Longitudinal Myocardial Function Assessed by Tissue Velocity, Strain, and Strain Rate Tissue Doppler Echocardiography in Patients With AL (Primary) Cardiac Amyloidosis

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Background—AL amyloidosis with heart failure is associated with decreased longitudinal myocardial contraction measured by pulsed tissue Doppler imaging. We sought to clarify whether new modalities of myocardial strain Doppler (change in length per unit length) or strain rate (the temporal derivative of strain) were more sensitive than tissue Doppler and could detect early regional myocardial dysfunction before the onset of congestive heart failure (CHF) in patients with AL (primary) amyloidosis.

Methods and Results—Ninety-seven biopsy-proven patients with AL amyloidosis were divided into 3 groups. Group 1 patients had no cardiac involvement (n=36), group 2 had heart involvement but no CHF (n=32), and group 3 had heart involvement and CHF (n=29). All patients underwent tissue velocity (TV) imaging, strain, and strain rate imaging (SR) at the basal, mid, and apical ventricle in 2 apical views. With the use of TV, differences in systolic function were only apparent between group 3 (basal mean value, 3.0±1.1 cm/s) and groups 1 and 2 (5.0±1.3 and 4.6±1.2 cm/s, respectively). In contrast, basal peak systolic SR (l/s) showed significant differences among all 3 groups (−2.0±0.4, −1.55±0.6, and −0.76±0.3 for groups 1 to 3, respectively, P<0.01). Basal strain also demonstrated statistically significant differences among the groups (−19±4%, −15±4.5%, and −8.0±5%; P<0.01).

Conclusions—Cardiac amyloidosis is characterized by an early impairment in systolic function at a time when fractional shortening remains normal. This abnormality precedes the onset of CHF and can be detected by strain and SR but is not apparent by TV imaging. (Circulation. 2003;107:2446-2452.)

Key Words: echocardiography ■ heart failure ■ ultrasonics ■ amyloid ■ cardiomyopathy

Cardiac AL (light-chain associated) amyloidosis is a cardiomyopathy associated with increased left ventricular (LV) wall thickness and normal or decreased LV cavity size. Severe congestive heart failure (CHF) may occur despite a normal or mildly reduced LV ejection fraction.1–7 Consequently, it is generally considered that CHF in cardiac amyloidosis is predominantly a diastolic phenomenon, with systolic dysfunction only occurring late in the disease.5,8–12

Recently we have shown, by using pulsed tissue Doppler echocardiography, that CHF in cardiac amyloidosis is associated with decreased peak systolic wall motion velocities at the level of the mitral annulus. Among patients without CHF but with echocardiographic evidence of amyloid infiltration of the LV, tissue Doppler detected only diastolic abnormalities and systolic function appeared preserved.13 Pulsed tissue Doppler, although a fairly sensitive method for the detection of regional wall motion abnormalities, measures the net myocardial velocity at the site of the tissue sample, and global cardiac motion such as translational artifacts influence this measurement. By measuring the difference in velocity between two tissue Doppler points oriented in the same plane and a known distance apart, a myocardial velocity gradient can be calculated that is not influenced by global motion. This is best measured in the longitudinal plane, where it is referred to as a longitudinal myocardial velocity gradient. Recent advances in 2-dimensional color-coded Doppler imaging have enabled the measurement of regional strain (defined as the change in length per unit length) and strain rate. Strain rate is the temporal derivative of strain and is calculated from simultaneously measured velocity gradients across a fixed distance.14 The accuracy of measurements of strain and strain rate Doppler imaging (SR) has been validated in an experimental model with sonomicrometry used as a reference method.15

We postulated that strain and SR measurements are more sensitive and accurate than tissue velocity (TV) imaging for evaluating regional longitudinal myocardial function. The purpose of this study was therefore to clarify whether strain or SR can detect early regional myocardial dysfunction in amyloidosis before the onset of CHF and to determine whether regional myocardial deformation abnormalities can be detected with strain or SR in these patients.
Methods

Study Population

The study population consisted of 97 consecutive patients with AL amyloidosis. The diagnosis of amyloidosis was made by biopsy study of an involved organ that demonstrated typical Congo red birefringence when viewed under polarized light. AL amyloidosis was confirmed by the finding of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow when evaluated by immunohistochemistry. Patients with familial, secondary, and senile cardiac amyloidosis were excluded, as were patients with a history of systemic hypertension, significant valvular heart disease, or atrial fibrillation. Cardiac involvement was defined as the mean value of LV thickness (half of the sum of the thickness of ventricular septum and posterior walls) >12 mm. The diagnosis of CHF was made by one of the investigators, who obtained a detailed history and examined each patient but who had no knowledge of the results of the TV and SR imaging results. CHF was defined as the existence of dyspnea on exertion, associated with orthopnea, paroxysmal nocturnal dyspnea, or appearance of heart failure and/or the finding of elevated jugular venous pressure with peripheral edema on chest radiography.

