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Speckle tracking echocardiography in cardiac amyloidosis

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Abstract
Speckle tracking echocardiography is an imaging method, based on analysis of 2D echocardiographic images, that is useful in providing information on tissue deformation in different cardiac diseases. Cardiac amyloidosis is a complex pathological entity that can be confused with other causes responsible for cardiac hypertrophy, and for this reason, it can be misdiagnosed, especially in the early stages. Cardiac magnetic resonance and endomyocardial biopsy are reference methods for specific diagnosis, but their use is limited by a number of factors, both of a logistical and technical nature. Considering the limits of standard 2D echocardiography, speckle tracking echocardiography can be a useful method to enhance the clinical suspicion, to provide prognostic information, and to address patients more appropriately towards reference methods for definitive diagnosis.

Keywords Cardiac amyloidosis · Speckle tracking echocardiography · Strain · Imaging

Introduction

Cardiac amyloidosis (CA) is characterized by clinically significant extracellular amyloid infiltration of the heart and usually has a poor prognosis. The diagnosis is challenging and relies on a high degree of clinical suspicion, a combination of imaging techniques, and often an endomyocardial biopsy. Considering the limits of standard 2D echocardiography and the not always easy availability of advanced diagnostic methods, new imaging techniques, such as two-dimensional speckle tracking echocardiography (2D-STE), can play a big part in CA assessment.

This review aims to describe the role of speckle tracking echocardiography as an accessible and non-invasive tool for cardiac amyloidosis assessment.

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General characteristics and diagnostic methods

Amyloidosis is a disease caused by an extracellular deposition of insoluble material called amyloid. It consists of fibrils formed by an aggregation of misfolded, insoluble, autologous proteins with the P component (pentameric protein, member of the serum proteins) and other glycoproteins. This proteinaceous material, viewed with electron microscopy, is oriented in a b-sheet structure. It binds Congo red dye with production of apple-green birefringence and has a distinct color when stained with sulfated Alcian blue [1].

The accumulation of misfolded protein in many tissues leads to multiple organ dysfunction [2]. Organs potentially involved are the kidney, gastrointestinal tract, liver, heart, and nervous tissue [3]. Cardiac amyloidosis (CA) can be an isolated form or part of a systemic disease.

There are more than 30 different types of proteins associated with amyloid and the classification depends on the protein that represents most of the deposits [4]. The 3 main types of amyloidosis associated with cardiac involvement are light-chain amyloidosis (AL), hereditary transthyretin amyloidosis (M-TTR), and wild-type transthyretin amyloidosis (WT-TTR) also known as senile systemic amyloidosis (SSA).

The development of CA varies with the type of amyloidosis: it is frequent in some forms of transthyretin amyloidosis and SSA, whereas in AL form, its development is variable and ranges from absent to severe. Secondary amyloidosis

(consequence of chronic inflammatory conditions) almost never affects the heart [3, 5].

The deposition of amyloid can be localized throughout the heart, leading to thickening of the walls. It can involve the ventricles and the atria, the perivascular tissue (particularly in the small vessels), the conduction system, and the valves. The infiltrative process could result in deterioration of ventricular filling with worsening of global systolic function in advanced stages [3, 6, 7].

The typical clinical presentation of CA is with the signs and symptoms of congestive heart failure. The features of right-sided heart failure almost always predominate [8].

There are electrocardiographic abnormalities in 90% of cases with cardiac involvement. The two most common abnormalities are low voltage of QRS complex and pseudo-infarct pattern most often in anterior precordial leads. Atrial fibrillation is frequent in about 15% of patients and ventricular tachycardia in about 5% of patients [9]. Atrioventricular block, intraventricular conduction delays, and bundle branch blocks may be seen [10].

The "gold standard" test for diagnosis of CA is endomyocardial biopsy, an invasive procedure performed by experienced team. Its use is limited by possible sampling errors, due to a variable distribution of amyloid deposits and its procedural risks.

