Identification of False Positive Exercise Tests With Use of Electrocardiographic Criteria: A Possible Role for Atrial Repolarization Waves

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Atrial repolarization waves are opposite in direction to P waves, may have a magnitude of 100 to 200 μV and may extend into the ST segment and T wave. It was postulated that exaggerated atrial repolarization waves during exercise could produce ST segment depression mimicking myocardial ischemia. The P waves, PR segments and ST segments were studied in leads II, III, aVF and V_4 to V_6 in 69 patients whose exercise electrocardiogram (ECG) suggested ischemia (100 μV horizontal or 150 μV upsloping ST depression 80 ms after the J point). All had a normal ECG at rest. The exercise test in 25 patients (52% male, mean age 53 years) was deemed false positive because of normal coronary arteriograms and left ventricular function (5 patients) or normal stress single photon emission computed tomographic thallium or gated blood pool scans (16 patients), or both (4 patients). Forty-four patients with a similar age and gender distribution, anginal chest pain and at least one coronary stenosis $\geq$80% served as a true positive control group.

The false positive group was characterized by 1) markedly downsloping PR segments at peak exercise, 2) longer exercise time and more rapid peak exercise heart rate than those of the true positive group, and 3) absence of exercise-induced chest pain. The false positive group also displayed significantly greater absolute P wave amplitudes at peak exercise and greater augmentation of P wave amplitude by exercise in all six ECG leads than were observed in the true positive group. Multivariable analysis revealed that exercise duration (p = 0.0001) and downsloping PR segments in the inferior ECG leads (p = 0.0004) were independent predictors of a false positive test. The combination of downsloping PR segments in two of three inferior leads plus either exercise duration $\geq$4 min or peak heart rate $\geq$125 beats/min identified false positive tests with a sensitivity of 84% and a specificity of 86% to 89%.

These results provide ECG criteria for predicting a false positive exercise test and support the hypothesis that exaggerated atrial repolarization waves may be a cause of a false positive exercise test.

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The exercise electrocardiogram (ECG) is an important first step in the evaluation of patients with suspected ischemic heart disease. Despite its pivotal role in cardiac diagnosis, the exercise ECG has limited specificity, reported to be approximately 77% in a recent meta-analysis of 132 studies (1). Factors known to be associated with a false positive exercise test (defined as ST segment depression in the absence of myocardial ischemia) include electrolyte abnormalities, drug use and repolarization abnormalities on the rest ECG. However, often none of these factors is present and in this situation, the cause of stress-induced ST segment depression in the absence of myocardial ischemia is unclear.

Some authors (2–7) have suggested that atrial repolariza-tion might contribute to ST segment depression during exercise testing. Other investigators (4,8–14) have demonstrated that atrial repolarization waves are usually opposite in direction to the P wave, have a magnitude of $\leq$200 μV and extend well into the ST segment. We postulated that exaggerated atrial repolarization waves could shift the ST segment in the absence of myocardial ischemia and that this phenomenon could be recognized by ECG criteria. To test the hypothesis, we studied the P wave, PR segment and ST segment in a group of patients with a false positive exercise test and compared them with findings in a similar group with a true positive test (that is, ST segment depression due to myocardial ischemia).

Methods

Patient selection. In this study, a positive exercise test was defined as ST depression 80 ms after the J point in at least one standard ECG lead of $\geq$100 μV for horizontal or downsloping ST segments or 150 μV for slightly upsloping ST segments (1). Patients were excluded from the study if

Table 1. Patient Characteristics

	False Positive Exercise Test (n = 25)		True Positive Exercise Test (n = 45)		
	No.	%	No.	%	p Value
Age (yr)	25	53 ± 1.5	43	57 ± 1.6	NS
Male patients	25	52	44	61	NS
Hypertension	25	40	42	67	0.043
Diabetes	25	0	41	27	0.005
Cigarette smoking	25	32	42	45	NS
Family history	25	48	44	48	NS
Hyperlipidemia	23	30	37	51	NS
Calcium channel blocking agent	25	16	42	50	0.008
Beta-adrenergic blocking agent	25	12	42	48	0.003

No. = number of patients analyzed for each variable; % = percent of patients with a variable present (age in years given as mean ± SE).

they had 1) an abnormal ECG at rest; 2) ST segment depression or change in T wave polarity induced by hyperventilation or a change from the supine to the standing position; 3) known cardiomyopathy or valvular disease, including mitral valve prolapse (clinical or echocardiographic diagnosis); 4) a tracing with excessive baseline artifact or wandering; 5) digitalis or direct-acting antiarrhythmic drug use within 8 days of the exercise test; or 6) prior coronary artery bypass surgery.

