Left ventricular (LV) hypertrophy is a frequent finding in echocardiography and an ongoing diagnostic challenge. Early diagnosis is important because treatment options and prognosis strongly depend on the underlying pathology and predominant cause. Common diseases associated with symmetrical concentric LV hypertrophy include isolated arterial hypertension (HP), cardiac amyloidosis (CA), Fabry disease (FD), and Friedreich ataxia (FA). Among these patient groups with various forms of concentric LV hypertrophy, prognosis is the worst in CA.

Clinical Perspective on p 1072

Increased LV wall thickness indicates cardiac involvement in patients with systemic amyloidosis, and the degree of hypertrophy is positively related to poor outcome.\(^1\)\(^-\)\(^5\) The hallmark of CA is known as the stiff heart syndrome, characterized by mild to moderate diastolic abnormalities in early stages and severe diastolic compromise with concurrent systolic dysfunction in advanced stages.\(^1\)\(^,\)\(^6\)\(^-\)\(^7\) In individual patients, however, it is frequently difficult to differentiate CA from other types of concentric LV hypertrophy because of the nonspecific patterns derived from routine echocardiography. Recent research focused on new echocardiographic modalities that might be more specific for CA diagnosis than conventional techniques. Belkin et al\(^8\) described a distinctive 2-dimensional (2D) echocardiographic pattern of preserved segmental wall motion at the base of the heart in CA.

Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy

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Background—Differentiation of cardiac amyloidosis (CA) from other causes of concentric left ventricular hypertrophy remains a clinical challenge, especially in patients with preserved ejection fraction at the early disease stages.

Methods and Results—Consecutive hypertrophic patients with CA, isolated arterial hypertension, Fabry disease, and Friedreich ataxia (n=25 per group) were investigated; 25 healthy volunteers served as a control group. Standard echocardiography was performed, and segmental longitudinal peak systolic strain (LSsys) in the septum was assessed by 2-dimensional speckle tracking imaging. Indices of left ventricular hypertrophy and ejection fraction were similar among all patient groups. Deceleration time of early filling was significantly lower in patients with CA (147±46 milliseconds) compared with those with isolated arterial hypertension, Fabry disease, or control subjects (all \(P<0.0125\)). Septal basal LSsys (−6±2%) was significantly lower in patients with CA compared with those with isolated arterial hypertension (−14±6%), Fabry disease (−12±5%), Friedreich ataxia (−16±2%), or control subjects (−17±3%; all \(P<0.001\)), whereas septal apical LSsys was similar among all patient groups and control subjects (all \(P>0.05\)). A data-driven cutoff value for the ratio of septal apical to basal LSsys ratio >2.1 differentiated CA from other causes of left ventricular hypertrophy (sensitivity, 88%; specificity, 85%; positive predictive value, 67%; negative predictive value, 96%). The prevalence of septal apical to basal LSsys ratio >2.1 plus deceleration time of early filling <200 milliseconds was 88% in CA but 0% in all other groups.

Conclusions—A systolic septal longitudinal base-to-apex strain gradient (septal apical to basal LSsys ratio >2.1), combined with a shortened diastolic deceleration time of early filling (deceleration time of early filling <200 milliseconds), aids in differentiating CA from other causes of concentric left ventricular hypertrophy. (Circ Cardiovasc Imaging. 2013;6:1066-1072.)

Key Words: amyloidosis ■ differential diagnosis ■ echocardiography ■ hypertrophy, left ventricular

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LV apex with hypokinesis in the basal to mid segments in 7 consecutive patients with endomyocardial biopsy–proven CA. Using 2D or 3-dimensional speckle tracking imaging (STI) technique, we and other groups recently reported that an intravall longitudinal base-to-apex strain gradient may be detectable in the majority of patients with CA.\(^1\)\(^\text{−}\)\(^\text{11}\) It remains unclear, however, whether this strain gradient pattern is specific for CA. Therefore, the purpose of the present study was to evaluate the diagnostic value of the septal systolic longitudinal strain in combination with diastolic parameters for differentiating CA from other causes of concentric LV hypertrophy.

