The Detection of Coronary Artery Disease with Radionuclide Techniques: A Comparison of Rest-Exercise Thallium Imaging and Ejection Fraction Response

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SUMMARY Fifty-two patients with suspected coronary artery disease underwent coronary angiography, thallium-201 myocardial imaging, and ECG-gated blood pool ventriculography at rest and at maximal exercise. In 11 patients without coronary artery disease, all thallium images were normal. The resting ejection fraction (EF) was normal in all 11 patients and increased during exercise in six, was unchanged in three, and decreased in two. Of the 41 patients with coronary artery disease, the thallium image was normal at rest and at exercise in six (15%), whereas the exercise EF was abnormal in these six. A new (18 patients) or enlarged (11 patients) defect appeared on the thallium image in 29 of 41 patients (71%) with coronary disease. Six of 41 patients (15%) had an abnormal rest thallium image that was unchanged with exercise. An abnormal rest and/or exercise image defect identified 35 of 41 patients (85%) with coronary artery disease. The resting EF was normal in 26 of the 41 patients (63%) and in 24 patients demonstrated an abnormal response to exercise. Fifteen patients (37%) had an abnormal resting EF, and 14 of these 15 demonstrated persistent abnormalities. Thus, an abnormal exercise EF response identified 38 of 41 (93%) patients with coronary disease. The specificity of the thallium image was 100% and for the exercise EF determination, 54% (p < 0.02). We conclude that an abnormal exercise EF response and the rest-exercise thallium image have similar sensitivities for detecting coronary disease; however, an abnormal exercise ejection fraction was significantly more sensitive than was a new thallium abnormality alone (93% vs 71%). Combined, the two studies detected all patients with coronary disease.

ACCURATE, NONINVASIVE METHODS for detecting coronary artery disease (CAD) are of considerable clinical importance. Standard ECG-treadmill stress testing has been widely used, but is controversial because it has a relatively low sensitivity and specificity.1, 2 Thallium-201 myocardial imaging has been reported to be superior to standard ECG-stress methods because it has improved sensitivity and specificity.3, 4 However, thallium imaging is rather expensive and is not sensitive enough to make screening in populations with a high disease prevalence clinically practical.6 Recently, Borer et al. reported that radionuclide measurement of ventricular function during exercise was highly sensitive for detecting CAD; however, this technique was not directly compared with thallium imaging.

The purposes of this study were 1) to compare the sensitivity and specificity of rest-exercise thallium myocardial imaging and supine rest-exercise radionuclide ventriculography for detecting coronary artery disease, and 2) to compare the duration of exercise, hemodynamic, electrocardiographic, and symptomatic parameters in the same patient population with both treadmill and supine bicycle exercise testing.

Methods Fifty-two patients with known or suspected CAD who had coronary angiography to evaluate chest pain, left ventriculography, rest-exercise 201TI myocardial imaging, and rest-exercise assessment of left ventricular function using radionuclide methods comprise the patient population. With exceptions noted below, the series includes all consecutive patients who had these four tests during the study. All studies were performed within 3 months of each other, and no patient with a history that suggested an intervening myocardial infarction or whose resting ECG changed was included. (Greater than 80% of the studies was performed within 2 weeks of the heart catheterization.) Patients with unstable angina, hemodynamically significant valvular lesions, mitral valve prolapse, or a clinically recognized nonischemic cardiomyopathy were excluded. At the time of the study, hypertension (> 160/90 mm Hg) was present in one patient with normal coronary arteries and in four of 41 patients with coronary artery disease; however, in no instance did the diastolic pressure exceed 100 mm Hg. Four other patients with CAD had a history of hypertension. Beta-blocking drugs or long-acting nitrates were not discontinued before these studies; however, no patient had taken nitrates on the morning of his test.

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Twenty-eight patients with CAD were taking propranolol (183 ± 100 mg, range 40–400 mg) and 13 were not. Two patients with normal coronary arteries were taking 60 and 80 mg/day.

Myocardial imaging was performed at rest using 1.5 mCi thallium-201 given intravenously after a 12-hour fast, and exercise imaging was performed by injection of a similar amount of thallium-201 at maximal symptom-limited exercise by the Bruce protocol as previously described from this laboratory.8 Imaging was performed on a gamma camera with a low-energy, medium-resolution collimator and a 20% window.9 Images were recorded directly from the gamma camera on Polaroid film with a tri lens camera. Three independent observers interpreted the images without knowledge of the results of coronary angiography. A consensus reading was used to resolve discrepancies.

