Multiple-lead QRS Changes with Exercise Testing
Diagnostic Value and Hemodynamic Implications

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SUMMARY To evaluate the diagnostic potential and hemodynamic significance of exercise-induced multiple-lead QRS changes, we studied exercise test responses in 230 patients with chest pain syndromes undergoing Bruce protocol exercise tests. When increases in the R waves of multiple ECG leads (ΣR) plus ST segment change > 1 mm were present, 74 of 75 patients (99%) had coronary disease; this was a higher percentage than that achieved with either measurement alone or when ST change was combined with increase in R in a single lead. Sixty-four of the 75 patients (85%) had multivessel disease, the most severe form of coronary artery disease. Left ventricular end-diastolic pressure (both at rest and after left ventriculography), presence and degree of resting ventricular asynergy, and ejection fraction were all significantly more abnormal in patients whose ΣR increased, regardless of ST-segment change. Further, in patients who stopped exercise because of cardiac symptoms, exercise duration and the product of heart rate times blood pressure were significantly lower when ΣR increased. Thus, the mechanism for the increase in ΣR with exercise in patients with coronary artery disease appears to be related to abnormalities in left ventricular function.

DESPITE CRITICISMS,1 the exercise test remains widely used in the evaluation of chest pain syndromes. However, because the problems associated with this use of exercise testing appear to be related in large part to the reliance on ST-segment changes as the sole criterion for diagnosing ischemia due to coronary artery disease, other ECG and non-ECG aspects of the exercise response have recently been used as diagnostic guides. These other features have included changes in heart rate and blood pressure (and the product of the two), exercise test duration, and increase in R-wave amplitude.2,3,4 The latter measurement, however, has been used only in a single ECG lead. The present study was designed 1) to evaluate the usefulness of multiple-lead QRS changes in diagnosing coronary artery disease in a symptomatic population, and 2) to determine the hemodynamic and ventriculographic implications of such QRS changes.

Materials and Methods

Patient Selection

The cardiac catheterization files of the Peter Bent Brigham Hospital were retrospectively reviewed for the period January 1, 1975 to July 1, 1977, and all patients without bundle branch block who had maximal, symptom-limited Bruce protocol5,6 exercise tolerance tests for evaluation of chest pain syndromes were identified. These exercise tests were performed in the hospital or its private out-patient facility, usually within 24 hours before diagnostic cardiac catheterization, but always within 6 weeks, and no patient had marked clinical deterioration between the exercise test and the catheterization. All tests were performed with continuous, single-lead monitoring, and 12-lead ECGs and cuff blood pressures were obtained every 3 minutes during exercise, at its completion, both standing and supine, and at 1, 3, 5 and 8 minutes of recovery, or every 3 minutes thereafter until the tracing returned to control. The Mason-Likar modification of the limb lead placements7 was used for all tests. Two hundred thirty-seven patients were identified, but in seven there were technical problems that did not allow comparison of postexercise ECGs with the resting tracings (usually one precordial lead having come loose during exercise); the other 230 patients formed the study group. Thirty-three of the patients were taking digitalis glycosides and 81 were taking propranolol; 16 had voltage criteria for left ventricular hypertrophy in the precordial leads;12 14 had electrocardiographic diagnosis of anterior myocardial infarction15 with small or no R waves in leads V1 to V4; and 20 had inferior infarctions12 with no R wave in aV1. No patient had true posterior myocardial infarction.13 Other characteristics of the population — sex ratio, age, prior chest pain history and exercise-induced chest pain (or the patient’s usual anginal equivalent) — are shown in table 1.

All patients in the study underwent 60 seconds of supine hyperventilation, and none had either ST-segment or QRS changes with hyperventilation. Additionally, no patient had further ST-segment or QRS changes when upright, before commencing exercise. The ECGs compared were the supine, prehyperventilation control tracing, and the supine, postexercise tracing showing the greatest degree of ST-segment change. This was usually the supine tracing recorded immediately after exercise (also used for tests without ST changes), but in four instances, it was the tracing recorded 1 or 3 minutes after exercise. R-wave height (or S-wave depth) was measured at the end of the PR segment and was the average of all beats measured for each time period in each lead.

