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ORIGINAL PAPER

# Left atrial strain imaging differentiates cardiac amyloidosis and hypertensive heart disease

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## Abstract

Echocardiographic diagnosis of cardiac amyloidosis (CA) can be difficult to differentiate from increased left ventricular (LV) wall thickness from hypertensive heart disease. The aim of this study was to evaluate left atrial (LA) function and deformation using strain and strain rate (SR) imaging in cardiac amyloidosis. We reviewed 44 cases of CA confirmed by tissue biopsy or a combination of clinical and cardiac imaging data. Cases were classified according two subgroups: amyloid light chain (AL) or amyloid transthyretin (ATTR). These subjects underwent 2D-Speckle tracking echocardiographic derived (STE) LA strain analysis. These were compared to 25 hypertensive (HT) patients with increased LV wall thickness. The three phases of LA function were evaluated using strain and strain rate parameters. Despite a similar increase in LV wall thickness, all LA strain parameters were significantly reduced in the AL cohort compared to the HT cohort (reservoir strain/LAs: 11.0 vs. 24.8%, $p < 0.05$). The ATTR cohort had significantly thicker LV walls and higher atrial fibrillation burden compared to AL and HT patients but similar reduction in LA strain values compared to AL group. A reservoir strain (S-LAs) cut off value of 20% was 86.4% sensitive and 88.6% specific for detecting CA compared to HT heart disease in this cohort. LA strain parameters were able to identify LA dysfunction in all types of CA. LA function in CA is significantly worse compared with hypertensive patients despite similar increase in LV wall thickness. In combination with other clinical and imaging features, LA strain may provide incremental value in differentiating cardiac amyloidosis from increased wall thickness secondary to hypertension.

**Keywords** Cardiac amyloidosis · Left atrial strain · Atrial deformation · Hypertension

## Introduction

Cardiac amyloidosis is an infiltrative cardiomyopathy caused by a group of disorders characterised by amyloid protein deposition in various organs. Cardiac amyloid (CA) is most commonly caused by immunoglobulin light chain (AL) amyloidosis due to a plasma cell dyscrasia, non-hereditary transthyretin (ATTRwt) amyloidosis or less commonly, hereditary TTR amyloidosis (ATTRm) due to a mutant TTR protein [1]. The atria can be involved in all types of cardiac amyloidosis as can be the ventricles and conduction system [2]. Atrial infiltration leads to atrial dysfunction, arrhythmias and atrial thrombus formation which are an important cause of morbidity in these patients [2].

Traditionally, invasive histologic diagnosis with cardiac or other tissue biopsy is central in the diagnosis of CA [3]. Cardiac biopsy has inherent risk of complications with variable detection rates, depending upon the nature of the tissue biopsied and extent of disease [4]. Bone scintigraphy and cardiac magnetic resonance imaging have an established role in the diagnostic pathway, particularly for TTR amyloidosis [4]. Scalia et al. demonstrated the value of bone scintigraphy with significant myocardial uptake in the diagnostic algorithm for CA [5]. In comparison, echocardiography is a bedside tool which is mobile and widely available in the diagnosis of cardiac amyloidosis but has limited specificity due to mimickers of increase in left ventricular (LV) wall thickness such as hypertensive heart disease, hypertrophic cardiomyopathy (HCM) and other cardiac infiltrative

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diseases [6]. Therefore, investigation of novel echocardiographic diagnostic tools, such as left atrial (LA) strain, is important to improve the diagnostic yield of non-invasive testing in CA.

Diagnosis of CA is important not only for prognostication but also has significant treatment implications. Fitzgerald et al. demonstrated regression of echocardiographic features of light chain CA post chemotherapy and peripheral blood stem cell transplantation [7]. For TTR amyloidosis, there has been increasing interest in the use of a variety of transthyretin stabilising and silencing drugs to prevent amyloidogenesis [8]. A recent breakthrough, phase 3 trial of the transthyretin stabiliser (tafamadis) showed reduced all-cause mortality and cardiovascular related complications in patients with TTR amyloid compared with placebo [9]. It is these scenarios where LA strain may play a useful role in guiding clinical management.

The aim of this study was to evaluate LA function and deformation using strain and strain rate (SR) imaging in cardiac amyloidosis and assess which LA strain parameter would be most useful to assist in cardiac amyloid diagnosis when compared to a cohort of patients with increased LV wall thickness due to hypertensive heart disease.

## Methods

### Study population

We retrospectively assessed medical and pathologic records for cases of cardiac amyloidosis diagnosed at this institution from 2004 to 2018. The echocardiographic database was then searched to identify fifty-eight cases with echocardiography acquisition. Of these fourteen were excluded due to suboptimal image quality (n = 8) or no available echocardiographic images in cases diagnosed at another centre (n = 6). Of the cases excluded due to suboptimal image quality, some cases were patients who came to our centre for native heart biopsy and the only imaging available to transfer to the TomTec database were those from the procedure lab. These studies generally did not have an adequately optimised LA view that could be used for strain analysis. Other were excluded due to inadequate image quality—foreshortened image, or suboptimal LA wall visualisation throughout the cardiac cycle. Notably, these were the only exclusions for the amyloid patient group—patients with arrhythmia, paced rhythm, LV systolic dysfunction or valvular heart disease were not excluded. In addition, 25 patients with isolated hypertensive heart disease were obtained by searching the echocardiographic database for cases with increased LV wall thickness, no significant aortic stenosis or HCM diagnosis, and no infiltrative heart disease at time of echocardiogram. Clinical records were then reviewed to ensure patients were treated for hypertension and had no other diagnosis that would contribute to the increased LV wall thickness. Ten healthy control patients with no history of hypertension, normal LA volumes and sinus rhythm were also included in the study. The study was approved by the ethics committee of the local institution.

