The "False Negative" Treadmill Exercise Test and Left Ventricular Dysfunction

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SUMMARY One hundred and fifteen consecutive symptomatic patients undergoing graded exercise testing, selective coronary angiography and left ventriculography were retrospectively evaluated. The sensitivity, specificity, and false negative response rates of the exercise tests were 79%, 81%, and 21%, respectively. Although the magnitude of a positive ST-segment response was related to more extensive vascular disease, the frequency of false negative responses was nearly identical in patients with single, double, or triple vessel disease (22%, 21%, 19%). Analysis of the false negative group demonstrated significant ventriculographic and hemodynamic abnormalities when compared to the true positive responders. Five out of six patients with the most serious motion disorders in the study fell into the false negative group. There were no significant differences in the extent, distribution, and severity of vascular involvement, or in the development of collateral circulation in the two groups. However, occluded vessels supplied abnormal ventricular segments more frequently in the false negative group (88% vs 38%); the absence of an "ischemic response" and the presence of segments of abnormal myocardium may be related.

Left ventricular dysfunction appears to be an important reason for a false negative response to exercise.

ELECTROCARDIOGRAPHIC EXERCISE STRESS TESTING has gained widespread acceptance as a noninvasive diagnostic tool in the evaluation of patients suspected of having ischemic heart disease. With the introduction of the multistage protocols, improved sensitivity over single stage methods was expected. Recent studies, however, have continued to demonstrate a high percentage of false negative responses in symptomatic patients.1 9 These reports attributed such responses to less extensive vascular disease. Others have suggested that left ventricular function may be a contributing factor.10 13 The present study was designed to assess further the relative influence of these parameters as determinants of the false negative response to exercise in symptomatic patients.

Methods

One hundred fifty patients referred to Rush-Presbyterian St. Luke's Medical Center for evaluation of chest pain syndromes during the period of January 1974 to January 1975 were retrospectively evaluated. The patients were chosen from a consecutive group after the exclusion of valvular or congenital heart disease, hypertension, previous cardiac surgery, left ventricular hypertrophy, bundle branch block, or inotropic drugs. Each patient underwent clinical evaluation, graded multistage submaximal exercise testing, selective coronary arteriography and left ventriculography. The data were analyzed for sex, age, presence of pathologic Q waves on electrocardiogram (ECG), exercise-induced angina, and ST-segment changes on the treadmill; degree of coronary artery disease, presence of collateral circulation, left ventricular wall motion, LV end-diastolic pressure and ejection fraction. Both treadmill and angiographic data were evaluated by two independent observers.

The patients were exercised according to an uninterrupted protocol at 1 mph at 0% inclination for 1 min, then at 3 mph at 4, 8, and 12% inclination for 3 min each. Leads I, II, III, V6 were recorded at control, during and immediately after exercise and then at 3 and 6 min thereafter. Exercise was considered complete if either an 85% maximal target rate was achieved or a symptomatic end point was reached (progressive chest pain, presyncope, fatigue or dyspnea) or if the patient developed serious arrhythmia.

A positive test response consisted of either depression or elevation of the ST segment 1 mm from baseline with straightening or downsloping extending for 0.08 sec in any monitored lead. In patients with resting ST-segment abnormalities, a change of at least 1 mm beyond the resting level constituted a positive test.10 14 The test was considered negative if the patient achieved an 85% target heart rate without significant ST changes. A false negative test consisted of the presence of significant coronary obstruction (as defined below) associated with a negative treadmill response. Patients failing to achieve a predicted target heart rate in the absence of significant ST changes were regarded uninterpretable responses. The development of exercise-induced chest pain was noted but not included in the definition of test responses. The data were subjected to Chi-square analysis. In those instances in which the number of patients was small, a test on a 2 x 2 contingency table was also done.