Myocardial images were interpreted in the following manner for the rest-exercise studies: normal/normal, normal/abnormal, abnormal/no change, and abnormal/increased size of defect. No equivocal or borderline categories were permitted.

Radionuclide left ventricular function studies were performed using ECG-synchronized blood pool imaging of 99mTc-labeled red blood cells.9 Images were acquired in the left anterior oblique projection using a gamma camera with a low-energy, high-sensitivity, parallel-hole collimator10 interfaced to a minicomputer.11 This system can acquire and store short-duration images in core memory with automatic transfer of images onto magnetic disc at operator determined counts/image or time/image criteria. Fourteen consecutive 40-msec images starting with the R wave of the ECG were routinely acquired for a 2-minute imaging period, as previously described.7

Supine exercise was done on a commercially available, multipurpose imaging table12 designed with a calibrated bicycle ergometer as an integral part of the table. The initial work load was 200 kg-m/min and increased in 200 kg-m/min increments every 4 minutes during exercise until the symptom-limited maximum was reached. Cardiac blood-pool images were acquired for three 2-minute periods at rest and then every 2 minutes during exercise and recovery.9, 12 Heart rate and ST-segment response to exercise were obtained from ECG recordings made at 1-minute intervals from a bipolar precordial lead (Vb), and blood pressure was measured with an arm sphygmomanometer every 2 minutes during rest and throughout exercise and recovery.

Coronary arteriography was performed by the Judkins approach using a GE Floricon 300 cineangiographic system with recording on 35-mm film at 30 or 60 frames/sec. The degree of coronary stenosis was determined from visual estimation of the coronary arteriogram by a staff cardiologist who was unaware of the radionuclide imaging study results. A significant stenosis was determined to be ≥ 50% diameter narrowing of a major coronary vessel or of a branch vessel that was estimated to be > 1.0 mm in diameter and at least half the length of the parent vessel.

Data Analysis

The interpretation of the thallium images and the coronary arteriograms have been described in the previous section. The 2-minute equilibrium blood pool images were recalled from magnetic disc and the left ventricular region of interest (ROI) identified on the end-diastolic image by use of an operator-interactive, commercially available, edge-detection program (MDS-MUGE). Background activity was determined by drawing a ROI adjacent to the inferior and lateral free walls of the left ventricle four or five channels removed from the ventricular border.7 Background activity was normalized to counts/channel and this value subtracted from the end-diastolic image and each of the 13 subsequent images of the composite cardiac cycle. The program then semiautomatically (with operator intervention as needed) defined a new left ventricular ROI for each 40-msec image. Ejection fraction (EF) was calculated by subtracting end-systolic from end-diastolic counts of the background-subtracted curves and dividing by the end-diastolic counts. When calculated in this manner, the EF correlates highly with values obtained from contrast angiography (r = 0.83; y = 0.76X + 11; n = 51) and is very reproducible (r = 0.94; see = 0.06 EF units).13

In addition to the EF calculated from the first baseline image using the variable ROI method, a second EF was calculated on the same image using a fixed ROI in which the area of interest is identified on the end-diastolic image and then applied to each of the subsequent images in the cardiac cycle. A time-activity curve was generated and the EF calculated in the standard manner. It has been shown that the EF calculated from the fixed ROI consistently underestimates that determined from the contrast ventriculogram and by the variable ROI since in systole, structures outside the left ventricle move into the fixed end-diastolic ROI and artificially elevate end-systolic counts;14 however, for an EF calculation, the fixed ROI method requires less technician and computer time (3–4 minutes) than the variable ROI method (10–15 minutes) and has a greater reproducibility.14 Because of the time constraints and the better reproducibility, we used the fixed ROI method to calculate the EF for each of the 2-minute images during rest, exercise and recovery, and used a correction factor so that the values correspond to those reported for contrast ventriculography. This correction factor was the difference between EF by variable ROI and fixed ROI, which was then added to the EF calculated by the fixed ROI for each 2-minute image during exercise.

