My Approach to Echocardiography for the Diagnosis of Amyloidosis

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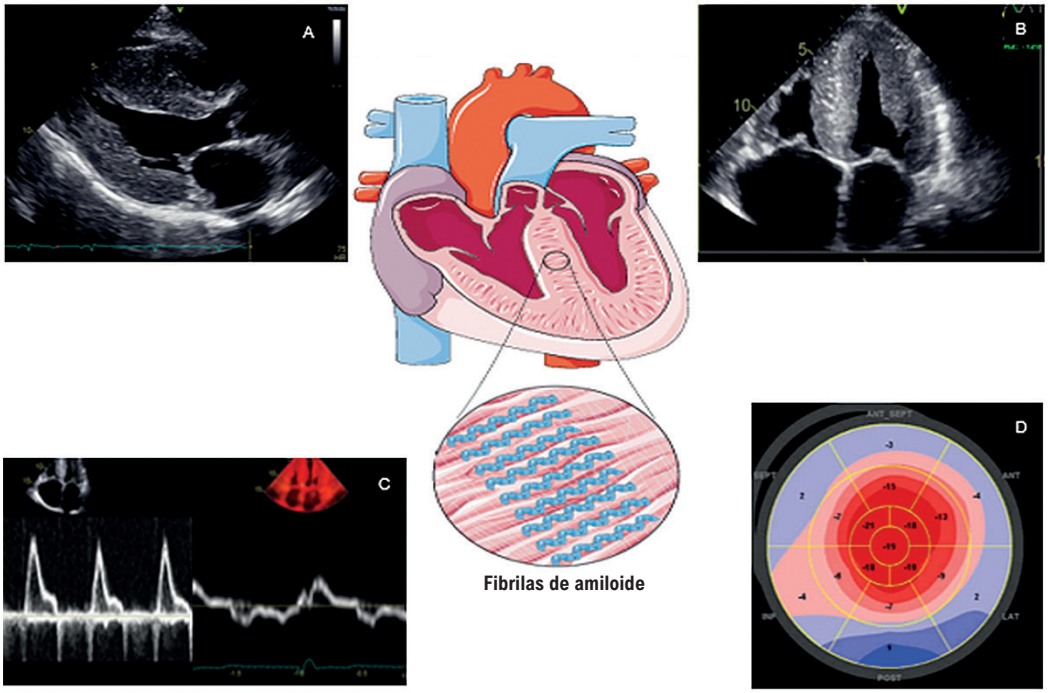
Central Illustration: My Approach to Echocardiography for the Diagnosis of Amyloidosis



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Classic echocardiographic findings of CA resulting from the deposition of amyloid fibrils in the heart: (A and B) normal-sized ventricles, enlarged atria, increased myocardial thickness with a granular sparkling appearance; thickening of the interatrial septum, atrial walls, and heart valves with mild pericardial effusion; (C) restrictive pattern of mitral inflow, tissue Doppler with reduced medial and lateral mitral annulus velocities, which may present the "5-5-5 sign" (e', a', s' wave velocity < 5 cm/s); (D) bull's eye image showing apical sparing: reduced myocardial deformation in the basal and middle segments and preserved deformation in the apical segments. (Source: the author).

Keywords

Amyloidosis; Echocardiography; Global Longitudinal Strain

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Abstract

Cardiac amyloidosis (CA) is a multisystemic, infiltrative disease characterized by the deposition of insoluble proteins, known as amyloid fibrils, in the interstitial space of different tissues, such as the heart, nervous system, gastrointestinal tract, and eyes. In the heart, it is characterized by a progressive myocardial thickening, evolving into a restrictive pattern. CA is being diagnosed with increasing frequency, probably due to the greater dissemination of related information and advances in diagnostic methods and therapies that modify its

course. Echocardiography is the first-line examination for diagnostic screening, monitoring, and differentiation from phenocopies.

Introduction

In cardiac amyloidosis (CA), deposition of insoluble amyloid fibrils in the interstitial space results in thickening of the ventricular and atrial walls and interatrial septum, in addition to infiltration of the conduction system. It can evolve into restrictive cardiomyopathy and arrhythmias.[1-4] Of the more than 30 types of amyloid fibrils, 2 are responsible for 98% of CA cases: immunoglobulin light chain, which is related to monoclonal gammopathy or multiple myeloma, and transthyretin, which is related to transthyretin amyloidosis and can be hereditary or wild-type.[1]

When there is an unexplained increase ≥ 12 mm in left ventricular (LV) myocardial thickness, associated with 1 or more of the signs in Table 1, CA must be considered.