**Methods**

**Study Population**

Consecutive patients with LV hypertrophy (ie, end-diastolic septal thickness ≥ 12 mm) experiencing CA, HP, FD, and FA (n=25 per group) were studied. In all patients with light-chain amyloidosis, ≥ 1 biopsy from endomyocardial tissue, bone marrow, rectum, kidney, or subcutaneous fat was positive for amyloid. The type of amyloid was assessed by immunohistochemistry. Patients with FD and FA were selected from the FD and FA reference centers of University Hospital of Würzburg, and all diagnoses were genetically confirmed. Hypertension was defined by a repeatedly measured systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or if the subject was receiving antihypertensive pharmacotherapy based on current guidelines.\(^1\)\(^\text{2}\) Patients with coronary artery disease, moderate to severe cardiac valve disease, and other endocrine or systemic diseases were excluded. Twenty-five healthy volunteers from the hospital staff and their relatives served as the control group. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

**Standard Echocardiography**

LV end-diastolic and end-systolic dimensions, as well as end-diastolic thickness of the posterior wall and the septum, were measured using standard M mode in parasternal LV long-axis views. LV ejection fraction (EF) was measured with the biplane Simpson method in apical 4- and 2-chamber views. Pulsed-wave Doppler was performed in apical 4-chamber views to obtain mitral valve inflow velocities for LV filling pattern evaluation (early filling [E wave] and late diastolic filling [A wave] velocities, E/A ratio, and deceleration time of early filling [DT]). Tissue Doppler early diastolic mitral annular velocity (E′) of the septal annulus was obtained in the apical 4-chamber view. Atrial fibrillation was present in 7 patients with CA, 2 patients with HP, and 2 patients with FD; in these subjects, E, E′, and DT (averaged from 3 cardiac circles) were measured. The stage of LV diastolic function was diagnosed according to the American Society of Echocardiography guidelines for the assessment of diastolic function.\(^1\)\(^\text{3}\)

**Speckle Tracking Imaging**

All longitudinal segmental strain measurements were performed offline using dedicated software (EchoPAC; GE, Horten, Norway). The 2D gray-scale images were recorded with a frame rate of 60 to 80 frames per second, and care was taken to ensure that the entire ventricular wall was clearly visible in all frames. A region of interest was created by manually outlining the endocardial border on an apical 4-chamber view at the end-systolic frame. The system automatically tracked the tissue within the region and divided the myocardium into standard segments. The tracking was visually checked and, if necessary, adjusted. The trace analysis was automatically displayed after validating the tracking. LV longitudinal peak systolic strain (LSSys) was extracted from basal, mid, and apical segments of the septum. The ratio between apical LSSys and basal LSSys (LSSys api/bas) was calculated as apical LSSys divided by basal LSSys.

**Electrocardiography**

A standard 12-lead ECG was recorded from each patient, with a paper speed of 50 mm/s and an amplification of 0.1 mV/mm. Low QRS voltage was defined as < 0.5-mV peak-to-peak QRS amplitudes in each limb lead and < 1.0 mV in each precordial lead.\(^1\)\(^\text{4}\) LV hypertrophy was defined by the Sokolow-Lyon criterion; that is, the sum of the S wave in V1 and the R wave in V5 or V6 is ≥ 3.5 mV.\(^1\)\(^\text{5}\) A pseudoinfarct pattern was defined as a QS wave pattern in 2 contiguous leads in the absence of previous myocardial infarction.

**Cardiac MRI**

Cardiac MRI was performed with a 1.5-T scanner (Magnetom Symphony Quantum, Siemens) using 2 conventional 6-channel body phased-array coils (Siemens, Erlangen, Germany) for signal detection. A stack of 15 slices ensured coverage of the whole LV. Late enhancement (LE) was obtained 10 to 15 minutes after the injection of 0.2 mmol/kg gadopentetate dimeglumine using an inversion recovery 2D turbo gradient echo sequence.

**Data Analysis**

Continuous data are presented as mean±SD and categorical variables as percentages. Differences in continuous data among the 5 patient groups were compared using 1- or 2-way ANCOVA after normalization if indicated, followed by appropriate post hoc tests for multiple comparisons (Tukey if equal variances assumed; Games-Howell if equal variances not assumed). Nonnormally distributed variables were normalized before analysis using natural logarithm or inverted values. Categorical data were compared across groups with a similar approach using the χ\(^2\) test for the overall test and Fisher exact for pairwise group tests, as appropriate. Because we aimed to contrast CA patients with control subjects and the other 3 patient groups, statistical significance was assumed at Bonferroni-adjusted \(P<0.0125\) (Tables 1 and 2) and \(P<0.0166\) (Table 3), respectively. Pairwise comparisons were only performed if the global test was significant.

