Impaired Left Ventricular Diastolic Filling in Patients with Coronary Artery Disease: Assessment with Radionuclide Angiography

ROBERT O. BONOW, M.D., STEPHEN L. BACHARACH, PH.D., MICHAEL V. GREEN, M.S., KENNETH M. KENT, M.D., PH.D., DOUGLAS R. ROISING, M.D., LEWIS C. LIPSON, M.D., MARTIN B. LEON, M.D., AND STEPHEN E. EPSTEIN, M.D.

SUMMARY To assess left ventricular (LV) diastolic filling at rest in patients with coronary artery disease (CAD), we analyzed high-resolution time-activity curves (10–20 msec/frame) obtained from gated radionuclide angiograms in 231 patients. Peak LV filling rate (PFR), expressed in end-diastolic volumes per second (EDV/sec), was subnormal in CAD patients (1.8 ± 0.6 [±SD] vs normal mean of 3.3 ± 0.6, p < 0.001) and time to PFR (TPFR), measured from end-systole to PFR, was prolonged (171 ± 41 msec vs normal mean of 136 ± 23 msec, p < 0.001). These indexes were also abnormal in the 141 patients with normal resting LV ejection fraction (PFR = 2.1 ± 0.5 EDV/sec; TPFR = 175 ± 36 msec) and in 123 patients without Q waves on the ECG (PFR = 2.1 ± 0.5 EDV/sec; TPFR = 168 ± 38 msec). Abnormal LV filling at rest (PFR < 2.5 EDV/sec or TPFR > 180 msec) was found in 91% of all patients with CAD, 86% of patients with normal resting LV ejection fractions, 85% of patients without Q waves, and 82% of patients with normal resting LV ejection fraction, no resting regional wall motion abnormalities and no Q waves. Thus, LV diastolic filling, evaluated noninvasively by radionuclide angiography, is abnormal in a high percentage of patients with CAD at rest independent of LV systolic function or previous myocardial infarction.

MANY PATIENTS with coronary artery disease have normal global and regional left ventricular systolic function at rest and develop abnormalities only during stress.1–8 Many investigators have also observed abnormalities in diastolic distensibility of the left ventricle during stress-induced angina.9–10 Several mechanisms have been proposed, including incomplete or impaired relaxation,11–12 altered diastolic tone,6,13 and tension prolongation during recovery from hypoxia.14,15 Diminished ventricular compliance has also been reported at rest in patients with coronary artery disease who had no evidence of either acute ischemia or previous myocardial infarction.16,17 However, the prevalence of abnormalities in left ventricular diastolic filling at rest in patients without previous infarction is unknown.

We analyzed high-temporal-resolution time-activity curves from gated equilibrium technetium-99m radionuclide cineangiograms to evaluate left ventricular diastolic filling at rest in 231 patients with coronary artery disease. Abnormalities in left ventricular diastolic filling were correlated with regional and global left ventricular systolic function, previous myocardial infarction, and the anatomic extent of coronary artery disease.

Methods

Patient Selection

We performed studies in 231 patients, ages 26–69 years, with coronary artery disease, between January 1978 and January 1980. No patient had any other cardiac abnormality. All patients underwent left-heart catheterization with contrast left ventriculography and coronary arteriography within 2 days of radionuclide scintigraphy, except for 24 patients (10%) who were catheterized at other institutions before their referral to the National Heart, Lung, and Blood Institute. In this latter group of patients, a maximum of 4 months elapsed between coronary arteriography and radionuclide cineangiography. All patients had > 50% reduction in luminal diameter of at least one major coronary artery. Two hundred fourteen patients were referred because of a recent history of angina pectoris and 105 because of a history of myocardial infarction (including 93 who complained of angina). Five patients were asymptomatic and were referred because of positive treadmill exercise ECGs. Studies were performed in all 231 patients at least 48 hours after cessation of propranolol and at least 4 hours after cessation of nitroglycerin. Patients were excluded from this study if they required continuous propranolol therapy while in the hospital.