ECG positivity was defined as 1 mm of ST-segment
elevation or depression (1.5 mm if slowly upsloping) in any lead but aVR, 80 msec after the end of the QRS complex. In patients taking digitalis glycosides, or with nonspecific ST-segment abnormalities at rest, a 1-mm increase in resting ST-segment abnormality was used as the criterion for ST-segment positivity. Tests that did not show this degree of ST-segment change and during which at least 85% of the maximal predicted heart rate for the patient's age and sex was achieved were considered nondiagnostic. If 85% of the maximal heart rate was not achieved, the test was considered negative. The sum of the R waves (ΣR) was defined as the R waves in aV1, aV2, aV3, V1 to V6 plus the S waves in V1 and V2. This was compared with the R wave in V4 (RV4). No change or an increase in an R-wave parameter were categorized as an abnormal response; a decrease was considered a normal response. Only directional change of the RV4 or ΣR was used in this analysis. No correlation could be made between absolute value of resting or exercise RV4 or ΣR and coronary disease, nor was the magnitude of R-wave change helpful diagnostically.

Cardiac catheterization and pressure measurement, left ventriculography and coronary angiography were performed by the standard methods used in our catheterization laboratory. The ventriculograms were performed either in the 30° right anterior oblique projection (111 patients), or in both 30° right anterior oblique and 60° left anterior oblique projections (119 patients). Because nearly half the patients did not have left anterior oblique studies, only the analyses of the right anterior oblique ventriculograms were used.

The coronary arteriograms and left ventriculograms were interpreted by three staff cardiologists and cardiovascular radiologists, and the consensus of their findings as represented on the final catheterization report was used to determine 1) the number* of significantly obstructed coronary arteries (>70% luminal diameter narrowing), and 2) the number of left ventricular wall segments (anterior, apical, inferior) showing abnormal wall motion. Abnormal wall motion, or asynery, was classified as hypokinetic (mild impairment), akinetic (severe impairment), or dyskinetic (paradoxical motion) using standard criteria based on the reduction or increase in local wall motion. An asynery index was constructed using the sum of the values of asynery for the three segments, with normokinesis assigned a value of 0, hypokinesis 1, akinesis 2, and dyskinesis 3. Left ventricular end-diastolic pressure was defined as the left ventricular pressure 40 msec after the onset of the QRS complex in the simultaneously recorded external ECG lead. All the patients had this value determined at rest, and 126 also had it measured 2–3 minutes after the left ventriculogram.

**Definition of Predictive Values**

- **Predictive value of an abnormal ST-segment or QRS response to exercise** was defined as the percentage of patients with the response who had at least one significantly obstructed coronary artery (true-positive ECG responses/true-positive + false-positive ECG responses).

- **Predictive value of a normal QRS or ST-segment response** was defined as the percentage of the patients with the response who had no significantly obstructed coronary artery (true-negative ECG responses/true-negative + false-negative ECG responses).

*The left main coronary artery was considered as two vessels, if significantly obstructed.
Predictive values for multivessel disease were defined in an analogous manner, except that the presence or absence of narrowing in two or more coronary arteries or the left main coronary artery was required.

Statistical Analyses

In evaluating the proportions of patients with a given ST-segment or R-wave response and the percentage of patients with R-wave increases and decreases showing ventricular wall motion abnormality, the chi-square test was used to test the null hypothesis that differences in proportions could have occurred by chance. For evaluating the group means of the hemodynamic and exercise data, an unpaired t test was used to test the null hypothesis that the differences noted in mean values were random variations. The asymmetry index did not distribute normally, due to a bulge of patients at the lowest possible value, 0. Because of this skew, a nonparametric test, the large-sample modification of the Wilcoxon rank-sum test, was used to test the similar null hypothesis. All data are expressed as the mean ± standard deviation, except for the asymmetry indices, which are expressed as the mean only.

Results

Patient Characteristics

There was no correlation between the age distribution of the patients and the presence or absence of R-wave or ST-segment abnormalities (table 1). The proportion of men was higher in each of the abnormal groups than in the whole population. A history of typical chest pain was more frequent than atypical pain. Exercise-induced chest pain was less common than a history of typical angina, and occurred most commonly when ST-segment change was present.

