Radionuclide Angiographic Assessment of Left Ventricular Diastolic Filling in Amyloid Heart Disease: A Study of Patients With Familial Amyloid Polyneuropathy

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To assess left ventricular diastolic filling in amyloid heart disease, 17 patients with familial amyloid polyneuropathy and 20 normal subjects were examined by radionuclide angiography. None of the patients showed clinical evidence of restrictive cardiomyopathy. All but two patients had normal left ventricular ejection fraction. Peak filling rate was significantly lower and time to peak filling rate was significantly greater in patients than in normal subjects (2.60 ± 0.52 versus 3.10 ± 0.44 EDV/s, p < 0.001, and 215 ± 53 versus 147 ± 18 ms, p < 0.001, respectively). The mean left ventricular filling volume during rapid diastolic filling and atrial systole in patients was 54.5 ± 19.5% and 44.2 ± 21.6% of the stroke volume, respectively, compared with 83.8 ± 6.6% (p < 0.001) and 20.0 ± 6.0% (p < 0.001), respectively, in normal subjects.

Although 10 of the 14 patients without clinical evidence of overt heart disease had normal ventricular wall thickness as well as normal ejection fraction, 8 of the 10 showed abnormal diastolic filling. In patients with familial amyloid polyneuropathy, indexes of diastolic filling were significantly related to ventricular wall thickness alone. The incidence and magnitude of abnormalities in time to peak filling rate and contribution of rapid filling as well as atrial systole to ventricular filling increased with age and duration of illness.

Thus, abnormal diastolic filling can be seen even in the early stage of familial amyloid polyneuropathy and may be related to myocardial amyloid deposition as well as to fibrosis. Careful consideration should be given to age and duration of illness when diastolic filling is assessed in this disorder.

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Recent studies (1-9) using invasive and noninvasive techniques have demonstrated alterations in left ventricular diastolic filling in a wide variety of cardiac diseases. In patients with amyloid heart disease, diastolic properties have usually been reported to be severely impaired, even in the absence of identifiable heart disease and abnormalities in systolic function, as well as ventricular wall thickening. To our knowledge, however, most of these studies have been accomplished by measuring indexes of left ventricular systolic and diastolic function with contrast ventriculography (10-13) and M mode and Doppler echocardiography (14-19); left ventricular diastolic filling appears not to have been investigated hitherto by radionuclide angiography.

This study was undertaken to analyze the left ventricular time-activity curve obtained by radionuclide angiography to determine left ventricular diastolic filling in patients with familial amyloid polyneuropathy, which shows long-term progression and variable degrees of amyloid infiltration into the heart. We also examined the effects of age and duration of illness on diastolic filling in this disorder.

Methods

Study patients. During the past 3 years we examined 17 patients with familial amyloid polyneuropathy (10 men and 7 women, aged 28 to 68 years [mean 47.1 ± 10.2]) who were referred to us from several locations in Nagano Prefecture in the central part of Japan (20). The diagnosis was based on neurologic findings and the confirmation of amyloid deposition in biopsy specimens obtained from the stomach, rectum or sural nerve. Duration of illness ranged from 1.5 to 12 years (mean 6.8 ± 3.0). Clinically overt heart disease was present in only three patients. No congestive heart failure,
restrictive cardiomyopathy, hypertension or any known concomitant heart disease was found in any of them at the time of entry into the study. Ten of the 17 patients underwent cardiac catheterization, and none had a dip and plateau pattern in the left ventricular pressure curves. Right ventricular endomyocardial biopsy, carried out in nine patients, disclosed histologic evidence of amyloid deposition in all nine. All patients underwent M-mode echocardiographic examination and radionuclide angiographic study.

We studied an additional 20 normal volunteers (10 men and 10 women, aged 28 to 68 years [mean 49.8 ± 11.1]) with no evidence of cardiovascular disease. Findings on their physical examination, including systemic blood pressure, chest roentgenogram and electrocardiogram (ECG), were normal, and they were used as normal control subjects. They also underwent echocardiographic and radionuclide angiographic studies. Informed consent was obtained from each subject included in the study.

Echocardiographic examination. M-mode echocardiograms derived from two-dimensional images were obtained with a Toshiba SSH-40A Sonolayergraph, with a 2.4 or 3.5 MHz transducer, or both, and the following measurements were made by standard techniques (21): 1) left ventricular internal end-diastolic and end-systolic diameter; and 2) ventricular septal wall thickness and left ventricular posterior wall thickness at end-diastole.