Receiver-operating characteristic (ROC) analysis was performed to identify the diagnostic yield of LSSys gradient and diastolic parameters for CA, respectively. The cutoff value of septal LSSys (LSSys septa) was derived from ROC analysis by maximizing the sum of the sensitivity and specificity. For this cutoff value, the 95% confidence interval (CI) was computed using the bias-corrected and accelerated method (with 10000 bootstrap resampling steps) as described by DiCicco and Efron\(^1\)\(^\text{6}\) and as implemented in MedCalc Software (version 12.7.2; last modified, August 2013; Ostend, Belgium). Diagnostic performance measures are reported as mean with their 95% CIs. Further statistical analysis was performed using IBM SPSS, version 20 for Windows (SPSS).

**Results**

**Clinical Characteristics**

Patients with FA were significantly younger compared with other patient groups and control subjects (Table 1). One patient with CA experienced pulmonary embolism with subsequent pulmonary infarction, and 1 patient experienced deep vein thrombosis of the leg. Although not systematically sought for, no intracardiac thrombus formation was detected in patients with CA using conventional echocardiography (n=25), transesophageal echocardiogram (n=1), or cardiac MRI (n=12). Contrast-enhanced cardiac MRI was performed in 12 patients with CA, 2 patients with HP, 20 patients with FD, and 5 patients with FA in this cohort. LE was documented in 9 of 12 patients with CA (75%; 7 diffuse, 1 basal posterolateral wall, 1 basal septal and
Table 1. Clinical and Echocardiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=25)</th>
<th>CA (n=25)</th>
<th>HP (n=25)</th>
<th>FD (n=25)</th>
<th>FA (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±7</td>
<td>66±10</td>
<td>67±13</td>
<td>61±8</td>
<td>25±10*†‡§</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (60)</td>
<td>14 (56)</td>
<td>12 (48)</td>
<td>14 (56)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Interventricular septal wall thickness, mm</td>
<td>9±1</td>
<td>14±2*</td>
<td>14±2*</td>
<td>14±2*</td>
<td>13±1*</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>9±1</td>
<td>14±2*</td>
<td>13±2*</td>
<td>13±2*</td>
<td>13±1*</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>50±4</td>
<td>42±6*</td>
<td>47±7</td>
<td>47±7</td>
<td>42±7*</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>66±6</td>
<td>58±12</td>
<td>61±11</td>
<td>64±7</td>
<td>65±7</td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.75±0.15</td>
<td>0.89±0.22</td>
<td>0.74±0.24</td>
<td>0.78±0.22</td>
<td>0.76±0.13</td>
</tr>
<tr>
<td>E/A</td>
<td>0.99±0.22</td>
<td>1.46±0.71</td>
<td>0.80±0.22†</td>
<td>1.15±0.53</td>
<td>1.54±0.45‡</td>
</tr>
<tr>
<td>DT, ms</td>
<td>221±52</td>
<td>147±46*</td>
<td>250±59†</td>
<td>251±82†</td>
<td>183±52§</td>
</tr>
<tr>
<td>E/E′</td>
<td>10±4</td>
<td>23±10*</td>
<td>14±5†</td>
<td>18±7*</td>
<td>8±2†§</td>
</tr>
<tr>
<td>Diastolic pattern (normal/abnormal relaxation/pseudonormal/ restrictive)</td>
<td>11/14/0/0</td>
<td>0/6/14/5*</td>
<td>0/21/4/0†</td>
<td>1/12/10/2</td>
<td>22/3/0/0†</td>
</tr>
</tbody>
</table>

CA indicates cardiac amyloidosis; DT, deceleration time of early filling; E, mitral inflow early diastolic velocity; E/A, early diastolic filling velocity (E) to late diastolic filling velocity (A) ratio; E/E′, mitral inflow velocity (E) to tissue Doppler annular velocity (E′) ratio; FA, Friedreich ataxia; FD, Fabry disease; HP, isolated arterial hypertension; and LV, left ventricle.

Bonferroni-adjusted P: †P<0.0125 vs control; ‡P<0.0125 vs CA; §P<0.0125 vs HP; §§P<0.0125 vs FA.

