SUMMARY  Preliminary studies have suggested that QRS-amplitude changes due to exercise-induced alterations in ventricular volume and function can improve the diagnostic value of the exercise test. To evaluate this, electrocardiographic data and equilibrium radionuclide angiographic images were recorded simultaneously in 18 normal subjects and 60 coronary artery disease patients at rest and during supine bicycle exercise. In 24 of the 60 coronary artery disease patients, left ventricular volumes were also calculated. The measured QRS amplitudes were the R waves in V₁, X, Y and Z, the Q wave in Z and the sum of amplitudes of R waves in X and Y and the Q wave in Z (ΣR). The mean left ventricular ejection fraction increased significantly from rest to peak exercise in the normal subjects; however, the mean left ventricular ejection fraction and mean volumes did not change significantly in the coronary patients. There was no significant difference in the mean QRS-amplitude changes during exercise between the coronary artery disease patients and the normal subjects in any of the measured leads. The sensitivity and specificity of exercise-induced QRS-amplitude changes for coronary disease were lower than ST-segment changes. For ST-segment changes, the sensitivity was 57% and specificity was 100%; the best sensitivity and specificity for QRS amplitude occurred in RZ, 48% and 67%, respectively. When ejection fraction was related to ΣR at rest and peak exercise for both normal subjects and coronary patients the correlations were fair (0.50, 0.51 respectively); however, the correlation between the magnitude of ΣR and ejection fraction change from rest to peak exercise was poor and did not improve with any other measured QRS amplitudes or by separating normal subjects from coronary patients with and without previous myocardial infarction. There were also poor correlations between end-diastolic and end-systolic volumes to QRS amplitudes at rest, peak exercise and their magnitude of change from rest to peak exercise. Thus, R-wave amplitude changes during exercise testing have little diagnostic value and are not related to exercise-induced changes in left ventricular function or volumes.

R-WAVE CHANGES in CM₅ have been reported to increase the diagnostic value of the exercise test. An increase in R-wave amplitude during exercise has been reported to indicate severe left ventricular dysfunction and coronary obstruction, while a decrease in R-wave amplitude is consistent with normal left ventricular function.¹ ² These changes are thought to be caused by an increase in end-diastolic volume during exercise and the Brody effect.³ The frequent S-wave increase in V₃ in normal subjects during exercise testing was postulated to be the result of increased myocardial function.⁴ Resting left ventricular ejection fraction obtained by contrast angiography has demonstrated a positive correlation with the sum of various Q- and R-wave amplitudes,⁵ but this has not been studied during exercise.

The gated equilibrium radionuclide angiography technique correlates well with angiographic studies of ejection fraction and is useful for detecting ejection fraction responses to exercise.⁶ ¹⁰ With this method, it is also possible to calculate end-diastolic and end-systolic volumes independent of geometric assumptions.¹¹ Thus, for the first time, QRS-amplitude changes during exercise could be simultaneously correlated with exercise-induced changes in left ventricular function and volumes. The aim of this study was to test the diagnostic value of exercise-induced QRS-amplitude changes and to evaluate the hypothesized mechanisms for these changes.

Methods

Patient Population

Sixty patients with coronary artery disease and 18 control subjects were studied. The control subjects were normal volunteers without clinical or electrocardiographic evidence of cardiovascular or pulmonary disease. The mean age was 41 years (range 30–57 years). The patients with coronary artery disease were males, and their mean age was 55 years (range 35–76 years). Coronary artery disease was documented by previous myocardial infarction (MI) at least 3 months before the study in 35 patients, coronary angiography in 10 patients, and angina pectoris with abnormal ECG and thallium treadmill test in the other 15 patients. An abnormal treadmill test was defined as more than 0.1 mV of flat or downsloping ST-segment depression or ST elevation in any of the 15 electrocardiographic/vectorcardiographic (ECG/VCG) leads other than aV₃R. Coronary artery disease was defined angiographically by the presence of at least a 70% decrease in the luminal diameter in one or more of the major coronary arteries. An abnormal thallium test
was defined as a perfusion defect at peak exercise filling during the recovery period or a perfusion defect remaining after redistribution. Ten of the coronary artery disease patients were treated with antianginal doses of propranolol (80–320 mg) and 15 of the patients were treated with either nitroglycerin or isosorbide dinitrate. All normal subjects and coronary artery disease patients were studied after they gave written informed consent.

