Serial Doppler Echocardiographic Follow-Up of Left Ventricular Diastolic Function in Cardiac Amyloidosis

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A spectrum of left ventricular diastolic filling abnormalities noted on Doppler echocardiography has been demonstrated in patients with cardiac amyloidosis. To determine how these filling abnormalities evolve over time and the significance of any change, serial pulsed wave Doppler studies of left ventricular inflow were performed over 12.6 ± 4.9 months in 41 consecutive patients (36 men and 15 women, mean age 59 ± 11 years) with typical two-dimensional echocardiographic features of cardiac involvement. The measurements were peak left ventricular inflow in early diastolic (E) and atrial contraction (A) velocities, E/A ratio, deceleration time and isovolumetric relaxation time.

Patients were classified by mean left ventricular wall thickness into an early group (<15 mm) of 24 patients and an advanced group (≥15 mm) of 17 patients. The total group showed an increased E/A ratio (1.7 ± 0.9 versus 1.4 ± 0.9, p = 0.009) and decreased deceleration time (164 ± 87 versus 174 ± 51 ms, p = 0.11) at follow-up compared with baseline study. The early group showed significant changes in the E/A ratio (1.0 ± 1.0 versus 1.2 ± 0.7, p = 0.011) between the two studies.

Seven patients (29%) in the early group showed a change from an abnormal relaxation or “normal” pattern to one of restriction, coincident with increased symptoms in six of these patients. Fifteen (88%) of the 17 patients in the advanced group did not show significant changes in the measures during the follow-up study, but these patients already showed a restrictive pattern.

Thus, significant changes in serial left ventricular flow velocity variables occur during short-term follow-up evaluation, predominantly in the early group with cardiac amyloidosis.

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Cardiac amyloidosis is characterized by abnormal diastolic function secondary to extracellular amyloid fibril deposition in the ventricular walls of the heart, which accounts for the “stiff heart” syndrome (1,2). Doppler echocardiography has been used as a noninvasive technique to assess left ventricular diastolic filling abnormalities in various diseases (3–7). Recent work from our institution (8,9) demonstrated that patients with cardiac amyloidosis show a spectrum of such filling abnormalities by Doppler echocardiography, corresponding to the degree of amyloid infiltration of the heart.

Patients with mildly increased mean left ventricular wall thickness (<12 but >15 mm) (early cardiac amyloidosis) show a left ventricular inflow pattern characteristic of abnormal relaxation, whereas patients with markedly increased mean left ventricular wall thickness (advanced cardiac amyloidosis) show a flow velocity pattern characteristic of restrictive physiology.

Preliminary observations (8,9) suggested that patients with cardiac amyloidosis may show a flow velocity pattern that evolves from abnormal relaxation through a “normal” or pseudonormal filling pattern and progresses to a restrictive filling pattern as the disease advances. To date, no serial echocardiographic Doppler studies have been performed in patients with cardiac amyloidosis to substantiate these observations. Thus, the purpose of this study was to determine whether left ventricular filling abnormalities by Doppler echocardiography change over time, the direction of such change and the significance of any change, in a large group of patients with cardiac amyloidosis.
Methods

Study patients. The study was performed on 41 consecutive patients (26 men and 15 women, mean age 59 ± 11 years) with biopsy-proved primary systemic amyloidosis with typical echocardiographic features of cardiac involvement. All patients were studied serially with two-dimensional echocardiography and Doppler echocardiography at least 6 months apart from July 1986 until August 1988. The mean follow-up time was 12.6 ± 4.9 months between the baseline and follow-up studies. All patients had positive biopsy results for amyloid from bone marrow, rectum, kidney or subcutaneous fat; seven patients had a positive endomyocardial biopsy result for amyloid. All patients were on a study protocol that included treatment with melphalan, prednisone, colchicine or alpha-tocopherol.

Patients were excluded if they had a significant history of hypertension, senile, familial or secondary amyloidosis (10), or regional wall motion abnormalities suggestive of coronary artery disease on two-dimensional echocardiography.

Echocardiographic examination. Two-dimensional and Doppler echocardiographic studies (pulsed and continuous wave) were performed with a phased array system (Hewlett-Packard) with a 2.5 MHz transducer. A complete two-dimensional echocardiographic examination was performed as previously described (11).