Equilibrium radionuclide angiography. Gated blood pool scintigraphy was performed with the patient at rest in the supine position with use of red blood cells labeled in vivo with 20 mCi of technetium-99m. All studies were performed within 1 week of the echocardiographic examination after the cessation of all cardiac medications, and all patients were in sinus rhythm at the time of the study. Imaging was accomplished with a conventional Anger camera equipped with a high resolution, parallel-hole collimator (Siemens, model ZLC 7500) interfaced to a minicomputer system (Shimadzu, model Scintipac 2400). A modified left anterior oblique projection that best isolated the left ventricle was used. The cardiac image sequence spanning the average cardiac cycle was constructed from several hundred cardiac cycles by computer-based ECG gating and by combined forward and reverse gating from the R waves. Extrasystolic and postextrasystolic cardiac cycles were excluded from the analyses. The data were digitized to a 64 × 64 pixel matrix for subsequent analysis and the cardiac cycle was formatted into 32 frames. Left ventricular and background regions of interest were identified and the high temporal resolution time-activity curve was generated from the cardiac image sequence after background correction.

From this time-activity curve and its first derivative, the following indexes of left ventricular systolic function and diastolic filling were measured (Fig. 1): 1) left ventricular ejection fraction; 2) peak filling rate; and 3) time to peak filling rate. The peak filling rate was determined by computing the first derivative of the filling curve and was expressed as end-diastolic volume per second (EDV/s). The time to peak filling rate was measured as the time from end-systole (minimal volume on the time-activity curve) to the time of peak filling rate and was expressed in milliseconds. The other two indexes of left ventricular diastolic filling were then measured by the method described by Bonow et al. (22) (Fig. 1): the relative contribution of rapid diastolic filling and atrial systole to total left ventricular filling volume. These measurements could be obtained in 17 of the 20 normal subjects and 13 of the 17 patients, who had a slow filling phase between the rapid diastolic filling and atrial systolic portions on the time-activity curves. Next, each value obtained from the patients was compared with that of the upper or lower range of the normal subjects.

Statistical methods. Data are expressed as mean ± SD and the analysis was performed in a blinded manner. The differences among the data were analyzed by the unpaired t test. Correlations between left ventricular function and clinical characteristics were assessed by linear regression analysis. A probability (p) value of <0.05 was considered to be statistically significant.

Results

Patient characteristics (Table 1). Age, gender distribution, heart rate, blood pressure and left ventricular chamber size did not differ significantly between patients with familial amyloid polyneuropathy and normal subjects. Thickened ventricular walls were present in only five patients (29%) but the thickness was significantly greater in patients than in normal subjects.
Radionuclide angiographic measurements in normal subjects (Table 2). Left ventricular ejection fraction averaged 59.0 ± 5.8% (range 50 to 73%). Peak filling rate ranged from 2.53 to 4.37 EDV/s (mean 3.10 ± 0.44) and time to peak filling rate ranged from 113 to 181 ms (mean 147 ± 18). Mean left ventricular filling volume during rapid diastolic filling was 83.8 ± 6.6% (range 69 to 91%) of the total stroke volume and mean filling volume during atrial systole was 20.0 ± 6.0% (range 10 to 30%) of the stroke volume. These data were nearly identical to those reported by Bonow et al. (22-24) in asymptomatic normal subjects.

Radionuclide angiographic measurements in patients with familial amyloid polyneuropathy (Table 2). Left ventricular ejection fraction for the entire group of 17 patients with familial amyloid polyneuropathy was slightly but significantly lower than that in the 20 normal subjects. The ejection fraction was >50% in 15 (88%) of the patients. Peak filling rate was significantly lower in patients with familial amyloid polyneuropathy than in normal subjects, and it was <2.53 EDV/s in 8 (47%) of the 17 patients. Time to peak filling rate was significantly greater in patients with familial amyloid polyneuropathy than in normal subjects, and exceeded 181 ms in 12 patients (71%). The mean left ventricular filling volume during rapid diastolic filling in the 13 patients in whom this could be measured was 54.5 ± 19.5% of total left ventricular stroke volume. The percent of rapid diastolic filling volume was <69% in nine patients (69%). The mean left ventricular filling volume during atrial systole in the patients was 44.2 ± 21.6% of the total stroke volume. The percent of atrial systolic filling volume was >30% in 9 (69%) of the 13 patients.

