Biventricular assessment of light-chain amyloidosis using 3D speckle tracking echocardiography: Differentiation from other forms of myocardial hypertrophy

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A B S T R A C T

Background: Given that in patients with cardiac amyloidosis (CA), deposition of amyloid protein is not restricted to the left ventricular (LV) myocardium, it can be hypothesized that the diagnostic value of deformation mechanics would be enhanced by considering right ventricular (RV) strain measures. The aim of the present study was to examine the potential utility of left ventricular (LV) and right ventricular (RV) deformation and rotational parameters derived from three-dimensional speckle-tracking echocardiography (3DSTE) to diagnose cardiac amyloidosis and differentiate this disease from other forms of myocardial hypertrophy.

Methods: Twenty-three patients with biopsy-proven light-chain (AL) amyloidosis, 23 patients with systemic arterial hypertension (HTN), 23 patients with hypertrophic cardiomyopathy (HCM), 23 athletes and 23 normal controls were prospectively studied by conventional echocardiography and 3DSTE. LV longitudinal strain (LV LS), LV circumferential strain (LV CS), RV global longitudinal strain and RV free-wall longitudinal strain (RV FW LS) were obtained by 3DSTE, as well as LV rotation and rotational velocities.

Results: LV and RV longitudinal strains were reduced in cardiac amyloidosis (CA) patients compared to controls. By multivariate analysis, LV basal LS (p = 0.002), LV peak basal rotation (p = 0.003), and RV basal FW LS (p = 0.014) were independently associated with CA in the overall population. A significant improvement in global $r^2$ value was noted with RV 3D-strain parameters over only LV-3DSTE + conventional indices for detection of CA (p < 0.001).

Comparison of ROC curves showed that the AUC using combined LV basal LS, LV basal rotation and RV basal FW LS had a higher discriminative value than the other echocardiographic parameters used for detecting CA (AUC 0.93, 95%CI 0.81–0.97).

Conclusions: Three-dimensional speckle tracking echocardiography reveals regional and global biventricular dysfunction in CA. Assessment of RV ventricular dysfunction has an additive value in differentiating CA from other causes of myocardial wall thickening.

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Cardiac amyloidosis (CA) is an infiltrative disease primarily caused by extracellular tissue deposition of amyloid fibrils in the myocardial interstitium [1,2]. Over half of patients with amyloidosis in its light chain (AL) variant show cardiac involvement at diagnosis, and this condition is the most important prognostic factor in the natural progression of the disease. Typical standard echocardiographic features in these patients include increased left (LV) and right ventricular (RV) wall thickness, biventricular diastolic dysfunction, granular/sparkling myocardial texture, enlarged left and right atria, and pericardial effusion, but no finding alone is specific [3]. Two-dimensional (2DSTE) and, more recently, three-dimensional speckle tracking echocardiography (3DSTE) have emerged as methods for detection of global and regional myocardial dysfunction in various cardiovascular diseases [4–6], and applied to the diagnosis of LV dysfunction in cardiac amyloidosis [7–11]. Although these novel echocardiographic imaging modalities have advanced our understanding of LV deformational mechanics, and facilitated the differentiation of physiologic left ventricular hypertrophy (LVH) from pathologic LVH, overlapping patterns in variant LVH forms often show challenges that limit their discriminatory utility. Moreover, RV dysfunction in AL-CA has only been studied to a very limited extent using 3DSTE [12] and it is not known if it has an additive value to differentiate this disease from other pathologic or physiologic cardiac hypertrophies.
The purpose of the present study was to investigate systolic and diastolic LV and RV mechanics in AL-CA by 3DSTE for potential differentiation of this condition from other causes of ventricular wall thickening.

1. Methods

1.1. Population

Twenty-three patients with light chain amyloidosis were studied. Subjects with hypertrophic cardiomyopathy (HCM), systemic arterial hypertension (HTN), and athlete's heart (ATHL) were also studied (n = 23 per group). All enrolled subjects had LV hypertrophy (mean LV wall thickness ≥ 12 mm) and preserved (≥50%) LV ejection fraction.

