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Reduced left atrial myocardial deformation irrespective of cavity size: a potential cause for atrial arrhythmia in hereditary transthyretin amyloidosis

Michael Y. Henein, Ole B. Suhr, Sandra Arvidsson, Björn Pilebro, Per Westermark, Rolf Hörnsten and Per Lindqvist

PUBLIC HEALTH AND CLINICAL MEDICINE, UMEÅ UNIVERSITY, UMEÅ, SWEDEN

ABSTRACT

Background: Cardiac amyloidosis (CA) is a myocardial disease and commonly under-diagnosed condition. In CA patients, atrial fibrillation might occur in the absence of left atrial (LA) enlargement.

Objectives: The aim of this study is to assess LA size and function, and its relationship with atrial arrhythmia in patients with hereditary transthyretin amyloidosis (ATTR).

Methods: Forty-six patients with confirmed ATTR amyloidosis on abdominal biopsy were studied. Assessment with 2D echocardiography and 2D strain showed 31 patients had increased LV wall thickness (LVWT) (septal thickness >12 mm), and 15 had normal LVWT. In addition to conventional measurements, LV and LA global longitudinal strain (GLS%) and strain rate (SR) were obtained. Western blot analysis was done to assess fibril type. ATTR patients with increased LVWT were compared with 23 patients with hypertrophic cardiomyopathy (HCM) and 31 healthy controls. ATTR amyloidosis patients also underwent 24 hour Holter monitoring to determine the presence of atrial arrhythmia.

Results: Atrial deformation during atrial systole was reduced in ATTR amyloidosis patients with increased LVWT independent of LA size and in contrast to HCM. Twenty of the ATTR amyloidosis patients (54%) had ECG evidence of significant atrial arrhythmic events. LA strain rate, during atrial systole, was the only independent predictor of atrial arrhythmia ($\beta = 3.28, p = .012$).

Conclusion: In ATTR cardiomyopathy with increased LVWT, LA myocardial function is abnormal, irrespective of atrial cavity size. Reduced LA myocardial SR during atrial systole, irrespective of cavity volume, E/e' and LV deformation, is also a strong predictor for atrial arrhythmic events.

Abbreviations: A': late atrial; AP4C: apical four-chamber; BSA: body surface area; CO: cardiac output; DT: deceleration time; E': early diastole; EDV: end diastolic volume; EF: ejection fraction; EST: end systolic volume; HCM: hypertrophic cardiomyopathy; HR: heart rate; IVST: inter-ventricular septum thickness; LA: left atrium; LASRa: LA strain rate during late diastole or atrial systole, atrial contraction; LASRe: LA strain rate during early ventricular filling phase/reservoir function; LASRs: LA strain rate during ventricular systole/reservoir function; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LV GLS%: peak left ventricular longitudinal strain/deformation during ventricular systole; LVSRe: LV strain rate during early ventricular filling phase; LVSRe: LV strain rate during ventricular systole; LVWT: left ventricular wall thickness; OT: outflow tract; PALS: peak atrial longitudinal strain/deformation during ventricular systole; PLAX: parasternal long axis; PWT: posterior wall thickness; ROI: region of interest; SR: strain rate; SV: stroke volume; VTI: velocity integral

Introduction

Anatomical and functional assessment of the left atrium (LA) have become an increasingly important part of cardiac examination, with LA size and function proves as independent predictors of survival and exercise performance in heart failure [1–3]. The LA function, both as a conduit and an active pump, significantly contributes to left ventricular (LV) filling as well as stroke volume.

Despite the known increased frequency of atrial fibrillation in patients with cardiac amyloidosis, and the confirmed diffuse infiltration of amyloid throughout the entire myocardium, studies have mainly focussed on LV structure and function. Thus, the relationship [4–6] between LA function and the frequently seen atrial arrhythmia in cardiac amyloidosis is not fully elucidated [6,7].

Conventional measurements of LA structure include longitudinal and transverse diameters, cavity area and volume. LA function is historically assessed by area and volume change during atrial systole, i.e. late diastole. Recently, LA myocardial functional assessment has become possible using speckle tracking echocardiography and 2D strain technology, from which myocardial segmental global strain and derived...
strain rate (SR) can be evaluated during different phases of the cardiac cycle. These variables have been tested in cardiac amyloidosis and shown to be abnormal in ATTR amyloidosis patients irrespectively of LA size [8,9]. However, no previous study has evaluated the relation between LA function using 2D strain and atrial arrhythmias.

