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The diagnostic performance of cardiac magnetic resonance in detection of myocardial involvement in AL amyloidosis

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AL amyloidosis; cardiac magnetic resonance; cardiomyopathy; echocardiography; late gadolinium enhancement

Summary

Background The non-invasive assessment of amyloid heart disease may be challenging. Cardiac magnetic resonance (CMR) represents a method of choice for assessment of left ventricular (LV) morphology and function, and it also provides a unique possibility to evaluate the presence of amyloid deposition by the late gadolinium enhancement (LGE) technique. However, so far, published studies have not been consistent in terms of described LGE patterns associated with amyloid cardiomyopathy.

Aims To compare echocardiographic and CMR assessment of LV morphology and function and to evaluate the presence and pattern of LGE in a population of patients with AL amyloid cardiomyopathy.

Methods Twenty-two consecutive patients with newly diagnosed AL amyloid cardiomyopathy and without contraindications to CMR were comprehensively examined by echocardiography and CMR.

Results Echocardiography and CMR did not differ in the evaluation of interventricular septal thickness, LV end-diastolic diameter and ejection fraction. Significant differences were found between echocardiographic and CMR estimates of LV end-diastolic volume ($P<0{\cdot}01$) and LV mass ($P<0{\cdot}001$). Various global LGE patterns (transmural homogenous or heterogeneous, subendocardial) were present in 17 patients (77%), patchy LGE was observed in one case (4·5%) and suboptimal nulling of the myocardium was reported in two subjects (9%).

Conclusions Echocardiography significantly overestimates LV mass and underestimates LV volumes in patients with AL amyloid cardiomyopathy as compared to CMR. As it is present in more than three quarters of individuals with AL amyloid cardiomyopathy, any type of global LGE pattern may be considered as pathognomic for amyloid heart disease.

Introduction

Amyloidosis is a group of diseases characterized by extracellular deposition of insoluble fibrillary protein called amyloid, which has specific chemical and morphological properties (Abbas, 2005). The various forms of amyloidoses are classified based on the underlying protein type and pathological process. Cardiac amyloidosis (CA), that is infiltration of cardiac tissues by amyloid, can be found in several types of amyloidosis (esp. AL, senile-cardiac and transthyretin amyloidosis). The most common form is systemic AL amyloidosis derived from immunoglobulin light chains. Cardiac involvement has been recognized as a crucial determinant of treatment possibilities as well as of prognosis in patients with AL amyloidosis (Falk, 2005; Dubrey *et al.*, 2011). Progressive accumulation of amyloid in the myocardial interstitium leads to thickened cardiac walls and diastolic dysfunction and eventually results in restrictive cardiomyopathy (Child *et al.*, 1976; Klein *et al.*, 1990, 1991; Hongo *et al.*, 1991). The current gold standard for diagnosis of amyloid cardiomyopathy is endomyocardial biopsy (EMB). However, this technique is invasive and specimens are taken just from only a few focal points, often only

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in the right ventricle. Diseased portions of the heart can therefore be easily missed. Furthermore, the procedure is associated with several major risks even if performed in experienced centres. Thus, the diagnosis of AL amyloid cardiomyopathy is usually based on echocardiographic findings, mainly left ventricular (LV) wall thickening, together with positive extracardiac biopsy for AL amyloidosis (Gertz *et al.*, 2005). Nevertheless, the interpretation of echocardiography can be challenging when other possible causes for LV hypertrophy coexist, for example arterial hypertension. In recent years, several studies suggested cardiac magnetic resonance (CMR) to be a valuable tool for non-invasive diagnosis of amyloid cardiomyopathy (Maceira *et al.*, 2005; Perugini *et al.*, 2006; Hosch *et al.*, 2008; Vogelsberg *et al.*, 2008; Austin *et al.*, 2009; Syed *et al.*, 2010). As CMR has been generally considered to be the gold standard for the assessment of ventricular volumes and mass, it would be expected to provide accurate measurements of LV morphology and function also in amyloid heart disease. However, the major advantage of CMR is its unique possibility of non-invasive tissue characterization. The late gadolinium enhancement (LGE) technique demonstrates myocardial abnormalities in cases with expanded interstitial space, such as ischaemic and non-ischaemic fibrosis or pathological myocardial infiltration (McCrohon *et al.*, 2003; Moon *et al.*, 2004; Elliott & Kim, 2005). Previously cited studies demonstrated high utility of LGE-CMR in the diagnosis of suspected amyloid cardiomyopathy; however, their results were not uniform in terms of described LGE patterns associated with amyloid heart disease.

Therefore, the aims of our study were as follows: (i) to compare echocardiographic and CMR assessment of LV morphology and function and (ii) to evaluate the presence and pattern of LGE in a population of patients with biopsy-proven AL amyloidosis and echocardiographic evidence of amyloid cardiomyopathy.

Methods

Study population

We prospectively examined 22 consecutive patients who were newly diagnosed with AL amyloid cardiomyopathy in the General University Hospital in Prague between March 2008 and June 2012 and did not have any contraindications to CMR (i.e. 56% of total 39 patients with AL amyloid heart disease newly diagnosed in this period). All enrolled patients had histological confirmation of amyloidosis by tissue biopsies (cardiac 9, extracardiac 13), evidence of markedly elevated serum-free light chain ratio, monoclonal protein in the serum or urine, monoclonal population of plasma cells in the bone marrow and exhibited cardiac involvement diagnosed by echocardiographic criteria (Gertz *et al.*, 2005). In all subjects, clinical assessment, ECG, echocardiography and LGE-CMR were performed. New York Heart Association (NYHA) functional class was ascertained at the time of their clinical evaluation with a cardiologist. The study was approved by institutional ethics committee, and all patients gave written informed consent.

Histopathological evaluation of biopsy samples

The presence of amyloidosis was diagnosed with Congo red staining and demonstration of red–green birefringence under cross-polarized light. Immunohistochemical stains were performed on tissue sections with the use of commercial antisera against κ and λ immunoglobulin light chains.

Electrocardiogram

Standard 12-lead electrocardiogram (ECG) was obtained and analysed for standard characteristics and maximal precordial and limb lead voltages. Low QRS voltage pattern was defined using the criteria described by Carroll *et al.* (1982): all QRS amplitudes in the limb leads (I, II, III, aVL and aVF) <0·5 mV or the sum of the S wave in V1 and the R wave in V5 or V6 of <1·5 mV in the precordial leads.

Echocardiography

All patients were examined at rest lying in the left lateral decubitus position. The measurements were made using a Vivid 7 or Vivid 9 (GE Healthcare, Milwaukee, WI, USA) ultrasound machines. M-mode measurements of the interventricular septal thickness (IVS), left ventricular end-diastolic diameter (LVEDD), posterior wall thickness (PW) and left atrial diameter (LA) were performed in parasternal long-axis view according to the recommendations of the American Society for Echocardiography (Lang *et al.*, 2005). Cardiac involvement with amyloid was defined as a mean left ventricular (LV) wall thickness (IVS and PW) >12 mm in the absence of arterial hypertension or other potential causes of left ventricular hypertrophy (Gertz *et al.*, 2005). LV mass was calculated by the method described by Devereux *et al.* (1986). LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF) were measured using the modified Simpson's method (Weyman, 1982). Diastolic function of the LV was assessed according to the current recommendations using mitral flow velocities and mitral annular velocities recorded by pulsed-wave Doppler and pulsed-wave tissue Doppler, respectively, in an apical four-chamber view (Nagueh *et al.*, 2009). Pseudonormal and restrictive filling patterns were considered representative for advanced LV diastolic dysfunction. All echocardiographic data were acquired over three consecutive beats and averaged using sweep speed of 50–100 cm s^{-1}.