A significant change in EF during exercise was defined as a deviation of ± 0.05 units from the mean of the three resting EF determinations. The rationale for this has previously been reported.8 * Briefly, it is:

In measuring the EF either at rest or after interven-
tions, both physiologic and statistical variations occur (the exact effect each exerts is very difficult to determine) that must be considered in interpreting the results. A single, resting EF is composed of a theoretical average EF and a random error term that accounts for the observed value being different from the theoretical average resting value. To decide if the next measurement of the EF is significantly different, a confidence interval must be defined. This confidence interval would be equal to the standard error of the mean (SEM) of the random error term if the theoretical true average EF were known, but it is not known. Therefore, the confidence interval about a resting EF is a function of the SEM of the theoretical true average EF plus the SEM of the random error term. One can approximate the theoretical average EF by making multiple measurements at rest; however, in practice, only a few resting measurements can be made. Thus, with a small number of resting observations (in our case, n = 3), the SEM for a single predicted value is slightly larger than the standard deviation of the observation:

\[ \text{se}(\bar{X}) = \sqrt{\frac{\text{se}(X)^2}{n}} + \text{se}(-\text{random error})^2 \]

where \( \bar{X} \) = next observation and \( X \) = mean of observations already made.

Thus, to construct confidence intervals about the resting EF to define a subsequent significant change with exercise, one must know the SEM-measured EF (\( \text{SE}(\bar{X}) \)) plus have some estimate of the random variability (random error) of the data (this can be expressed in terms of pooled variance). To obtain this latter information, we made three serial, 2-minute EF measurements at rest in 30 consecutive patients who were not included in the 52 patients reported here. Ninety-four percent of the individual observations were within ± 0.03 EF units of the mean of their three consecutive observations and all within ± 0.06 units. Using these data, the pooled variance was determined and was 0.000444. Therefore, from the mean of the three resting values and knowledge of pooled variance in our laboratory, a 95% confidence level for significant change for a single subsequent EF measurement at maximal exercise was established. The 95% confidence limit for an individual patient is \( \bar{X} \pm 0.049 \) EF units. We assume that the EF should increase in the normal person and use the confidence limit to decide if the increase is greater than that which can be attributed to physiologic and statistical noise.

Throughout this report, the baseline value reported is the mean of the three resting EF values. Failure to increase the EF during supine exercise by more than 0.05 EF units could not be distinguished from physiologic and statistical noise alone and was our criteria for an abnormal response. This 0.05-unit increase was similar to the minimum increase in EF of 7% in the normal patients used by Borer et al.\(^6\) Figures 1 and 2 are examples of typical normal and abnormal studies.

**Statistical Analysis**

Within the subgroups of patients, the difference between rest and maximal exercise EF values were compared using the paired \( t \) test. Intergroup differences for EF were compared by the \( t \) test for difference between two means.

The difference in sensitivity and specificity for the thallium myocardial image and the exercise ven-
tricular function study were compared using the McNemar test for significance of change in related samples. A statistically significant difference of \( p < 0.05 \) was used throughout.

**Results**

**Population Characteristics**

There were 50 male patients and two females, average age of 51 ± 8 years (mean ± sd, range 33–64 years). Forty-one patients had coronary narrowing of > 50% lumen diameter, whereas 11 had no (10 patients) or insignificant (one patient) disease (henceforth referred to as normal coronary arteries). The mean age of patients with CAD was 52 ± 8 years (range 33–64 years); the mean age of those with normal coronary arteries was 45 ± 8 years (range 35–57 years; \( p = 0.01 \)).

In patients with CAD, the heart rate increased from 68 ± 12 beats/min to 122 ± 20 beats/min during treadmill exercise and from 62 ± 11 beats/min to 104 ± 19 beats/min during supine bicycle exercise. Systolic blood pressure increased from 123 ± 19 mm Hg to 141 ± 30 mm Hg with treadmill exercise and from 132 ± 18 mm Hg to 164 ± 24 mm Hg with supine exercise. All patients had increased systolic blood pressure during supine exercise, whereas 11 patients decreased the systolic blood pressure or failed to increase by greater than 15 mm Hg during treadmill exercise. Pressure-rate product (\( P \times R \times 10^{-2} \)) at maximal exercise was the same for the upright treadmill (172 ± 49) and the supine bicycle exercise (173 ± 50) (\( p > 0.05 \)).