This was an observational case-control study. Amyloidosis patients were prospectively recruited between 2014 and 2017 from those evaluated in the Hematology Department at our University Hospital. At the time of the echocardiographic examination, the study participants had been previously diagnosed with amyloidosis. For inclusion, at least one biopsy specimen from endomyocardial tissue, bone marrow, rectum, kidney, subcutaneous fat, or other involved organ had to be positive for amyloid. The diagnosis of AL amyloidosis was confirmed by detection of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow. Cardiac involvement was considered [2] when LV wall thickness ≥12 mm was detected in the absence of potential causes for wall thickness increase, and at least one of the following additional criteria were met: 1) positive Congo red stain for amyloid at endomyocardial biopsy; 2) RV free wall thickness >5 mm; 3) symptoms of heart failure graded according to New York Heart Association functional class ≥2; 4) cardiac troponin T > 0.01 ng/mL and/or NT-proBNP > 332 pg/mL in the absence of hypertension history or other known cardiopathies.

The clinical diagnosis of HCM was based on the demonstration of LV hypertrophy in the absence of another disease process and/or abnormal loading conditions that could reasonably account for the magnitude of hypertrophy [13]. Patients having LV outflow obstruction or an apical type of HCM were excluded. Systemic hypertension was defined by a repeatedly measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or if the subject was receiving optimal antihypertensive pharmacotherapy based on current guidelines [14]. Athlete's heart was defined as that condition associated with increased left ventricular thickness, cardiac chamber enlargement and modest aortic root dilatation to accommodate increased physiologic demands [15,16], and was studied in strength-trained athletes. Exclusion criteria for all groups were atrial fibrillation (n = 2), at the time of the echocardiographic examination and poor image quality (n = 2). Patients with coronary artery disease, moderate or greater valvular heart disease, dilated cardiomyopathy, atrial fibrillation, congenital heart disease, obesity (body mass index ≥ 30 kg/m²), chronic obstructive pulmonary disease, endocrinological, liver, kidney, or neoplastic diseases were also excluded from the study. Twenty-three healthy subjects without cardiovascular disease chosen from the hospital staff and their relatives were enrolled as controls. The study was approved by the local Institutional Research Committee. All patients gave written consent. All of them were in sinus rhythm at the time of echocardiographic evaluation.

1.2. Echocardiography

Patients were examined in the left lateral decubitus position using a Vivid E9 commercial ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) with phased-array transducers. Measurements of cardiac chambers were made by two-dimensional trans-thoracic echocardiography according to established criteria [17-19]. Three-dimensional echocardiographic speckle-tracking data were obtained [6,8,12] and analyzed on a separate software workstation (EchoPAC BT13, 4D Auto-LVQ, GE Vingmed-Ultrasound, Horten, Norway) by a single investigator blinded to the disease status of the participants. LV peak global strain and averaged peak strain at three levels (basal, midventricular, and apical) were assessed. Following a frame-by-frame analysis, a three-dimensional RV speckle tracking analysis was performed with a methodology previously described [6,12-23]. Three-dimensional global longitudinal strain of the whole RV was determined using the Echo PAC BT13 (Fig. 1). Global longitudinal strain of RV free-wall only (FW LS) was then calculated (Fig. 1).

1.3. Statistics

Categorical variables are presented as numbers and percentages and continuous data are expressed as mean ± SD. Linear correlations, univariate and multivariate analysis were used for comparisons. Patients were divided into five groups (AL-CA, HCM, HTN, ATHL, and controls). Echocardiographic parameters of LV-RV function (standard, 3DSTE) were compared between groups using Student’s unpaired t-tests. Differences among three or more groups were assessed using one-way analysis of variance with post hoc comparisons by Bonferroni test. Differences were considered statistically significant when the p value was <0.05. To identify independent factors associated with CA univariate analysis and multivariate forward stepwise logistic regression analysis were performed. Variables with p values <0.05 in univariate analysis were entered into a multivariate model and tested for collinearity. Variation inflation factor, eigenvalue, and condition index were assessed. Receiver operating characteristic curves were used to determine diagnostic accuracy for detection of CA. The optimal cut-off values of echo parameters were derived from ROC analysis by maximizing the sum of the sensitivity and specificity. The incremental value of RV-3DSTE echocardiographic parameters in detecting CA over conventional echocardiographic variables and LV-3DSTE indices was assessed by calculating the χ² increase of the multivariate model in logistic regression analysis, including DT and E/Ea on the basis of their potential clinical relevance in CA diastolic dysfunction. Global χ² value was measured in 3 steps. Step 1 included LV conventional parameters (DT and E/Ea) + LV basal LS. Step 2 included DT + E/Ea + LV basal LS + LV basal rotation. Step 3 included DT + E/Ea + LV basal LS + LV basal rotation + RV FW basal LS. Intra- and inter-observer variability of strain measurements was evaluated in 10 randomly selected patients. To analyze intraobserver variability, measurements of strain parameters were made by the same investigator at multiple sites in different patients on 2 different occasions. For interobserver variability, a second investigator randomly made measurements at the above different sites (same recorded loops) without knowledge of other echocardiographic parameters. The intraobserver and interobserver variabilities were determined as the absolute difference between each observer’s value divided by the mean of both measurements and expressed as a percentage (coefficient of variation). For the assessment of reproducibility of measurements intra-class correlation coefficients were also calculated with good agreement defined as having a coefficient = 0.80.