CMR protocol

Electrocardiogram-gated CMR was performed in a breathhold with a 1·5-T system (Philips Gyroscan Intera T15, Philips Medical Systems, Best, Netherlands). After initial scout images, multiple long-axis and short-axis cine steady-state free

precession images were obtained from the atrioventricular ring to the LV apex. The sequence parameters were as follows: echo time (TE) 1·46 ms, repetition time (TR) 2·9 ms, flip angle 60°, matrix 204 × 192, field of view (FOV) 320–440 mm with phase FOV 0·75–1·0 and 8 mm slice thickness without any interslice gap. LGE images covering the LV in multiple short-axis and long-axis views were obtained between 1 and 15 min after an intravenous bolus of 0·2 mmol kg^{-1} gadoterate meglumine (Dotarem; Guerbet, S.A., Villepinte, France) with segmented inversion recovery fast gradient echo sequences (TE 1·19 ms, TR 3·7 ms, flip angle 15°, matrix 209 × 164, FOV 310 mm). Due to the well-known difficulties with determining the optimal inversion time (TI) to null myocardium in case of CA, selection of optimal TI for LGE images was accomplished using a multi-TI cine fast gradient echo sequence, which generates 40 images in a single slice location with increasing TIs. Multiple sets of images were obtained to optimize LGE images.

CMR analysis

Left ventricular end-diastolic diameter, LVEDV, LV mass, LVEF and IVS were measured by tracing epicardial and endocardial borders manually with commercial software (Extended MR Work Space 2.6.3.4; Philips). Papillary muscles were excluded from LV mass. LGE images were reviewed by consensus of two readers (T.P. and M.M.). The presence of LGE was assessed as none, patchy focal, global subendocardial and global transmural homogenous or heterogeneous patterns; suboptimal nulling of the myocardium was also taken into the consideration (Austin *et al.*, 2009).

Intra-observer and interobserver variability of CMR measurements

Intra-observer variability was determined by having reader repeat measurements of LVEDD, LVEDV, LV mass, LVEF and IVS in 10 subjects who were randomly selected. Interobserver variability was determined by having a second reader measure these variables. Intra-observer and interobserver variabilities were assessed by the coefficient of variability for differences.

Statistical analysis

Data are expressed as mean ± standard deviation or as a number and percentage of subjects. Differences between echocardiographic and CMR parameters were compared with the unpaired Student's t-test. A value of $P<0·05$ was considered statistically significant. Statistical analysis was performed with commercially available JMP 5.1. statistical software (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

Results

The clinical, ECG, echocardiographic and CMR variables are summarized in Table 1. A majority of patients were in NYHA class III or IV, indicating advanced stage of heart failure. Low QRS voltage on ECG was found in half of the study population. In all, LV was not dilated. Decreased LVEF <50% was present in four patients as assessed by echocardiography and in six individuals as evaluated by CMR. Advanced LV diastolic dysfunction, that is pseudonormal or restrictive filling pattern, was found in 50% of subjects. There were no statistical significant differences between echocardiographically and CMR derived values of IVS, LVEDD and LVEF. However, statistically significant difference was noticed between echocardiographic and CMR estimates of LVEDV ($P<0·01$) and LV mass ($P<0·001$), respectively. The results of analysis of intra-observer and interobserver variability of CMR measurements are given in Table 2.

Table 1 Clinical, ECG, echocardiographic and CMR variables of the study population.

Age (years)	65 ± 9
Male gender (%)	15 (68)
NYHA class III/IV (%)	13 (59)
Low QRS voltage on ECG	11 (50)
Echocardiographic parameters	
IVS (mm)	14 ± 2
LVEDD (mm)	45 ± 5
LV mass (g)	223 ± 53***
LVEDV (ml)	92 ± 29**
LVEF (%)	59 ± 11
Pseudonormal or restrictive filling pattern	11 (50)
LA (mm)	46 ± 7
Cardiac magnetic resonance parameters	
IVS (mm)	15 ± 3
LVEDD (mm)	43 ± 6
LV mass (g)	140 ± 47
LVEDV (ml)	123 ± 42
LVEF (%)	59 ± 11

Data are expressed as mean ± SD or as a number and percentage of subjects.
IVS, Interventricular septal thickness; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume, LVEF, left ventricular ejection fraction.
**P<0·01, ***P<0·001 for echocardiographic vs. CMR parameters.

Table 2 Intra-observer and interobserver variability of CMR measurements.

	Intra-observer variability (%)	Intra-observer variability (%)
IVS	9·0	8·5
LVEDD	3·8	5·4
LV mass	6·8	6·1
LVEDV	6·4	8·5
LVEF	3·9	4·7

IVS, Interventricular septal thickness; LVEDD, left ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume, LVEF, left ventricular ejection fraction.

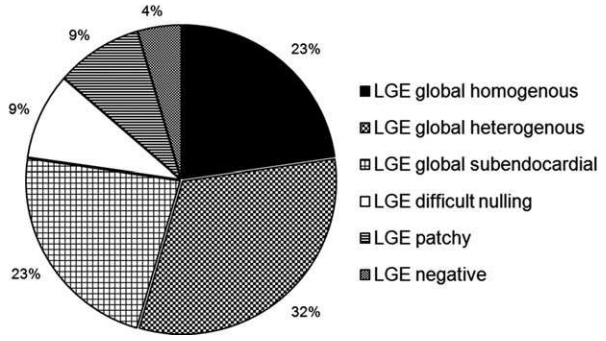

Figure 1 Pie chart demonstrating the prevalence of various LGE patterns.

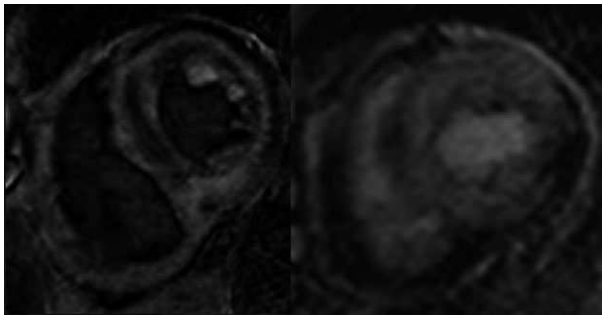

Figure 2 The examples of global subendocardial (left) and transmural homogenous (right) LGE patterns in patients with amyloid cardiomyopathy.

The presence of LGE patterns is shown in Fig. 1. Global transmural homogenous or heterogeneous LGE patterns were found in 5 (23%) and 7 subjects (32%), respectively, a global subendocardial LGE pattern was found in five individuals (23%) (Fig. 2). Any type of global LGE pattern was thus present in 17 patients (77%). Suboptimal nulling of the myocardium was reported in another two subjects (9%). A patchy LGE pattern was observed in one case (4·5%), and in one individual, no LGE was present. There were no statistically significant differences in echocardiographic as well as CMR variables between patients with any type of global LGE pattern and other studied individuals.

During the study period, 11 patients (50%) have died. Any type of global LGE pattern was present in nine of them: global transmural homogenous or heterogeneous patterns in seven subjects, a global subendocardial pattern in two individuals; patchy type of LGE as well as the absence of any LGE pattern was found in two other deceased patients.