Study patients. Twenty-five retrospectively identified patients with a positive exercise test but no diagnosed heart disease or known cause for such a test result formed the false positive group. Nineteen patients were identified consecutively by reviewing all those with a normal stress radionuclide study (93 patients) or a normal coronary arteriogram (158 patients) between December 1, 1988 and December 30, 1989. Six additional patients had studies performed before that time. Five of the 25 patients had coronary arteriography showing no coronary stenosis of ≥30% and normal left ventricular function. Sixteen patients had a normal stress radionuclide study (10 single photon emission computed tomography thallium and 6 gated blood pool scans) while exercising to a peak systolic blood pressure-heart rate product of ≥25,000. Three patients had both normal coronary arteriography and a normal stress radionuclide study. One patient with a 50% mid-left anterior descending coronary artery stenosis and a normal stress radionuclide study was also considered to be in the false positive group. Twenty-two patients in the false positive group were tested to evaluate a chest pain syndrome; two were evaluated because of palpitation and one patient was self-referred because of risk factors for coronary disease.

The true positive group consisted of 44 patients identified at random and retrospectively with a history consistent with angina pectoris, a positive exercise test and coronary arteriography within 4 months of the exercise test showing at least one ≥80% stenosis in a major coronary artery. Exer-

cise test files were reviewed consecutively by medical record number to identify patients meeting these criteria. Because the age and gender distribution of the false positive group was already known, some potential true positive tests were arbitrarily excluded when it appeared that the control group was becoming too heavily weighted with elderly men. However, this exclusion took place before review of the exercise ECG.

Patient characteristics (Table 1). The false positive and true positive groups were similar in mean age (false positive 53 ± 1.5 years, true positive 57 ± 1.6 years) and gender distribution (false positive 52% male, true positive 61% male). A history of hypertension or diabetes mellitus was significantly more common in the true positive group and more patients in this group were taking a calcium channel or beta-adrenergic blocker. Of the 10 patients with a false positive test and a history of hypertension, 3 were receiving a diuretic. In two of these patients, the serum potassium level determined within 1 week of the exercise test was normal. The potassium level was not determined in the third patient.

The study was approved by the Committee on the Protection of the Rights of Human Subjects of the University of North Carolina, Chapel Hill.

Exercise testing. Patients were exercised on a motorized treadmill (Marquette model 1800) using the standard Bruce protocol. Continuous monitoring of ECG leads II, V_4 and V_5 was performed, with a 12 lead tracing performed every minute. End points for the test were the development of exertion-limiting symptoms (angina, fatigue, dyspnea, claudication), a decrease in systolic blood pressure >10 mm Hg from the pretest level, ventricular tachycardia or horizontal ST segment depression >200 μV. Blood pressure was measured by mercury sphygmomanometer at the end of each 3 min stage, at intermediate intervals when indicated and at peak exercise. The supine ECG was monitored in the
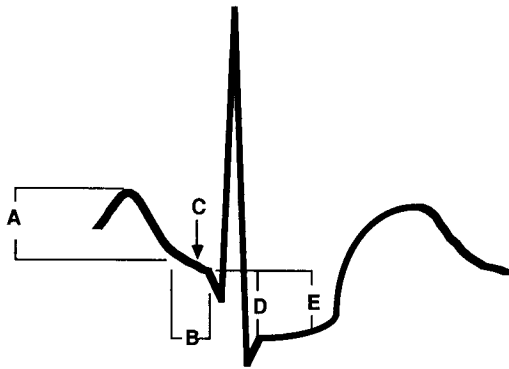
Figure 1. This representation of an electrocardiographic (ECG) complex indicates the points used for ECG measurements. A = P wave amplitude; B = PR segment duration; C = PR segment slope; D = J point depression; E = ST segment depression at 80 ms after the J point.

recovery period, with 12 lead tracings each minute until the ECG returned to baseline values.

Exercise test analysis. Tracings were analyzed at peak exercise when ST segment depression was maximal. In each tracing, leads II, III, aVF, V_4, V_5 and V_6 were examined as shown in Figure 1. The P wave amplitude was measured from the peak of the P wave to the beginning of the PR segment, defined as that point where there was a change in the downslope of the P wave. The PR segment duration was measured in the lead where the PR segment was most clearly defined (usually lead II). The ST segment slope was classified as flat, slightly upsloping or markedly upsloping. The J point depression and ST segment depression were referred to the PR-Q junction, with ST segment depression measured at 80 ms after the J point. The PR segment slope was determined by visual inspection and classified as flat, slightly downsloping or markedly downsloping (Fig. 2). Amplitudes and PR segment duration were determined to the nearest 50 μV or 10 ms.

Figure 2. Examples of the three PR segment slope classifications taken from actual electrocardiographic tracings. Arrow indicates PR segment.

