SPECIAL ARTICLE

Practical Points for Echocardiography in Cardiac Amyloidosis

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OBJECTIVE

This document was created by an American Society of Echocardiography Amyloidosis Taskforce as a practical accompaniment to the recently published multisociety Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis.[1,2] In this document we will outline the common echocardiographic imaging findings of cardiac amyloidosis (CA), highlighting red flags that should raise suspicion for the diagnosis. We will also provide tips for image acquisition and interpretation. Based on the comprehensive multisociety document on imaging of CA,[1,2] this document will also provide recommendations for standard reporting of an echocardiogram in a patient with CA.

WHAT IS CA?

Cardiac amyloidosis is a form of infiltrative cardiomyopathy due to deposition of amyloid fibrils in the myocardium.[3]

Most cases of CA result from 2 protein precursors (Figure 1):

- Monoclonal immunoglobulin light chain amyloidosis (AL) produced by bone marrow plasma cells
- Transthyretin (TTR), a serum transport protein for thyroid hormone and retinol that is synthesized primarily by the liver. The resulting amyloid TTR (ATTR) amyloidosis is further subtyped into wild-type (wtATTR) or hereditary/variant (vATTR), the latter resulting from genetic variants in the TTR gene.

Systemic AL amyloidosis is a rare disease with an incidence of less than 50 cases per million person-years, with equal distribution between sexes. The disease generally presents from the fifth to seventh decade, although it may occur at all ages from the fourth decade onward. Wild-type ATTR CA is more common, with a prevalence as high as 10% in older patients with increased wall thickness and heart failure with preserved ejection fraction and up to 16% in older patients with aortic stenosis (AS).[4-7] One of the most common mutations associated with vATTR amyloid is V142I (legacy nomenclature, V122I), which has been reproducibly demonstrated in 3.4% of African Americans, with a lower penetrance.[8]

There is significant heterogeneity in clinical course, prognosis, and treatment approach between AL and ATTR; however, echocardiographic features are similar.

Cardiac involvement leads to atrial arrhythmias, conduction system disease, and progressive heart failure. Echocardiography is commonly one of the first investigations to raise the suspicion for CA, where early and successful diagnosis is dependent on the awareness of the sonographer and reader of the cardinal features of the disease. As the efficacy of newer therapeutics are dependent on early diagnosis, it has never been more vital for the imaging team to be aware of these features.

ECHOCARDIOGRAPHY OVERVIEW

Echocardiography plays a major role in the noninvasive evaluation of CA. The advantages of this imaging modality are safety, availability, portability, relatively low cost, and ability to provide hemodynamic and diastolic function assessments. While echocardiography is not sufficient by itself to definitively diagnose and differentiate the type of CA (AL vs ATTR), it is an essential part of the diagnostic, prognostic, and ongoing management of patients with this disorder.

RED FLAGS (COMMON FEATURES ON IMAGING)

There are several typical morphologic and functional features of CA that should raise suspicion, so-called red flags (Figure 2):

- Increased left ventricular (LV) and right ventricular (RV) wall thickening
- Biatrial enlargement
- Increased LV wall thickness with low-voltage criteria on associated electrocardiogram (ECG)
- Diastolic dysfunction (≥grade II) with elevated LV filling pressures
- Severely reduced mitral annular tissue Doppler velocities
- Reduced global longitudinal strain (GLS) with apical sparing
- Low-flow, low-gradient AS, paradoxical rather than classical
- Pericardial effusion
- Increased atrial septal thickness
- Diffuse valve thickening
- Preserved ejection fraction with low stroke volume index

When these features are present in certain patient populations, CA should be considered as the possible underlying etiology (Table 1).

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Abbreviations
2D = Two-dimensional
AL = Light chain amyloidosis
AS = Aortic stenosis
ATTR = Transthyretin amyloidosis
CA = Cardiac amyloidosis
ECG = Electrocardiogram
EF = Ejection fraction
GLS = Global longitudinal strain
IVS = Interventricular septum
LA = Left atrium
LV = Left ventricle, ventricular
LVEF = Left ventricular ejection fraction
ROI = Region of interest
RRSR = Relative regional strain ratio
RV = Right ventricle, ventricular
vATTR = Variant ATTR
wtATTR = Wild-type ATTR

Tips for Assessing Cardiac Structure

All two-dimensional (2D) and Doppler echocardiographic acquisition and measurements in patients with suspected or known CA should follow the American Society of Echocardiography/European Association of Cardiovascular Imaging chamber quantification guidelines.[9,10]

Interventricular septum (IVS) measurement: this can be challenging due to RV structures including trabeculations, crista supraventricularis, and the moderator band. Wall thickness may be verified in the parasternal short-axis view (Figure 3).

Right ventricular wall measurement: RV wall thickness is best evaluated from the subcostal window with zoomed focus on the right ventricle (RV). Two-dimensional or M-mode echocardiographic measurements should be taken at end diastole. The measurement should be obtained ~1 cm below the tricuspid annulus at the level of the anterior tricuspid leaflet tip when the valve is fully open. Using breathing techniques and a zoomed view on the RV can help optimize this measurement (Figure 4).

Left atrial (LA) measurement: LA foreshortening is a common issue encountered in the standard apical views, focusing on the LV. Dedicated LA views, which demonstrate the full length of the atrium, should be acquired in the apical 4-chamber and 2-chamber views (Figure 5).

DOPPLER ECHOCARDIOGRAPHIC FEATURES IN CARDIAC AMYLOIDOSIS

Infiltration of amyloid fibrils in the myocardium results in abnormal LV relaxation and progressive diastolic dysfunction. The degree of diastolic dysfunction is often a reflection of the disease course, with more severe forms of dysfunction manifesting later in the disease.