This study aims to evaluate LA function in patients with hereditary transthyretin (her ATTR) amyloidosis. Patients diagnosed with hereditary ATTR amyloidosis and LV myocardial thickening (increased LVWT) will then be compared with a group of patients with known hypertrophic cardiomyopathy (HCM) in order to determine predictors of LA arrhythmia, as well as healthy controls.

**Patients and methods**

Forty-six patients with abdominal fat tissue biopsy and genetically proven hereditary ATTR amyloidosis, (median age 67 ± 10 year, 26% females) who underwent clinical evaluation at Umeå University hospital between 2003 and 2015 were retrospectively studied. One patient had TTR A45S mutation and the other patients carried the TTR V30M mutation. Based on inter-ventricular septal thickness >12 mm, and in the absence of other pathologies, ATTR patients were classified into two groups; one group consisting of 32 patients with amyloid hypertrophy of the myocardium (inter-ventricular septal thickness >12 mm), and the other consisting of 14 patients with normal myocardial thickness (septal thickness <12 mm). Twenty-three patients with echocardiographically confirmed diagnosis of HCM, (inter-ventricular septum thickness (IVST) >15 mm) in the absence of any other causative pathology (median age 60 ± 20 years (46% females), were also included for comparison. In addition, 31 healthy controls taken from the population who were on no medications and had no history of cardiovascular or systemic disease (median age 61 ± 10 years, 38% females), comprised a control group.

**Echocardiographic analysis**

Patients and controls underwent a comprehensive echocardiographic examination, including 2D, M-Mode, pulsed and tissue Doppler echocardiography using Vivid 7 or E9 (GE Vingmed Ultrasound, Horten, Norway). All patients were in sinus rhythm. For both ATTR and HCM patients, the echocardiographic study was undertaken close to the time of sinus rhythm, as well as healthy controls.

**Myocardial deformation measurements**

Deformation measurements were made offline using the GE EchoPac system (version BT 13, 113.0, Waukesha, WI). From the A4C view, LV and LA longitudinal endocardial deformation were determined by manually tracing along the endocardial border in the end-systolic frame using the point-and-click technique, which created a horseshoe shaped region of interest (ROI) within the cavity. The software algorithm thereafter automatically defined and LA into six regional segments, Figure 1. Tracking quality was checked and, if needed, was manually corrected to ensure optimal tracking of each segment. Only segments deemed appropriately and accurately tracked were included in the analysis with attention paid to avoid inclusion of the pulmonary veins and the LA appendage. The six regional segments were then averaged to generate global peak LV and LA longitudinal deformation. The software required at least 4/6 segments to be accurately tracked to ensure proper analysis and thus was a pre-requisite to include the patient in this study [11].

Strain and SR recordings were averaged from 3 cardiac cycles. To assess the longitudinal deformation of the LA, the following parameters were calculated, with the reference point set at the onset of the QRS complex of the superimposed ECG.

1. PALS (peak atrial longitudinal strain/deformation during ventricular systole),
2. LASRs (LA strain rate during ventricular systole/reservoir function),
3. LASRe (LA strain rate during early ventricular filling phase/conduit function),
4. LASRa (LA strain rate during late diastole or atrial systole, atrial contraction),
5. LV GLS% (peak ventricular longitudinal strain/deformation during ventricular systole),
6. LVSRs (LV strain rate during ventricular systole),
7. LVSRs (LV strain rate during early ventricular filling phase),
8. LVSRa (LV strain rate during late diastole or atrial systole).
Amyloid fibril type determination

The diagnosis of ATTR amyloidosis was confirmed by histopathological examination of Congo red stained abdominal fat biopsy specimens under polarised light [12]. It was possible to determine transthyretin amyloid fibril type (Type A ATTR fibrils consisting of fragmented and full length TTR and type B consisting of full length TTR only) in unfixed abdominal adipose tissue biopsies by gel electrophoresis and western blotting method, as previously described [13,14], in 36 patients.

Holter ECG monitoring

All 46 patients with cardiac amyloidosis underwent 24 h Holter monitoring to determine the presence and frequency of atrial arrhythmic events. Significant atrial arrhythmia was defined as more than 5 consecutive supraventricular beats or more than a total of 1000 supraventricular beats in a 24 h period.

All recordings were performed using a standard recording unit (Tracker II, Reynolds Medical Ltd, UK or Braemer DL 700, Braemer Inc. Burnsville, MN). All recordings were automatically analysed by a PC-based Holter System (Danica Replay Unit, Danica, Borlänge, Sweden or Aspect Holter System, GE Healthcare, Stockholm Sweden).