Echocardiographic findings correlated with "stiff heart" syndrome were published in the mid-1970s. Since then, echocardiography has become a fundamental tool for diagnosing and monitoring these patients.[3]

The echocardiographic patterns of CA depend on the type of cardiac involvement. In the initial phase of the disease, changes are more discreet, characterized by increased LV wall thickness (12-15 mm), mild diastolic dysfunction, and preserved ejection fraction (EF).[3]

As the disease progresses to the intermediate stage, signs of increased myocardial thickness ("hypertrophic" stage) are observed, characterized by marked thickening of the LV wall (> 15 mm), right ventricle (RV) (≥ 5 mm), interatrial septum (> 5 mm), and heart valves (> 5 mm), in addition to biatrial dilation and progression of diastolic dysfunction to a restrictive pattern, including mild pericardial effusion but preserved EF.[3]

In the advanced stage of the disease, all forms converge into infiltrative restrictive cardiomyopathy associated with biventricular systolic dysfunction and heart failure symptoms refractory to medical therapy.[3]

Main echocardiographic findings

Unexplained increase in LV wall thickness

The most striking feature of CA is the unexplained increase in LV wall thickness (≥ 12 mm) (Figure 1). The increased myocardial thickness in CA is, in reality, a 'pseudohypertrophy' caused by the progressive infiltration of amyloid protein into the extracellular space. Therefore, the term "hypertrophy" is incorrectly applied in this case, since the condition is due to extracellular deposition of amyloid protein and not to an increase in cardiomyocytes (which occurs as a physiological mechanism during intense physical activity or post-loading).[1,4,5],

Table 1 – Summary of red flags for suspected CA[4]

HF with preserved EF in patients aged > 60 years (ATTR)
Low-flow/low-gradient aortic stenosis, increased wall thickness at age > 60 years (ATTR)
Unexplained HF with hepatomegaly, macroglossia, and periorbital purpura (AL)
Men aged > 50 years with bilateral carpal tunnel syndrome (ATTR)
Spinal stenosis and spontaneous biceps rupture (ATTR)
Unexplained HF associated with sensorimotor polyneuropathy and neuropathic pain of unknown origin (ATTR)
Autonomic dysfunction, orthostatic hypotension, and erectile dysfunction (ATTR/AL)
Hypotension or normotension in previously hypertensive patients (ATTR/AL)
Vitreous opacity and corneal dystrophy
BNP disproportionately elevated to HF stage
Persistently elevated troponin level
ECG with low voltage, pseudoinfarction pattern and AV conduction disturbances
Discrepancy between ECG findings (no signs of LV overload) and imaging methods with increased myocardial thickness).

AL: immunoglobulin light chain amyloidosis; ATTR: transthyretin amyloidosis; HF: heart failure; EF: ejection fraction; AS: aortic stenosis; BNP: brain natriuretic peptide; ECG: electrocardiogram; LV: left ventricle.

Amyloid protein is deposited during the early stages, predominantly in the basal segments but subsequently progressing to apical segments of the LV. The posterobasal portion of the interventricular septum is the region of initial deposition, which mimics hypertrophic cardiomyopathy, making differential diagnosis challenging in some cases. As the disease progresses, deposition becomes more widespread and ventricular walls thickness increases in a symmetrical and concentric pattern, with a relative wall thickness > 0.42.[1-6] Although the increased thickness is concentric and diffuse, some cases may present with an asymmetric pattern, thus asymmetry does not exclude CA.[1-3]

The myocardium of these patients often has a granular, "sparkling" appearance, resulting from the greater echogenicity of the amyloid protein in relation to the surrounding myocardium. Since shifting from fundamental to harmonic imagery can confuse this phenotype, the fundamental image is preferable to the harmonic image for correct identification.[1] Although it is considered a very suggestive finding, it is not a pathognomonic sign of CA, since its specificity is 81% and its sensitivity is 36% and the phenomenon can also be found in hypertrophic cardiomyopathy, chronic renal failure, and other storage diseases.[1,2,5]

LV thickness and mass are greater in wild-type ATTR than other forms of CA, probably due to longer accumulation of amyloid protein than in immunoglobulin light chain amyloidosis or hereditary ATTR. Patients with immunoglobulin light chain amyloidosis may present a favorable clinical picture when there is a slight increase in myocardial thickness, which is explained by the cardiotoxic effect of light chain proteins. However, these subtypes cannot be differentiated by echocardiographic findings (Figure 1)..[1,2]

RV free wall thickness ≥ 5 mm

The RV is frequently affected, especially in advanced stages of the disease, which is also suggestive of infiltrative cardiomyopathy.[2] It must be measured in the subcostal plane at end diastole.[6] In addition to RV thickness, systolic function parameters must be analyzed, such as tricuspid annular displacement velocity (s' wave), tricuspid annular plane systolic excursion, and fractional area change (Figure 2). Dysfunction indicates a worse prognosis.[2,5]