The following Doppler indices are recommended to assess diastolic function and LA pressures (Figure 6):

1. Pulsed-wave Doppler of mitral inflow: while grade I diastolic dysfunction may be present early in the course of disease, most patients demonstrate grade II or III diastolic dysfunction by the time the disease is detected.
2. Tissue Doppler of the mitral annulus: septal and lateral annular velocities are often very low (~ 5 cm/sec), reflecting abnormal myocardial relaxation and compliance.
3. Pulsed-wave Doppler of the pulmonary veins: pulmonary vein velocities reflect LV diastolic dysfunction and atriopathy, with a progressive decline in the pulmonary S wave (due to elevated LA pressure) and concurrent increase in the D wave with disease progression. An increased pulmonary vein atrial reversal velocity, reflecting increased LV end-diastolic pressure, may be seen (Figure 7).

Tips for Appropriate Doppler Techniques

Pulsed-wave Doppler assessment of mitral valve inflow is imperative for evaluating diastolic function. Sample volume size (optimally 1-3 mm) can affect the appearance of the waveform. Correct positioning of the sample volume is also crucial; the sample volume should be placed at the leaflet tips (Video 1). Placing

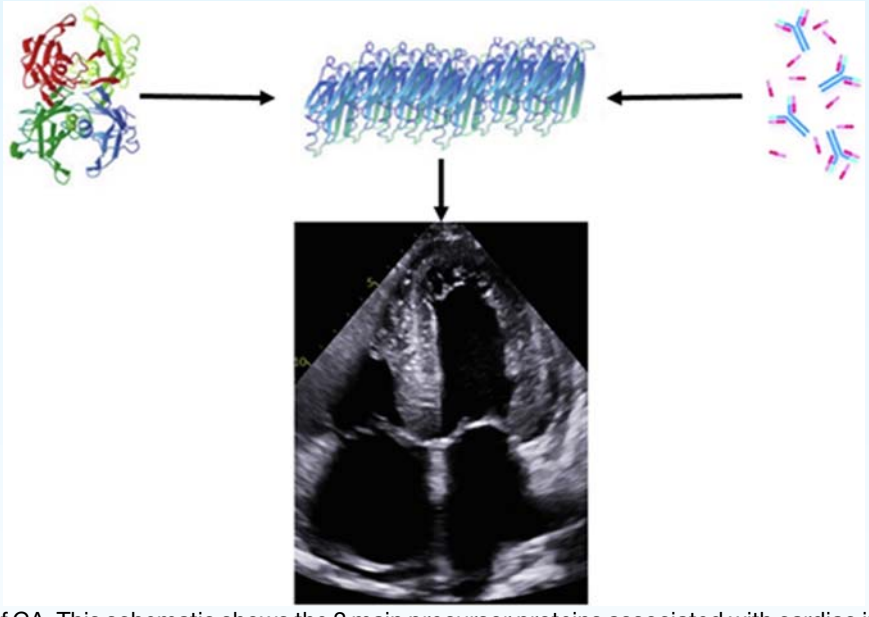

Figure 1 Pathogenesis of CA. This schematic shows the 2 main precursor proteins associated with cardiac infiltration in amyloidosis. Transthyretin (left panel) or abnormal light chains (right panel) produced by the plasma cells misfold, aggregate, and form amyloid fibrils that deposit in the extracellular space. Both types have a similar appearance when stained with Congo red; immunofluorescence and/or mass spectrometry are/is required to distinguish the type of precursor protein. Similarly, no echocardiographic features distinguish the type of amyloid infiltration.

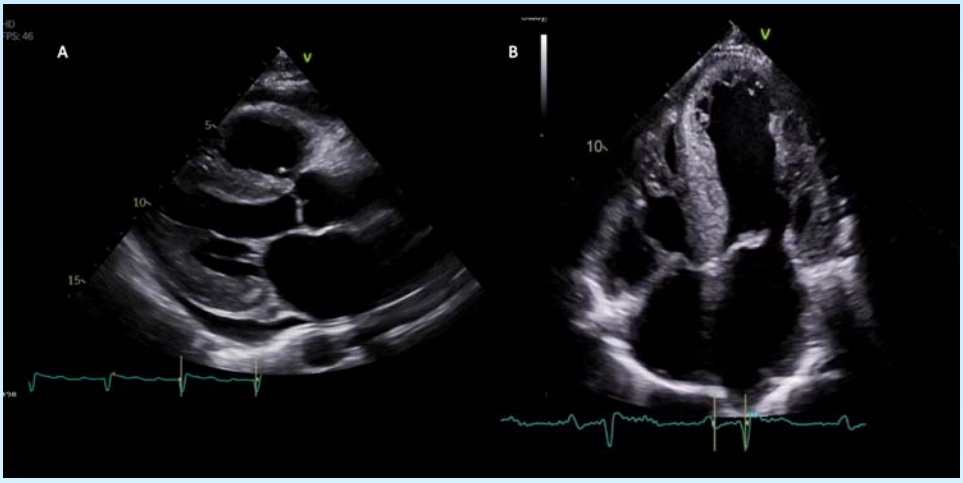

Figure 2 Typical echocardiographic findings. **(A)** Parasternal long-axis view: the ventricular wall thickness is increased, there is atrial dilation, and a small pericardial effusion is seen. **(B)** Apical 4-chamber view. Increased biventricular wall thickness, biatrial dilation, and valvular thickening are shown.