Cardiovascular magnetic resonance (CMR) is a reference standard for the diagnosis of cardiac amyloidosis and, in addition, is an excellent tool for risk stratification and disease tracking [11]. It offers precise measurement of cardiac walls and it is also useful for definition of the myocardium; gadolinium has an interstitial distribution, and in amyloidosis, normal myocardium is replaced by amyloid fibrils with an increase in interstitial cardiac mass. Then, gadolinium stays longer in the tissue giving the late gadolinium enhancement (LGE). CMR shows a characteristic pattern of non-coronary, usually subendocardial, pattern of delayed gadolinium enhancement, both within the ventricular myocardium and in the atrium agree with the transmural histological distribution of amyloid protein and the cardiac amyloid load [9, 12]. Transmural patterns of LGE distinguished ATTR from AL cardiac amyloidosis [13]. LGE pattern is absent in approximately 30% of patients and the analysis of myocardial gadolinium signal intensity decay after gadolinium injection improves the accuracy of CMR for CA diagnosis [14].

In this context, CMR is useful and precise but it is often not available or feasible because of movement artifacts due to cardiac arrhythmias or the presence of implantable device non-MR compatible. Furthermore, it requires an interpretation by highly trained physicians. Although its routine use is progressively increasing, availability and expertise is still lacking in several centers [6, 15].

Echocardiography is crucial for clinical suspicion and initial assessment of cardiac involvement.

Amyloid infiltration leads to the thickening ($\geq$ 12 mm) of ventricular walls with a concentric pattern because LV cavity is not dilated [16]. The myocardial texture is seen as abnormal and described as "granular sparkling" or "brilliant" because of its increased echogenicity derived from amyloid fibrils deposits [17]. Global LV systolic function assessed by ejection fraction is normal or nearly normal until the late stages of disease [18]. Longitudinal contractile dysfunction (measured by mitral annular displacement) can be observed in the early stages [19]. Diastolic dysfunction is an element of amyloid cardiac disease and the Doppler alterations depend on the stage of the disease. Mild or moderate LV diastolic dysfunction may develop in the first phases of the disease; then during later stages, we can find a severe restrictive filling pattern with E/A ratio > 2 and increased E/E′ [3, 9]. Elevated LV filling pressure could lead to left atrial enlargement [20] and also to post-capillary pulmonary hypertension with consequent right ventricular cavity enlargement [7]. It is possible to find a small pericardial effusion; the presence of which is associated with worse prognosis [9].

Standard 2D echocardiography can support the diagnostic suspicion but cannot absolutely give a conclusive and, mostly, an early diagnosis of CA, which is critical especially in most common AL amyloidosis. In fact, patients with advanced heart disease are not suitable candidates for effective hematologic treatment. Findings suggestive of CA, such as increased wall thickness, impaired systolic and diastolic function, and reduced myocardial tissue velocities, are regularly attributed to more prevalent pathologies, and may not be evident in the initial stages. Further, these findings may not be as common in CA as initially described, based on studies of patients with confirmed cardiac involvement [21, 22].

Left ventricular strain imaging

New echocardiographic techniques such as tissue Doppler strain rate imaging, speckle tracking based, and three-dimensional echocardiographic LV analysis have been shown to allow the detection of cardiac amyloid at a subclinical stage when other echocardiographic measurements are normal [23].

In particular, 2D-STE has been found more sensitive and more reproducible than Doppler imaging and has shown promise for the early diagnosis of CA [24].

2D-STE helps to differentiate cardiac amyloid from other causes of left ventricular hypertrophy (LVH), such as hypertensive heart disease and hypertrophic cardiomyopathy. More generally, it showed an incremental value in differentiating between primary and secondary LVH and in the differential diagnosis with storage diseases [25].

Cardiac amyloid profoundly alters all left ventricular strain parameters (longitudinal, radial, circumferential). In CA, longitudinal strain is often lower than in other groups, but the entity of this difference largely depends on the stage of the

disease. Patients with different diseases, all characterized by LVH, in different stages of progression, may have reduced global strain in the same range, so it is difficult to differentiate left ventricular hypertrophies from one another solely on the basis of global strain impairment (Table 1).

Sun et al. [31] showed that standard deviation of time to peak strain was significantly higher in the groups with hypertrophic cardiomyopathy and amyloidosis compared with the control group, indicating the asynchronized contraction pattern that underlies the pathology of these patients.

In one study [32], endocardial and epicardial longitudinal and circumferential strain and radial strain were found to be significantly lower in hypertrophic cardiomyopathy and ATTR cardiac amyloidosis patients compared with control subjects.

