Prognostic Significance of Ultrasound Myocardial Tissue Characterization in Patients With Cardiac Amyloidosis

Jun Koyama, MD; Patricia A. Ray-Sequin, BS; Rodney H. Falk, MD

Background—Cycle-dependent variation of myocardial integrated backscatter (CV-IB) is an objective measurement that may detect myocardial abnormalities. However, no data exist about the prognostic value of CV-IB in primary cardiac amyloidosis.

Methods and Results—We prospectively examined 208 consecutive biopsy-proven patients with primary amyloidosis. The magnitude of CV-IB was analyzed at the interventricular septum and left ventricular (LV) posterior wall and its prognostic value was compared with standard Doppler measurements with to the Tei index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time). One hundred thirty-three patients had cardiac involvement (mean LV thickness >12 mm). Forty-one patients (20%) (32 cardiac deaths) died during a mean follow-up of period of 307±156 days. Univariate analysis showed that the CV-IB at the LV posterior wall was the best predictor of cardiac death (P<0.0001) and all-cause death (P<0.0001). The Tei index did not identify patients at risk of death. Multivariate analysis showed that CV-IB at the LV posterior wall was the only independent predictor of both cardiac and overall deaths.

Conclusions—Among patients with cardiac amyloidosis, CV-IB at the LV posterior wall is a powerful predictor of clinical outcome and is superior to standard echocardiographic/Doppler flow indexes. (Circulation. 2002;106:556-561.)

Key Words: amyloid ▪ prognosis ▪ echocardiography

Cardiac amyloidosis is characterized by increased left ventricular (LV) wall thickness, normal or decreased LV cavity size, and congestive heart failure (CHF) with normal or near-normal fractional shortening.1-7 A marked increase in wall thickness, reduced LV systolic function,2 shortened deceleration time, and increased early diastolic filling velocity to atrial filling ratio7 have all been proposed as predictors of cardiac death, but it has been suggested that a Doppler-derived index of combined systolic and diastolic myocardial performance (known as the Tei index) is a more useful predictor of clinical outcome.8 Because most of these studies were retrospective or contained very few patients, we sought to examine prospectively a large group of patients to reevaluate these parameters. Furthermore, because cardiac amyloidosis is associated with abnormal echogenicity, we investigated the prognostic value of acoustic quantification with cyclic variation (CV) of integrated backscatter (IB) from the myocardium during the cardiac cycle.9-12

Acoustic quantification has been performed with IB ultrasonic imaging under a variety of conditions such as the aging heart,13 dilated cardiomyopathy,14,15 hypertrophic cardiomyopathy,16-18 myocardial ischemia,19-21 diabetes mellitus,22,23 and cardiac allograft rejection.24,25 and various abnormalities have been described. We sought to clarify the prognostic value of cycle-dependent variation of myocardial integrated backscatter (CV-IB) analysis in primary (AL) amyloidosis and to compare its prognostic value with that of the previously described 2-dimensional and Doppler flow data.2,5-8

Methods

Patient Population
Two hundred thirty-four consecutive biopsy-proven patients with AL amyloidosis entered the study. All patients were evaluated at the Boston University Amyloidosis Treatment and Research Center between March 21, 2000, and April 11, 2001. The diagnosis of amyloidosis was made when the biopsy specimen of an involved organ, viewed under polarized light, demonstrated typical Congo red birefringence. A monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow (evaluated by immunohistochemistry) confirmed AL amyloidosis. Patients with familial, secondary (AA), or senile amyloidosis were excluded. Patients with AL amyloid and poor echocardiographic quality (n=16), atrial fibrillation (n=3), hypertension (n=5), or significant valvular heart disease (n=2) were also excluded, leaving 208 patients. Cardiac involvement in AL amyloidosis is generally considered to be present when increased wall thickness is present in the absence of hypertension, valvular disease, or criteria for LV hypertrophy on the ECG. Thus, cardiac involvement was defined as a mean value of LV thickness (half of the sum of the thickness of interventricular septum and posterior walls) ≥12 mm.

All echocardiograms were reviewed by two readers who concurred on the presence or absence of cardiac involvement. Of the 208 patients, 133 had cardiac involvement and 75 had no echocardiographic features of amyloidosis. The latter group was defined as group 1 (noncardiac amyloid). CHF was defined as dyspnea on exertion, associated with orthopnea, paroxysmal nocturnal dyspnea,
or a chest radiographic appearance of heart failure and/or the presence of elevated jugular venous pressure. The diagnosis of CHF was made by one of the investigators, who obtained a detailed history and examined each patient without knowledge of the results of the IB.