FLAT

SLIGHTLY
DOWNSLOPING

MARKEDLY
DOWNSLOPING
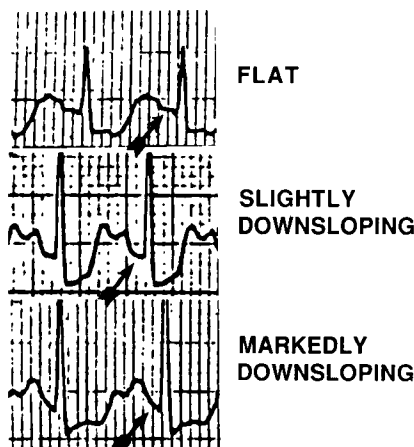
The reader did not know the clinical data. Intraobserver reproducibility was assessed by rereading the same tracings in a similar blinded fashion 1 week later. A random sample of 4 false positive and 12 true positive tracings (96 separate lead tracings) was assessed by a second observer using the same techniques and criteria. The reproducibility of all ECG measurements was studied by intraclass correlation. The reliability coefficients were about 0.7 (range 0.41 to 0.92), confirming the similarity of the readings by the two observers. The reliability coefficients for the PR segment slope, particularly in leads II, III and aVF, were higher (intraobserver r = 0.86, 0.92 and 0.92; interobserver r = 0.87, 0.88 and 0.74, respectively).

Cardiac catheterization. Selective coronary arteriography was performed in multiple projections using cranial and caudal angulation to visualize all parts of the coronary vessels. A ventriculogram was obtained in the right anterior oblique and in most cases the left anterior oblique projection. The films were analyzed by two observers who were aware only that the exercise test was positive.

Thallium scintigraphy. Exercise was performed using supine bicycle ergometry, beginning at a work load of 200 kilopond-meters (kp-m)/min, increasing by 100 kp-m/min every minute. When one of the end points described for exercise ECG was approached, 2 mCi of thallium-201 was injected intravenously and exercise continued for 90 s. Single photon emission computed tomographic imaging was performed within 10 min of injection (GE Starcam and software) with redistribution images obtained 4 h later. Images were interpreted visually by two observers aware only that the exercise test was positive. The study was considered normal if myocardial perfusion was homogeneous during stress and redistribution imaging.

Radionuclide ventriculography. This was performed with the patient on a supine bicycle and use of the exercise and monitoring protocol described for thallium scintigraphy. Stress images were obtained in the right anterior oblique view during the first pass of in vivo radiolabeled red blood cells (20 mCi of technetium-99m pertechnetate). After a 10 to 15 min recovery period, stress was repeated with the work load at a level that could be maintained for 3 min and equilibrium images were obtained in a left anterior oblique projection modified to best separate the left and right ventricles. The patient was allowed to recover and images at rest were obtained in both positions by the equilibrium technique. The details of image data acquisition and analysis have been reported previously (15). Cine studies created by display of an endless loop of frame data from the cardiac study were used to evaluate wall motion.

Studies were interpreted by two observers with knowledge only of a positive exercise test. A normal study was defined as an increase in ejection fraction of $\geq$0.05 percent points plus normal wall motion at rest and with stress. Two patients with an ejection fraction at rest of >0.70, an increase with stress of <0.05 and normal wall motion were considered normal (16).

Table 2. Exercise Variables in False Positive Versus True Positive Groups

	False Positive Exercise Test		True Positive Exercise Test		
	Value	No.	Value	No.	p Value
Exercise duration (min)					
All patients	8.1 ± 0.7	25	5.0 ± 0.3	44	0.0003
Excluding Ca and beta	8.8 ± 0.8	18	4.1 ± 0.4	14	0.0002
Peak exercise HR (beats/min)					
All patients	156 ± 3.4	25	127 ± 3.0	44	0.0001
Excluding Ca and beta	158 ± 4.5	18	137 ± 5.5	14	0.0070
Exercise chest pain (% experiencing)	24 ± 8.7	25	82 ± 5.9	44	<0.0001
Baseline systolic BP (mm Hg)	132 ± 4.0	25	135 ± 3.5	41	NS
Peak systolic BP (mm Hg)	179 ± 5.6	25	168 ± 4.3	41	NS

Beta = patients taking a beta-adrenergic blocking agent; BP = blood pressure; Ca = patients taking a calcium channel blocking agent; HR = heart rate; No. = number in each group or subset.

Statistical analysis. The distribution of baseline and exercise variables were described for each group, using frequencies and percents for categoric variables and mean and SE for continuous variables. The groups were compared by using the Wilcoxon rank sum test for continuous variables and the chi-square test for categoric variables. Pairwise associations for ordered categoric variables and continuous variables were evaluated with Spearman rank correlation methods. Baseline and exercise P wave amplitudes were compared with use of the Wilcoxon signed rank and paired t tests. Stepwise linear regression methods were used to develop the predictive model for discriminating between false positive and true positive tests, and sensitivity and specificity calculations were used for its evaluation.

Results

Exercise variables (Table 2). The false positive group had a longer mean exercise duration (8.1 ± 0.7 vs. 5 ± 0.3 min, $p = 0.0003$) and higher peak heart rate (156 ± 3.4 vs. 127 ± 3 beats/min, $p = 0.0001$). These differences persisted ($p < 0.01$) when patients in each group receiving a beta-blocking or calcium channel blocking drug were excluded from analysis. The false positive group also had a significantly smaller number of patients experiencing chest pain during exercise (24% vs. 82%, $p < 0.0001$). There was no significant difference between baseline or peak systolic blood pressure in the two groups.