Table 2. Longitudinal Systolic Strain and Thickness in the Septum

<table>
<thead>
<tr>
<th></th>
<th>Control (n=25)</th>
<th>CA (n=25)</th>
<th>HP (n=25)</th>
<th>FD (n=25)</th>
<th>FA (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal peak systolic strain (LSSys), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical</td>
<td>−20±5</td>
<td>−20±7</td>
<td>−22±8</td>
<td>−17±7</td>
<td>−21±4</td>
</tr>
<tr>
<td>Mid</td>
<td>−18±4</td>
<td>−10±4*</td>
<td>−15±6†</td>
<td>−15±5†</td>
<td>−15±3†</td>
</tr>
<tr>
<td>Basal</td>
<td>−17±3*</td>
<td>−6±2*</td>
<td>−14±6†</td>
<td>−12±5†</td>
<td>−16±2†§</td>
</tr>
<tr>
<td>LSSys&lt;sub&gt;ap/bas&lt;/sub&gt;</td>
<td>1.2±0.3</td>
<td>3.3±1.6*</td>
<td>1.8±0.9†</td>
<td>1.7±1.8†</td>
<td>1.3±0.3†</td>
</tr>
<tr>
<td>Septal wall thickness (end diastole, apical 4-chamber view), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical</td>
<td>10±1</td>
<td>13±2*</td>
<td>14±2*</td>
<td>15±3*</td>
<td>13±1†§</td>
</tr>
<tr>
<td>Mid</td>
<td>10±1</td>
<td>16±2*</td>
<td>15±2*</td>
<td>17±4*</td>
<td>13±1†§</td>
</tr>
<tr>
<td>Basal</td>
<td>10±1</td>
<td>15±2*</td>
<td>15±2*</td>
<td>16±5*</td>
<td>13±1†§</td>
</tr>
</tbody>
</table>

CA indicates cardiac amyloidosis; FA, Friedreich ataxia; FD, Fabry disease; HP, isolated arterial hypertension; and LSSys<sub>ap/bas</sub>, ratio between apical LSSys and basal LSSys.

Bonferroni-adjusted P: †P<0.0125 vs control; ‡P<0.0125 vs CA; §P<0.0125 vs HP; §§P<0.0125 vs FA.

Table 3. Electrocardiography Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CA (n=25)</th>
<th>HP (n=25)</th>
<th>FD (n=25)</th>
<th>FA (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>18 (72)</td>
<td>22 (88)</td>
<td>22 (88)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (28)</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Paced</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Low QRS voltage, n (%)</td>
<td>13 (52)</td>
<td>1 (4)*</td>
<td>1 (4)*</td>
<td>1 (4)*</td>
</tr>
<tr>
<td>Left ventricular Sokolow index, mV</td>
<td>1.3±0.6</td>
<td>2.2±0.9*</td>
<td>3.1±1.6*</td>
<td>1.8±0.9†</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n (%)</td>
<td>0 (0)</td>
<td>4 (16)</td>
<td>12/24 (50)*</td>
<td>1 (4)</td>
</tr>
<tr>
<td>I° atrioventricular block, n (%)</td>
<td>6/18 (33)</td>
<td>3/22 (14)</td>
<td>4/22 (18)</td>
<td>0 (0)*</td>
</tr>
<tr>
<td>Right or left bundle branch block, n (%)</td>
<td>12 (48)</td>
<td>6 (24)</td>
<td>7/24 (29)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Pseudoinfarct changes, n (%)</td>
<td>12 (48)</td>
<td>1 (4)*</td>
<td>0/24 (0)*</td>
<td>0 (0)*</td>
</tr>
</tbody>
</table>

CA indicates cardiac amyloidosis; FA, Friedreich ataxia; FD, Fabry disease; HP, isolated arterial hypertension.

Bonferroni-adjusted P: *P<0.0166 vs CA; †P<0.0166 vs HP.

Standard Echocardiographic Evaluation

Standard echocardiographic parameters are listed in Table 1. LV wall thickness and LV EF (all >55%) were similar among the 4 patient groups. DT was significantly shorter in the CA group than in the control, HP, and FD groups. E/E′ was significantly higher in the CA group than in the control, HP, and FA groups. ROC analysis showed that DT outperformed E/E′ in differentiating CA from HP, and FA. The areas under the ROC curve for DT and E/E′ were 0.86 (95% CI, 0.78–0.94) and 0.79 (95% CI, 0.67–0.90), respectively. Advanced diastolic dysfunction (pseudonormal or restrictive pattern) was absent in the control and FA groups but was observed in 76% of patients with CA, 16% with HP, and 48% with FD.

