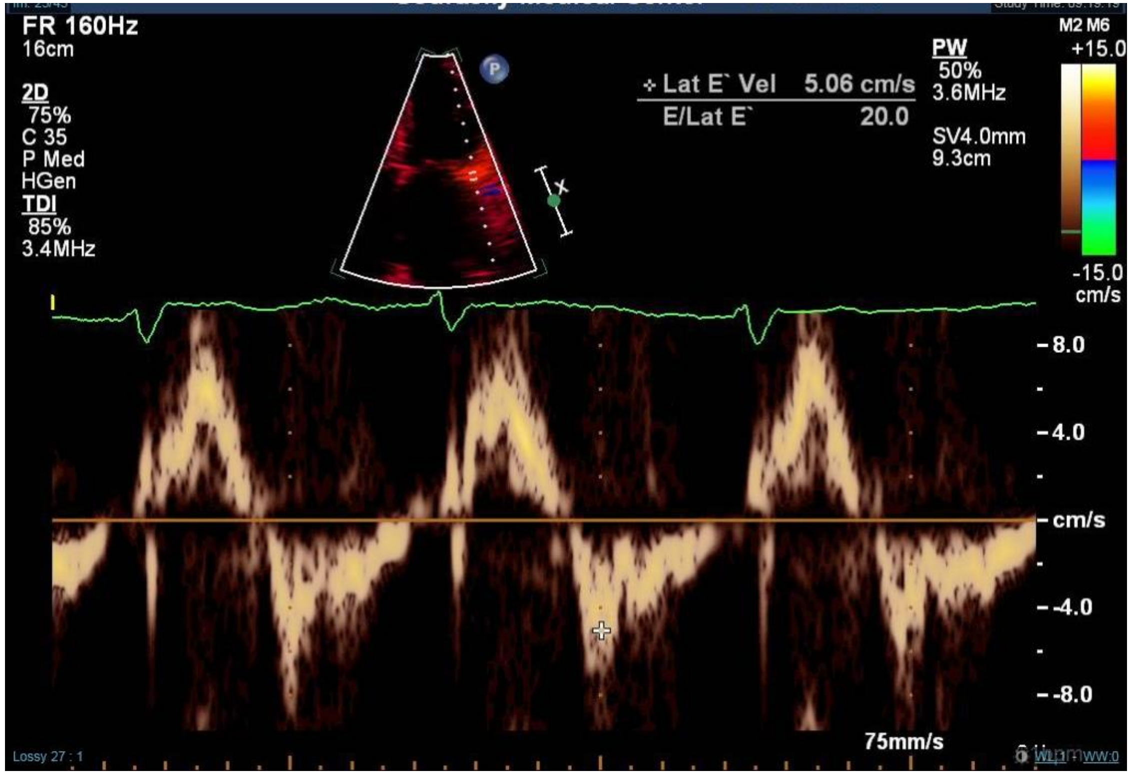
Clinical Cases – Elevated filling pressure

Case N1



- Reduced e' septal (4)
- Elevated E/e' (25)

Case N2



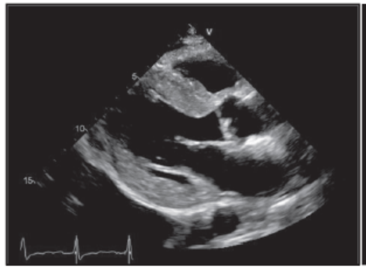
- Reduced e' lateral (5)
- Elevated E/e' (20)

ATTR Diagnosis

1. Case N1?

2. Case N2?

3. Both?



Increased LV wall thickness without dilated LV on echocardiogram

LVH>12mm

+ ≥1 of the following Red-flags

Category	Red-flags
Demographic	Elderly men over the age of 60 years
Family history	Progressive neuropathy
	HF at early age

Right ventricular hypertrophy on Echo

Biatrial enlargement with normal ventricular chamber size on Echo

Atrial septal or cardiac valve thickening on Echo

Pericardial effusion on Echo

Restrictive filling pattern on Echo

Apical sparing pattern on Echo

	Atrial fibrillation on ECG
	Right ventricular hypertrophy on Echo
	Biatrial enlargement with normal ventricular chamber size on Echo
	Atrial septal or cardiac valve thickening on Echo
	Pericardial effusion on Echo
	Restrictive filling pattern on Echo
	Apical sparing pattern on Echo
	CMR with LGE
Alert signs	Intolerance to standard HF medications: ACE-I, ARB, beta-blockade, CCB, digitalis
	Symptomatic hypotension or resolution of hypertension in previously hypertensive patients

Yamamoto et al. Transthyretin cardiac amyloidosis: an update on diagnosis and treatment. *ESC Heart Failure 2019; 6: 1128-1139*

