A RECURRING clinical conundrum is the recognition of cardiac amyloid.1-7 The diagnosis is usually suggested by the combination of insidious congestive heart failure4, 6-10 and low voltage on the electrocardiographic leads;5, 8-11 established by the presence of a dip and plateau in the left ventricular (LV) diastolic pressure contour and different right and left ventricular diastolic pressures at cardiac catheterization;3, 12-14 and confirmed by tissue biopsy. However, recent reports indicate that cardiac amyloid is not characterized by a single hemodynamic picture1 and that hemodynamic data should not be relied upon for diagnosis.14

Consideration of the pathophysiology of cardiac amyloid, which is an infiltration of the myocardium by noncontractile material resulting in increased ventricular wall thickness8, 9, 15-18 and intramyocardial restriction, suggested to us that an alternative means of recognizing its presence is to examine the profile of regional LV wall dynamics and cavity function using computer-assisted analysis of the LV echograms in a large number of patients with the disease. We assessed the relative contributions to LV dysfunction of amyloid deposition per se and increased wall thickness, by using as a model for comparison the regional and global dynamics obtained from patients with aortic stenosis and normal coronary arteries and similarly increased wall thickness and cavity size. In addition, because patients with nonobstructive hypertrophic cardiomyopathy may resemble patients with amyloid both clinically and echocardiographically, we determined whether this technique might distinguish between these conditions.

Patients

The study population was composed of four groups.

Normal Subjects

LV echograms were obtained from 20 normal volunteers (mean body surface area 1.77 m²), 12 female and eight male, ages 19–63 years (mean 48 years). All were asymptomatic and had normal exercise tolerance, physical examination, chest roentgenograms and 12-lead ECGs.

Patients with Amyloid

LV echocardiograms were recorded in 20 patients with biopsy-proved amyloidosis (mean body surface area 1.69 m²) (fig. 1), 12 female and eight male, ages 41–76 years (mean 59 years). All had grade III or IV (New York Heart Association [NYHA] classification) congestive heart failure. Ten patients had direct histologic evidence of cardiac amyloid, three pericardial and myocardial biopsies at thoracotomy and seven complete autopsies. In the other 10 patients, amyloidosis was diagnosed by biopsy of at least two tissues (rectum 10, muscle five, kidney three, marrow two, gingiva two and tongue one). Nineteen patients had primary amyloidosis. One patient had amyloidosis associated with multiple myeloma, but had not been taking cytotoxic drugs that might have affected LV contractility before or at the time of echocardiography.
All patients were in sinus rhythm, except for one who was in controlled atrial fibrillation at the time of echocardiography. No patient had more than a trivial pericardial effusion echocardiographically. The ECGs and chest roentgenograms were similar to those of patients previously reported.5-10,12-19 The ECGs confirmed the presence of sinus rhythm in 19 patients and atrial fibrillation in one patient. The most frequent ECG abnormality was nonspecific ST-segment and T-wave changes (65%). Thirty percent of the patients had first-degree atrioventricular block. 30% had left-axis deviation, 15% had right-axis deviation and 10% had right bundle branch block: no patient had left bundle branch block. Chest roentgenograms showed cardiomegaly (cardiothoracic ratio > 50%) in 80% of the patients. Five patients underwent cardiac catheterization. LV end-diastolic pressure ranged from 10–21 mm Hg (mean 17 mm Hg) and cardiac index from 1.9–3.2 l/min/m² (mean 2.4 l/min/m²). Three patients had a dip and plateau in the LV diastolic pressure contour. Two patients underwent coronary arteriography, and both had normal coronary arteries.

**Patients with Aortic Stenosis**

LV echocardiograms were performed in 15 patients with aortic stenosis (mean body surface area 1.71 m²). Eight were female and seven were male, ages 37–77 years (mean 63 years). All patients were in NYHA functional class III or IV and had clinically severe aortic stenosis without aortic regurgitation. ECGs demonstrated sinus rhythm and LV hypertrophy in every patient, but no patient had left bundle branch block. All patients had undergone cardiac catheterization before aortic valve replacement. LV outflow tract gradients varied from 55 to 109 mm Hg (mean 82 mm Hg). LV end-diastolic pressures varied from 7 to 27 mm Hg (mean 16 mm Hg) and cardiac index from 1.7 to 3.9 l/min/m² (mean 2.7 l/min/m²). LV angiograms showed no segmental wall motion abnormalities. Aortography demonstrated no hemodynamically significant aortic regurgitation and selective coronary arteriography showed normal coronary anatomy in all 15 patients. These patients had wall and septal thicknesses and LV cavity diameters similar to those of patients with amyloid; thus, we could investigate the effects of increased wall thickness on global and regional LV dynamics.