Of the 12 patients with at least one abnormality of left ventricular diastolic filling, 7 had a diminished peak filling rate and prolonged time to peak filling rate; this was accompanied by a reduced contribution of rapid diastolic filling and an enhanced contribution of atrial contraction to ventricular filling in five of them in whom the latter two indexes could be measured (Fig. 2). One patient showed a depressed peak filling rate with normal time to peak filling rate and the remaining four exhibited a normal peak filling rate but prolonged time to peak filling rate in association with abnormal contributions of rapid diastolic filling and of atrial systole. In three of these four patients, left ventricular filling predominantly occurred during atrial contraction, resulting in striking changes in the time-activity curve (Fig. 3). These three patients had significantly greater ventricular wall thickness and longer duration of illness compared with the other nine patients (ventricular septal wall thickness, 15.3 ± 1.7 versus 11.5 ± 1.7 mm, p < 0.01; posterior wall thickness, 13.7 ± 2.4 versus 11.1 ± 1.4 mm, p < 0.05; duration of illness, 10.0 ± 1.6 versus 6.1 ± 2.7 years, p < 0.05, respectively), although no other differences were found in the clinical and echocardiographic findings or ejection fraction.

### Table 1. Clinical and Echocardiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients With FAP</th>
<th>Normal Subjects</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.1 ± 10.2</td>
<td>49.8 ± 11.1</td>
<td>NS</td>
</tr>
<tr>
<td>Men/women</td>
<td>10/7</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>6.8 ± 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64.2 ± 6.8</td>
<td>67.4 ± 7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>111 ± 12</td>
<td>117 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>71 ± 9</td>
<td>72 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>VST (mm)</td>
<td>12.2 ± 2.3</td>
<td>10.1 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>11.5 ± 1.9</td>
<td>9.7 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>44.7 ± 1.9</td>
<td>45.8 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>29.9 ± 2.0</td>
<td>30.1 ± 1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP = blood pressure; duration = duration of illness; EDD = end-diastolic diameter; ESD = end-systolic diameter; FAP = familial amyloid polyneuropathy; HR = heart rate; PWT = left ventricular posterior wall thickness; VST = ventricular septal wall thickness.

### Table 2. Radionuclide Angiographic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Patients With FAP</th>
<th>Normal Subjects</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>54.6 ± 4.1</td>
<td>59.0 ± 5.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PFR (EDV/s)</td>
<td>2.60 ± 0.52</td>
<td>3.10 ± 0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPFR (ms)</td>
<td>215 ± 53</td>
<td>147 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RDF (% of SV)</td>
<td>54.5 ± 19.5</td>
<td>83.8 ± 6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS (% of SV)</td>
<td>44.2 ± 21.6</td>
<td>20.0 ± 6.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The numbers in parentheses indicate the range of each value: AS = contribution of atrial systole; EF = ejection fraction; PFR = peak filling rate; RDF = contribution of rapid diastolic filling; SV = stroke volume; TPFR = time to peak filling rate.
Figure 3. Left ventricular time-activity curve obtained from a 61 year old man with biopsy-proved cardiac amyloidosis. Left ventricular diastolic filling predominantly occurs during atrial systole (AS). This results in a striking change in the shape of the time-activity curve with an apparently normal peak filling rate but with prolonged time to peak filling rate in association with abnormal contribution of rapid diastolic filling and of atrial contraction to ventricular filling. EDV = end-diastolic volume.

Of the 14 patients without clinical evidence of overt heart disease, 10 showed normal ventricular wall thickness and ejection fraction >50% but 8 (80%) of the 10 had some abnormality in the indexes of diastolic filling. These included diminished peak filling rate in four patients, prolonged time to peak filling rate in six, a decrease in rapid diastolic filling volume in three of five patients and an increase in atrial systolic filling volume in three.

In patients with familial amyloid polyneuropathy there was a significant correlation between the relative rapid diastolic filling volume and relative atrial systolic filling volume of the left ventricle (r = -0.97, p < 0.001). In addition, the indexes of diastolic filling were significantly related to ventricular wall thickness (Table 3), although no significant correlations were found between these indexes and heart rate, blood pressure, left ventricular chamber size or ejection fraction. Furthermore, the incidence and magnitude of abnormal time to peak filling rate and of enhanced contribution of atrial systole to ventricular filling increased significantly, and those of reduced rapid diastolic filling increased with advancing age and duration of illness (Tables 4 and 5).