We also studied 45 normal volunteers, ages 21–63 years, without evidence of cardiovascular or pulmonary disease. Cardiac catheterization was not performed, but physical examination (including blood pressure), chest x-ray, electrocardiography, and echocardiography were normal in all subjects. Echocardiography was performed within 3 days of radionuclide cineangiography. Echocardiographic measurements of the left ventricular transverse dimension at end-

From the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
Address for correspondence: Robert O. Bonow, M.D., Building 10, Room 7B-15, National Institutes of Health, Bethesda, Maryland 20205.
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diastole were made at a level in the ventricular cavity just caudal to the tips of the mitral leaflets and at a point in the cardiac cycle corresponding to the peak of the R wave.

Electrocardiography

Twelve-lead ECGs were performed in all patients. ECGs were considered diagnostic of previous myocardial infarction if Q waves were 40 msec or longer. One hundred eight patients had diagnostic Q waves.

Gated Blood Pool Cardiac Scintigraphy

Radionuclide cineangiography was performed in the supine position. Before imaging, red blood cells were labeled in vivo with 15–20 mCi of technetium-99m. Imaging was accomplished using a conventional Anger camera equipped with a high-sensitivity parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. A computer-based procedure gated to the ECG, previously described, was used to collect and organize data into a series of images or frames (framing rate up to 100 frames/sec) spanning the average cardiac cycle, which were displayed in a rapid-sequence, endless-loop movie format. After left ventricular and background regions of interest were labeled, high-temporal-resolution (10–20 msec/frame) time-activity curves were generated by summing the radioactivity in the ventricle during many beats. Cardiac cycles that fell outside a physician-selected range of acceptable cardiac cycle lengths were automatically excluded from analysis to prevent distortion of the time-activity curve by extrasystoles, postextrasystolic cycles, and wide spontaneous variations in sinus cycle length. Exclusion of cardiac cycles of extremely short or long cycle length preserves the portion of the time-activity curve describing left ventricular diastolic events. Blood radioactivity is proportional to blood volume, so after background correction, the time-activity curve represents a measure of relative left ventricular volume changes with time.

After images and time-activity curves were obtained at rest, imaging was repeated in each patient during supine bicycle exercise, except for eight patients who had developed angina at rest after cessation of propranolol therapy and were considered too symptomatic to perform exercise testing. At the time of the radionuclide study, however, none of these eight patients complained of chest pain at rest. In the remaining patients, exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased in a stepwise fashion by 25 W at 2-minute intervals until the development of angina or limiting fatigue or dyspnea. In patients who developed angina, exercise continued until angina reached at least the severity typically causing the patient to stop exercising. Heart rate and blood pressure (by cuff sphygmomanometry) were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only that portion of the data series that occurred during maximal exercise, encompassing the final 1.5–2 minutes of exercise, was selected for analysis.

After completion of imaging, left ventricular ejection fraction at rest and during exercise was determined by computer analysis of the time-activity curves as previously described. Regional left ventricular function at rest and during exercise was determined subjectively by visual inspection of the movies and by inspection of the count-based functional stroke volume map (or “difference image”), constructed by computer subtraction of the end-systolic image from the end-diastolic image. A study was considered abnormal if regional wall motion abnormalities were observed during exercise. Many patients had regional abnormalities at rest as well (see Results section). In the first 140 consecutive patients, regional wall motion was interpreted by three independent observers who were unaware of the results of coronary arteriography. The three observers were in unanimous agreement about regional wall motion during exercise in 132 of 140 studies (94%). In the remaining patients, regional left ventricular function was interpreted by a single observer.

Peak left ventricular ejection rate and filling rate were then computed from the time-activity curve (10–20 msec/point). A computer algorithm chose a short span of points (always the larger of either five points or 100 msec) on the time-activity curve coinciding with the systolic ejection or rapid diastolic filling. The span of points was then increased from this minimum until an inflection point of the proper sign (negative-sloping second derivative for determination of filling rate) was achieved with no local maxima or minima. For resting studies, this procedure usually resulted in the inclusion of 10 or fewer points. This portion of the time-activity curve was then fitted to a third-degree polynomial function using a least-squares technique (Fig. 1). The fit was weighted according to the statistical fluctuations expected for each point. Errors in the coefficients of the polynomial, combined with the assumed Poisson errors in the end-diastolic counts and background counts, were used to determine the errors in peak filling rate. The time of occurrence of the peak filling (or ejection) rate was determined by computing the resultant polynomial equation for the time at which the second derivative of the polynomial was equal to zero, using the R wave (peak slope of the R-to-S transition) as the onset reference for time. The value of the peak filling (or ejection) rate was then determined by computing the first derivative of the polynomial equation at time of peak filling (or ejection). Both peak ejection rate and peak filling rate were computed in left ventricular counts per second; these values were normalized for the number of left ventricular counts at end-diastole. Hence, both ejection and filling rates are subsequently expressed as end-diastolic counts (volume) per second (EDV/sec). This does not imply knowledge of actual left ventricular end-diastolic volume.