**Patients with Nonobstructive Hypertrophic Cardiomyopathy**

LV echocardiograms were recorded in 12 patients with nonobstructive hypertrophic cardiomyopathy associated with long-standing hypertension (mean body surface area 1.75 m²). Four were female and eight were male, ages 29–66 years (mean 47 years). Patients had dyspnea and were in NYHA functional class II to IV, but none had either syncope or angina pectoris. All patients were in sinus rhythm and had LV hypertrophy on the ECG; however, none had left bundle branch block. These patients were selected because they presented with a clinical and echocardiographic picture similar to that of patients with amyloid, i.e., with progressive dyspnea and heart failure. No patient had undergone cardiac catheterization.

**Methods**

Echocardiograms were obtained with an Ekeline 20 ultrasonoscope using a 2.25-MHz transducer with a repetition frequency of 1000 Hz. Recordings were made on a Honeywell 1856A strip-chart recorder at paper speeds of 50 or 100 mm/sec with simultaneous ECGs. Echocardiograms were obtained from the right and left sides of the septum and from the endocardium and epicardium of the posterior LV wall at the level of the chordae tendineae of the mitral valve with patients in the left semilateral decubitus position. Only echocardiograms that were clear and continuous throughout the cardiac cycle were accepted for analysis.

Echocardiograms were digitized as previously described20 with a Hewlett-Packard 9874A digitizer and processed by a Hewlett-Packard 9825A computing system with floppy disc storage. Data points were generated for both right and left sides of the septum and for the endocardial and epicardial surfaces of the posterior wall so that strings of x,y coordinates at 10-msec intervals were obtained for the four surface boundaries. Echoes were calibrated with points defining a time interval of 1000 msec, a depth of 5 cm, and two successive Q waves on the ECG enclosing the cardiac cycle to be analyzed. Graphic records and computer printouts were made from an on-line Hewlett-Packard 9872A incremental plotter and 9870 printer, of continuous LV dimension (D), septal (VS) and posterior wall (PW) thicknesses, and their respective rates of changes expressed either in cm/sec (dD/dt) or normalized to refer to unit cavity diameter (Vcf) or unit septal
and posterior wall thickness (1/VS · dVS/dt and 1 PW · dPW/dt, respectively) (figs. 2 and 3). From these data, the following indexes of cavity, septal and posterior wall dynamics were examined.

LV Cavity Dynamics

*The percent shortening of cavity minor axis* was calculated by subtracting end-systolic dimension (ESD) from end-diastolic dimension (EDD), and expressing this difference as a percentage of end-diastolic dimension:

\[
\frac{EDD - ESD}{EDD} \times 100\%.
\]

The peak rate of increase of LV dimension during diastole was calculated as the largest positive value of instantaneous dD/dt (diastole), where D is LV dimension (cm) and t is time (seconds). This measurement is hereafter called the filling rate.

The normalized peak rate of left ventricular dimensional shortening in systole was identified as the maximal value of \( \frac{1}{D} \cdot \frac{dD}{dt} \) (systole), which was derived by dividing the instantaneous rate of dimensional shortening, dD/dt, by instantaneous LV dimension, D. This normalized peak shortening rate is taken to represent the peak Vcf.

The duration of rapid filling phase was defined as the time from minimum LV dimension to the time when the LV filling rate decreased to 20% of its maximum value. This point corresponds to the end of the rapid filling phase in normal subjects, and is seen as a discontinuity of the plot of continuous LV dimension. The minimum LV dimension was defined as the point at which dD/dt changes from negative to positive.

The time of mitral valve opening was measured as the time from minimum LV dimension to the onset of mitral valve opening, which was defined as the initial separation of the mitral valve leaflets. This interval was taken to represent isovolumic relaxation.