Equipment and Imaging Techniques

Multiple ECG gated equilibrium radionuclide angiography was performed after complete mixing throughout the vascular space of 20–25 mCi 99mTc tagged to human serum albumin, administered via a peripheral arm vein as previously described. Imaging was performed by positioning the detector of an Anger-type single-crystal scintillation camera over the chest in a 40–50° left anterior oblique and 5–10° caudad tilt in order to isolate the left ventricle optimally from the left atrium. Data acquisition was accomplished using a commercially available nuclear medicine computer system, Medical Data System PAD (MUGA), which divided the RR interval into 28 equal time periods (frames) of 20–40-msec duration, depending on heart rate. It then assembled several hundred heart cycles at corresponding times to generate composite images throughout the cardiac cycle. In a 2-minute acquisition, usually 2500–7000 counts could be accumulated in the left ventricular region of interest at end-diastole in one 40-msec frame (counts corrected for background). To generate a time-activity curve, a rectangular region of interest was arbitrarily placed around the left ventricle at end-diastole. A computer algorithm (MUGE) automatically determined the edge of the left ventricle using a combination of the second derivative and a count-rate threshold of 5% per element as guidelines. Each subsequent frame was processed at the same threshold so that throughout all 28 frames a “variable” region of interest was used to determine the changing count rate within the left ventricle. A computer-assigned background region of interest outside the lower quadrant of the left ventricle was used to correct for noncardiac activity.

The ejection fraction was then calculated from the time-activity curve according to the formula:

\[
EF = \frac{ED_c - ES_c}{ED_c} \times 100
\]

where \( ED_c \) = left ventricular counts at end-diastole (usually the first frame of the time activity curve corrected for background) and \( ES_c \) = left ventricular counts at end-systole (nadir of curve corrected for background). The ejection fraction calculated by this technique has been shown to correlate well with those determined from biplane cineangiography, with a correlation coefficient in our laboratory of 0.91. The inter- and intraobserver variations of ejection fraction calculated by equilibrium radionuclide angiography in our laboratory is 0.04 ejection fraction units. Thus, in any single patient a significant change of ejection fraction was considered only when the change was at least ±0.05 ejection fraction units. End-systolic and end-diastolic volumes were calculated from 24 coronary artery disease patients using a radionuclide method free of geometric assumptions as previously described by Slutsky et al. Briefly, both at rest and peak exercise, the end-diastolic and end-systolic counts were divided by the number of processed heart beats and normalized for counts in milliliters of plasma drawn from a peripheral vein while the patient was at rest and again at peak exercise. Using this technique the correlation of radionuclide angiographic volumes with biplane contrast angiographic volumes was 0.98.

ECG/VCG Technique

Twelve ECG leads and three orthogonal Frank leads were obtained using 14 electrodes. Consistent electrode placement was accomplished using the Dalhouise square. The chest electrodes were small silver electrodes that did not interfere with imaging. The data were acquired using a specially developed, microcomputer-assisted, 15-lead ECG/VCG recorder (Marquette Data Logger) that records on paper and continuously stores on floppy discs. In this way we could obtain accurate peak exercise ECG/VCG changes. ST-segment changes were considered in any of the 15 ECG/VCG leads. To measure the QRS amplitudes, the isoelectric line was always defined as the PR interval and the highest and lowest amplitudes were averaged from consecutive beats during 10 seconds at rest and during the last minute of exercise. The measured QRS amplitudes were R wave in V1, R wave in X, R wave in Y, R wave in Z, Q wave in Z, as well as \( \Sigma R \), which is equal to RX + RY + QZ.