Clinical course. All patients were followed up for a mean of 34.2 ± 7.9 months (range 28 to 47). None of them died of cardiovascular disease during the follow-up period. However, congestive heart failure with pulmonary edema occurred in two patients 10 and 15 months, respectively, after the radionuclide angiographic studies. They had shown marked reduction in rapid diastolic filling volume and enhanced atrial systolic filling volume with normal ejection fraction (Fig. 3). The duration of illness was longer (10 and 12 years, respectively) and the ventricular walls were markedly thickened in both patients.

Discussion

Abnormal diastolic function in familial amyloid polyneuropathy. The major findings of this study of patients with familial amyloid polyneuropathy are 1) abnormal left ventricular diastolic filling is common and can be identified before the development of clinically overt heart disease, ventricular wall thickening and abnormal systolic function; 2) the degree of diastolic filling abnormalities is not related to heart rate, blood pressure, left ventricular chamber size or left ventricular ejection fraction, but to left ventricular wall thickness.

| Table 4. Effect of Age on Left Ventricular Diastolic Filling in 17 Patients With Familial Amyloid Polyneuropathy |

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of patients</th>
<th>PFR (EDV/s)</th>
<th>TPFR (ms)</th>
<th>RDF (% of SV)</th>
<th>AS (% of SV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 yr</td>
<td>10</td>
<td>2.41 ± 0.27 (60%)</td>
<td>182 ± 22 (90%)</td>
<td>66.0 ± 9.0 (50%)</td>
<td>30.8 ± 10.5 (50%)</td>
</tr>
<tr>
<td>&gt;50 yr</td>
<td>7</td>
<td>2.36 ± 0.76 (71%)</td>
<td>225 ± 11 (100%)</td>
<td>36.0 ± 17.4 (100%)</td>
<td>65.8 ± 16.8 (100%)</td>
</tr>
</tbody>
</table>

The numbers in parentheses indicate the incidence of abnormalities in each value. Abbreviations as in Table 2.

Table 5. Effect of Duration of Illness on Left Ventricular Diastolic Filling in 17 Patients With Familial Amyloid Polyneuropathy

<table>
<thead>
<tr>
<th>Duration of Illness</th>
<th>No. of patients</th>
<th>PFR (EDV/s)</th>
<th>TPFR (ms)</th>
<th>RDF (% of SV)</th>
<th>AS (% of SV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 5 Years</td>
<td>6</td>
<td>2.56 ± 0.30 (67%)</td>
<td>189 ± 42 (33%)</td>
<td>75.0 ± 5.9 (90%)</td>
<td>19.3 ± 0.5 (0%)</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>11</td>
<td>2.49 ± 0.73 (63%)</td>
<td>212 ± 40 (91%)</td>
<td>48.3 ± 17.9 (90%)</td>
<td>51.7 ± 19.1 (0%)</td>
</tr>
</tbody>
</table>

The numbers in parentheses indicate the incidence of abnormalities. Abbreviations as in Table 2.
thicknes;
3) the incidence and magnitude of abnormalities in
indexes of diastolic filling increase with advancing age and
duration of illness; and 4) congestive heart failure occurs in
some patients with marked abnormalities of diastolic filling
despite normal systolic function.

Previous studies. A number of investigators (10–15) have
reported abnormalities in diastolic filling in patients with
amyloid heart disease in the advanced stage with the use of
catheter systems or M-mode and pulsed Doppler echocar-
diography. Some of them (11,12) noted an acceleration of
early rapid diastolic filling followed by a cessation of filling in
mid- to late diastole in patients who had a dip and plateau
waveform in the left ventricular diastolic pressure curve.
Additionally, a uniformly depressed filling was revealed in
the absence of this waveform in some patients (10,12). On
the other hand, Tyberg et al. (13) demonstrated that left
ventricular filling rate was constantly reduced throughout
diastole despite the presence of a dip and plateau pattern. St.
John Sutton et al. (15), using digitized M-mode echocardiog-
raphy, found abnormal diastolic filling manifested as a re-
duced peak filling rate of rapid diastolic filling in patients
with thickened ventricular walls and left ventricular systolic
dysfunction; some of these patients showed a dip and
plateau pattern.

