Influence of Resting Left Ventricular Function on the Left Ventricular Response to Exercise in Patients with Coronary Artery Disease

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SUMMARY First-pass radionuclide angiography was used to assess the left ventricular response to submaximal exercise in 150 patients with coronary artery disease (CAD). To test the hypothesis that resting systolic left ventricular function as determined by left ventricular ejection fraction (LVEF) was a predictor of the hemodynamic response to exercise, the study group included patients with a wide range of resting LVEF (0.12–0.82). The influences of resting LVEF, resting end-diastolic volume, the number of diseased vessels, exercise end point and exercise double product on the change in LVEF (ΔLVEF) during exercise were tested using multiple linear regression analyses. Resting LVEF was a highly significant predictor of the ΔLVEF (p = 0.0001). Exercise duration was not related to either the resting LVEF or the ΔLVEF. For the 112 patients in whom coronary anatomy was known, resting LVEF retained its significance as a predictor of ΔLVEF (p = 0.002) even after adjustment for the significance of the extent of CAD (p = 0.0007) and the exercise end point (p = 0.06). Patients with normal resting LVEF showed the most profound decreases in LVEF, the highest frequency of new regional dysfunction and the largest relative increase in end-diastolic volume during exercise. As rest LVEF decreased, the magnitude of the ΔLVEF and the frequency of new regional dysfunction decreased. Therefore, left ventricular function at rest is an important determinant of the direction and magnitude of change in left ventricular function during exercise.

IN PATIENTS without cardiovascular disease, both the fraction of blood ejected from the ventricle and regional wall excursion increase during exercise. In patients with coronary artery disease, the left ventricular ejection fraction (LVEF) usually decreases and abnormalities of regional contraction appear. Prior myocardial infarction may reduce the ejection fraction and produce abnormal wall motion at rest. Studies performed in experimental animals indicate that global ventricular function may be preserved during regional ischemia by compensatory increases in contractility of the nonischemic myocardium. Hence, myocardial infarction may reduce the amount of myocardium available for maintaining global function during subsequent regional ischemia. Ventricular dysfunction at rest may thus be expected to predispose to further deterioration in global function during exercise stress in patients with coronary artery disease. In contrast to this view, we observed that despite extensive coronary artery disease and markedly reduced ventricular function at rest, LVEF usually increases or is maintained during exercise. The purpose of the present study was to evaluate this apparent inconsistency between the extent of ventricular dysfunction at rest and ventricular function during exercise. Ventricular function was measured during exercise in a large group of patients with a wide range of resting ventricular function. The independent effect of resting ventricular function on the ventricular response to exercise was analyzed.

Methods

Patient Population

The study group consisted of 150 patients with coronary artery disease documented by coronary arteriography or prior myocardial infarction who underwent radionuclide angiography during the period from July 1, 1978 to March 1, 1979. There were 134 men with a mean age of 53 ± 9 years (range 25–83 years) and 16 women with a mean age of 55 ± 10 years (range 38–70 years) (p = NS). The diagnosis of coronary artery disease was established by coronary arteriography in 112 patients and by a history of myocardial infarction in 38 patients. Coronary arteriography and biplane left ventriculography were performed by Judkins’ technique using standard procedures. Significant stenosis of a coronary artery was defined as occlusion greater than 75% of luminal diameter. In the group of 112 patients with coronary anatomy documented by arteriography, there were 26 patients with one-vessel, 36 with two-vessel and 50 with three-vessel disease. A history of myocardial infarction was accepted if two of the following three criteria were met: chest pain, typical evolutionary QRS or T-wave changes on the ECG or the presence of CPK-MB fraction in serum. Patients who had undergone previous coronary artery or left ventricular surgery were excluded. No patient had taken propranolol for at least 24 hours. Digitalis, nitrates and other vasodilators were not routinely discontinued.

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For comparison, the population was divided into three groups based on the resting LVEF as determined by radionuclide angiography: group 1, resting LVEF < 0.25; group 2, resting LVEF 0.26–0.50; and group 3, resting LVEF > 0.50.