Study Protocol

Both the normal subjects and patients were studied first in the supine basal state and then during a graded supine bicycle exercise with up to three levels of increasing work load, each lasting 3 minutes. The test was discontinued because of any of the following: angina, more than 0.3 mV ST depression or fatigue. The supine exercise test was performed on an imaging table supporting an electronically braked bicycle ergometer (Uniwor 845T, Quinton Instruments) that kept a constant work load over a pedal speed range of 40–70 rpm. This allowed the work done by each patient at each level of exercise to be held constant over the 3 minutes. The ejection fraction and the 15 scalar leads were recorded in the supine resting state, and then the supine bicycle exercise was performed. Equilibrium data were recorded for 5 minutes at rest and continuously throughout the exercise period. The data from the last 2 minutes of the peak 3-minute work load level were analyzed to avoid the rapid changes in heart rate and other hemodynamic variables that usually occur in the first minute of a new exercise level and affect the accuracy of the ejection fraction calculations. Blood pressure was taken with an arm cuff at rest and at peak exercise.
Statistical Analysis

Statistical analysis used the t test for paired and nonpaired samples with a level of significance of <0.01. The correlation coefficients were significant at a level of <0.05. All the results are presented as the mean ± SD. Sensitivity and specificity were defined as described by Yerushalmy. Briefly, sensitivity is defined as the percentage of coronary disease patients with an abnormal response TP/(TP + FN); specificity is defined as the percent of subjects without coronary disease with a normal test TN/(TN + FP). To compare the combined sensitivity and specificity of the various ECG/VCG variables, Youden's J-summary index was used, which has an algebraic equivalent to the sum of sensitivity plus specificity minus 1. The best summary index is closest to 1, while negative summary indices indicate little diagnostic value.

Results

In table 1 the heart rates, systolic blood pressures, ejection fractions and QRS amplitudes (RV\textsubscript{s}, RX, RY, RZ, QZ, \Sigma R) are presented at rest and peak exercise for the normals, all the coronary artery disease patients and the coronary artery disease patients with and without previous MI. The mean heart rate and systolic blood pressure increased significantly from rest to peak exercise in all the groups. The mean heart rates at rest were not significantly different between the groups; however, the mean exercise heart rate was significantly higher in the normal subjects. In the normals the mean heart rate increased by 72 beats/min, but in the coronary artery disease patients it increased by only 52 beats/min (p < 0.001). There was no significant difference in the mean systolic blood pressure at rest and peak exercise between the normals and coronary artery disease patients. The mean ejection fraction at rest was significantly higher (p < 0.001) in the normals (0.62 ± 0.06) than in all the coronary artery disease patients (0.54 ± 0.11) or the group with previous MI. (0.49 ± 0.11). However, in the coronary artery disease patients without previous MI, the resting ejection fraction was similar to that of normals (0.62 ± 0.06). At peak exercise, the normal subjects had a mean increase of 0.12 ejection fraction units from the resting value. The coronary artery disease patients did not significantly change the mean ejection fraction from rest to peak exercise in either those with or without a previous myocardial infarction.

ECG/VCG Changes

The mean R-wave amplitudes in \textit{V\textsubscript{s}}, X and \Sigma R decreased significantly from rest to peak exercise both in normals and in coronary artery disease patients. There was no significant difference in the mean R-wave amplitudes in \textit{V\textsubscript{s}} or X either at rest or peak exercise between normal subjects and coronary patients. The mean \Sigma R amplitude was significantly lower (p < 0.001) at rest and at peak exercise in all the coronary artery disease patients (rest 1.98 ± 0.64 mV, peak exercise 1.68 ± 0.64 mV) and in patients with previous MI (rest 1.79 ± 0.63 mV, peak exercise 1.51 ± 0.56 mV), relative to the normal subjects (rest