2. Results

2.1. Reproducibility and feasibility

Ninety-two subjects with pathologic and physiologic left ventricular hypertrophy were included in the study. Hundred and thirty-four subjects were initially evaluated. Thirteen patients were excluded from the study due to coexistent disease (n = 11) or poor image quality (n = 2). LV and RV 3DSTE measurements from all segments were not feasible in a total of 29 subjects (11 and 26 subjects respectively) due to inadequate myocardial tracking. The overall feasibility of LV 3DSTE was 89% (92/103), and overall feasibility of RV 3DSTE was 78% (92/118). Reproducibility of 3DSTE parameters was shown to be acceptable. Intra-observer and inter-observer coefficients of variation for LV measures ranged from 3% up to 7%, and from 4% up to 9%, respectively, and for RV measures ranged from 4% up to 9%, and from 5% up to 12%, respectively. Intra-observer and inter-observer intra-class coefficients were for LV measures from 0.84 to 0.96, and from 0.82 to 0.91, respectively, and for RV measures from 0.83 to 0.92, and from 0.78 to 0.87, respectively.

2.2. Clinical data

Baseline characteristics of patients and athletes are summarized in Table 1. No differences were present between the three groups of patients in body mass index, body surface area, and heart rate. Low QRS voltage was present in 9 (39%) CA patients. Echo sparkling texture was present in 16 (70%) CA patients, in 10 (43%) HCM patients, and in 9 (39%) HTN patients. The same proportion of patients was medicated with beta-blockers, ACE inhibitors, calcium channel blockers, and diuretics.

2.3. Echocardiographic and strain data

Conventional 2D echocardiographic data are presented in the associated “data in brief” article [26]. All groups had increased mean LVMi and RVWti compared to controls. CA patients had significantly reduced LV deceleration time. MV and TV E/Ea were increased in CA, HCM and HTN patients.

Three-dimensional speckle tracking echocardiographic parameters are summarized in Table 2. LV longitudinal and circumferential strain were reduced in CA patients compared to controls with the most prominent impairment at the basal segments (see also Fig. 1). Peak
twist was lower in CA and HTN patients compared to controls. Peak basal rotation was impaired in CA patients compared to HTN and HCM. RV global and free-wall LS were reduced in CA patients compared to controls with the most prominent impairment at the basal segments (Fig. 1, Table 2). RV base-apex deformation difference was higher compared to controls but lower with respect to LV. LV LS apical/basal ratio was 2.9 ± 1.5 and RV FW LS apical/basal ratio was 1.4 ± 0.8 (p < 0.01). LV relative apical sparing was 1.3 ± 0.7, and RV relative apical sparing was 1.1 ± 0.4 (p < 0.05).

CA patients had higher mean RVSP than controls (45 ± 14 vs 22 ± 6 mmHg, p < 0.01). There were 7 (30%) CA patients with RVSP ≥ 35 mmHg. When restricting our analysis to those with an RVSP < 35 mmHg, we found that RV Global LS and RV FW LS were unchanged compared to the whole group (−16.5 ± 2.4% vs −15.9 ± 2.6%, and 15.1 ± 2.5% vs −14.7 ± 2.4%, respectively, p > 0.05).