### Echocardiography/LA strain

Echocardiographic imaging was obtained as a part of routine medical care. Image acquisition was carried out by different sonographers using several commercially available ultrasound systems to acquire echocardiographic images. Images were chosen to carry out LA strain assessment if there were adequate optimised apical four and two-chamber views. Standard 2D images were triggered to the QRS complex (R-R gating) and saved in a cine-loop and stored in Digital Imaging and Communications in Medicine (DICOM) format. All 2D and Doppler recordings along with measurements were performed according to guideline recommendations. This included non-foreshortened windows with visualisation of the LA walls throughout the cardiac cycle. Derived echocardiographic pulmonary to LA ratio (ePLAR) was carried out for all cases. ePLAR is an echocardiographic parameter (ratio of the maximum tricuspid regurgitant velocity divided by the E/e′) which can accurately differentiate patients with pre-capillary and post-capillary pulmonary hypertension [10]. LA strain assessment was performed offline using a 2D speckle tracking vendor independent software. This program employs algorithms designed specifically for LA analysis (2D Cardiac Performance Analysis, TomTec-Arena version 4.6, TomTec Imaging systems, Unterschleissheim, Germany). A single observer with experience in LA strain analysis performed strain measurements offline and was blinded to patient clinical details such as type of cardiac amyloidosis and disease duration. For cases with arrhythmia including atrial fibrillation (AF) or paced rhythm, all LA strain measurements were carried out on 3 cardiac cycles and averaged. A second operator blinded to patient clinical data and strain analysis by the primary observer, performed LA strain and strain rate analysis to assess interobserver agreement for 10 randomly selected patients in each cohort.

To assess 2D speckle tracking derived LA strain and SR, the LA endocardial borders in the apical four and two-chamber views were manually traced using a point and click technique on an end systolic frame. The TomTec software automatically generates an epicardial line to create the region of interest and allow tracking of the LA endocardium. The LA myocardium is automatically divided into three segments (septal, lateral, and roof), with a LA longitudinal deformation curve generated for each segment. A fourth curve generated is the average of each of the three segments, and this

was used for data collection. The average strain and strain rate measurements were analysed for the three major LA functions (reservoir, conduit and contractile) [11]

- Reservoir function (S-LAs) was measured in systole with the strain value corresponding to the first peak between the ECG R and T wave.
- Conduit function occurs in early diastole and is the calculated difference between reservoir and contractile strain values (S-LAe = S-LAs – S-LAa).
- Contractile function (S-LAa) is measured in late diastole in timing with the ECG P wave. Strain rate is determined from the SR curve, with the reservoir strain rate (SR-LAs) being the peak positive value in systole, while the conduit (SR-LAe) and contractile strain rate (SR-LAa) values correspond to the two peak negative values of the curve in diastole (see Fig. 1).

For cases that were not in sinus rhythm, contractile and conduit strain could not be assessed.

### Statistical analysis

Continuous data were presented as mean values ± SD. Data were analysed using standard statistical software (SPSS version 26 and Microsoft excel 2016). Absolute mean strain measurements were compared between subgroups using paired t-test for variables in each group for the echocardiographic parameters. A P value of $< 0.05$ was considered statistically significant. A receiver operating curve (ROC) curve was constructed for reservoir strain to assess its diagnostic performance for CA. Area under the curve (AUC), sensitivity and specificity were calculated from the true/false, positive/negative classifications using standard definitions. A threshold was then selected for a reservoir strain value that could optimally distinguish CA from HT or controls. Interobserver variability was assessed using intraclass correlation coefficients (ICCs) in 10 CA and 15 HT/control cases.

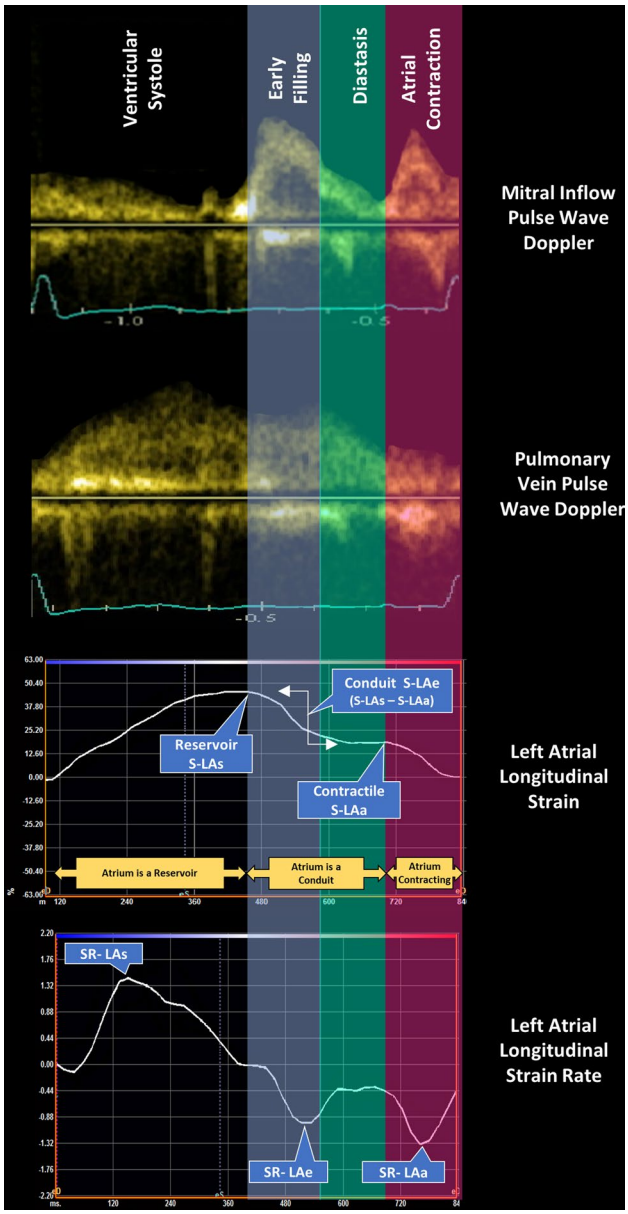


**Fig. 1** LA strain and SR curves summarising measurement of the three LA functions with comparison to the traditional Doppler parameters including mitral inflow and pulmonary venous pulse wave Doppler traces (From Rausch et al.) [11]