Of the 133 patients with cardiac amyloidosis, 61, defined as group 3, had prior or current evidence of CHF. The 72 with cardiac amyloid but no CHF were defined as group 2. Follow-up data were obtained from correspondence with patients' families or from the attending physician. Written informed consent was obtained from each patient.

Standard Ultrasound Examination and Measurements
Ultrasound examinations were performed with a commercially available echocardiographic machine (Sonos 5500, Hewlett-Packard). Standard M-mode measurements of the LV were made. Transmural flow velocity was recorded from the apical 4-chamber view, with the sample volume at the mitral valve tips. The sample volume was also placed in the area of the anterior mitral valve leaflet to record simultaneous LV outflow tract and transmural flow profiles (Figure 1). Pulsed Doppler of pulmonary venous and LV outflow tract velocity patterns was recorded, positioning the sample volume at the right upper pulmonary vein 1 cm below the ostium and just below the aortic valve, respectively, in the apical 4-chamber view.

Analysis of Doppler flow was performed with computerized planimetry (Color Cineview Plus, TomTec Imaging Systems). Three or more consecutive beats were averaged for each measurement. The peak velocity of early (E) and late filling (A) waves, E/A ratio, deceleration time of E wave and peak velocities of systolic (S), diastolic (D), A waves, and the D/S ratio of pulmonary venous flow were measured. (Figure 1). Isovolumic relaxation time was measured as the time between the end of LV outflow tract flow and the onset of transmural flow (Figure 1). Isovolumic contraction time was measured as the time between the R wave and the onset of LV outflow. Ejection time was measured as the duration of LV outflow velocity profile. The Tei index was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time.8

Acquisition and Analysis of IB Data
A software package (Acoustic Densitometry) incorporated into the echocardiography machine was used with a wide-band sector transducer (S4) (Figure 2). This provides an IB image in which the gray level is displayed proportional to the IB power. Sixty frames from consecutive cardiac cycles (30 Hz) are displayed, captured into cine-loop memory, and digitally stored on magneto-optical disk. The dynamic range of the IB image is ~64 dB. The parasternal short-axis view of the LV was obtained at the level of the chordae. The time-gain compensation was adjusted to give equal gain at each depth of the LV in each patient. For IB analysis, the backscatter images were retrieved from the optical disk into the system memory. An 11×11- or 21×21-pixel elliptical region of interest was placed in

Figure 1. Measurements of Doppler time intervals, Doppler-derived index of combined systolic and diastolic myocardial performance (Tei index), and indexes of pulmonary venous flow. Tei index was calculated as sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time. PCG indicates phonocardiogram; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; ET, ejection time; PVF, pulmonary venous flow; S, systolic wave; D, diastolic wave; A, atrial wave.

Figure 2. Two-dimensional IB image from parasternal short-axis view at chordae level (upper left) and IB measurements at interventricular septum (upper right) and posterior wall (lower left) in patient with cardiac amyloidosis. Magnitudes of cyclic variation of IB were calculated as difference between minimal and maximal values in a cardiac cycle (lower left).
the interventricular septum and posterior wall, and the region of interest was manually adjusted to avoid specular reflections from interfaces between endocardium and blood. From the time-intensity waveforms, the magnitude of CV-IB was calculated as the difference between the minimal and maximal values in a cardiac cycle, averaged over 3 consecutive beats (Figure 2). Two cine loops were acquired consecutively to analyze 3 cardiac cycles. All data from the ultrasound examination were analyzed by one investigator, who was unaware of patients’ clinical information.

Statistics

Data are expressed as mean value±SD. Statistical analyses were done with a commercially available software program (StatView 5.0, SAS Institute Inc). Comparisons of the values of CV-IB between the interventricular septum and LV posterior wall were made by means of the 2-tailed paired t test. Differences among 3 groups were assessed with the χ2 test for categorical variables, and comparisons of continuous variables among 3 groups were made by means of 1-way factorial analysis of variance, followed by the Scheffe test. A probability value <0.05 was considered significant.

The median values of variables were used to divide patients into two groups when survival free of cardiac death and overall survival were estimated by use of the Kaplan-Meier method.26 We also evaluated values defined in previous studies to divide patients into two groups.2,7,8 To determine suitable cutoff points of CV-IB, we constructed receiver operating characteristic curves to determine values in which sensitivity was as close as possible to specificity. The area under the curve was measured to determine a summary measure of performance. Univariate analyses were followed by a log-rank test. Multivariate analyses to determine the relative contribution of variables were examined by Cox proportional hazards regression model.27 A 0.05 level of significance was applied to determine whether variables were added or removed from the model.