Baseline ECG variables. There were no differences in rest heart rate or P wave amplitude. There was a weak but significant association in all ECG leads between the baseline PR segment slope and exercise test results, such that a downsloping PR segment classification in the rest tracing was associated with a subsequent false positive exercise test (leads II, III, aVF $r = 0.46, 0.33$ and 0.39, $p < 0.01$; leads V_4, V_5 and V_6 $r = 0.26, 0.29$ and 0.34, $p < 0.05$ respectively,).

Exercise ECG variables. In addition to the differences in exercise duration, maximal heart rate and the presence or absence of chest pain, the two groups were distinguished on the basis of P wave amplitude, PR segment duration and slope, J point depression and ST segment slope. The groups were not distinguished on the basis of ST segment depression.

P wave amplitude. The mean P wave amplitude at peak exercise was greater in each lead in the false positive group and this difference was statistically significant in leads II, V_4, V_5 and V_6 (Fig. 3A). The false positive group demonstrated a significantly greater increase in P wave amplitude from baseline to peak exercise in all six leads (Fig. 3B). The false positive group did attain a higher mean exercise heart rate and there was a weak correlation between P wave amplitude and heart rate that was significant only in leads II, V_4 and V_6 ($r = 0.26, 0.31$ and 0.30, $p < 0.05$, respectively).

PR segment duration. The mean PR segment duration was significantly shorter in the false positive group (43 ± 1.5 vs. 55 ± 1.6 ms, $p = 0.0001$). This may have been due to the higher mean heart rate in the false positive group because PR segment duration correlated inversely with heart rate (that is, the faster the rate, the shorter the PR segment; $r = 0.52$, $p = 0.0001$).

PR segment slope. There was a very strong association between PR segment slope and a false positive test such that in any given lead, the more downsloping the classification of PR segment slope (Fig. 2), the more likely a false positive test (leads II, III and aVF $r = 0.57, 0.57$ and 0.62; leads V_4, V_5 and V_6 $r = 0.57, 0.50$ and 0.46, respectively, $p < 0.0001$). There was also a relation between higher heart rate and a more downsloping PR segment, but this was not as strong as that between PR segment slope and a false positive exercise test (leads II, III and aVF $r = 0.44, 0.42$ and 0.47; leads V_4, V_5 and V_6 $r = 0.53, 0.42, 0.41$, respectively, $p < 0.001$). Of the six ECG leads studied in each patient, an increase in the
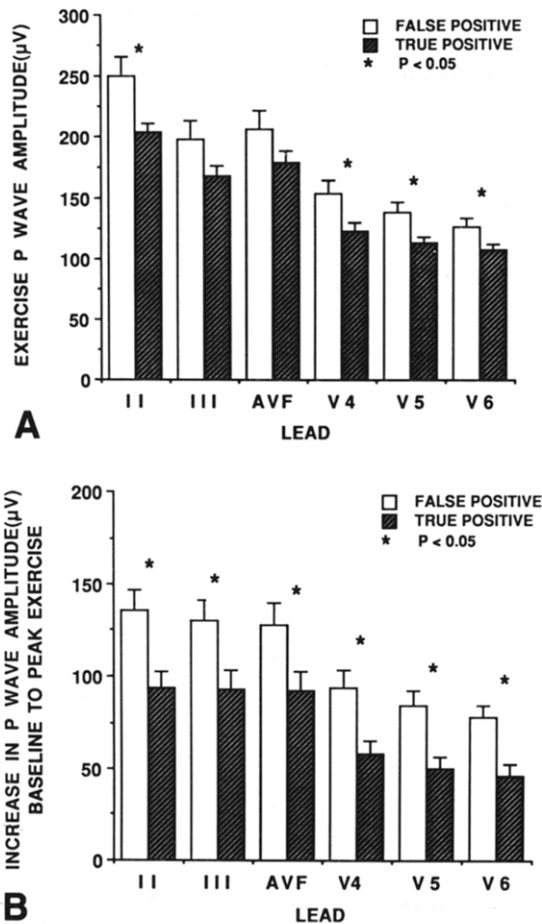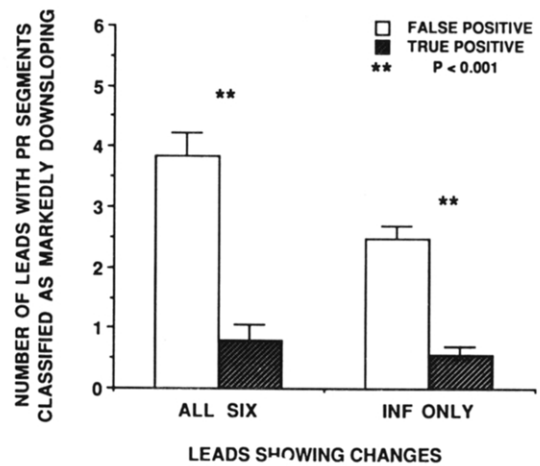
Figure 3. A, Mean P wave amplitude (±SE) in each electrocardiographic lead at peak exercise. B, Mean increase in P wave amplitude (±SE) from rest to peak exercise in each lead.