Coronary Arteriography

Of the 230 patients, 68 (31 men and 37 women) had normal coronary anatomy, 43 (31 men and 12 women) had one-vessel obstruction, 59 (51 men and eight women) had two-vessel obstruction, 60 (54 men and six women) three-vessel obstruction, and seven (five men and two women) had left main coronary obstruction.

Predictive Values for Coronary Artery Disease of Increases in ΣR, RV₅ and ST Change

Figure 1 shows the predictive values for coronary artery disease of an increase in ΣR, increase in RV₅ and ST-segment change. All were highly predictive of coronary artery disease, with ΣR the best predictor, but there was not a significant difference between these parameters. We then looked at combinations of QRS and ST changes (table 1). If ≥ 2 mm of ST-segment depression or 1 mm ST elevation was present, ST-segment change alone was very highly predictive of coronary obstructive disease, and there was no need to consider QRS changes. However, for the group with 1-1.9 mm ST depression, ST-segment change alone was less impressive as a predictor of coronary disease. When increases in ΣR were added, a statistically significant improvement in predictive value over ST change alone occurred for this subgroup (p < 0.05). Increases in RV₅ and ST depression did not significantly improve the predictive power over ST change alone (p > 0.10). Most important, if there was at least 1 mm of ST-segment depression and ΣR also increased, coronary disease was invariably present (74 of 75).

Because the prevalence of coronary artery disease was lower in women than in men (41% vs 81%), the predictive values were lower: 60% (15 of 25) for ST-segment changes and increases in RV₅ vs 70% (16 of 23) for increased ΣR. The difference was not statistically significant.

The predictive value for multivessel disease of increase in ΣR, RV₅ and ST change was 0.76 (76 of 101), 0.64 (70 of 110), and 0.72 (98 of 137), respectively. These figures do not differ significantly from each other. However, 64 of the 75 patients (85%) with increases in ΣR and ST depression had multivessel disease, including 19 of 24 patients (80%) with 1-1.9 mm ST depression and 45 of 51 (88%) with ≥ 2 mm ST depression.

If ST change was not present (negative or nondiagnostic tests), the predictive value of ΣR was also less, yet 73% (19 of 26) of these patients had coronary disease. All of these tests were, by definition, falsely negative by ST criteria alone.

Figure 2 and tables 1 and 2 show that the absence of ST change, or a decrease in ΣR, or a decrease in RV₅ were all poor predictors of the absence of coronary artery disease, and the differences between them are, again, insignificant. In women, with their lower frequency of significant coronary disease (41% vs 81% in men), the negative predictive values were better: 0.71 (27 of 38) with no ST depression and decrease in RV₅ and 0.75 (30 of 40) with decreased ΣR had normal coronary anatomy.
Table 3 shows predictive values for positive and negative R-wave and ST-segment change for patients taking cardioactive medications or with left ventricular hypertrophy and/or myocardial infarction. Each of these patient groups has very high prevalence of coronary artery disease: 0.91 (21 of 23) for the digitalis group, 0.79 (56 of 71) for the propranolol patients, 0.80 (eight of 10) for those taking both drugs, 0.88 (14 of 16) for those with left ventricular hypertrophy, 1.0 (14 of 14) for those with anterior and 0.95 (19 of 20) for those with inferior infarction. As expected, predictive values are very high for positive tests, and very low for negative ones. In 28 instances, 8R and RV5 changed in opposite directions, and in 20 of these (12 of 17 in patients with coronary disease and eight of 11 without coronary disease), 8R correctly predicted presence or absence of coronary obstruction. However, this difference in predictive power did not reach statistical significance. (p = 0.08).

Exercise Tolerance and Changes in QRS

In comparing exercise and catheterization variables, the patients are categorized as having normal or abnormal R-wave changes with exercise by 8R only. Figure 3A shows the duration of exercise for patients limited by chest pain (63, 28%), fatigue (155, 69%), and dyspnea (seven, 3%); patients limited by dyspnea were excluded from this part of the analysis.