Statistics

Statistical analysis was performed using commercially available software packages (IMB SPSS statistics, version 24). Data are presented as mean ± SD. The differences between groups were assessed using parametric t-test. Non-parametric Mann–Whitney test was used for comparison between small groups such as healthy controls versus non cardiomyopathy ATTR amyloidosis and ATTR amyloidosis cardiomyopathy versus HCM patients. Fisher Exact probability test was used to test differences in prevalence and Chi-Square test to test difference in categorical variables. To identify independent predictors of atrial arrhythmic events on Holter recordings,

Figure 1. (A) Left ventricular (LV) deformation including strain rate during systole (SRs), early diastole (SRe) and atrial contraction (Sra). (B) Left atrial (LA) deformation including strain rate during reservoir phase (SRs), conduit phase (SRe) and atrial or booster contraction (Sra).
we used binary logistic regression (backward) method. A p value <.05 was considered statistically significant.

### Results

**ATTR amyloidosis versus controls**

Demographic and conventional echocardiographic data are presented in Table 1. Compared to healthy controls, heart rate (HR), septal thickness and LA and LV deformation were different in ATTR amyloidosis patients (p < .05 for all). Thirty-six ATTR amyloidosis patients were analysed and subcategorised by fibril type; 17/36 patients were determined to have type A and 19/36 to have type B ATTR fibril. Sixteen of 17 (94%) patients with type A had LV wall thickness >12 mm compared with 11/19 (58%) of those with type B, who had wall thickness of ≤12 mm. The difference in LVWT between type A and B fibrils was significant (p < .001).

**ATTR amyloidosis with versus without increased LV septal thickness**

Comparing ATTR amyloidosis patients with and without myocardial thickening showed that the former were slightly older (p < .001), had larger LA diameter (p < .05), reduced LA systolic and diastolic deformation (p < .05), and had lower LV GLS, LVSRs and LVSRe (p < .05 for all) (Table 2).

**ATTR amyloidosis with normal septal thickness versus controls**

Compared to controls, ATTR amyloidosis patients with normal myocardial thickness (≤12 mm) were younger (p < .001), tended to have lower body weight (p < .05), had faster HR (p < .001), lower systolic blood pressure (p < .05), smaller LA diameter (p < .05) and lower SV (p < .05) (Table 2). LVEF was not significantly different between the groups, neither were LA and LV deformation parameters. Patients with type A fibrils (94% had increased wall thickness) had lower LASRa compared to those with type B (58% had normal wall thickness (p < .001), Figure 3(A).

**ATTR amyloidosis with increased wall thickness versus HCM**

Compared to HCM, ATTR amyloidosis patients with myocardial thickening were slightly older (p = .024), had less septal thickening (p = .05), a smaller LA diameter (p = .016) and LAVI (p < .022) but higher LASRa (p < .031) (Table 2). In addition, they had higher LVSRe (p = .006). LASRa was related to LA volume only in HCM patients (r = 0.74, p = .025), Figure 2.

**Predictors of atrial arrhythmia**

Holter analysis showed that 20 patients (54%) with ATTR amyloidosis displayed significant atrial arrhythmia. Binary logistic regression (backward testing) was applied to identify independent predictors of atrial arrhythmia among the following parameters: LASRa, GLS, LA volume and E/e’. LASRa proved to be the only independent predictor of atrial arrhythmia (β = 3.28, p = .012), Figure 3(A). Patients with fragmented fibrils (75%) had significantly (p = .004) more atrial arrhythmia events than those with full length fibrils (20%), Figure 3(B). Comparing LA diameter, LAVI and LA deformation measures in ATTR amyloidosis patients with or without atrial arrhythmias on Holter ECG, LASRa was the only parameter that was in difference between the 2 groups (p = .006). The reproducibility of LASRa measurements has previously been shown by the authors to be quite satisfactory [15].

