Clinical research

Left atrial myopathy in cardiac amyloidosis: implications of novel echocardiographic techniques

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Aims To assess left atrial (LA) function and determine the prevalence of LA dysfunction in AL amyloidosis (AL) using conventional and strain echocardiography.

Methods and results LA ejection fraction, LA filling fraction, LA ejection force, peak LA systolic strain rate (LAsSR), and LA systolic strain (LA e) were determined in 95 AL patients (70 with and 25 without echocardiographic evidence of cardiac involvement, abbreviated CAL and NCAL, respectively), 30 age-matched controls (CON), and 20 patients with diastolic dysfunction and LA dilatation (DD). Peak LAsSR >2 standard deviations below mean CON value was used as the cut-off for normal LA function. LA ejection fraction was lower in CAL when compared with CON (40.4 ± 13.6 vs. 67.0 ± 6%, P = 0.01). Left atrial septal strain rate and strain were lower in CAL (0.8 ± 0.5 s⁻¹ and 5.5 ± 4%, respectively) compared with CON (1.8 ± 0.8 s⁻¹ and 14 ± 4%, respectively, P < 0.0001), NCAL (1.6 ± 0.8 s⁻¹ and 13 ± 7%, respectively, P < 0.0001) and DD (1.3 ± 0.4 s⁻¹ and 10 ± 2%, respectively, P < 0.0001). Based on peak LA systolic strain rate criteria, the cut-off values for normal LA function were −1.1 s⁻¹ and −1.05 s⁻¹ for lateral and septal walls. Using these criteria, LA dysfunction was identified in 32% (lateral LA criteria) and 60% (septal LA criteria) of CAL patients. Lateral and septal LAsSR were lower in CAL patients with vs. those without symptoms of heart failure. Inter- and intra-observer agreement was high for LA strain echocardiography.

Conclusion LA function assessment using strain echocardiography is feasible with low intra- and inter-observer variability. LA dysfunction is observed in AL patients without other echocardiographic features of cardiac involvement and may contribute to cardiac symptoms in CAL.

KEYWORDS
Amyloidosis;
Strain;
Atrial function;
Echocardiography

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Introduction

AL amyloidosis (AL; also known as primary amyloidosis) is characterized by extracellular infiltration of various organs, including the heart, by fibrillar deposits derived from monoclonal light chain fragments. Clinical evidence of cardiac involvement occurs in 30–50% of AL patients and usually presents as diastolic dysfunction. The left atrium modulates left ventricular (LV) filling through three components: an expansion component during ventricular systole, a conduit component during early ventricular diastole, and an active contractile component during late ventricular diastole. The active contractile component of the left atrium has an important role in patients with diastolic dysfunction, where the ‘atrial kick’ is critical to ventricular filling. AL amyloidosis is known to affect all cardiac chambers. Left atrial (LA) involvement could potentially impair LA systolic function, which could further compromise ventricular filling and contribute to symptoms related to diastolic dysfunction. We evaluated LA systolic function in AL amyloidosis patients using conventional and strain echocardiography.

Methods

Study population

The protocol was approved by the Institutional Review Board. We enrolled 145 subjects: 95 consecutive patients with AL amyloidosis, 30 healthy age-matched subjects (CON), and 20 subjects with enlarged LA and diastolic dysfunction but no evidence of AL amyloidosis (DD).

All AL patients were newly diagnosed and had not received any treatment prior to enrolment in the study. All AL patients had a fat and/or bone marrow biopsy positive for Congo red birefringence and monoclonal protein in serum/urine. AL patients had no history of hypertension, diabetes, coronary artery or significant valvular heart disease, or tobacco use. CON were asymptomatic individuals from the community, age >55 years, no co-morbidities and normal echo-Doppler examination including ejection fraction (EF) >0.55, normal wall motion, normal diastolic function, and ventricular wall thickness <12 mm. DD subjects consisted of age-matched individuals with diastolic and enlarged LA by echocardiography and no amyloidosis. These individuals were identified by screening the daily echocardiography reports.

All enrolled subjects had a 12-lead EKG. We excluded patients with bundle branch block or AV block, pacemaker and atrial fibrillation. Presence/absence of heart failure symptoms (CHF) was noted from medical records and patient interview in all the subjects.