A parasternal short-axis view at the mid-left ventricular level was used to derive the following M-mode measurements: left ventricular end-systolic and end-diastolic dimensions and ventricular septal and left ventricular posterior wall thickness. Mean left ventricular wall thickness was measured as half the sum of the septal and free wall thicknesses. Ejection fraction was calculated by modification of the method of Quinones et al. (12).

Doppler examination. A complete pulsed and continuous wave Doppler examination was performed as previously described (13). In pulsed wave recordings, the lowest available wall filter settings were used. A heat-sensitive nasal respirometer was used to record the phase of respiration simultaneously with the Doppler tracing on the strip chart recorder at a paper speed of 50 to 100 mm/s.

Left ventricular inflow velocities were recorded from the apical four chamber view by using pulsed wave Doppler methods with the sample volume positioned between the leaflet tips of the mitral valve.

The isovolumetric relaxation time (interval from the aortic valve closure to mitral valve opening) was obtained by using either pulsed wave Doppler measurements of the left ventricular inflow and outflow tract velocities or more frequently by using continuous wave Doppler measurements with the beam directed across the left ventricular outflow tract and adjusted for recording aortic valve closure and onset of left ventricular inflow velocity simultaneously (9).

Figure 1. Diagram of a normal left ventricular inflow velocity recording with greater peak early (E) and smaller peak late (A) velocities. The deceleration time (DT) is the time from the peak E velocity to the extrapolation of the decline of this velocity to the baseline value. Isovolumetric relaxation time (IVRT) is the time from aortic valve closure (AVC) to mitral valve opening (MVO). It is obtained by using either pulsed wave Doppler recording of the left ventricular inflow and outflow tract velocities or, more frequently, by using continuous wave Doppler ultrasound with the beam directed across the left ventricular outflow tract and adjusted for simultaneous recording of aortic valve closure and the onset of left ventricular inflow velocity.

Doppler measurements. Peak flow velocities of left ventricular inflow in early diastole (E) and with atrial contraction (A) were measured from the baseline to the maximal flow velocity. The early to late peak velocity ratio (E/A) was calculated for each cardiac cycle. The deceleration time was measured as the time from peak E velocity to the extrapolation of the decline of the velocity to the baseline value (Fig. 1). All measurements were analyzed with a computer-interfaced digitizing tablet, except for the deceleration time, which was measured by hand. Mean values were obtained by averaging at least one beat during inspiration and one beat during expiration for each of three respiratory cycles (six cardiac cycles).

Reproducibility. The low intraobserver and interobserver variability (± SD) for left ventricular inflow velocity measurements in our laboratory in patients with amyloidosis has been previously reported (9).

Statistical analysis. An independent sample t test was used for analysis of baseline differences in Doppler variables between the amyloid groups. A paired t test was used to assess significance of serial changes. Finally, an independent sample t test was used to assess significance of the amyloid subgroup differences in serial changes. A p value <0.05 was considered to be significant. Data for echocardiographic and Doppler measurements are presented as mean values ± 1 SD.

Results

Subgrouping by wall thickness. For the purpose of analysis, the study cohort was classified on the basis of left
ventricular wall thickness into a group with early amyloidosis (wall thickness >12 but <15 mm) and a group with advanced amyloidosis (wall thickness ≥15 mm), similar to our previous study (9).

The early group consisted of 24 patients (13 men and 11 women) with a mean left ventricular wall thickness of 13.5 ± 0.8 mm. Three patients (13%) had congestive heart failure and were taking cardiac medications. Two patients (8%) had decreased systolic function detected by echocardiography (ejection fraction <50%) and 12 patients (50%) had left atrial enlargement.

The advanced group was composed of 17 patients (13 men and 4 women) with a mean left ventricular wall thickness of 17 ± 2 mm. Seven patients (41%) had congestive heart failure and were taking cardiac medications. 11 (65%) had decreased systolic function and 10 (59%) had left atrial enlargement. The clinical and echocardiographic features of both study groups during the baseline study are shown in Table 1.

Left ventricular inflow velocities at baseline. The early group showed a decreased E/A ratio and an increased peak A velocity and deceleration time compared with values in the advanced group at baseline study (Table 2). In the early group, 12 (50%) of the 24 patients showed an abnormal relaxation pattern (defined as a decreased E/A ratio <1 or a prolonged isovolumetric relaxation time >90 ms, or both). 1 SD above normal), 7 (29%) had a "normal" pattern and 5 (21%) had a restrictive pattern (defined as a decreased deceleration time ≤150 ms).