Discussion

The results of our study demonstrate several important issues related to diagnostics of AL amyloid cardiomyopathy. First, echocardiographic and CMR measurements of IVS, LV diameters and LVEF are comparable; however, in comparison with CMR, M-mode and two-dimensional echocardiography significantly overestimate LV mass and underestimates LV volumes in patients with AL amyloid cardiomyopathy. Although, according to our best knowledge, our study is the first to study this topic in detail in AL amyloidosis, these findings are not surprising. Several previous studies have clearly demonstrated that M-mode echocardiography overestimates LV mass, especially in patients with LV hypertrophy, whether due to arterial hypertension or as an expression of hypertrophic cardiomyopathy (Allison *et al.*, 1993; Bottini *et al.*, 1995; Missouris *et al.*, 1996; Devlin *et al.*, 1999). This LV mass overestimation is the result of assumptions made in the calculation of mass from M-mode recordings which are invalid when LV geometry is abnormal. Furthermore, the worsening of spatial resolution with increasing depth may influence the accuracy of M-mode measurements of LV posterior wall thickness and ultimately lead to an incorrect estimate of LV mass. The underestimation of LV volumes by two-dimensional echocardiography relative to CMR has also been documented in a number of studies (Bellenger *et al.*, 2000; Darasz *et al.*, 2002). Exclusion of the volume of the LV outflow tract and, more importantly, foreshortening of the LV in apical views clearly play a role in echocardiographic underestimation of LV volumes. Furthermore, two-dimensional echocardiographic method for assessment of LV volumes requires heart shape to conform to a geometric model. Poor endocardial border delineation may also contribute to less accuracy of echocardiographic volumetry of the LV. Our findings are very important for planning of future studies focused on the evaluation of the efficacy of specific haematological therapy on LV mass and function in patients with AL amyloid cardiomyopathy. Two-dimensional echocardiography will be sufficient for serial follow-up of LV ejection fraction; however, if changes in LV mass should be the endpoint then CMR represents a preferable method for evaluation. Furthermore, all CMR measurements are highly reproducible as demonstrated by analysis of intra-observer and interobserver variability. Nevertheless, there is a clear potential for real-time three-dimensional echocardiography to replace CMR in complex assessment of LV mass and function in patients with amyloid heart disease as its estimates of LV volumes, LVEF and LV mass are comparable to CMR measurements including subjects with hypertrophied LV (Chang *et al.*, 2013).

Secondly, our results confirm high utility of LGE-CMR in the diagnosis of AL amyloid cardiomyopathy. Maceira *et al.* (2005) were first to examine patients with CA by LGE-MRI and compared their findings with observations in hypertensive controls. These authors found a distinctive global subendocardial pattern of LGE in 69% of amyloid patients which was not present in hypertensive individuals. Patients with LGE exhibited greater LV mass than unenhanced patients. In one LGE-CMR positive patient, an autopsy was performed showing substantial interstitial expansion with amyloid which was dominantly present in the subendocardial region. Very similar findings were subsequently presented by Vogelsberg *et al.* (2008) and Austin *et al.* (2009). On the other hand, Perugini

et al. (2006) found LGE in 76% patients with confirmed diagnosis of amyloid heart disease; however, high variability of LGE distribution was described with the mid-ventricular regions being more often involved. So far the largest series of 120 patients with amyloidosis studied by CMR was published by Syed *et al.* (2010). Cardiac histology was available and positive in 35 individuals; the remaining patients were divided into those with and without echocardiographic evidence of CA. Of the 35 patients with histologically proven amyloid cardiomyopathy, abnormal LGE was present in 97%. A global transmural LGE pattern, either homogenous or heterogeneous, was found in 60% and a global subendocardial LGE pattern was observed in 23% of patients. Thus, a global LGE pattern of some type was present in 83% subjects. Patchy, focal LGE was found in 6% and so-called suboptimal nulling of the myocardium, where adequately nulled 'black' images of the myocardium could not be obtained despite the use of multiple inversion times, was present in 8% of patients with biopsy-proven amyloid cardiomyopathy. A global LGE pattern was associated with greater interstitial amyloid deposition on right ventricular histologic specimens. Among patients without cardiac histology, LGE was present in 86% of those with echocardiographic signs of CA and in 47% of those without evidence of amyloid heart disease by echocardiography. However, in patients without echocardiographic evidence of amyloid cardiomyopathy, the presence of LGE was associated with worse clinical, ECG and cardiac biomarkers profiles. The prevalence of each LGE pattern in this non-cardiac histology group was as follows: global transmural 37%, global subendocardial 16%, suboptimal nulling 10%, focal patchy 12% and absent in 14% of patients. The results of our study are well in line with findings reported by Syed *et al.* (2010). A global LGE pattern of any type was observed in almost 80% of our patients with verified AL amyloid cardiomyopathy; suboptimal nulling of the myocardium and patchy focal LGE pattern were also present in similar percentage compared to Syed *et al.* Based on our results, we believe, in accordance with other authors (Syed *et al.*, 2010), that any type of global LGE – subendocardial, homogenous or heterogeneous transmural patterns – represents a rather unique LGE pattern highly specific for amyloid heart disease. Indeed, LGE-CMR findings in other cardiomyopathies are clearly different. In hypertrophic cardiomyopathy, the most common differential diagnosis, LGE typically involves the middle third of the hypertrophied ventricular wall in a patchy, multifocal distribution (Mahrholdt *et al.*, 2005). The peculiar pattern characterized by intramural LGE in the basal posterolateral region of the LV is characteristic for Fabry disease-related LVH, which represents another form of 'non-sarcomeric' hypertrophic cardiomyopathy like amyloid cardiomyopathy (Moon *et al.*, 2003). The involvement of subendocardium is typical for coronary artery disease, where the LGE pattern follows a 'wave front' of ischaemia with subsequent necrosis and fibrosis and extends in various degrees from subendocardium to epicardium (Wu *et al.*, 2001). However, compared with amyloid heart disease, this 'ischaemic-type' of LGE is regional, not global, limited to the territory of the affected coronary artery. In agreement with others, we strongly suggest that detection of suboptimal nulling of the thickened LV myocardium is a cause for concern in amyloid heart disease patients (Syed *et al.*, 2010). While it is important to rule out technical issues or incorrect selection of inversion time as potential causes, this finding may be indicative of amyloid interstitial infiltration, especially if the blood pool appears unusually dark (Maceira *et al.*, 2005). The dark blood pool results from similar myocardial and blood T1 values because of high myocardial uptake and rapid blood washout of the gadolinium. Interestingly, in a few patients with amyloid cardiomyopathy focal patchy LGE may be present. Syed *et al.* (2010) suggest that patchy LGE may reflect earlier stages of amyloid infiltration. Indeed, the only patient in our cohort with this LGE pattern expressed only borderline thickening of the IVS. However, focal LGE may be found in many other heart diseases as a result of fibrosis or inflammation and thus cannot be considered a specific finding for amyloid cardiomyopathy (Mahrholdt *et al.*, 2005). Finally, while the prognostic significance of LGE-CMR in AL amyloid cardiomyopathy has been studied in recent years, results have been conflicting. In a retrospective study conducted by Mekinian *et al.* (2010) involving 29 patients with AL amyloidosis, the presence of LGE was associated with a significantly increased risk of death, in particular of cardiac origin, but was not independent of clinical heart failure. On the other hand, Ruberg *et al.* (2009) did not find the presence of LGE to be a significant predictor of survival in their cohort of 28 patients with AL amyloid cardiomyopathy. Although the results of our study support the idea that the presence of LGE, and especially its global pattern, is related to increased risk of death in patients with AL amyloid cardiomyopathy, we strongly believe that further studies with higher numbers of patients are clearly needed to assess the prognostic utility of LGE-CMR in AL amyloidosis.