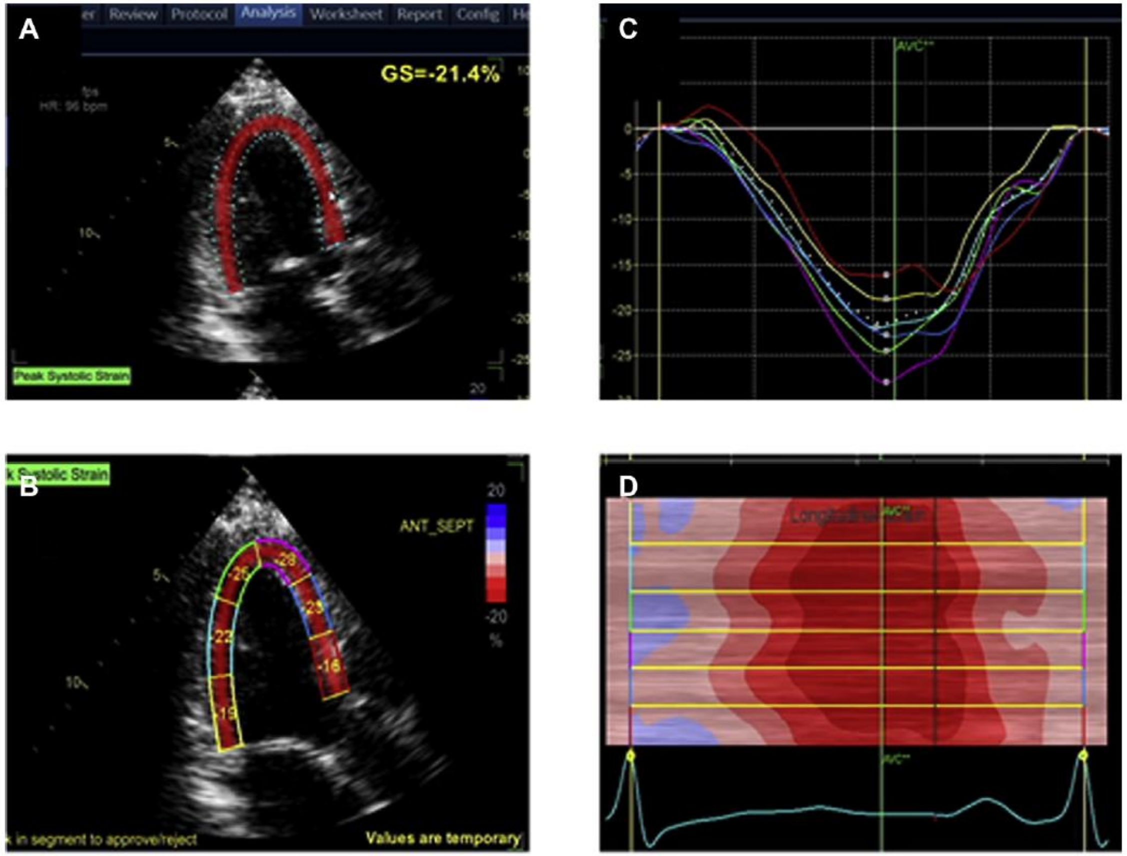
Which Echocardiographic parameters can support further diagnosis tests for ATTR-CM?

Echocardiography – Speckle-tracking

- LV deformation, or strain, unique features (“speckles”) within the heart can be identified.
- Groups of these speckles can then be tracked from frame to frame over multiple segments simultaneously allowing the calculation of strain and strain rate.

- Represents the percent change in LV fiber length from relaxed to contractile state.
- Strain measures LV deformation in longitudinal, radial, and circumferential directions.

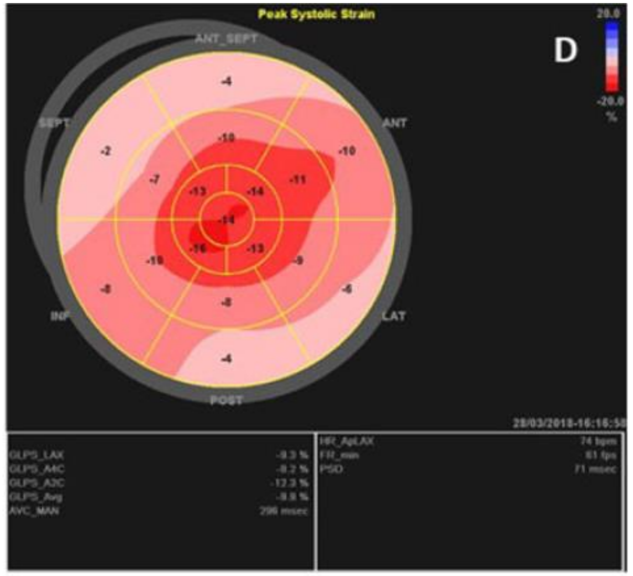
FIGURE 1 Display of Segmental and GLS



1. Santoro C, Arpino G, Esposito R, Lembo M, Paciolla I, Cardalesi C, Simone GD, Trimarco B, Placido SD, Galderisi M. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. European Heart Journal - Cardiovascular Imaging 2017;18(8):930-936.
2. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr. 2014;27(9):911–39
3. Liu et al. Strain Imaging in Cardio-Oncology. JACC cardiooncology 2020

2D Speckle Strain Echocardiography

- **Apical Sparing - Hallmark**.