Further, epicardial circumferential strain was significantly lower in ATTR cardiac amyloidosis than in hypertrophic cardiomyopathy. The peak systolic radial strain and strain rate have been reported to be indicative of LV segments with cardiac amyloidosis involvement, as confirmed by cardiac magnetic resonance imaging in a patient with secondary amyloidosis [33].

Another study [34] demonstrates that a systolic septal longitudinal base-to-apex strain gradient (septal apical/basal longitudinal systolic ratio > 2.1), combined with a shortened diastolic deceleration time of early filling (deceleration time of early filling < 200 ms), aids in differentiating cardiac amyloidosis from other causes of concentric LV hypertrophy.

Growing evidences [26–29] focus on an important aspect: the regional variations in longitudinal strain from base to apex (Fig. 1), with the most prominent impairment in the basal segments and no or minor involvement of the cardiac apex, a so-called relative apical sparing pattern. It may indicate relatively less amyloid deposition in the apex than in the base and this assumption is consistent with CMR pattern of gadolinium distribution.

Recently, Ternacle et al. [6] demonstrated a strong negative correlation between the amyloid burden measured by histopathology and segmental LV LS in all 3 types of amyloidosis (AL, M-TTR, and WT-TTR). Amyloid deposits were more abundant in the basal and mid-cavity sections of the explanted hearts. In these sections, LGE was more marked and was associated with longitudinal strain impairment, indicating regional contractile dysfunction. All patients with impaired LS in at least 1 basal segment exhibited LGE.

Phelan et al. [28] analyzed 55 consecutive patients with CA that were compared with 30 control patients with LV hypertrophy (15 with HCM and 15 with AS) and illustrate that a pattern of relative "apical sparing" of LS in the LV apex as assessed using 2-D STE is highly sensitive and specific for the diagnosis of CA.

Comparison of ROC curves for detecting CA showed that the AUC using relative apical LS was significantly larger than the other more traditional echocardiographic parameters used for diagnosing CA, including deceleration time, E/E′, ejection fraction, and global LS.

This pattern was integrated into a relative apical longitudinal strain formula:

(average apical longitudinal strain/(average basal + mid longitudinal strain).

Relative apical longitudinal strain (LS) of 1.0, defined using this equation, was sensitive (93%) and specific (82%) in differentiating CA patients from controls (area under the curve 0.94).

An apical sparing pattern in LS was consistently found regardless of the subtype of amyloid. However, patients with TTR CA were found to have significantly lower average apical LS than those with AL amyloidosis.

Using parametric polar maps or bull's eye plots (Fig. 1b), LS regional variations in strain are easily recognizable and showed different patterns for each disease subgroup: apical sparing pattern in patients with cardiac amyloidosis, isolated impairment of septal LS in septal hypertrophic cardiomyopathy, patchy reduction in longitudinal strain in left ventricular hypertrophy related to aortic stenosis [30].

Table 1 Strain patterns in different types of left ventricular hypertrophy

Type of left ventricular hypertrophy	Strain pattern	Typical impairment on STE
Athlete's heart	Normal GLS	None
Hypertrophic cardiomyopathy	Reduced GLS	IVS
Arterial hypertension	Normal/Reduced GLS	IVS
Cardiac amyloidosis	Reduced GLS	Apical sparing
Fabry disease	Reduced GLS	Basal posterior-lateral
Aortic stenosis	Reduced GLS and GRS	Basal LV segments/patchy
Aortic regurgitation	Reduced GLS	Diffused
Mitral regurgitation		
Initial disease	Normal/supranormal GLS	None
Advanced disease	Reduced GLS	Basal segments, lateral wall

GLS, global longitudinal strain; *GRS*, global radial strain; *IVS*, interventricular septum; *LV*, left ventricular; *STE*, speckle tracking echocardiography [25–30]