In the advanced group, 12 (71%) of the 17 patients showed a restrictive pattern, 3 (18%) had an abnormal relaxation pattern and 2 (12%) showed a "normal" pattern.

### Table 1. Clinical and Echocardiographic Features at Baseline in 41 Patients With Cardiac Amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Total Group (n = 41)</th>
<th>Early Cardiac Amyloidosis Group (n = 24)</th>
<th>Advanced Cardiac Amyloidosis Group (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>59 ± 41</td>
<td>58 ± 10</td>
<td>61 ± 13</td>
</tr>
<tr>
<td><strong>Gender (M/F [no.])</strong></td>
<td>26/15</td>
<td>13/11</td>
<td>13/4</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>81 ± 12</td>
<td>79 ± 11</td>
<td>83 ± 13</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>124 ± 18</td>
<td>123 ± 17</td>
<td>127 ± 20</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>75 ± 14</td>
<td>73 ± 15</td>
<td>78 ± 12</td>
</tr>
<tr>
<td><strong>CHF (no.)</strong></td>
<td>10 (24%)</td>
<td>3 (12%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td><strong>MVVT (mm)</strong></td>
<td>15 ± 2</td>
<td>13 ± 0.8</td>
<td>17 ± 2</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>59 ± 12</td>
<td>63 ± 7</td>
<td>53 ± 15</td>
</tr>
<tr>
<td><strong>LA (mm)</strong></td>
<td>42 ± 7</td>
<td>40 ± 6</td>
<td>41 ± 8</td>
</tr>
</tbody>
</table>

BP = blood pressure; CHF = congestive heart failure; EF = ejection fraction; F = female; LA = left atrium; M = male; MVVT = mean left ventricular wall thickness.

Total group. The overall group of 41 patients showed an increased left ventricular mean wall thickness and a decreased ejection fraction from baseline to follow-up study. The mean E/A ratio increased significantly: there was an increasing trend in the mean peak E velocity (p = 0.06) and a decreasing trend in the mean peak A velocity (p = 0.14) and the mean deceleration time (p = 0.11) (Table 3).

Early group. The mean follow-up time in the early subgroup was 13.6 ± 5.3 months. Mean left ventricular wall thickness increased and ejection fraction decreased significantly from baseline to follow-up study (Table 2). Similarly, the E/A ratio increased significantly (1.2 ± 0.7 versus 1.6 ± 1.0; p = 0.01) from baseline to the follow-up study. The deceleration time and isovolumetric relaxation time did not change significantly, whereas the peak E velocity showed an increasing trend (p = 0.15) and the A velocity showed a decreasing trend (p = 0.19) from the baseline to follow-up study.

### Table 2. Serial Echocardiographic and Doppler Variables in Cardiac Amyloidosis Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Early Cardiac Amyloidosis Group (n = 24)</th>
<th>p Value for Serial Change</th>
<th>Advanced Cardiac Amyloidosis Group (n = 17)</th>
<th>p Value for Serial Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>79 ± 11</td>
<td>77 ± 14</td>
<td>0.19</td>
<td>83 ± 13</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>63 ± 7*</td>
<td>57 ± 9</td>
<td>0.001*</td>
<td>53 ± 15</td>
</tr>
<tr>
<td><strong>MVVT (mm)</strong></td>
<td>13.5 ± 0.8*</td>
<td>14.1 ± 1.5</td>
<td>0.04*</td>
<td>17 ± 2</td>
</tr>
<tr>
<td><strong>Peak E vel (cm/s)</strong></td>
<td>74 ± 21</td>
<td>80 ± 19</td>
<td>0.15</td>
<td>87 ± 29</td>
</tr>
<tr>
<td><strong>Peak A vel (cm/s)</strong></td>
<td>72 ± 24*</td>
<td>66 ± 28</td>
<td>0.19</td>
<td>60 ± 31</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>1.2 ± 0.7*</td>
<td>1.6 ± 1.0</td>
<td>0.01*</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td><strong>DT (ms)</strong></td>
<td>190 ± 43*</td>
<td>179 ± 61</td>
<td>0.24</td>
<td>152 ± 54</td>
</tr>
<tr>
<td><strong>IVRT (ms)</strong></td>
<td>82 ± 22</td>
<td>75 ± 19</td>
<td>0.35</td>
<td>78 ± 22</td>
</tr>
</tbody>
</table>

* p < 0.05 between groups with early and advanced cardiac amyloidosis baseline study; † significant difference between baseline and follow-up study (p < 0.05).

