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M-mode and Two-dimensional Echocardiographic Features in Cardiac Amyloidosis

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SUMMARY Twenty-eight patients with cardiac amyloidosis were studied by echocardiography — 26 by M-mode and 13 by two-dimensional (2D) studies. All had heart failure and biopsy-proved amyloidosis. M-mode features included (1) normal left ventricular (LV) dimension in all; (2) thickened ventricular septum (88%), LV posterior wall (77%), and right ventricular (RV) anterior wall (79%); (3) decreased thickening of ventricular septum (96%) and of LV posterior wall (65%) and reduced LV global function (62%); (4) left atrial enlargement (75%); and (5) pericardial effusion (58%). Two-dimensional echocardiography provided additional features: (1) thickened papillary muscles (five of 13); (2) thickened valves (four of 13); (3) better appreciation of thickened RV wall; and (4) a characteristic "granular sparkling" appearance of thickened cardiac walls — presumably secondary to the amyloid deposit — which was noted in 12 of 13 patients. Thus, M-mode echocardiography is helpful in the recognition of cardiac amyloidosis. However, the better appreciation with 2D echocardiography of thickened cardiac walls with a "granular sparkling" appearance in patients with unexplained cardiac failure is virtually diagnostic of cardiac amyloidosis.

CLINICALLY SIGNIFICANT cardiac amyloidosis accounts for 5–10% of all forms of isolated non-coronary cardiomyopathy. Although the clinicopathologic findings of such an unusual form of heart disease have been well described,1–9 only a few investigators have reported the echocardiographic features of amyloid cardiomyopathy.10–18 and their observations and conclusions are based on small numbers of patients. Two-dimensional echocardiography has increased our ability to diagnose several forms of cardiac disease. However, to our knowledge, there have been no reports on two-dimensional echocardiographic features of amyloid heart disease.

The purpose of this retrospective study was to analyze in detail the M-mode echocardiographic features in a relatively large group of patients with systemic amyloidosis, and to describe the two-dimensional echocardiographic features of this disease.

Methods

Patients

The study population comprised 28 patients, all of whom were examined at the Mayo Clinic. All had biopsy-proved amyloidosis. Clinical profile, ECG findings, chest roentgenogram, and pathologic findings of these patients are presented in table 1. Thirteen patients (cases 1–13) had tissue-proved cardiac amyloidosis (eight autopsies, three biopsies during pericardectomy and two transvenous endomyocardial biopsies). Fifteen patients (cases 14–28) had evidence of heart disease in the presence of tissue-proved amyloidosis elsewhere in the body. Eleven patients had both M-mode and two-dimensional echocardiograms, 15 had only M-mode, and two had only two-dimensional examination. Six patients underwent cardiac catheterization, four of whom had coronary arteriography, which was normal in all. Detailed hemodynamics will not be discussed.

M-mode Echocardiography

M-mode echocardiograms were obtained with a commercially available ultrasonoscope (Smith Kline Instruments, Ekoline 20A) and recorded with a multichannel strip-chart recorder (Cambridge or Honeywell 1856). Studies were performed with a 2.25-MHz transducer with a repetition rate of 1000 Hz.

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Patients were studied supine or in a left semilaterally decubitus position, with the transducer placed at the left sternal border.

All measurements except left atrial dimension were made at the level of the chordae of the mitral apparatus. The end-diastolic measurements for cavity size and wall thickness were taken at the peak of the R wave of the ECG. The right ventricular anterior wall was measured when the epicardial and endocardial surfaces could be clearly identified. Systolic measurements of left ventricular (LV) internal dimension and septal thickness were done at the nadir of septal motion; posterior wall thickness was measured at the peak of its anterior motion. Excursion of the ventricular septum and that of the LV posterior wall were measured at their maximal amplitudes of motion. Left atrial dimension was taken at end-ventricular systole at the level of the aortic valve leaflets, and the measurements included posterior aortic wall thickness. Percent systolic thickening (\%ΔTh) of the septum and posterior wall was calculated as

\[
\left[\frac{(Ths - Thd)}{Thd}\right] \times 100
\]

where Ths is end-systolic thickness and Thd is end-diastolic thickness. Global LV function was estimated by percent change in LV dimension (\%ΔD) determined as

\[
\left[\frac{(Dd - Ds)}{Dd}\right] \times 100
\]

where Dd and Ds are LV end-diastolic and end-systolic dimensions, respectively. LV mass was calculated according to the formula

\[
\left[\frac{(Dd + 2 \times ThPW)^3 - (Dd)^3}{1.05}\right]
\]

where ThPW is end-diastolic LV posterior wall thickness.