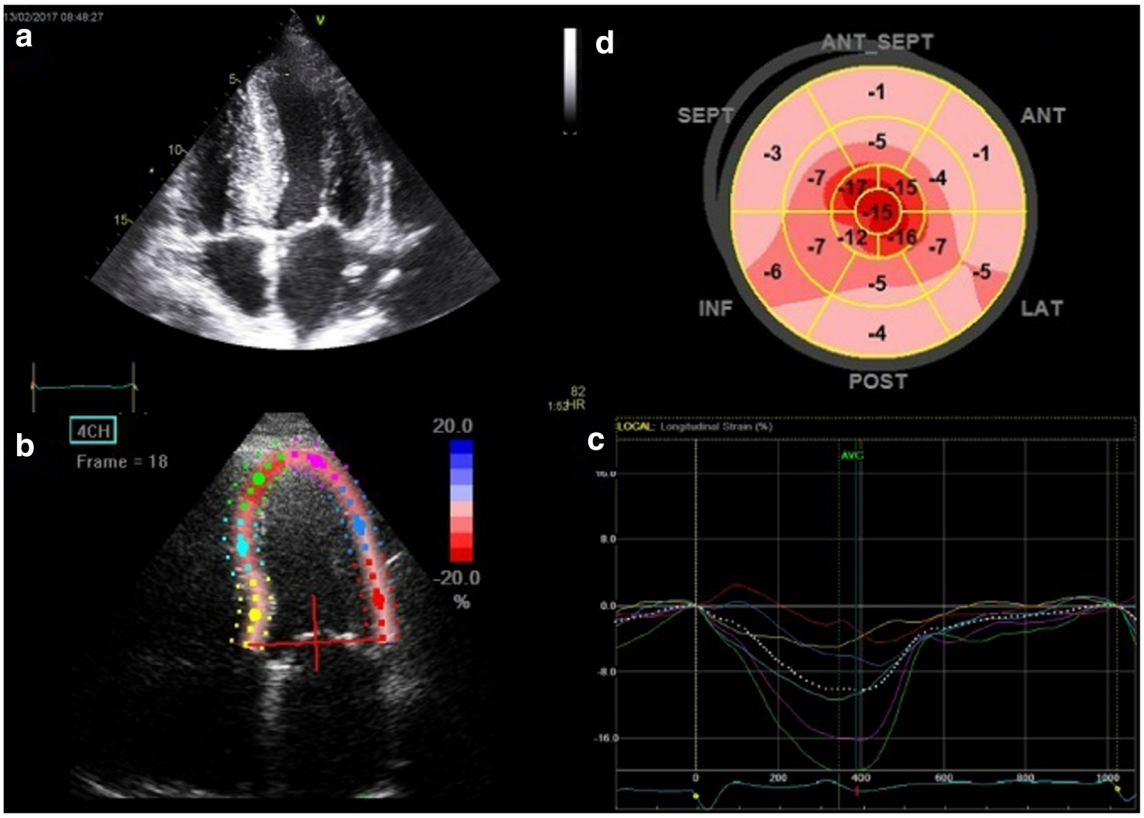

Fig. 1 **a** An apical 4-ch view showing an hypertrophic left ventricle with "granular sparkling" aspect, consistent with amyloidosis suspicion. **b** Delineation of the six segments composing the region of interest for strain acquisition. **c** Strain curves showing regional differences of LV LS in a heart affected by amyloidosis: some segments have a clearly better deformation pattern, with a LS of − 16% and over, against an average of − 8%. **d** A bull's eye plot showing a relative "apical sparing" pattern of LS, suggestive of cardiac amyloidosis

However, there is uncertainty about the early presentation of this pattern. The relative apical sparing longitudinal strain pattern was originally described in advanced CA patients whose median LV wall thickness was over 14 mm. Recently, it was reported that the finding is also clinically useful for detecting CA in less advanced patients with a borderline or mildly thickened LV wall (≤ 14 mm) [27].

Strain imaging can also give important insights on disease progression and prognosis, although it has to be cleared whether improvement in patient's heart condition can alter the relative apical sparing pattern.

About that, in a study [35] that assessed 2D global longitudinal strains of the LV and cardiac serological biomarkers in 206 consecutive patients with biopsy-proven systemic AL amyloidosis, only diastolic dysfunction and 2D global LS remained as independent predictors of survival in the multivariate analysis.

In a retrospective study [36] evaluating 97 patients with CA from 2004 to 2013 (59 AL, 38 transthyretin with diagnosis based on endomyocardial biopsy or advanced imaging criteria coupled with either extracardiac biopsy or genetic analysis), a high relative regional strain ratio demonstrated to be adversely prognostic.

Further, Liu et al. [37] compared 44 biopsy-proven systemic AL amyloidosis patients with LV hypertrophy and 30 normal controls, and multivariate analysis showed that NYHA class and mid-septum systolic longitudinal strain were independent predictors for survival.