Several variables were used to describe global left ventricular systolic function. These were left ventric-
Variables used to express left ventricular diastolic filling were peak left ventricular filling rate and the time to peak filling rate (measured from end-systole to the time of peak left ventricular filling rate).22

Statistical Methods

Data were analyzed by the t test, using unpaired data, by the chi-square method, and by linear regression analysis as appropriate. The data from the normal volunteers were analyzed to derive confidence limits for normal. These data were first analyzed by the analysis of variance test of Shapiro and Wilk24 to establish whether they conformed to a normal distribution. For normal distributions, confidence limits were generated from the mean and standard deviation of the data. For data that did not conform to a normal distribution, confidence limits were derived by the univariate statistical analysis system (S.A.S., Inc.).

Results

Normal Volunteers

Systolic Function

Left ventricular ejection fraction at rest for the 45 normal volunteers ranged from 45–72% (mean 55 ± 6% [± sd]). During maximum exercise, ejection fraction increased in all subjects, to 56–90% (mean 68 ± 7%). No individual had regional abnormalities of wall motion at rest or during exercise. The values of other variables of left ventricular systolic function (peak left ventricular ejection rate, time to peak ejection rate, and time to end-systole) in these subjects are listed in table 1.

Diastolic Filling

Peak left ventricular filling rate in the normal volunteers (table 1, fig. 2) ranged from 2.5–5.0 EDV/sec (mean 3.3 ± 0.6 EDV/sec). These data did not conform to a normal distribution (p < 0.01 by the

Table 1. Variables Describing Left Ventricular Systolic Function and Diastolic Filling

<table>
<thead>
<tr>
<th>Variables Describing Left Ventricular Systolic Function and Diastolic Filling</th>
<th>Patients with CAD and subnormal rest LV ejection fraction (n = 90)</th>
<th>Patients with CAD and normal rest LV ejection fraction (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV systolic function at rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>55 ± 6</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>Peak LV ejection rate (EDV/sec)</td>
<td>2.7 ± 0.5</td>
<td>1.9 ± 0.5*</td>
</tr>
<tr>
<td>Time to peak ejection rate (msec)</td>
<td>182 ± 44</td>
<td>196 ± 28</td>
</tr>
<tr>
<td>Time to end-systole (msec)</td>
<td>344 ± 33</td>
<td>342 ± 28</td>
</tr>
<tr>
<td>LV diastolic filling at rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LV filling rate (EDV/sec)</td>
<td>3.3 ± 0.6</td>
<td>1.3 ± 0.4*</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>136 ± 22</td>
<td>170 ± 48*</td>
</tr>
</tbody>
</table>

Data are mean ± sd.

*p < 0.001 vs normal subjects.

Abbreviations: CAD = coronary artery disease; LV = left ventricular; EDV = end-diastolic volumes.
Shapiro-Wilk method24). The 95% confidence limits for peak filling rate were 2.6 and 4.7 EDV/sec; the 99% confidence limits were 2.5 and 5.0 EDV/sec. Time to peak filling rate (table 1, fig. 3) ranged from 90–180 msec (mean 136 ± 22 msec). These data did conform to a normal distribution (p = 0.572). The 95% confidence limits for time to peak filling rate were 92 and 179 msec; the 99% confidence limits were 90 and 181 msec. Peak left ventricular filling rate in the normal volunteers correlated significantly with left ventricular ejection fraction (fig. 4) but with a low correlation coefficient (r = 0.51, p < 0.001). Peak filling rate did not correlate with the time to peak filling rate (r = 0.26) (fig. 5). Neither peak left ventricular filling rate nor the time to peak filling rate correlated with heart rate (r = 0.08; r = −0.32), with age (r = 0.04; r = 0.34), or with echocardiographic left ventricular
end-diastolic transverse dimension \( (r = 0.08; \ r = 0.17) \).