Septal Dynamics

*The percent systolic septal thickening* was determined by subtracting minimum diastolic thickness (VSd) from maximum systolic thickness (VSs) and expressing the difference as a percent of minimum diastolic thickness:

\[
\frac{VSs - VSd}{VSd} \times 100\%.
\]

The normalized peak rate of systolic septal thickening was calculated as \( \frac{1}{VS} \cdot \frac{dVS}{dt} \) (systole). This was the maximal value obtained by dividing the instanta-
neous rate of systolic thickening $\frac{dV_S}{dt}$ (systole by instantaneous septal thickness).

The normalized peak rate of diastolic septal thinning was calculated as $\frac{1}{V_S} \cdot \frac{dV_S}{dt}$ (diastole). This was the minimum value obtained by dividing the rate of septal thinning by its instantaneous septal thickness.

The delay of peak septal thickness in relation to peak posterior wall thickness was determined by subtracting the time from the onset of the QRS to peak posterior thickness from the time from the onset of QRS to peak septal thickness.

**Posterior Wall Dynamics**

The percentage systolic thickening was obtained by subtracting minimum posterior wall diastolic thickness (PWd) from maximum systolic thickness (PWs), and expressing the difference as a percentage of minimum diastolic thickness:

$$\frac{PWs - PWd}{PWd} \times 100\%.$$  

The normalized peak rate of systolic posterior wall thickening was calculated as $\frac{1}{PW} \cdot \frac{dPW}{dt}$ (systole). This was the maximal value obtained by dividing the rate of posterior wall thickening, $\frac{dPW}{dt}$ (systole), by instantaneous posterior wall thickness.

The normalized peak rate of diastolic posterior wall thinning was calculated as $\frac{1}{PW} \cdot \frac{dPW}{dt}$ (diastole). This was identified as the minimal value obtained by dividing the rate of posterior wall diastolic thinning by the instantaneous posterior wall thickness.

**Validity of Methods**

Validation of echocardiographic measurements of the LV minor axis and its rate of change was established by comparison with angiographic data from previous studies.22-24

**Reproducibility**

Reproducibility was assessed as the root-mean-square difference between pairs of determinations of
LV dimension at end-systole and end-diastole, and of peak rate of increase in LV dimension during filling. These were performed for 25 pairs of measurements made by two observers on the same record and also in 15 patients all in sinus rhythm, between pairs of records made at different times in the same patient. For duplicate determinations on the same record, the root-mean-square difference was 1.6 mm for end-systolic and 1.7 mm for end-diastolic difference and 1.5 cm/sec for peak rate of increase of LV dimension.

### Statistical Methods
The numerical data in the tables and in the Results section are arithmetic group means ± sp. Statistical comparisons were made between the groups by analysis of variance.52

### Results

#### Normal Subjects

**Global Function**

Group mean values for LV end-diastolic and end-systolic dimensions, percent cavity shortening, peak Vcf, peak LV filling rate, the duration of the rapid diastolic filling period and the delay in mitral valve opening with respect to minimum LV diameter for normal subjects are shown in table 1 (figs. 2, 4 and 5).

#### Regional Function

Maximum systolic and minimum diastolic posterior wall and septal thicknesses, their respective percent systolic thickening, the interval between peak septal and peak posterior wall thickness, and the normalized peak velocities of systolic thickening and diastolic thinning of the septum and posterior wall are listed in table 2 (figs. 2, 6 and 7).

#### Patients with Amyloid

**Global Function**

Among patients with amyloid, the group mean value for LV cavity diameter and end-diastole was normal, although in four of 20 (20%), individual values were smaller than normal. Mean end-diastolic LV diameter was significantly (p < 0.01) larger than normal (table 1). Percent systolic shortening and the mean value for peak Vcf were significantly reduced (p < 0.01) (table 1, figs. 3 and 4). Although the group means for systolic phase indexes (percent shortening and peak Vcf) were significantly reduced, in 20% of patients they were within normal limits, indicating preserved contractile function in this subgroup. In contrast, peak LV diastolic filling rate was significantly abnormal (p < 0.01) in every patient, with a group mean value more than 3 standard deviations below normal (table 1, fig. 5). This value is comparable to that in mitral stenosis.21,22 In spite of the reduction in peak rate of LV filling, the duration of the rapid diastolic filling period was normal, and was followed by a period of diastasis, during which there was little or no change in LV diameter (fig. 3). In 13 patients, the initial separation of the mitral valve leaflets could be clearly identified. In these patients, mitral valve opening was significantly delayed (p < 0.01) with respect to minimum LV dimension, indicating prolonged isovolumic relaxation (table 1).