### Discussion

**Findings**

In the group of ATTR amyloidosis patients, cardiac structure and function was abnormal compared to age matched controls. Despite maintained LA size, myocardial deformation function was reduced as was that of the LV, despite normal LVEF and stroke volume. The only significant LV structural abnormality was increased septal and posterior wall thickness, and the only functional disturbance was reduced myocardial deformation during both systole and diastole. Amyloid fibril analysis also showed a close association between LV myocardial thickness and the type A ATTR fibrils.
Table 2. Conventional and deformation echocardiography and demographics in ATTR with or without increased wall thickness, HCM and controls.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>ATTR w/o increased wall thickness</th>
<th>ATTR w/ increased wall thickness</th>
<th>p-value</th>
<th>HCM</th>
<th>ns</th>
<th>Controls</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 ± 10</td>
<td>52 ± 14</td>
<td>.017</td>
<td>68 ± 9;***</td>
<td>60 ± 20</td>
<td>.024</td>
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<td>Gender, females, n(%)</td>
<td>21 (52)</td>
<td>8 (53)</td>
<td>ns</td>
<td>8 (28)</td>
<td>11 (48)</td>
<td>ns</td>
<td></td>
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<td>SBP, mmHg</td>
<td>132 ± 18</td>
<td>123 ± 10</td>
<td>.031</td>
<td>132 ± 16</td>
<td>139 ± 24</td>
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<tr>
<td>DBP, mmHg</td>
<td>76 ± 7</td>
<td>76 ± 7</td>
<td>ns</td>
<td>76 ± 10</td>
<td>81 ± 14</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 ± 8</td>
<td>170 ± 11</td>
<td>ns</td>
<td>174 ± 10</td>
<td>173 ± 13</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 ± 11</td>
<td>66 ± 14</td>
<td>&lt;.001***</td>
<td>72 ± 10</td>
<td>81 ± 18</td>
<td>.011</td>
<td></td>
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<tr>
<td>LA diameter, mm</td>
<td>38 ± 6</td>
<td>32 ± 5</td>
<td>.037*</td>
<td>37 ± 5?</td>
<td>42 ± 8</td>
<td>.016</td>
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<tr>
<td>LAVI, ml/m²</td>
<td>31 ± 10</td>
<td>25 ± 11</td>
<td>ns</td>
<td>31 ± 11*</td>
<td>42 ± 17</td>
<td>.022</td>
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**LA deformation**

<table>
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<tr>
<th>Measurement</th>
<th>ATTR w/o increased wall thickness</th>
<th>ATTR w/ increased wall thickness</th>
<th>p-value</th>
<th>HCM</th>
<th>ns</th>
<th>Controls</th>
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<tr>
<td>PALS, %</td>
<td>29 ± 10</td>
<td>28 ± 7</td>
<td>ns</td>
<td>21 ± 7†,*</td>
<td>18 ± 14</td>
<td>ns</td>
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<tr>
<td>LASRs, 1/s</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>ns</td>
<td>1.0 ± 0.41*</td>
<td>0.8 ± 0.4</td>
<td>ns</td>
<td></td>
</tr>
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<td>LASRe, 1/s</td>
<td>−1.4 ± 0.5</td>
<td>−1.4 ± 0.6</td>
<td>ns</td>
<td>−0.8 ± 0.41,*</td>
<td>−0.7 ± 0.5</td>
<td>ns</td>
<td></td>
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<tr>
<td>LASRs, 1/s</td>
<td>−1.7 ± 0.6</td>
<td>−1.8 ± 0.5</td>
<td>ns</td>
<td>−1.3 ± 0.51,*</td>
<td>−0.9 ± 0.6</td>
<td>.031</td>
<td></td>
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<tr>
<td>Septal thickness, mm</td>
<td>10 ± 1</td>
<td>10 ± 2</td>
<td>ns</td>
<td>16 ± 3†,*</td>
<td>18 ± 5</td>
<td>.05</td>
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<tr>
<td>Posterior wall, mm</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>ns</td>
<td>12 ± 2†,*</td>
<td>11 ± 2</td>
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<tr>
<td>LVDVI, ml/m²</td>
<td>54 ± 10</td>
<td>49 ± 11</td>
<td>ns</td>
<td>49 ± 14</td>
<td>90 ± 33</td>
<td>ns</td>
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<tr>
<td>LSVI ml/m²</td>
<td>20 ± 6</td>
<td>18 ± 4</td>
<td>ns</td>
<td>16 ± 4.5</td>
<td>29 ± 13</td>
<td>ns</td>
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<tr>
<td>LVEF, %</td>
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<td>ns</td>
<td>67 ± 6</td>
<td>65 ± 11</td>
<td>ns</td>
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<tr>
<td>SV, ml</td>
<td>78 ± 14</td>
<td>68 ± 13</td>
<td>.028*</td>
<td>75 ± 17</td>
<td>78 ± 18</td>
<td>ns</td>
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<td>CO ml/min</td>
<td>4.9 ± 0.9</td>
<td>5.2 ± 0.8</td>
<td>ns</td>
<td>5.3 ± 1.1</td>
<td>5.0 ± 1.1</td>
<td>ns</td>
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<tr>
<td>E/A</td>
<td>1.2 ± 0.5</td>
<td>1.1 ± 0.3</td>
<td>ns</td>
<td>1.0 ± 0.5</td>
<td>1.2 ± 0.5</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>DT, ms</td>
<td>220 ± 54</td>
<td>200 ± 51</td>
<td>ns</td>
<td>221 ± 78</td>
<td>201 ± 49</td>
<td>ns</td>
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<tr>
<td>E/e</td>
<td>6.9 ± 1.8</td>
<td>8 ± 3</td>
<td>ns</td>
<td>9.7 ± 4.3</td>
<td>10.0 ± 4.5</td>
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</table>