Quarta et al. [38] analyzed 172 patients with cardiac amyloidosis (80 AL, 36 ATTRm, 56 ATTRwt) by standard echocardiography and 2D speckle tracking imaging-derived LV longitudinal, radial, and circumferential strains and demonstrated that LS and advanced NYHA class were negative predictors of survival. Instead, TTR-related causes were favorable predictors.

Also, 3D echocardiography has shown some potential in evaluation and diagnosis of CA, although stronger evidence is needed to validate this method. There are evidences [15, 39] of intraventricular segmental dyssynchrony in CA subjects on 3D echocardiography. Further, using 3D-STE–derived measurements, there are evidences of significant alterations in segmental LV rotation in CA including near absence of left ventricular twist [40].

Left atrial strain imaging

Although left ventricular alterations are predominant in the setting of CA, left atrial (LA) function is very often significantly impaired and its analysis can provide further insights about pathophysiology of CA. LA or bi-atrial enlargement is a

common finding in CA and LA size has been reported to be a poor prognostic indicator in affected patients [41].

However, LA enlargement is an anatomical measurement and does not necessarily reflect its function [42]. Myocardial deformation imaging is a robust and sensitive echocardiographic technique for the quantitative assessment of LA function.

Nochioka et al. [43] showed that each phase of LA function (reservoir, conduit, pump) assessed by 2D-STE was severely impaired and highly correlated to left ventricular deformation but independent of LA size. The impairment of both passive and active LA function suggests a combination of both LV and intrinsic LA failure in the pathophysiology of LA dysfunction. Further, despite the known different clinical courses, LA function was more impaired in ATTRwt compared to AL amyloidosis.

However, this study includes only patients in advanced stage of the disease, whereas a recent study [44] showed that functional LA parameters are progressively altered in light-chain amyloidosis patients according to the stage of the disease. In particular, a decrease in 3D peak atrial longitudinal strain was associated with worse outcome, independently of LA volume. The relationship between LA function and new onset of AF in patients with AL amyloidosis is of high clinical interest, although it was not an endpoint of the study. This association needs to be confirmed by further prospective studies.

Finally, atrial standstill derived from markedly increased LV diastolic pressures and intrinsic LA dysfunction is probably at the base of the possibility of left atrial thrombosis in CA [45]. Left atrial thrombi may occur in cardiac amyloidosis even in sinus rhythm [46]. In this context, the study of LA function, also with STE, could represent a useful clinical tool to identify CA patients with higher thromboembolic risk.

Based on these evidences, the assessment of LA function in CA should be performed routinely in the clinical practice.

Right ventricular strain imaging

The importance of the right ventricular (RV) involvement has often been underestimated in CA patients, and the role of its contractile and systo-diastolic performance was undervalued. Nowadays, few data are available about RV involvement in amyloidosis, mainly focusing on chamber enlargement and RV systolic function [47–49]. Moreover, little is known about the relationship between RV dysfunction and LV dysfunction.

However, the assessment of RV function can provide valuable information about the stage and prognosis of amyloidosis. In particular, a study [51] showed that, in patients with AL amyloidosis, an RV longitudinal strain less negative than − 17% identifies a cohort of patients with marked RV dysfunction and at high risk of death. The prognostic significance of