Results

The clinical characteristics are shown in Table 1. There were more men in the groups with cardiac involvement (groups 2 and 3) and the heart rate was significantly greater in group 3 than in that in other 2 groups.

Two-Dimensional Echocardiographic and Doppler Measurements

No echocardiographic or Doppler features differentiated group 2 from group 1, other than the predefined wall thickness (Table 1). Patients in group 3 had more abnormalities than either of the other 2 groups; LV systolic dimension and left atrial diameter were significantly greater in group 3 than in groups 1 and 2, the LV diastolic dimension in group 3 was smaller than in group 1, and the LV fractional shortening was smaller in group 3 than in the other 2 groups. Transmitral flow, pulmonary venous flow, and Doppler time intervals are shown in Table 1. Patients in group 3 showed greater values in peak E-wave velocity, peak E/A ratio of transmitial flow, peak D-wave velocity, and peak D/S ratio of pulmonary venous flow. The Tei index in group 3 was greater than that in group 1, and patients in group 3 showed smaller values in peak transmitial A wave, peak S, and A velocity of pulmonary venous flow, isovolumic relaxation time, and ejection time compared with the other groups. The E-wave deceleration time in group 3 was significantly smaller than in group 1, but the isovolumic contraction time was not different among the 3 groups.

### TABLE 1. Echocardiographic and Doppler Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.4±10</td>
<td>60.1±11</td>
<td>59.0±10</td>
</tr>
<tr>
<td>Male/female</td>
<td>28/48</td>
<td>50/22</td>
<td>35/26</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±10</td>
<td>71±11</td>
<td>79±12‡</td>
</tr>
<tr>
<td>Mean LVThd, mm</td>
<td>10.0±1.2</td>
<td>14.1±1.7</td>
<td>16.5±2.5†</td>
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<td>LVDD, mm</td>
<td>46.4±6.5</td>
<td>45.1±6.7</td>
<td>43.2±7.5§</td>
</tr>
<tr>
<td>LVDS, mm</td>
<td>27.9±5.7</td>
<td>27.1±6.0</td>
<td>30.7±7.0§</td>
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<tr>
<td>LVFS, %</td>
<td>39.8±8.4</td>
<td>40.0±9.2</td>
<td>29.0±9.9†</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>36.6±6</td>
<td>38.8±6</td>
<td>43.9±7.7§</td>
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<tr>
<td>TMF-E, m/s</td>
<td>0.71±0.2</td>
<td>0.78±0.25</td>
<td>0.94±0.23‡</td>
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<td>TMF-A, m/s</td>
<td>0.74±0.2</td>
<td>0.80±0.21</td>
<td>0.50±0.24*</td>
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<td>TMF-E/A</td>
<td>1.01±0.5</td>
<td>1.05±0.56</td>
<td>2.24±1.21†</td>
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<td>TMF E-DT, ms</td>
<td>165±48</td>
<td>156±56</td>
<td>135±37§</td>
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<tr>
<td>PVF-S, m/s</td>
<td>0.59±0.16</td>
<td>0.53±0.15</td>
<td>0.34±0.17†</td>
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<td>PVF-D, m/s</td>
<td>0.45±0.14</td>
<td>0.50±0.16</td>
<td>0.61±0.18‡</td>
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<tr>
<td>PVF-A, m/s</td>
<td>0.30±0.13</td>
<td>0.32±0.15</td>
<td>0.23±0.14§</td>
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<td>PVF-D/S</td>
<td>0.83±0.49</td>
<td>1.06±0.60</td>
<td>2.40±1.41†</td>
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<td>ICT, ms</td>
<td>82±20</td>
<td>85±22</td>
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<tr>
<td>IVRT, ms</td>
<td>72±16</td>
<td>77±21</td>
<td>62±22‡</td>
</tr>
<tr>
<td>ET, ms</td>
<td>300±34</td>
<td>288±36</td>
<td>244±30†</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.52±0.12</td>
<td>0.57±0.16</td>
<td>0.61±0.14§</td>
</tr>
</tbody>
</table>

Th indicates thickness at end diastole; LVDD, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening; LAD, left atrial diameter; TMF, transmitial flow; E, peak early diastolic wave velocity; A, peak atrial filling wave velocity; DT, deceleration time; PVF, pulmonary venous flow; S, peak systolic wave velocity; D, peak diastolic wave velocity; ICT, isovolumic contraction time; IVRT, isovolumic relaxation time; and ET, ejection time.