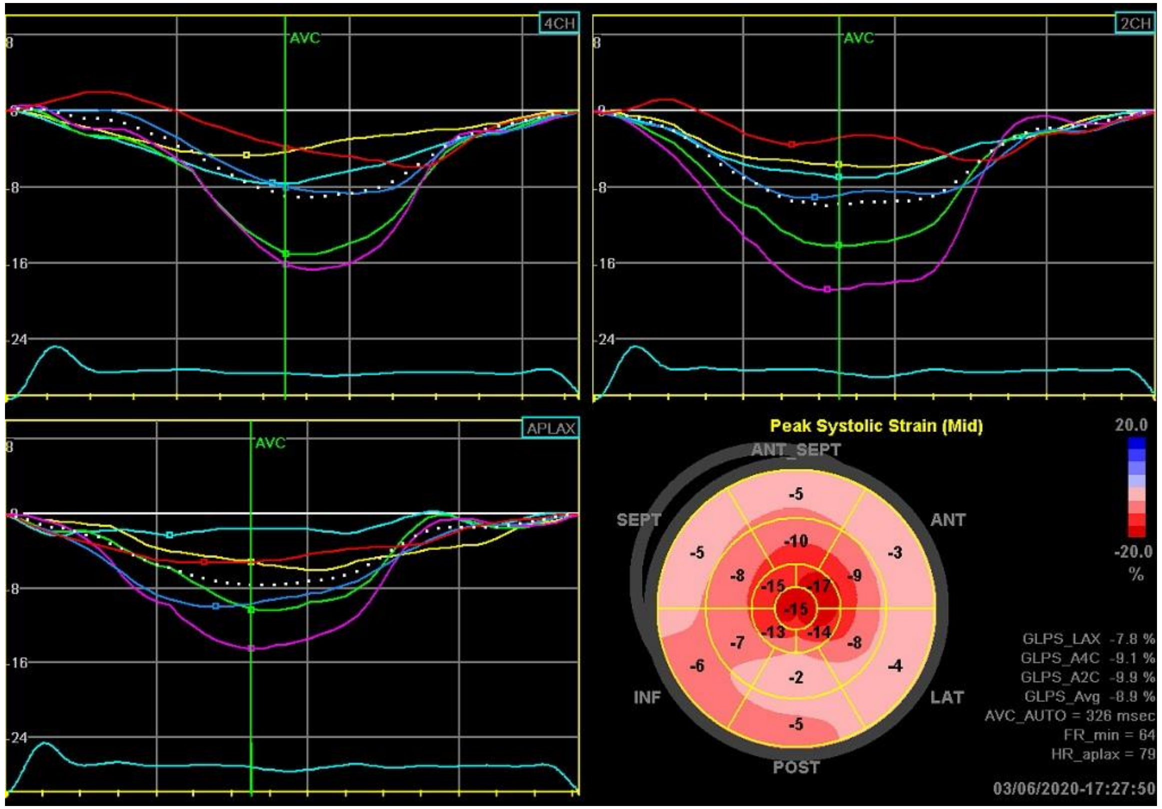
- The pathophysiological mechanism underlying this finding is unclear.
- <u>Suggested three main mechanisms:</u>
  1. Less amyloid deposition at the apex compared to the base
  2. The greater diversity of myocyte and matrix orientation at the apex compared to the base.
  3. A greater tendency towards myocyte apoptosis in the basal segments related to the LV outflow tract turbulent flow and higher wall stress.

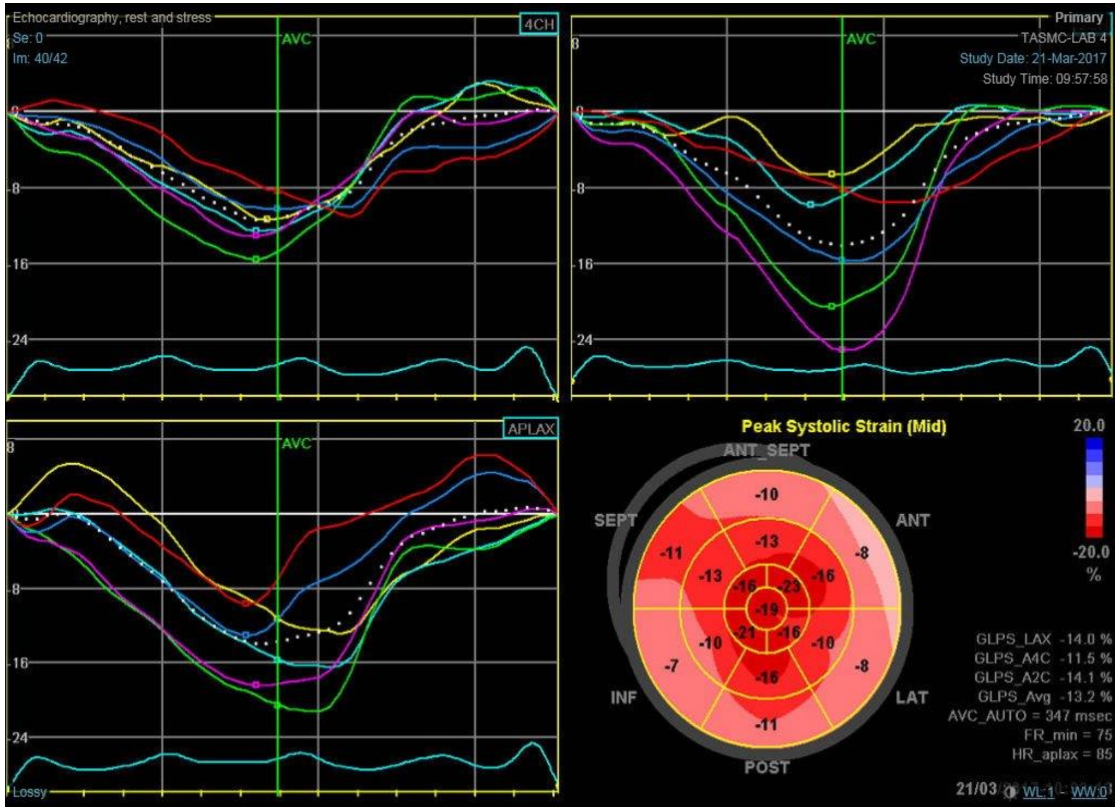
Jurcur et al. Multimodaliy imaging in cardiac amyloidosis: a primer for cardiologists. European Heart Journal. 2020*; 21: 833-844*

Apical Sparing

Case N1

Case N3





How we define apical sparing ?
Need for Cut-off values

Ventricular Structure and Function

Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy

Dan Liu, MD*; Kai Hu, MD*; Markus Niemann, MD; Sebastian Herrmann, MD; Maja Cikes, MD, PhD; Stefan Störk, MD, PhD; Philipp Daniel Gaudron, MD; Stefan Knop, MD; Georg Ertl, MD; Bart Bijnens, PhD; Frank Weidemann, MD

Background—Differentiation of cardiac amyloidosis (CA) from other causes of concentric left ventricular hypertrophy remains a clinical challenge, especially in patients with preserved ejection fraction at the early disease stages.