We are well aware of the limitations of our study. Firstly, the number of studied patients is limited. However, CA is a rather infrequent diagnosis and our study cohort did not significantly differ from other previously published series regarding the number of patients (Maceira *et al.*, 2005; Perugini *et al.*, 2006; Austin *et al.*, 2009). Secondly, cardiac histology was not available in all subjects. This would certainly increase the validity of our study. Nevertheless, routine clinical diagnosis of CA does not require performance of EMB if typical echocardiographic features of amyloid cardiomyopathy together with positive extracardiac biopsy for amyloid are present (Gertz *et al.*, 2005). Therefore, in all but one previously published studies cardiac histology was not performed in all subjects (Maceira *et al.*, 2005; Perugini *et al.*, 2006; Austin *et al.*, 2009; Syed *et al.*, 2010). Thirdly, we did not include a control group to study the sensitivity and specificity of LGE-CMR. We agree with Syed *et al.* (2010), that given the scarce presence of amyloid cardiomyopathy, a valid assessment of these patients would require a large control population which it would be very difficult to establish.

Conclusions

Echocardiography and CMR are comparably effective in the assessment of one-dimensional LV morphological characteristics as well as in the evaluation of LVEF in patients with AL amyloid cardiomyopathy. However, two-dimensional echocardiography significantly overestimates LV mass and underestimates LV volumes in these patients as compared to CMR. Any type of global LGE pattern – transmural (homogenous or heterogeneous) or subendocardial – can be found in more than three quarters of individuals with AL amyloid heart disease. Therefore, CMR represents a reliable non-invasive imaging method for the assessment of myocardial involvement in patients with AL amyloidosis. A global transmural or subendocardial LGE pattern may be considered pathogenomic for amyloid cardiomyopathy.

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Conflict of interest

The authors have no conflict of interest.

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WILEY Echocardiography

Simplified apical four-chamber view evaluation of relative apical sparing of longitudinal strain in diagnosing AL amyloid cardiomyopathy

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Aim of the study: To assess the diagnostic utility of a simplified approach to relative apical sparing of longitudinal strain (RAS LS) using only an apical four-chamber view (A4C) in patients with AL amyloid cardiomyopathy (ALAC).

Methods: We retrospectively evaluated echocardiographic recordings of 20 patients with ALAC, 20 patients with Fabry disease-related cardiomyopathy (FD), and 20 patients with concentric hypertensive left ventricular hypertrophy (HLVH) matched for mean LV mean thickness. Peak segmental LS values of the interventricular septum and lateral LV wall were measured in the A4C using two-dimensional speckle-tracking echocardiography. RAS LS was calculated as average apical LS/(average basal LS + average midventricular LS).

Results: Relative apical sparing of longitudinal strain values in patients with ALAC (1.23 ± 0.64) were significantly higher than those in FD patients (0.75 ± 0.19, $P < 0.05$) as well as in individuals with HLVH (0.75 ± 0.23, $P < 0.05$), but with a significant overlap. The optimal RAS LS value differentiating ALAC from FD and HLVH with 70% sensitivity and 75% specificity was 0.88 (AUC 0.79). In multivariate modeling, RAS LS was significantly additive to traditional predictors of ALAC (low QRS voltage and pseudoinfarct ECG patterns, pericardial effusion, E/e′ ratio, E-wave deceleration time; $P < 0.05$ for all models).

Conclusions: Simplified RAS LS evaluation represents an attractive approach for diagnostics of ALAC. However, because of considerable overlap with other disorders with hypertrophic phenotype, the analysis of RAS LS in the A4C should be combined with other traditional echocardiographic and ECG predictors in differentiating ALAC from other forms of concentric LV wall thickening.

KEYWORDS
amyloidosis, apical sparing, cardiomyopathy, Fabry disease, speckle tracking

1 | INTRODUCTION

Progressive extracellular deposition of insoluble fibrillary proteins within various organs is the common feature of a group of diseases called systemic amyloidoses. Clinically relevant cardiac involvement is present in amyloid light-chain (AL) amyloidosis and in hereditary or senile transthyretin-related amyloidosis.[1] In AL amyloidosis, amyloid cardiomyopathy is the major determinant of outcome. Early recognition and prompt initiation of therapy are thus of utmost importance as the median survival of untreated patients with AL amyloidosis

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is very poor, reaching only several months from the onset of heart failure.[2]

Echocardiography is still the mainstay for the noninvasive diagnosis of cardiac amyloidosis. However, concentric left ventricular (LV) wall thickening as the main finding suggestive of amyloid heart disease is regularly found in more prevalent heart pathologies including arterial hypertension and hypertrophic cardiomyopathy. Recently, relative apical sparing (RAS) of longitudinal strain (LS) by speckle tracking was described as a specific echocardiographic sign of cardiac amyloidosis useful in the differential diagnosis of unclear LV hypertrophy.[3] Furthermore, is has been also shown that RAS LS may serve as an independent prognostic factor in patients with amyloid heart disease.[4] However, the evaluation of RAS LS using standard approach, which is based on the assessment of regional LS of all LV walls, may not be feasible in numerous patients due to suboptimal visualization of anterior as well as anteroseptal wall in apical two-chamber and long-axis view, respectively.[5,6] Because the apex-to-base LS gradient is present in all LV walls in cardiac amyloidosis, we aimed to assess the diagnostic utility of a simplified approach to RAS LS evaluation using only an apical four-chamber view (A4C) to distinguish AL amyloid cardiomyopathy (ALAC) from other myocardial pathologies characterized by concentric LV hypertrophy matched for the same degree of mean LV wall thickness (MLVWT).

2 | METHODS

2.1 | Patient population

We retrospectively analyzed echocardiographic, ECG, clinical, and laboratory data of 20 patients with ALAC, 20 patients with Fabry disease-related cardiomyopathy (FD), and 20 patients with hypertensive left ventricular hypertrophy (HLVH). First, we identified ALAC individuals from the echocardiographic database of our institution, who were examined between January 2014 and December 2016 and in whom the diagnosis of ALAC was confirmed by current diagnostic criteria including histological confirmation of amyloidosis by tissue biopsies (endomyocardial biopsy in 11 subjects and extracardiac biopsy in 9 individuals).[7] Among these, only patients on stable sinus rhythm without bundle branch block and implanted pacemaker, with adequate two-dimensional (2D) images in A4C and without history of heart surgery, regional wall-motion abnormalities, or significant valvular heart disease were selected and constituted the final group of 20 ALAC patients that was further analyzed. Then, we identified 40 control patients with concentric LV hypertrophy matched for MLVWT: 20 patients with FD and 20 individuals with HLVH. Concentric LV hypertrophy was defined according to current guidelines as LV mass index > 115 g/m^2 for men and >95 g/m^2 for women with relative wall thickness above 0.42.[8] All these control subjects were examined during the same time period as ALAC patients and with the same echocardiographic machine. Again, in all of them, stable sinus rhythm without bundle branch block and implanted pacemaker, adequate 2D images in A4C and no history of heart surgery, absence of regional wall-motion abnormalities, or significant valvular heart disease were required. The diagnosis of FD was confirmed by the detection of α-galactosidase A deficiency in leukocytes and plasma and then confirmed by genetic analysis.[9] In individuals with HLVH, no other cause of LV hypertrophy than arterial hypertension was found. The study was approved by institutional ethics committee and ran in accordance with the Declaration of Helsinki, and all patients gave written informed consent.