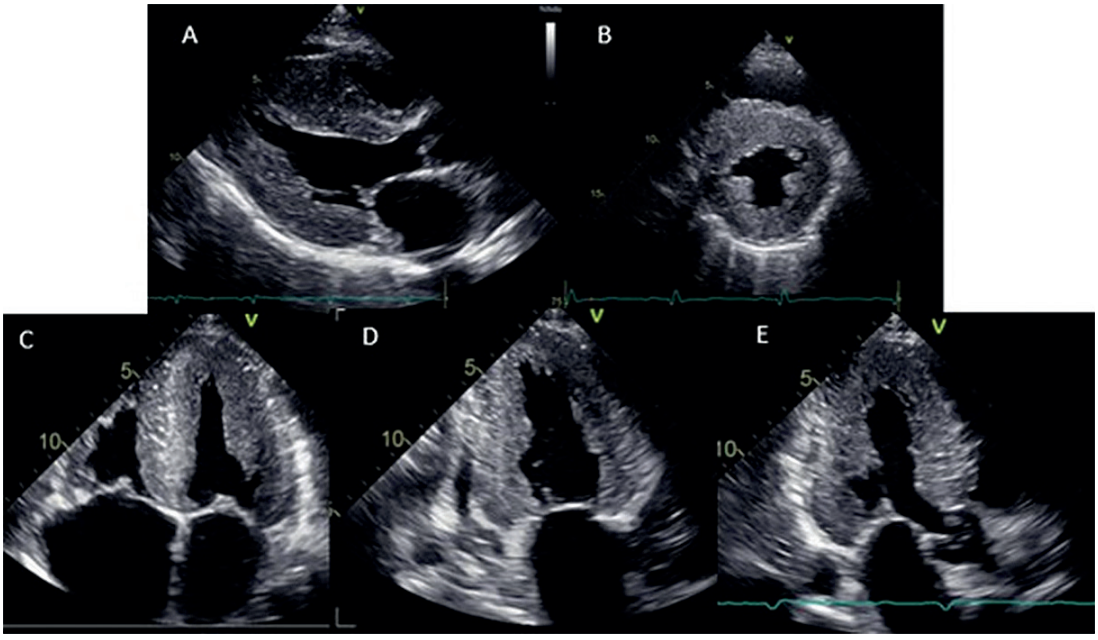

Figure 1 – *Typical CA findings: (A and B) parasternal longitudinal and short axis sections at the level of the papillary muscles, diffuse increase in myocardial thickness, with a granular, shimmering appearance of the LV and discrete pericardial effusion; (C, D, and E) apical 4-chamber, 2-chamber, and 3-chamber views: ventricles of normal dimensions with increased thickness, dilation of the atria, and increased thickness of the heart valves and interatrial septum. (Source: the author).*

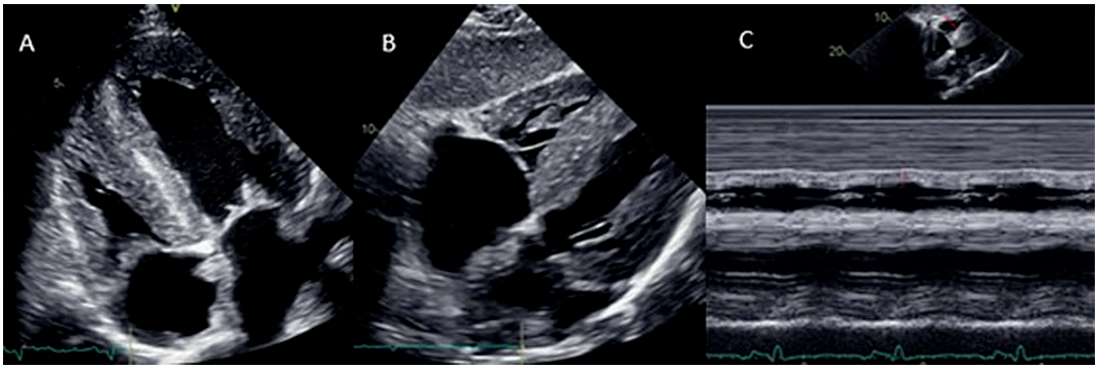

Figure 2 – *(A) apical 4-chamber view focused on the RV; (B and C) subcostal view and M-mode at the tip of the leaflets in diastole to measure the RV free wall; increased thickness of the RV free wall and interatrial septum.*

Interatrial septum th> 5 mm

Thickening of interatrial septum may occur as a result of deposition of amyloid fibrils.[1,2,6] Falk et al. demonstrated that a combination of increased myocardial echogenicity and increased interatrial septum thickness has 60% sensitivity and 100% specificity for diagnosing CA[7] (Figures 1C and 2B).