Table 2. Predictive Value of 8R, RV5, and ST Depression with Exercise

<table>
<thead>
<tr>
<th>Presence of CAD</th>
<th>Absence of CAD</th>
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<tbody>
<tr>
<td></td>
<td>ΣR</td>
</tr>
<tr>
<td>All tests</td>
<td>93/101</td>
</tr>
<tr>
<td>(n = 230)</td>
<td>(0.93)</td>
</tr>
<tr>
<td>ECG positive tests</td>
<td>24/24</td>
</tr>
<tr>
<td>(1-1.9 mm) (n = 62)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>ECG markedly positive tests</td>
<td>50/51</td>
</tr>
<tr>
<td>(≥ 2 mm) (n = 75)</td>
<td>(0.98)</td>
</tr>
<tr>
<td>Negative tests</td>
<td>7/9</td>
</tr>
<tr>
<td>(≥ 85% heart rate for age) (n = 48)</td>
<td>(0.77)</td>
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<tr>
<td>Nondiagnostic tests</td>
<td>12/17</td>
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<tr>
<td>(&lt; 85% heart rate for age) (n = 45)</td>
<td>(0.71)</td>
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Abbreviations: ΣR = R in aV1, aVF, V1 to V6 plus S in V1 to V2 (mm); † = increase; ‡ = decrease; RV5 = R wave in V5 (mm); ST = 1 mm or greater ST depression with exercise; CAD = coronary artery disease.
unless normal pulmonary function studies were recorded on their charts. Patients limited by dyspnea had significantly shorter exercise duration, on the average, if SR increased with exercise. In addition, in the same patients, peak double products (fig. 3B) were significantly lower in patients with increased SR. Those taking digitalis had similar exercise findings. Those taking propranolol (alone or with digitalis) also had comparable exercise tolerance whether or not SR increased (6.2 ± 2.7 vs 6.1 ± 2.8 minutes), but significantly lower peak double products if SR increased (15.8 ± 4.4 vs 18.6 ± 5.5 mm Hg/min, p < 0.05).

Hemodynamics and Wall Motion and the Change in SR

For the group as a whole, all hemodynamic and wall motion parameters evaluated were significantly different and deviated from normal to a greater extent when SR increased with exercise. Specifically, left ventricular end-diastolic pressure both at rest and, when measured, after left ventriculography, was significantly higher in patients with increased SR (fig. 4A). More asynergy was present in those patients, evaluated at rest (fig. 4B), and they had lower resting ejection fraction (fig. 4C).

Of 11 patients with hypotension at peak exercise, 10 (91%) had increases in SR. This included the only patient with a false-positive increase in SR who had exercise-induced hypotension and proved to have a congestive cardiomyopathy at catheterization.

Table 4 shows that these comparisons were statistically significant between patients showing increases and decreases in SR, whether ST depression of 1–1.9 mm, ST depression ≥ 2 mm, no ST depression at greater than 85% of predicted heart rate, or no ST depression at less than 85% of predicted heart rate occurred. The presence of propranolol therapy, with or without digitalis, also did not alter these comparisons. There were two exceptions, where the trend, though in the same direction, did not reach statistical significance.

Patients with coronary artery disease were significantly more likely to have ventricular asynergy if SR increased (77%, 72 of 93) than if it decreased (36%, 27 of 74) (p < 0.005).

False-positive Increase in SR

There were eight false-positive increases in SR in patients with no significant coronary disease. One had a final diagnosis of congestive cardiomyopathy, and was the only patient with abnormal ventricular wall motion or an abnormal ejection fraction in this group. Three others had abnormal left ventricular end-diastolic pressure at rest, which became more abnormal after ventriculography. Two had abnormal left ventricular end-diastolic pressure only after ventriculography, and two had no detectable cardiac abnormality at catheterization. For comparison, of the 55 patients with no coronary obstruction and a decrease in SR (true negatives), none had abnormal ejection fractions, three (5%) had mildly abnormal wall motion, 10 (18%) had an abnormal resting left ventricular end-diastolic pressure, 11 (20%) had an abnormal end-diastolic pressure after ventriculography and 42 (77%) had no detectable abnormality at catheterization.

Discussion

Changes in the ECG During Exercise as Predictors of Coronary Artery Disease

It is clear from the data presented here that increases in R-wave voltage with exercise, especially in multiple leads, are highly predictive of coronary artery disease, at least in a symptomatic population. Furthermore, the combination of increased SR and
prevalent, while false-negative results are less so. Even when there are no changes in the ST segments, however, increase in ΣR still usually indicates coronary disease.