Table 1 At-risk populations where CA should be considered

At-risk populations	Type (most likely)*
Monoclonal gammopathy, multiple myeloma, or known extra cardiac amyloid	AL
Unexplained heart failure with hepatomegaly, macroglossia, periorbital purpura	AL
Heart failure and unexplained peripheral sensorimotor neuropathy	vATTR or AL
Non–African American individuals, with unexplained heart failure and increased wall thickness (not explained by hypertensive heart disease or other conditions)	AL, wtATTR, non-V142I vATTR
Men >50 years, with bilateral carpal tunnel syndrome†/biceps tendon rupture/spinal stenosis	wtATTR
African American individuals, ages >60 years, with increased wall thickness and/or unexplained heart failure	vATTR
ATTR genetic variant carrier	vATTR
Age >60 years with low-flow, low-gradient AS and increased wall thickness	wtATTR

*The most likely amyloid type is indicated, but definitive tissue typing is required. Light chain amyloidosis always requires cardiac or noncardiac tissue; nuclear scintigraphy may be used in the proper clinical context if AL is excluded.
†Carpal tunnel syndrome, especially bilateral, may be present with any type of amyloid.

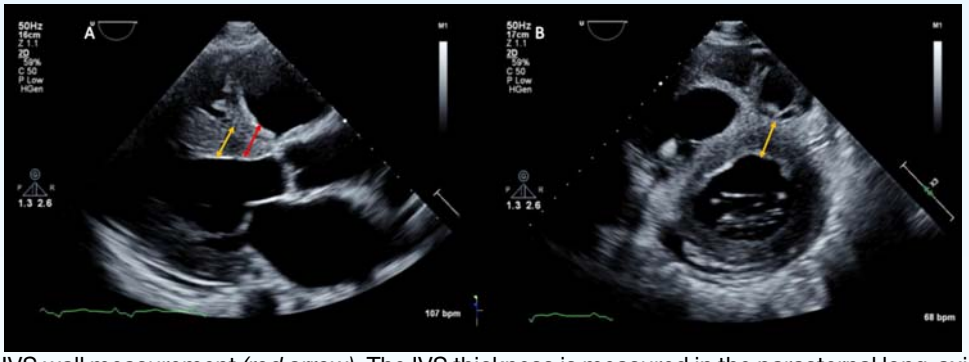

Figure 3 Erroneous IVS wall measurement *(red arrow)*. The IVS thickness is measured in the parasternal long-axis view **(A)**. If there is uncertainty, the wall thickness should be verified in the short-axis view **(B)**, ensuring RV structures are not included in the IVS measurement. Correct measurements are shown with the *orange arrow*.

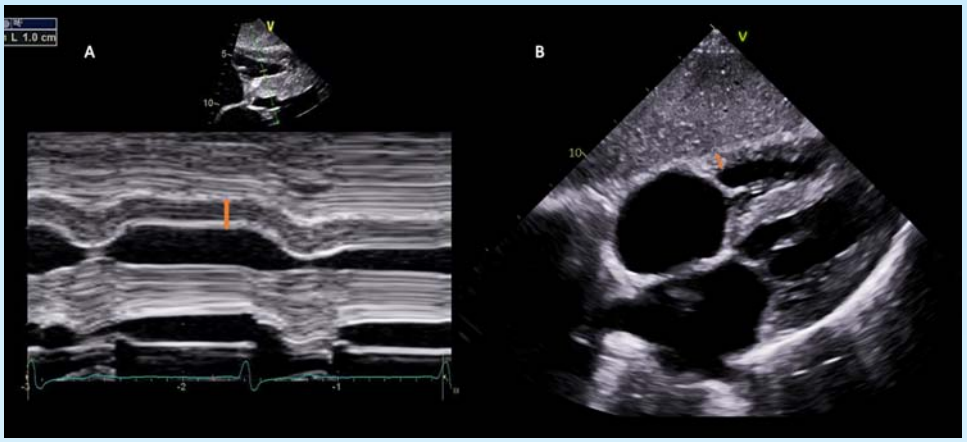

Figure 4 **(A)** M-mode echocardiography is used in the subcostal 4-chamber view to measure the RV free wall thickness. **(B)** Two-dimensional RV wall thickness measurement in the subcostal 4-chamber view. Correct measurements are shown with the *orange arrow*.

the sample volume too far into the left ventricle (LV) can underestimate the E and A velocities and cause the modal velocity to be ill-defined.

Accurate tissue Doppler velocities are important when evaluating CA. Common pitfalls include small sample volume size (5-10 mm is the suggested sample size), incorrect sample volume position (correct placement should be just on the ventricular side of the annulus in the basal myocardium), poor Doppler alignment (the cursor should be aligned with the axis of movement of the annular plane), and variability with breathing (recording at end expiration is recommended; Video 2).

LV FUNCTION AND 2D SPECKLE-TRACKING IN CARDIAC AMYLOIDOSIS

Amyloid fibril infiltration impairs myocardial function, often with a normal appearing LV ejection fraction (LVEF). As the disease progresses the LVEF decreases. A midrange or even severely reduced LVEF may be present in vATTR, especially due to V142I mutation.

Two-dimensional speckle-tracking imaging is used to measure myocardial deformation. Global longitudinal strain is useful for diagnosing and quantifying myocardial dysfunction in CA. When it is abnormal, it reflects contractile dysfunction.