2.2 | Echocardiography

All echocardiograms were performed on Vivid 9 ultrasound system (GE Healthcare, Chicago, IL, USA) with adequate quality of 2D images in A4C amenable to assessment of speckle-tracking strain. Adequate 2D image quality was defined as a frame rate > 50 frames per second and the absence of dropout or artifacts and inadequate visualization of any segment of the septal or lateral wall, respectively, in the A4C. Interventricular septal thickness (IVS), LV end-diastolic diameter (LVEDD), LV posterior wall thickness (PW), and left atrial diameter (LAD) were assessed by 2D measurements in the parasternal long-axis view. LV mass was then calculated using the modified Devereux formula[10] and indexed to body surface area; relative wall thickness was defined as 2 × PW/LVEDD. Mean LV wall thickness (MLVWT) was computed as (IVS + PW)/2. Left ventricular volumes and ejection fraction (LVEF) as well as left atrial volume (LAV) were measured in the A4C using single plane Simpson's method. Transmitral flow was recorded using pulsed-wave Doppler between the tips of mitral valve leaflets in the A4C, and peak early diastolic velocity (E), its deceleration time (DT), and peak late diastolic velocity (A) were measured. Early diastolic tissue Doppler velocity (e′) was measured using pulsed-wave technique on septal and lateral mitral annulus and then averaged. All measurements were performed in accordance with current recommendations.[8,11] The presence of pericardial effusion was evaluated in all routine echocardiographic views.

Longitudinal strain (LS) assessment was done using the dedicated workstation (EchoPAC, v.113, Advanced Analysis Technologies; GE Healthcare). In the A4C, LV endocardium was manually identified and the frame-by-frame tissue speckle tracking of the LV myocardium was automatically done throughout the cardiac cycle. The quality of tracking was checked, and manual adjustments of endocardial borders with automatic reanalysis were done if necessary. Peak systolic LS values from basal, midventricular, and apical segments of the LV were averaged to obtain three regional LS values in the A4C. The relative apical sparing longitudinal strain (RAS LS) was calculated as[3]:

RAS LS = apical LS/(basal LS + midventricular LS).

2.3 | Electrocardiogram

ECG recordings of adequate quality were available in 58 study subjects (97%). The low voltage on limb leads was defined as QRS amplitude of ≤0.5 mV in all limb leads. A pseudoinfarct pattern was defined as the presence of QS-waves in 2 consecutive anterior leads.[12]

2.4 | Clinical and laboratory data

Blood pressure and heart rate were measured at the time of echocardiography. All other clinical and laboratory data were extracted from patients' medical records.

2.5 | Statistical methods

Continuous variables were summarized using mean ± standard deviation (SD) and categorical variables using proportions. For testing of difference between baseline continuous variables, Kruskal-Wallis test was used with the Dunn post hoc test to compare the different groups, due to non-normal distribution of continuous data. Chi-square test or Fisher's test with post hoc adjustment using the Holm method was used for categorical data, as appropriate. Power of different variables to differentiate between ALAC and other groups was assessed using logistic models, and optimal cutoffs were defined based on the ROC analysis, using the point closest to the upper left edge as the optimal cutoff value. For multivariate modeling, we used nested logistic models to assess additive predictive power of RAS LS to established predictors of cardiac amyloidosis: the presence of pericardial effusion, low voltage on ECG, and DT and E/e′ as non-invasive estimates of LV filling pressures. Likelihood ratio test was used to compare the different models. The inter-observer variability and intra-observer variability for RAS LS assessment were assessed using Bland and Altman analysis in all ALAC subjects. Statistical analysis was done using the R software version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Germany). A *P*-value < 0.05 was considered significant.

3 | RESULTS

The clinical and laboratory characteristics of all studied subjects are shown in Table 1. The patients with FD were significantly younger and had lower heart rate than ALAC subjects. Blood pressure values were significantly lower in ALAC patients compared with two other study groups. Heart failure symptomatology expressed by NYHA class was higher in ALAC individuals than in FD as well as HLVH subjects.

Routine echocardiographic and ECG data are given in Table 2. By definition, MLVWT was similar in all study groups; furthermore, IVS also did not statistically differ among study groups. In FD, LV mass index was significantly higher than in ALAC as well as HLVH patients. In HLVH, LVEDD was higher and LAV index was smaller compared with two other study groups. The patients with FD expressed significantly better LVEF than ALAC individuals. The Doppler parameters of LV diastolic function and LV filling pressures were significantly worse in ALAC patients compared with FD as well as HLVH subjects. Pericardial effusion and low voltage on ECG were also more often present in ALAC patients.

The results of strain analysis are shown in Table 3 and Figure 1. The average basal values as well as midventricular peak systolic LS values were significantly lower in ALAC patients compared with FD as well as HLVH subjects ($P < 0.05$). With respect to average apical peak systolic LS, there was no difference between ALAC and FD patients; however, in HLVH subjects the value of averaged peak apical systolic LS was significantly higher compared with two other study groups ($P < 0.05$). The RAS LS was significantly higher in ALAC patient than in two other study groups ($P < 0.05$). The ROC analysis showed an optimal value of 0.88 for RAS LS to differentiate ALAC from FD and HLVH (AUC 0.79, sensitivity 70%, specificity 75%). However, there was a significant overlap in RAS LS among study groups as seen in Figures 2, 3.

Relative apical sparing of longitudinal strain as well as E/A ratio, DT, e′, E/e′, pericardial effusion, low voltage on ECG, and pseudoinfarct ECG pattern were identified to be significant univariate predictors of ALAC as presented in Table 4. Using nested multivariate modeling, the significant added predictive power of RAS LS to established predictors of ALAC—either low voltage or pseudoinfarct ECG pattern, pericardial effusion, and either E/e′ ratio or DT as two parameters of LV filling pressures—was demonstrated, as shown in Figure 4.

TABLE 1 Clinical and laboratory characteristics

Variable	ALAC (n = 20)	FD (n = 20)	HLVH (n = 20)
Age (years)	64 ± 12	54 ± 9*	62 ± 14
Sex (male)	14 (70)	11 (55)	17 (85)
BSA (m^2)	1.90 ± 0.17	1.74 ± 0.12*	2.10 ± 0.17**,***
HR (bpm)	78 ± 15	64 ± 9*	69 ± 11
SBP (mm Hg)	107 ± 16	133 ± 20*	141 ± 23**
DBP (mm Hg)	64 ± 14	78 ± 10*	75 ± 15**
NYHA class III or IV	15 (75)	2 (10)*	1 (5)**
Diabetes mellitus	1 (5)	0 (0)	10 (50)**,***
Hyperlipidemia	8 (40)	7 (35)	10 (50)
Hemoglobin (g/L)	127 ± 16	138 ± 13	138 ± 18
Creatinine (μmol/L)	186 ± 135	126 ± 117*	143 ± 135

Data are expressed as mean ± SD or as a number and percentage of subjects.
ALAC = AL amyloid cardiomyopathy; BSA = body surface area; DBP = diastolic blood pressure; FD = Fabry disease; HLVH = hypertensive left ventricular hypertrophy; HR = heart rate; NYHA = New York Heart Association; SBP = systolic blood pressure.
*$P < 0.05$ FD vs ALAC.
**$P < 0.05$ HLVH vs ALAC.
***$P < 0.05$ HVLH vs FD.