To assess the incremental value of RV-3DSTE echocardiographic parameters in detecting CA over traditional and LV-3DSTE parameters, global χ² value was measured in 3 steps, as described in the methods section. A significant improvement in global χ² value was noted with RV 3D-strain parameters over only LV-3DSTE + conventional indices for detection of CA. The χ² values improved from 77.2 vs 84.6 (p = 0.003) and from 84.6 to 93.4 (p < 0.001).

By multivariate analysis (data-in-brief, ref. 26), LV basal LS (p = 0.002), LV peak basal rotation (p = 0.003), and RV FW basal LS (p = 0.014) were independently associated with CA. Comparison of ROC curves for detecting CA (Fig. 2) showed a good discriminative power of LV basal LS (AUC 0.89, 95%CI 0.77–0.95). By combining LV basal LS with LV basal rotation and RV basal FW LS a higher discriminative value was obtained for discerning CA (AUC 0.93, 95%CI 0.81–0.97).

3. Discussion

The major findings of the present study were: 1) 3DSTE parameters show segmental and global biventricular dysfunction in patients with AL-CA and appear sensitive for the recognition of this disease; 2) assessment of RV ventricular dysfunction has an additive value in differentiating AL-CA from other forms of myocardial wall thickening.

3.1. LV and RV mechanics in CA

It was shown [11,12,27] that patients with CA have combined systolic and diastolic LV abnormalities with impairment of strain and twisting/untwisting, and that the extent of impairment depends on the stage of the disease as twist increases in the early stage in patients with systemic amyloidosis and no evidence of cardiac involvement and is reduced in patients with evident amyloidosis cardiac involvement. RV myocardial assessment in AL amyloidosis is scant compared...
Table 1
Age, anthropometric and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 23)</th>
<th>CA (n = 23)</th>
<th>HCM (n = 23)</th>
<th>HTN (n = 23)</th>
<th>ATHL (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.1 ± 9.5</td>
<td>62.1 ± 10.6</td>
<td>57.4 ± 11.1</td>
<td>60.1 ± 12.8</td>
<td>28.5 ± 9.4</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Male -No(%)</td>
<td>12(25)</td>
<td>12(25)</td>
<td>11(48)</td>
<td>13(57)</td>
<td>12(52)</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area -cm²</td>
<td>1.87 ± 0.28</td>
<td>1.92 ± 0.19</td>
<td>1.93 ± 0.21</td>
<td>1.91 ± 0.18</td>
<td>1.94 ± 0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index -kg/m²</td>
<td>22.0 ± 2.1</td>
<td>22.7 ± 2.2</td>
<td>22.7 ± 3.1</td>
<td>22.6 ± 2.7</td>
<td>23.3 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>HR -bpm</td>
<td>68.5 ± 9.2</td>
<td>65.7 ± 7.4</td>
<td>65.1 ± 8.2</td>
<td>67.4 ± 7.86</td>
<td>57.0 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>SBP -mmHg</td>
<td>122.7 ± 7.1</td>
<td>121.9 ± 6.6</td>
<td>123.8 ± 7.4</td>
<td>130.8 ± 7.9</td>
<td>126.1 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>DBP -mmHg</td>
<td>75.4 ± 5.8</td>
<td>71.6 ± 5.7</td>
<td>72.1 ± 4.9</td>
<td>77.1 ± 4.5</td>
<td>71.4 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class II -No(%)-</td>
<td>0 (3.9)</td>
<td>7 (30)</td>
<td>5 (22)</td>
<td>6 (26)</td>
<td>0</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Echo sparking texture -No(%)-</td>
<td>0 (0)</td>
<td>18 (70)</td>
<td>10 (43)</td>
<td>9 (39)</td>
<td>0</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Pericardial effusion -No(%)-</td>
<td>0 (0)</td>
<td>4 (17)</td>
<td>3 (13)</td>
<td>3 (13)</td>
<td>0</td>
<td>&lt;0.05**</td>
</tr>
<tr>
<td>Pleural effusion -No(%)-</td>
<td>0 (0)</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Low QRS voltage -No(%)-</td>
<td>0 (0)</td>
<td>9 (39)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>cTnT-ng/ml.</td>
<td>/</td>
<td>0.07 ± 0.03</td>
<td>0.09 ± 0.02</td>
<td>0.05 ± 0.02</td>
<td>/</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine -mg/dL.</td>
<td>/</td>
<td>1.4 ± 0.25</td>
<td>1.1 ± 0.19</td>
<td>1.3 ± 0.15</td>
<td>/</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs -No(%)-</td>
<td>/</td>
<td>5 (22)</td>
<td>5 (22)</td>
<td>7 (30)</td>
<td>/</td>
<td>NS</td>
</tr>
<tr>
<td>β-blockers -No(%)</td>
<td>/</td>
<td>4 (17)</td>
<td>5 (22)</td>
<td>7 (30)</td>
<td>/</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel blockers -No(%)</td>
<td>/</td>
<td>/</td>
<td>1 (4)</td>
<td>2 (9)</td>
<td>/</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics -No(%)</td>
<td>/</td>
<td>9 (39)</td>
<td>6 (26)</td>
<td>7 (35)</td>
<td>/</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACE = Angiotensin Converting Enzyme; ARBs = Angiotensin Receptor Blockers; ATHL = athlete’s heart; CA = cardiac amyloidosis; cTnT = cardiac troponin T; DBP = diastolic blood pressure; HCM = hypertrophic cardiomyopathy; HR = heart rate; HTN = systemic hypertension; LVOT = left ventricular outflow; NS = not significant; RVP = right ventricular systolic pressure; SBP = systolic blood pressure. Low voltage is defined according to AHA criteria (<0.5 mV total QRS amplitude in each extremity lead and <1.0 mV in each precordial lead).

