Left Ventricular Diastolic Performance At Rest and During Exercise in Patients With Coronary Artery Disease

Assessment with First-pass Radionuclide Angiography

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SUMMARY We used first-pass radionuclide angiography to assess filling fraction during the first third of diastole, peak filling rate and peak filling rate during the first third of diastole as indexes of left ventricular diastolic performance at rest and after upright bicycle exercise in 32 normal patients and 68 patients with coronary artery disease. The mean filling fraction was unchanged from rest to exercise in normal patients (47 ± 15% vs 46 ± 13%; NS). Even in 49 coronary patients with normal (≥50%) ejection fraction at rest, filling fraction was less than that in normal patients at rest (35 ± 11% vs 47 ± 15%, p < 0.001). Despite similar resting heart rates, patients with coronary disease had lower (p < 0.001) peak filling rate and peak filling rate during the first third of diastole than normal patients. With exercise, filling fraction decreased (p < 0.001) from the resting value in coronary patients. These data suggest that (1) indexes of diastolic performance can be noninvasively assessed at rest and during exercise using first-pass radionuclide angiography, (2) abnormalities in early diastolic performance are often present at rest in patients with coronary artery disease despite normal systolic performance, and (3) exercise-induced ischemia results in increased early diastolic dysfunction in patients with coronary disease.

ABNORMALITIES in left ventricular diastolic performance are common in patients with coronary artery disease.1,2 Myocardial relaxation during early diastole is an active, energy-dependent process and previous investigations have shown that hypoxia may impair the rate of myocardial relaxation.3 Abnormalities in diastolic performance during ischemia may occur in the absence of impaired systolic performance.4,6 The noninvasive assessment of left ventricular diastolic performance in the patient with coronary artery disease either at rest or during physiologic stress such as exercise has been difficult by traditional techniques.

Use of first-pass angiocardiography and gated cardiac blood pool imaging have shown that the response of left ventricular systolic performance to exercise is a sensitive marker of left ventricular ischemia.5,8 Few data are available, however, concerning the application of radionuclide techniques to the evaluation of left ventricular diastolic performance, at rest or during exercise-induced ischemia, in patients with coronary artery disease.

The purposes of the present investigation were (1) to define left ventricular peak filling rate, peak filling rate during the first third of diastole and filling fraction during the first third of diastole as indexes of left ventricular diastolic performance at rest in normal subjects and in patients with coronary artery disease using first-pass radionuclide techniques; (2) to determine the effects of exercise on these indexes of diastolic performance and compare the response in normal subjects to that of patients with coronary artery disease during exercise-induced ischemia; and (3) to investigate the comparative effects of exercise on systolic and diastolic performance in normal subjects and patients with coronary artery disease.

Materials and Methods

Patient Population

The study group consisted of 68 patients (58 males and 10 females) with documented coronary artery disease. Clinical characteristics are summarized in table 1. Fifty-six patients had significant angiographically documented stenosis (>50% reduction in luminal diameter) of at least one major coronary artery and 12 patients had electrocardiographic evidence (ΔQ waves ≥0.04 second in duration) of previous transmural...
myocardial infarction. Twenty-six patients had had an inferior infarction and eight an anterior infarction; three patients had evidence of both inferior and anterior infarction. Twelve patients had electrocardiographic evidence of left ventricular hypertrophy and five patients were taking digoxin for congestive heart failure. Twenty-eight patients were receiving propranolol for angina pectoris (mean dosage 110±68 mg/day; range 40–240 mg/day). Patients with significant valvular heart disease or New York Heart Association class IV angina were excluded from the study.

Thirty-two normal patients and subjects without clinical or electrocardiographic evidence of cardiac disease served to define normal values (table 1). Twenty-four normal subjects were healthy volunteers and eight patients had normal cardiac catheterization and coronary angiography during evaluation for atypical chest pain.