Figure 4. Mean number of leads (±SE) at peak exercise with PR segments classified as markedly downsloping. ALL SIX = electrocardiographic leads II, III, aVF plus V_4, V_5 and V_6; INF ONLY = inferior leads II, III and aVF.

number of PR segments classified as "markedly downsloping" was strongly associated with a false positive test (r = 0.63, p = 0.0001). The false positive group demonstrated markedly downsloping PR segments in 3.8 ± 0.4 of six leads compared with 0.8 ± 0.2 of six leads for the true positive group, with the changes tending to concentrate in the three inferior ECG leads (Fig. 4). Figure 5 demonstrates markedly downsloping PR segments in the inferior and lateral ECG leads of a false positive exercise test.

J point depression. The magnitude of J point depression was significantly greater in the false positive group in leads II, III, aVF and V_4 (Fig. 6).

ST segment slope. The false positive group had slightly fewer positive leads with horizontal ST depression (3 ± 0.4 vs. 4 ± 0.2 leads, p = 0.04) and more leads with upsloping ST depression (1.5 ± 0.4 vs. 0.5 ± 0.2 leads, p = 0.006). Only 3 of 25 patients in the false positive group and 1 of 44 patients in the true positive group had a positive exercise test with only upsloping and no horizontal ST segment depression. Figure 5 illustrates the significant horizontal ST depression in the false positive group.

ST segment depression. The groups were similar in mean number of leads with diagnostic ST segment depression (4.5 ± 0.3 vs. 4.5 ± 0.2 leads in the false positive vs true positive group, respectively). The magnitude of ST depression measured at 80 ms after the J point was similar in both groups in every lead except lead III, in which the false positive group had more ST depression (Fig. 7).

Multivariable analysis. Although some of the ECG changes that characterized the false positive tests were also correlated with the higher heart rate attained by the patients with these tests, the appearance of markedly downsloping PR segments in the inferior ECG leads was an independent predictor of a false positive test. Multivariable analysis using a linear regression model including exercise and ECG variables revealed that the independent predictors of a false positive test were exercise duration (p = 0.0001) and the presence of markedly downsloping PR segments in the inferior leads (p = 0.0004). Peak exercise heart rate did not enter the model as an independent predictor of a false positive test. The results of multivariable analysis were applied retrospectively to identify false positive exercise tests with optimal sensitivity and specificity. The combination of exercise time ≥4 min plus markedly downsloping PR segments in two of three inferior leads identified a false positive test with a sensitivity of 84% and a specificity of 89% (Fig. 8). When a peak exercise heart rate ≥125 beats/min was substituted for exercise duration, the two variables allowed prediction of a false positive test with a sensitivity of 84% and a specificity of 86%. If only the patients attaining a heart rate of 125 beats/min or an exercise duration of 4 min are examined, the sensitivity of the PR segment slope criterion remains approximately 85%, although the specificity decreases to approximately 75% (Fig. 8 and 9).
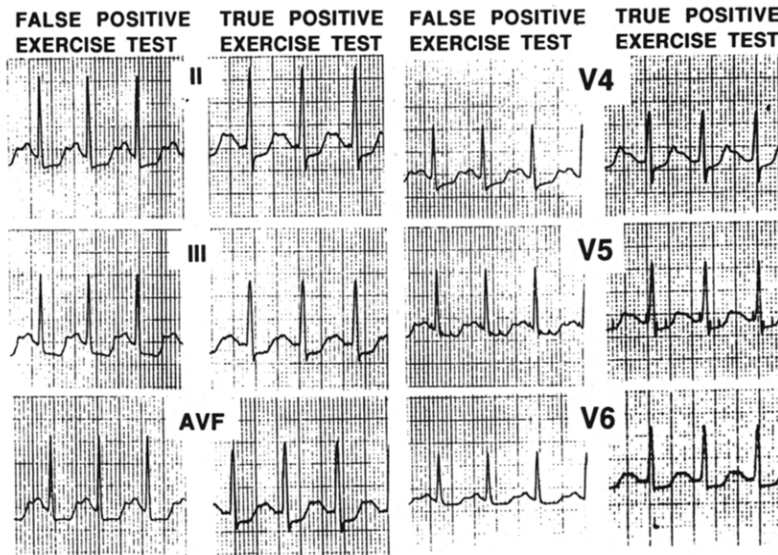
Figure 5. Lead by lead comparison of true and false positive exercise tests at similar heart rates. In the false positive test, the PR segments, particularly in electrocardiographic leads II, III and aVF, are more downsloping compared with the horizontal PR segments in the true positive test. Also note significant horizontal ST segment depression in the false positive test.