Table 2
Three-dimensional speckle tracking values in patients, athletes and controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 23)</th>
<th>CA (n = 23)</th>
<th>HCM (n = 23)</th>
<th>HTN (n = 23)</th>
<th>ATHL (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Global LS (%)</td>
<td>−20.3 ± 2.5</td>
<td>−12.8 ± 2.3</td>
<td>−14.7 ± 2.6</td>
<td>−13.5 ± 2.2</td>
<td>−21.4 ± 2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>LV Global RS (%)</td>
<td>2.9 ± 15.8</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>LV Global AS (%)</td>
<td>−22.9 ± 13</td>
<td>−23.8 ± 2.7</td>
<td>−22.1 ± 2.9</td>
<td>−25.2 ± 3.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>LV Global (%/sec)</td>
<td>13.1 ± 4.1</td>
<td>9.2 ± 3.2</td>
<td>14.4 ± 3.1</td>
<td>11.8 ± 4.2</td>
<td>13.9 ± 2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>LV peak twist (%)</td>
<td>10.1 ± 3.6</td>
<td>8.9 ± 4.3</td>
<td>9.7 ± 3.4</td>
<td>9.8 ± 3.9</td>
<td>10.9 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>LV peak basal ROT (%)</td>
<td>−5.8 ± 2.5</td>
<td>−3.2 ± 2.3</td>
<td>−6.1 ± 1.7</td>
<td>−5.7 ± 1.1</td>
<td>−6.2 ± 1.6</td>
<td>0.0004</td>
</tr>
<tr>
<td>LV PUV (°/sec)</td>
<td>0.93 ± 16</td>
<td>−82.8 ± 20</td>
<td>−83.1 ± 17</td>
<td>−86.2 ± 22</td>
<td>−96.8 ± 17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV time to PUV (msec)</td>
<td>455 ± 42</td>
<td>458 ± 41</td>
<td>439 ± 38</td>
<td>443 ± 46</td>
<td>389 ± 45</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ACE = Angiotensin Converting Enzyme; ARBs = Angiotensin Receptor Blockers; CA = cardiac amyloidosis; cTnT = cardiac troponin T; DBP = diastolic blood pressure; HCM = hypertrophic cardiomyopathy; HR = heart rate; HTN = systemic hypertension; LVOT = left ventricular outflow; NS = not significant; PUV = peak untwisting diastolic velocity; ROT = rotation; RS = radial strain; RV = right ventricle; RVFE = three-dimensional right ventricular ejection fraction (3DSTE).


with reports of LV wall thickness as a criterion for cardiac involvement [12,28], and there is controversy about the time of onset of RV dysfunction, whether early [29] or late [30].