3.1 | Reproducibility

The inter-observer variability for measurement RAS LS showed an absolute bias between the two readings of −0.01 ± 0.23 (mean ± SD). The bias for intra-observer variability was 0.02 ± 0.28 (mean ± SD).

TABLE 2 Echocardiographic and electrocardiographic characteristics

Variable	ALAC (n = 20)	FD (n = 20)	HLVH (n = 20)
IVS (mm)	15.5 ± 2.2	15.5 ± 3.1	14.6 ± 1.0
MLVWT (mm)	14.8 ± 2.0	14.5 ± 2.0	14.1 ± 0.7
RWT	0.64 ± 0.15	0.56 ± 0.12	0.52 ± 0.09**
LVMI (g/m^2)	141 ± 32	178 ± 52*	139 ± 13***
LVEDD (mm)	45 ± 5	49 ± 5	53 ± 5**,***
LVEF (%)	59 ± 9	67 ± 7*	61 ± 8
LAD (mm)	47 ± 5	44 ± 6	45 ± 4
LAVI (mL/m^2)	43 ± 9	47 ± 14	38 ± 6**,***
E (cm/s)	90 ± 22	74 ± 16*	70 ± 19**
A (cm/s)	47 ± 25	71 ± 18*	77 ± 20**
E/A	2.61 ± 1.60	1.08 ± 0.31*	0.94 ± 0.30**
DT (ms)	187 ± 50	229 ± 52	259 ± 52**
e′ (cm/s)	4.5 ± 1.2	6.5 ± 1.5*	9.6 ± 9.4**
E/e′	22.1 ± 10.1	12.1 ± 4.3*	9.5 ± 4.2**
Pericardial effusion	15 (75)	0 (0)*	1 (5)**
Low QRS voltage on ECG	14 (70)	0 (0)*	1 (5)**
Pseudoinfarct pattern on ECG	10 (50)	0 (0)*	1 (5)**

Data are expressed as mean ± SD or as a number and percentage of subjects.
A = peak late mitral diastolic flow velocity; ALAC = AL amyloid cardiomyopathy; DT = deceleration time of early mitral diastolic flow velocity; E = peak early mitral diastolic flow velocity; e′ = average of medial and lateral early diastolic mitral annular tissue velocities; FD = Fabry disease; HLVH = hypertensive left ventricular hypertrophy; IVS = interventricular septal thickness; LAD = left atrial diameter; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MLVWT = mean left ventricular wall thickness; RWT = relative wall thickness.
*P < 0.05 FD vs ALAC.
**P < 0.05 HLVH vs ALAC.
***P < 0.05 HVLH vs FD.

TABLE 3 Apical four-chamber longitudinal strain analysis

Variable	ALAC (n = 20)	FD (n = 20)	HLVH (n = 20)
Basal LS (%)	5.2 ± 2.9	11.4 ± 2.0*	13.4 ± 3.3**
Mid LS (%)	9.4 ± 2.3	12.8 ± 2.6*	15.7 ± 3.1**,***
Apical LS (%)	15.7 ± 3.3	18.1 ± 5.8	21.1 ± 4.9**
RAS LS	1.23 ± 0.64	0.75 ± 0.19*	0.75 ± 0.23**

Data are expressed as mean ± SD.
ALAC = AL amyloid cardiomyopathy; AS LS = relative apical sparing of longitudinal strain; FD = Fabry disease; HLVH = hypertensive left ventricular hypertrophy; LS = longitudinal strain.
*P < 0.05 FD vs ALAC.
**P < 0.05 HLVH vs ALAC.
***P < 0.05 HVLH vs FD.

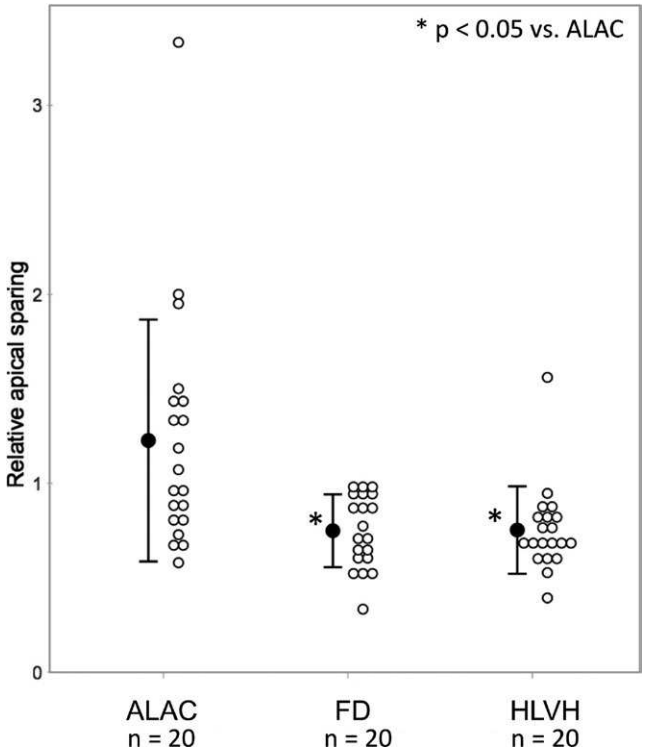

FIGURE 1 Relative apical sparing of longitudinal strain in the A4C in ALAC, FD, and HLVH patients (A4C = apical 4-chamber view; ALAC = AL amyloid cardiomyopathy; FD = Fabry disease-related cardiomyopathy; HLVH = hypertensive left ventricular hypertrophy; RAS LS = relative apical sparing of longitudinal strain)

4 | DISCUSSION

The present study shows that simplified evaluation of RAS LS using only the A4C may be used in noninvasive diagnostics of ALAC; however, because some degree of RAS LS in the A4C is also found in other forms of concentric LV wall thickening, the analysis of this parameter should be always combined with other traditional echocardiographic and ECG predictors of ALAC.