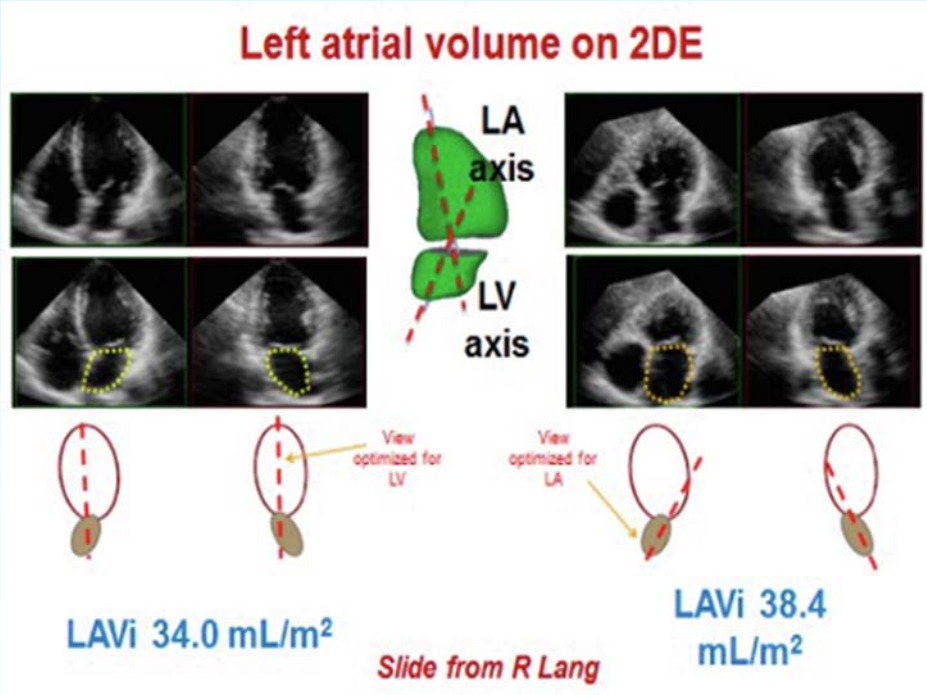

Figure 5 Left atrial foreshortening (R Lang slide). Nonforeshortened LA imaging is not always in the same plane as for the LV. Care should be taken to obtain focused on-axis views that include the left atrium (LA) at its maximal size while visualizing the pulmonary veins. Zoomed views of the LA can help define atrial borders. In cardiac amyloid, the LA is often dilated, and accurate volumes must be obtained to help with diagnosis. LAVi, LA volume indexed. Slide courtesy of Dr. Roberto Lang.

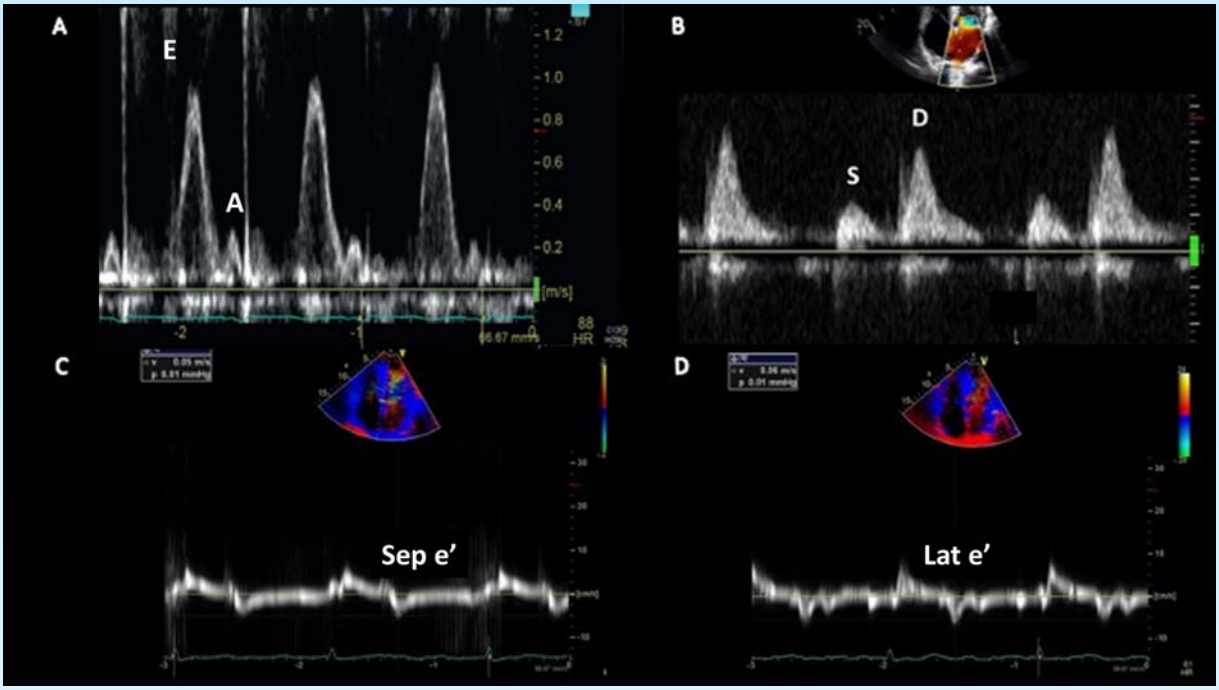

Figure 6 Typical Doppler velocity waveforms in amyloidosis. **(A)** Mitral inflow demonstrates a high E-wave velocity with a small A-wave velocity, E/A >2, and short deceleration time of 100 msec. **(B)** Pulmonary vein velocities exhibit systolic (S) blunting. Mitral annular tissue Doppler imaging velocities at the septal **(C)** and lateral **(D)** aspects of the annulus are reduced, leading to an average E/e' >14. Sep e'= septal e' velocity, Lat e'= lateral e' velocity.

Measures of LV Strain

Global longitudinal strain: GLS is a unitless measure of longitudinal deformation with more negative values denoting greater deformation or more pronounced shortening. Therefore, values nearing 0% indicate akinesis, positive values indicate dyskinesis, and negative values indicate shortening/contraction. Normal values of GLS vary between vendors; normal is usually considered to be more negative than −20% with an SD of ± 2% (lower limit of normal −16% to −18%, depending on vendor; Figure 8).