Thirty-six patients defined as group 1 (noncardiac amyloid) had no echocardiographic features of cardiac amyloidosis. Sixty-one patients had echocardiographic evidence of cardiac involvement, 29 of whom had a history or current symptoms of CHF. The 32 patients with evidence of cardiac amyloid but no CHF were defined as group 2 [CHF (–) group], and the remaining 29 patients with CHF were defined as group 3 [CHF (+) group]. The institutional review board approved the protocol, and written informed consent was obtained from each patient before the ultrasound examination.

Standard Ultrasound Examination

All ultrasound examinations were performed with a commercially available echocardiographic machine (Vivid Five System, Vingmed- General Electric). The thickness of the interventricular septum and LV posterior wall and the LV end-diastolic and end-systolic diameters were determined from the M-mode at the level of chordae, and LV fractional shortening was calculated. Pulsed Doppler echocardiography of transmitral and pulmonary venous flow velocities were performed, positioning a sample volume at the level of the mitral tips and the right upper pulmonary vein 1 cm below the ostium. The sample volume was then placed in the area of the anterior mitral valve leaflet to record the LV outflow tract flow and the transmitral flow profiles simultaneously to calculate isovolumic relaxation time. All pulsed Doppler flows were recorded on VHS videotape at a speed of 100 mm/s.

The off-line analyses of transmitral flow and pulmonary venous flow were performed with the use of dedicated software (Echopac 6.3.6, GE Vingmed Ultrasound). Three consecutive beats were measured and averaged for each measurement. The peak velocities of early and late filling waves, early/late filling ratio of peak velocities, and deceleration time of early filling wave were measured from transmitral flow velocities, and the peak velocities of systolic, diastolic, and atrial contractile waves, diastolic/systolic ratio of peak velocities, were also measured from the pulmonary venous flow velocities. Isovolumic relaxation time was measured as the time interval between the end of LV outflow tract flow and the onset of transmitral flow.

Tissue Doppler Data Acquisition

Apical 2- and 4-chamber views were acquired (Figure 1). Two-dimensional color tissue Doppler recordings with second harmonic imaging were collected with a frame rate 84 to 147 frames per second (mean value of 97 frames per second) during brief apnea after expiration. Pulse repetition frequency was adjusted to avoid aliasing. Three consecutive cardiac cycles were recorded as 2-dimensional cine loops, and the acquired raw data were saved for off-line analysis.

Analysis of Tissue Velocity, Strain, and Strain Rate Imaging

Color 2-dimensional digital data from 3 cardiac cycles were analyzed off-line with research software incorporated in the Vivid Five System (Echopac 6.3.6, GE Vingmed Ultrasound). Sample volumes were placed on basal, mid, and apical LV at the septum, lateral, inferior, and anterior walls in the apical views (Figure 1). The SR is the percentage deformation per second and is measured in s⁻¹ or /s. It is equal to the spatial myocardial velocity gradient expressed by the equation SR = (v(x) − v(x + Δx))/Δx, and strain can be determined by combining the strain rate values from a given time interval as described previously. An offset (“sample volume”) of Δx = 10.8 or 11.1 mm was used in all studies. This was done, and the mean values from 3 cardiac cycles were calculated. (Figure 1). The sample volumes were placed in the inner half of the myocardium to keep the angle between the Doppler beam and the longitudinal shortening direction of the wall (or the direction of endocardium) as small as
possible (at least <30°). Because minor displacement of the sample volume may make a large difference in the strain waveform, we considered the sample volume position to be adequate when there was good reproducibility of the strain waveform over 3 consecutive cardiac cycles. The peak systolic strain in each segment was determined as the difference in strain measured from the onset of the QRS complex to the nadir of the strain tracing. For SR, the peak systolic SR, peak early diastolic SR, and peak late diastolic SR were measured. The technique of raw data storage and reconstruction permits the measurement of TV, SR, and strain curves from exactly the same sample volumes as strain and SR, and the same sample volume in same image at each site. Thus, TV waves were obtained from the same sample volumes as strain and SR, and peak systolic TV, peak early diastolic TV, and peak late diastolic TV were measured.