Group 1 consisted of 37 patients, 33 men and four women. The resting LVEF ranged from 0.12–0.25 (mean 0.20 ± 0.04). Group 2 consisted of 51 patients, 46 men and five women. The resting LVEF ranged from 0.26–0.50 (mean 0.38 ± 0.07). Group 3 consisted of 62 patients, 55 men and seven women. The resting LVEF ranged from 0.51–0.82 (mean 0.63 ± 0.07).

Exercise Protocol

Radionuclide angiograms were performed with the patient in the erect position, at rest and during exercise. After the radionuclide angiogram at rest, exercise was performed on a bicycle ergometer (Fitron, Lumex Inc.). Blood pressure was recorded by cuff manometric technique at 2-minute intervals during and after exercise until stable. The ECG was monitored continuously, and an eight-lead ECG (I, II, III, aVR, aVL, aVF, V6 and V4) was recorded every minute during and after exercise until stable. Work load was measured in kilopond meters per minute (kpm/min). All patients began exercise at a work load of 200 kpm/min. The work load was then increased by 100 kpm/min every minute. Exercise was terminated when one of the following occurred: (1) pain suggestive of myocardial ischemia, (2) electrocardiographic evidence of ischemia, (3) hypotension, (4) frequent premature ventricular complexes or ventricular tachycardia, (5) severe fatigue or shortness of breath or (6) achievement of 85% predicted maximal heart rate. The exercise test was considered adequate if the patient developed chest pain or ECG changes consistent with myocardial ischemia or reached 85% of the predicted maximal heart rate.

ECG Interpretation

Standard 12-lead ECGs were analyzed for the location of any prior myocardial infarction (Q wave > 0.04 second). Infarct locations were designated as anterior, inferior or multiple. A significant ST-segment change with exercise was defined as deviation of the J point ≥ 0.1 mV and a horizontal or downsloping ST segment with a duration of 0.08 second.

RNA Technique

Radionuclide angiography was performed from the anterior projection using a multicrystal gamma camera (Baird-Atomic System Seventy-Seven) equipped with a one-inch, parallel-hole collimator. Ten or 15 mCi of technetium-99m pertechnetate were injected for the resting measurement and 15 mCi were injected for exercise measurements. Details of the technique have been published. A 1-inch, 20-gauge Teflon cannula was introduced into an external jugular vein after anesthesia with 1% xylocaine. The radioisotope was dissolved in less than 1 ml of normal saline and flushed in as a bolus with 10–20 ml of saline. Precordial counts were recorded in binary form at 25-msec intervals for 1 minute.

Data Collection and Analysis

All RNA data were stored on magnetic disks and subsequently transferred to magnetic tapes for permanent storage. Radionuclide data were processed using the computer and software of the Baird system after correction for background measured just before injection and for detector nonuniformity and electronic dead time count loss of the instrument. A curve representing count changes within the left ventricle was used to identify the times of end-systole and end-diastole of individual beats. Sequential addition of data from three to six beats starting at end-diastole produced an average or representative cardiac cycle. LVEF was calculated from the background-corrected representative cycle as

\[
\frac{ED\ counts - ES\ counts}{ED\ counts \times 100}
\]

where ED = end-diastolic and ES = end-systolic. A computer program outlined the ED and ES perimeters at the 21% isocount contour of the end-diastolic image. The aortic valve plane was identified from dynamic images and by isolation of the zone demarcating alternate count increases and decreases during diastole and systole. The area of the ED image was obtained by planimetry and the length was measured using a sonic digitizing device (Graf-Pen) coupled to a PDP-11/45 computer. The left ventricular end-diastolic volume (EDV) was calculated by the area-length method of Sandler and Dodge.

Regional left ventricular function was assessed by analysis of wall motion using both the cinematic display of the average cycle and the static display of the superimposed ED and ES perimeters. The static radionuclide angiographic left ventricular image was divided into three zones representing the anterior, apical and inferior walls.