### Radionuclide Technique

First-pass radionuclide angiocardiography was performed using a computerized multicrystal scintillation camera (Baird-Atomic System 77). All studies were performed in the anterior position while patients were seated on a bicycle ergometer (Tunturi Corp.). An indwelling polyethylene catheter was placed in an antecubital vein for injection of radionuclide. A 10-lead electrocardiographic lead system was used to monitor heart rate and ST-segment response. While patients were seated at rest, 15–20 mCi of technetium-99m pertechnetate dissolved in less than 1 ml of saline were injected and flushed with saline. Data were accumulated at 20-msec intervals as the radionuclide bolus entered the central circulation. The entire study was completed within 15–30 seconds. After the rest study, all patients performed upright bicycle exercise with 100-kilopond-meter increments in work load every 3 minutes. Electrocardiographic recordings and blood pressure measurements were obtained every 3 minutes. All patients were exercised to symptom-limiting fatigue or electrocardiographic evidence of ischemia (defined as horizontal or downsloping ST-segment depression ≥1 mm and lasting ≥0.06 second). The exercise data are summarized in table 1. At completion of maximal exercise, all patients were instructed to stop pedaling abruptly, and a repeat first-pass radionuclide angiogram was acquired within 5–10 seconds. Heart rate obtained during the exercise first-pass radionuclide angiogram did not decrease by more than 5 beats/min from the peak exercise heart rate. All patients remained in normal sinus rhythm.

Left ventricular ejection fraction was calculated using the radionuclide technique of Marshall et al. Ejection fraction determined by this radionuclide technique is reproducible, has a low intrinsic variability and correlates closely with angiographic estimates of left ventricular ejection fraction. In this laboratory, left ventricular ejection fraction determined by first-pass radionuclide technique correlated well with angiographic estimates in 20 patients with coronary artery disease (r = 0.90).

The data output by the camera computer was further analyzed using a MUMPS* data management system. The tabular record from the scintillation camera is used as the source document for manual entry of frame-by-frame counts. Provision has been made for analysis of several cardiac cycles. A representative cycle is analyzed as if it were a single-beat record. After completion of data entry and operator verification of accuracy, analysis proceeds in three phases: time series smoothing, variable extraction and statistical summarization.

Because processing algorithms in the second phase must deal with the derivative of the time series of counts, and the input data frequently contain irregu-

### Table 1. Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Normal patients (n = 32)</th>
<th>Coronary artery disease (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 ± 10</td>
<td>56 ± 10*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>8 AWMI, 26 IWMII, 3 AWMI + IWMII</td>
</tr>
<tr>
<td>Propranolol (mg/day)</td>
<td>0</td>
<td>110 ± 68</td>
</tr>
<tr>
<td>Digoxin (number of patients)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>75 ± 16</td>
<td>75 ± 17*</td>
</tr>
<tr>
<td>Peak exercise heart rate (beats/min)</td>
<td>148 ± 23</td>
<td>130 ± 27*</td>
</tr>
<tr>
<td>Double product</td>
<td>23,560 ± 3,866</td>
<td>20,700 ± 6,008†</td>
</tr>
<tr>
<td>Positive stress ECG</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Abnormal EF exercise response</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

*p < 0.001 vs normal patients.

†p < 0.05 vs normal patients.

Abbreviations: AWMI = anterior wall myocardial infarction; IWMII = inferior wall myocardial infarction; EF = ejection fraction; double product = heart rate (beats/min) × systolic blood pressure (mm Hg).

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larities or “noise” not attributable to a physiologic or anatomic phenomenon, the first processing phase consists of a five-point parabolic smoothing algorithm implemented by a digital filter. The frequency response of the smoothing filter is oscillatory, reaching 70% of its DC value at approximately 12 Hz, and its first zero (an accepted measure of band width) at 19.8 Hz. End effects of the filter are avoided by entry of at least three points before the first diastolic frame and three points after the final diastolic frame. This smoothing process tends to minimize large, artificial excursions in the derivative due to the “noise” in the input data.

The time series is then analyzed on a beat-to-beat basis, extracting variables of clinical and research interest, e.g., end-diastolic and end-systolic and stroke counts, ejection fraction, filling fraction, peak filling rate during diastole and rates for segments of diastole. End-diastolic and end-systolic volumes were defined as maximal and minimal counts, respectively, obtained from the left ventricular region of interest. Variables were expressed as raw data or automatically normalized to end-diastolic counts. For computation of peak filling rate during the first third of diastole, the time interval from end-systole to end-diastole was divided into thirds, and the maximal value of the derivative within each segment was determined (fig. 1). A tabular summary of beat-by-beat data was printed from the original and calculated data.