The mean values from the septum, lateral, inferior, and anterior walls were calculated at the basal, mid, and apical LV segments. Thus, there were 12 values for each patient. To simplify the analysis, the values at each wall were combined and averaged to give a mean basal, mid, and apical value. One investigator, who was unaware of the patients' clinical status, analyzed all data from the ultrasound examination.

Statistics
Statistical analyses were done with a commercially available software program (Stat View 5.0, SAS Institute Inc). Differences among 3 groups were assessed with the 1-way factorial ANOVA, followed by the Scheffé test. Data are expressed as mean values ±SD. A difference was considered significant when the probability value was <0.05.

Results
The clinical characteristics are shown in Table 1. There were more men in group 2, and the heart rate was significantly higher in group 3 than in the other 2 groups.

Two-Dimensional Echocardiography
No echocardiographic features differentiated group 2 from group 1 other than left atrial diameter and the predefined wall thickness (Table 1). Patients in group 3 had more abnormalities than either of the other 2 groups, as shown in Table 1.

Standard Doppler Flow Measurements
Indexes of transmitral flow, pulmonary venous flow, and isovolumic relaxation time are shown in Table 2. Similar to the 2-dimensional echocardiographic features, no Doppler flow features differentiated group 2 from group 1. As anticipated, patients in group 3 showed more abnormalities than either of the other 2 groups.

Tissue Velocity Imaging
TV imaging data are presented in two forms. In the top line of Figures 2 through 4, respectively, systolic, early diastolic, late diastolic, and isovolumic relaxation time are shown.

Table 1. Patient and Echocardiographic Characteristics (n=97)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean LV Thickness</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>&lt;12 mm</td>
<td>(n=36)</td>
<td>(n=32)</td>
<td>(n=29)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59±10</td>
<td>56±10</td>
<td>58±11</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>14/22</td>
<td>24/8</td>
<td>12/17</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>73±13</td>
<td>74±12</td>
<td>82±18*</td>
</tr>
<tr>
<td>LV thickness (septum), mm</td>
<td>9.9±1.6</td>
<td>14.6±2.2†</td>
<td>15.8±2.6†</td>
</tr>
<tr>
<td>LV thickness (posterior), mm</td>
<td>10.3±1.2</td>
<td>14.6±2.3†</td>
<td>16.3±3.6†‡</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>48±6</td>
<td>47±7</td>
<td>42±56‡</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>28±6</td>
<td>27±6</td>
<td>30±4</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>42±8</td>
<td>42±9</td>
<td>29±9†‡</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>39±7</td>
<td>43±7*</td>
<td>46±6§</td>
</tr>
</tbody>
</table>

*P<0.05 vs noncardiac amyloid group, †P<0.001 vs noncardiac amyloid group, ‡P<0.05 vs CHF (–), §P<0.001 vs noncardiac amyloid, and ¶P<0.0001 vs CHF (–).

Table 2. Doppler Flow Data (Mean±SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=36)</td>
<td>(n=32)</td>
<td>(n=29)</td>
</tr>
<tr>
<td>Transmirtal flow peak E velocity, m/s</td>
<td>0.68±0.15</td>
<td>0.71±0.19</td>
<td>0.86±0.25†</td>
</tr>
<tr>
<td>Transmirtal flow peak A velocity, m/s</td>
<td>0.65±0.19</td>
<td>0.68±0.23</td>
<td>0.35±0.23§</td>
</tr>
<tr>
<td>Transmirtal flow E/A</td>
<td>1.16±0.56</td>
<td>1.23±0.74</td>
<td>2.99±1.68§</td>
</tr>
<tr>
<td>Deceleration time of transmirtal flow, ms</td>
<td>212±52</td>
<td>209±60</td>
<td>169±90†‡</td>
</tr>
<tr>
<td>Pulmonary venous flow peak S velocity, m/s</td>
<td>0.52±0.19</td>
<td>0.49±0.16</td>
<td>0.26±0.14§</td>
</tr>
<tr>
<td>Pulmonary venous flow peak D velocity, m/s</td>
<td>0.46±0.14</td>
<td>0.48±0.18</td>
<td>0.61±0.17†‡</td>
</tr>
<tr>
<td>Pulmonary venous flow peak A velocity, m/s</td>
<td>0.24±0.06</td>
<td>0.25±0.07</td>
<td>0.20±0.09</td>
</tr>
<tr>
<td>Pulmonary venous flow, D/S</td>
<td>1.07±0.76</td>
<td>1.10±0.71</td>
<td>2.93±1.57§</td>
</tr>
<tr>
<td>Isovolumic relaxation time, ms</td>
<td>91±22</td>
<td>90±24</td>
<td>77±35</td>
</tr>
</tbody>
</table>