Mechanism(s) of Exercise-induced QRS Change

Our data appear consistent with the hypothesis that the change in QRS voltage associated with maximal exercise is a result of left ventricular dysfunction. Bonoris and associates⁸,⁹ assume that the Brody effect¹¹ is responsible: increases in the volume of a heart chamber increase the radially directed electrical forces from the chamber walls, resulting in a larger amplitude of the QRS in an electrocardiographic lead. Normally, exercise or rapid atrial pacing leads to a diminution of the left ventricular volumes at both end-systole and end-diastole.¹⁸-²² However, when ischemia is induced by exercise and end-systolic volume is measured, most²²,²³ but not all²⁴ investigators find an increase in end-systolic volume of up to 50%.²⁵ Lesser increases in this volume are seen with atrial pacing.¹⁹-²¹

In normal patients, R waves decrease with exercise,²⁶ and it is tempting to infer causation from the association of volume change and increase in R wave. However, this may not be the sole explanation for the changes we saw in our patients with coronary disease.

Holland and Arnzendorf²⁶ have reviewed, from the perspective of solid-angle theory, the factors that modify the size of the QRS complex in any recording lead. These include the position of the heart with respect to that lead (including the Brody effect), the velocity of electrical conduction in the myocardium, the sequence of activation (for example, the presence of conduction blocks), the resting myocardial membrane voltage and the properties of the heart as a volume conductor, which include the intracellular properties such as hypertrophy of the cells and extracellular ones such as the content of the extracellular space, both tissue content (fibrosis, etc.) and ion concentrations.

Changes affecting some of the other (that is, not volume related) properties determining QRS voltage may occur with ischemia. Experimental studies in several species with ischemic stress²⁷-²⁹ severe enough to cause myocardial necrosis have shown increases in the QRS duration concomitant with the increases in QRS size during the hyperacute phases of ischemia. These conduction changes appear²⁹,³⁰ to result from increases in local extracellular potassium due to leakage from ischemic cells. Conduction delay, by causing some areas of the left ventricle to depolarize later than others, can allow the electrical forces from those areas to appear unopposed by forces directed away from them, from the opposite ventricular wall, and thus can increase the size of the QRS deflection.

Whether these changes occur in humans at all, even temporarily, and whether they can be associated with the less marked ischemia characteristic of exercise testing, is not known. Kilpatrick³¹ has reported that in some coronary disease patients with exercise vector-
cardiograms, transient changes in intraventricular conduction occur that are consistent with the experimental results cited above. Our data do not allow us to differentiate between these two mechanisms of R-wave increase with exercise, but this differentiation could be made by analysis of QRS duration in cardiograms recorded before and after exercise.

The possible reasons for the statistical trend toward better reliability of multiple leads in interpretation of exercise-induced R-wave changes include the development of a change in cardiac position with the deeper inspiration of peak exercise and early recovery, which could cause larger changes in RV than those due to exercise. If this occurred, these changes should add to those seen in the right precordial leads due to exercise, and summing of multiple R and S waves should cause positional effects to cancel out, leaving those due to an abnormal response to exercise. Additionally, when the RV is small, it may not change detectably with exercise, resulting in a false-positive response in a normal patient.

Hemodynamic Implications

It is important to consider the exercise and catheterization measurements that we have shown to correlate with an increase in $\Sigma R$. We have previously shown that mean peak exercise double product is lower in patients with coronary artery disease than in those with normal coronary arteries, and that exercise duration tends to be less. Double product correlates with maximum myocardial oxygen uptake and exercise duration with the Bruce protocol relates to left ventricular function. Both of these parameters were significantly lower in patients in whom $\Sigma R$ increased than in those in whom it did not, all of whom were limited by cardiac symptoms. This implies that increases in $\Sigma R$ relate to inadequate functional reserve due to coronary disease.

In addition, left ventricular wall motion is more commonly and more severely abnormal in patients with increases in $\Sigma R$. In the present study, this refers only to resting wall motion, but we can speculate that during or after exercise, wall motion abnormalities are even more prevalent, contributing to the increased volumes required for the Brody effect. Ten of 11 patients (91%) with hypotension, a sign of severely depressed left ventricular function, had increases in $\Sigma R$.