Apical sparing: while there is a normal base-to-apex gradient in GLS, this has been found to be far more pronounced in CA. In CA, the apical segmental strain values are greater than those in the basal and middle segments. When plotted on a bull's-eye map, this will generate a characteristic "apical-sparing" pattern (Figure 9).[11]

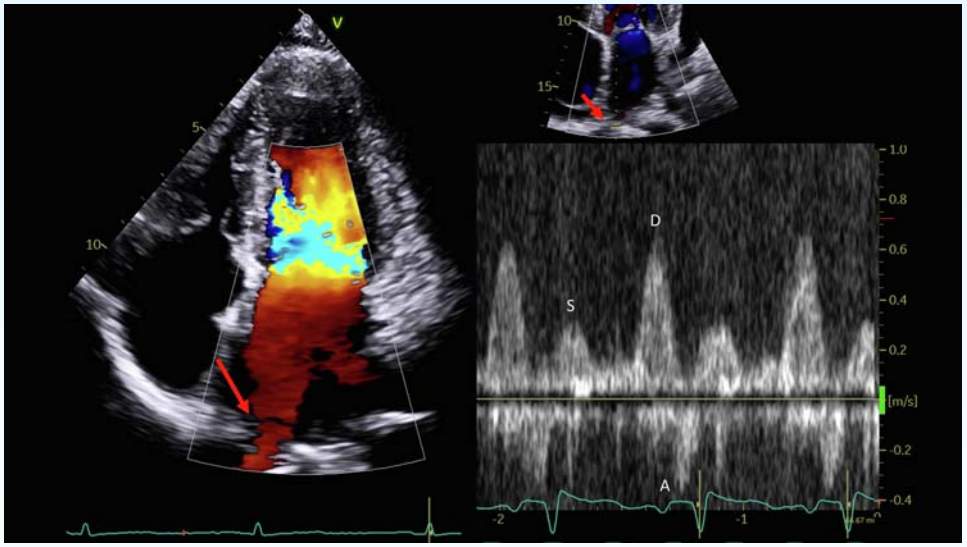

Figure 7 Color and spectral Doppler echocardiography of pulmonary vein (PV; *red arrow*). As shown in the *top image*, it is important to place the sample volume 1-2 mm into the PV. The pulsed-wave Doppler waveform shows a blunted systolic inflow (S), with higher velocity diastolic flow (D) and marked atrial reversal (A).

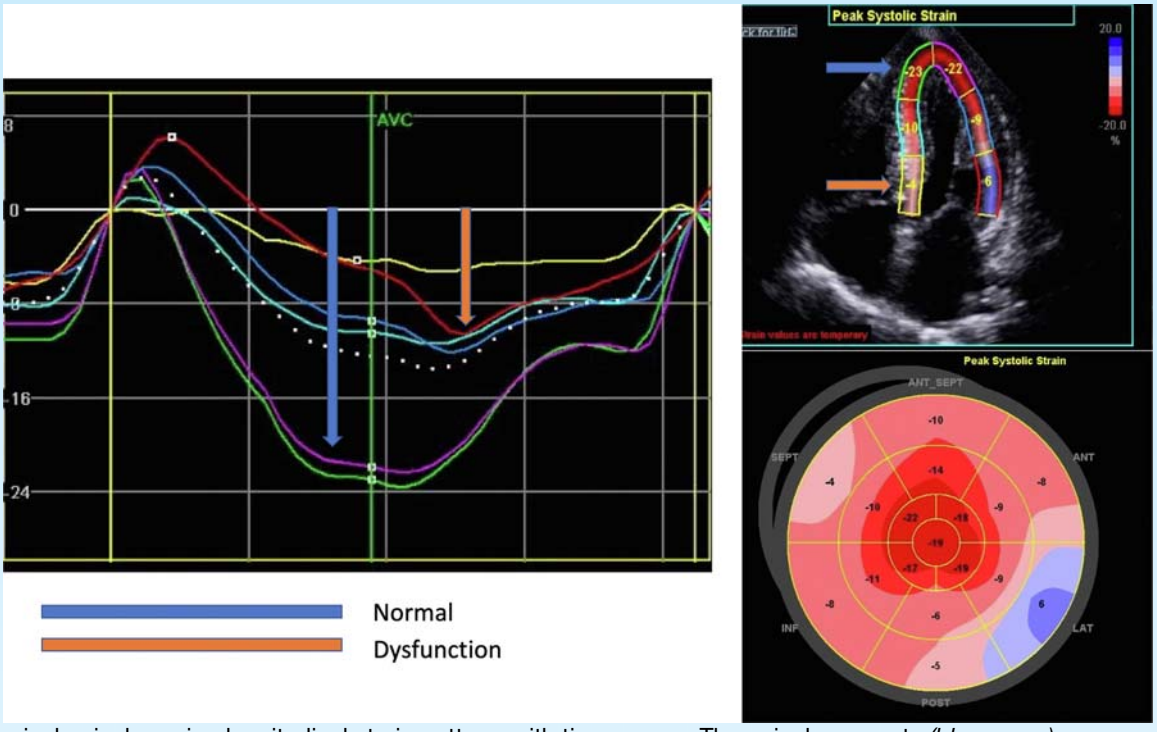

Figure 8 Typical apical-sparing longitudinal strain pattern, with time curves. The apical segments *(blue arrow)* are more preserved than the basal segments *(orange arrow)* assessed visually and quantitatively by the negative displacement from the 0 line. AVC, aortic valve closure.