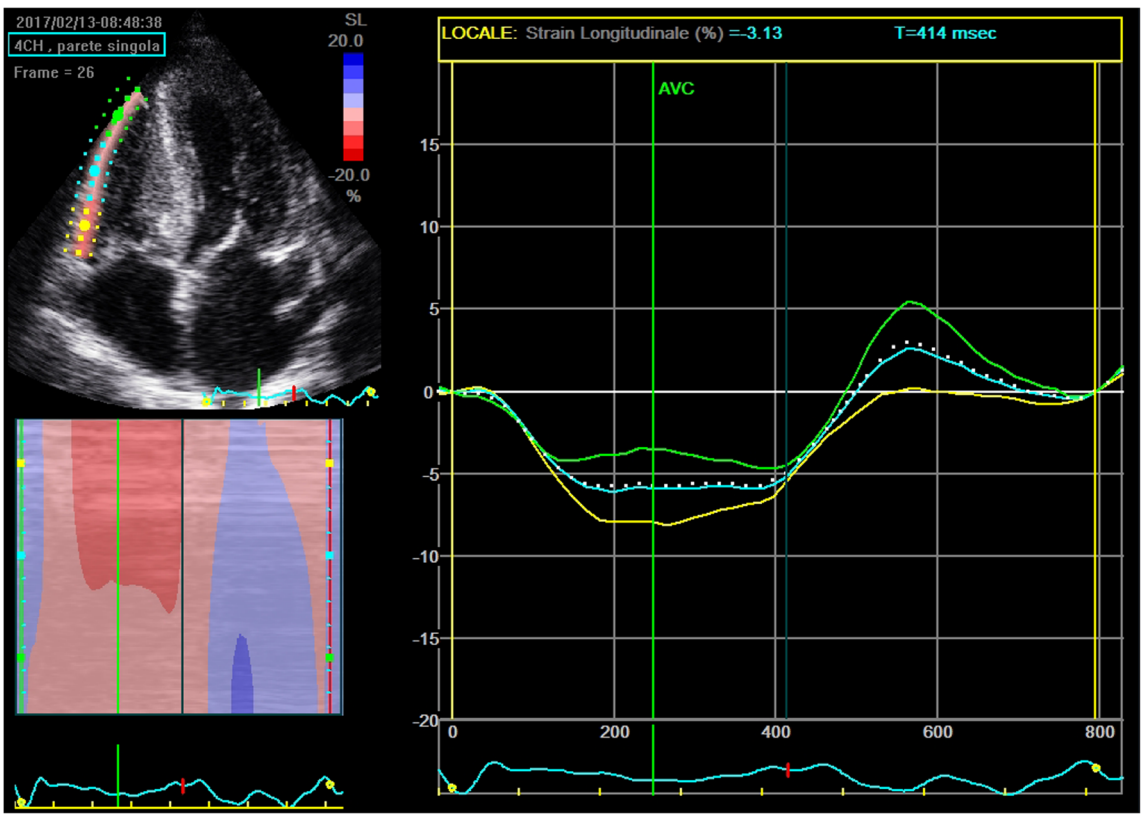

Fig. 2 A right ventricular free wall strain severely impaired (− 6%) in a patient affected by cardiac amyloidosis

RV longitudinal strain persisted after adjusting for the cardiac biomarker NT-proBNP, for indexes of systolic and diastolic LV function, for pulmonary artery systolic pressure, and for diastolic RV dysfunction, as assessed by tricuspidal E′ and E/E′. RV longitudinal strain was the only echocardiographic predictor of prognosis, superior to the standard 2D, Doppler flow, and tissue velocity measurements.

RV longitudinal could be added to TAPSE as a valuable RV-derived prognostic marker in patients with cardiac AL amyloidosis (Fig. 2).

Clinical perspectives

Strain deformation analysis with 2D-STE can provide data that, while based on standard echocardiographic images, provide early information on the development of the disease, with earlier modifications than the traditional echocardiographic indices (E/e′, global systolic function, LA size, mitral annular dysfunction).

Strain analysis is angle independent, semiquantitative and relatively operator independent, and can also be useful in the differential diagnosis with other forms of heart disease characterized by concentric hypertrophy, especially in earlier-stage disease. About that, we highlighted the importance of the peculiar pattern of LV myocardial longitudinal shortening called "apical sparing" that seem to be sensible and specific for differential diagnosis, although further evidences are needed to validate this pattern in early-stage disease, and eventually in response of specific therapy. The progressive reduction of the ventricular strain showed a correlation with the extent of fibrosis documented as LGE in CMR and also with the NYHA class.

As a feasible and reproducible technique for quantification of myocardial deformation, LV longitudinal function by LS and 2D global LS provided incremental prognostic value regarding cardiovascular outcome in amyloidosis and seemed to be superior to standard echocardiography and cardiac biomarkers.

Further valuable information about stage and prognosis is provided also by the integrated assessment of RV function and LA function.

Conclusions

Assessment of LV, RV, and LA function by STE can be useful in CA, guiding the clinician in the diagnostic process, especially when gold standard methods are not readily available. Strain parameters may also represent prognosticators. Therefore, considering the growing evidence supporting an important role of STE in this field, we highlight the role of multimodality imaging and suggest that speckle tracking analysis could be performed routinely as a part of cardiac amyloidosis evaluation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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