<p>| Table 1. Mean (± SD) Heart Rates, Systolic Blood Pressures, Ejection Fractions and QRS Amplitudes of the Normal Subjects and Coronary Artery Disease Patients at Rest and Peak Exercise |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>EF</th>
<th>RV\textsubscript{s} (mV)</th>
<th>RX (mV)</th>
<th>RY (mV)</th>
<th>RZ (mV)</th>
<th>QZ (mV)</th>
<th>\Sigma R (mV)</th>
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<tr>
<td>NL (n = 18)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>rest</td>
<td>72 ± 10</td>
<td>125 ± 13</td>
<td>0.62 ± 0.06</td>
<td>1.38 ± 0.38</td>
<td>1.07 ± 0.37</td>
<td>1.02 ± 0.51</td>
<td>0.63 ± 0.26</td>
<td>0.42 ± 0.16</td>
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<tr>
<td>Pex</td>
<td>144 ± 17</td>
<td>184 ± 21</td>
<td>0.74 ± 0.06</td>
<td>1.16 ± 0.54</td>
<td>0.88 ± 0.23</td>
<td>0.97 ± 0.48</td>
<td>0.76 ± 0.34</td>
<td>0.36 ± 0.18</td>
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<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>rest</td>
<td>64 ± 10</td>
<td>131 ± 17</td>
<td>0.54 ± 0.11</td>
<td>1.38 ± 0.50</td>
<td>1.06 ± 0.34</td>
<td>0.64 ± 0.33</td>
<td>0.75 ± 0.30</td>
<td>0.25 ± 0.21</td>
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<tr>
<td>Pex</td>
<td>116 ± 21</td>
<td>173 ± 25</td>
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<td>1.14 ± 0.41</td>
<td>0.87 ± 0.31</td>
<td>0.60 ± 0.32</td>
<td>0.80 ± 0.27</td>
<td>0.22 ± 0.20</td>
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<tr>
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<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
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<tr>
<td>rest</td>
<td>67 ± 11</td>
<td>131 ± 15</td>
<td>0.49 ± 0.11</td>
<td>1.30 ± 0.52</td>
<td>1.00 ± 0.35</td>
<td>0.56 ± 0.29</td>
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<tr>
<td>Pex</td>
<td>117 ± 21</td>
<td>170 ± 23</td>
<td>0.48 ± 0.12</td>
<td>1.06 ± 0.40</td>
<td>0.80 ± 0.29</td>
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<tr>
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<tr>
<td>rest</td>
<td>63 ± 8</td>
<td>131 ± 17</td>
<td>0.62 ± 0.06</td>
<td>1.50 ± 0.46</td>
<td>1.15 ± 0.30</td>
<td>0.77 ± 0.35</td>
<td>0.66 ± 0.21</td>
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</tr>
<tr>
<td>Pex</td>
<td>116 ± 22</td>
<td>179 ± 28</td>
<td>0.64 ± 0.11</td>
<td>1.28 ± 0.40</td>
<td>0.98 ± 0.32</td>
<td>0.70 ± 0.36</td>
<td>0.76 ± 0.21</td>
<td>0.26 ± 0.19</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± sd. Abbreviations: NL = normal subjects; CAD = coronary artery disease patients; MI = myocardial infarction; HR = heart rate; SBP = systolic blood pressure; EF = ejection fraction; Pex = peak exercise.
2.51 ± 0.81 mV, peak exercise 2.21 ± 0.67 mV) and the patients without previous MI (rest 2.25 ± 0.58 mV, peak exercise 1.94 ± 0.66 mV). Mean R-wave amplitude in Y did not change significantly from rest to peak exercise in any of the groups of patients. However, at rest and peak exercise, the mean R-wave amplitude in Y was significantly lower in the coronary artery disease patients compared with the normals. Mean R-wave amplitude in Z did not change significantly in normals, coronary artery disease patients or coronary artery disease patients with previous MI; however, it did increase significantly in patients without a previous MI. The trend of the R wave in Z amplitude was to increase during exercise. The Q-wave amplitude in Z did not change significantly in the normals, however, it did decrease significantly in the coronary artery disease patients. The mean resting and peak exercise Q waves in Z were significantly lower in amplitude in the coronary artery disease patients than in the normals.