Valve involvement

Thickening of the heart valves (> 5 mm) can also occur due to amyloid deposition, resulting in insufficiency or stenosis. Moderate-to-severe insufficiency of the tricuspid and mitral valves and increased pulmonary pressure indicate more advanced heart disease.[1,6] It is estimated that up to 15% of individuals with severe aortic stenosis and up to 30% of those with the low-flow low-gradient subtype have associated CA.[1,8] Most patients have low cardiac output, which is explained by cavity reduction and mitral insufficiency, leading to reduced stroke volume. This finding explains reduced aortic transvalvular velocity in the presence of significant stenosis.[9]

Ventricular diastolic dysfunction

Diastolic dysfunction of varying degrees is almost always present in both ventricles and is considered the earliest echocardiographic sign (Figure 3). The severity of diastolic dysfunction is related to the degree of amyloid infiltration in the myocardium.[1,3] In the early stages of the disease, an abnormal relaxation pattern is found (grade I diastolic dysfunction). This stage is similar to the ventricular filling patterns found in hypertension and hypertrophic cardiomyopathy.[3]

At advanced stages, the ventricles become increasingly rigid and less compliant, with a significant pressure increase and little diastolic filling volume (restrictive physiology). The following will be found in the LV: short deceleration time (< 150 ms), E/A ratio > 2, increase in E wave, marked reduction in A wave, the "5-5-5" sign in tissue Doppler (ie, reduction of all velocities < 5 cm/s, which is highly suggestive of advanced stage CA), E/e' ratio > 14, left atrial (LA) dilation and dysfunction (Figure 3).[2,5,6]

The following will be found in the RV: E/e' ratio > 6, right atrial dilation with increased systolic pressure in the pulmonary artery and increased diameter of the inferior vena cava.[1,3] Spontaneous contrast will be noted in the atria, in addition to a propensity for thrombus formation, even in sinus rhythm.[1]

LV systolic function

EF remains within normal values for nearly the entire course of the disease. Decreased EF is a marker of advanced disease, but reduced longitudinal contractile function occurs early.[3] Therefore, LV systolic function should be assessed with additional methods, such as mitral annular systolic velocity (abnormal when s' wave < 6 cm/s) and the Tei index (abnormal > 0.40).[3] As described above, reduced end-systolic volume index may be an early predictor of decreased systolic function independent of EF, and should also be evaluated.[2]

In all patients with suspected CA, myocardial deformation should be assessed through speckle tracking, since it provides a more sensitive assessment of LV systolic function.[6] Global longitudinal strain is useful for diagnosing incipient myocardial dysfunction in CA. When it is abnormal (generally < 13%) it reflects contractile dysfunction:[1,3] the lower and closer to 0% it becomes, the more advanced the disease.[6] Such a tool should also be used to assist in differential diagnosis of other pathologies involving increased myocardial thickness.[3,5]

In polar mapping, reduced myocardial deformation in the middle and basal segments is associated with preserved deformation in the apical regions, known as apical sparing or "cherry on top" pattern **(Figure 4).** This finding, which is due to greater deposition of amyloid protein in the basal and middle myocardial segments, is frequent but not pathognomonic.[3,10]

Apical sparing can be determined visually or by dividing the average strain of the apical segments by the average strain of the middle plus basal segments. Values > 1 are

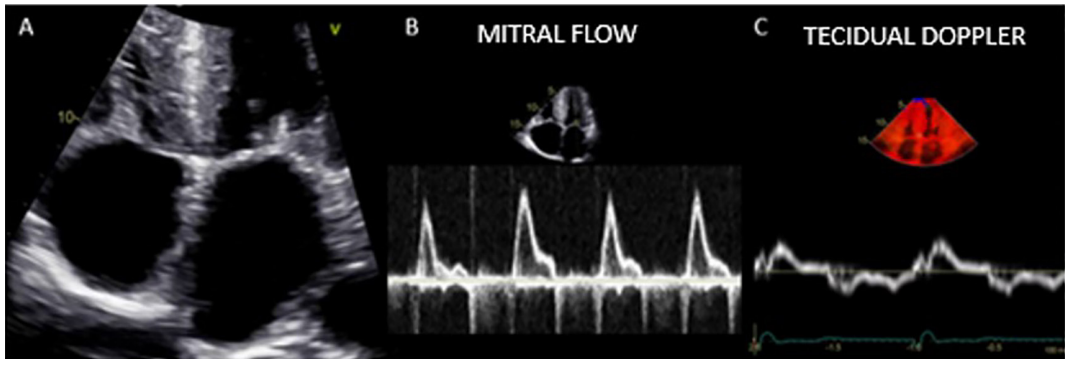

Figure 3 – *Apical 4-chamber view of the atria and use of pulsed Doppler and tissue Doppler: (A) dilation of the atria with increased thickness; (B) restrictive LV filling pattern; (C) 5-5-5 sign; reduction in e', a' and s' wave speeds (< 5 cm/s).*

suggestive of CA and can be found in earlier stages of the disease.[3] An apical sparing index > 1 allows differentiation of patients with CA from other causes of increased ventricular thickness (sensitivity 93%, specificity 82%).[1,3,10]