All data were processed using the MUMPS language on a Digital Equipment Corporation PDP-11/60 computer controlled by an Interpretive Data Services operating system (IDSM-11).

The radionuclide-determined indexes of left ventricular diastolic performance were compared with changes in left ventricular dimension derived from manually digitized M-mode echocardiograms in 17 patients without coronary artery disease or left ventricular dyssynergy. All patients were in sinus rhythm and heart rates between radionuclide and echocardiographic studies differed by 10 beats/min or less. The echocardiographically determined peak rate of change of left ventricular diastolic dimension was normalized to end-diastolic dimension, and peak filling rate was normalized to end-diastolic counts. The peak rate of change of diastolic dimension and peak filling rate correlated significantly (p < 0.001, r = 0.65). Similarly, the change in diastolic dimension from end-systolic dimension to diastolic dimension during the first third of diastole, when divided by diastolic dimension during the first third of diastole, correlated closely with filling fraction (r = 0.78, p < 0.001).

The variability of these diastolic indexes assessed by the radionuclide technique was determined in a separate group of 20 patients. Two first-pass radionuclide angiograms 15–30 minutes apart were performed with the patients at rest seated on a bicycle ergometer. All patients remained clinically stable between studies. The results of these two determinations (table 2) were used to define significant (p < 0.05) increase or decrease in diastolic indexes: ejection fraction, > 5%; filling fraction, > 8%; first third peak filling rate, > 0.84 sec⁻¹; and peak filling rate, > 0.84 sec⁻¹.

**Statistical Analysis**

Data are expressed as the mean ± SD. One-way analysis of variance was used to analyze differences between multiple groups. If the F statistic was significant (p < 0.05), t tests were used to determine where the difference occurred. Univariate comparisons between two groups were made using the t test. Data within individual groups were compared with the paired t test. Comparison of frequency distributions between groups was performed by Fisher’s exact chi-square test.

Predictive accuracy was defined as the number of true-positive and true-negative responses divided by the total population.

**Results**

**Normal Patients**

**Ejection Fraction**

Mean left ventricular ejection fraction in the 32 normal patients was 67 ± 9% (range 50–88%) and increased during exercise to 82 ± 8% (range 62–95%, p < 0.001). All normal patients had an absolute increase in ejection fraction of at least 6% during exercise (mean increase 15 ± 7%, range 6–31%) (fig. 2).

**Diastolic Indexes**

At rest, the mean filling fraction in normal patients was 47 ± 15% (range 21–84%) and did not change.
TABLE 2. Variability of Diastolic Indexes Assessed By First-pass Radionuclide Angiography in 20 Patients

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>p</th>
<th>r</th>
<th>Mean difference (± si)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>63 ± 15%</td>
<td>NS</td>
<td>0.97</td>
<td>0 ± 4%</td>
<td>(0-5%)</td>
</tr>
<tr>
<td>Filling fraction</td>
<td>40 ± 15%</td>
<td>NS</td>
<td>0.97</td>
<td>3.11 ± 2.21%</td>
<td>(0-8%)</td>
</tr>
<tr>
<td>First third peak filling rate</td>
<td>2.38 ± 0.98 sec⁻¹</td>
<td>NS</td>
<td>0.90</td>
<td>0.46 ± 0.25 sec⁻¹</td>
<td>(0.04-0.84 sec⁻¹)</td>
</tr>
<tr>
<td>Peak filling rate</td>
<td>2.98 ± 1.2 sec⁻¹</td>
<td>NS</td>
<td>0.89</td>
<td>0.50 ± 0.25 sec⁻¹</td>
<td>(0.04-0.84 sec⁻¹)</td>
</tr>
</tbody>
</table>