Figure 1 demonstrates the distribution of QRS-amplitude changes from rest to peak exercise between normals and coronary artery disease patients. An increase or no change in R wave was considered to be a normal response to exercise; a decrease was considered normal. However, the Q wave in the Frank scalar Z lead corresponds to the R wave in lead V2 of the standard ECG, while the R wave of the Frank scalar Z lead corresponds to the S wave in lead V2. Thus for lead Z, any decrease or no change in the R wave at peak exercise was considered an abnormal response and any increase in RZ at peak exercise was considered a normal response. The R wave in V5 increased or did not change at peak exercise compared with the preexercise amplitude in only 12 of the 60 coronary artery disease patients (for a sensitivity of 20%) and decreased in 14 of the 18 normals (for a specificity of 78%). The R wave in X increased or did not change in 10 of the 60 coronary artery disease patients (for a sensitivity of 17%) and decreased in 14 of the 18 normals (for a specificity of 78%). The R wave in Y increased or did not change at peak exercise in 30 of the 60 coronary artery disease patients (for a sensitivity of 50%) but decreased in only six of the 18 normal subjects (for a specificity of 34%). The R wave in Z decreased or did not change in 29 of the 60 coronary artery disease patients (sensitivity 48%) and increased in 12 of the 18 normals (specificity 67%).

The R waves increased or did not change in nine of the 60 coronary artery disease patients (sensitivity 15%) and decreased in 16 of 18 normals (specificity 89%). Thirty-four of the 60 coronary artery disease patients (sensitivity 57%) had abnormal ST changes at peak exercise, while none of the normals showed similar changes (specificity 100%). Thus, the sensitivity and specificity of ST changes at peak exercise were better than any of the QRS-amplitude changes and according to the summary index, the QRS changes reflecting the best sensitivity and specificity occurred in RZ (table 2).

Radionuclide Ejection Fraction Changes

Figure 2 shows the changes in ejection fraction from rest to peak exercise for each of the 18 normal subjects and each of the 60 coronary artery disease patients.
The coronary artery disease patients had a significantly lower mean resting ejection fraction than the normals. At peak exercise the mean ejection fraction increased significantly in the normals and did not change in the coronary artery disease patients. Every normal subject increased the peak exercise ejection fraction from a normal resting ejection fraction (≥0.50) by at least 0.05 ejection fraction units. Of the coronary artery disease patients, 44 had either a decrease or change in the peak exercise ejection fraction from rest.

Of the 16 coronary artery disease patients that increased peak exercise ejection fraction by at least 0.05 ejection fraction units, four had an abnormal resting ejection fraction (<0.50); three were taking antianginal doses of propranolol and three had isolated right coronary artery stenosis. Of the remaining six, three stopped exercise because of fatigue, and three because of angina or significant ST changes.

Volume Changes

In figure 3 the end-diastolic and end-systolic volume changes from rest to peak exercise for 24 of the coronary artery disease patients are presented. Both the mean end-diastolic and end-systolic volumes did not change significantly from rest to peak exercise. However, nine patients had increased end-diastolic volume from rest to peak exercise, of whom seven (78%) had accompanying angina or abnormal ST changes at peak exercise, compared with only five of the 15 patients (33%) that decreased or did not change.
end-diastolic volume at peak exercise. Of the nine patients who had increased end-diastolic volume at peak exercise only one also had an increase in one of the QRS amplitudes (RV5, from 1.1 mV at rest to 1.2 mV at peak exercise); the other seven patients decreased all QRS amplitudes measured at peak exercise.