Methods and Results—Consecutive hypertrophic patients with CA, isolated arterial hypertension, Fabry disease, and Friedreich ataxia (n=25 per group) were investigated; 25 healthy volunteers served as a control group. Standard echocardiography was performed, and segmental longitudinal peak systolic strain (LSsys) in the septum was assessed by 2-dimensional speckle tracking imaging. Indices of left ventricular hypertrophy and ejection fraction were similar among all patient groups. Deceleration time of early filling was significantly lower in patients with CA (147±46 milliseconds) compared with those with isolated arterial hypertension, Fabry disease, or control subjects (all *P*<0.0125). Septal basal LSsys (−6±2%) was significantly lower in patients with CA compared with those with isolated arterial hypertension (−14±6%), Fabry disease (−12±5%), Friedreich ataxia (−16±2%), or control subjects (−17±3%; all *P*<0.001), whereas septal apical LSsys was similar among all patient groups and control subjects (all *P*>0.05). A data-driven cutoff value for the ratio of septal apical to basal LSsys ratio >2.1 differentiated CA from other causes of left ventricular hypertrophy (sensitivity, 88%; specificity, 85%; positive predictive value, 67%; negative predictive value, 96%). The prevalence of septal apical to basal LSsys ratio >2.1 plus deceleration time of early filling <200 milliseconds was 88% in CA but 0% in all other groups.

Conclusions—A systolic septal longitudinal base-to-apex strain gradient (septal apical to basal LSsys ratio >2.1), combined with a shortened diastolic deceleration time of early filling (deceleration time of early filling <200 milliseconds), aids in differentiating CA from other causes of concentric left ventricular hypertrophy. (***Circ Cardiovasc Imaging*. 2013;6:1066-1072.**)

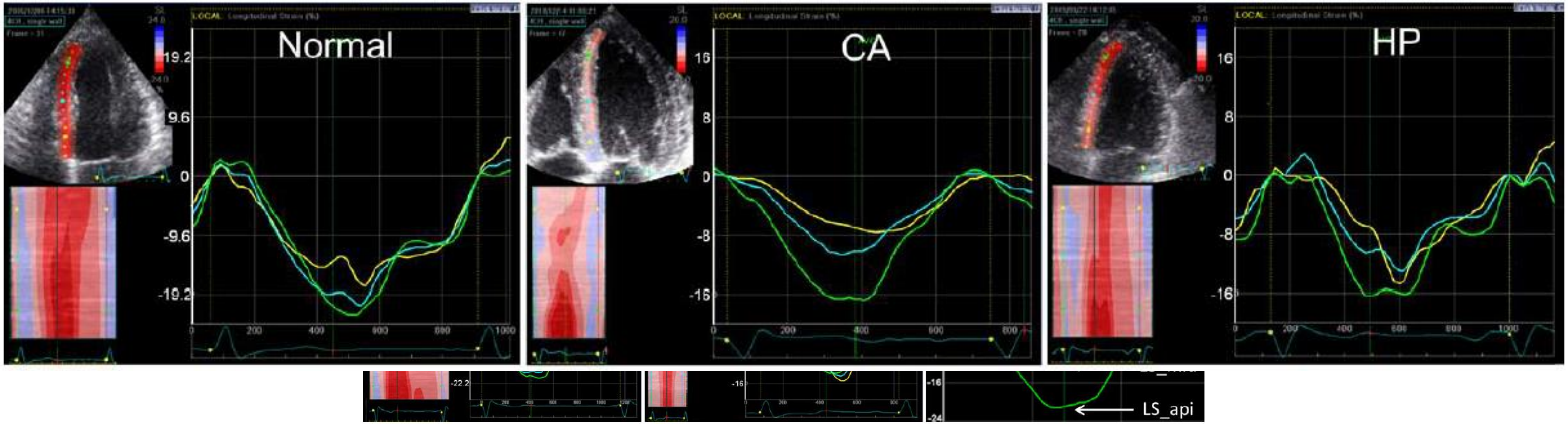
Table 1. Clinical and Echocardiographic Characteristics

	Control Subjects (n=25)	CA (n=25)	HP (n=25)	FD (n=25)	FA (n=25)
Age, y	63±7	66±10	67±13	61±8	25±10*†‡§
Male, n (%)	15 (60)	14 (56)	12 (48)	14 (56)	18 (72)
Interventricular septal wall thickness, mm	9±1	14±2*	14±2*	14±2*	13±1*
LV posterior wall thickness, mm	9±1	14±2*	13±2*	13±2*	13±1*
LV end-diastolic diameter, mm	50±4	42±6*	47±7	47±7	42±7*
LV ejection fraction, %	66±6	58±12	61±11	64±7	65±7
E, m/s	0.75±0.15	0.89±0.22	0.74±0.24	0.78±0.22	0.76±0.13
E/A	0.99±0.22	1.46±0.71	0.80±0.22†	1.15±0.53	1.54±0.45*‡
DT, ms	221±52	147±46*	250±59†	251±82†	183±52‡§
E/E′	10±4	23±10*	14±5†	18±7*	8±2†‡§
Diastolic pattern (normal/abnormal relaxation/pseudonormal/ restrictive)	11/14/0/0	0/6/14/5*	0/21/4/0†	1/12/10/2	22/3/0/0†

Liu et al. Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy. *Circ Cardiovasc Imaging*. 2013;6:1066-1072