ST-segment depression (≥ 1 mm J point, with horizontal or downsloping ST 0.06 second after the J point) occurred in 18 patients during upright exercise and in 19 patients during supine exercise. One patient had ST elevation during both types of exercise. The degree of ST depression was essentially identical with both modes of exercise (fig. 3).

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**Figure 1.** An example of a rest-exercise left ventricular ejection fraction (EF) and thallium myocardial perfusion study in a patient with normal coronary arteries. Duration of supine exercise in minutes is displayed on the horizontal axis and the EF and work load are on the vertical axis. A progressive increase in the EF during exercise is seen. The marked increase in EF after exercise is associated with lowering the feet to the level of the body and with a rapid decrease in blood pressure. This occurs in normals as well as in the diseased state. Two standard views of the rest and exercise thallium images are displayed above with a summary of the interpretation of the rest-exercise study in the box on the right. LAO = Left anterior oblique; CAD = coronary artery disease; PTBG = patient identification.

**Figure 2.** Example of a combined study in a patient with a single left anterior descending coronary stenosis. The exercise thallium image is abnormal in the anteroseptal region and the ejection fraction is unchanged until maximal exercise is reached, when it decreases. Abbreviations as in figure 1.
Angina was the limiting symptom in 25 patients during treadmill testing, compared with 22 during supine testing \((p > 0.05)\). Dyspnea or fatigue were the limiting factors during supine exercise in 17 patients, compared with 14 patients during the treadmill exercise \((p > 0.05)\) (fig. 3). Limiting symptoms were not recorded on the supine exercise form for two patients.

For the 11 patients with normal coronary arteriograms, the resting heart rates for the upright and supine exercise, respectively, were \(72 \pm 11\) beats/min vs \(66 \pm 9\) beats/min \((p < 0.05)\). At maximal exercise, the respective heart rates were \(161 \pm 23\) beats/min and \(125 \pm 21\) beats/min \((p = 0.001)\).

In these same 11 patients, systolic blood pressure at rest was \(123 \pm 13\) mm Hg and \(126 \pm 16\) mm Hg \((p < 0.05)\) for the treadmill and supine bicycle, respectively. At maximal exercise, the values were \(165 \pm 19\) mm Hg and \(189 \pm 31\) mm Hg, with the difference significant at the \(p = 0.04\) level. These values were also significantly higher than the same measurements in the patients with CAD. In the normal group, pressure-rate product was the same at rest for the two types of exercise, \(88 \pm 15\) and \(83 \pm 13\); however, at maximal exercise, the product was higher for the treadmill \((267 \pm 59)\) compared with the supine bicycle exercise \((237 \pm 62)\) \((p = 0.04)\).

ST changes of myocardial ischemia were seen in only one of the 11 normal patients. The patient developed 4.5 mm of ST depression in stage I of both types of exercise and stopped at the end of this stage with fatigue and dyspnea. The only explanation for these findings was a history of hypertension and a thickened ventricle by echocardiography. The resting ECG and contrast ventriculogram were normal.

Two patients in the group with normal coronary arteries stopped supine exercise with chest pain felt to be angina, and one of these patients stopped on the treadmill with similar pain. Neither had ST changes of ischemia. The remaining patients stopped with fatigue and/or dyspnea.

Thallium Myocardial Imaging

Both rest and exercise images were normal in all 11 patients with normal coronary arteries and in six of 41 patients \((15\%)\) with CAD (fig. 4). In 18 patients \((44\%)\) with CAD a normal rest image became abnormal with exercise. Six CAD patients \((15\%)\) had an abnormal rest image that was unchanged with exercise. Eleven patients \((27\%)\) with CAD had an abnormal resting image that demonstrated increased abnormality with exercise (table 1). An abnormality thus appeared in 41% of all images at rest. The sensitivity \((\frac{\#\text{true positive}}{\#\text{patients with disease}})\) of a new exercise-induced defect or an increase in a previous rest defect was 71% for patients with CAD. The sensitivity of a rest and/or an exercise defect on a thallium myocardial image in detecting CAD was 85% \((35\text{ of }41\text{ patients})\) in this group of patients. The specificity \((\frac{\#\text{true negative}}{\#\text{patients without disease}})\) of either a rest or an exercise defect was 100% \((11\text{ of }11\text{ patients})\).