significantly during exercise (mean 46 ± 13%, range 26–68%) (fig. 2). The mean change in filling fraction from rest to exercise was −0.6 ± 10% (range −20 to 20%). Eight patients had an increase in filling fraction in response to exercise, and 18 patients had no change in filling fraction during exercise. Six normal subjects had a decrease in filling fraction from rest to exercise. Four of the six normal patients with a decrease in filling fraction from rest to exercise had a filling fraction ≥ 60% at rest. Peak filling rate at rest averaged 3.13 ± 0.85 sec⁻¹ and increased with exercise to 5.61 ± 1.38 sec⁻¹ (p < 0.001). The mean increase in peak filling rate was 2.48 ± 1.35 sec⁻¹ (range 0.39–5.55 sec⁻¹) (table 3). Peak filling rate during the first third of diastole averaged 2.86 ± 0.92 sec⁻¹ and increased during exercise to 3.84 ± 1.05 sec⁻¹ (p < 0.001) (mean increase 0.98 ± 1.16 sec⁻¹) (table 3).

Patients with Coronary Artery Disease

Ejection Fraction

At rest, the mean left ventricular ejection fraction in the 68 patients with coronary artery disease averaged 57 ± 13% (range 21–79%), which was less than that in normal subjects (p < 0.001). The ejection fraction was normal in 49 patients with coronary artery disease and abnormal in 19 (table 3). The mean left ventricular ejection fraction did not change during exercise (57 ± 13% vs 57 ± 16%, p = NS) in patients with coronary artery disease and was significantly less than that in normal patients (p = 0.001). In both groups with normal and abnormal ejection fraction at rest, there was no change in mean ejection fraction during exercise.

Of the 68 patients with coronary disease, 23 (16 with normal ejection fraction at rest and seven with abnormal ejection fraction at rest) had a normal ejection fraction response during exercise and 45 (33 with normal and 12 with abnormal ejection fraction at rest) had an abnormal response during exercise (figs. 3 and 4). There were no significant differences with respect to resting or exercise heart rates or double product between patients with a normal or abnormal response of ejection fraction during exercise.

Diastolic Indexes

The mean filling fraction at rest in patients with coronary artery disease was 30 ± 13% (range 2–59%), which was significantly (p < 0.001) less than that in normal patients (fig. 5). Even in patients with normal left ventricular ejection fraction at rest, the mean filling fraction was significantly less than that in normal patients (35 ± 11% vs 47 ± 15%, p < 0.001). For the 19 patients with abnormal ejection fraction at rest, the mean filling fraction was 18 ± 9% and was less (p < 0.001) than that in coronary patients with normal resting ejection fraction (table 3).

With exercise, the mean filling fraction decreased from the resting values in patients with coronary dis-

**FIGURE 2.** Rest and exercise left ventricular ejection fraction and filling fraction in normal patients. Dots represent individual patients; open circles represent mean values. Mean left ventricular ejection fraction significantly increased during exercise, and all patients had an absolute increase in ejection fraction of at least 6% in response to exercise. Filling fraction did not significantly change from rest to exercise.
TABLE 3. Left Ventricular Ejection Fraction and Diastolic Indexes in Normal Patients and Coronary Artery Disease Patients at Rest and Exercise

|                      | Normal patients (n = 32) | Coronary artery disease
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Normal EF at rest (n = 49)</td>
<td>Abnormal EF at rest (n = 19)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest EF (%)</td>
<td>67 ± 9</td>
<td>63 ± 7*</td>
</tr>
<tr>
<td>Exercise EF (%)</td>
<td>82 ± 8</td>
<td>62 ± 14†</td>
</tr>
<tr>
<td>ΔEF (%)</td>
<td>15 ± 7</td>
<td>-1 ± 13†</td>
</tr>
<tr>
<td>Diastolic indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest FF (%)</td>
<td>47 ± 15</td>
<td>35 ± 11†</td>
</tr>
<tr>
<td>Exercise FF (%)</td>
<td>46 ± 13</td>
<td>24 ± 14†</td>
</tr>
<tr>
<td>ΔFF (%)</td>
<td>-0.6 ± 10</td>
<td>-10 ± 13†</td>
</tr>
<tr>
<td>Rest PFR (sec⁻¹)</td>
<td>3.13 ± 0.85</td>
<td>2.66 ± 0.66†</td>
</tr>
<tr>
<td>Exercise PFR (sec⁻¹)</td>
<td>5.61 ± 1.38</td>
<td>4.07 ± 1.21†</td>
</tr>
<tr>
<td>ΔPFR (sec⁻¹)</td>
<td>2.48 ± 1.35</td>
<td>1.42 ± 1.10†</td>
</tr>
<tr>
<td>Rest first third PFR (sec⁻¹)</td>
<td>2.86 ± 0.92</td>
<td>2.03 ± 0.60†</td>
</tr>
<tr>
<td>Exercise first third PFR (sec⁻¹)</td>
<td>3.84 ± 1.05</td>
<td>2.58 ± 0.83†</td>
</tr>
<tr>
<td>ΔFirst third PFR (sec⁻¹)</td>
<td>0.98 ± 1.16</td>
<td>0.55 ± 0.70</td>
</tr>
</tbody>
</table>