Interestingly, an initial observation on the difference in wall-motion pattern between the apex and the rest of the LV in cardiac amyloidosis has been reported by Belkin et al[13] using visual assessment of regional kinetics of the ventricle. The authors described a distinctive 2D echocardiographic pattern of preserved segmental wall motion at LV apex with hypokinesis in basal to midsegments in seven consecutive patients with biopsy-proven cardiac amyloidosis. In their landmark paper, Phelan et al[3] were first to describe a phenomenon of relative "apical sparing" of LS in the LV apex as assessed using 2D speckle tracking to be an easily recognizable, accurate, and reproducible parameter of amyloid heart disease. In comparison with the patients with ALAC or transthyretin-related amyloid cardiomyopathy to subjects with other forms of LV hypertrophy (hypertrophic cardiomyopathy, aortic stenosis) matched for mean LV thickness, a value of RAS LS assessed in all three apical views >1.0 differentiated cardiac

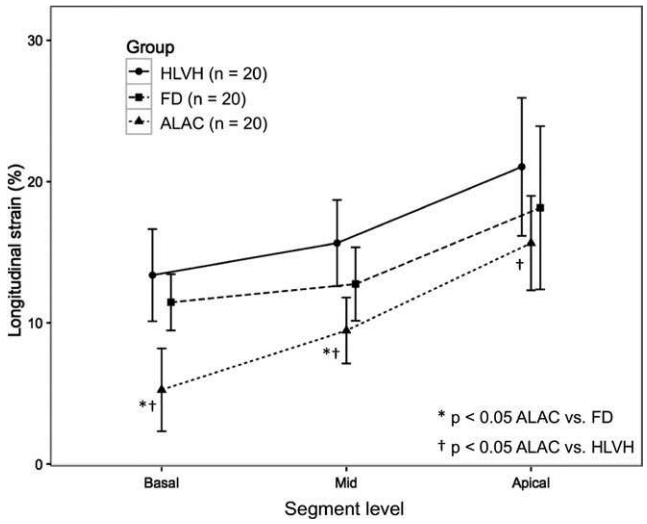

FIGURE 2 Differences in peak segmental left ventricular longitudinal strain in the A4C among ALAC, FD, and HLVH patients (A4C = apical 4-chamber view; ALAC = AL amyloid cardiomyopathy; FD = Fabry disease-related cardiomyopathy; HLVH = hypertensive left ventricular hypertrophy)

amyloidosis from controls with 93% sensitivity and 82% specificity. Moreover, in a logistic regression multivariate analysis, RAS LS had incremental value in predicting amyloid heart disease over more traditional parameters. A visual evaluation of RAS LS has been subsequently studied by Korean authors.[14] Visually assessed RAS LS was found in two-thirds of patients with cardiac amyloidosis, except in those with preserved LVEF, normal LV wall thickness, and only mildly decreased global LS, that is, in patients with probably less advanced amyloid heart disease. Though calculated RAS LS was higher in cardiac amyloidosis than in other causes of LV hypertrophy (hypertrophic cardiomyopathy, hypertensive disease, aortic stenosis), RAS LS alone not was not sufficient to discriminate amyloid heart disease because significant overlap was evident between amyloid heart disease and control group. In this study, the optimal cutoff point of RAS LS to differentiate cardiac amyloidosis from other causes of LV hypertrophy was 0.65, with 72% sensitivity and 78% specificity. A systolic septal longitudinal base-to-apex strain gradient was noted in patients with cardiac amyloidosis by Liu et al.[15] This 2D strain parameter reflects relatively preserved systolic deformation in

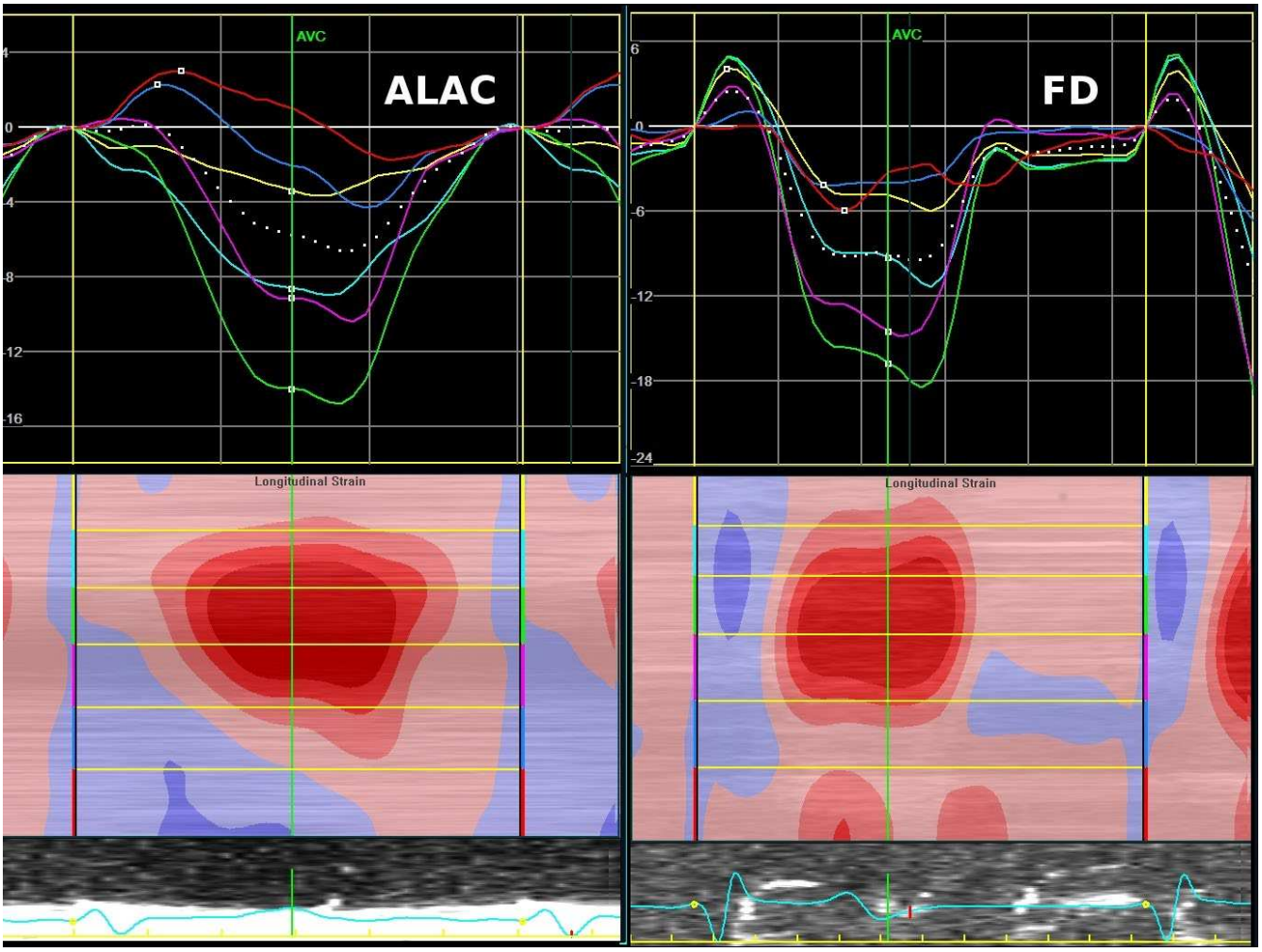

FIGURE 3 Examples of visually similar patterns of relative apical sparing of longitudinal strain in the A4C view in a patient with ALAC and FD, respectively (A4C = apical 4-chamber view; ALAC = AL amyloid cardiomyopathy; FD = Fabry disease-related cardiomyopathy)

TABLE 4 Significant univariate predictors of ALAC

Variable	OR (95% CI)	*P*-value	ROC AUC (95% CI)	Optimal cutoff value	Sensitivity (%)	Specificity (%)
RAS LS	67.9 (4.8–953.1)	0.002	0.79 (0.66–0.92)	>0.88	70	75
E/A	7.4 (2.3–24.0)	<0.001	0.80 (0.65–0.95)	>1.67	65	98
DT	0.98 (0.96–0.99)	0.002	0.78 (0.65–0.91)	<192	60	85
e′	0.37 (0.22.–0.63)	<0.001	0.87 (0.78–0.96)	<5.0	75	79
E/e′	1.35 (1.14–1.59)	<0.001	0.88 (0.78–0.98)	>14.6	80	84
Pericardial effusion	117 (18–2367)	<0.001		Presence	75	98
Low voltage on ECG	86 (14–1720)	<0.001		Presence	70	97
Pseudoinfarct pattern on ECG	3.6 (1.8–6.6)	0.001		Presence	50	97