The relationship between EF and global longitudinal strain is called the EF strain ratio. This echocardiographic parameter has the highest sensitivity (91.7%) and specificity (89.7%) for diagnosing CA. Values > 4.1 can differentiate CA from hypertrophic cardiomyopathy, aortic stenosis, and systemic arterial hypertension.[11]

The septal apical/basal ratio is the ratio of apical to basal strain in the septum. When > 2.1, it can help differentiate other causes of increased myocardial thickness.[6,11]

Myocardial work, a modern tool for assessing myocardial systolic function, integrates afterload into strain analysis to estimate intraventricular pressure during the cardiac cycle. Global constructive work, global work index, and global work efficiency values are lower in CA than in hypertrophic cardiomyopathy, being associated with increased all-cause mortality (Figure 4C).[12]

Strain assessment should include the RV and LA. Reduced RV strain, especially in the free wall (average of the 3 segments with absolute values < 17%) is associated with worse prognosis, and an apical preservation pattern can be found.[5,13] The reduction in LA strain is greater than in hypertrophic cardiomyopathy and is associated with reduced LV systolic and diastolic function[13] (Figures 5 and 6).

Pericardial effusion

Pericardial effusion, present in > 50% of cases, is often mild, and may be mild-to-moderate, but rarely progresses to cardiac tamponade. However, when present, it is associated with a worse prognosis. Pleural effusion is also common[1,6] (Figure 1A).

Table 2 presents echocardiographic findings highly suggestive of CA (see Videos 1-3).

Differential diagnosis

The main differential diagnoses must be considered for diseases involving myocardial thickening that mimic hypertrophic cardiomyopathy, also known as phenocopies. These range from hypertensive cardiomyopathy (most common) to rarer diseases, such as sarcomeric hypertrophic cardiomyopathy, Anderson-Fabry disease, Friedreich's ataxia, PRKAG2, and Danon disease. Recognizing the main clinical characteristics, in association with echocardiography findings and myocardial deformation assessment, allows clearer identification of these pathologies.[15]

Conclusions

Through transthoracic echocardiography with longitudinal strain analysis, the main findings of CA can be identified, allowing early diagnosis, prognosis, and better monitoring of these patients.