Values are mean ± so.
* p < 0.05 (normals vs CAD with EF ≥ 50%); 
† p < 0.001 (normals vs CAD with EF ≥ 50%); 
‡ p < 0.05 (CAD with EF ≥ 50% vs CAD with EF < 50%); 
§ p < 0.001 (CAD with EF ≥ 50% vs CAD with EF < 50%).

Abbreviations: Δ = change from rest to exercise; EF = ejection fraction; FF = filling fraction; PFR = peak filling rate.

ease (30 ± 13% to 22 ± 13%, p < 0.001). The mean change in filling fraction during exercise was significantly less in patients with coronary disease than in normal patients (−8 ± 12% vs 0 ± 10%, p = 0.002). The 16 patients with normal ejection fraction at rest who had a normal ejection fraction response during exercise had no significant change in filling fraction during exercise (37 ± 15% vs 36 ± 16%). In contrast, 33 patients with coronary disease who had normal ejection fraction at rest but who had an abnormal ejection fraction response during exercise had a significantly lower filling fraction during exercise compared with the resting value (33 ± 10% vs 18 ± 8%, p < 0.001).

In the 19 patients with abnormal ejection fraction at rest, there was no difference in filling fraction at rest between patients who had a normal or abnormal ejection fraction response during exercise. In this sub-

FIGURE 3. Rest and exercise ejection fraction and filling fraction in 23 coronary artery disease patients with a normal ejection fraction response to exercise. Although the mean left ventricular ejection fraction increased during exercise (55 ± 15% to 67 ± 17%, p < 0.001), the mean filling fraction did not change (31 ± 16% vs 31 ± 16%, p = NS).
DIASTOLIC PERFORMANCE IN CAD/Reduto et al.

FIGURE 4. Rest and exercise ejection fraction and filling fraction in 45 patients with coronary artery disease who had an abnormal ejection fraction response during exercise. In response to exercise, the mean ejection fraction significantly decreased compared with the resting value (58 ± 13% vs 51 ± 12%, p < 0.001). The filling fraction also decreased with exercise (29 ± 12% vs 17 ± 7%, p < 0.001).

FIGURE 5. Filling fraction at rest in the 32 normal patients, 49 patients with coronary artery disease (CAD) and normal (≥50%) ejection fraction (EF) and 19 patients with CAD and abnormal EF. Filling fraction is displayed along the vertical axis. Even in patients with CAD and normal EF at rest, the mean filling fraction was less than that in normal patients (p < 0.001). MI = myocardial infarction; IWMI = inferior wall MI; AWMI = anterior wall MI.
group, filling fraction during exercise did not differ between patients with a normal or abnormal ejection fraction response during exercise (figs. 3 and 4).

Thirty-two of the patients with coronary artery disease had a decreased filling fraction and only three patients had an increased filling fraction. Each of these three patients had a normal ejection fraction response to exercise.

Although there was no difference in resting heart rate in normal patients compared with patients with coronary artery disease, the mean peak filling rate was significantly less in patients with coronary disease than in normal patients (2.39 ± 0.75 sec⁻¹ vs 3.13 ± 0.85 sec⁻¹, p < 0.001) (table 3). The mean increase in peak filling rate during exercise was less in patients with coronary disease than in normal subjects (1.41 ± 1.06 vs 2.48 ± 1.35 sec⁻¹, p < 0.001). The mean peak filling rate during the first third of diastole at rest in patients with coronary artery disease was significantly less than that in normal patients (1.83 ± 0.72 vs 2.86 ± 0.92 sec⁻¹, p < 0.001) (table 3). During exercise, the peak filling rate during the first third of diastole was also less than that in normal subjects (2.45 ± 0.86 vs 3.84 ± 1.05 sec⁻¹, p < 0.001).