**LV deformation**

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<th>Measurement</th>
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<th>ATTR w/ increased wall thickness</th>
<th>p-value</th>
<th>HCM</th>
<th>ns</th>
<th>Controls</th>
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<tbody>
<tr>
<td>GLS, %</td>
<td>−18 ± 3</td>
<td>−19 ± 3</td>
<td>ns</td>
<td>−16 ± 4†,***</td>
<td>−15 ± 4</td>
<td>ns</td>
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</tr>
<tr>
<td>LSVRs, 1/s</td>
<td>−0.9 ± 0.1</td>
<td>−1.0 ± 0.2</td>
<td>ns</td>
<td>−0.9 ± 0.2†,*</td>
<td>−0.9 ± 0.2</td>
<td>ns</td>
<td></td>
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<tr>
<td>LSVRe, 1/s</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>ns</td>
<td>0.9 ± 0.3††,***</td>
<td>0.8 ± 0.2</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>LSVRa, 1/s</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td>ns</td>
<td>0.9 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>.006</td>
<td></td>
</tr>
</tbody>
</table>

A and a: atrial contraction; CO: cardiac output; DBP: diastolic blood pressure; DT: deceleration time; DVI: diastolic volume indexed for BSA; E and e: early diastolic; EF: ejection fraction; GLS: global longitudinal strain.; LA: left atrial; LV: left ventricular; PALS: peak atrial longitudinal systolic strain; s: systolic; SBP: systolic blood pressure; SR: strain rate; SVI: systolic volume indexed for BSA; SV: stroke volume

*, †: p < .05, ††: p < .01, †††: p < .001 using Mann–Whitney test.

Figure 2. Relationships between LASRa (left atrial strain rate during atrial contraction) and LAVI (left atrial volume indexed for BSA) in transthyretin amyloid (ATTR) amyloidosis with (filled thin line) and without (thin small dotted line) increased left ventricular (LV) wall thickness, healthy controls (dotted line) and hypertrophic cardiomyopathy (HCM) (thick line).
In Swedish hereditary ATTR V30M amyloidosis, there are two distinct fibril types [13,14,16,17]. Type A fibrils are composed mainly of N-terminally truncated TTR molecules starting at positions 46, 49 and 52 while type B fibrils consist of full-length TTR molecules. Interestingly, ATTR amyloidosis with type A fibrils has been shown to be associated with a risk of progressive cardiomyopathy and is characterised by an increasing myocardial thickness [13,17].

Fibril type A is associated with a decreased LV myocardial function [14] and, in the present study, was also associated with decreased LA function and with increased atrial arrhythmic events. Although no differences in LA and LV myocardial function were found between ATTR patients with normal wall thickness and controls, those with septal thickness >12 mm displayed a smaller LA size and higher LASR during atrial systole, compared with those of HCM. In addition they also had lower LASRa compared with that of normal wall thickness ATTR patients and healthy controls. Interestingly, no correlation between LASRa and LA size was noted in the ATTR amyloidosis patients when compared to the HCM patients, where a significant correlation between the severity of LV wall thickness compared to the relatively normal wall thickness, commonly seen in the type B ATTR amyloidosis patients. However, the relationship found between LA strain rate and prevalence of atrial arrhythmia, was relatively independent of LV deformation, thus, suggesting a different aetiology. The fourth finding was the positive relationship between reduced LA strain rate and atrial arrhythmic events, irrespective of cavity size and LV wall thickness. Interestingly, this relationship was more pronounced in patients with type A compared to those with type B ATTR. Finally, the significant association between the type A fibrils, LA dysfunction, atrial arrhythmia and LV wall thickness is likely to be associated with a poorer prognosis or decreased survival previously reported in ATTR amyloidosis patients with cardiac involvement [17], although this aspect was not the focus of this study.