Two-sample t tests were used to compare the means of measurements from patients with amyloidosis proved in cardiac tissue and those with biopsies elsewhere in the body (table 2). Ninety-five-percent confidence intervals for the difference between population means were also calculated.

### Two-dimensional Echocardiography

Two-dimensional echocardiographic examinations were performed with a commercially available sector scanner (Varian Associates, phased-array ultrasonograph, model V-3000) with an 84° sector angle. The transducers, with a frequency of 2.25 MHz, had 32 piezoelectric crystals in linear array. Images were recorded directly on a ¼-inch video cassette with a Sony VO-2800 video recorder or on 1-inch reel-to-reel tape with an IVC 817 video recorder. Patients were examined supine or turned into a partial left lateral decubitus position. The cross-sectional views of the heart were obtained from the parasternal, apical and subxiphoid positions with the technique previously described.14 The long and short axes and the four-chamber view could be visualized from each transducer position in most of the patients.

Two-dimensional studies were interpreted independently by at least two investigators. Measurements that were analyzed included size of cardiac chambers, LV function, presence of pericardial effusion, and thickness of ventricular walls, papillary muscles, cardiac valves and interatrial septum. By qualitative analysis, these measurements were designated normal or abnormal. Abnormalities were graded as mild, moderate or severe.

### Results

#### Clinopathologic Data

Clinopathologic data from each patient are presented in table 1. Eighteen men and 10 women were studied, ages 28–77 years (mean 61 years). All had congestive heart failure. Restrictive cardiomyopathy or constrictive pericarditis was clinically diagnosed in 13 patients (46%). In four of these patients (cases 1, 3, 7 and 12), thoracotomy was performed to rule out noncalcific constrictive pericarditis. ECGs were abnormal in all cases and chest x-ray films showed cardiomegaly in 25 patients (89%). Primary amyloidosis was the pathologic diagnosis in 23 cases, and the remaining five patients had cardiac amyloidosis associated with multiple myeloma. Thirteen patients (cases 1–13) had tissue-proven cardiac amyloidosis and 15 cases (14–28) had heart disease with biopsy-proved amyloidosis in other tissues, most often the rectum (14 patients) and the kidneys (five patients).