Rest-Exercise Radionuclide Left Ventricular Angiography

The mean EF decreased from \(0.53 \pm 0.14\) at rest to \(0.49 \pm 0.14\) \((p < 0.001)\) at maximal exercise in the patients with CAD and increased from \(0.60 \pm 0.05\) to \(0.63 \pm 0.09\) \((p > 0.05)\) in the normal group.

The resting EF was normal \((\geq 0.50)\)* in all 11 patients with normal coronary arteries and increased during exercise in six, was unchanged in three, and decreased in two (table 1). In patients with CAD, the resting EF was normal in 26 \((63\%)\). Of these, two demonstrated an increase, 10 no change, and 14 a decrease in EF at maximal exercise. In the 15 patients \((37\%)\) whose resting EF was abnormal \((< 50\%)\), the

*Normal value of the EF for both contrast ventriculography and radionuclide ventriculography in our laboratory is \(0.66 \pm 0.16\), mean \(\pm\) sd.
EF at maximal exercise increased in one, was unchanged in 10, and decreased in four (table 1). An abnormal exercise EF response thus identified 38 of 41 patients (93%) with CAD (fig. 4). If an abnormal rest study is considered a positive test even though the EF increases with exercise, then the rest-exercise EF study detected 39 of 41 patients (95%). The specificity of an abnormal response was six of 11 (54%).

In 39 of the 41 patients with CAD, limiting symptoms were recorded at maximal supine exercise. Angina was associated with an increase in EF in one patient, a decrease in EF in 14 patients, and with no change in nine. Dyspnea or fatigue were limiting in three patients whose EF increased, in four patients with a decrease and in eight patients in whom there was no change. The number of patients who stopped with angina and had a decrease in EF was not different from those who stopped with fatigue or dyspnea (p > 0.05).

Combined Studies

Of the six patients with CAD and a normal rest-exercise thallium image, all six demonstrated an abnormal rest-exercise EF study. Conversely, of the three patients with CAD and a normal rest-exercise ventriculogram, rest and/or exercise thallium studies were abnormal in all three. Combined, the two tests detected all patients with CAD. The specificity of thallium of 100% and that for ventriculography of 54% was significantly different at the p = 0.02 level, but there was no difference between the sensitivities of these two techniques.

Eighteen of 24 patients (75%) with a normal rest thallium image developed an exercise-induced or enlarged image defect. Twenty-four of 26 (92%) patients with a normal resting EF developed an abnormal EF response to exercise. These differences are not significant. Both the rest EF and the rest thallium images were normal in 18 patients. The exercise thallium image was normal in three, all of whom had an abnormal EF response. Fifteen patients had an exercise thallium defect and EF response was abnormal in 13 (87%) (p = NS).

Figure 5 is a comparison of the change in the EF between rest and maximal exercise as a function of the results of the myocardial image for each patient.

Effect of Propranolol

Twenty-eight patients with CAD were on propranolol (183 ± 100 mg, range 40–400 mg), and 13 were not. The mean resting EF of those on propranolol was 0.54 ± 0.14 vs 0.52 ± 0.14 for those on no drug (p > 0.05). At maximal exercise, the EFs

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<tr>
<th>Table 1. Summary of Rest-Exercise Myocardial Image and Exercise Ejection Fraction Studies</th>
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<tr>
<td>Thallium myocardial image</td>
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<tr>
<td>Rest/exercise</td>
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<tr>
<td>Normal/normal</td>
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<td>Normal/abnormal</td>
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<td>Abnormal/enlarged defect</td>
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<td>total</td>
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*Number of patients in each category who have coronary disease or normal coronary arteries.
†Resting radionuclide ejection fraction greater than or less than 0.50.
‡Change with exercise. Increase = > 0.05 units above mean of three resting values. No change = within ± 0.05 units of mean. Decrease = > 0.05 units below mean.
were 0.49 ± 0.14 and 0.48 ± 0.14, respectively \((p > 0.05)\). Of those on the drug, 10 had a resting EF < 0.50 and 18 an EF > 0.50, while of those not on the drug, five had a resting EF < 0.50 and eight an EF > 0.50 \((p > 0.05)\). The response to exercise for those on and off propranolol was also compared relative to the result of the rest-exercise thallium study (table 2). The EF either fell or was unchanged during exercise in all categories of thallium abnormalities, regardless of the presence or absence of drug. The decrease was statistically significant only in the subgroups of patients who demonstrated a new or enlarged thallium defect. When analyzed on the basis of a normal or abnormal resting EF, there was a significant decrease in EF with exercise for both drug and nondrug groups when the resting EF was normal \((0.62 ± 0.07 \text{ to } 0.56 ± 0.07 \text{ and } 0.62 ± 0.08 \text{ to } 0.54 ± 0.09, \text{ respectively})\). A similar decrease occurred in the propranolol group with an abnormal rest EF \((0.41 ± 0.12 \text{ to } 0.36 ± 0.14), \text{ whereas there was no}