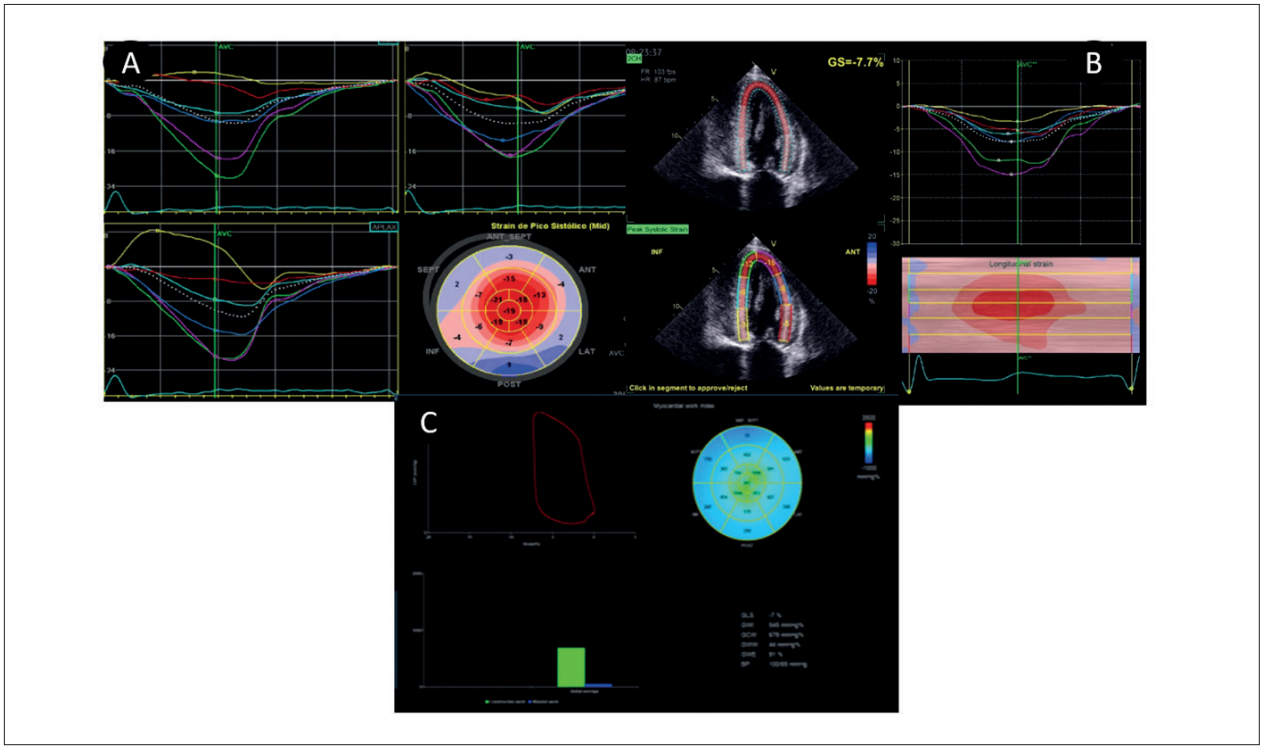

Figure 4 – *(A) parametric representation in bull's eye format and LV longitudinal strain curves showing apical preservation (cherry-on-top) pattern: reduced deformation in the middle and basal segments (light red) with preserved apical segments (dark red) and reduced global longitudinal strain (absolute value 7.7%); (B) longitudinal 4-chamber image with reduced deformation in the middle and basal segments and preserved deformation in the apical segments; (C) polar map with estimated myocardial work.*

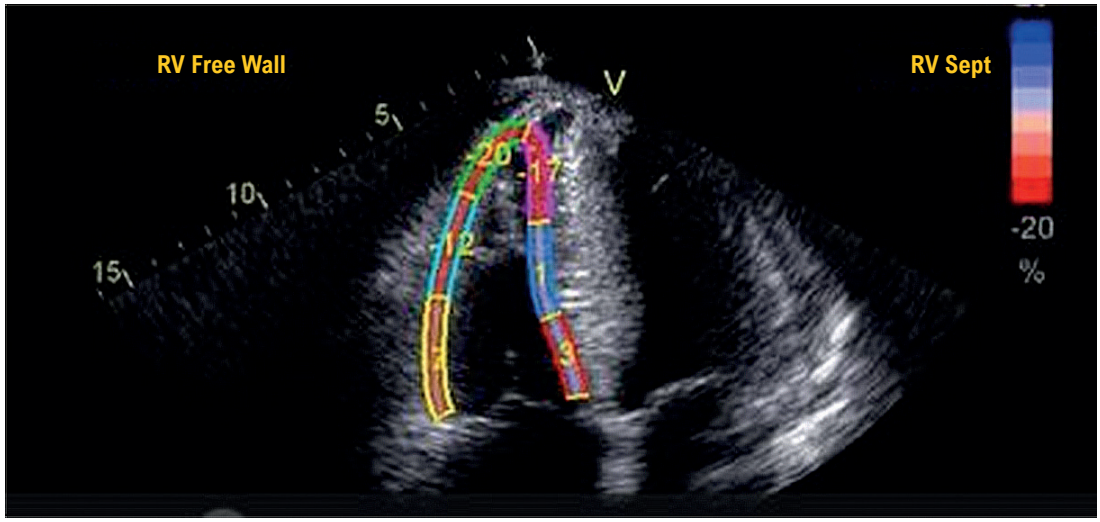

Figure 5 – *Apical 4-chamber view of the RV: reduced RV free wall strain (average of the 3 segments). RV: right ventricle.*