Using the static display of the ED and ES perimeters, wall motion was categorized as hypokinetic if the ES perimeter indicated less than normal systolic excursion, akinetic if the ES and ED perimeters were superimposed and dyskinetic if the ES perimeter was extended beyond the ED perimeter. A wall motion abnormality was then graded from 0–6, where 0 = normal, 1 = < ½ wall hypokineti, 2 = > ½ wall hypokinetic, 3 = < ½ wall akinetic, 4 = > ½ wall akinetic, 5 = < ½ wall dyskinetic and 6 = > ½ wall dyskinetic. A grade greater than 0 was considered a wall motion abnormality when present at rest or when present during exercise if the rest grade was 0. If a wall motion abnormality was present at rest, the exercise wall motion grade had to exceed the resting grade by more than 2 to be considered significantly worse with exercise.

In addition, regional function was evaluated using a regional ejection fraction image that was generated by
subtracting ES counts from ED counts and dividing by the ED counts for each crystal in the left ventricular image. Differences in regional function were displayed using a 16-color coded image, each color representing approximately a 6% difference in regional ejection fraction. The regional ejection fraction image was considered to be abnormal at rest if at least one-third of a wall showed a four-count color difference from the most intense color in the ventricle. The same criterion applied to the exercise image if the resting image was normal. If a resting abnormality was present, an additional four-count color change involving one-third of the wall was necessary to be considered a significant change with exercise.12

Statistical Methods

A paired t test was used to analyze changes from rest to exercise in the same subject. A multiple linear regression analysis was used to assess the significance of the resting LVEF, exercise end point, number of diseased vessels, resting EDV and the exercise double product (heart rate × mean exercise blood pressure) as predictors of the change in LVEF from rest to exercise. Individual linear regression analyses were performed where indicated. Any p value < 0.05 was considered significant.

Results

Resting Left Ventricular Function

The heart rate at rest ranged from 50–120 beats/min (mean 79.9 ± 16.6 beats/min). The resting blood pressure was 123.2 ± 16.8/81.4 ± 12.7 mm Hg (range 88–178/50–130 mm Hg). The LVEF at rest ranged from 0.12–0.82 (mean 0.43 ± 0.18). Neither resting heart rate nor blood pressure showed a significant linear correlation with resting LVEF. The EDV at rest ranged from 70–378 ml. There was a significant inverse relationship between LVEF and EDV at rest (r = 0.69). The resting EDVs of the three subgroups were 246 ± 59 ml for group 1, 195 ± 58 ml for group 2 and 132 ± 35 ml for group 3.

Regional contraction abnormalities were present at rest in 100%, 86% and 8% of groups 1, 2 and 3 respectively. No patient had a discrete, potentially resectable aneurysm.

Exercise Left Ventricular Function

Exercise End Point

Of the 150 patients, 46 (31%) stopped exercise because of a horizontal or downsloping ST segment shift ≥ 0.1 mV, 21 (14%) stopped because of chest pain but had no ECG changes, 36 (24%) reached 85% predicted maximal heart rate without chest pain or ECG changes and 47 (31%) stopped because of fatigue.

Exercise Tolerance

The duration of exercise ranged from 90–840 seconds. Exercise duration was not significantly related to resting LVEF (fig. 1). Further, exercise durations in patients whose LVEF decreased during exercise were not significantly different from those in patients whose LVEF increased during exercise (fig. 2). Because the work load was increased every minute, the peak work load attained was proportional to the duration of exercise.

Heart Rate and Blood Pressure

The heart rate of the 150 patients averaged 134.4 ± 20.1 beats/min (range 80–170 beats/min) during exercise. There was no correlation between the heart rate during maximal exercise and resting LVEF (r = 0.003). The mean maximal heart rates of the three LVEF subgroups were 133.6 ± 18.7, 135.6 ± 19.7 and 134.0 ± 21.0 beats/min for groups 1, 2 and 3, respectively.

The mean blood pressure at peak exercise for the entire group was 157.4 ± 27.2/85.6 ± 15.6 mm Hg (range 70–230/20–120 mm Hg). Peak systolic blood pressure tended to be lower as resting LVEF decreased; the mean peak systolic pressure was 142.5 ± 24.9 mm Hg in group 1, 157.6 ± 22.1 mm Hg
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FIGURE 3. Left ventricular ejection fraction response to exercise (ΔLVEF) vs resting LVEF. Patients with normal resting LVEF show the greatest variability as well as the most profound decreases in LVEF with exercise. As resting LVEF decreases, the magnitude of the decrease in LVEF with exercise also diminishes. Patients with resting LVEF < 0.25 rarely have decreased LVEF with exercise.

in group 2 and 167.1 ± 26.5 mm Hg in group 3. However, peak systolic pressure was variable in each group and a linear regression analysis between peak systolic pressure and resting LVEF showed a weak correlation (r = 0.33).