#### Patients with Hypertension

**Global Function**

Group mean values for minimum systolic and minimum diastolic septal and posterior wall thicknesses were significantly (p < 0.01) greater than normal (table 2). Fifteen percent of the patients had asymmetric septal hypertrophy (ASH) (ratio of the septal to posterior wall end-diastolic thicknesses > 1.3). However, in all patients, the normal close time relations between peak septal and posterior wall thicknesses and minimum LV cavity diameter were preserved. The percent systolic thickening of both the septum and the posterior wall were significantly reduced (p < 0.01) (table 2). Group mean values for peak rates of septal and posterior wall systolic thickening were also significantly reduced (p < 0.01), the former more so than the latter (table 2). Similarly, the group mean rates of septal and wall diastolic thinning were both significantly reduced, and there was little individual

### Table 1. Left Ventricular Function: Global Dimensions and Dynamics in Normal Subjects and in Patients with Amyloid and Patients with Aortic Stenosis

<table>
<thead>
<tr>
<th>Study group</th>
<th>No. of pts</th>
<th>Mean BSA (m²)</th>
<th>EDD (cm)</th>
<th>ESD (cm)</th>
<th>Fractional shortening (%)</th>
<th>dD/dt (cm/sec)</th>
<th>Peak Vcf (circ/sec)</th>
<th>Rapid filling period (msec)</th>
<th>Isovolumic relaxation period (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20</td>
<td>1.77</td>
<td>4.5</td>
<td>2.7</td>
<td>40.2</td>
<td>14.5</td>
<td>2.7</td>
<td>160</td>
<td>0 ± 5</td>
</tr>
<tr>
<td>Amyloid</td>
<td>20</td>
<td>1.6</td>
<td>4.1±</td>
<td>3.2±</td>
<td>23.9±±</td>
<td>6.4±±</td>
<td>1.9±±</td>
<td>200</td>
<td>50 ± 25*</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>15</td>
<td>1.71</td>
<td>4.3</td>
<td>2.6</td>
<td>38.8</td>
<td>10.6*</td>
<td>2.6</td>
<td>200</td>
<td>60 ± 30*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>1.74</td>
<td>4.9</td>
<td>3.2*</td>
<td>37.0</td>
<td>10.7*</td>
<td>2.5</td>
<td>190</td>
<td>50 ± 15*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±0.6</td>
<td>±0.8</td>
<td>±3.9</td>
<td>±2.8</td>
<td>±0.7</td>
<td>±55</td>
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<td></td>
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</tbody>
</table>

*p < 0.01 vs normal subjects.

*†p < 0.01 vs aortic stenosis.

*‡p < 0.01 vs hypertension.
Table 2. *Left Ventricular Function: Regional Dimensions and Dynamics in Normal Subjects and in Patients with Amyloid and Patients with Aortic Stenosis*

<table>
<thead>
<tr>
<th>Study group</th>
<th>No. of pts</th>
<th>VS thickness (cm)</th>
<th>% VS thickening</th>
<th>PW thickness (cm)</th>
<th>% PW thickening</th>
<th>1 dVS (sec⁻¹)</th>
<th>1 dPW (sec⁻¹)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>VS dt</td>
<td>PW dt</td>
</tr>
<tr>
<td>Normal</td>
<td>20</td>
<td>0.7 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>53 ± 13</td>
<td>0.9 ± 0.2</td>
<td>69 ± 23</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>Amyloid</td>
<td>20</td>
<td>1.6* ± 0.5</td>
<td>2.0* ± 0.4</td>
<td>17 ± 8*†‡</td>
<td>1.4* ± 0.3</td>
<td>24 ± 9*†‡</td>
<td>1.5*†‡</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>15</td>
<td>1.5* ± 0.3</td>
<td>1.9* ± 0.4</td>
<td>31 ± 12*</td>
<td>1.3* ± 0.3</td>
<td>47 ± 18</td>
<td>2.3 ± 1.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>1.4* ± 0.2</td>
<td>1.8* ± 0.3</td>
<td>39 ± 14*</td>
<td>1.3* ± 0.1</td>
<td>47 ± 13</td>
<td>2.9* ± 0.8</td>
</tr>
</tbody>
</table>

*p < 0.01 vs normal subjects.
†p < 0.01 vs aortic stenosis.
‡p < 0.01 vs hypertension.