Discussion

Causes of false positive ST depression. Depression of the ST segment due to subendocardial myocardial ischemia is the result of local changes in cellular membrane potential at rest and the shape of the action potential (17). These changes result in current flow that causes TQ segment elevation and ST segment depression, both of which are registered on the body surface ECG as ST depression (17). Depression of the ST segment in the absence of myocardial ischemia may be due to alterations in the action potential produced by electrolyte abnormalities, cardioactive drugs, pericarditis and nonischemic myocardial disease (17). Catecholamine and autonomic influences affect the duration of repolarization and primarily influence the T wave but have not been shown to cause isolated ST segment abnormalities (18,19). The electrophysiologic basis for stress-induced ST segment depression in the absence of heart disease or other factors known to influence the action potential is obscure. We

examined the hypothesis that the ECG manifestations of atrial repolarization could produce ST segment shifts mimicking ischemia.

Previous investigations of atrial repolarization. Several features of the atrial repolarization wave have been examined (4,8–14), mostly in patients or animals with atrioventricular (AV) block. The atrial repolarization wave has been found to be almost always directed opposite to the P wave (8,9). Thus, the atrial repolarization wave is normally inverted in leads in which the P wave is upright. The magnitude of the atrial repolarization wave correlates directly with the amplitude of the P wave (8,10). Hayashi et al. (8) found the average atrial repolarization wave amplitude to be 0.38 times the P wave amplitude, with a range of 0.22 to 0.45 in patients with complete AV block and an otherwise normal heart. This would indicate that a 250 μV positive P wave would be followed by a negative atrial repolarization wave of

Figure 6. Mean J point depression ($\pm$SE) in each electrocardiographic lead at peak exercise.
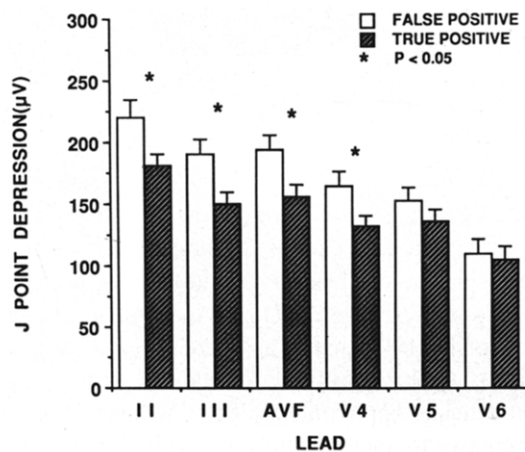
Figure 7. Mean ST segment depression ($\pm$SE) 80 ms after the J point in each electrocardiographic lead at peak exercise in false and true positive (POS) tests.
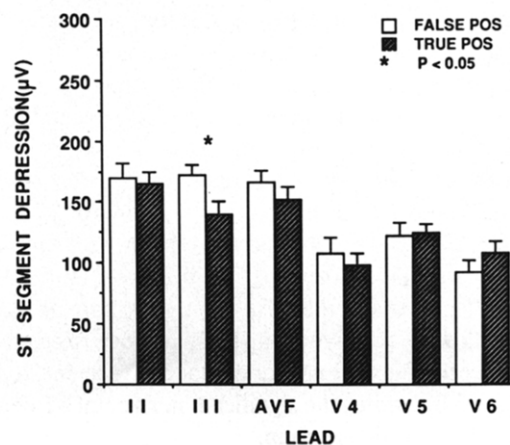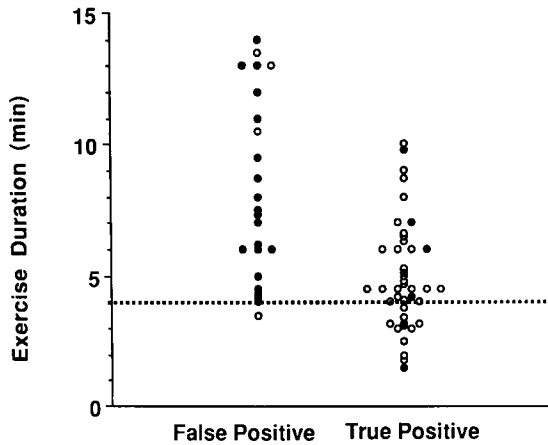
Figure 8. Exercise duration combined with PR segment slope to identify false positive tests. **Open circles** = none or one PR segment in electrocardiographic leads II, III or aVF classified as markedly downsloping; **filled circles** = two or three PR segments in leads II, III or aVF classified as markedly downsloping. The combination of exercise duration ≥4 min and markedly downsloping PR segments in two or more inferior leads identifies 21 of 25 false positive tests (sensitivity 84%) and misclassifies 5 of 44 true positive tests (specificity 89%).