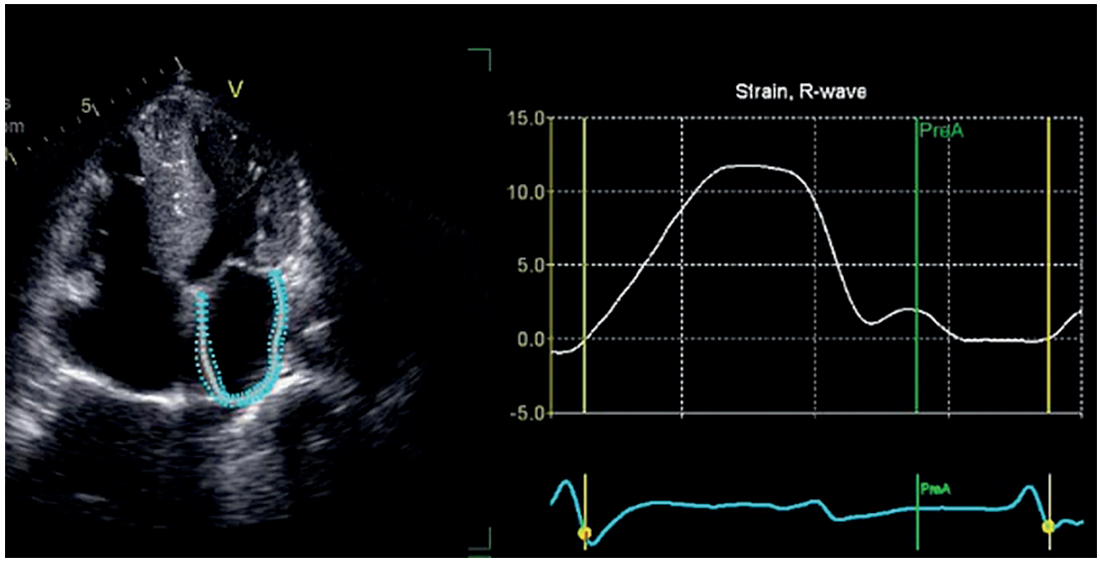

Figure 6 – *Apical 4-chamber view to assess LA strain.*

Author Contributions

Writing of the manuscript: Silva LLM, Vilela AA; critical revision of the manuscript for intellectual content: Vilela AA, Paladino Filho AT, Assef JE.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

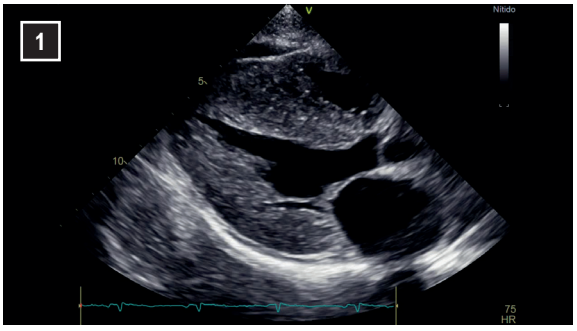
Ethics Approval and Consent to Participate

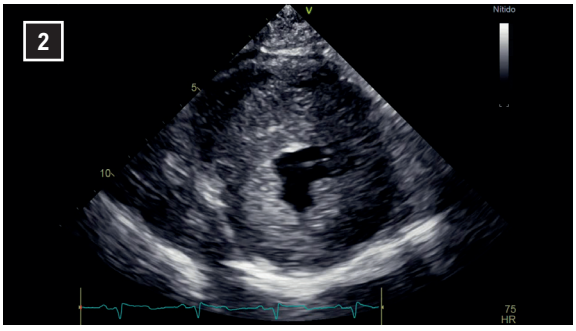
This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2 – Echocardiographic findings indicative of CA

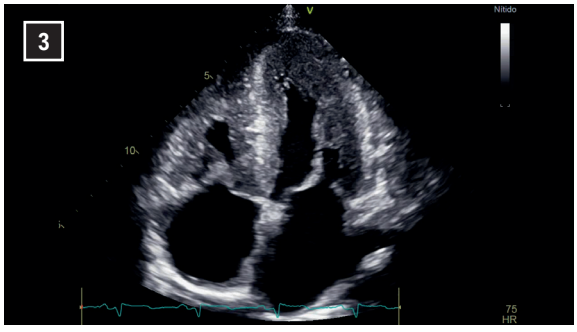
Highly suggestive:
• Increased LV and/or RV wall thickness
• Increased LV mass with relative posterior wall thickness > 0.6
• Normal or small ventricles and atrial dilation
• Granular, sparkling appearance associated with interatrial septal thickening
• Restrictive fill pattern
• E/e' ratio > 11
• Global longitudinal strain ≤ 13% (absolute value)
• Typical longitudinal LV deformation with apical preservation
• Septal apical/basal longitudinal strain > 2.1
• E', a' and s' wave velocities of the septal or lateral mitral annulus < 5 cm/s (DT)
• Small mitral A wave (< 30 cm/s) in sinus rhythm
• Mild pericardial and/or pleural effusion

LV: left ventricle; RV: right ventricle; DT: Tissue Doppler. Adapted from Expert Consensus Recommendations[2,4,6,14]





Videos 1 and 2 – *Parasternal longitudinal section and short axis in the papillary muscle plane: normally-sized ventricles, LA dilation, diffuse increase in wall thickness with a granular sparkling appearance, and slightly impaired contractility.*
Link video 1: http://abcimaging.org/supplementary-material/2024/3703/2024-0056_AR_video_1.mp4
Link video 2: http://abcimaging.org/supplementary-material/2024/3703/2024-0056_AR_video_2.mp4



Video 3 – *Apical 4-chamber view with normally-sized ventricles, significant dilation of the LA, diffuse increase in myocardial wall thickness with a granular sparkling appearance in both ventricles, the interatrial septum, and the heart valves, as well as mild impairment of myocardial contractility.*
Link: http://abcimaging.org/supplementary-material/2024/3703/2024-0056_AR_video_3.mp4

References

1. Pinto IM, Smanio PEP, Vilela AA, Quagliato PC, Segundo EMV Neto, Vasconcelos LA, et al. Amiloidose Cardíaca: Ainda uma Doença Rara? Rev Soc Cardiol Estado de São Paulo. 2021;31(2):187-97. doi: 10.29381/0103-8559/20213102187-97.