A vel = left ventricular inflow velocity at atrial contraction; DT = deceleration time; E vel = left ventricular inflow velocity in diastole; EF = ejection fraction; IVRT = isovolumetric relaxation time; MVVT = mean left ventricular wall thickness.
Table 3. Serial Echocardiographic and Doppler Variables in Total Patient Group With Cardiac Amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Total Group (n = 41)</th>
<th>p Value for Serial Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 12</td>
<td>81 ± 15</td>
</tr>
<tr>
<td>EF (%)</td>
<td>59 ± 12</td>
<td>54 ± 11</td>
</tr>
<tr>
<td>MVWT (mm)</td>
<td>15 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Peak E vel (cm/s)</td>
<td>79 ± 25</td>
<td>85 ± 23</td>
</tr>
<tr>
<td>Peak A vel (cm/s)</td>
<td>68 ± 27</td>
<td>62 ± 28</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.4 ± 0.8</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>174 ± 51</td>
<td>164 ± 57</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>80 ± 22</td>
<td>75 ± 20</td>
</tr>
</tbody>
</table>

*Significant difference between baseline and follow-up. Abbreviations as in Table 2.

changed pattern (defined as a change in deceleration time ≥30 ms and E/A ≥0.3). The change was from abnormal relaxation to "normal" in two patients and normal to restrictive in five patients. Two (29%) of the seven patients showed an increased mean ventricular wall thickness at the follow-up study. Six (86%) of these seven patients became symptomatic, with arrhythmia (atrial fibrillation) or congestive heart failure at the time of the follow-up study (Fig. 2 and 3).

Advanced group. The mean follow-up time was 11.3 ± 4.1 months between the two studies. In this group, however, there was no significant change in the peak E velocity, A velocity, E/A ratio, deceleration time and isovolumetric relaxation time between baseline and follow-up study (Table 2). One patient showed a significantly changed pattern (same definition as for early group) from "normal" to restriction. Another patient showed further shortening of deceleration time from 140 to 90 ms (Fig. 4). Increased symptoms of congestive heart failure developed in both patients. There was no significant change in mean left ventricular wall thickness between the two studies.

Discussion

Pattern of left ventricular diastolic abnormalities in cardiac amyloidosis. Previous investigations (14–18) of diastolic function in cardiac amyloidosis have yielded controversial results. Initial studies (15) demonstrated the classic hemodynamic "dip and plateau" pattern during cardiac catheterization similar to that in constrictive pericarditis. In contrast, other investigations reported relaxation abnormalities with a prolonged isovolumetric relaxation time by using digitized M-mode echocardiography (16) and a uniformly delayed left ventricular diastolic filling volume and filling rate during left ventriculography (17). Still others (18) suggested atrial systolic failure as the mechanism to explain the abnormal diastolic filling seen in cardiac amyloidosis.

Recently, we documented (9) a spectrum of left ventricular diastolic filling abnormalities by Doppler echocardiography in a series of 53 patients with cardiac amyloidosis. Left ventricular diastolic patterns ranged from abnormal relaxation through "normal" to restriction, which was related to the degree of amyloid infiltration as measured by mean left ventricular wall thickness. Early cardiac amyloidosis with a mildly increased wall thickness showed a decreased peak E velocity, an increased peak A velocity, a decreased E/A ratio, a normal deceleration time and a prolonged isovolumetric relaxation time, suggesting abnormal relaxation. In contrast, advanced cardiac amyloidosis with a markedly increased wall thickness showed a markedly shortened deceleration time, characteristic of restriction. Furthermore, there were six patients with definite cardiac involvement by echocardiography who showed a "normal" pattern. We hypothesized that patients with cardiac amyloidosis may represent a continuum of left ventricular diastolic function abnormalities that may evolve from abnormal relaxation through a "normal" or pseudonormal phase and progress to a restrictive phase as the disease advances.

Changes in Doppler flow patterns during follow-up. The results of this study confirm that at short-term (13.6 months)
follow-up study, left ventricular inflow patterns show a significant change, particularly in the group with early amyloidosis. The E/A ratio increased significantly between the baseline and follow-up study in the early group, whereas deceleration time and isovolumetric relaxation time demonstrated no significant change. Seven patients (29%) in this group showed a significant change in Doppler flow patterns from either abnormal relaxation or "normal" to restriction. Also, six of these patients showed an increase in symptoms at the time of the follow-up study.