Abbreviations: VS = ventricular septal; PW = posterior wall; \( \frac{1}{VS \, dt} \) = normalized rate of change of septal thickness; \( \frac{1}{PW \, dt} \) = normalized rate of change of posterior wall thickness.

patients with aortic stenosis (table 1, fig. 4). The peak rate of LV cavity filling was significantly decreased (\( p < 0.01 \)), but was still significantly greater than that in patients with amyloid (table 1, fig. 5). Isovolumic relaxation was prolonged, indicating abnormal diastolic function with preservation of systolic cavity function.
the presence of factors in addition to increased wall thickness in determining regional function in amyloid.

**Patients with Nonobstructive Cardiomyopathy**

*Global Function (table 1)*

Mean LV cavity size at end-systole in patients with nonobstructive cardiomyopathy was similar to that in patients with amyloid, and significantly greater than

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**Regional Function**

Group mean values for maximal systolic and minimal diastolic septal and posterior wall thicknesses were selected to be similar to those in patients with amyloid (table 2). The group mean value for peak rate of systolic wall thickening was at the lower limit of normal, in contrast to that in patients with amyloid, and although there was a substantial and significant reduction in the group mean value for diastolic wall thinning, this reduction was not as severe as that in amyloid (table 2, figs. 6 and 7). The changes in wall dynamics in patients with amyloid who had similarly increased wall thickness were significantly greater than those in patients with aortic stenosis, indicating

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**Figure 6.** (top) Normalized peak rates of septal systolic thickening and (bottom) septal diastolic thinning in normal subjects and in patients with amyloid, aortic stenosis and hypertrophic nonobstructive cardiomyopathy associated with hypertension.

**Figure 7.** (top) Normalized peak rates of left ventricular wall systolic thickening and (bottom) diastolic thinning in normal subjects and in patients with amyloid, aortic stenosis, and hypertrophic nonobstructive cardiomyopathy associated with hypertension.
normal. LV end-diastolic dimension was normal, and significantly greater than in amyloid, accounting for the greater percent fractional shortening. Peak Vcf was normal, but the mean value for the peak rate of LV cavity filling during early diastole decreased to a degree similar to that in aortic stenosis, but it was still significantly greater than that in patients with amyloid (fig. 5). However, the isovolumic relaxation period was similarly prolonged in the patients with aortic stenosis or with amyloid.

**Regional Function (table 2)**

Mean values for end-systolic and end-diastolic posterior wall thickness were significantly greater than normal, but similar to those in both patients with aortic stenosis or amyloid (table 2). The percent systolic thickening of the septum and posterior LV wall was indistinguishable from that in aortic stenosis, but significantly greater than that in amyloid. Peak rates of systolic wall thickening varied widely, overlapping with the value of patients with amyloid and aortic stenosis, and the group mean value was not significantly different from that in patients with amyloid (figs. 6 and 7). Peak diastolic wall thinning rates were markedly reduced, and although there was overlap with the amyloid patients, the reduction in the group mean value was significantly less than that in patients with amyloid, but was similar to that in patients with aortic stenosis (figs. 6 and 7). Thus, the abnormalities in wall dynamics in patients with nonobstructive hypertrophic cardiomyopathy were indistinguishable from those in patients with aortic stenosis and, except for peak rates of systolic wall thickening, they were significantly less severe than those in patients with amyloid.