Correlation of Ejection Fraction to QRS Amplitudes

Figure 4 shows the correlation coefficients between ejection fractions and QRS amplitudes at rest and peak exercise and their magnitude of change from rest to peak exercise for normal subjects and coronary artery disease patients together, for normal subjects, for all the coronary artery disease patients, and for the patients with and without previous MI. In all these five groups there was a fair correlation between most of the R-wave amplitudes and ejection fraction both at rest and peak exercise. In most of the cases at peak exercise the correlation coefficients were somewhat lower than at rest. However, the correlation between the magnitude of change of ejection fractions and change of QRS amplitudes during exercise was never significant. The best correlations were obtained in the combined normals and coronary artery disease patients at rest (r = 0.50) and peak exercise (r = 0.51). Figure 5 is an example of the correlation obtained from both the normals and the coronary artery disease patients for the \( \Sigma R \) at rest and peak exercise and the magnitude of changes from rest to peak exercise. At rest, the correlation coefficient was 0.50 and at peak exercise it was 0.51. Both these correlations were significant (\( p < 0.001 \)). However, the correlation coefficient between the change of ejection fraction and \( \Sigma R \) amplitude changes from rest to peak exercise was not significant. Fourteen subjects had a \( \Sigma R \) amplitude of less than 1.5 mV, and only two of them were normals; eight of the 12 coronary artery disease patients in this group also had resting ejection fractions of less than 0.50 (fig. 5, rest). At peak exercise there were 24 coronary artery disease patients and two normal subjects who had \( \Sigma R \) amplitude of less than 1.5 mV and 14 of them, all with coronary artery disease, also had reduced peak ejection fractions of less than 0.50 (fig. 5, peak exercise).

Volumes and QRS Amplitudes Correlations

In figure 6, the correlation coefficients between end-diastolic and end-systolic volumes and R-wave amplitudes are presented at rest, peak exercise and for the magnitude of change from rest to peak exercise. All these correlations were poor, although they were again somewhat better at rest and peak exercise than for the magnitude of change from rest to peak exercise.

QRS Changes During Treadmill Testing

To test if similar results would be obtained, 25 of the coronary artery disease patients had a treadmill exercise test done within 24 hours of the supine bicycle exercise test. R-wave amplitudes in V5 were measured at rest and at maximal treadmill exercise. During the treadmill exercise test the mean R-wave amplitude in V5 decreased significantly (\( p < 0.001 \)) from 1.35 ± 0.63 mV at rest to 1.16 ± 0.53 mV at peak exercise (fig. 7).

Discussion

Recently, Bonorini et al.\textsuperscript{1, 2} recommended the use of R-wave amplitude changes during exercise to improve the sensitivity and specificity of the exercise test. As previously hypothesized\textsuperscript{3, 4, 15-18} they suggested that exercise-induced changes in left ventricular function and volume cause the QRS-amplitude changes. However, these theories have never been validated, mainly because of technical problems involved in simultaneously studying left ventricular function, volume and QRS amplitude during exercise. Nuclear cardiology and newer ECG techniques make it possible to measure dynamic changes in left ventricular function, volumes and the ECG continuously during exercise. The equilibrium radionuclide angiography technique has been extensively validated by us\textsuperscript{9} and others\textsuperscript{6-8, 10} and found to be very accurate. Thus, for the first time, the relationship of exercise-induced
Figure 5. The correlation between ejection fraction and mV ΣR amplitude at peak exercise and at rest (left) and the magnitude of change from rest to peak exercise (Δ) (right). Closed circles represent normal subjects (NL) and open circles represent coronary artery disease patients (CAD).

Figure 6. The correlation coefficients between end-diastolic volumes (EDV) and end-systolic volume (ESV), and QRS amplitudes (RV5, RX, RY, RZ, ΣR) at rest, peak exercise and the magnitude of change from rest to peak exercise (Δ).
changes in left ventricular volume and function to the electrocardiogram could be assessed.