## Results

### Demographics and clinical parameters

Patients with cardiac amyloidosis were on average older than the hypertensive and control groups (mean age: CA 76 ± 10 years vs. HT 63 ± 12 years and control 57 ± 9 years, $p < 0.05$). The ATTR amyloid group were the oldest with a mean age of 80 years. In all groups there was a male preponderance. There were high rates of AF in the amyloidosis groups, particularly the ATTR group where 54% of patients had AF, which may reflect disease duration and severity at time of diagnosis. Table 1 outlines the patient demographic and clinical data for all patient groups.

The ATTR group included 2 patients with ATTRm, whilst the remainder were ATTRwt amyloid cases. Histologic confirmation of amyloid diagnosis was available in all AL amyloid cases and 67% of ATTR amyloid cases. Cases of ATTR amyloid with no available histologic confirmation were diagnosed using clinical, laboratory and multimodality imaging data. Both amyloid and hypertensive patients had varying degrees of comorbidities that are known to impact

**Table 1** Demographic and clinical parameters for amyloid, hypertensive and control subgroups

| | AL N = 11 | ATTR N = 33 | HT N = 25 | Control N = 10 |
|---|---|---|---|---|
| Age (years) | 72 (53–90) | 80 (63–91) | 63 (44–88) | 57 (41–70) |
| Male gender (n,%) | 9 (81%) | 26 (78%) | 22 (88%) | 6 (60%) |
| SPB (mmHg) | 112 | 125 | 161 | 125 |
| DBP (mmHg) | 71 | 70 | 85 | 73 |
| Heart rate (bpm) | 68 | 68 | 69 | 65 |
| BMI (kg/m) | 26.1 | 24.6 | 31 | 27 |
| Sinus Rhythm | 9 (82%) | 15 (45%) | 10 (100%) | 10 (100%) |
| Histology available | 11 | 22 | - | - |
| Cardiac | 5 | 12 | | |
| BMAT | 2 | 5 | | |
| Other | 4 | 5 | | |
| Histology positive | 11/11 | 17/22 | - | - |
| Histology negative | 0/11 | 5/22 | - | - |
| Cardiac imaging abnormal | | | | |
| TTE | 11 | 33 | - | - |
| Cardiac MRI | 4 | 12 | | |
| Nuclear scan | 1 | 24 | | |
| Comorbidities | | | | |
| HT | 5 (45%) | 15 (45%) | 25 (100%) | 0 |
| CKD | 10 (90%) | 29 (87%) | 10 (40%) | 0 |
| CAD | 4 (36%) | 12 (36%) | 17 (68%) | 0 |
| Diabetes | 1 (9%) | 6 (18%) | 5 (20%) | 0 |

*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *BMAT* bone marrow and trephine, *TTE* transthoracic echocardiogram, *cardiac MRI* cardiac magnetic resonance imaging, *FLC* free light chains, *SEPP* serum electrophoresis, *Urine BJP* urine Bence-Jones protein, *HT* hypertension, *CKD* chronic kidney disease, *CAD* coronary artery disease

on LA strain values including coronary artery disease, diabetes, and chronic kidney disease (CKD).

With regards to the hypertensive group, the majority (92%) were on two or more antihypertensive agents.

## Standard echocardiographic parameters

The baseline echocardiographic data according to subgroup is summarised in Table 2. The ATTR group had thicker LV walls compared to the AL group (1.8 vs. 1.4 cm, $p < 0.05$). Both CA groups had severe biatrial enlargement and on average, low normal to mild LV systolic dysfunction. Filling pressures assessed using E/e′ were elevated in both CA groups, with no significant difference between the two groups ($p = 0.13$). Derived echocardiographic pulmonary to LA ratio (ePLAR) was reduced in both CA groups below 0.25, consistent with elevated filling pressures due to left heart disease. As expected, the CA groups had higher grades of diastolic dysfunction compared with the hypertensive group. Lastly, it is important to note that two amyloid patients had previously undergone a mitral valve replacement (S-LAs were 16.3 and 6.3%), and two had severe mitral regurgitation at time of strain analysis (S-LAs were 2.4 and 3.2%) (summarised in Table 2).

Comparatively, the HT group had a mild to moderate increase in LV wall thickness and upper limit of normal LA size assessed by LA volume indexed to body surface area (LAVI). This group had high normal LV filling pressures (average E/e′ 13.22) and mildly reduced ePLAR values (0.21 m/s).

## LA strain and strain rate parameters

Table 3 summarises the LA strain and SR findings according to subgroup. LA strain and strain rate were measured in 44 patients with CA, though conduit and contractile strain could not be measured in 2 AL cases (18%) and 18 (54%) of ATTR cases due to AF or paced rhythm. All HT and control patient cases were in sinus rhythm. All parameters of LA function were severely reduced in the amyloid group compared to control patients ($p < 0.05$) (Fig. 2). Interestingly, despite thicker LV walls, the ATTR group had similarly low strain values as the AL group (reservoir strain, S-LAs: 11.0% vs. 9.8%, $p = 0.67$). Atrial fibrillation was more common in the CA cohort. Those patients with CA and AF/paced rhythm had significantly lower reservoir strain values than those in sinus rhythm (S-LAs 6.3% vs. 13.4%, $p = < 0.05$). Importantly, the cardiac amyloid group included patients with variable degrees of LV systolic dysfunction and atrial fibrillation. As LV systolic function declined, there was a decline in LA reservoir function (S-LAs- EF > 52%: 12.1%; EF 40–52%: 9.1%; EF < 40%: 7.3%).