Stress ECG

Twenty-eight patients with coronary artery disease had a positive stress ECG (fig. 6). There was no difference in heart rate change from rest to exercise in patients with or without a positive stress ECG (55 ± 21 vs 56 ± 26 beats/min). While the mean change in ejection fraction from rest to exercise was abnormal both in patients with and without positive stress ECG, the mean decrease in ejection fraction during exercise was significantly greater in patients with a positive stress ECG than in patients with a negative test (−5 ± 12% vs 4 ± 10%, p < 0.002). Twenty-one of 28 patients with a positive stress ECG had an abnormal ejection fraction response to exercise (fig. 6). The mean decrease in filling fraction during exercise was significantly greater in patients who had ischemic electrocardiographic changes during stress than in patients who did not (−13 ± 13% vs −5 ± 11%, p = 0.007).

Propranolol

Twenty-eight patients were receiving propranolol for angina pectoris. Patients who were receiving propranolol had a lower heart rate than those who were not receiving propranolol (66 ± 12 vs 81 ± 17 beats/min, p < 0.001). Similarly, exercise heart rate was lower in patients receiving propranolol than in patients not receiving propranolol (112 ± 20 vs 143 ± 24 beats/min, p < 0.001, but the mean ejection fraction at rest was similar in the groups (60 ± 12% vs 54 ± 14%). The propranolol-treated group, however, had a higher ejection fraction during exercise than patients not taking propranolol (64 ± 17% vs 52 ± 14%, p < 0.002).

The mean filling fraction at rest was higher in the propranolol group than in the remaining coronary artery disease patients (36 ± 14% vs 25 ± 11%, p < 0.001). With exercise, filling fraction remained higher in the propranolol-treated group than the non-treated patients (30 ± 14% vs 16 ± 7%, p < 0.001). Despite a lower resting and exercise heart rate in the propranolol group, peak filling rate and peak filling rate during the first third of diastole at rest and during exercise were not significantly different in patients receiving compared with those not receiving propranolol.

Relationship of Filling Fraction to Ejection Fraction, Extent of Coronary Artery Disease and Infarct Size

For the population as a whole, ejection fraction and filling fraction correlated significantly at rest (p < 0.001, r = 0.75) (fig. 7) and during exercise (p < 0.001, r = 0.82) The absolute changes in filling fraction and ejection fraction from rest to exercise correlated significantly (p < 0.001, r = 0.59) (fig. 8).

Coronary angiography was performed in 56 of the 68 patients with coronary artery disease. Significant one-, two-, and three-vessel coronary artery disease was present in 17, 16, and 23 patients, respectively. Among the patients with an abnormal response of ejection fraction during exercise, patients with three-vessel disease were significantly more common (chi-square p = 0.003) than patients with one- or two-vessel disease. In addition, the mean change in ejec-

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Response during exercise in coronary artery disease patients with respect to stress ECG, ejection fraction (EF) and filling fraction (FF).
tion fraction from rest to exercise was greater in patients with one-vessel disease than in those with three-vessel disease (4 ± 9% vs. −3 ± 12%, p < 0.05). While there was no significant relationship of filling fraction to extent of coronary artery disease, there was a trend toward a greater decrease in filling fraction from rest to exercise in patients with three-vessel disease (−11 ± 12%) than patients with one-vessel disease (−5 ± 10%). In patients with inferior wall infarction, heart rate, ejection fraction and filling fraction at rest or during exercise were not significantly different from those in patients with anterior infarction.

The sensitivity, specificity and predictive accuracy of the stress ECG and the response of ejection fraction or filling fraction to exercise in detecting exercise-induced ischemia is summarized in Table 4. Since, by definition, all normal patients had a negative stress ECG and increased ejection fraction during exercise, the specificity and predictive accuracy of these variables was 100%. Twenty-eight of 68 patients (41%) with coronary artery disease had electrocardiographic evidence of ischemia, while 45 patients had an abnormal ejection fraction response during exercise (sensitivity 66%). The combination of a positive stress ECG and an abnormal ejection fraction response resulted in a sensitivity of 76%. An abnormal filling fraction response to exercise was noted in 32 of 68 coronary artery disease patients and six of 32 normal patients (sensitivity 49%, specificity 81%). Combining abnormal responses of both filling fraction and ejection fraction with a positive stress ECG resulted in a sensitivity of 81% in detecting exercise-induced ischemia (Table 4).