The magnitude and direction of exercise-induced volume changes either in normals or coronary patients is still controversial. Rushmer et al. used microcrystal ultrasound transducers in conscious dogs and concluded that the heart dimensions often become smaller during exertion. However, using the same technique in swimming dogs, Erickson et al. showed an increase in end-diastolic left ventricular diameter during exercise. Using epicardial metal markers, Braunwald et al. showed only small changes in both end-diastolic and end-systolic dimensions during supine exercise. Using the thermodilution technique in normals and patients with a variety of heart diseases, Gorlin et al. found variable changes in end-diastolic volume during supine exercise. Using the echocardiographic technique, Stein et al. demonstrated a slight decrease in end-systolic dimension without a significant change in end-diastolic dimension during supine exercise in normal subjects. Using contrast angiography and nuclear angiography, it was demonstrated that coronary artery disease patients who developed angina during supine exercise usually increased both the end-diastolic and end-systolic volumes, while patients who did not develop angina usually did not change significantly the left ventricular volumes. In another study, using erect bicycle exercise, both normals and coronary artery disease patients increased the end-diastolic volume during exercise. Thus, previous studies suggest that differences in exercise position and severity of coronary disease account for different volume responses to exercise. In the present study the 24 coronary artery disease patients in whom we could obtain volumes using the radionuclear angiography technique did not change significantly either the mean end-diastolic or end-systolic volumes from rest to peak supine exercise. However, of nine patients that increased end-diastolic volume during exercise, seven developed angina or significant ST changes at peak exercise.

Ejection fraction changes during exercise have been extensively investigated with radionuclide angiography. Most investigators agree that ejection fraction increases during exercise in normal subjects, while most coronary artery disease patients show no change or a decrease. In the present study the normal subjects increased the ejection fraction significantly by a mean of 0.12 ejection fraction units and each subject increased the ejection fraction by at least 0.05; the coronary artery disease patients did not significantly change the mean ejection fraction from rest to peak exercise. However, 16 of the 60 coronary artery disease patients increased the ejection fraction at peak exercise by more than 0.05. Of these 16 patients, four had an abnormal resting ejection fraction (<0.50), which as an isolated finding is diagnostic of left ventricular dysfunction. Of the other 12 patients, three were taking antianginal doses of propranolol and three had isolated right coronary lesions, both causes of a false-negative ejection fraction response to exercise as shown previously by our group. Thus the other six patients (10%) are true false-negative responders. Of the six, three patients did not develop angina or ST changes during exercise and stopped because of fatigue. We can speculate that in these patients the exercise challenge was not enough to cause a mismatch between oxygen demand and supply.

QRS-amplitude changes during exercise are as controversial as volume changes. Bonoris et al. measured exercise-induced R-wave changes in CMR in a highly selected group of coronary artery disease patients and in normal subjects. Most of these patients were false-positive or false-negative responders by ST-segment criteria. They defined an abnormal response as an increase or no change in R-wave amplitude and a normal response as a decrease in R-wave amplitude at
peak exercise from rest. Using these criteria, the sensitivity and specificity of R-wave amplitude changes during exercise were better than ST changes. They also compared R-wave changes during exercise to the severity of angiographic lesions and concluded that exercise-induced increases in R-wave amplitude occurred with left ventricular dysfunction.1 Katzeff and Edwards4 predicted an electromechanical association between S-wave amplitudes and cardiac mechanical function. In normal subjects, they reported an increasing S-wave voltage in a horizontal bipolar lead with increasing work load and concluded that the amplitude of the S wave in certain leads acts as an indicator of left ventricular function. Kentala et al.15 studied the variation of R wave from V₆ during progressive bicycle exercise testing as an index to predict the results of physical training in patients with coronary artery disease. They concluded that the R-wave changes were greatest in the cardiac patients who responded to exercise training, and the smaller the dynamic changes of the QRS amplitude during exercise testing the worse the training results. In another paper Kentala and Luurila16 showed that R-wave amplitude changes occurred with postural changes and exercise in healthy subjects and patients surviving acute MI.