#### M-mode Echocardiographic Data

Table 2 is a summary of the M-mode echocardiographic data in 26 patients. (In cases 13 and 14 only two-dimensional studies were done.) Figures 1–3 are representative examples of the M-mode findings. LV end-diastolic dimension was normal (Dd = 35–56 mm) in 22 patients; four had decreased dimension. Increased thickness of the ventricular septum (VS > 11 mm) was noted in 23 patients (88%) and increased thickness of the LV posterior wall (PW > 11 mm) in 20 of the 26 cases (77%) (fig. 1). Seven patients (27%) had asymmetric septal hypertrophy (VS/PW ratio > 1.3); four patients had a VS/PW ratio of 1.5 or more. The right ventricular dimension was normal in 20 patients and enlarged (RV > 26 mm) in six. The right ventricular anterior wall was thickened (RVAW > 7 mm) in 15 of the 19 cases (79%) in whom it could be well identified (fig. 2). Left atrial enlargement (LA > 40 mm) was noted in 13 patients (50%). Systolic thickening of the ventricular septum was decreased (\%ΔTh < 30%) in 25 cases (96%) (fig. 3), with hypokinetic motion of the septum in seven (excursion < 3 mm). In 17 patients (65%) systolic thickening of the LV posterior wall was decreased (\%ΔTh < 50%), and six patients (23%) had hypokinesis (excursion < 8 mm). Global LV function, estimated by the percent
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
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<th>Clinical presentation</th>
<th>ECG</th>
<th>Chest x-ray</th>
<th>Diagnosis</th>
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<td>61</td>
<td>M</td>
<td>CHF (4 mo), pericardial effusion</td>
<td>1° AV block, low anterior forces</td>
<td>Marked cardiomegaly</td>
<td>Pericardial biopsy and autopsy</td>
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<td>CHF (1 yr), restrictive cardiomyopathy</td>
<td>1° AV block, RAD, low anterior forces</td>
<td>↑ LV size, pulmonary congestion</td>
<td>Autopsy</td>
</tr>
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<td>Pericardial and myocardial biopsies</td>
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<td>Autopsy</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
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<td>CHF (3 yr), ? restriction vs. effusion</td>
<td>Junctional rhythm, LAD, low anterior forces</td>
<td>Cardiomegaly, pulmonary congestion</td>
<td>Myocardial biopsy</td>
</tr>
<tr>
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<td>F</td>
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</tr>
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<td>RBBB, RAD, low voltage</td>
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<tr>
<td>11</td>
<td>76</td>
<td>M</td>
<td>CHF (1 yr), restrictive cardiomyopathy</td>
<td>At. fib., LAD, RBBB, inferolateral infarct pattern</td>
<td>Cardiomegaly, pleural effusion</td>
<td>Myocardial biopsy</td>
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<td>Breast cancer 2 yr before, CHF (6 mo), pericardial effusion</td>
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<td>Slight cardiomegaly, right pleural effusion</td>
<td>Pericardial and myocardial biopsies</td>
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<tr>
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<td>1° AV block, inferior infarct pattern</td>
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<td>Low anterior forces, diffuse T-wave abnormalities</td>
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<td>CHF (4 yr), restrictive cardiomyopathy</td>
<td>Low voltage, low anterior forces, T-wave abnormality</td>
<td>Cardiomegaly, bilateral pleural effusions</td>
<td>Rectal biopsy</td>
</tr>
<tr>
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<td>M</td>
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<td>LAD, low anterior forces</td>
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<td>Rectal biopsy</td>
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<td>M</td>
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<td>1° AV block, LAD, low anterior forces</td>
<td>Cardiomegaly</td>
<td>Rectal biopsy</td>
</tr>
</tbody>
</table>

Abbreviations: LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; CHF = congestive heart failure; 1° = first-degree; AV = atrioventricular; RBBB = right bundle branch block; RAD = right-axis deviation; LV = left ventricle; LAD = left-axis deviation; At. fib. = atrial fibrillation; ↑ = increase.
change in LV dimension, was abnormal (%ΔD < 30%) in 16 patients (62%). The LV mass was increased in 17 of the 26 patients (65%) compared with 443 normal subjects analyzed in our institution (normal ninety-fifth percentile estimates are 245 g for males and 205 g for females) (St. John Sutton MG, Lovett JL, Giuliani ER: unpublished data).

Fifteen patients (58%) had pericardial effusion. In most, the amount of pericardial fluid was small or moderate (figs. 1 and 3), but one patient (case 1) had a large accumulation of pericardial fluid. Two patients showed echocardiographic features of pulmonary hypertension, and six had apparent thickening of the mitral leaflets.

When the M-mode echocardiographic data from patients with amyloidosis proved by cardiac biopsies were compared with those from patients who had biopsies on other tissues (table 2), the mean values did not show any significant difference; echocardiographically, therefore, they could be grouped together.
Two-dimensional Echocardiographic Data

Table 3 is a summary of the data evaluated in 13 patients with two-dimensional sector echocardiograms (cases 10–22). LV size was considered normal in 11 patients and smaller than normal in two. Global LV function was normal in seven cases and reduced in six. Ventricular septum and LV free wall had increased thickness in all cases (fig. 4); one patient had a ventricular septum asymmetrically thicker than the LV free wall. Papillary muscles were also considered abnormally thickened in five of 13 cases. The right ventricular anterior wall appeared unusually thickened in 11 of 13 cases (fig. 5). The right ventricle was enlarged in two cases; however, one of these patients had associated pulmonary hypertension. The left atrium was enlarged in nine patients and the right atrium was enlarged in eight. Four of the 13 patients had thickened cardiac valves: mitral valve in all four, tricuspid in three, aortic in two and pulmonic in one (figs. 4 and 6). The interatrial septum was inordinately thickened in three cases. Six patients had pericardial effusion.
effusion, which was small in four cases and moderate in two (fig. 5). The most impressive two-dimensional finding, however, which was not apparent on the M-mode echocardiograms, was a "granular sparkling" appearance of the thickened ventricular myocardium.