**Patients with Coronary Artery Disease**

**Systolic Function**

Ninety of the 231 patients with coronary artery disease had subnormal left ventricular ejection fractions at rest (less than 45\%). Patients with subnormal resting ejection fractions also had diminished peak left ventricular ejection rates (mean 1.9 \pm 0.5 EDV/sec vs normal 2.8 \pm 0.5 EDV/sec, \( p < 0.001 \)), whereas this variable was normal in the 141 patients with normal resting ejection fraction (table 1). Regional wall motion abnormalities at rest were detected in 86 of the 90 patients (96\%) with subnormal resting ejection fractions, and electrocardiographic Q waves were present in 77 of the 90 patients (86\%). In contrast, of 141 patients with normal resting left ventricular ejection fractions (45\% or greater), resting wall motion abnormalities were observed in only 25 patients (18\%), and Q waves were present in only 31 patients (22\%). The differences in the prevalence of wall motion abnormalities and Q waves between patients with subnormal and those with normal resting ejection fraction were highly significant (\( p < 0.001 \)).

**Diastolic Filling**

Peak left ventricular filling rate in all 231 patients with coronary artery disease ranged from 0.5–4.1 EDV/sec (mean 1.8 \pm 0.6 EDV/sec) and was significantly lower (\( p < 0.001 \)) than that in the 45 normal volunteers (fig. 2). Peak filling rate correlated significantly with ejection fraction (\( r = 0.73, \ p < 0.001 \)) (fig. 4), but did not correlate with heart rate. Only 35 patients (15\%) had normal peak filling rates of 2.5 EDV/sec or greater. The time to peak filling rate ranged from 90–340 msec (fig. 3) and was prolonged compared with that in the normal volunteers (171 \pm 41 msec vs normal 133 \pm 22 msec, \( p < 0.001 \)). The time to peak filling rate exceeded the 99\% confidence limit for normal (180 msec) in 81 patients (35\%). When analysis of the two diastolic filling variables was combined, 211 patients (91\%) were outside the 99\% confidence limits (table 2). Resting heart rates were not different between patients with coronary artery disease (75 \pm 13 beats/min) and the normal volunteers (78 \pm 15 beats/min). In the patients with coronary artery disease, neither peak left ventricular filling rate nor the time to peak filling rate correlated with left ventricular end-diastolic pressure (\( r = -0.12 \) and \( r = -0.14 \), respectively).

Because the majority of patients with subnormal resting ejection fractions had evidence of previous infarction, and because myocardial fibrosis reduces left ventricular diastolic distensibility,16, 17, 25, 26 analysis of left ventricular diastolic filling was repeated after subgrouping patients with coronary artery disease on the basis of resting left ventricular ejection fraction (table 1, figs. 2–4).

**Patients with Subnormal Resting Ejection Fraction.** The 90 patients with subnormal ejection fraction at rest had a mean peak left ventricular filling rate of 1.3 \pm 0.4 EDV/sec (table 1, fig. 2), significantly lower than the normal volunteers (\( p < 0.001 \)). The highest peak filling rate in this group, observed in only one patient, was 2.5 EDV/sec, the lower limit of normal. Similarly, time to peak filling rate was higher than that of the normal volunteers (table 2, fig. 3). Thirty-two patients (36\%) had a time to peak filling rate greater than 180 msec, the upper limit of normal.

**Patients with Normal Resting Ejection Fraction.** Peak left ventricular filling rates in the 141 patients with normal left ventricular ejection fractions were also significantly lower (\( p < 0.001 \)) than those in the normal volunteers (table 1). Thirty-four of these patients (24\%) had peak filling rates of 2.5 EDV/sec or greater (fig. 2) and were considered within the normal range. However, when these 34 patients with both normal ejection fraction and normal filling rate were compared with normal volunteers with the same ejection fraction (fig. 4), peak filling rates were substantially lower in the coronary disease patients than in the normal subjects. Moreover, combined analysis of both peak filling rate and time to peak filling rate further segregated the normal volunteers and the coronary disease patients with normal ejection fractions (fig. 5). Because these two variables were not directly related in these patients (\( r = -0.16 \)), they were used as independent measures of left ventricular diastolic filling. Only 20 patients (14\%) fell within the normal range defined by the 99\% confidence limits: a peak left ventricular filling rate of 2.5 EDV/sec or greater and a time to peak filling rate of 180 msec or less (table 2, fig. 5).