Our results confirm that LV longitudinal and circumferential strain are reduced in CA patients compared to controls as well as LV twist and untwisting velocity. In addition, in spite of a reported satisfactory
negative correlation between RV strain and RVEF [24], we found impairment of RV longitudinal strain in the presence of normal RVEF in line with previous studies showing that LS is more sensitive compared to ejection fraction in detecting early changes in ventricular performance [28]. CA patients had higher mean RVSP and LV filling pressure (E/Ea) than controls, but when we restricted our analysis to those with RVSP <35 mmHg, we observed unchanged differences in RV regional strain between CA patients and controls. Thus, although high RV systolic pressure is an ominous finding in CA patients [28], RV dysfunction is probably the result of complex mechanisms that include high RV afterload and impaired RV contractility because of amyloid deposition. Advantages and disadvantages of 3D over 2D speckle tracking have been reported by ourselves and other authors [6,31,32]. The 3D mode avoids foreshortening of apical views, consumes less time in data acquisition and offline-analysis, and helps to solve the problem of out-of-plane motion present in the 2D modality tracking motion of speckles in all three dimensions. However, this advantage is achieved at the expense of lower frame/volume rate, lower temporal resolution and higher dependence on image quality with possible inappropriate tracking due to dropouts in the endocardial border in patients with poor acoustic windows.

3.2. Comparison with other forms of myocardial hypertrophy

Our findings corroborate other published reports [26,33–36] that LV longitudinal strain was markedly decreased in AL-CA patients with the most prominent reduction in the basal level, and contribute novel observations that may help in the strategy for differentiating CA from isolated arterial hypertension and other causes of concentric LV hypertrophy. Some interesting aspects of LV rotational mechanics have been obtained. LV peak untwisting velocity appeared equally reduced and delayed in all groups of patients suggesting impairment of LV relaxation and early diastolic filling. LV twist was increased in HCM, decreased in CA, and moderately decreased in HTN. This confirms previous studies on systemic hypertension [37] that showed no differences in peak systolic twist among patients with different degrees of concentric LVH. Significant basal hyperrotation was the most frequent pattern encountered in our CA patients and this is in agreement with what previously described [38] using feature-tracking cardiovascular magnetic resonance (CMR). Whereas increased LV twist in HCM patients is mainly attributable to increased apical rotation (due to the relative wall thickness and consequent twisting force produced by the epicardial myofibers compared with the endocardial fibers), decreased LV twist in CA patients is mainly attributable to decreased basal rotation (due to the infiltrative damage of LV subepicardial myofibers). The present study supports and further extends this concept, since the significant correlation we obtained between LV basal LS and basal rotation is consistent with the apical sparing pattern of myocardial strain frequently present in CA patients. All our patients had preserved LVEF and diastolic dysfunction. Global longitudinal strain 2DSTE-derived can be used as a prognostic marker in patients with AL amyloidosis and preserved LVEF [10]. Whether 3DSTE helps in monitoring LV changes with disease progression cannot be concluded from our findings but this was not the aim of the study.

To the best of our knowledge, no study has compared RV deformation changes in CA with other forms of myocardial hypertrophy. Global longitudinal RV strain was found to be largely impaired in HCM compared with athletes [39], reduced in patients with eccentric and concentric LVH from systemic hypertension compared with those with normal geometry and concentric remodeling [40], superior to more conventional functional parameters of RV systolic function for distinguishing HCM from HTN [41]. Regional myocardial deformation differences within the RV were also described in athletes, with a significant reduction of systolic strain in the basal portion of the RV free wall, but its meaning remains unclear [42]. It was hypothesized [42] that the heterogeneous RV morphology induces predominant damage to the basal region during exercise because of higher Laplace local wall stresses. The general population also presents a trend to have reduced strain in the inlet portion of RV free wall [42] but in athletes the fall is higher [43]. The predominant decrease in RV basal deformation is even greater in CA although apical sparing pattern is less pronounced compared to LV. These peculiar aspects of RV strain, contrasting with the frequent RV apical impairment in chronic pulmonary