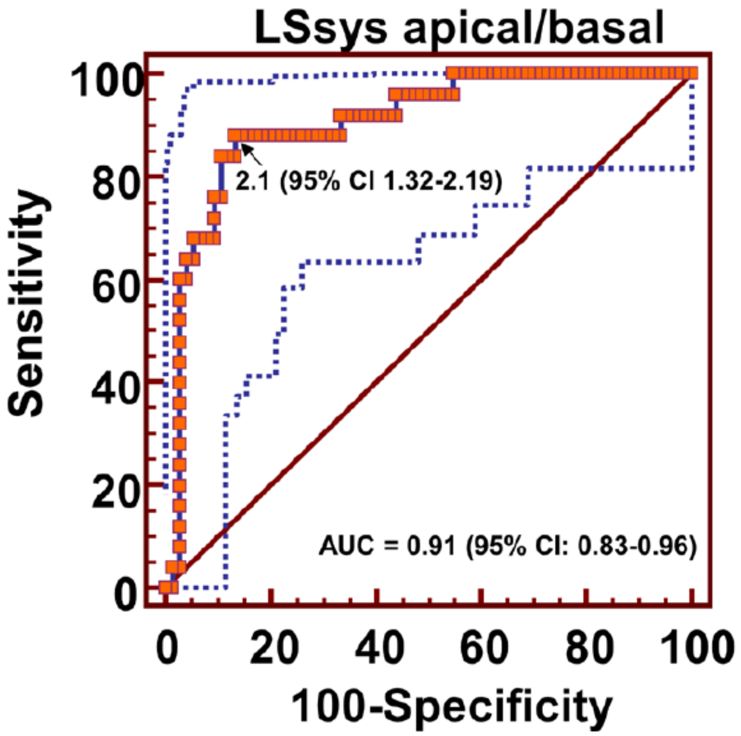
Table 2. Longitudinal Systolic Strain and Thickness in the Septum

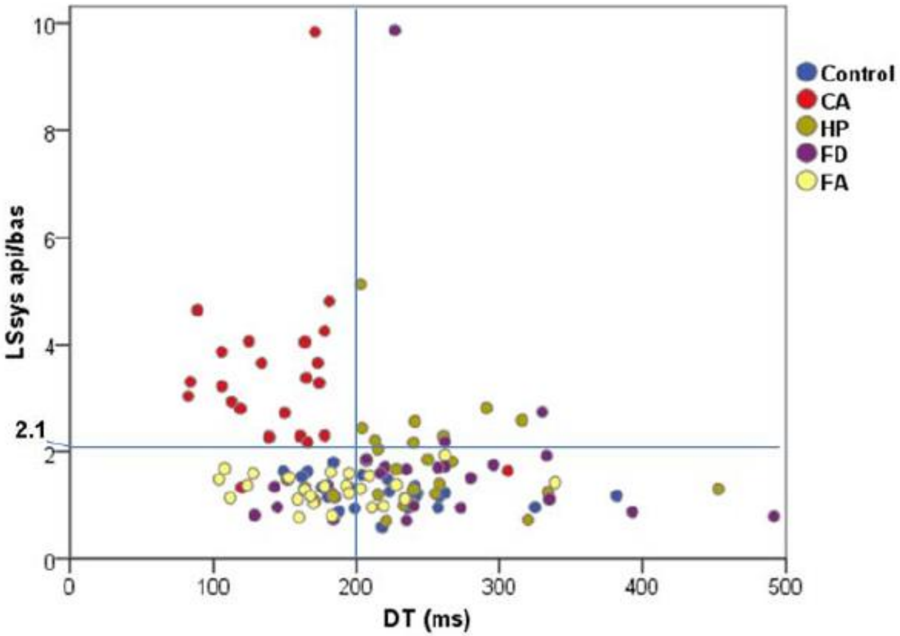
	Control (n=25)	CA (n=25)	HP (n=25)	FD (n=25)	FA (n=25)
Longitudinal peak systolic strain (LSsys), %					
Apical	−20±5	−20±7	−22±8	−17±7	−21±4
Mid	−18±4	−10±4*ll	−15±6†ll	−15±5†ll	−15±3†ll
Basal	−17±3ll	−6±2*ll#	−14±6†ll	−12±5*†ll	−16±2†§ll
$LSsys_{api/bas}$	1.2±0.3	3.3±1.6*	1.8±0.9†	1.7±1.8†	1.3±0.3†
Apical	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mid	10±1	16±2*ll	15±2*	17±4*	13±1*†§
Basal	10±1	15±2*ll	15±2*	16±5*	13±1*†‡§



Liu et al. Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy. *Circ Cardiovasc Imaging*. 2013;6:1066-1072

similar among all patient groups and control subjects (all *P*>0.05). A data-driven cutoff value for the ratio of septal apical to basal LSsys ratio >2.1 differentiated CA from other causes of left ventricular hypertrophy (sensitivity, 88%; specificity, 85%; positive predictive value, 67%; negative predictive value, 96%). The prevalence of septal apical to basal LSsys ratio >2.1 plus deceleration time of early filling <200 milliseconds was 88% in CA but 0% in all other groups.





Liu et al. Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy. *Circ Cardiovasc Imaging*. 2013;6:1066-1072

Cardiomyopathies

Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis

A Head-to-Head Comparison of Deformation and Nondeformation Parameters

Efstathios D. Pagourelias, MD, PhD; Oana Mirea, MD, PhD; Jürgen Duchenne, MSc; Johan Van Cleemput, MD, PhD; Michel Delforge, MD, PhD; Jan Bogaert, MD, PhD; Tatyana Kuznetsova, MD, PhD; Jens-Uwe Voigt, MD, PhD

***Background*—**A plethora of echo parameters has been suggested for distinguishing cardiac amyloidosis (CA) from other causes of myocardial thickening with, however, scarce data on their head-to-head comparison. This study aimed at comparing the diagnostic accuracy of various deformation and conventional echo parameters in differentiating CA from other hypertrophic substrates, especially in the gray zone of mild hypertrophy (maximum wall thickness ≤16 mm) or normal ejection fraction (EF).