All LA strain parameters between the AL and ATTR groups were similar and subtype differentiation based on LA strain alone was not possible. Strain rate values were also significantly reduced in the amyloid groups compared to controls.

The hypertensive group also had a mild reduction in all strain and strain rate parameters ($P < 0.05$ for all parameters) compared to controls. Despite similar degrees of increased LV wall thickness (particularly to the AL amyloid group), the hypertensive group had significantly higher atrial strain values than the amyloid cases. Reservoir strain (S-LAs) were 11.0%, 9.8% and 24.8% in the AL, ATTR and HT groups respectively. A receiver operating curve (ROC) analysis was carried out to assess ability of LA reservoir strain to detect disease when comparing the cohorts. This analysis revealed an AUC of 0.93 (95% confidence interval, 0.88–0.98). Using a reservoir strain cut off value of 20%, there is an 86.4% sensitivity and 88.6% specificity for detecting CA (see Fig. 3). The lower

**Table 2** Baseline echocardiographic data for amyloid, hypertensive and control subgroups

| | AL N = 11 | ATTR N = 33 | HT N = 25 | P value AL vs HT | P value ATTR vs HT | Control N = 10 |
|---|---|---|---|---|---|---|
| LVEDD (cm) | 4.5 ± 0.8 | 4.4 ± 0.65 | 4.7 ± 0.9 | < 0.05 | < 0.05 | 4.5 ± 0.5 |
| IVS (cm) | 1.4 ± 0.3 | 1.8 ± 0.3 | 1.44 ± 0.2 | 0.8 | < 0.05 | 0.9 ± 0.14 |
| LVPW (cm) | 1.3 ± 0.3 | 1.6 ± 0.3 | 1.42 ± 0.3 | 0.3 | 0.03 | 0.9 ± 0.1 |
| LVEDV/BSA (mlm$^2$) | 54 ± 16 | 57 ± 17 | 57 ± 13 | 0.5 | 0.5 | 49 ± 5.8 |
| LV mass (g) | 245 ± 76 | 325 ± 81 | 298 ± 84 | 0.8 | 0.24 | 134 ± 34 |
| LV mass indexed to BSA (g/m$^2$) | 136 ± 42 | 175 ± 39 | 135 ± 35 | 0.96 | < 0.05 | 70 ± 10.6 |
| LA volume (ml) | 91.8 ± 24 | 110 ± 38 | 91.5 ± 18 | 0.97 | 0.05 | 53 ± 15 |
| LA volume/BSA (ml/ m$^2$) | 51 ± 14 | 58 ± 18.8 | 41 ± 12 | 0.04 | < 0.05 | 26 ± 4.2 |
| RA volume/BSA (ml/m$^2$) | 46 ± 14 | 45 ± 20.3 | 27 ± 9.0 | < 0.05 | < 0.05 | 19 ± 5.6 |
| Ejection fraction (%) | 45 ± 11 | 50 ± 13 | 60 ± 5.9 | < 0.05 | < 0.05 | 58 ± 3 |
| E wave (cm/s) | 95.5 ± 32 | 78 ± 22 | 69 ± 14 | < 0.05 | 0.02 | 62 ± 13 |
| Deceleration time (cm/s) | 202 ± 79 | 192 ± 80 | 200 ± 45 | 0.9 | 0.3 | 174 ± 47 |
| A wave (cm/s) | 59.5 ± 30 | 73 ± 44 | 71 ± 21 | 0.22 | < 0.05 | 59 ± 11 |
| EA ratio | 2.4 ± 1.3 | 1.6 ± 1.2 | 1.05 ± 0.4 | < 0.05 | 0.08 | 1.1 ± 0.3 |
| e′ septal (cm/s) | 3.6 ± 1.0 | 4 ± 1.4 | 5.7 ± 1.8 | < 0.05 | < 0.05 | 7.4 ± 2.2 |
| e′ lateral (cm/s) | 5.8 ± 3.3 | 5 ± 1.4 | 6.9 ± 2.5 | 0.3 | < 0.05 | 10.8 ± 3.6 |
| Average E/e′ | 25 ± 10 | 20.5 ± 7.2 | 13.2 ± 5.7 | < 0.05 | 0.01 | 6.2 ± 1.7 |
| TR velocity (m/s) | 2.4 ± 0.6 | 2.7 ± 0.32 | 2.5 ± 0.3 | 0.5 | 0.17 | 2.2 ± 0.09 |
| ePLAR (m/s) | 0.12 ± 0.05 | 0.13 ± 0.04 | 0.21 ± 0.08 | 0.02 | < 0.05 | 0.3 ± 0.03 |
| Diastolic function grade | | | | | | |
| 1 | 2 | 2 | 13 | | | 0 |
| 2 | - | 6 | 6 | | | 0 |
| 3 | 6 | 5 | 1 | | | 0 |
| Elevated filling pressures | 1 | 16 | 0 | | | 0 |
| Indeterminate | 2 | 4 | 5 | | | 0 |
| Normal | 0 | 0 | 0 | | | 10 |
| Mitral regurgitation grade (n) | | | | | | |
| 0, 0–1 or 1 | 8 | 21 | 23 | | | 10 |
| 2 | 2 | 7 | 2 | | | 0 |
| 3 | 1 | 0 | 0 | | | 0 |
| 4 | - | 2 | 0 | | | 0 |
| MVR | 1 | 1 | 0 | | | 0 |
| RVSP (mmHg) | 37 ± 13 | 41 ± 8.7 | 26 ± 3.9 | | | 23 ± 1.5 |

*LVEDD* left ventricular end diastolic diameter, *IVS* interventricular septal thickness, *LVPW* left ventricular posterior wall thickness, *LVEDV/BSA* left ventricular end diastolic volume indexed to body surface area, *TR velocity* tricuspid regurgitant jet peak velocity, *ePLAR* echocardiographic pulmonary to LA ratio, *RVSP* right ventricular systolic pressure

the reservoir strain value, the higher the specificity for CA—11.4% or less, was 100% specific but 77.3% sensitive for CA compared to HT heart disease in this cohort.