Septal Longitudinal Systolic Strain

Figure 1 illustrates examples of STI-derived longitudinal strain curves at apical, mid, and basal segments of the septum from a normal subject and patients with CA, HP, FD, and FA. Mean values for septal apical LSSys were similar among all patient groups and control subjects. However, septal mid and basal LSSys values were significantly lower in the CA group than in the control, HP, FD, and FA groups. Consequently, the septal LSSys<sub>ap/bas</sub> ratio was significantly higher in the CA group than in all other groups (Table 2). To better understand the relationship between regional myocardial function and morphology of the septum, the regional septal wall thickness...
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was measured in 2D images from an apical 4-chamber view. In the CA group, the septal end-diastolic wall thickness was significantly higher at the basal and mid segments compared with apical segments. A trend for the same finding was also seen in HP and FD groups (Table 2).

Electrocardiography
As shown in Table 3, low QRS voltages and QRS pseudoinfarct changes were more frequently seen in the CA group than in the HP, FD, and FA groups (P<0.05). LV Sokolow index was significantly lower in the CA group than in other patient groups. Fifty percent of patients with FD presented more severe LV hypertrophy assessed by ECG criteria. Conversely, LV hypertrophy was suggested in none of patients with CA and in only 16% of patients with HP by ECG.

Diagnostic Use of LSsys ap/bas and DT
The diagnostic performance of LSsys ap/bas was optimal at a cutoff value of 2.1 (bootstrapped 95% CI, 1.32–2.19; Figure 2, left), differentiating CA from HP, FD, and FA with a sensitivity, specificity, positive predictive value, and negative predictive value of 88% (68%–97%), 85% (75%–92%),

Figure 1. Examples of longitudinal strain curves at apical (green), mid (blue), and basal (yellow) septum in various groups. CA indicates cardiac amyloidosis; FA, Friedreich ataxia; FD, Fabry disease; HP, isolated arterial hypertension; and LS, longitudinal peak systolic strain.

Figure 2. The receiver-operating characteristic (ROC) analysis of the ratio between apical LSsys and basal LSsys (LSsys ap/bas) for differentiating cardiac amyloidosis (CA) from isolated arterial hypertension (HP), Fabry disease (FD), and Friedreich ataxia (FA; left) and scatterplot of LSsys ap/bas in the study groups (right). The diagnostic performance of LSsys ap/bas was optimal at a cutoff value of 2.1 (bootstrapped 95% confidence interval [CI], 1.32–2.19), differentiating CA from HP, FD, and FA with a sensitivity of 88% (68%–97%) and a specificity of 85% (75%–92%). The corresponding area under the ROC curve was 0.91 (95% CI, 0.83–0.96). AUC indicates the area under the ROC curve.
67% (48%–81%), and 96% (87%–99%), respectively. The corresponding area under the ROC curve was 0.91 (95% CI, 0.83–0.96; Figure 2, left). The prevalence of septal LSsys_api/bas >2.1 in patients with CA (88%) was significantly higher than in the control (0%), HP (32%), FD (12%), and FA (0%) groups (Figure 2, right). Figure 3 shows that the prevalence of LSsys_api/bas >2.1 plus a DT <200 milliseconds was 88% in the CA group but 0% in the control and all other patient groups (sensitivity, 88%; specificity, 100%; positive predictive value, 100%; negative predictive value, 96%).

Discussion
The major finding of this study is that a systolic septal longitudinal base-to-apex strain gradient (LSsys_api/bas >2.1), combined with a shortened diastolic DT (DT <200 milliseconds), could be used to differentiate CA from other forms of concentric LV hypertrophy such as HP, FD, and FA.