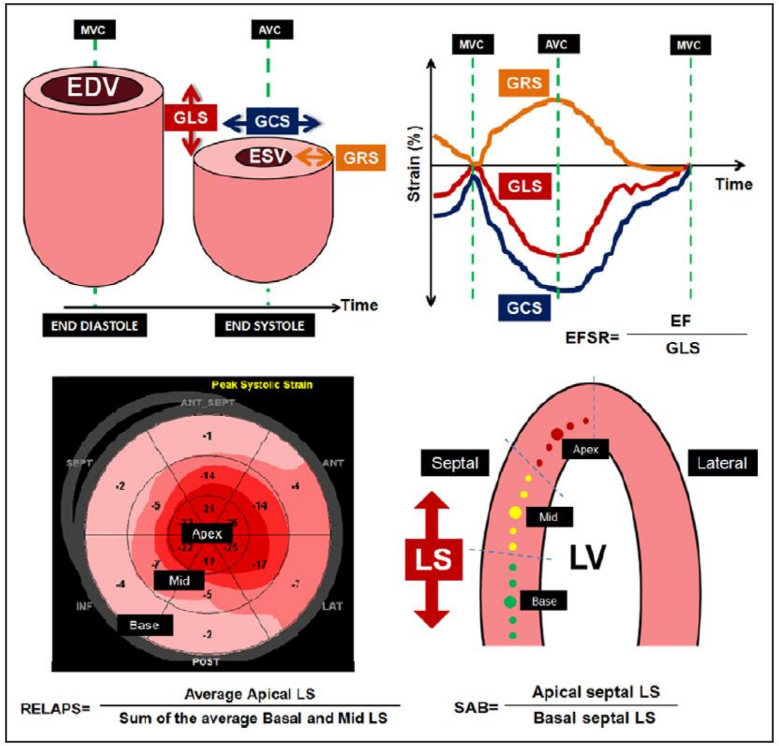
***Methods and Results*—**We included 100 subjects, of which 40 were patients with newly diagnosed, biopsy-proven CA (65.5±10.8 years, 65% male, 62.5% amyloidosis light chain [AL] type), 40 patients with hypertrophic cardiomyopathy matched for demographics and maximum wall thickness (60.1±14.8 years, 85% male), and 20 hypertensives with prominent myocardial remodeling. Quantifiable conventional morphological and functional parameters along with multidimensional strain and strain-derived ratios indices, previously suggested to diagnose CA, were analyzed. EF global longitudinal strain ratio showed the best performance to discriminate CA (area under the curve, 0.95; 95% confidence intervals, 0.89–0.98; $P<0.00005$). Traditional echo indices showed overall low sensitivities and high specificities (among them myocardial contraction fraction ratio had the highest area under the curve, 0.80; 95% confidence intervals, 0.7–0.87; $P<0.0001$). In the challenging subgroups (maximum wall thickness ≤16 mm and EF>55%), EF global longitudinal strain ratio remained the best predicting parameter of CA diagnosis (multiple logistic regression models $P<0.00005$ and $P=0.0002$, respectively) independent of the CA type.

***Conclusions*—**Our study demonstrated that in patients with thickened hearts, EF global longitudinal strain ratio has the best accuracy in detecting CA, even among the most "challenging" patient subgroups as those with mild hypertrophy and normal EF. **(*Circ Cardiovasc Imaging*. 2017;10:e005588. DOI: 10.1161/CIRCIMAGING.116.005588.)**

Table 2. Echocardiographic Morphological and Functional Parameters

	CA Group, n=40	HCM Group, n=40	Hypertensive Group, n=20	*P* value
Standard morphology and systolic function parameters				
IVSd, mm	17.6±3.9*	18.2±3.8†	13±1.5	<0.0005‡
MWT, mm	18±3.8*	18.2±3.8†	13±1.5	<0.0005‡
LVEDD, mm	41.3±6.1*,§	44.2±5.4†	53.4±3.8	<0.0005‡
PWTd, mm	15±3.2§	10.9±2.4	11.5±0.9	<0.0005‡
EF, %	56±12.7§	65±8.2	61.2±9.1	0.001‡
LAVI, mL/m^2	41±17	36.6±20.1	33±6.4	0.202
LVMI, g/m^2	163.1±53.2§	129.2±35.8	139.1±15.7	0.001‡
Eccentricity index	1.1±0.2*,§	1.7±0.4	1.1±0.1	<0.0005‡
RWT	0.77±0.2	0.5±0.12	0.43±0.05	<0.0005‡
MCF	0.26±0.14*,§	0.36±0.09†	0.46±0.09	<0.0005‡
Diastolic function				
E/A	2±1.4*,§	1.1±0.45	0.86±0.23	<0.0005‡
E/E′ lat	18.4±11*,§	8±3.4	7.7±3.0	<0.0005‡
DT, ms	188.3±51§	224.8±64†	185.3±47.3	0.007‡
Diast. Dysf. Grade				
I	13 (32.5%)	23 (57.5%)	13 (65%)	<0.0005‡
II	8 (20%)	14 (35%)	7 (35%)	
III	19 (47.5%)	3 (7.5%)		
Deformation parameters				
GLS, %	−11±4.1*,§	−17.9±2.7	−19.2±2.3	<0.0005‡
GCS, %	−16.3±5.5*,§	−22.1±4.9	−24.7±3.9	<0.0005‡
GRS, %	8.4±4.1*,§	14.4±4.8	14.1±5.4	<0.0005‡
TORSION, °	9.8±3.7*	9.8±2.4	12±5.7	0.01‡