Conventional echocardiography and strain echocardiography

Conventional (standard projections) and strain echocardiography were performed using a Vivid 7 machine with a 3.5-MHz phased array transducer. Echocardiographic criteria (presence of diastolic dysfunction, ventricle wall thickness >12 mm, thickened valves, pericardial effusion, and ‘granular’ sparkling appearance of myocardium) were used to identify AL patients with cardiac involvement. Standard echo-Doppler criteria were used to grade global diastolic dysfunction. LA filling fraction (atrial time–velocity integral/total time–velocity integral) and LA ejection force [0.5 × 1.06 × mitral orifice area × (peak A velocity)]2 were used to assess LA function by conventional echocardiography.7–9 LA volume was measured using the area-length technique in 4- and 2-chamber apical projections and indexed to body surface area.10 Ventricular septal thickness was measured in parasternal long and short axis views. LV EF was estimated using biplane Simpson’s method and LV dysfunction defined as an EF <0.55.

For strain echocardiography, narrow-sector, high frame rate (~200 Hz) images of the LA lateral and septal walls were obtained from the apical 4-chamber view. Peak LA systolic strain rate (LAsSR) and LA systolic strain were determined from the LA lateral and septal walls, using a strain (offset) length of 12 mm, at a level ~5 mm superior to the atrio-ventricular junction. All values were averaged over four consecutive cardiac cycles. Peak LAsSR was the peak negative value at the time of atrial contraction. The atrial systolic wave was integrated to yield LA systolic strain (Figure 1). To determine variability of strain echocardiography parameters, peak LAsSR and strain measurements were repeated by the same observer (intra-observer) or by a second observer (inter-observer) in 12 randomly selected subjects from the study group. All strain echocardiography analysers were blinded to clinical and conventional echocardiographic data. Peak atrial and lateral septal sSR was used to quantify LA function, and values >2 standard deviations below mean sSR of the CON group were considered abnormal. Segments with poor signal quality were not analysed. Patients with or without echocardiographic evidence of cardiac involvement were abbreviated CAL and NCAL, respectively.

Statistics

Sample size calculations were performed using a single end point variable of left atrial septal strain rate. Based on the initial 20 AL patients, we calculated the sample size for a two-sided Student’s t-test using a common standard deviation of 0.5 s–1, α = 0.05 and a desired power of 80% to be 17 patients per group. The expected difference in means for this calculation was 0.5 s–1 which translates to an effect size of 1.

Data were summarized as mean ± SD for continuous variables and as frequency (percentage) for nominal variables. Analysis of variance was used to perform overall comparisons among the four groups (CAL, NCAL, CON, DD) for continuous variables. Where the overall P-value indicated statistical significance, two-sided Student’s t-tests, with the Tukey HSD adjustment for multiple comparisons, were used to perform all possible pairwise comparisons. The degree of association between LAsSR and right ventricular systolic pressure was estimated using the Pearson coefficient of correlation. Intra- and inter-observer variability of strain and strain rate measurements of the left atrium were assessed using the inter- and intra-class correlation coefficient (ICC) and by Bland–Altman methods.11–13

Results

Echocardiographic features of cardiac involvement were present in 66 AL patients (CAL) and absent in 25 patients (NCAL). Endomyocardial biopsy was available and positive for CAL in 15 AL patients including four with non-diagnostic echocardiograms resulting in 70 CAL
Figure 1  Representative strain echocardiography image of the atrial septum in a control subject (A; arrow = region of interest). The atrial strain rate signal (B) depicts ventricular systole (VS), early ventricular relaxation (EVR), and atrial systole (AS). Atrial systolic wave was integrated (hatched area) to yield atrial strain (C). Peak atrial strain is the most negative point on the curve (arrow).