In the present study, R-wave changes during exercise had the same directions in normal subjects as in coronary artery disease patients. In both normals and unselected coronary artery disease patients, the sensitivity and specificity of QRS-amplitude changes were less than for ST changes. No single lead could separate normals and coronary patients using the R-wave amplitude criteria, including RV₅ and RX. Among the nine patients who increased end-diastolic volume at peak exercise, only one also increased the R-wave amplitude in V₆ (from 1.1 mV at rest to 1.2 mV at peak exercise). A possible explanation for these different results could be that we used supine bicycle exercise rather than treadmill or erect bicycle exercise. To examine this, 25 of the coronary artery disease patients were retested on a treadmill and RV₅ amplitude was measured at rest and peak exercise. There was again a significant decrease in RV₅ amplitude from 1.35 ± 0.63 mV at rest to 1.16 ± .53 mV at peak exercise (p < 0.001) and only two patients increased the amplitude of R wave in V₆ from rest to peak exercise. Another possible explanation is that others may only allow their coronary patients with severe disease to perform submaximal exercise. During submaximal exercise, most subjects have an increased R-wave amplitude, but decrease it at higher work loads. As we described previously,30 exercise-induced R-wave changes in the Z vectorcardiogram lead had somewhat better sensitivity and specificity than amplitudes measured in other leads. Using the sum of R-wave amplitudes from X, Y and Z did not improve the sensitivity or specificity of the test.

The relationship between QRS amplitudes and left ventricular volumes and function at rest has been extensively investigated. The Brody effect,3 which explains the effect of intracardiac blood on QRS potentials by augmentation of the initial portion of the QRS complex and attenuation of the latter portion, was derived from models31,32 and animal experiments.33 However, human studies have not all agreed with this theory of why an increase in left ventricular end-diastolic volume should increase R-wave amplitude. Baxley et al.34 and Vine et al.35 found a positive correlation between QRS voltage and left ventricular end-diastolic volume while Talbot et al.37 found an inverse correlation for volume and QRS voltage.

The relationship of QRS amplitudes and ejection fraction was studied previously at rest. Gottwik et al.3 and Askennaz et al.38 compared QRS amplitudes obtained from the orthogonal Frank system with left ventricular ejection fraction measured by contrast angiography. They found that the sum of RX + RY + RZ correlated significantly with ejection fraction, and this correlation even improved with the ejection fraction of postextrasystolic beats. However, these studies were not simultaneous ECG-function-volume studies and were done only at rest. In the present study we found a fair positive correlation at rest and peak exercise between R waves and ejection fractions and, as in the previous works3,38 we also found that the best correlations were obtained using ΣR. However, when we correlated the magnitude of exercise-induced changes in QRS amplitudes in the various leads to ejection fraction changes, the correlations were not significant. For left ventricular volumes, there were no significant correlations either at rest or peak exercise or between the magnitude of changes between rest and peak exercise. We could not find any improvement in the correlation coefficients when we separated the normals from coronary patients, and coronary patients with or without previous MI. Thus, although we agree that there is a positive correlation between R-wave amplitude and left ventricular ejection fraction either at rest or peak exercise, this relationship does not explain the changes that occur in the QRS amplitudes during exercise.

Other mechanisms than changes in left ventricular volume and function must be responsible for exercise-induced QRS-amplitude changes. Changes in wall thickness during exercise could result in alterations in size or number of individual muscle fiber dipoles. Changes in the position of the heart in the thorax during exercise and in the amount of air in the lungs during exercise can affect the conductivity of the chest. These are hypothesized mechanisms that require further investigation.

In summary, during maximal exercise there is a significant increase in ejection fraction in normals, no change or a decrease in ejection fraction in most of the coronary artery disease patients, no significant volume changes in coronary patients who are not developing angina pectoris, and a similar decrease in R-wave amplitude during maximal exercise both in normals and coronary artery disease patients.

Thus, our study has not confirmed the direction of exercise-induced QRS changes in coronary patients or
their relationship to left ventricular volume and function. We feel that further research is needed before exercise-induced QRS changes can be used to make diagnostic decisions.

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