<p>| Table 2. Prevalence of Left Ventricular Diastolic Filling Abnormalities in Patients with Coronary Artery Disease* |
|-------------------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th>All patients with CAD (n = 231)</th>
<th>Patients with negative ECG (no Q wave) (n = 123)</th>
<th>Patients with normal rest LV EFR (n = 141)</th>
<th>Patients with normal rest LV EFR and negative ECG (n = 110)</th>
<th>Patients with normal rest LV EFR, normal wall motion and negative ECG (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LV filling rate (rest)</td>
<td>85%</td>
<td>76%</td>
<td>76%</td>
<td>73%</td>
</tr>
<tr>
<td>Combined peak LV filling rate and time to peak filling rate (rest)</td>
<td>91%</td>
<td>85%</td>
<td>86%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Abnormal values based on 99\% confidence limits for normal data.
Abbreviations: CAD = coronary artery disease; LV = left ventricular; LV EFR = LV ejection fraction.
Figure 6. (A) Unretouched time-activity curves from a normal subject (top) and from a patient with one-vessel coronary artery disease and normal resting ECG (bottom). (B) Schematic representations of the two curves. Heart rate (70 beats/min), ejection fraction (56%), and ejection rate (3.2 EDV/sec) are identical. Time to peak ejection rate and time to end-systole (TES) are similar (197 vs 193 msec and 340 vs 320 msec). In the patient with coronary artery disease, however, peak filling is diminished compared to the normal subject (1.6 vs 3.3 EDV/sec) and time to peak filling rate (TPFR) is prolonged (207 vs 128 msec).

Figure 7. Peak left ventricular (LV) filling rates in patients with coronary artery disease and normal LV ejection fraction (LVEF), subdivided into patients with stenosis of one, two or three major coronary arteries or patients with stenosis of the left main coronary artery. The 12 patients with left main coronary artery disease also had stenosis of at least one other major coronary artery. Abbreviations and symbols are as in figure 2.

fig. 5). Figure 6 illustrates differences between normal and abnormal left ventricular diastolic filling in two patients with identical, normal ejection fractions, one with normal coronary arteries and one with coronary artery disease.

Exclusion of patients with previous myocardial infarction. Patients with normal left ventricular ejection fraction at rest were subdivided to further exclude patients with previous myocardial infarction. Of 110 patients with normal left ventricular ejection fraction at rest plus ECGs without Q waves, 91 patients (83%) had either subnormal peak left ventricular diastolic filling rates, prolonged times to peak filling rate, or both (table 2). Exclusion of another 11 patients with regional wall motion abnormalities at rest (possibly indicating myocardial scar) resulted in 99 patients with normal resting ejection fraction, normal resting regional wall motion, and ECGs without Q waves; 81 of these patients (82%) had either subnormal peak left ventricular filling rates, prolonged times to peak filling rate or both (table 2). Fifty-seven of these 99 patients were asymptomatic or mildly symptomatic and have been treated with medical therapy, while the other 42 patients had moderate-to-severe angina and underwent coronary artery bypass surgery. Peak left ventricular filling rates were identical in these two subgroups (2.2 ± 0.5 EDV/sec), as were times to peak filling rates (176 ± 35 msec in the group with mild symptoms, 173 ± 37 msec in the group with more severe symptoms).

Patients without evidence of previous myocardial infarction by resting radionuclide angiography and by electrocardiography had echocardiographic left ventricular end-diastolic dimensions (50 ± 5 mm) that were not different than those observed in the normal individuals (48 ± 6 mm). Radionuclide peak left ventricular diastolic filling in these patients did not correlate with echocardiographic left ventricular diastolic dimension (r = 0.14).