**Discussion**

Cardiac amyloid accounts for 5–10% of all noncoronary cardiomyopathy. The clinical presentation invariably includes congestive heart failure, and this was the case in every patient in the present study. The histologic abnormalities that provide the background for such LV dysfunction consist of deposition of a noncontractile protein in the intercellular space in the atrial and ventricular myocardium, the pericardium, semilunar and atrioventricular valve leaflets, and, less commonly, in the walls of the coronary arteries. Within the myocardium, these deposits insidiously increase in size, causing pressure necrosis of juxtaposed myocardial fibers so that histologically, the myocardium has a honeycomb appearance, wherein the vacuolated areas represent atrophic myocardial cells and the matrix amyloid. Although amyloid is occasionally preferentially deposited in the subendocardium, resulting in conduction disturbances, more often it is distributed throughout the myocardium, resulting in increased septal and right and left ventricular wall thicknesses and a concomitant reduction in LV cavity size. Thus, the macroscopic changes in LV architecture in amyloid resemble those in patients with secondary LV hypertrophy due to chronic pressure overload. The temporal sequence of these morphologic changes is unknown, since the development of symptoms that result in the patients’ presentation occur late in the course of the disease and usually denote the onset of congestive heart failure.

Recent reports have suggested that the so-called characteristic hemodynamic findings12 of a dip and plateau in LV diastolic pressure and different right and left ventricular diastolic pressures are not always present, and therefore cannot be relied upon for diagnostic purposes.14 Therefore, we investigated a noninvasive means of determining the diagnosis of cardiac amyloid, using computer-assisted analysis of the LV echocardiograms. Few echocardiographic studies of this type have been published, and they have shown no constant abnormality. They tended to emphasize morphologic rather than functional features, useful in supporting rather than making the diagnosis of amyloid.

Although LV cavity size at end-diastole was normal in 80% and small in 20% of the amyloid patients, mean end-systolic dimension was above normal. Systolic cavity function, evaluated in terms of percent shortening and peak Vcf, was significantly decreased. However in 20% of patients, all of whom had normal LV cavity size, both of these variables were still within the lower range of normal, concordant with previous hemodynamic and angiographic assessments of systolic function. In contrast, diastolic LV cavity function was abnormal in every patient, in that the mean value for peak rate of increase in LV dimension in diastole (peak filling rate) was significantly reduced, to a degree similar to that in patients with mitral stenosis. Although amyloid may cause thickening of the mitral valve, seen in approximately 50% of our patients as an increased number of echoes from the valve leaflets, it does not result in obstructive mitral valve disease, and this was evident by the normal echographic mitral valve motion pattern in all patients. The plot of continuous LV dimension in amyloid patients also showed important differences from patients with mitral stenosis (fig. 3): (1) Despite the slow filling rate, there was a discrete rapid filling period. (2) The duration of this rapid filling period was normal. (3) Rapid filling was followed by a normal period of diastasis during which there was little or no change in LV dimension. Thus, the resistance of LV filling in amyloid was not at the level of the mitral valve, but was a manifestation of intramyocardial restriction due to reduced ventricular distensibility. Further evidence for reduced compliance in cardiac amyloid was provided echocardiographically by the delay in mitral valve opening with respect to minimum LV dimension, indicating prolonged isovolumic relaxation, which is consistent with the previously reported abnormal diastolic pressure-volume relations.12-14 The continuous LV dimension plot (fig. 3) showed no suddenly arrested rapid increase in LV diameter during early diastolic filling to correspond with the early dip and plateau in the LV diastolic pressure tracing often observed in amyloid.

Posterior wall and septal thicknesses were signifi-
cantly increased, and 15% of the patients had ASH, suggesting that in a minority of patients, amyloid deposition may have been greater in the septum than in the free wall. However, even in the patients with ASH, the close time relations in normal subjects\(^1\) between peak septal thickness, peak posterior wall thickness and minimum LV cavity dimension were maintained. The mean percent systolic thickening of the septum and posterior wall were decreased, but systolic and diastolic dynamics were more markedly impaired. Group mean values for peak rate of systolic thickening of the septum and posterior wall were significantly decreased, but septal and posterior wall diastolic thinning rates were more greatly impaired. The comparatively greater reduction in regional diastolic dynamics than regional systolic dynamics would account for the more pronounced impairment of cavity filling than ejection, and the latter has also been described hemodynamically.\(^1,3,8,12-14\) The relative preservation of systolic function even in the presence of severe diastolic abnormalities until late in the course of the disease may in part, account for the delayed onset of symptoms in cardiac amyloid.