Pagourelias et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017



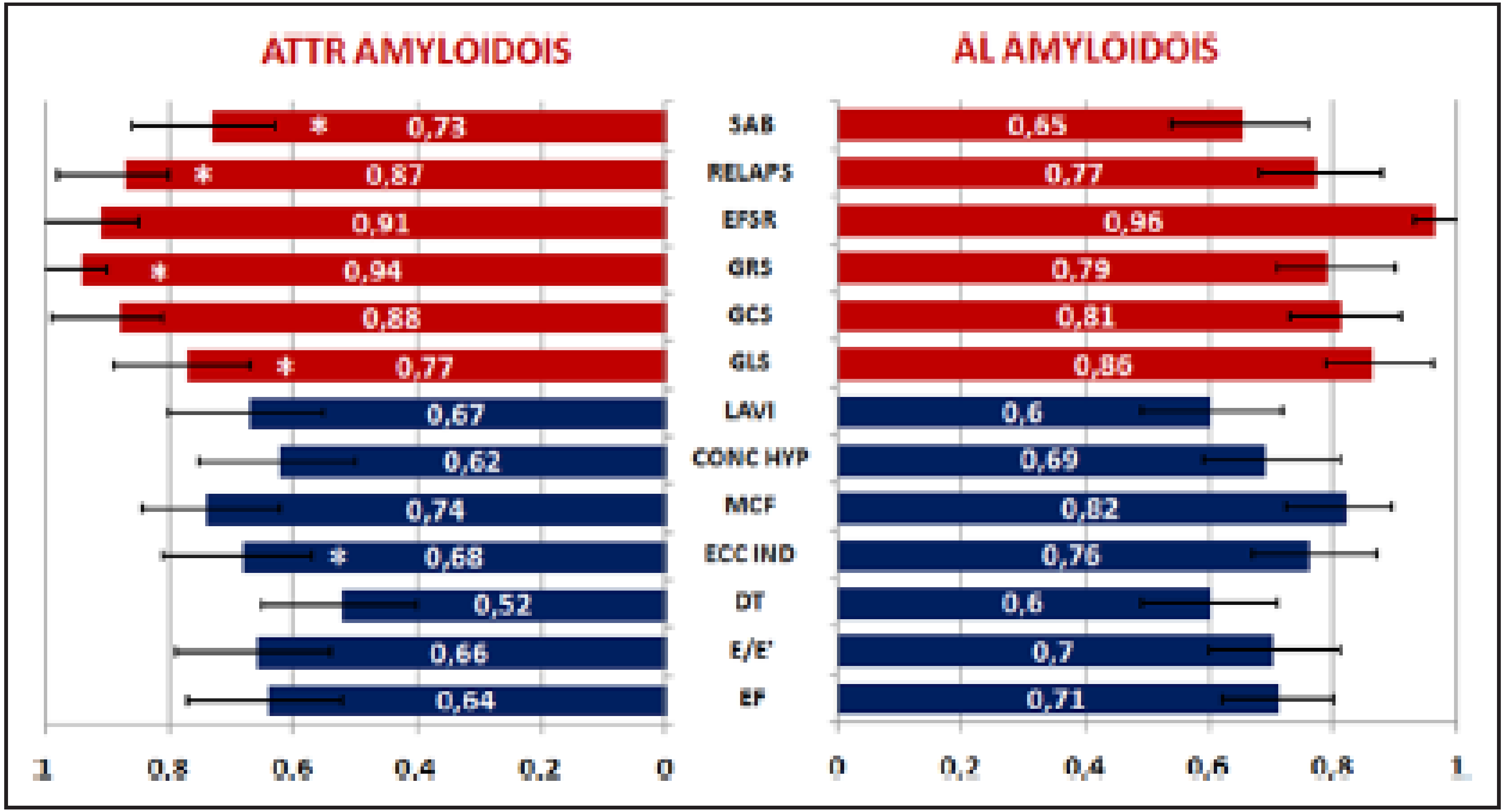
$$\text{RELAPS}=\frac{\text{Average Apical LS}}{\text{Sum of the average Basal and Mid LS}}\qquad \text{SAB}=\frac{\text{Apical septal LS}}{\text{Basal septal LS}}$$

$$\text{EFSR}=\frac{\text{EF}}{\text{GLS}}$$

Table 4. Bootstrapped ROC Curve Characteristics and Cut-Off Points of Deformation Echo Parameters for Differential Diagnosis of Amyloidosis

Variable	AUC	95% CI	*P* Value	Cutoff	95% CI	Sens, %	95% CI	Spec, %	95% CI	+LR	95% CI	−LR	95% CI
GLS, %	0.85	0.77–0.89	<0.0001	>−15.1	>−16.7 to >−13.1	87.5	73–96	71.7	59–83	3.09	2–4.7	0.17	0.08–0.4
GCS, %	0.83	0.73–0.90	<0.0001	<−18.3	>−22.2 to >−17.4	86.2	68.3–96.1	57.1	43.2–70.3	2.01	1.4–2.8	0.24	0.09–0.6
GRS, %	0.82	0.72–0.90	<0.0001	≤9.01	≤5.33 to ≤9.78	65.5	45.7–82.1	89.3	78–96	6.1	2.7–13.6	0.39	0.2–0.6
EFSR	0.95	0.89–0.984	<0.0001	>4.1	>3.6 to >4.1	89.7	75.8–97.1	91.7	81.6–97.2	10.8	4.6–25.1	0.11	0.04–0.3
RELAPS	0.78	0.68–0.86	<0.0001	>0.87	>0.79 to >1	62.5	43.8–77.3	85	73.4–92.9	4.17	2.2–8	0.44	0.3–0.7
				>1.0*	…	37.5	22.7–54.2	93.3	83.8–98.2	5.63	2–15.7	0.67	0.5–0.9
SAB	0.67	0.57–0.76	0.0024	>3.1	>1.7 to >3.7	47.5	31.5–63.9	86.7	75.4–94.1	3.56	1.7–7.3	0.61	0.4–0.8
				>2.1*	…	65	48.3–79.4	53	41.6–67.9	1.44	1–2.1	0.64	0.4–1.0