**Data interpretation**

Despite LV involvement caused by amyloid depositions in the ATTR amyloidosis group [18], and irrespective of LV wall thickness, there was no significant difference in LA size when compared to the control group. This is an unexpected finding, since the LA, described as the “Cinderella of the left heart”, is commonly enlarged in any form of LV disease [19,20]. This finding therefore suggests that LA myocardial infiltration with the amyloid limits LA distension, as has previously been found in cardiac examinations on patients with AL or ATTR amyloidosis [7,8,21]. This suggestion is also supported by the significantly reduced LA SR function during the atrial contraction phase, particularly in patients with increased LV wall thickness. The second finding was that type A fibril composition (presence of TTR fragments) exerted an impact on LA function, despite maintained LA size. Patients with type A fibrils had worse LA SR function compared with those with type B fibrils, which is probably related to the severity of LV wall thickness compared to the relatively normal wall thickness, commonly seen in the type B ATTR amyloidosis patients. The third finding was that type A fibril composition (presence of TTR fragments) exerted an impact on LA function, despite maintained LA size. Patients with type A fibrils had worse LA SR function compared with those with type B fibrils, which is probably related to the severity of LV wall thickness compared to the relatively normal wall thickness, commonly seen in the type B ATTR amyloidosis patients. However, the relationship found between LA strain rate and prevalence of atrial arrhythmia, was relatively independent of LV deformation, thus, suggesting a different aetiology. The fourth finding was the positive relationship between reduced LA strain rate and atrial arrhythmic events, irrespective of cavity size and LV wall thickness. Interestingly, this relationship was more pronounced in patients with type A compared to those with type B ATTR. Finally, the significant association between the type A fibrils, LA dysfunction, atrial arrhythmia and LV wall thickness is likely to be associated with a poorer prognosis or decreased survival previously reported in ATTR amyloidosis patients with cardiac involvement [17], although this aspect was not the focus of this study.

**Clinical application**

Even though malnutrition and opportunistic infections are the main cause of death in ATTR V30M patients, heart failure and arrhythmia including atrial fibrillation and cerebrovascular complication are increasingly acknowledged in late onset and liver transplanted ATTR V30M amyloidosis patients [22,23]. Since heart failure is a common cause of death in ATTR patients [24], LA function should be routinely and thoroughly assessed and monitored as it is shown to be an integral part of cardiac function in health and disease. This proposal is supported by the significantly reduced LA function using speckle tracking found in these patients,
irrespective of its size and LV wall thickness. The LA deformation function is easily obtainable by echocardiography, and should hence be used for screening and assessment of early subclinical myocardial involvement and may be useful as a predictor for future risk for atrial arrhythmic events. The significant association between fragmented fibrils and LA dysfunction supports the need for closer cardiac follow up. More rigorous screening and monitoring methods in these patients may serve to prevent rapid deterioration of LA function and determine the need and time-point for medical intervention, pressure off loading and anti-arrhythmic medications.

Limitations
The small number of patients included in this study carried its known limitations, particularly with regards to statistical significance and relevance of findings. The absence of cardiac biopsy in these patients weakens the explanation of atrial infiltration, although the findings are consistent. However, a previous study from our group has shown the presence of amyloid infiltration in the heart of hereditary ATTR patients irrespectively of fibril type [18]. Our findings in hereditary ATTR cannot be automatically transferred to other types of amyloidosis. Patients had Holter monitoring for only 24h, which may be too short a period of time to identify patients in whom atrial arrhythmic events are less frequent. An event recorder sampling for longer time may be preferable, or 3 weeks thumb ECG recordings [25]. It can be argued that 2D strain measures of LA function are dependent on LV and LA function since they are structurally and functionally connected. However, a previously published study showed LA deformation during atrial contraction to be independent of LV mechanics [26].

Conclusion
In ATTR cardiomyopathy with increased LVWT, LA myocardial function is abnormal, irrespective of atrial cavity size. Reduced LA myocardial SR during atrial systole, irrespective of cavity volume, E/e' and LV deformation, is also a strong predictor for atrial arrhythmic events. The close relationship between the ATTR fibril type A, LA deformation and arrhythmia, supports the need for regular monitoring of atrial function, rather than atrial size, to detect patients at high risk of developing atrial arrhythmias.

Disclosure statement
The authors report no conflicts of interest.

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References