We compared LV dynamics in patients with amyloid to those of a group of patients with aortic stenosis, who were selected simply as a model of similarly increased wall thickness and normal cavity size, and not because there was diagnostic confusion between amyloid and aortic stenosis. We sought to determine whether the amyloid deposition itself resulted in LV dysfunction over and above that due to increased wall thickness. Such a comparison might initially appear not to be valid, since the myocardial fibers in aortic stenosis are hypertrophied and those in amyloid are not, and there might be further impairment resulting from the hypertrophy itself. However, any additional impairment would tend to minimize differences that might have existed between aortic stenosis and amyloid.

The patients with aortic stenosis had some abnormalities of LV function qualitatively similar to those in patients with amyloid, in that diastolic cavity function (peak LV filling rate and isovolumic relaxation) was impaired, although significantly less so than that occurring in amyloid. In contrast to amyloid, systolic cavity function (peak Vcf and fractional shortening) in patients with aortic stenosis was normal, as was regional systolic function measured in terms of peak rate of wall thickening. However, although the mean value for peak rate of diastolic wall thinning in patients with aortic stenosis was below normal, this reduction was significantly smaller than that in the patients with amyloid. Patients with aortic stenosis have a normal coronary anatomy; we interpreted the impaired diastolic and yet normal systolic function as having resulted from changes in LV distensibility secondary to increased wall thickness. Although diastolic abnormalities did result from increased wall thickness, since wall thickness was similar in patients with amyloid and aortic stenosis, the significantly greater impairment in diastolic LV dynamics and the additional systolic abnormalities in cardiac amyloid could be ascribed to the presence of amyloid per se causing severe intramyocardial restriction.

Two major differential diagnoses to be considered in patients with cardiac amyloid are constrictive pericarditis and nonobstructive hypertrophic cardiomyopathy; since these patients may present with virtually identical clinical features, and may not even be distinguished on the basis of hemodynamics, as both can have restrictive physiology. Although we have no data regarding patients with pericardial constriction, we did compare our amyloid patients with patients with nonobstructive hypertrophic cardiomyopathy.

The LV end-diastolic cavity size in patients with hypertrophic nonobstructive cardiomypathy was significantly greater than that in patients with amyloid: end-diastolic diameter and end-diastolic wall thickness were similar. However, computer analysis of regional and cavity function distinguished between amyloid and hypertrophic cardiomyopathy when these two populations were considered on the basis of group mean values, although with much less certainty as individuals, due to the overlap in LV function in these two diseases. Except for the peak rates of systolic wall thickening, which were similar, systolic and diastolic regional and global LV function in hypertrophic nonobstructive cardiomyopathy was significantly less impaired than that in amyloid, but was indistinguishable from that in patients with aortic stenosis.

Thus, two major pathophysiologic mechanisms appeared to contribute to the genesis of LV dysfunction: increased wall thickness and deposition of a matrix of rubbery tissue in the LV wall, with loss of myocardial fibers by pressure necrosis. There may, in addition, be some contribution in a few patients from myocardial ischemia due to obstructive intramural coronary artery amyloid.\(^3,27,28\), but we could not assess this separately. The combination of these factors resulted in intramyocardial restriction that was expressed in terms of characteristic echocardiographic findings: normal or small LV cavity size, with increased wall and septal thickness: reduced peak LV filling rate; normal rapid filling period; prolonged isovolumic relaxation; reduced percent shortening and peak Vcf in 80%; and greater reduction in diastolic than systolic regional dynamics. These data indicate that cardiac amyloid is manifest initially more as diastolic than systolic LV failure, corroborating previous hemodynamic findings.\(^1\) The final stages in the natural history of this disease are, of course, marked by severe impairment of both systolic and diastolic regional and global LV function.

We conclude that the extreme uniformity of these severely abnormal echocardiographic findings in this large group of patients enables cardiac amyloid to be diagnosed and differentiated from nonobstructive hypertrophic cardiomyopathy. The presence of these findings should strongly suggest the diagnosis of cardiac amyloid, which can be confirmed directly by tissue biopsy.

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