This uniform hyperrefractile appearance was observed in 12 of 13 patients and involved all cardiac walls in six cases; in the six other patients it predominated in the ventricular septum and LV posterior wall.

Discussion

The heart is often involved in amyloidosis, and approximately one-third of patients with amyloidosis...
suffer a cardiac-related death. Cardiac amyloid deposits are characteristically extensive and cause myocardial dysfunction manifested as congestive heart failure and, ultimately, death. 

Autopsy studies have demonstrated fairly consistent findings in patients with cardiac amyloidosis. Heart weight is increased. The myocardium is involved more often than the pericardium or epicardium; both atria and ventricles may be diffusely or focally affected. Usually, there is pronounced thickening of the myocardial wall, which results in a stiff and noncompliant ventricle. The LV cavity is often normal in size, and the left atrium is dilated. LV papillary muscles frequently contain extensive amyloid deposits. Valvular involvement is common and affects all four valves, which become thickened and flat and show occasional verrucous amyloid deposits.

The clinical presentation was congestive heart failure in all of the patients described in this study. In 13 cases there was clinical suspicion of restrictive cardiomyopathy or constrictive pericarditis. The difficulties in the differential diagnosis between cardiac amyloidosis and constrictive pericarditis are well known; this resulted in exploratory thoracotomy in four patients. All patients also showed electrocardiographic abnormalities similar to those previously described.

M-mode Echocardiography

The echocardiographic evaluation of functional and anatomic features in this series of patients with amyloidosis was concordant with described pathologic findings. The M-mode echocardiographic studies showed increased thickness of the ventricular septum and LV posterior wall in the majority of patients.

Figure 6. (A) Two-dimensional echocardiogram and illustration of subcostal four-chamber view with image orientation recommended by American Society of Echocardiography. In this 70-year-old man (case 10), the ventricular septum (VS) and atrial septum (AS) showed increased dimension. The tricuspid valve (TV) also appeared to be inordinately thickened. On complete examination, mitral and aortic valves also appeared to show thickened leaflets. (B) Seventy-six-year-old man (case 11) (same patient as in figure 4). Shown are a parasternal section of the right ventricular outflow tract (RVO), main pulmonary artery (MPA) and bifurcation into right and left pulmonary arteries (RPA and LPA). The pulmonary valve (PV) shows thickened leaflets. Note the increased thickness and refractile appearance of the outflow ventricular septum, between aorta (Ao) and pulmonary valve (PV). LA = left atrium; RA = right atrium; TV = tricuspid valve; RV = right ventricle; MV = mitral valve; LV = left ventricle; S = superior; I = inferior; L = left; R = right; A = anterior; P = posterior.
The ventricular septum was more affected than the LV posterior wall: 25 patients (96%) had decreased systolic thickening of the ventricular septum and 17 (65%) showed decreased systolic thickening of the LV posterior wall. This finding is also probably related to the uneven deposition of amyloid that can occur in the cardiac walls, with consequent loss of regional or global contractility.

Pericardial effusion was detected in 15 of 26 M-mode echocardiograms (58%). Except for one case (fig. 2), the amount of fluid observed was small or moderate. Pericardial amyloidosis may be nodular or diffuse; it was found in three of four cases at the time of pericardial biopsy. However, the fact that all patients had features of congestive heart failure and some had associated nephrotic syndrome precludes a definite conclusion as to the cause of the pericardial effusion in these cases.

### Two-dimensional Echocardiography

Evaluation by the two-dimensional technique confirmed all the M-mode echocardiographic findings (table 3). Cardiac walls were thickened, and in one case there was septal-LV free wall asymmetry. The left ventricle had normal or small dimensions and in some cases had reduced function. Left atrial enlargement and small or moderate pericardial effusions were also observed.