Pagourelias et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017

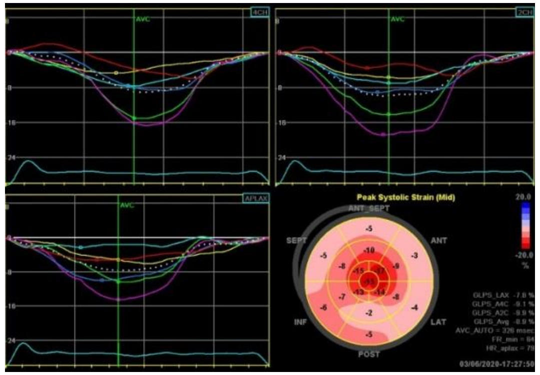


Pagourelias et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017

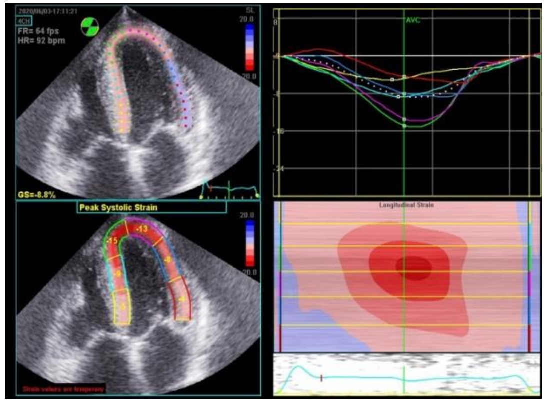
Clinical Cases – Speckle Strain

Case N1

- RELAPS – 14.8 / 11.9 = **1.2** (>1)



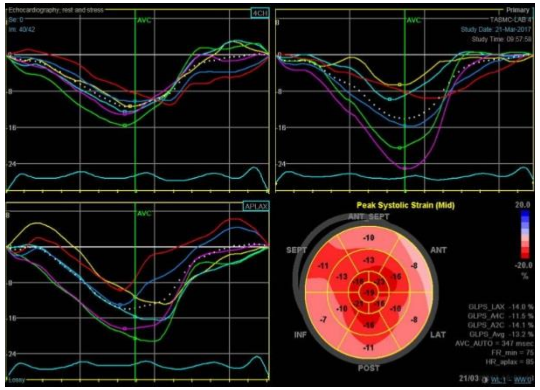
- SAB – 15 / 5 = **3** (>2.1)



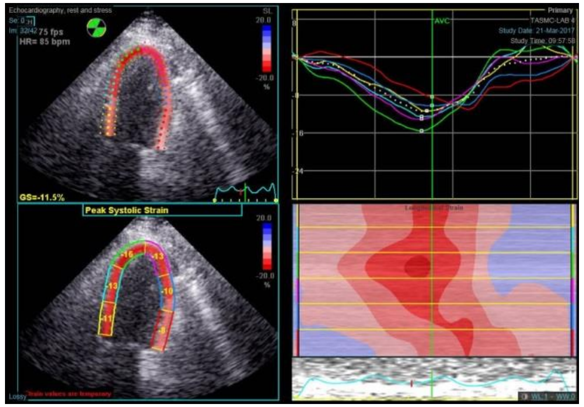
- EFSR – 40 / 8.9 = **4.5** (>4.1)

Case N2

- RELAPS – 14.4 / 21.16 = **0.68** (>1)



- SAB – 16 / 11 = **1.45** (>2.1)



- EFSR – 55 / 13.2 = **4.16** (>4.1)

Clinical Case 1 – Further workup

- Summary – IVS 17, DT 136, E/A 2.5, E/e’ 25, SAB > 2.1 and EF/GLS > 4.1

- Cardiac MRI – Diffuse LGE
- EMB – Positive Congo red
- Positive PYP scan – grade III
- Negative bone marrow
- Negative genetic test

- Diagnosis of **ATTRwt CM**

Summary

FIGURE 1 Further Evidence to Support a Suspicion of ATTR-CM

"Red flags" for ATTR-CM

- Reduction in longitudinal strain with apical sparing
- Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on EKG)
- Atrioventricular block, in the presence of increased left ventricular wall thickness
- Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum and right ventricular free wall
- Marked extracellular volume expansion, abnormal nulling time for the myocardium or diffuse late gadolinium enhancement on CMR
- Symptoms of polyneuropathy and / or dysautonomia
- History of bilateral carpal tunnel syndrome
- Mild increase in troponin levels on repeated occasions

TABLE 2 Noninvasive Testing Features Suggestive of ATTR-CM

Electrocardiography
Low voltages in context of increased echocardiographic wall thickness
Caution: low voltage seen in <50% of cases with ATTR-CM (18)
Echocardiography
1. Increased LV wall thickness with/without right ventricular wall thickness
2. Apical sparing regional longitudinal strain pattern (>2:1 ratio) or increased LVEF to global longitudinal strain ratio (>4)

Witteles et al. JACC: HEART FAILURE 2019, Ruberg et al. JACC. 0 1 9 : 2 8 7 2 – 9 1