60 to 120 μV. The P wave amplitude increases with exercise (20,21) and the rest amplitudes of both P and atrial repolarization waves increase as heart rate increases (8,10,13). In one study (4), negative atrial repolarization waves ≤190 μV were observed during exercise at a heart rate of 120 beats/min.

The duration of the atrial repolarization wave has been reported (8,11,12) to be considerably longer than that of the P wave. Hayashi et al. (8) showed the duration of interval from the onset of the P wave to the end of the atrial repolarization wave to be 2.7 to 4 times the P wave duration (mean P wave and atrial repolarization wave duration 450 ms). Other investigators (11) reported atrial repolariza-

Figure 9. Peak exercise heart rate combined with PR segment slope to identify false positive tests. The combination of peak heart rate ≥125 beats/min and PR segments classified as markedly downsloping in two or more inferior electrocardiographic leads identifies 21 of 25 false positive tests (sensitivity 84%) and misclassifies 6 of 44 true positive tests (specificity 86%). Format as in Figure 8.
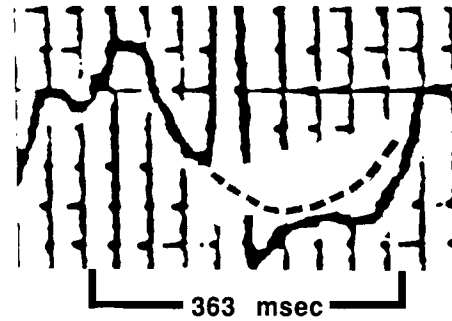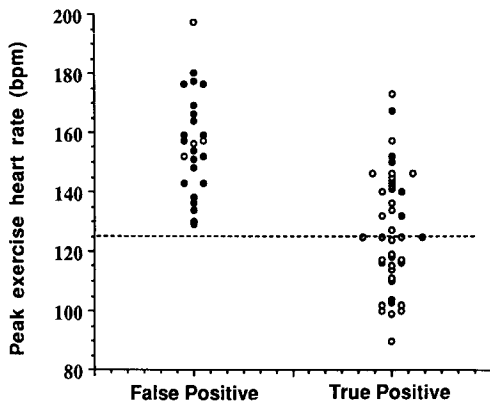
Figure 10. Illustration of the extent to which an exaggerated atrial repolarization wave might influence the ST segment. The lead II electrocardiographic complex is from a false positive test at a heart rate of 134 beats/min. The **dotted line** indicates the hypothetical atrial repolarization wave. The duration of the P wave plus the atrial repolarization wave (363 ms) represents the 95% upper confidence limit above the mean P wave and atrial repolarization wave duration at that heart rate, derived from the data of Kesselman et al. (12).

tion waves lasting up to 600 ms after the onset of the P wave. It has also been found (8,15) that the atrial repolarization wave shortens predictably as heart rate increases.

The potential extension of the atrial repolarization wave into the ST segment can be estimated. In 20 patients in the false positive group with an ECG recorded at a heart rate between 145 and 155 beats/min, the mean (±SD) interval from the onset of the P wave to the onset of the ST segment was 220 ± 22 ms. Regression equations predicting P wave and atrial repolarization wave duration from atrial rate were developed (8,12). These equations predict mean P wave and atrial repolarization wave durations of 272 and 276 ms, respectively, at a heart rate of 150 beats/min. A retrospective analysis of the data of Kesselman et al. (12), which includes measurements at PP intervals <300 ms, allows calculation of 95% confidence intervals about the mean P wave and atrial repolarization wave duration at a heart rate of 150 beats/min. The 95% upper confidence limit value is 340 ms. When the measured P wave and QRS duration is compared with these estimates of P wave and atrial repolarization wave duration, the mean extention of the atrial repolarization wave beyond the end of the QRS complex is 56 ms (276 − 220 ms). In some patients with a longer period of atrial repolarization and a shorter PR interval, the atrial repolarization wave could extend up to 140 ms (340 − 200 ms) beyond the end of the QRS complex. Thus, it might be expected that only a small number of normal individuals will develop an atrial repolarization wave during exercise that is of sufficient duration and magnitude to cause horizontal ST segment depression (Fig. 10).

The PR segment represents the plateau phase of the atrial action potential, much as the ST segment reflects the plateau phase of the ventricular action potential. Because the plateau of the atrial action potential is shorter and more downsloping than that of the ventricular action potential (22), the PR segment is not isoelectric and merges with the atrial repolarization wave.

Other investigators have addressed the effect of atrial repolarization waves on the exercise ECG in normal individuals without exercise-induced ST segment depression by studying P wave and ST segment vectors using orthogonal lead ECGs (20) or changes in body surface isopotential maps (23). These investigators (20,23) concluded that the influence of atrial repolarization waves on the ST segment is minimal. Conversely, these studies (20,23) did not assess atrial repolarization in individuals with ST depression, who are the subject of this investigation.