### Table 4. Combined Noninvasive Testing for Detection of Exercise-induced Ischemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive stress ECG</td>
<td>41%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Abnormal EF response</td>
<td>66%</td>
<td>100%</td>
<td>100%</td>
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<td>Abnormal EF response and/or</td>
<td>76%</td>
<td>81%</td>
<td>88%</td>
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<td>positive stress ECG</td>
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<td>Abnormal FF response</td>
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<td>88%</td>
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<td>89%</td>
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<td>positive stress ECG</td>
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<td>Abnormal FF response and/or</td>
<td>81%</td>
<td>81%</td>
<td>90%</td>
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<tr>
<td>abnormal EF response and/or</td>
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<tr>
<td>positive stress ECG</td>
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</table>

*Refers to patients with coronary artery disease only.

Abbreviations: EF = ejection fraction; FF = filling fraction.

### Discussion

Although the response to exercise of left ventricular systolic performance has been investigated hemodynamically and angiographically,12,14 few data are available regarding the effects of exercise on left ventricular diastolic performance.4 Using first-pass radionuclide techniques, we sought to delineate the responses of various diastolic indexes to upright exercise and to evaluate the comparative effects of exercise-induced ischemia on systolic and diastolic measures of left ventricular performance.

In the present investigation, failure to increase ejection fraction by at least 6% was used to define exercise-induced ischemia. We believed that the left ventricular ejection fraction response to exercise stress would increase sensitivity in the detection of left ventricular ischemia compared with the stress ECG alone. Using identical first-pass techniques, Berger et al.4 showed ejection fraction response was more sensitive than the development of wall motion abnormalities in...
detecting exercise-induced ischemia. Because all coronary patients in this investigation had either angiographically documented coronary artery stenosis or evidence of prior transmural infarction, we believed that the response of left ventricular ejection fraction would afford maximal sensitivity in identifying exercise-induced ischemia.

In the present study, the sensitivity of an abnormal ejection fraction response in detecting exercise-induced ischemia was 66%. These data are similar to those of Okada et al.,\textsuperscript{18} who used gated cardiac blood pool imaging techniques and found a sensitivity of 64% in detecting exercise-induced ischemia in patients with coronary disease utilizing both an abnormal ejection fraction response and the development of segmental abnormalities as markers of exercise-induced ischemia. In contrast, Borer et al.\textsuperscript{8} found regional dysfunction or a subnormal ejection fraction response in 95% of patients with coronary artery disease. A number of variables may be responsible for these apparent discrepancies. First, 34% of the coronary patients in the present investigation had three-vessel disease, whereas 50% of patients in the study of Borer et al. had three-vessel disease. Second, propranolol may have afforded protection against exercise-induced ischemia; 28 of our 68 coronary patients were receiving this agent, compared with none of the patients reported by Borer et al.\textsuperscript{8}

Gibson and Brown\textsuperscript{16} and DeMaria et al.\textsuperscript{17} have shown an excellent correlation between the rate of change of echocardiographically measured left ventricular dimension and angiographically determined left ventricular volume. Because our technique of assessing left ventricular diastolic performance is new, the radionuclide-derived diastolic indexes were compared with changes in left ventricular dimension obtained from M-mode echocardiograms in patients without coronary artery disease or dyssynergia; there was a significant ($p < 0.001$) relationship over a wide range of left ventricular performance.\textsuperscript{11} The radionuclide techniques and computer algorithm used to derive these diastolic indexes appear to be reproducible, as evidenced by the low observed variability of these measurements.