Longitudinal Base-to-Apex Strain Gradient in CA Patients With Preserved EF

The diagnosis of CA remains a clinical challenge, requiring cardiac biopsy and histological evaluation to arrive at a definite diagnosis; however, histology is not available in several patients with suspected CA. It is therefore important to find noninvasively derived sensitive and specific diagnostic markers that aid in the diagnostic workup of CA. Conventional echocardiography has been used to identify the structural and functional changes of patients with CA.1,17–19 However, typical conventional echocardiographic findings suggestive for the diagnosis of CA mostly appear only in advanced stages and may be absent in individual patients with suspected CA.13,20 Two-dimensional STI is currently being developed as an objective methodology for the assessment of regional myocardial deformation and function in cardiovascular diseases.21 Using the 2D STI technique, we recently demonstrated a pronounced intrawall longitudinal base-to-apex strain gradient with preserved LSsys at apical segments and significantly reduced LSsys at basal and mid segments in patients with CA.11 This strain gradient is related to disease progression and is helpful in predicting the prognosis of patients with CA. In addition, the gradient was superior to other routine echocardiographic parameters such as LV wall thickness and EF for clinical staging. Nevertheless, it remains unknown whether the observed strain gradient in patients with CA is a pathognomonic feature for patients with CA or whether it is also present in other forms of concentric hypertrophy. In the present study, we found that this typical strain gradient pattern was present in the majority of patients with CA but not in patients with HP, FD, and FA with similar types of concentric LV hypertrophy. Consistent with our findings, Phelan et al10 reported that the presence of relatively preserved apical longitudinal strain assessed by a 2D STI bull’s-eye plot could differentiate patients with CA from patients with LV hypertrophy caused by hypertrophic cardiomyopathy and aortic stenosis. Baccouche et al9 also demonstrated intrawall longitudinal regional strain gradient in patients with CA using 3-dimensional STI. However, the patients with CA enrolled in both of these studies were at the late stage of the disease with severe LV hypertrophy and significantly reduced EF. In our study, we focused on regional strain changes in patients with CA at an earlier stage with preserved EF (>55%).

Potential Mechanisms of the Longitudinal Strain Gradient

The underlying pathophysiology for the documented longitudinal base-to-apex systolic strain gradient in patients with CA might be multifactorial. The different wall stress faced by the septal basal, mid, and apical segments might contribute to the observed strain differences among these regions. It is known that the wall stress at the basal segment is higher than at the mid and apical segments because of the nonspherical ventricular geometry and the largest local radius of the LV curvature in the basal part of the septum.22,23 The propensity to develop increased apoptosis, collagen formation, and subsequent fibrosis might be higher in segments with elevated wall stress,23 which may partly explain the phenomenon of significantly lower strain values of patients with CA at the basal compared with the apical segments. However, the factor of unequal wall stress is similarly encountered in patients with FD and FA and even more exaggerated in HP, where this additionally leads to significant postsystolic deformation at the basal septum (Figure 1).2 However, in CA, the increased wall thickness is caused by extracellular protein deposition, which is in contrast to the real cellular hypertrophy presented in patients with HP, FD, and FA. Thus, it can be speculated that the increased wall stress on segments, together with extracellular protein deposition, in CA might have much more effect on cardiac deformation than increased wall stress in patients with HP, FD, and FA with true cellular hypertrophy.

The difference in wall thickness at the basal, mid, and apical segments might also play a role in the observed septal longitudinal base-to-apex strain gradient in patients with CA. Phelan et al10 showed that the LV wall thickness determined by cardiac MRI at the basal and mid segments increased more than at the apex in patients with CA. This may indicate relatively
less amyloid deposition in the apex. Brenner et al\textsuperscript{24} reported that human light-chain proteins could directly impair active force through an increase in cellular oxidant stress. Thus, it is possible that less deformation impairment at the apical segment of patients with CA is linked to a lower amount of amyloid deposition at this region, resulting in the observed preserved longitudinal strain at the apical segment in patients with CA. A greater diversity of myocardial fibers and matrix orientations at the apical segment compared with the basal segment of patients with CA could also contribute to a preserved deformation at the apical segments.\textsuperscript{24–26}

It is of note that this strain gradient was also observed in 32\% of the patients with HP. Interestingly, in 7 of 8 (87\%) of these HP patients with a strain gradient, a septal bulge (localized increase in wall thickness of the basal septum) was detected. Thus, the inhomogeneity in morphology might be responsible for the detected septal longitudinal base-to-apex strain gradient in some of the patients with HP. In line with this finding, Baltabaeva et al\textsuperscript{22} found that longitudinal peak systolic strain rate and end-systolic strain were significantly reduced at the basal septal segment, whereas they were preserved at mid and apical segments in patients with hypertension compared with nonhypertensive control subjects and that marked post-systolic thickening was present in that segment.