*P<0.01 vs noncardiac amyloid, †P<0.05 vs CHF (–), ‡P<0.001 vs noncardiac amyloid, §P<0.001 vs CHF (–), and ¶P<0.05 vs noncardiac amyloid (by Scheffé test).
and late diastolic values are presented individually for each of the four walls at the basal, mid, and apical segments. Note that tissue velocities for all groups are highest at the base and decrease as the sample volume is moved apically. These changes in velocity have been previously described and were present in all the walls evaluated (Figures 2 through 4). Because of the similar findings in the four walls, and in order to render the data less complex, the mean values of basal, mid, and apical values of TV derived from these walls were calculated and are shown in the top line of Figure 5. Unless otherwise stated, discussion of the TV, strain, and SR values refer to the combined data illustrated in Figure 5. As can be seen, peak systolic TV did not differ between group 2 and group 1 at any site, but, similar to our previous findings, it was lower in the heart failure group (group 3) at the base and mid ventricle than in either other group. In contrast to the indexes of systolic TV, peak early diastolic TV at the LV base was statistically different among all 3 groups. Peak late diastolic TV was significantly lower in all 3 segments in group 3 when compared with either of the other groups, but it did not distinguish between groups 1 and 2.

**Early Diastolic Indices**

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**Figure 2.** Peak systolic indexes of TV, SR, and strain on basal, mid, and apical left ventricle at the septum, lateral, inferior, and anterior walls. Group 1, Noncardiac amyloid; group 2, CHF (·); group 3, CHF (+): *P<0.05 vs group 1, †P<0.01 vs group 1, ‡P<0.001 vs group 1, * *P<0.05 vs group 2, ††P<0.01 vs group 2.

**Figure 3.** Peak early diastolic indexes of TV, SR, and strain. Also see Figure 2.
Strain Rate Imaging
In contrast to the inability of systolic TV measurements to differentiate between patients without cardiac amyloidosis (group 1) and those with asymptomatic cardiac involvement (group 2), SR clearly documented that an increased wall thickness was associated with a decrease in systolic function in asymptomatic patients at the base and mid-ventricle (Figure 5). In addition, group 3 had greater abnormalities in
peak systolic SR than group 2 at all 3 sites. In contrast to the superior efficacy of SR over TV to demonstrate reduced systolic function, there appeared to be no advantage of this modality for the assessment of diastolic function among the 3 groups (Figure 5).

**Strain Imaging**

As anticipated, strain was lowest at all 3 sites in the group with heart failure. As with SR, strain imaging better detected differences of longitudinal systolic function between group 1 and 2 than did TV.

**Discussion**

This study demonstrates the limitations of standard 2D and Doppler echocardiography for detecting early abnormalities in cardiac function and the value of newer echocardiographic modalities. The 3 groups of patients all had a mean normal ejection fraction, yet differed in terms of myocardial infiltration and presence of CHF. In contrast to standard echocardiography, strain and SR were able to demonstrate that significant differences in systolic function occur as cardiac amyloid infiltration progresses to CHF. Tissue velocity, although a little better than standard 2D echocardiography for the detection of functional abnormalities, was not as good as strain/SR. Standard Doppler echocardiography measures velocities of blood flow and is well established for the assessment of hemodynamics and for detecting global abnormalities of diastolic function. In the present study, Doppler characteristics among patients with evidence of myocardial infiltration but no clinical CHF did not differ statistically from those in patients with normal wall thickness. Tissue velocity imaging, a technique that is capable of detecting regional systolic and diastolic function, also failed to differentiate between groups 1 and 2. It did, however, confirm a greater degree of diastolic dysfunction in the patients with evidence of myocardial infiltration, but this difference was present only in the basal left ventricular segments and only in early diastole.