The present study. Given this information, one would predict characteristic ECG changes in patients with false positive ST depression due to large atrial repolarization waves. First, a test that is false positive because of atrial repolarization would be expected to occur at more rapid heart rates when P wave and atrial repolarization wave amplitudes are augmented. Second, such a false positive test might have a shorter PR segment duration, shifting the deepest part of the atrial repolarization wave further into the ST segment and tending to cause horizontal ST segment depression. Third, because of the characteristics of the atrial action potential and the short transition segment between the P wave and the atrial repolarization wave, a deep atrial repolarization wave would be expected to be accompanied by a downsloping PR segment in leads in which the P wave is tallest (that is, inferior ECG leads). Furthermore, one would expect these false positive tests to demonstrate taller P waves and perhaps a greater augmentation of P wave amplitude with exercise. Finally, one might also expect patients with a false positive test to show indications of exaggerated atrial repolarization waves on the rest tracing.

The results of this study agree with these predictions. The patients with a false positive test achieved a significantly higher heart rate than did patients with a true positive test. The PR segments were shorter in the false positive than in the true positive tests. A false positive test was associated with downsloping PR segments in all leads, particularly leads II, III and aVF. Although these features were to some extent a function of the higher heart rate attained by patients with a false positive test, a downsloping PR segment carried independent predictive value for a false positive test. With exercise, the false positive group demonstrated taller P waves in all six ECG leads studied, although the difference was significant in only four. The increase in P wave amplitude with exercise was significantly greater in all leads in the false positive group. Furthermore, there was a significant association between a downsloping PR segment at rest and a subsequent false positive test.

The finding of a mean value for J point depression to be slightly greater than that for ST depression at 80 ms after the J point in a false positive test is also consistent with the effects of atrial repolarization. Previously reported data (4,8,12) suggest that in most individuals, the duration of atrial repolarization is such that its effects will be maximal at the J point and the ST segment will be upsloping. Indeed, upsloping ST depression is well known to carry a low

specificity for the presence of coronary artery disease (24). Our study suggests that atrial repolarization may also cause horizontal ST segment depression identical to that seen in patients with myocardial ischemia (Fig. 5). This most likely reflects the positioning of the deepest portion of the atrial repolarization wave late in the ST segment as a result of either a short PR segment or a prolonged atrial repolarization wave, or both. Patients with myocardial ischemia during exercise testing may also reflect the effects of atrial repolarization, particularly if they are able to attain a high heart rate. Thus, a true positive test in patients who attained a higher peak exercise heart rate was also more likely to show downsloping PR segments (Fig. 9).

Limitations. One limitation of this study is the potential for unrecognized ischemia in the patients with a test termed "false positive." If a large proportion of the patients classified as having a false positive test had ischemia (that is, the test was, in fact, true positive), the characteristic PR segment changes seen to separate false positive and true positive tests would be much less useful as a marker for a genuine false positive test. In this study, the exclusion of patients who did not attain a high rate-pressure product during the stress radionuclide test (only one patient did not attain 85% of the maximal predicted heart rate) makes it unlikely that a significant number of our patients classified as normal by stress radionuclide tests alone had functionally significant coronary artery disease (25,26). It is important to note that the standard for the demonstration of functionally significant coronary artery disease is not yet clarified (27). The demonstration of a >50% coronary artery stenosis in a patient with a normal radionuclide study at an adequate exercise end point does not necessarily imply that the radionuclide study missed an ischemia-producing lesion. However, other data suggest (28,29) that of the five patients with angiographically normal coronary arteries who did not undergo functional testing, only two might have had an abnormal radionuclide study implying "microvascular ischemia."

The measurement techniques utilized were not computerized and some were qualitative. The key variable, PR segment slope, was assessed qualitatively, although only markedly downsloping PR segments turned out to be important in the final analysis, thus decreasing reliance on more subtle changes in this difficult to visualize portion of the exercise ECG. Finally, the highly selected nature of the two study groups (designed to obtain clearly ischemic and nonischemic groups) prevents the application of the study findings to all patients referred for exercise testing.

Conclusions. The implications of ST depression during an exercise test are significant. Patients may be made aware of an adverse prognosis, treated empirically for coronary artery disease or referred directly for coronary angiography with its attendant risks and expense. This study suggests some simple clinical and ECG criteria that might be used to predict a false positive exercise test in patients with a normal rest ECG and no apparent reason for a false positive result. Our

findings are in accord with other reports associating a higher exercise heart rate, longer exercise time and absence of chest pain during exercise with a lower probability that a positive exercise test is caused by myocardial ischemia (30–34) and with a favorable long-term prognosis (35). In this setting, the finding of short, steeply downsloping PR segments, particularly in the inferior ECG leads, is an independent marker of a false positive exercise test even in the presence of significant horizontal ST segment depression. Patients with these clinical and ECG exercise findings perhaps require additional noninvasive efforts to prove they have stress-induced myocardial ischemia before empiric treatment or invasive testing is recommended. Finally, the utility of these criteria needs to be assessed prospectively in a large number of patients undergoing exercise testing.

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