*There was little change in the Doppler measurements between the two studies in the group with advanced amyloidosis. Only one patient showed a significant change in Doppler flow patterns from "normal" to restriction, whereas one patient showed a further shortening of deceleration time concomitant with increased symptoms (Fig. 4). The negligible changes from baseline to follow-up (11.3 months) in the advanced group are not surprising because this group already showed restrictive physiology at baseline.*

**Previous studies.** Our study agrees with the recent study by Appleton et al. (19), who proposed an interchangeable continuum of left ventricular diastolic filling patterns between abnormal relaxation (pattern I), "normal" and restriction (pattern II) in various diseases by comparing Doppler echocardiographic data with cardiac catheterization hemodynamic data. They showed that the left ventricular inflow pattern was more reflective of diastolic hemodynamics not unique to an individual disease, but rather reflective of the filling characteristics (for example, dilated cardiomyopathy in its advanced stages may show restrictive filling by Doppler echocardiography) (9,19,20).

Our study also agrees with the findings of Cueto-Garcia et al. (21,32), who documented serial echocardiographic changes in 14 (52%) of 27 patients over a 19 month observation period. They showed that the mean left ventricular wall thickness changed from $12.4 \pm 2.6$ to $16.6 \pm 2.3$ mm compared with a change of $14.9 \pm 2.3$ to $15.5 \pm 2.4$ mm in our study. We did not find a consistent serial change in mean ventricular wall thickness and Doppler flow patterns. An explanation for this poor correlation is that the follow-up time in this study was too short. With a longer follow-up time, we would expect a stronger correlation between the continuums of left ventricular diastolic filling patterns.
degree of amyloid deposition (mean ventricular wall thickness) and a change in Doppler flow patterns. The other possibility is that Doppler flow patterns, which reflect a physiologic assessment of diastole, may be an earlier sign of dysfunction than an increase in wall thickness, which reflects an anatomic assessment.

Mechanisms for changing left ventricular filling pattern in cardiac amyloidosis. The mechanisms have not been clearly established. We speculate that in early cardiac amyloidosis with lesser degrees of amyloid infiltration, the relaxation process may be disturbed from either alteration of calcium fluxes or inhomogeneity between relaxation and contraction of the myocardial cells (23-25). Over time, as the degree of amyloid deposition increases, left atrial pressure rises secondary to increased stiffness of the ventricle, resulting in a shortening of the isovolumetric relaxation time as well as a return of the E/A ratio to normal (19). In advanced disease with greater amyloid infiltration of the ventricular walls of the heart and subsequent loss of myocardial cells from pressure necrosis (16), there is a more marked decrease in compliance of the ventricle, which accounts for the "stiff ventricle" and the subsequent restrictive process (9).

Limitations of the study. A major limitation of this study is that multiple factors can affect left ventricular flow velocity patterns. Recent investigations (5,26-30) demonstrated that changes in preload, afterload and heart rate, the aging process and the location of the pulsed wave Doppler sample volume may all influence left ventricular filling characteristics. Because of the lack of simultaneous cardiac hemodynamic data with the Doppler flow patterns, it is unknown whether a higher left atrial pressure in the absence of a change in left ventricular compliance could explain the change in the Doppler flow patterns. It is possible that in patients whose relaxation pattern changed from abnormal to "normal," a higher left atrial pressure could have developed at the time of the follow-up study. However, none of the left ventricular inflow patterns changed in the other direction (from "normal" to abnormal relaxation) it seems unlikely that a change in left atrial pressure accounted for these differences. Moreover, the heart rate in the patients was not different enough in the two studies to explain the change in the Doppler pattern.

In our study, there may be a selection bias favoring healthier patients. This bias would explain the small degree of change in the Doppler measurements because the patients with the most advanced disease may not live long enough to have a second Doppler study at least 6 months later.

Conclusions. This study clearly shows that Doppler-determined left ventricular inflow patterns change in a short-term follow-up time over 13.6 months in patients with early cardiac amyloidosis. It corroborates the hypothesis that ventricular diastolic function deteriorates as the disease advances, with flow velocity patterns evolving from abnormal relaxation, through a pseudonormal pattern to a restrictive pattern.

References
20. Appleton CP, Hlatky LK, Popl RL. Demonstration of restrictive ventric-