Ejection Fraction

The LVEF at peak exercise ranged from 0.12–0.83. The maximal increase was 0.23, and the maximal decrease was 0.30. There was a significant but weak inverse relationship between LVEF at rest and the change in LVEF during exercise (r = -0.36, fig. 3). There was considerable variability in the change in LVEF with exercise (ΔLVEF), and the variability was greatest in the patients with a normal LVEF at rest. In patients with markedly decreased resting function, the range of the ΔLVEF was quite small. In group 1, 78% of the patients increased their ejection fractions with exercise, compared with 43% of patients in group 2 and 37% patients in group 3 (fig. 4). In contrast, the LVEF decreased during exercise in only five of 37 patients in group 1 (14%), compared with 19 of 51 (37%) and 32 of 62 (52%) in groups 2 and 3, respectively. Hence, during exercise the LVEF increased when the resting LVEF was low (0.04 ± 0.05, p = 0.0001), remained unchanged (–0.004 ± 0.08, p = 0.7) when the resting LVEF was intermediate, and decreased (–0.04 ± 0.13, p = 0.01) when the resting LVEF was normal.

Multiple linear regression analyses were performed to determine whether the resting LVEF, the resting EDV, the extent of coronary disease, the exercise end point and the exercise double product were predictors of the ejection fraction response to exercise. The first analysis excluded the extent of coronary disease because these data were unavailable in 38 patients with myocardial infarction. Both the resting LVEF (p = 0.0001) and the exercise end point (p = 0.02) were significant predictors of ΔLVEF. A separate analysis of the 112 patients whose coronary anatomy was known showed that the resting LVEF retained its significance as a predictor of ΔLVEF (p < 0.002), even when adjusted for the extent of coronary disease (p = 0.007) and the exercise end point (p = 0.06).

Patients in each of the three LVEF groups were separated into three subgroups according to the number of coronary arteries with significant stenosis, to examine the effect of the interaction between this variable and the resting LVEF on the ΔLVEF with exercise (table 1). In groups 2 and 3, the greater the ex-

<p>| Table 1. Left Ventricular Ejection Fraction and Extent of Coronary Artery Disease |
|----------------------------------------|----------------------------------------|----------------------------------------|
| 1-vessel CAD | 2-vessel CAD | 3-vessel CAD |</p>
<table>
<thead>
<tr>
<th>n</th>
<th>ΔLVEF</th>
<th>n</th>
<th>ΔLVEF</th>
<th>n</th>
<th>ΔLVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>(LVEF &lt; 0.25)</td>
<td>3</td>
<td>0.03 ± 0.06</td>
<td>3</td>
<td>-0.04 ± 0.05</td>
</tr>
<tr>
<td>Group 2</td>
<td>(LVEF 0.26–0.50)</td>
<td>9</td>
<td>0.04 ± 0.06</td>
<td>9</td>
<td>-0.02 ± 0.08</td>
</tr>
<tr>
<td>Group 3</td>
<td>(LVEF &gt; 0.50)</td>
<td>14</td>
<td>0.01 ± 0.13</td>
<td>24</td>
<td>0.00 ± 0.10</td>
</tr>
</tbody>
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Abbreviations: LVEF = left ventricular ejection fraction; CAD = coronary artery disease.
tent of coronary disease, the more abnormal the ejection fraction response to exercise. In contrast, in group 1, the extent of coronary disease did not appear to influence the ejection fraction response, although there were only three patients with one-vessel disease and three patients with two-vessel disease in this group.

The interaction of the exercise end point and resting LVEF on ΔLVEF is shown in Table 2. Patients in groups 2 and 3 who exercised to chest pain or significant ST-segment changes had decreased ejection fractions during exercise, whereas patients in group 1 who reached similar end points actually had increased ejection fractions. In all three groups, patients who stopped exercising because of fatigue had the least abnormal change in ejection fraction.