The interventricular septal thickness did not distinguish between amyloid and hypertensive groups, with significant overlap between the two groups (Fig. 4). Likewise, LAVI was elevated to similar degrees in the majority of HT and amyloid cases, and failed to distinguish the two different pathologies (Fig. 5). When comparing S-LAs to E/e′ values, there was a trend towards higher E/e′ values in cases with worsening LA reservoir strain (Fig. 6).

### Inter observer variability

All study measurements were performed by a single investigator. Ten cases were randomly selected from the amyloid group and 15 cases from the HT/control cohorts to assess interobserver reproducibility. There was good to excellent interobserver variability between the two blinded strain readers with interclass correlation coefficients ranging from 0.77 to 0.97 (Table 4). This was consistent with our previous study which demonstrated good intraobserver

**Table 3** LA strain and strain rate values for amyloid, hypertensive and control groups

| | AL N = 10 | ATTR N = 33 | HT N = 10 | P value Amyloid vs HT | Control N = 10 | P value Amyloid vs Control |
|---|---|---|---|---|---|---|
| S-LAs (%) | 11.0 ± 7.4 | 9.8 ± 7.5 | 24.8 ± 6.4 | p ≤ 0.05 | 38.1 ± 6.1 | p ≤ 0.05 |
| S-LAe (%)[a] | 5.9 ± 4.0 (n = 8) | 6.9 ± 4.1 (n = 15) | 13.1 ± 3.9 | p ≤ 0.05 | 19.9 ± 7.1 | p ≤ 0.05 |
| S-LAa (%)[a] | 5.7 ± 4.4 (n = 8) | 6.6 ± 5.1 (n = 15) | 11.8 ± 4.5 | p ≤ 0.05 | 18.1 ± 4.9 | p ≤ 0.05 |
| SR-LAs ($s^{-1}$) | 0.39 ± 0.18 | 0.42 ± 0.27 | 0.95 ± 0.25 | p ≤ 0.05 | 1.3 ± 0.15 | p ≤ 0.05 |
| SR-LAe ($s^{-1}$) | 0.27 ± 0.14 | 0.36 ± 0.17 | 0.7 ± 0.2 | p ≤ 0.05 | 1.1 ± 0.3 | p ≤ 0.05 |
| SR-LAa ($s^{-1}$)[a] | 0.4 ± 0.32 (n = 8) | 0.5 ± 0.4 (n = 15) | 1.0 ± 0.3 | p ≤ 0.05 | 1.4 ± 0.5 | p ≤ 0.05 |

*AL* light chain cardiac amyloid, *ATTR* transthyretin cardiac amyloid, *HT*, hypertension, *S-LAs* peak systolic or 'reservoir strain', *S-LAe* conduit strain, *S-LAa* contractile strain, *SR-LAs* peak systolic SR, *SR-LAe* early diastolic SR, *SR-LAa* late diastolic SR

[a]Note for those cases in AF/paced rhythms, contractile and conduit strain could not be calculated due to absence of normal atrial contractile function. Therefore, these groups have smaller numbers of data points, and this is annotated with a separate cohort number)

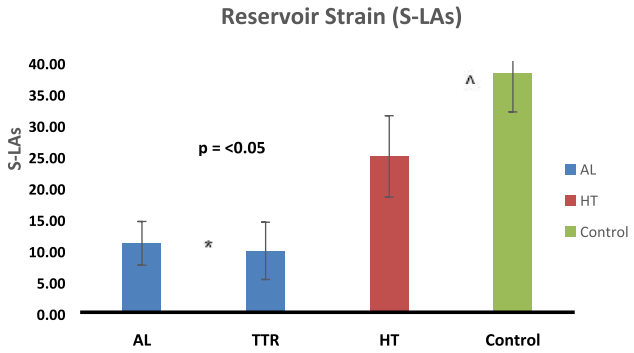


**Fig. 2** Reservoir (peak systolic) LA strain values in amyloid, HT, and control groups. *p < 0.05 versus control; ^p < 0.05 versus HT

and interobserver reproducibility of LA strain using the Tomtec strain analysis software [12].

## Discussion

This study aimed to assess the differences in left atrial strain in CA compared to a population with increased left ventricular wall thickness due to hypertensive heart disease. There were four primary important findings:

1. LA strain is an important emerging echocardiographic tool which is significantly reduced in CA.
2. Despite similar LV wall thickness, LA strain was significantly reduced in the amyloid groups compared to the HT group.
3. LA strain could not differentiate between CA subtypes in this small population, although the AL group had lower strain values for the same degree of wall thickening as the HT group.

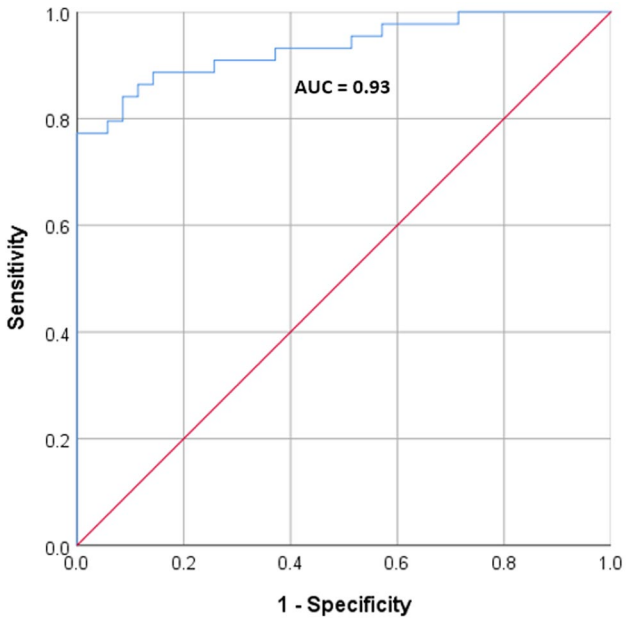


**Fig. 3** Receiver operating curve analysis of LA reservoir strain (S-LAs) to detect the presence of CA. AUC 0.93. A reservoir strain (S-LAs) value of 20% was 86.4% sensitive and 88.6% specific for detecting CA compared to those in the HT/control cohorts with no disease