Myocardial relaxation represents a complex interaction of both active and passive processes. During early isovolumic diastole when the peak rate of relaxation occurs, myocardial relaxation is an active, energy-dependent process resulting from the dissociation of actin and myosin.\textsuperscript{18} In the isolated cardiac muscle preparation, catecholamines enhance the rate of myocardial relaxation.\textsuperscript{19} Myocardial ischemia, in contrast, may attenuate the rate and extent of relaxation by reducing available substrate for ATP-dependent dissociation of actin and myosin.\textsuperscript{20} Additionally, acidosis appears to increase the affinity of sarcoplasmic reticulum for calcium, thereby resulting in prolongation of relaxation time.\textsuperscript{21}

Recent studies carried out by exercising normal controls and coronary patients at cardiac catheterization indicate that, concomitant with the onset of ischemia manifested by angina, significant shifts in the slope of the diastolic log pressure-volume relation occur. In addition, the time constant of isovolumic pressure fall was lengthened during exercise in patients with coronary artery disease and angina or left ventricular dyssynergy; no change occurred in normal controls.\textsuperscript{4} These data obtained by standard invasive techniques further support the data obtained in our investigation by noninvasive methods.

In the present investigation, filling fraction as an index of early diastolic performance was significantly less in patients with coronary artery disease and normal systolic performance, even in the resting state, than in normal patients. However, the sensitivity and predictive accuracy of an abnormal filling fraction response to exercise compared with the ejection fraction response provide no additional diagnostic advantage. The abnormal filling fraction values at rest nevertheless suggest that diastolic function is sensitive to abnormalities resulting from chronic coronary artery disease. Even in the resting state, low-grade subclinical ischemia, myocardial fibrosis or both may result in impaired early diastolic filling, which was even more pronounced in patients with abnormal systolic performance.

In response to exercise-induced ischemia, as defined by an abnormal response of ejection fraction during exercise, 33 of 45 patients had a decrease in filling fraction during exercise, compared with six of 32 normal patients. These data imply that exercise-induced ischemia frequently impairs early diastolic filling coincident with the development of abnormalities in global systolic performance. In the 23 patients with coronary artery disease who had a normal ejection fraction response during exercise, the response of filling fraction to exercise was more varied — three patients had an increase and five had a decrease. Similarly, while the majority of normal patients exhibited an increase of no change in filling fraction during exercise, six normal patients had a decrease in this index during exercise. Four of these six normal patients had a resting filling fraction of 60% or more, while all patients with coronary disease had a resting value less than 60%. While this decrease in filling fraction may represent a false-positive response for exercise-induced ischemia, incomplete myocardial relaxation may be a normal physiologic response in certain patients during rapid heart rates. Studies by Weisfeldt et al.\textsuperscript{22} of pressure-ventricular dimension relationships in the intact canine ventricle showed a failure of the myocardium to return to a fully relaxed state after rapid pacing rates.

The left ventricular filling rate has been evaluated as an index of left ventricular compliance in several angiographic and echocardiographic studies. Using angiographically derived left ventricular volume curves, Hammermeister and Warbasse\textsuperscript{23} saw reduced filling rates in patients with coronary artery disease compared with normal subjects. In the present investigation, peak filling rate and peak filling rate during the first third of diastole were significantly lower at rest in patients with coronary artery disease than in normal patients, despite similar heart rates. These
data would also support the observation that early
diastolic relaxation is impaired in coronary artery
disease.

Coltart et al.24 showed that propranolol may result
in an increase in diastolic volume for a given pressure
so that static ventricular compliance appears to be in-
creased. In the present investigation, filling fraction
was higher at rest and during exercise in propranolol-
treated patients than in those not receiving pro-
pranolol. Despite lower resting and exercise heart
rates in the propranolol-treated group, peak filling
rate and peak filling rate during the first third of
diastole did not differ significantly from those in
patients with coronary artery disease not receiving
propranolol. These data imply that propranolol may
exert a beneficial effect upon early diastolic ventricu-
lar performance in patients with coronary artery dis-
ease.

In conclusion, our results indicate that exercise-
induced abnormalities in left ventricular filling frac-
tion occur in the majority of patients manifesting
evidence of ischemia defined by an abnormal response
of systolic function to exercise. The finding that filling
fraction decreases during exercise in certain normal
subjects suggests that incomplete myocardial relaxa-
tion may be a normal physiologic response during
rapid heart rates.

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