### End-diastolic Volumes

The mean EDV for all patients in the study increased with exercise, from 183.1 ± 68.1 to 214.3 ± 66.2 ml (p < 0.0001). The absolute changes in EDV with exercise are shown for the three groups in Figure 5. EDV increased significantly in all the groups although the change in group 1 (14 ± 39.6 ml) was smaller than those of groups 2 (33.2 ± 38.4 ml) and 3 (37.7 ± 34.2). There was an inverse linear relationship (r = -0.50) between resting EDV and the percentage change in EDV during exercise (Fig. 6). Hence, as the resting heart size increased, the relative increase in EDV with exercise became progressively smaller.

### Regional Left Ventricular Function

All group 1 patients, 90% of group 2 patients and 51% of group 3 patients had regional wall motion abnormalities during exercise (Fig. 7). Compared with the resting study, new or additional regional dysfunction was detected in 33% of the 150 patients in the study and was more commonly detected in patients with normal resting function. In addition, exercise-induced regional dysfunction was present significantly more often (p = 0.0004, Fischer's exact test) in patients who had pain or ischemic ECG changes during exercise (Fig. 8). The lower frequency of exercise-induced regional dysfunction in group 1 patients persisted even when the different frequencies of exercise-induced ischemia (pain or ECG changes) were considered. Hence, of the patients with clinical evidence of ischemia, new or additional regional abnormalities were detected in only 10% of group 1 patients.

### Figure 5

Change in end-diastolic volume (EDV) from rest (R) to exercise (E) in groups 1, 2 and 3. EDV was largest in group 1, intermediate in group 2 and normal in group 3. EDV increased with exercise in all groups.
Whether or not the left ventricular response to stress is altered by the presence of abnormal left ventricular function at rest has not been thoroughly studied, as previous reports have included few patients with markedly abnormal resting left ventricular function. To examine that question, we studied the effect of exercise stress on global and regional left ventricular function. First-pass radionuclide angiography was used to measure LVEF and EDV and to assess regional wall motion. The validity and reproducibility of those measurements using this technique have been reported.3, 14, 15

The study population was divided into three groups by their resting ejection fractions. These groups reflect commonly used clinical categories of normal, mildly to moderately impaired and severely impaired left ventricular function. However, to avoid the statistical bias that may result from arbitrary subdivisions, all statistical analyses were performed on the entire cohort.

The results of the study clearly show the heterogeneous nature of the response to exercise in patients with coronary artery disease, confirming previous findings.2, 3, 14 In addition, the significance of the resting LVEF as a determinant of ΔLVEF was confirmed by multiple linear regression analysis. Moreover, the influence of resting function retained its statistical significance when adjusted for the extent of coronary disease and the presence of pain or ST-segment changes during exercise, both of which have been shown to be important determinants of the left ventricular response to exercise.2, 3, 14

Despite individual variability, as a group, patients with normal resting function showed the most profound decreases in ejection fraction. As the resting LVEF decreased, the magnitude of the changes in LVEF decreased so that patients with mildly to moderately depressed resting LVEF showed no change in ejection fraction during exercise and patients with severely depressed resting function actually had increased ejection fractions with exercise.

Similarly, the prevalence of exercise-induced regional dysfunction was much more common in patients with normal resting function than in patients with abnormal resting function. That relationship persisted even after the differences in the frequency of exercise-induced ischemia were considered. In patients who developed pain or ECG changes during exercise, regional function deteriorated in only 10% of those with a resting LVEF < 0.25, compared with 59% and 51% of those with intermediate and normal resting LVEF, respectively.