4. LA strain is a highly reproducible parameter which is important for potential future clinical application.

Cardiac amyloidosis (CA) is often a challenging diagnosis to make by non-invasive assessment tools. LA strain is a novel, evolving echocardiographic technique which allows detailed assessment of the three phasic LA functions, and could assist in echocardiographic assessment of patients suspected to have CA [1]. In cardiac amyloid, LA strain can

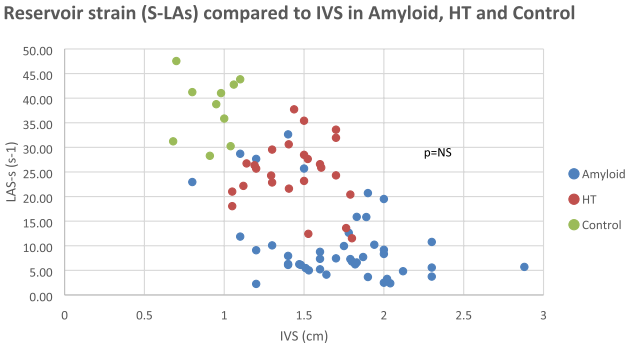


**Fig. 4** Reservoir (peak systolic) LA strain compared to interventricular septal thickness in amyloid, HT, and control groups

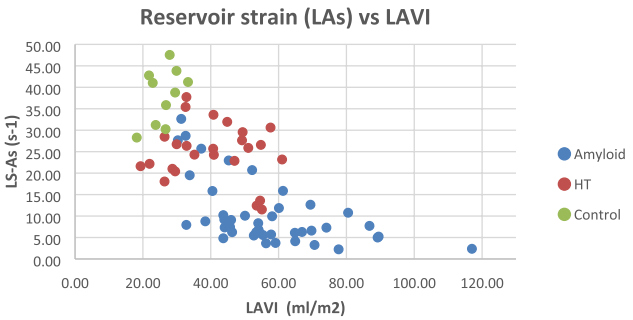


**Fig. 5** Left atrial volume indexed to body surface area (LAVI) compared to reservoir (peak systolic) LA strain values in amyloid, HT, and control groups

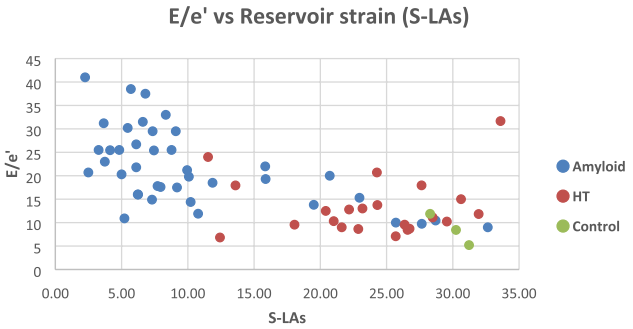


**Fig. 6** Reservoir (peak systolic) LA strain compared to E/e′ values in amyloid, HT and controls

be reduced due to multiple mechanisms: amyloid protein deposition in the LA walls, worsening LV diastolic dysfunction, increasing left atrial volume and higher rates of AF. In this retrospective study we sought to assess the degree of LA dysfunction (using LA strain) in patients with diagnosed CA and compared this to a hypertensive cohort. The results demonstrated that all LA functions assessed using strain and SR imaging were markedly reduced in the CA group compared to healthy controls. Additionally, LA functions

**Table 4** LA strain interobserver variability in cardiac amyloid cases (n = 10)

| Variable | Cardiac Amyloid ICC (n = 10) | HT/Control ICC (n = 15) |
|---|---|---|
| S-LAs (%) | 0.94 (0.65–0.97) | 0.95 (0.86–0.98) |
| S-LAe (%) | 0.77 (0.4–0.95) | 0.95 (0.85–0.98) |
| S-LAa (%) | 0.96 (0.74–0.99) | 0.89 (0.7–0.96) |
| SR-LAs ($S^{-1}$) | 0.94 (0.8–0.98) | 0.93 (0.79–0.97) |
| SR-LAe ($S^{-1}$) | 0.90 (0.58–0.97) | 0.94 (0.84–0.98) |
| SR-LAa ($S^{-1}$) | 0.97 (0.79–0.99) | 0.86 (0.61–0.95) |

*ICC* interclass correlation coefficient, *S-LAs* peak systolic or 'reservoir strain', *S-LAe* conduit strain, *S-LAa* contractile strain, *SR-LAs* peak systolic SR, *SR-LAe* early diastolic SR, *SR-LAa* late diastolic SR

were significantly worse in the CA group compared to those with increased LV wall thickness due to HT. Importantly, ROC analysis suggested a reservoir strain cut point of 20% was reliable for detecting CA (sensitivity 86.4%, specificity 88%).Additionally, the lower the reservoir strain value the more specific it was for CA rather than HT. No HT cases had a reservoir strain value below 11.4%. Clinically, when encountering an unclear case with increased LV wall thickness, a very low reservoir strain value (less than 20%) in the absence of severe left ventricular or valvular dysfunction, makes CA more likely as a differential diagnosis.