GLS Ratios

The original description of this regional variation in GLS seen in CA provided a ratio of apical strain to mid and basal strain (relative regional strain ratio [RRSR]), suggesting that this value was highly sensitive and specific for the diagnosis of CA compared to other causes of increased LV wall thickness when assessed in selected populations with increased wall thickness.[11] Since that time, other ratios have been suggested for the diagnosis of CA. The septal apical-to-basal (SAB) ratio uses the 4-chamber septal apical and basal segmental longitudinal strain values.[12] The ejection fraction-to-strain ratio uses the discrepancy between the 2D LV systolic ejection fraction and the strain value that can be seen in CA.[13] These ratios have not been validated as screening tools in larger populations. The variation across vendors in the discriminatory ability of the RRSR ratio has been demonstrated and is driven by differences in regional strain[14] (Figure 9). The RRSR and SAB cutoffs quoted in Table 2 were developed using the same vendor software (EchoPAC Advanced Analysis Technologies; GE Medical Systems) in select populations with increased wall thickness. In addition, strain values may differ across layers of the LV such that longitudinal strain is highest at the endocardium and lowest at the epicardium, highlighting the importance

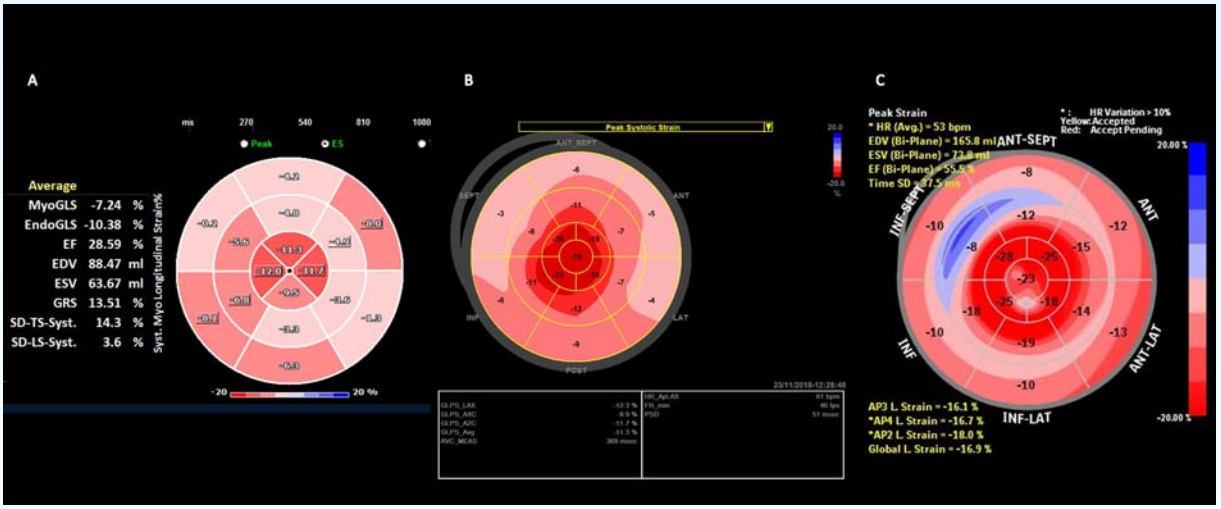

Figure 9 Variation across vendors. This figure shows the apical-sparing pattern of longitudinal strain for 3 different subjects using 3 different vendors: **(A)** TomTec, **(B)** GE EchoPAC, **(C)** Philips QLab.

Table 2 Longitudinal strain ratios that have been described, with the diagnostic cutoffs used in the original publications: proposed ratios incorporating LV GLS for diagnosis of CA

Ratio		Cutoff
RRSR[9]	Average apical segment LS/ average combined mid + basal segment LS	>1.0
SAB LS ratio[10]		>2.1
Ejection fraction to strain ratio[13]		>4.1

LS, Longitudinal strain.

of region of interest (ROI) location (Figure 11, Video 3). There is also variability across vendors pertaining to calculation of GLS and default layer selected, varying from a full-thickness calculation to midmyocardial or endocardial. Using GLS ratios can improve specificity at the cost of reduced sensitivity over visual assessment (Table 2). The key concept is to perform strain imaging in patients referred for possible amyloidosis or with echocardiographic red flags noted during the examination; this can be done by the sonographer during image acquisition or after the study. In patients with subtle or no wall thickening, abnormal GLS with an apical-sparing pattern may be the clue to the diagnosis. It is important to also consider concomitant pathologies that may affect the strain pattern, such as prior infarct or marked LV dyssynchrony (Figure 10).

When to Seek Additional Information With Speckle-Tracking

Two-dimensional speckle-tracking with strain analysis should be performed in the following scenarios:

1. The study is suggestive of CA.
2. The clinical pretest probability is high (see Table 1 on at-risk populations).
3. There is undifferentiated LV wall thickening.

See the tips for strain analysis in Table 3 (Figures 9–11, Videos 3 and 4).

REPORTING

The expert consensus document set out several features to note in the echocardiographic report (Tables 4 and 5).[1,2] Raising the differential diagnosis of CA is appropriate if suggestive features are present in an at-risk population.

Standardized reporting suggestions are as follows:

1. When findings are suspicious for CA, a statement should be included in the final impressions (not buried elsewhere in the report).
2. Suggested wording:
   a. Findings are strongly suggestive of CA/infiltrative cardiomyopathy.