2. Moody WE, Turvey-Haigh L, Knight D, Coats CJ, Cooper RM, Schofield R, et al. British Society of Echocardiography Guideline for the Transthoracic Echocardiographic Assessment of Cardiac Amyloidosis. Echo Res Pract. 2023;10(1):13. doi: 10.1186/s44156-023-00028-7.

3. Di Nunzio D, Recupero A, de Gregorio C, Zito C, Carerj S, Di Bella G. Echocardiographic Findings in Cardiac Amyloidosis: Inside Two-dimensional, Doppler, and Strain Imaging. Curr Cardiol Rep. 2019;21(2):7. doi: 10.1007/s11886-019-1094-z.

4. Yilmaz A, Bauersachs J, Bengel F, Büchel R, Kindermann I, Klingel K, et al. Diagnosis and Treatment of Cardiac Amyloidosis: Position Statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021;110(4):479-506. doi: 10.1007/s00392-020-01799-3.

5. Perry R, Selvanayagam JB. Echocardiography in Infiltrative Cardiomyopathy. Heart Lung Circ. 2019;28(9):1365-75. doi: 10.1016/j.hlc.2019.04.017.

6. Cuddy SAM, Chetrit M, Jankowski M, Desai M, Falk RH, Weiner RB, et al. Practical Points for Echocardiography in Cardiac Amyloidosis. J Am Soc Echocardiogr. 2022;35(9):31-40. doi: 10.1016/j.echo.2022.06.006.

7. Falk RH, Plehn JF, Deering T, Schick EC Jr, Boinay P, Rubinow A, et al. Sensitivity and Specificity of the Echocardiographic Features of Cardiac Amyloidosis. Am J Cardiol. 1987;59(5):418-22. doi: 10.1016/0002-9149(87)90948-9.

8. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, et al. Prevalence and Outcome of Dual Aortic Stenosis and Cardiac Amyloid Pathology in Patients Referred for Transcatheter Aortic Valve Implantation. Eur Heart J. 2020;41(29):2759-67. doi: 10.1093/eurheartj/ehaa170.

9. Matteo S, Anna C, Federico S, Daniele M, Gioele F, Beatrice DP, et al. Stroke Volume and Myocardial Contraction Fraction in Transthyretin Amyloidosis Cardiomyopathy: A Systematic Review. Front Cardiovasc Med. 2023;10:1085824. doi: 10.3389/fcvm.2023.1085824.

10. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative Apical Sparing of Longitudinal Strain Using Two-dimensional Speckle-tracking Echocardiography is Both Sensitive and Specific for the Diagnosis of Cardiac Amyloidosis. Heart. 2012;98(19):1442-8. doi: 10.1136/heartjnl-2012-302353.

11. Pagourelias ED, Duchenne J, Mirea O, Vovas G, van Cleemput J, Delforge M, et al. The Relation of Ejection Fraction and Global Longitudinal Strain in Amyloidosis: Implications for Differential Diagnosis. JACC Cardiovasc Imaging. 2016;9(11):1358-9. doi: 10.1016/j.jcmg.2015.11.013.

12. Roger-Rollé A, Cariou E, Rguez K, Fournier P, Lavie-Badie Y, Blanchard V, et al. Can Myocardial Work Indices Contribute to the Exploration of Patients with Cardiac Amyloidosis? Open Heart. 2020;7(2):e001346. doi: 10.1136/openhrt-2020-001346.

13. Huntjens PR, Zhang KW, Soyama Y, Karmpalioti M, Lenihan DJ, Gorcsan J 3rd. Prognostic Utility of Echocardiographic Atrial and Ventricular Strain Imaging in Patients With Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2021;14(8):1508-19. doi: 10.1016/j.jcmg.2021.01.016.

14. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2-Evidence Base and Standardized Methods of Imaging. Circ Cardiovasc Imaging. 2021;14(7):e000029. doi: 10.1161/HCI.0000000000000029.

15. Fernandes F, Antunes MO, Hotta VT, Rochitte CE, Mady C. Deposit Diseases as Differential Diagnosis of Left Ventricular Hypertrophy in Patients with Heart Failure and Preserved Systolic Function. Arq Bras Cardiol. 2019;113(5):979-87. doi: 10.36660/abc.20180370.