Although an uncommon disorder, recognition of cardiac involvement in patients diagnosed with systemic amyloidosis has important prognostic and treatment implications. Hypertension, hypertrophic cardiomyopathy and other infiltrative conditions that cause increased LV wall thickness can mimic CA and decrease the specificity of echocardiography for diagnosing CA [4].

LA function using strain parameters has been studied in several recent amyloid cohorts. Nochioka et al. in 2017 described in a multicentre study of 124 patients with CA in sinus rhythm. There was no significant difference in mean reservoir strain values for AL, ATTRm or ATTRwt with values of 19.3%, 20.1% and 16.1% respectively [1]. These values are higher than those in the current study (AL 11.0%, ATTR 9.8%). This difference may be explained by high rates of more advanced disease, inclusion of AF cases and diastolic dysfunction, with larger LAVI and higher E/e′ in the current study. Notably, the CA patients in the current study in sinus rhythm, had mean reservoir strain of 13%. Mohty et al. in 2017 assessed LA strain in 77 patients with AL amyloidosis and graded patients according to the Mayo Clinic (MC) staging system (a score including B type natriuretic peptide and troponin T levels to stage severity of cardiac involvement) [13]. They showed a progressive reduction in LA strain with worsening Mayo clinic staging with peak strain values of 20% in MC class 1 and 11% in MC class 3 [13]. Additionally,

they showed that a reservoir strain of < 14% was associated with increased mortality independent of LA volume.

Despite similar LV wall thickness, LA strain was significantly reduced in the CA group compared to the hypertensive population (illustrated in Fig. 3). This supports the potential role of LA wall amyloid infiltration in addition to other factors such as diastolic dysfunction and LA enlargement. LA strain in amyloid has also been compared to other pathologies with increased LV wall thickness. De Gregorio et al. assessed LA function in 32 patients—16 with TTR amyloid and 16 with HCM [14]. Similar to our comparison of hypertensive heart disease with CA, the HCM group had a lesser reduction in strain (mean reservoir strain 20%) than the ATTR group (mean reservoir strain 14.1%) despite similar LAVI and LV systolic function. This study additionally included cardiac magnetic resonance imaging (cMRI) and found higher prevalence of LA wall delayed gadolinium enhancement in the CA group than HCM [14].

The LA plays an important role in modulating LV filling and likewise there are adaptive changes by the LA in response to LV diastolic dysfunction. CA begins with predominately diastolic dysfunction, progressing in more advanced disease to cause LV systolic dysfunction. Sing et al. demonstrated the significant drop in LA reservoir strain values as diastolic dysfunction worsened, with LA strain superior to LAVI when categorizing diastolic dysfunction grade [15]. This study confirms findings of other studies, that worsening diastolic function (suggested by higher E/e′ values) can be seen as progressive reduction in LA reservoir strain [1].

Importantly, not only LA size but also function, may be a prognostic marker in CA. Historically there has been extensive investigation of the role of LV global longitudinal strain (GLS) not only as a diagnostic tool but also for prognostication in cardiac amyloid [16, 17]. Buss et al. showed in a series of over 200 patients with systemic light chain amyloidosis that reduced LV global longitudinal strain was an independent predictor of survival [16]. LV strain has also been used to track treatment response—Fitzgerald et al. demonstrated normalisation of LV GLS in AL amyloid after treatment with chemotherapy and blood stem cell transplantation [18]. Recent studies have also investigated the prognostic role of LA size and function in CA. LA size (determined by M-mode imaging) in a study by Mohty et al. in 2011 was shown to be an independent predictor of increased 5 year mortality in patients with CA [19]. Early studies have assessed prognostic significance of LA strain imaging in light chain amyloidosis. Tuzovic et al. assessed LA strain in 41 patients with AL amyloid undergoing chemotherapy treatment [20]. There were small improvements in LA function measures post chemotherapy with a modest association with haematologic response. More studies in this area are required to confirm prognostic value of LA strain in CA in a larger cohort.

Atrial fibrillation is commonly associated with cardiac amyloidosis, with one recent study of 238 patients with CA showed 44% of patients had AF at time of diagnosis [21]. In the current study, AF was present in 18% of AL group and 54% of ATTR group, with high rates likely due to presence of advanced CA particularly in the ATTR cohort. Many prior studies of LA strain in cardiac amyloidosis excluded patients with AF, likely as the atrial myopathy associated with AF itself causes reduction in LA strain values and additionally, the conduit and contractile strain functions cannot be measured [22]. Notably in this study, even CA cases in sinus rhythm had lower strain values than those in the hypertensive group. Thus, screening for LA dysfunction in CA patients with early disease may also allow identification of subclinical atrial myocardial dysfunction and high-risk patients for future arrhythmic events.

LA strain allows detailed assessment of the three phasic functions of the LA and has been shown to be a reproducible technique which can be carried out in the majority of echocardiographic cases [12]. Rausch et al. have previously shown good inter- and intraobserver variability with ICC values > 0.88 and > 74–82 respectively for strain values [12]. Several studies have recently documented normal LA strain values according to gender and age ranges [23–25]. LA strain may be of incremental value in the imaging diagnosis of CA with significantly reduced values compared to normal and other populations. Additionally, identification of early atrial dysfunction may identify CA patients who are at higher risk of disease progression, arrhythmias or LA thrombus and assist in selecting patients who may benefit from more frequent disease monitoring or a change in medical therapy.

## Study limitations

There are several limitations to this study that should be noted. Firstly, not all CA cases were biopsy proven. For CA cases without biopsy, diagnosis was made based upon clinical and multimodality imaging as is done in real world practice, particularly for the ATTR group. Secondly, given the small number of amyloid cases in the subgroups, this study is underpowered to assess a true difference between the amyloid subtypes, and similar strain values between AL and ATTR groups may either be due to chance, or the fact that patients referred for biopsy, particularly cardiac biopsy may have more advanced disease. Given the retrospective nature of the study, the amyloid patients had variable disease duration at time of LA strain analysis, including variable LV systolic function and ventricular wall thickness. Additionally, early CA may have more normal LA function and therefore strain values than

more advanced cases and it would be interesting to study LA function in this subgroup.