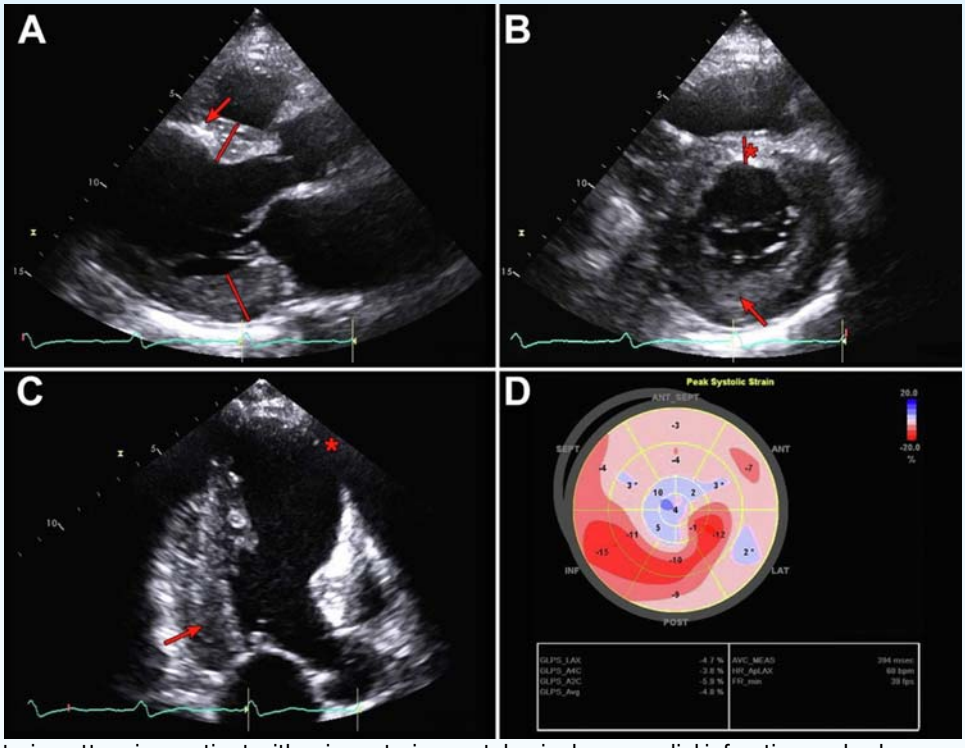

Figure 10 Atypical strain pattern in a patient with prior anterior septal apical myocardial infarction and subsequent amyloid infiltration in the noninfarcted segments. **(A)** Thickening of the basal segments *(solid lines)* due to amyloid infiltration; the *arrow* demonstrates scarred segment from previous myocardial infarct. **(B)** *Asterisk* at scarred segment; the *arrow* demonstrates posterior wall thickening. **(C)** The *arrow* shows inferolateral thickening; the *asterisk* shows anterior-apical scar. **(D)** Classic apical-sparing pattern is absent due to infarction. Cardiac amyloid was proven by endomyocardial biopsy.

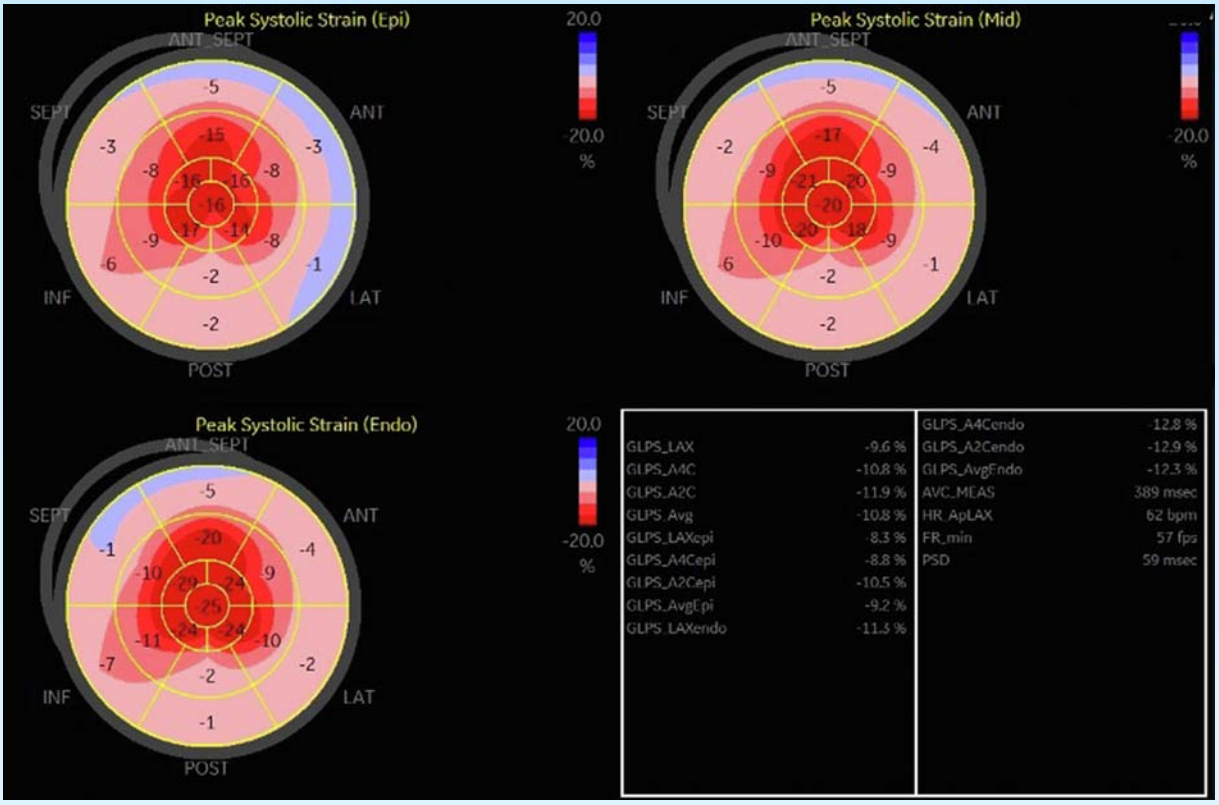

Figure 11 Global longitudinal strain values at the endocardial, mid, and epicardial layers. There is a notable gradient from endocardium to epicardium in the apical segments, showing the potential impact of misplacing the ROI.

b. Findings are suggestive of possible CA/infiltrative cardiomyopathy.
c. The following findings suggest possible CA: [free form].
d. Findings are not suggestive of CA/infiltrative cardiomyopathy.
e. Findings are equivocal for CA/infiltrative cardiomyopathy.