*P<0.0001 vs group 1, †P<0.0001 vs group 2, ‡P<0.001 vs group 2, §P<0.05 vs group 1, ‖P<0.01 vs group 2 by Scheffe test.

### Integrated Backscatter

The cyclic variation of integrated backscatter (CV-IB) in the interventricular septum and LV posterior wall are shown in Table 2. In contrast to the traditional echo-Doppler features (Table 1), which could not differentiate between groups 1 and 2, there was a significant and progressive decrease in CV-IB in the posterior wall among all 3 groups, whereas the septal CV-IB differed only between groups 1 and 3.

### Prognostic Value of Echo/Doppler Indexes and CV-IB

Of the 209 patients, 41 died during a mean follow-up period of 307±156 (162 to 547) days. Thirty-two of 41 deaths were cardiac related (either sudden or caused by CHF). Group 3

### TABLE 2. Cyclic Variation of Integrated Backscatter

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=75)</th>
<th>Group 2 (n=72)</th>
<th>Group 3 (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS, dB</td>
<td>5.4±3.2</td>
<td>4.6±2.4</td>
<td>3.8±1.7*</td>
</tr>
<tr>
<td>PW, dB</td>
<td>6.7±2.2</td>
<td>5.9±2.1</td>
<td>4.2±1.8†</td>
</tr>
</tbody>
</table>

IVS indicates interventricular septum; PW, left ventricular posterior wall.

*P<0.01 vs group 1, †P<0.0001 vs group 1, ‡P<0.0001 vs group 2, §P<0.05 vs group 1, ‖P<0.001 vs IVS, ††P<0.01 vs IVS.
showed significantly poorer prognosis than that of the other 2 groups (Figure 3).

Univariate analysis showed that CV-IB in the LV posterior wall, E/A ratio of transmitral flow, left atrial diameter, deceleration time of transmitral E wave, D/S ratio of pulmonary venous flow, and LV fractional shortening were predictors of all death and cardiac death (Table 3 and Figure 4). Univariate analyses that used published cutoff values showed that E/A ratio of transmitral flow (2.1) was only the predictor of all-cause and cardiac death, whereas fractional shortening (0.30), mean LV thickness (15 mm), and Tei index (0.77) were not predictors. Multivariate analysis showed that the CV-IB at the LV posterior wall and the deceleration time of transmitral E wave were independent predictors of overall death, and the CV-IB at the LV posterior wall was the only independent predictor of cardiac death (Table 3).

The receiver-operating characteristic analysis (Figure 4) indicated that 4.7 dB was the best cutoff value to predict patient outcome within 5 months (the minimum follow-up period of this study). This cutoff value (4.7 dB) was a stronger predictor of adverse outcome than the median value (5.35 dB, Figure 4).

Because CHF itself was a strong variable (discontinuous) to predict adverse outcome, a subgroup analysis was made in group 3 (n = 61). The median value of CV-IB (4.3 dB) still significantly distinguished patients with all-cause and cardiac death (Figure 5). The receiver-operating analysis indicated that 4.0 dB was the best cutoff value, predicting patient outcome within 5 months in group 3 (Figure 5), and this value (4.0 dB) was a stronger predictor of all-cause and cardiac death than median value (4.3 dB, Figure 5).

**Discussion**

In a previous 2-dimensional echocardiographic study of patients, it was suggested that an increased mean LV wall thickness and decreased fractional shortening were the most important echocardiographic predictors of poor outcome in AL amyloidosis. In the present, larger study, univariate

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**Figure 3.** Overall survival and survival free of cardiac death in each group with light-chain (AL) amyloidosis. Group 3 showed poorer outcome than in the other 2 groups. Small vertical lines in graphs represent censor time. Group 1, noncardiac amyloid; group 2, cardiac involvement without CHF; and group 3, cardiac involvement with CHF.

**Figure 4.** Overall survival and survival free of cardiac death in patients with AL amyloidosis (n = 209). Median value (5.35 dB) and receiver operating characteristic curve–derived cutoff value (4.7 dB) predict adverse outcomes in all groups.