All hypertensive cases were in sinus rhythm, compared to amyloid cases where there were AF or paced rhythm. This may have contributed to the lower strain values, but even CA cases in sinus rhythm had significantly lower strain values than the hypertensive group. Additionally, the HT group had variable disease severity, and thus variable wall thickness. HT was the only comparator group (i.e. no HCM or other infiltrative pathologies were included) and was chosen because it is one of the most common causes of increased LV wall thickness.

Importantly, the results are only applicable to the multi-vendor strain analysis software (TomTec) and cannot be generalized to other vendor specific software for LA strain analysis. TomTec was used due to the retrospective nature of the study carried out in a large multi-vendor echocardiography laboratory. Image quality (non-foreshortened view of the LA and the LA wall visualisation throughout the cardiac cycle) is important in LA strain analysis, and as such, 14 amyloid cases were excluded due to suboptimal image quality.

## Conclusions

All left atrial strain and strain rate parameters are significantly reduced in patients with cardiac amyloidosis. Patients with hypertensive heart disease also had reduced strain values, though to a significantly lesser degree than the CA group. LA strain is a potential echocardiographic tool to add incremental value in diagnosis of infiltrative pathologies such as CA and in differentiating between increased LV wall thickness due to CA or the more common cause of hypertensive heart disease.

**Author contributions** KR—concept and design, data collection, primary author of manuscript. GMS—concept and design, critical revision of article. KS—interobserver variability data collection. NE—data collection, critical revision of article. AL—concept and design, drafting article, critical revision of article. DGP—concept and design, critical revision of article. JC—concept and design, oversight of data collection, statistical analysis, drafting article, critical revision of article.

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### Compliance with ethical standards

**Conflict of interest** All the authors declared that they have no conflict of interest.

## Appendix

### Data including study vendor, year of study and strain values for the amyloid and hypertensive cohorts

| Disease state | Vendor | Year of study | Reservoir strain (S-LAs | Conduit strain (S-LAe) | Contractile strain (S-LAa) |
|---|---|---|---|---|---|
| AL | GE | 2017 | 11.87 | | |
| AL | Phillips | 2018 | 7.94 | 4.895 | 3.045 |
| AL | Phillips | 2016 | 8.77 | 5.85 | 2.92 |
| AL | Phillips | 2010 | 22.955 | 7.75 | 15.205 |
| AL | Phillips | 2015 | 6.795 | 3.11 | 3.685 |
| AL | Phillips | 2015 | 9.09 | 4.87 | 4.22 |
| AL | Phillips | 2011 | 7.44 | 4.455 | 2.985 |
| AL | GE | 2017 | 2.245 | 1.385 | 0.86 |
| AL | Phillips | 2017 | 27.655 | 16.285 | 11.37 |
| AL | GE | 2015 | 12.64 | 4.805 | 7.835 |
| AL | GE | 2017 | 3.65 | | |
| ATTR | GE | 2015 | 12.64 | 4.805 | 7.835 |
| ATTR | GE | 2017 | 3.65 | | |
| ATTR | GE | 2018 | 6.245 | 3.995 | 2.25 |
| ATTR | Phillips | 2016 | 3.27 | 2.73 | 0.535 |
| ATTR | GE | 2016 | 5.46 | 3.58 | 1.88 |
| ATTR | GE | 2017 | 10.21 | | |
| ATTR | Phillips | 2019 | 5.00 | | |
| ATTR | GE | 2018 | 4.13 | | |
| ATTR | GE | 2017 | 5.57 | | |
| ATTR | GE | 2017 | 15.84 | 5.40 | 10.45 |
| ATTR | GE | 2017 | 15.87 | 6.53 | 9.34 |
| ATTR | GE | 2018 | 6.10 | | |
| ATTR | Phillips | 2014 | 19.51 | | |
| ATTR | Phillips | 2018 | 10.78 | 8.18 | 2.60 |
| ATTR | GE | 2017 | 6.60 | | |
| ATTR | Phillips | 2018 | 7.71 | | |
| ATTR | Phillips | 2017 | 3.73 | | |
| ATTR | GE | 2019 | 6.22 | | |
| ATTR | Phillips | 2015 | 10.08 | | |
| ATTR | Phillips | 2015 | 25.70 | 15.47 | 10.24 |
| ATTR | GE | 2015 | 9.95 | 3.41 | 6.54 |
| ATTR | GE | 2016 | 5.70 | 4.63 | 1.07 |
| ATTR | GE | 2015 | 7.30 | | |
| ATTR | GE | 2014 | 5.21 | | |
| ATTR | GE | 2015 | 6.10 | | |
| ATTR | GE | 2017 | 4.82 | | |
| ATTR | GE | 2013 | 7.34 | | |
| ATTR | Phillips | 2010 | 20.71 | 6.92 | 13.79 |

| Disease state | Vendor | Year of study | Reservoir strain (S-LAs | Conduit strain (S-LAe) | Contractile strain (S-LAa) |
|---|---|---|---|---|---|
| ATTR | HP7500 | 2004 | 2.49 | | |
| ATTR | Phillips | 2017 | 6.30 | 4.61 | 1.69 |
| ATTR | Phillips | 2018 | 28.70 | 4.94 | 15.77 |
| ATTR | Phillips | 2016 | 9.18 | | |
| ATTR | Siemens | 2016 | 2.37 | | |
| ATTR | Phillips | 2017 | 8.34 | 5.48 | 2.86 |
| ATTR | GE | 2015 | 32.64 | 15.91 | 13.65 |

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