change in the nondrug group \((0.37 ± 0.10 \text{ to } 0.37 ± 0.11)\). Only two of the group with normal coronary arteries were on propranolol, one on 60 mg/day and the other 80 mg/day. The resting EFs were 0.58 and 0.68, respectively, and both decreased with exercise; however, neither the rest nor the maximal exercise EF values for these two patients were statistically different from the corresponding values of the three patients in whom the EF did not change during exercise.

**Discussion**

Noninvasive tests for the detection and diagnosis of CAD have evolved gradually over the past 20 years since the early work of Masters and Rosenfeld. A better understanding of the overall usefulness has also evolved during this period. Rest and exercise thallium myocardial imaging combined with treadmill exercise testing is often used for detecting abnormal myocardial perfusion as a manifestation of occlusive CAD. In patients who undergo coronary angiography for suspected or known CAD, several large studies have shown that ST changes of ischemia during exercise, combined with a new or enlarged defect on the thallium myocardial image, result in a test with a sensitivity of 75–90% and a specificity of 85–100%. These results are superior to treadmill testing alone, in which the sensitivity ranges from 55–65% and the specificity from 90–95%.

Borer et al. first described radionuclide left ventriculography at rest and maximal exercise as a means of detecting CAD. In this and two subsequent reports, these authors have shown that an abnormal response, defined as failure to increase the EF, a decrease in the EF, or development of regional dysfunction as an indicator of coronary disease was very sensitive for the detection of CAD — in the range of 95%, with a specificity of almost 100%.

However, the sensitivity of their technique has recently been questioned by Berger et al., who reported a much lower sensitivity for new regional wall motion abnormalities with exercise for detection of CAD.

Because these early reports suggested a significant improvement in the accuracy of the exercise EF study over thallium imaging for detecting CAD, a comparison of the two tests in the same population with known disease, thereby defining the relative sensitivity and specificity, was indicated for three reasons: First, if the exercise EF method had clearly superior sen-

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**Table 2. Effect of Propranolol on Ejection Fraction Change**

<table>
<thead>
<tr>
<th>Thallium image</th>
<th>Propranolol</th>
<th>No propranolol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rest/exercise</td>
<td>Ejection fraction</td>
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<tr>
<td>Normal/normal</td>
<td>n = 4</td>
<td>0.53 ± 0.13</td>
</tr>
<tr>
<td>Normal/abnormal</td>
<td>n = 11</td>
<td>0.62 ± 0.08</td>
</tr>
<tr>
<td>Abnormal/no change</td>
<td>n = 5</td>
<td>0.44 ± 0.13</td>
</tr>
<tr>
<td>Abnormal/enlarged defect</td>
<td>n = 8</td>
<td>0.51 ± 0.17</td>
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</tbody>
</table>

*Mean ± sd.
†Statistically different at \( p < 0.05 \).
sitivity and specificity, it would be a better screening tool than thallium; second, if the studies were additive in terms of diagnostic results, the appropriate testing sequence could be established; and third, it was necessary to compare the hemodynamic and electrocardiographic changes and the limiting symptoms during supine exercise to those during upright exercise.

Our results must be clarified. The sensitivity and specificity of thallium myocardial imaging alone were slightly higher in this group of patients than in those previously reported at our institution. When thallium-201 studies were combined with the rest-exercise ECG, the results were better than most previous reports with the exception of that of Vogel et al., who used a new thallium-201 tomographic imaging technique. Our improved results may be due, in part, to 4 years of additional experience in interpreting the thallium images, in the radiopharmaceutical preparation, in gamma-camera resolution, and to unrecognized differences in the patient population. In addition, the high specificity may have been secondary to the small number of normal patients in the present study.