These results of tissue velocity imaging confirm our previous observations, performed by pulsed tissue Doppler, that systolic tissue velocities in cardiac amyloidosis do not detect early abnormalities in longitudinal systolic function until CHF supervenes. The observations that strain and SR are abnormal earlier than TV point to some of the limitations of the latter technique. One major drawback is that TV cannot differentiate tissue movement due to active contraction from passive motion that results either from translational motion of the whole heart or from a “tethering” of normal surrounding tissue on a segment of diseased myocardium.15,16

As recently described by Edvardsen et al,17 it is likely that the differences in tissue Doppler values by TV imaging seen between apex and base do not represent intrinsic differences in tissue velocities, as this gradient was not seen when strain rate was measured by either echocardiography or MRI. Rather, the difference is a function of the greater motion of the whole heart at the base compared with the mid and apical regions. Reference to Figures 2 through 5 indicates that the differences in tissue velocities from base to apex that are so apparent with TV imaging are much less prominent when strain or SR are measured at the identical points. These modalities are much less affected by passive myocardial motion and tend to be uniform throughout the heart in normal subjects. Because they are minimally affected by passive motion, data derived from strain and SR should be expected to give a more sensitive reading of myocardial function. In this study, we confirmed our hypothesis that strain and SR are more sensitive than TV. Peak systolic SR was able to detect lower basal and mid LV values once wall thickening was present. This occurred before the onset of CHF, and once CHF was present, the systolic abnormalities were even more prominent. Peak early and late diastolic SR was also lower in group 2 compared with group 1.

**Study Limitations**

Despite the intriguing findings of this new technology, certain limitations should be stressed. Strain measurements are angle-dependent,14,15 and the angle between the ultrasound beam and LV axis must be small. We performed strain and SR measurements to keep the angle as small as possible (≤30 degrees). Because of the curvature of the apex, this resulted in the need to perform some of the apical measurements in the proximal part of the apical segments, but this should not have affected the results of the study. With the currently available technology, a limitation of SR is a relatively poor signal-to-noise ratio. To minimize this effect, we measured and averaged 3 cardiac cycles. Although this has the advantage of averaging out much of the noise, it has a disadvantage because identical sample volumes throughout the cardiac cycles are difficult to precisely maintain, due to beat-to-beat motion. It is therefore important to obtain the raw data from which these measurements are derived during breath holding, preferably at end expiration.

A Δr of 10.8 or 11.1 mm was used to measure strain and SR. It is possible to measure values over a greater or lesser distance, and this may affect the values obtained. Because of the consistent use of this setting in this study, the validity of the comparative values among the 3 groups was ensured, but caution is warranted when comparing our values with values obtained over a different sample distance. Finally, a potential criticism of this study relates to the definition of group 1 as having no cardiac amyloidosis, based on a normal wall thickness. As amyloidosis is a generalized disease, it might be expected that minor deposition could occur in the heart, undetectable by echocardiographic measurement of wall thickening. Although this might be possible, it is extremely rare for patients with AL amyloidosis affecting other organs to manifest signs of cardiac dysfunction unless wall thickening is present. In addition, the values obtained in group 1 are similar to (unpublished) normal values from our laboratory and to published normal data for TV17,18 and strain/SR17 obtained with the same imaging system.

**Possible Application of Strain and SR in AL Amyloidosis**

The treatment of AL amyloidosis with high-dose intravenous melphalan and autologous stem cell transplant is a new and effective therapy for AL amyloidosis, although it is best tolerated in patients without severe heart disease.7,19,20 If effective, as defined by a hematologic response, cardiac
function assessed by standard echocardiography usually stabilizes, but regression of echocardiographic evidence of heart disease is not usually apparent despite clinical improvement in CHF. Strain and SR are sensitive methods for assessing cardiac function and may possibly detect changes in cardiac function after chemotherapy. Furthermore, evaluation of patients with these modalities at the time of presentation may help to determine prognosis and thus aid in the appropriate selection of patients for aggressive chemotherapy.

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References
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