A = peak late mitral diastolic flow velocity; ALAC = AL amyloid cardiomyopathy; DT = deceleration time of early mitral diastolic flow velocity; E = peak early mitral diastolic flow velocity; e′ = average of medial and lateral early diastolic mitral annular tissue velocity; RAS LS = relative apical sparing of longitudinal strain.

the apical region of the IVS compared to its midsegments and basal segments. The prevalence of the systolic septal longitudinal base-to-apex strain gradient > 2.1 in subjects with cardiac amyloidosis reached 88% and was significantly higher than in patients with LV hypertrophy due to arterial hypertension, FD, and Friedreich ataxia. Recently, high RAS LS has been shown to be independently predictive of all-cause mortality or heart transplantation in cardiac amyloidosis despite adjustment for established adversely prognostic factors.[4]

Our results further extend findings from previously published studies. In routine clinical practice, adequate visualization of LV walls in apical 2-chamber and long-axis views allowing correct 2D strain analysis is sometimes impossible and traditional approach for the evaluation of RAS LS cannot be used.[5] We demonstrate that a simplified approach to assess RAS LS only in the A4C may be used as a reproducible parameter to differentiate ALAC from other forms of concentric LV wall thickening with the same degree MLVWT. The optimal cutoff value for RAS LS in the A4C derived in our study is different from cutoff points given in previous studies,[3,14] which probably reflects the principle methodological difference of our study to assess this parameter only in one apical view. However, the sensitivity and specificity values of optimal RAS LS value derived in our study are very similar to those published by Lee et al.[14]

Despite being statistically significantly different, RAS LS assessed in the A4C alone cannot be used to discriminate ALAC from other causes of concentric LV wall thickening because of significant overlap. This observation is similar to findings of other authors.[14] Nevertheless, our results show that addition of RAS LS in the A4C on the top of more traditional echocardiographic (E/e′, DT, pericardial effusion) and ECG (low QRS voltage and pseudoinfarct patterns) provides significant added diagnostic value in predicting ALAC. We consider this finding to be very important from clinical point of view. In the process of differential diagnosis among ALAC and other forms of concentric LV hypertrophy, RAS LS, at least if evaluated only in the A4C, should not be used in isolation, but

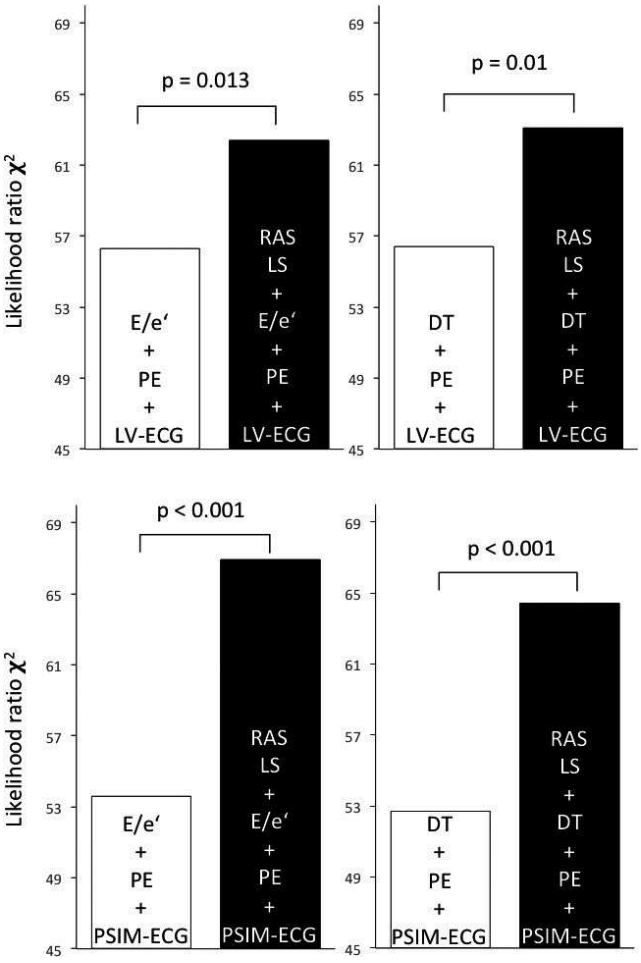

FIGURE 4 Four nested multivariate models demonstrating significant added diagnostic value of relative apical sparing of longitudinal strain in the A4C to established predictors of ALAC (A4C = apical 4-chamber view; DT = deceleration time of early mitral diastolic flow velocity; e′ = average of medial and lateral early diastolic mitral annular tissue velocity; E = peak early mitral diastolic flow velocity; LV-ECG = low voltage ECG pattern; PE = pericardial effusion; PSIM = pseudoinfarct ECG pattern; RAS LS = relative apical sparing of longitudinal strain)

in combination with other known parameters, echocardiographic as well as nonechocardiographic. Only such complex approach allows clinician to increase the diagnostics accuracy of noninvasive diagnostics of ALAC.

According to current knowledge, RAS LS is very likely related to regional differences in amyloid extracellular deposition and concomitant fibrosis. In a recent study, Williams et al[16] nicely demonstrated a base-to-apex gradient in quantitative late gadolinium enhancement burden in patients with cardiac amyloidosis. The major histological basis for late gadolinium enhancement in amyloid hearts is most probably interstitial expansion from amyloid infiltration as shown by Maceira et al.[17] Furthermore, an increased uptake of ^{99m}Tc-hydroxymethylene diphosphonate in basal and mid-cavity segments compared to lower uptake of apical segments of the LV was demonstrated in patients with transthyretin-related cardiac amyloidosis reflecting higher amyloid burden in nonapical regions.[18] However, segmental differences in amyloid deposition supporting this idea are still to be proved on histopathological basis.

4.1 | Limitations

The absence of patients with transthyretin-related cardiac amyloidosis may be considered as a limitation of our study. However, the phenomenon of apical sparing was previously documented by other authors also in this form of amyloid heart disease.[3,4] Another possible limitation represents the retrospective and observational character of our study with relatively small number of patients. Not all our patients underwent endomyocardial biopsy for a definitive diagnosis of ALAC. However, in those who did not undergo heart biopsy, the diagnosis of AL amyloidosis was confirmed by positive histological finding of amyloid infiltration in extracardiac tissue and no other cause for increased LV wall thickness was present as stated in current recommendations.[7]

5 | CONCLUSIONS

The simplified assessment of RAS LS only in the A4C represents an attractive tool for noninvasive diagnostics of ALAC. However, due to the significant overlap with other causes of concentric LV wall thickening, the analysis of RAS LS in the A4C should be combined with other traditional echocardiographic and ECG predictors of ALAC.

AUTHORS 'CONTRIBUTIONS

Michal Fikrle, Tomas Palecek: conception and design of the study, acquisition of data, analysis of the data, drafting of the article, and final version of the article; Josef Marek: acquisition of data, analysis of the data, statistics, drafting of the article, and final version of the article; Petr Kuchynka: Acquisition of data, drafting of the article, and final version of the article; and Ales Linhart: acquisition of data and final version of the article.

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