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 30)</th>
<th>DD (n = 20)</th>
<th>NCAL (n = 25)</th>
<th>CAL (n = 70)</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 ± 7</td>
<td>65 ± 9</td>
<td>59 ± 10</td>
<td>61 ± 10</td>
<td>0.05</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>10 (33)</td>
<td>13 (65)</td>
<td>10 (33)</td>
<td>41 (82)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body surface area, kg/m²</td>
<td>1.89 ± 0.2</td>
<td>1.83 ± 0.2</td>
<td>1.87 ± 0.2</td>
<td>1.87 ± 0.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart rate, b.p.m.</td>
<td>69.4 ± 11</td>
<td>62 ± 12</td>
<td>69.3 ± 12</td>
<td>79 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>128 ± 10</td>
<td>136 ± 26</td>
<td>118 ± 19</td>
<td>115 ± 18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66.4 ± 5.4</td>
<td>59.8 ± 16.1</td>
<td>64.1 ± 5.4</td>
<td>56.2 ± 12.8</td>
<td>0.005</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>5.0 ± 0.6</td>
<td>5.1 ± 0.7</td>
<td>4.7 ± 0.5</td>
<td>4.5 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic diameter, cm</td>
<td>2.8 ± 0.9</td>
<td>3.2 ± 0.8</td>
<td>2.9 ± 0.4</td>
<td>3.0 ± 0.6</td>
<td>0.30</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>43.4 ± 17</td>
<td>37 ± 9</td>
<td>46.6 ± 5</td>
<td>32.7 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>LV wall thickness, cm</td>
<td>0.8 ± 0.1</td>
<td>1.1 ± 1.9</td>
<td>1.1 ± 1.6</td>
<td>1.6 ± 3.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV mass indexed to body surface area, g/m²</td>
<td>76 ± 21</td>
<td>106 ± 29</td>
<td>89 ± 29</td>
<td>149 ± 48</td>
<td>&lt;0.0001</td>
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<tr>
<td>LA volume index, mm³/m²</td>
<td>20.5 ± 3.8</td>
<td>45.7 ± 16.4</td>
<td>25.4 ± 5.3</td>
<td>32.2 ± 9.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>E/A ratio</td>
<td>1.0 ± 0.2</td>
<td>1.8 ± 0.9</td>
<td>1.0 ± 0.4</td>
<td>1.8 ± 1.1</td>
<td>&lt;0.0001</td>
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<td>E/e’ ratio</td>
<td>9.7 ± 3.1</td>
<td>14.9 ± 5.8</td>
<td>10.7 ± 3.8</td>
<td>21.1 ± 8.7</td>
<td>&lt;0.0001</td>
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<td>Deceleration time, ms</td>
<td>209 ± 25</td>
<td>213 ± 53</td>
<td>215 ± 37</td>
<td>181 ± 46</td>
<td>&lt;0.0001</td>
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<td>ACE-inhibitors or angiotensin receptor blockers</td>
<td>–</td>
<td>7</td>
<td>6</td>
<td>22</td>
<td>0.42</td>
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<tr>
<td>β-blockers</td>
<td>–</td>
<td>10</td>
<td>2</td>
<td>13</td>
<td>0.12</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>2</td>
<td>1</td>
<td>6</td>
<td>0.64</td>
</tr>
<tr>
<td>Diuretics</td>
<td>–</td>
<td>6</td>
<td>11</td>
<td>37</td>
<td>0.03</td>
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<tr>
<td>Digitalis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>0.37</td>
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</tbody>
</table>

Data are mean ± SD, or frequency (%).
LV, left ventricle; LA, left atrium; E/A, early to late diastolic of mitral inflow; E/e’, early diastolic mitral inflow to early tissue Doppler; LVEF, left ventricular ejection fraction; ACE angiotensin-converting enzyme.
patients. Baseline characteristics are presented in Table 1. Electrocardiogram revealed 'p' waves in all and a prolonged PR interval (175 ± 42 ms) in 14 AL patients. All AL patients had 'A' waves on mitral inflow and pulmonary vein Doppler signal by conventional echocardiography.

There were 33 (47%) patients with heart failure in the CAL, four in the DD, and none in the NCAL and CON groups. Mean LVEF was within normal range and similar in the CAL (59.03 ± 1.7%) and DD (59.25 ± 3.0%, P = 0.94) groups but significantly lower compared with CON and NCAL subjects (66.4 ± 5.9 and 64.1 ± 5.4%, respectively, P = 0.01 for both). Echocardiographic data were available in all subjects. Acceptable quality LA lateral wall strain data were available in 78% of subjects.

The following conventional echocardiography parameters were used to quantify LA systolic function, and data from pair-wise comparisons are presented (Figure 2): LAEF, LA filling fraction, and LA ejection force. Mean LAEF was lower in CAL compared with CON, NCAL, and DD (40 ± 14, 67 ± 6, 40 ± 14, and 50 ± 13%, respectively, all P < 0.02, Figure 2A). There was no statistical difference in LAEF between NCAL and DD (58 ± 12 vs. 50 ± 13%, respectively, P = 0.06). Mean LA filling fraction was significantly different between the DD and NCAL (0.34 ± 0.1 vs. 0.50 ± 0.1, respectively, P = 0.008) and between DD and CON (0.34 ± 0.1 vs. 0.42 ± 0.09, respectively, P = 0.009) but was similar between other pairs (P = 0.57 for CAL vs. CON, P = 0.10 for CAL vs. NCAL, P = 0.19 for CAL vs. DD, Figure 2B). Mean LA ejection force was similar in all four groups (P = 0.83).