The right ventricular wall could be more easily visualized and thickening could be better appreciated by two-dimensional echocardiography. In 11 of 13 two-dimensional studies (85%), the right ventricular free wall was considered thicker than normal, and this confirmed the widespread infiltration of cardiac walls previously reported in pathologic studies. Right atrial dimension could also be assessed, and it

### Table 3. Two-Dimensional Echocardiographic Findings in Patients With Amyloidosis

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<tr>
<th>Case</th>
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<th>RVW</th>
<th>PM</th>
<th>Valves</th>
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<th>LV</th>
<th>RV</th>
<th>LA</th>
<th>RA</th>
<th>Sparkling Intensity</th>
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<td>†</td>
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<td>++</td>
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<td>+ all</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>†</td>
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<td>↓↓↓</td>
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<td>↑</td>
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</tr>
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**Abbreviations:** † = mild; ++ = moderate; +++ = accentuated (increase in thickness or intensity of sparking); ↓ = increased, ↓↓↓ = decreased; N = normal; VS = ventricular septum; LVW = left ventricular free wall; RVW = right ventricular anterior wall; PM = papillary muscle; IAS = interatrial septum; LV = left ventricle; RV = right ventricle; LA = left atrium; RA = right atrium; MV = mitral valve; TV = tricuspid valve.

*VS thicker than LVW.
appeared to be augmented in eight patients (62%); one of these patients had associated pulmonary hypertension.

Two-dimensional echocardiography provided some additional features not appreciated by the M-mode technique. Among the 13 studies, five showed increased papillary muscle thickness, four had thickened valves, and three had a thickened interatrial septum. However, the most interesting and characteristic finding was a diffuse hyperrefractile "granular sparkling" appearance of the thickened myocardium, which was observed in 12 of 13 patients (92%). This is presumably secondary to the amyloid deposit and resultant pathologic changes.

This constellation of two-dimensional echocardiographic findings — including thickened right and left ventricular and septal walls with a "granular sparkling" appearance of the myocardium, normal or small LV cavity, and mildly enlarged atria — is virtually diagnostic of cardiac amyloidosis. In two recent patients (cases 13 and 22), the diagnosis of amyloid heart disease was correctly predicted by two-dimensional echocardiographic studies. On the basis of two-dimensional findings, biopsies were recommended and they resulted in the diagnosis of this disease.

Differential Diagnosis

Clinical and echocardiographic differential diagnoses must be considered. Although cardiac amyloidosis may mimic ischemic and valvular heart disease, the most important clinical differentiation involves constrictive pericarditis. Our data and other reports clearly indicate that echocardiography is extremely helpful in this differentiation. The findings of thickened cardiac walls and associated features noted in amyloid heart disease have not been seen in constrictive pericarditis.

From the echocardiographic standpoint, hypertrophic cardiomyopathies, either obstructive or nonobstructive, and other forms of infiltrative cardiomyopathies should be considered in the differential diagnosis. Obstructive hypertrophic cardiomyopathy is another condition in which we have seen a hyperrefractile appearance of the ventricular septum. However, the pattern is not diffuse; it does not involve other walls and it usually is more intense at the base of the hypertrophied septum. Some other features that can be seen in hypertrophic obstructive cardiomyopathy, such as systolic anterior motion of the mitral apparatus, midsystolic closure of the aortic valve, and normal to hyperdynamic LV posterior wall motion, would also be helpful in the diagnosis of this disease. Differentiation from nonobstructive hypertrophic cardiomyopathy is more difficult, but again the refractile appearance is not diffuse and not as impressive and does not involve the right ventricular wall or the valve leaflets. High voltage on the ECG, indicative of LV hypertrophy, would also be helpful in the diagnosis of this form of hypertrophic cardiomyopathy.

Regarding the other infiltrative cardiomyopathies, patients with hemochromatosis also have thickened cardiac walls, but they usually show ventricular dilatation. Associated clinical features and age would exclude the majority of cases with other types of infiltrative disease. We have not observed the two-dimensional echocardiographic features found in advanced cardiac amyloidosis in any other situation.

In summary, the M-mode echocardiogram can suggest amyloid heart disease when it shows thickened ventricular walls in the presence of a small or normal-sized left ventricle, dilated left atrium, and a small amount of pericardial effusion. However, two-dimensional echocardiography adds substantial diagnostic information and defines the extent of cardiac involvement. In an older patient with unexplained congestive heart failure, two-dimensional findings of thickened right and left ventricular myocardium, normal LV cavity dimension, and a diffuse hyperrefractile "granular sparkling" appearance are virtually diagnostic of amyloid heart disease.

References

M-mode and two-dimensional echocardiographic features in cardiac amyloidosis.
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