Although the sensitivities of combined rest-exercise thallium and rest-exercise EF determinations in detecting CAD were not significantly different, a smaller percentage of patients (71%) developed an exercise-induced or enlarged defect on the thallium image than demonstrated an abnormal exercise EF response (93%; p = 0.01). A normal resting EF tended to become abnormal more frequently (92%) with exercise than did a normal rest thallium image (75%), although these differences were not significant. When both studies were normal at rest, each had an equal chance of being abnormal with exercise.

Other investigators have used the development of a regional area of dysfunction on the exercise ventriculogram to identify abnormal function, and believe that it permits detection of disease that would otherwise be undetected. They also believe it improves specificity. We have chosen not to include qualitative regional function analysis because in our experience with rest-exercise ventricular function studies in patients with CAD in the past 2 years, less than one-fourth have developed new exercise-induced regional function abnormalities that we can identify; therefore, absence of a regional abnormality even with a fall in EF would not have discriminated normal subjects from those with CAD. Similarly, Berger et al. found new exercise-induced regional abnormalities in less than 50% of their patients with coronary disease. In addition, if one excludes by careful clinical and/or echocardiographic evaluation patients with valvular heart disease or cardiomyopathies, including mitral valve prolapse — both of which produce global exercise ventricular function abnormalities — then the global EF response should be relatively specific for CAD. Our qualitative and quantitative experience and approach to regional function will be reviewed in another report.

The incidence of false-positive tests (failure to increase EF during exercise) in this study was much higher than that reported by others. Reasons for the differences are not clear. The ages of the patients were similar and, except for one patient with hypertension, all were free of recognized cardiovascular disease at the time of the exercise test. Retrospectively, we were able to postulate possible reasons for the false-positive studies that are discussed below. In any event, we believe that our experience is representative of the results that would be achieved if the method were applied to a similar population of patients referred to a diagnostic center for evaluation of chest pain. We anticipate that the results in normal volunteers would be different.

The false-positive exercise ejection fraction studies have four possible explanations: 1) The presence of β blockade, which has been shown to reduce the resting EF slightly and to blunt (but not eliminate) the normal increase in EF during exercise; however, the dose at which this effect is seen is unknown. 2) Wisenberg et al. reported that in four normal patients who were taking 160 mg/day of propranolol, the mean maximal exercise EF (0.77) was lower than the control maximal value (0.82); at 533 mg/day, the maximal exercise value was 0.75. No study has reported that propranolol will convert a normal response to a decrease in the EF, which was the case in two of our patients. Therefore, for these two patients with normal coronary arteries on low-dose propranolol (< 80 mg/day), it is unlikely that the drug produced a fall in the EF. 2) The presence of a coronary stenosis, which was underestimated in severity, was a possibility in one patient with a right coronary narrowing of 40%. 3) The presence of an unrecognized myopathic process which only in retrospect was a possible explanation in two of the patients. One had a mild viral syndrome at the time of onset of his chest pain and T-wave abnormalities several months before the exercise study; however, he continued to have chest pain after the viral syndrome resolved. There were no symptoms or chest x-ray findings of congestive failure at any time. Das et al. reported no increase in EF in patients who previously had documented viral myocarditis but who had completely normal ventricular function studies at rest. The other patient who may have had a myopathic process had a history of poorly controlled hypertension, a thick ventricle on an echocardiogram, but no ECG evidence of hypertrophy or ischemia and a normal resting contrast left ventricular angiogram. 4) A variation of the normal increase in EF may have occurred in two of our patients whose EFs progressively increased and reached (but did not exceed) our 95% confidence limit of + 0.05 EF units.