### Diastolic Filling in Patients With CA

In early-stage CA with mild amyloid infiltration, the myocardial relaxation process is altered by calcium overload.\textsuperscript{26,29} In advanced CA, the severe amyloid infiltration of the ventricular walls and the subsequent remodeling and replacement fibrosis\textsuperscript{19} finally lead to the stiff heart syndrome with a restrictive filling pattern. Although the specific longitudinal base-to-apex strain gradient was found in the majority of patients with CA, there was still a slight overlap between the CA group and the HP group. To further differentiate patients with CA from patients with HP, we complemented it with a routine echocardiographic parameter assessing diastolic function. Experimental and clinical studies suggested that DT of early diastolic filling is related to LV stiffness and that DT shortens in proportion to a decrease in LV compliance.\textsuperscript{30,31} Our study showed that complementing the systolic strain gradient with the DT parameter could improve the diagnostic accuracy for echocardiographic detection of CA.

Consistent with the cardiac MRI study by Syed et al.,\textsuperscript{32} we found that diffuse LE as a possible sign of interstitial deposition of amyloid was common in patients with CA (58\% in our sample). In line with previous reports, our study underlines the notion that the presence and type of LE pattern are helpful in differentiating CA (diffuse LE) from FD (patchy LE) and hypertensive heart disease (no LE).\textsuperscript{31}

### Clinical Impact

The present study indicates that combining an established conventional diastolic function parameter (DT) together with advanced systolic function parameters (peak systolic strain) could be a feasible strategy for differentiating CA from other causes of concentric LV hypertrophy. Short DT (<200 milliseconds) and higher septal LSsys_{ap/bas} ratio (>2.1) are suggestive of CA (specificity, 100\%; sensitivity, 88\%). These parameters are simple and available in patients with both sinus and atrial fibrillation rhythms. Hypertrophic patients suspected for CA could be identified by measuring DT and LSsys_{ap/bas} ratio during daily echocardiographic examinations.

### Limitations

The patient sample was relatively small, which could have introduced some bias and subsequent overoptimism on the proposed cutoff values. Certainly, prospective studies with larger sample size are warranted to confirm these results and to test their relevance for clinical practice. In addition, not all types of hypertrophic conditions were included. However, hypertrophic cardiomyopathy is an asymmetrical hypertrophy and thus is relatively easily discernible from CA. Furthermore, in patients with aortic stenosis, the symmetrical hypertrophy is related to the aortic valve abnormalities that can be identified by conventional echocardiography. No intracardiac thrombus formation was detected in patients with CA, although autopsy and in vivo transesophageal echocardiogram studies suggest a prevalence rate between 15\% and 30\%.\textsuperscript{34,35} Because the systematic search for thrombotic disease was outside the focus of this investigation, the reason for this discrepancy may be related to the low specificity of transesophageal echocardiogram in detecting intracardiac thrombus.

### Conclusions

The septal longitudinal base-to-apex strain gradient (LSsys_{ap/bas} >2.1), combined with a short DT (DT <200 milliseconds), is a good diagnostic parameter for differentiating CA from other causes of concentric LV hypertrophy.

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### Disclosures

None.

### References


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**CLINICAL PERSPECTIVE**

The present study suggests that combining an established conventional diastolic function parameter (deceleration time of early filling) with advanced systolic function parameter (septal peak systolic strain [LSsys]) is a feasible strategy for differentiating cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Short deceleration time of early filling (<200 milliseconds) and higher septal ratio between apical LSsys and basal LSsys (>2.1) are suggestive of cardiac amyloidosis (specificity, 100%; sensitivity, 88%). These parameters are simple and available in patients with both sinus and atrial fibrillation rhythms. Hypertrophic patients suspected to have cardiac amyloidosis could be identified by measuring the deceleration time of early filling and the ratio between apical LSsys and basal LSsys during routine echocardiographic examinations.
Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy

Dan Liu, Kai Hu, Markus Niemann, Sebastian Herrmann, Maja Cikes, Stefan Störk, Philipp Daniel Gaudron, Stefan Knop, Georg Ertl, Bart Bijnens and Frank Weidemann

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