These discrepancies of results among earlier studies
might be partly due to the investigators’ omission from their
assessment of the effect of aging and associated disease
processes on left ventricular diastolic filling. Recently,
pulsed Doppler echocardiographic studies (17–19) of cardiac
amyloidosis that included suitable age-matched control sub-
jects demonstrated different patterns of abnormal left ven-
tricular diastolic filling depending on whether the patient
manifested impaired relaxation or increased chamber stiff-
ness with resultant restriction of the left ventricle. Abnormal
relaxation with prolonged isovolumic relaxation time and
augmentation of atrial contraction were characteristic in
patients in whom echocardiographic evidence of cardiac
involvement was absent or mild (18,19). In contrast, ad-
vanced disease with restrictive cardiomyopathy and marked
ventricular wall thickening were associated with increased
transmural flow velocity of early rapid filling and decreased
flow velocity of atrial systole (17,19).

Cardiac involvement in familial amyloid polyneuropathy.
Familial amyloid polyneuropathy is a hereditary systemic
amyloidosis with polyneuropathy that shows long-term pro-
gression and variable degrees of myocardial amyloid infiltr-
atior. In contrast to other forms of amyloid heart disease such
as primary amyloidosis, amyloid deposition in this disorder
is generally remarkable in the subendocardium and valves
and less so in the myocardium. As we have previously
demonstrated (16,25), the incidence and magnitude of echo-
cardiographic abnormalities in patients with familial amyloid
polyneuropathy are mild to moderate compared with those
in primary amyloidosis. Thus, there are great differences in
the disease process, which may result from different types of
amyloid protein, and extremely different left ventricular
filling patterns would be expected in these two conditions.

Present study. The majority of our patients were consid-
ered to be in an early stage of the myocardial amyloid
infiltrative process (16,25) because most of them exhibited
neither marked ventricular wall thickening nor abnormal
systolic function and none had restrictive cardiomyopathy.
The abnormal diastolic filling pattern that was observed
included a decrease in the rate and volume, as well as a
prolongation, of rapid diastolic filling and an enhanced atrial
systolic filling. These findings corresponded well with those
of pulsed Doppler echocardiographic studies (18,19). Fur-
thermore, we confirmed the finding of prior echocardiog-
raphic studies (14,16,25) that abnormal diastolic filling can
be detected even in the absence of clinically overt heart
disease, ventricular wall thickening or abnormal systolic
function.

The mechanism that contributed to an abnormal diastolic
filling appeared to be increased ventricular wall thickness;
this might be attributed to intramyocardial amyloid infil-
tration with resultant loss of myocardial fibers as well as
fibrosis because indexes of abnormal diastolic filling were
significantly related to ventricular wall thickness, whereas
no significant correlations were found between any of these
indexes and other clinical findings. Another possible mech-
anism is myocardial ischemia resulting from amyloid depo-
sition in the intramural coronary arteries, as shown by
autopsy studies (26–29).

Clinical implications. Of the four indexes of left ven-
tricular diastolic filling obtained, the percent of rapid diastolic
filling volume showed a significant inverse correlation with
that of atrial systolic filling volume in patients with familial
amyloid polyneuropathy. Moreover, the time to peak filling
rate and the contribution of atrial contraction increased and
the contribution of rapid diastolic filling decreased with
advancing age and duration of illness, whereas the peak
filling rate was independent of these factors. Some of the
patients with greater wall thickness and longer duration of
disease showed a striking change in the left ventricular
time-activity curve, in which diastolic filling is mainly ac-
complished during atrial systole. This resulted in an appar-
etly normal peak filling rate but with marked abnormalities
in the other three indexes. Thus, reduced early diastolic
filling volume is compensated for by the augmentation of
atrial contraction with increasing age and duration of disease
in patients with familial amyloid polyneuropathy. These
findings indicate that age and duration of disease should be
carefully considered when diastolic filling is assessed by
radionuclide angiography in this disorder.

Some patients in this study developed congestive heart
failure. They had a longer duration of illness and thickened
ventricular walls and also showed marked abnormalities in
left ventricular diastolic filling with normal systolic function.
at the time of the radionuclide angiographic studies. As several investigators (30,31) have pointed out, decreased ventricular compliance and elevation of the pulmonary capillary wedge pressure often cause pulmonary congestion despite normal systolic function in various cardiac diseases. In addition, in patients with familial amyloid polyneuropathy, left ventricular systolic function has been reported to be preserved until late in the course of the disease (16). Thus, abnormal diastolic function is suggested as a possible mechanism for the occurrence of congestive heart failure in the present patients. To establish the precise mechanism more frequent serial studies are necessary.

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References