Left ventricular end-diastolic pressure is determined by several factors that are both intrinsic and extrinsic to the left ventricular myocardium. In our study, this pressure was significantly higher in patients with exercise-induced increases in $\Sigma R$, and remained so when measured after the stress of left ventriculography. Ejection fraction was also significantly less in those with increased $\Sigma R$. Increases in R wave were not present in many cases of coronary artery disease, presumably because even in the presence of severely obstructed coronary arteries, left ventricular function was relatively well preserved at rest and with

<table>
<thead>
<tr>
<th>Table 4. Wall Motion and Hemodynamics of Patients with Increased and Decreased $\Sigma R$ with Exercise</th>
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<tr>
<td>All tests (n = 230, 126 with LVEDP)</td>
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<tr>
<td></td>
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<tr>
<td>ECG positive tests (n = 61, 31 with LVEDP)</td>
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<tr>
<td>Markedly positive tests (n = 76, 33 with LVEDP)</td>
</tr>
<tr>
<td>Negative tests (≥ 85% predicted heart rate) (n = 48, 30 with LVEDP)</td>
</tr>
<tr>
<td>Nondiagnostic tests (&lt; 85% maximum heart rate) (n = 45, 32 with LVEDP)</td>
</tr>
<tr>
<td>Tests on patients receiving propranolol (n = 81)</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.005$.
§ $p < 0.001$.

Abbreviations: Positive test = 1-1.9 mm ST depression with exercise; markedly positive test = > 2 mm ST depression with exercise; LVEDP = left ventricular end-diastolic pressure; LVEDPA = left ventricular end-diastolic pressure after left ventriculography; AI = asynergy index at rest; EF = ejection fraction; $\Sigma R$ = sum of R waves; † = increase; ‡ = decrease.

QRS CHANGES WITH EXERCISE/Berman et al. 59

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exercise. Thus, false-negative results remain a problem, just as with ST-segment changes.

Other work has shown negative prognostic value for QRS increases with exercise, at least in terms of ability to improve exercise tolerance with exercise training after myocardial infarction. Because the presence and severity of asynergy have been shown to be prognostic in this disease, QRS changes on the ECG may be prognostically important in terms of survival on medical therapy. Additionally, the group with increases in $\Sigma R$ contained 44 of our 52 patients with abnormally low (<50%) ejection fractions, and all six with ejection fractions of 30% or less. Low ejection fraction, especially under 30%, has been shown to predict poor survival in coronary disease.

Digitalis and R-wave Changes

R-wave analysis may be especially useful in patients receiving digitalis, because there is a great deal of controversy surrounding the value of ST-segment changes. We did not find any difference in the usefulness or limitations of QRS analysis in our patients, whether they were receiving digitalis or not. Bonor and associates excluded digitalized patients from their analysis, citing work by Manoach and coworkers showing that QRS voltage in the limb leads of cats increased after digitalization. Pipperbe and associates state that this does not occur in humans, and cite previous work from their laboratory in which QRS changes were absent in the ECgs of normal men receiving a large digitalizing dose that was sufficient to cause ST-segment changes.

Theoretically, in the presence of digitalis drugs, changes in activity of the sodium-potassium ATPase could cause alterations in local extracellular potassium concentration sufficient to cause QRS changes. These could be more pronounced if exercise-induced ischemia is also present and could cause problems with interpretation of QRS changes with exercise. However, as reviewed by Schwartz et al., the experimental evidence in both human and nonhuman species is unclear, both as to the presence of this potassium shift and, if it occurs, whether the changes in electrolytes remain localized, as they must if QRS changes are to occur. Based on the limited number of patients in this study, we feel that QRS changes are potentially very useful in analyzing exercise tests in patients receiving digitalis drugs.

The False-positive R-wave Increase

Our group of patients with increases in $\Sigma R$ and normal coronary anatomy is small. Most had an abnormal diastolic pressure at rest and/or with ventriculography, and only two of eight had a totally normal cardiac catheterization, as opposed to three-quarters of those with decreased $\Sigma R$ and normal coronary arteries. These data suggest that any patient showing an increase of $\Sigma R$ with exercise is very likely to have some cardiac abnormality, even if he or she has normal coronary arteries.

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