Fig. 2. ROC curves comparing different standard and 3DSTE echocardiographic parameters for their accuracy to predict CA. 3D = three-dimensional; AUC = area under the curve; DT = deceleration time; CI = confidence interval; E = inflow early diastolic velocity; Ea = annular early diastolic velocity; FW = free-wall; LS = longitudinal strain; LV = left ventricular; ROT = rotation. †p < 0.001 compared to peak basal ROT; ‡p < 0.005 compared to LV basal LS; p < 0.001 compared to RV basal FW LS.
hypertension [6], can help in distinguishing CA from other forms of myocardial hypertrophy in the presence of challenging aspects of LVH in patients with HTN or symmetrical HCM, since it is known that an increasing LV septal longitudinal base-to-apex strain gradient is not a pathognomonic feature for patients with CA and can be caused by a morphological inhomogeneity (septal bulge) in some of the patients with HTN or HCM.

The mechanisms of LV longitudinal strain gradient in patients with CA were hypothesized to be multifactorial, related to a dominant deposition of amyloid protein at the basal and, later, apical subendocardium [44], to a greater diversity of myocyte and matrix orientations at the apex compared with the base [33], or to higher basal wall stress associated to extracellular protein deposition compared to patients with other forms of myocardial hypertrophy and true cellular hypertrophy [34]. The prominent reduction of basal RV FW strain is a representative marker of the large regional nonuniformity associated with cardiac amyloidosis as it occurs in LV. The lower base-apex difference in RV longitudinal strain compared to LV may be explained by the greater complexity of RV geometry organized in terms of three component parts, inlet, trabeculated apical myocardium, and outlet (infundibulum or conus). Another explanation could be the different orientation of the myocardial fibers through LV and RV walls. Whereas the thicker LV wall contains obliquely oriented myocardial fibers superficially, longitudinally oriented myofibers in the subendocardium, and predominantly circular fibers in between, in the relatively thin RV wall circumferential and longitudinal orientations predominate with the superficial myofibers arranged circumferentially in the subepicardium and invaginating at the right ventricular apex in spiral fashion to form the deep or subendocardial myofibers aligned longitudinally towards the base.

3.3. Clinical implication

Our study shows that the integration of the new 3DSTE echocardiographic techniques added useful information for the assessment of biventricular function in cardiac amyloidosis. Combining LV 3DSTE strain and torsion parameters together with RV 3DSTE assessment helps in differentiating CA from other forms of myocardial hypertrophy and reveals a higher sensitivity in comparison with conventional echocardiography. Low LV basal longitudinal strain, LV peak basal rotation, and RV basal longitudinal strain are suggestive of CA with a specificity of 86% and a sensitivity of 92%. This triad of basal segmental parameters could be clinically useful in patients with increased ventricular wall thickness suspected for CA especially in the presence of other unclear echocardiographic indices [3] or atypical CA manifestations [45] or when CMR is not available or not applicable because of severe claustrophobia, presence of pacemakers, or severe renal dysfunction. Their incremental role in clinical decision-making needs further studies to determine whether assessment of biventricular dysfunction is helpful in these patients to follow the effects of cardiac therapy with loop diuretics, aldosterone receptor antagonists and angiotensin–converting enzyme inhibitors, in addition to hematological therapy.

3.4. Limitations

The low temporal resolution of 3DSTE that affects the ability to track anatomic details frame by frame and requires multibeat (six beats) is a technical limitation as well as the fact that RV strain analysis was performed with use of the software aimed for the LV analysis. This methodology has been shown to work in a clinical scenario [6,12,23–25]. However, a dedicated RV 3DSTE software package that takes specific factors into account may be desirable [46] to further improve the feasibility and reproducibility of RV measurements.

Second, we did not discuss the systolic and diastolic dysfunction in different types of systemic amyloidosis. However, a very similar pattern of LV myocardial deformation was shown in all pathogenetic subtypes [33,47].

Third, not all amyloidosis patients had an endomyocardial biopsy performed. However, additional criteria to confirm cardiac involvement were adopted.

Last, the present study covered only a small number of patients in a single center protocol, thus a larger study is required to confirm our findings.

4. Conclusions

Three-dimensional speckle tracking echocardiography reveals regional and global biventricular dysfunction in AL-CA patients that may be helpful for the differential diagnosis with other forms of myocardial hypertrophy. The clinical significance of this biventricular dysfunction should be further evaluated.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References