Similar pair-wise analysis was performed to analyse strain echocardiography parameters. Mean peak LAaSR of lateral and septal walls was lower in CAL (0.9 ± 0.6 s\(^{-1}\) lateral, 0.8 ± 0.5 s\(^{-1}\) septal) compared with CON (2.4 ± 1.3 s\(^{-1}\) lateral, 1.8 ± 0.8 s\(^{-1}\) septal), DD (1.3 ± 0.6 s\(^{-1}\) lateral, 1.3 ± 0.4 s\(^{-1}\) septal), NCAL (1.5 ± 0.8 s\(^{-1}\) lateral, 1.6 ± 0.8 s\(^{-1}\) septal, P < 0.0001) (Figure 2C). Compared with controls, lateral peak LAaSR was lower in DD and NCAL (P < 0.0009 for both). However, lateral and septal LA systolic strain were similar in DD and NCAL (P = 0.69 and P = 0.07, respectively). Lateral and septal LA systolic strain were lower in CAL (5.5 ± 4% lateral, 6 ± 3% septal) compared with CON (19 ± 4% for lateral, 14 ± 4% for septal, both P < 0.0001) and NCAL (11 ± 5% lateral, 13 ± 7% septal, both P < 0.0001, Figure 2D). There was no statistical difference in septal LA systolic strain between CON and NCAL (P = 0.52), and lateral and septal LA systolic strain between DD and NCAL (P = 0.69 and P = 0.07, respectively).

There was no correlation between septal LAaSR parameters and right ventricular pulmonary pressure (R = 0.36, P = 0.06).

Mean LAEF and peak LAaSR were able to demonstrate a statistical difference in five of six possible pairs. However, only peak LAaSR was significantly lower in AL patients with, vs. without, heart failure (–0.7 ± 0.4 vs. –1.1 ± 0.7 s\(^{-1}\), respectively, P = 0.03) while LAEF was similar in both groups (41 ± 16 vs. 50 ± 16%, respectively, P = 0.06, Figure 3).

Based on peak LAaSR in CON, the cut-off value for normal LA function was –1.1 s\(^{-1}\) and –1.05 s\(^{-1}\) for

![Figure 2](image-url)

**Figure 2** Left atrial ejection fraction (LAEF; A), LA filling fraction (LAFF; B), LA systolic strain rate (LAaSR; C), and LA systolic strain (LAs; D) were lower in CAL compared with all other groups.
lateral and septal walls, respectively. Using these criteria, LA dysfunction was identified in 32% (lateral LA criteria) and 60% (septal LA criteria) of CAL patients.

Intra- and inter-observer reproducibility of LA strain measurements was high. Inter-observer ICC was 0.90 for peak LA systolic strain rate, 95% confidence interval (CI) of 0.61–0.91, and 0.91 for LA systolic strain (95% CI: 0.70–0.97). Intra-observer ICC for peak LAsSR was 0.87 (95% CI 0.52–0.97) and 0.89 (95% CI 0.58–0.97) for LA systolic strain. The mean (±1SD) inter-observer difference was 0.06 ± 0.05 s⁻¹ (95% CI: −0.5–0.7) for peak LAsSR and 4.9 ± 0.76% (95% CI: 5.7–7.5) for LA systolic strain. The mean (±1SD) intra-observer difference was 0.07 ± 0.31 s⁻¹ (95% CI: −0.04–0.16) for peak LAsSR and 0.9 ± 3.4% (95% CI: −3.4–6.3) for LA systolic strain (Figure 4).

Discussion

Our study demonstrates LA systolic dysfunction in AL patients. The LA dysfunction appears to be independent of global LV systolic and diastolic function, and LA dilatation. Abnormal LA function, using strain echocardiography criteria, was identified in a significant number of CAL patients and mean peak LAsSR was lower in those with, vs. those without, CHF. Furthermore, mean peak LAsSR was lower in NCAL compared with CON, suggesting LA involvement in the absence of the classic echocardiographic features of cardiac AL. Assessment of LA function by strain echocardiography was feasible in all subjects and showed high inter- and intra-observer reproducibility.

In AL, extracellular amyloid deposition in the heart results in mechanical impairment of ventricular diastolic filling and manifests as progressive diastolic dysfunction leading to a restrictive cardiomyopathy. Impaired diastolic filling usually results in increased left ventricular, atrial and pulmonary vascular pressures, and usually presents as reduced exercise tolerance and diastolic heart failure.