Influence of number of diseased coronary arteries. Patients with normal left ventricular ejection fraction were further subdivided on the basis of the anatomic extent of coronary artery disease. Patients with stenosis of one, two or three major coronary arteries, or patients with stenosis of the left main coronary artery, did not differ with respect to peak left ventricular filling rates (fig. 7) or time to peak filling rate (fig. 8). Peak filling rates and times to peak filling rate in each subgroup were significantly different from normal (p < 0.001). The prevalence of abnormalities of left ventricular diastolic filling did not appreciably diminish, as successive subgrouping of these patients on the basis of left ventricular function and previous myocardial infarction eliminated subjects with more severe manifestations of coronary artery disease (table 3).
tion fraction during exercise. One hundred six of the 107 patients had regional wall motion abnormalities during exercise (fig. 9). The remaining 34 patients had an increase in ejection fraction with exercise, of whom 28 (82%) fulfilled our definition of a normal exercise response (an increase in ejection fraction during exercise to 55% or greater, or an increase in 5% compared to a normal resting value). Seven of the 34 patients had regional wall motion abnormalities at rest and an additional 12 patients developed new regional wall motion during exercise. The remaining 15 patients had normal wall motion and ejection fraction at rest and during exercise. Patients with a decrease in ejection fraction during exercise did not differ from patients whose ejection fraction increased during exercise, with respect to either resting peak filling rate (2.11 ± 0.49

\[ \text{vs} \ 2.04 ± 0.48 \ \text{EDV/sec} \] (fig. 9) or time to peak filling rate (173 ± 35 vs 180 ± 39 msec). The resting diastolic filling variables in the 15 patients with normal regional and global systolic function during exercise (peak filling rate at rest, 2.23 ± 0.39 EDV/sec and time to peak filling rate at rest, 189 ± 47 msec) also did not differ from those of the other patients.

![Figure 8](https://example.com/figure8.png)

**Figure 8.** Time to peak left ventricular (LV) filling rate in patients with coronary artery disease, subdivided as in figure 7. Abbreviations and symbols are as in figure 2. The dashed line at 180 msec is considered the upper limit of normal.

![Figure 9](https://example.com/figure9.png)

**Figure 9.** Peak left ventricular (LV) diastolic filling rates in the 141 patients with normal resting LV ejection fraction (LVEF), subdivided into the 107 patients with either no change or a fall in ejection fraction during exercise (left) and the 34 patients with an increase in ejection fraction during exercise (right column). The three symbols used refer to regional wall motion at rest and during exercise (Ex) as shown in the legend. Twelve of 15 patients with normal regional and global systolic function during exercise had subnormal peak filling rates at rest.

**Table 3. Prevalence of Left Ventricular Diastolic Filling Abnormalities in Patients with Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Anatomic extent of coronary artery disease</th>
<th>Patients with negative ECG (no Q waves)</th>
<th>Patients with normal rest LVEF</th>
<th>Patients with normal rest LVEF and negative ECG</th>
<th>Patients with normal rest LVEF, normal wall motion and negative ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel disease</td>
<td>78% (37)</td>
<td>82% (44)</td>
<td>78% (36)</td>
<td>79% (33)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>85% (34)</td>
<td>88% (41)</td>
<td>84% (31)</td>
<td>83% (29)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>92% (38)</td>
<td>91% (44)</td>
<td>91% (32)</td>
<td>85% (27)</td>
</tr>
<tr>
<td>Left main disease</td>
<td>79% (14)</td>
<td>75% (12)</td>
<td>73% (11)</td>
<td>70% (10)</td>
</tr>
<tr>
<td>Total</td>
<td>85% (123)</td>
<td>86% (141)</td>
<td>83% (110)</td>
<td>82% (99)</td>
</tr>
</tbody>
</table>

*Peak left ventricular filling rate and time to peak filling rate (determined at rest), based on 99% confidence limits for normal data.

Abbreviations: LVEF = left ventricular ejection fraction.
sis, with alterations in the distensibility characteristics of the left ventricle.\textsuperscript{16, 17, 25, 28, 29} Abnormalities in isovolumic relaxation and diastolic distensibility have also been observed in patients during angina induced by exercise and by rapid atrial pacing.\textsuperscript{4-10} Several mechanisms of angina-induced alterations in left ventricular diastolic pressure-volume relations have been hypothesized, including incomplete or impaired relaxation,\textsuperscript{4-9, 11, 12} altered diastolic tone,\textsuperscript{6, 13} or tension prolongation during recovery from hypoxia.\textsuperscript{14, 15}

In addition, previous studies using contrast angiography or M-mode echocardiography have suggested that diminished left ventricular compliance and regional relaxation abnormalities may occur at rest in patients with coronary artery disease in the absence of either acute ischemia or previous myocardial infarction.\textsuperscript{16, 17, 27} However, most patients in each of these studies had regional wall motion abnormalities by contrast angiography compatible with prior infarction. Thus, the prevalence and magnitude of abnormalities in left ventricular diastolic filling in a large number of patients with coronary artery disease without previous myocardial infarction, and in whom regional and global left ventricular systolic function is normal, has not been reported.