**Table 3.** Univariate Mantel-Cox and Multivariate Cox Proportional-Hazards Analysis (Log-Rank Test, n = 209)

|                    | All Death (n=41) | Heart Rate (bpm) | Univariate Mantel-Cox Analysis |
|--------------------|-----------------|------------------|
|                    | \( \chi^2 \)     | \( P \)          | \( \chi^2 \)     | \( P \)          |
| CV-IB PW (5.35 dB) | 25.6            | <0.0001          | 19.1            | <0.0001          |
| TMF E/A (0.99)     | 11.3            | 0.0008           | 12.2            | 0.0005           |
| LAD (39.5 mm)      | 10.6            | 0.001            | 12.1            | 0.0005           |
| TMF-DT (154 ms)    | 8.62            | 0.003            | 7.18            | 0.0007           |
| PVF D/S (0.85)     | 8.37            | 0.004            | 15.0            | 0.0001           |
| %FS (0.382)        | 6.61            | 0.010            | 6.85            | 0.009            |
| LVThm (12.9 mm)    | 5.63            | 0.018            | 3.34            | 0.07             |
| Heart rate (72 bpm)| 2.54            | 0.1              | 2.49            | 0.1              |
| CV-IB IVS (4.30 dB)| 0.62            | 0.4              | 0.002           | 0.9              |
| Tei index (0.55)   | 0.11            | 0.7              | 1.01            | 0.3              |
|                    |                 |                  |                 |                  |
| Multivariate       |                 |                  |                 |                  |
| CV-IB PW (5.35 dB)| 11.5            | 0.0007           | 9.15            | 0.0025           |
| TMF-DT (154 ms)    | 3.98            | 0.0461           | ...             | ...              |

Abbreviations as in Tables 1 and 2.
analysis confirmed that a decreased fractional shortening was a predictor of both overall and cardiac death, although the mean LV thickness was not helpful to predict cardiac death. Previously published cutoff values of fractional shortening (0.30) and mean LV thickness (15 mm) were not predictors of death in our series of patients.\(^2\)

Left ventricular inflow filling variables have been described as independent predictors of cardiac death in cardiac amyloidosis, and, consistent with this, we found that univariate analysis demonstrated that the E/A ratio and deceleration time of transmitral flow were significant predictors of cardiac death in our series of patients.\(^2\) This study was supported by a research grant from the Japan Health Sciences Foundation (Drs Koyama and Falk), and the General Clinical Research Sciences Foundation (Dr Koyama), the Sue Sellors Finley Amyloid Fund (Drs Koyama and Falk), and the General Clinical Research Center M01RR00533. The authors gratefully acknowledge the advice and helpful comments of Professor J.G. Miller.

Advantages of the Present Study
We prospectively examined the largest published consecutive number of patients with AL amyloidosis\(^2,6,8\) and confirmed that previously published values of transmural Doppler E/A ratio and E-wave deceleration time are strong predictors of adverse outcome,\(^7\) whereas mean LV thickness and fractional shortening were not predictors of death.\(^2\) We also demonstrated that the CV-IB at the LV posterior wall is the most sensitive marker among multiple ultrasonic variables for predicting poor outcome. The CV-IB in myocardium is believed to be independent of heart rate, preload, and afterload and to follow changes in intrinsic myocardial contractility.\(^30\) This may partly explain why it is a more sensitive prognostic indicator than load-dependent LV inflow filling variables.\(^31\)

Our study confirmed that the existence of CHF itself is a strong predictor of adverse outcome (Figure 3).\(^7,8\) However, even when we restricted the analysis to the subgroup of patients with CHF (Figure 5), CV-IB still had prognostic significance.

Limitations
Although CV-IB is affected by age,\(^13\) there was no significant difference in the mean ages among groups in our study. Cardiac involvement was defined as a mean value of LV thickness >12 mm in patients with AL amyloid confirmed by a biopsy from any site. Thus, many patients were diagnosed as having cardiac amyloidosis without endomyocardial biopsy. However, on the basis of autopsy studies, it generally is accepted that the finding of LV thickening by echocardiography in the absence of diseases associated with LV hypertrophy is highly specific for the finding of cardiac amyloid deposition at biopsy or autopsy.\(^32\)

Conclusions
Cyclic variation of integrated backscatter at the LV posterior wall is a useful and powerful predictor of clinical outcome in patients with AL cardiac amyloidosis, compared with the traditional Doppler flow indexes. This finding may help to select patients for treatment, particularly when high-dose intravenous melphalan with autologous stem cell transplantation is considered.\(^7,33\)

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