In compliant ventricles, diastolic filling predominantly occurs early in diastole. In non-compliant ventricles there is increased dependence on the late diastolic filling mediated by atrial contraction. Left atrial systolic failure in this setting further compromises ventricular filling and usually results in new or worsening heart failure symptoms. This presentation is typified by patients with diastolic dysfunction who develop acute atrial fibrillation (loss of atrial kick) and present with diastolic heart failure.

Although reduced exercise tolerance in AL patients may be due to impairment of other organ systems, altered cardiac function is probably the most important contributor to their functional limitation. Left atrial dysfunction may contribute to exacerbation of symptoms in these patients.

The prevalence of atrial dysfunction in AL is unknown and it is unclear whether it is independent of cardiac involvement. Case reports indicate that atrial dysfunction is associated with evidence of amyloid infiltration in the atria. Murphy et al. found that LA kinetic energy was lower in CAL compared with NCAL and controls (10 subjects in each group) suggesting that atrial involvement may be related to the cardiac AL phenotype. We used conventional and novel echocardiography tools to assess LA function. Strain echocardiography has been validated as an accurate measure of systolic function, and is less susceptible to cardiac translational motion and tethering compared to tissue velocities. The utility of strain echocardiography in depicting cardiac dysfunction has been demonstrated in a multitude of
experimental and clinical studies. Furthermore we have lately validated strain echocardiography in isolated muscle strips of similar thickness to the atrial wall. Image acquisition and analysis of LA strain echocardiography parameters was feasible in the majority of patients and took ~5 min per subject. Data quality and intra- and inter-observer reproducibility were good.

Our data suggest that LA dysfunction is a common component of the CAL phenotype. Interestingly, LA functional parameters demonstrated abnormal function in NCAL subjects compared with CON suggesting that LA function may be affected even in the absence of the traditional echocardiographic features of CAL. In order to assess the contribution of diastolic dysfunction and LA dilatation to abnormal LA function, we compared the AL subjects with individuals with diastolic dysfunction and LA dilatation similar to that of the AL patients (DD group). Our data demonstrate that peak LAsSR and LA systolic strain were significantly lower in CAL compared with the DD group indicating that strain echocardiography parameters were able to detect subtle differences in LA function not recognized by most conventional echocardiographic parameters. Thus it appears that AL involvement affects LA function over and above the dysfunction occurring due to diastolic dysfunction and LA dilatation per se. Also, in the CAL group, peak LAsSR was lower in those with, vs. those without, heart failure. Although convincingly attributing symptoms to LA dysfunction would be challenging, these data somewhat support our hypothesis that loss of atrially mediated ventricular filling in CAL influences symptoms.

Electrical ‘standstill’ has been reported in AL. However, despite evidence of LA dysfunction on conventional and strain echocardiography, all patients had visible ‘p’ waves on electrocardiography. Thus our data suggest a poor correlation between electrical and mechanical atrial activity. Similarly, mitral inflow Doppler signal may not be a sensitive measure of atrial mechanical activity. All AL subjects had ‘A’ waves on mitral inflow Doppler, albeit indistinct and poorly developed in many cases.

Previously published data indicate that septal annular late diastolic velocity is different in CAL, NCAL, and controls. However, our study was not adequately powered to test whether LAsSR offers incremental information over septal annular late diastolic velocities. In our study, LAEF appeared to reliably discriminate between the various clinical groups. However, determination of LAEF by Simpson’s technique is relatively more involved than the single measurements performed in strain echocardiography. Measurement of peak LAsSR may provide a simple, single, and easy measurement of LA systolic function and could potentially be used to monitor LA activity in other cardiac diseases.

Limitations

Echocardiographic criteria, not endomyocardial biopsy, were used to define cardiac involvement in AL. However, this is standard clinical practice in most large volume centres managing amyloidosis. Thus, it is conceivable that some of the patients with normal conventional echocardiography may have had early cardiac amyloid infiltration. However, the converse is also true and a negative biopsy does not rule out cardiac involvement. Similarly, there are reports of isolated atrial amyloidosis in the setting of a normal conventional echocardiogram.

Strain signal quality can be an issue in clinical imaging but to avoid noisy signals we imaged single wall (LA lateral and septal walls) as parallel as possible to the probe. Using this technique, septal wall data were available in all and lateral wall data in 78% subjects. There was no independent validation of LA function. Likewise, there was no invasive assessment of LA and LV pressures.

Conclusions

Left atrial systolic dysfunction is frequent and may contribute to symptoms of heart failure in CAL. LA involvement may occur in the absence of classic echocardiographic features of AL. Quantification of LA systolic function by strain echocardiography is feasible and demonstrates good reproducibility in a clinically diverse population.

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References

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