The results of the current study indicate that abnormal indexes of left ventricular diastolic filling, determined noninvasively by radionuclide angiography, are present under resting conditions in 91% of patients with coronary artery disease. Among 108 patients with electrocardiographic evidence of previous myocardial infarction, 103 (95%) had abnormal diastolic filling, manifested by subnormal peak left ventricular filling rates or prolonged times to peak filling rates, presumably reflecting, at least in part, alterations in left ventricular distensibility produced by myocardial fibrosis. Abnormal indexes of resting left ventricular diastolic filling, however, were also present in 82% of patients in whom there was no evidence of previous infarction by either ECG or radionuclide angiogram (table 2) and in whom resting left ventricular ejection fraction, and every other quantitative measurement of resting left ventricular systolic function, was normal (table 2, figs. 4, 5). Although the abnormalities of left ventricular diastolic filling are common in patients with coronary artery disease, they are not specific for coronary artery disease and may appear in patients with valvular heart disease and hypertrophic cardiomyopathy.\textsuperscript{28, 51}

The differences between the diastolic filling characteristics of patients with coronary artery disease without prior infarction and those of normal volunteers could not be explained on the basis of any differences in age, in heart rate or in left ventricular end-diastolic size (as determined by echocardiography) between the two groups. The extent of the diastolic filling abnormalities in patients with normal systolic function and without myocardial infarction did not correlate with the level of left ventricular end-diastolic pressure, with the anatomic severity of coronary artery disease (table 3, figs. 7, 8), or with the severity of angina pectoris (as determined by whether patients felt their symptoms were sufficiently controlled to continue medical therapy, or whether symptom severity was such that they opted for surgical therapy).

The cause of abnormal left ventricular diastolic filling, even in the absence of abnormal systolic function or evidence of active ischemia, is therefore unexplained. Periods of myocardial ischemia may produce irreversible changes in left ventricular relaxation and filling without altering systolic function. Also, clinically inapparent ischemia, sufficiently mild so as not to cause angina or affect contractile function, may lead to reversible abnormalities of diastolic filling. Alternatively, abnormalities of diastolic relaxation and filling may persist for longer periods following episodes of ischemia than do abnormalities of systolic contraction. If such a disparity in the persistence of ischemia-induced abnormalities between systolic and diastolic function exists, then in patients with no previous infarction and normal left ventricular systolic function at rest, abnormal diastolic filling may represent the residual manifestation of ischemic episodes experienced by the patients hours earlier.

In the absence of quantitative left ventricular volume measurements and analysis of simultaneous diastolic pressure-volume relations, the abnormalities in left ventricular diastolic filling that we have presented cannot be attributed directly to abnormalities in left ventricular compliance. Moreover, the mechanism responsible for prolonging the time to peak filling rate cannot be determined without also determining the precise instant of mitral valve opening, which cannot be accomplished with certainty by analyzing intraventricular volume changes alone. Thus, a prolonged time to peak filling rate might involve prolongation of isovolumic relaxation, prolongation of rapid diastolic filling, or prolongation of both of these phases. In addition, in the absence of quantitative left ventricular volume estimation, the peak left ventricular filling rates (which are a measure of rapid diastolic filling) cannot be expressed as absolute volume changes, but only as changes relative to end-diastolic volume.

Despite these methodologic limitations, our data indicate that abnormalities in left ventricular diastolic filling can be detected using noninvasive radionuclide techniques and that these diastolic filling abnormalities are independent of left ventricular systolic function (table 1, figs. 2, 3), as previously described.\textsuperscript{15, 17, 82} Our data also indicate that abnormalities in left ventricular diastolic filling at rest are common in patients with coronary artery disease, even in subgroups without previous myocardial infarction and with normal regional and global left ventricular systolic function.

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