In studies of stress-induced ischemia, Sharma et al.17 used contrast angiography and Rerich et al.2 used radionuclide scanning to demonstrate increases in EDV and end-systolic volume during ischemia. In the present study, there was an inverse relationship between the increase in EDV during exercise and the resting EDV.
The observation that the frequency and magnitude of exercise-induced left ventricular dysfunction decreases as resting LVEF decreases seems inconsistent with what might be expected from the results of animal studies, which suggest that global function is preserved by the enhanced contractility of non-ischemic myocardium until the ischemic area reaches a critical mass. Myocardial fibrosis secondary to infarction might be expected to reduce the ability to sustain global function during subsequent ischemia. One might predict that a reduced ejection fraction at rest would predispose to a further deterioration in ventricular function during an exercise stress; but the results of the present study indicate that ventricular function frequently improves or is maintained in patients with diminished resting function. Of the patients with a resting LVEF < 0.25, 78% actually increased their ejection fractions during exercise.

Several factors may have contributed to these unexpected findings. A systematic inaccuracy in the radionuclide technique could have accounted for the results. However, this explanation is unlikely, as studies have demonstrated a good correlation between contrast and radionuclide ejection fractions, including a study from this laboratory in patients with severe left ventricular dysfunction. Failure to perform adequate exercise is also an unlikely explanation for the finding, as 57 of 84 patients with abnormal resting LVEF attained 85% of predicted maximal heart rate or had pain or ECG changes during exercise, compared with 46 of 62 with normal resting function (NS). Another hypothesis is that our patients with low resting ejection fractions were not representative of all those with abnormal resting function. Certain patients who might have developed deterioration in ventricular function during exercise might have been excluded because of the severity of clinical symptoms at rest. Further, the effects of cardiotoxic medications other than propranolol were not assessed and may have contributed to our findings.

However, the results of the present study seem most consistent with the hypothesis that the frequency and magnitude of global and regional left ventricular dysfunction during exercise in patients with coronary artery disease depend on the mass of potentially ischemic myocardium present at rest. As the ventricle becomes progressively fibroosed, there is not only less myocardium capable of maintaining global function, there is also less muscle mass in jeopardy and consequently proportionally less dysfunction induced by stress. Once extensive fibrosis has occurred, any additional regional dysfunction during stress-induced ischemia must be relatively small. This view is supported by the observation that ECG evidence of ischemia is frequently not observed during exercise in patients with left ventricular dysfunction at rest.

Despite the influence of resting systolic function on the hemodynamic response to exercise, there was no relationship between the resting LVEF or ΔLVEF and exercise tolerance as measured by exercise time. Many patients in this study with severely compromised resting function achieved exercise times comparable to those achieved by patients with normal resting function. The lack of correlation between resting LVEF and exercise tolerance has been documented.

This study also confirmed the importance of both the extent of coronary artery disease and the exercise end point on the hemodynamic response to exercise noted previously. Exercise-induced left ventricular dysfunction is more likely to occur with more extensive coronary disease and in the presence of exercise-induced ST-segment changes. Eighteen patients in the present study (13 with a history of typical angina and nine with multivessel disease) had a normal left ventricular response to exercise despite adequate exercise and normal or minimally reduced resting ejection fractions. It is likely that the exercise response is influenced by multiple variables. The importance of the location of a stenosis in a coronary artery, the percentage diameter occlusion, presence of collateral vessels, coexistence of mitral insufficiency, sympathetic tone and cardiac medications merit further investigation.

The results of this study have important implications for the clinical use of radionuclide angiocardiography in the evaluation of patients with coronary artery disease. Neither global nor regional deterioration with exercise can be detected with enough frequency to warrant use of this technique to detect ischemia in patients with low ejection fractions at rest. Because there was no correlation between exercise capacity and resting LVEF or ΔLVEF, the value of radionuclide measurements during exercise in that group of patients does not seem to be of value in assessing the suitability for or benefits derived from any therapeutic intervention. However, prognostically significant information may be derived from exercise data in patients with low ejection fractions. The prognosis in patients with a low resting LVEF who show additional dysfunction with exercise may be different from that in patients whose ventricular function does not deteriorate with exercise. However, too few patients were studied and the follow-up was too short to evaluate that possibility.

In contrast, in patients with normal or mildly to moderately depressed left ventricular function at rest, the magnitude and frequency of changes during exercise are significantly greater. Hence, radionuclide angiography should be useful for quantifying both the effects of ischemia and the effects of therapy on the ischemic response in these patients.

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