False-negative studies (an increase in EF with exercise) have been reported by others, but apparently are infrequent. A false-negative study could be ex-

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*All thallium imaging was performed on the same model cameras from the same vendor. The camera used for the current study is a latter production model with slightly improved resolution characteristics.
explained by: 1) failure of the patient to exercise to max-
imum. This seems unlikely on the basis of the limiting
symptoms, ST changes, and pressure-rate product
achieved by two of our patients with false-negative
studies. The other patient with the false-negative
response had abnormal resting function. He stopped
supine exercise with fatigue after achieving a pressure-
rate product greater than on the treadmill. From the
above, a submaximal effort was unlikely to be the
cause of the false-negative response in these patients.
2) The presence of scar in an otherwise normal ventri-
cle with the normal portion demonstrating hypercon-
tractility is possible, but cannot be proved or dis-
proved in our study. 3) A normal variant is possible. 4)
Technical error due to underestimating the resting
EF or in calculating the maximal value is possible.
The latter is unlikely because of the multiple resting
samples that are made and because the analysis was
repeated to exclude an error in the instance of a false-
negative study.

Finally, Rainwater et al. and Wisenberg et al. have
reported that the exercise EF improved slightly
without change in the resting EF after propranolol in
men with CAD. In neither study, however, did pro-
pranolol cause an exercise EF response that had been
abnormal before the drug to normalize. Rather, only
the magnitude of the decrease in EF was reduced.
While our data cannot directly indicate the effect of
propranolol, the sensitivity of the exercise EF for
detecting CAD was the same for our patient group on
propranolol as for the group not on the drug. Also,
only one of the three patients with CAD whose EF in-
creased was taking propranolol.

In comparing the merits of supine vs upright exer-
cise, studies of cardiac output during supine and up-
right exercise have shown that higher values for max-
imal output are obtained during upright exercise and
that the highest output is produced by treadmill exer-
cise. At submaximal levels of exercise, the cardiac
output is the same for both the treadmill and the sit-
ting bicycle at any level of oxygen consumption. For
these reasons and because upright exercise is a more
natural form of exercise, these two forms of stress
testing have been used most often for assessing heart
function and detecting electrocardiographic evidence
of myocardial ischemia. Supine exercise has several
technical advantages over upright exercise when per-
formed in conjunction with ECG-gated blood pool im-
aging. However, because supine exercise might not
produce as much stress on the heart and therefore
would be less likely to induce abnormal function, we
undertook the comparison of heart rate, blood
pressure, pressure-rate product, ECG changes, and
symptom limitations with both positions of exercise in
the same patients. As anticipated, the systolic blood
pressure was higher and the heart rate lower during
supine compared with upright exercise, but in the
patients with CAD the pressure-rate product was the
same for the two tests, indicating that in our popula-
tion the patients' limiting symptoms probably oc-
curred at the same level of myocardial oxygen con-
sumption. Moreover, the ST response was similar for
the two positions of testing. This further supports our
contention that the myocardial oxygen consumption
was the same for both positions of exercise and that
changes in heart position did not alter the ability to
detect ST-segment change. When combined, ST-
segment changes and an abnormal rest and/or exer-
cise EF study detected 98% of patients with CAD in
the supine exercise study. The specificity for our study
was unchanged because the one normal patient with a
false-positive ST-segment response also had an abnor-
mal EF response. In a larger patient population, par-
icularly one with more females, the combined spec-
ificity would probably be even lower.

Two additional, extremely important findings are: 1)
Patients who develop exertional hypotension on up-
right exercise testing have not done so during supine
exercise; and 2) the development of arrhythmias has
not forced termination of supine exercise testing. This
has also been our experience in testing more than 75
survivors of sudden cardiac death who have a high
incidence of upright, exercise-induced arrhythmias (un-
published data).

In summary, we have demonstrated: 1) that in
patients being evaluated for suspected coronary dis-
eease, an abnormal EF response to supine exercise is
not significantly more sensitive than rest-exercise
thallium myocardial imaging for the detection of
CAD, but is more sensitive than exercise-induced
thallium abnormalities alone; 2) that in this series in
which patients with chest pain, normal coronary
arteries, and no clinically identifiable noncoronary
disease, the exercise EF response was nonspecific; and
3) that when rest-exercise thallium myocardial imag-
ing and rest-exercise EF testing are combined, it is
possible to detect almost all patients with CAD. We
have also shown that no information was lost in terms
of maximal pressure-rate response, ST-segment
changes, or in symptoms during supine bicycle exer-
cise compared with upright maximal treadmill testing
in this series of patients with CAD. Therefore, com-
bining the rest-exercise EF response with the ST-
segment change may permit detection of almost all
patients with CAD, but with a low specificity.

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