Specific wording regarding further evaluation for infiltrative cardiomyopathy will vary according to local availability and expertise. Echocardiographers are encouraged to consider standardized wording appropriate to their practice, including screening for monoclonal gammopathy (serum-free light chain assay, serum and urine protein electrophoresis with immunofixation) and consideration of nuclear cardiac scintigraphy, cardiac magnetic resonance imaging, and tissue biopsy, if clinically indicated. Depending on institutional practice and resources, links to a diagnostic algorithm and specific testing order sets may be helpful.

Table 3 Tips for performing strain analysis

Parameter	Comment
Increased gain	Higher gain results in more speckles; need good endocardial definition.
Consistent sector width and depth	Wide enough to include the full wall thickness and apex and extend beyond annulus to allow capture of entire LV throughout cardiac cycle (Video 3).
ROI	Include 90% of the myocardium as error can occur if too narrow, favoring epicardial or endocardial regions. If too wide can lead to abnormal values, often lower (Video 4).
ECG gating and timing of end diastole and end systole to aortic valve opening and closing	It is very important for evaluation of end-systolic versus peak strain values; deformation after aortic valve closure is not relevant. If ECG gating is incorrect, e.g., tracking p wave, may need to manually adjust off-line (Video 4).
Longitudinal follow-up	Consistent vendor (Figure 9).

Table 4 Standardized acquisition and interpretation of echocardiography for CA (adapted from Expert Consensus Recommendations)

Parameter for acquisition and reporting	Abnormal parameter	Notes
LV wall thickness	Increased LV wall thickness (>1.2 cm) and increased relative wall thickness (>0.42)	Discordance between increased LV wall thickness relative to ECG QRS voltage is particularly suggestive, but normal ECG voltage can also be seen.
Myocardial echogenicity	Increased echogenicity of the myocardium (sparkling, hyperrefractile "texture" of the myocardium)	Not highly specific (differential diagnosis includes end-stage renal disease or other infiltrative cardiomyopathies); highly suggestive in conjunction with severely reduced longitudinal function of the LV.
Atrial size and function	Atrial enlargement and dysfunction (see diastolic function)	Nonspecific but important finding to support the diagnosis and potentially provide insight into risk for stroke or arterial embolism.
Interatrial septum and valves	Increased thickening of the interatrial septum and valves (>0.5 cm)	Nonspecific but suggestive of the diagnosis.
Pericardial effusion	Pericardial effusion	Nonspecific but when coupled with other echo signs is suggestive of the diagnosis.
Diastolic function	Grade II or worse diastolic dysfunction with high E/A ratio (>1.5) and reduced E deceleration time (<150 msec).	Doppler diastolic function is helpful in determining prognosis. Severely reduced A wave velocity can be due to LA failure, which can be helpful in determining risk of stroke. An A wave <30 cm/sec portends a higher risk of thromboembolism in sinus rhythm in CA. Assessment of pulmonary vein atrial reversal may be suggestive of increased LV end-diastolic pressure and atrial function.
Estimated PA systolic and right atrial pressure	Increased pressures (>35 mm Hg for PA, ≥10 mm Hg for right atrium)	These are important parameters to estimate volume status and optimize diuretic dosing.
Mitral annular tissue Doppler velocities	Reduced tissue Doppler s', e', and a' velocities	If present, the "5-5-5" sign (all tissue Doppler imaging velocities <5 cm/sec) can be useful and is typically highly suggestive of the diagnosis but may not be sensitive for the diagnosis in early forms of the disease.
Longitudinal LV strain	Decreased global longitudinal LV strain	2D and speckle-tracking echocardiography shows characteristic appearance of myocardial deformation in patients with CA.
Longitudinal LV strain bull's-eye map	Relative preservation of apical longitudinal strain compared to basal and mid-LV longitudinal strain (average apical LS/average combined mid + base LS of >1)	Characteristic bull's-eye pattern is likely the most specific sign to rule in the diagnosis of CA

LS, Longitudinal strain; *PA*, pulmonary artery.

Table 5 Categories of echocardiographic findings in CA (adapted from Expert Consensus Recommendations)

Not suggestive	Normal LV wall thickness Normal LV mass Normal atrial size Septal or lateral mitral annular e' velocity >10 cm/sec
Strongly suggestive*	Increased LV and/or RV wall thickness Increased LV mass Restrictive filling pattern Typical apical-sparing LV longitudinal strain pattern Septal or lateral mitral annular e' velocity <5 cm/sec Biatrial enlargement Small mitral A wave in sinus rhythm Small pericardial and or pleural effusions
Equivocal	Findings not described above

*In the absence of a history of poorly controlled hypertension.

SERIAL ASSESSMENT USING ECHOCARDIOGRAPHY

Several studies looking at echocardiographic assessment of disease progression and response to therapy have shown potential benefit for the use of echocardiography in the following areas:

1. To demonstrate changes in cardiac disease in response to treatment in patients with AL and ATTR CA[15,16]
2. To determine whether patients with cardiac amyloidosis need to be anticoagulated for stroke prophylaxis[17]
3. To diagnose progressive cardiac involvement after liver transplantation in patients with vATTR amyloidosis[18]
4. To assess LVEF in patients with AL amyloidosis who are being considered for stem cell transplantation[19]

Emerging data suggest that echocardiographic LV GLS may be a marker of disease progression and response to therapy.[20]

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2022.06.006.

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