Selective coronary arteriography was performed by the percutaneous femoral technique or using the brachial approach. Significant coronary artery disease was considered present if there was luminal narrowing of 60% or greater in at least one major vessel. Left main coronary artery stenosis was considered functionally equivalent to double vessel disease. Significant lesions were further subdivided into moderate (60-80%), severe (80-99%), and occluded categories (100%). Collateral circulation was defined as present if an obstructed artery was opacified by antegrade flow via bridge vessels or through the conus branch, and when filling of distal vessels was noted via retrograde flow through distal anastomosis. The RAO projection for selective left ventriculography was utilized to detect contraction abnormalities as well as to determine the ejection fraction according to the modified method of Greene,14 utilizing the formula

$$EF = \frac{EDV - ESV \times 100}{EDV}$$

Pressures were measured with Statham P23db strain gauges.
Results

General Characteristics

There were 150 consecutive patients evaluated for the study. From this group 115 patients (77%) were selected for having attained target heart rate or symptomatic end point and had interpretable treadmill tests. These comprise the actual study population. The age range for the 87 males was 32-68 years (mean age 47) and for the 28 females it was 29-64 (mean age 48). Their resting ECGs revealed: a normal pattern in 44 patients, nonspecific changes in 43 patients, pathologic Q waves in 22 patients (anterior 9, inferior 13) and minor conduction disturbances in 6 patients. There were 53 patients without significant coronary artery disease, 18 patients with single vessel, 28 patients with double vessel and 16 patients with triple vessel disease. Of the 35 excluded patients (see Methods) the incidence of single, double and triple vessel disease was identical to that of the study population. Ventriculographic contraction abnormalities were noted in 25 (40%) of the patients with significant coronary artery disease. These occurred in four patients (22%) with single vessel, 13 patients, (46%) with double vessel and eight patients (50%) with triple vessel disease.

Treadmill Test Correlations with Coronary Angiography

The overall treadmill sensitivity

\[
\left( \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \times 100 \right)
\]

for the study was 79% and the overall specificity

\[
\left( \frac{\text{true negative}}{\text{true negative} + \text{false positive}} \times 100 \right)
\]

was 81%. The rate of false positive responses was 19% and the rate of false negative responses was 21%.

Table 1 relates the maximal ST-segment exercise responses with the extent of significant coronary artery disease in the 115 patients studied. As shown, progressive ST-segment change (1 mm - 2 mm) was associated with a greater occurrence of combined double and triple vessel disease. No relationship existed between the maximal ST-segment response and the presence of collateral circulation. The distribution of single, double, and triple vessel disease was similar in the false negative group (first column). Additionally, among those patients with either single, double or triple vessel disease, the frequency of false negative exercise tests were nearly identical — 22%, 21%, and 19% respectively.

The distribution of treadmill responses as correlated with ventriculography is shown in figure 1. Of the 56 negative exercise responses there were 13 patients with false negative tests (12 males, 1 female) and 12 of them (92%) demonstrated ventriculographic motion disorders. Of the 59 positive ECG exercise responses there were 49 patients with true positive tests and 13 of them (26%) showed similar ventriculographic abnormalities (P < 0.0001). There were no significant differences in the incidence of single, double, or triple vessel disease in the false negative and true positive groups. None of the ten patients in the false positive group (8 females, 2 males) demonstrated ventriculographic motion disorders.

In the 62 patients with significant coronary artery disease the presence of either an abnormal ventriculogram (25 patients) or an electrocardiographic pattern of infarction (22 patients) were associated with positive exercise ischemic response rates of 52 and 59% respectively. Contrariwise either a normal ventriculogram (37 patients) or the lack of an electrocardiographic pattern of infarction (40 patients) was associated with positive exercise response rates of 97 and 90% respectively.

Determinants of Treadmill Test Responses

The false negative and true positive groups were next analyzed in detail in order to ascertain the relative influence of vascular and left ventricular determinants on the ischemic response to exercise.

Electrocardiographic Patterns

Diagnostic resting electrocardiographic patterns of infarction were observed in nine patients (69%) of the false negative group and in 13 patients (27%) of the true positive group (P < 0.01, fig. 2). The sites of infarction were similar in both groups, with inferior wall patterns noted in 44% of the false negative group and 69% of the true positive group (NS). Anterior infarction patterns were present in 56% and 31% of the two respective groups (NS). The incidence of nonspecific ST wave abnormalities was 15% in the false negative and 28% in the true positive group (NS, fig. 2).

During exercise a mean maximal heart rate of 158 beats/min (140-175) was attained in the false negative group and 141 beats/min (85-210) in the true positive group.

| Table 1. Correlation of Maximal ST-Segment Change with the Arteriographic Extent of Significant Coronary Artery Disease (115 patients) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| No. vessels involved with SCAD | | | | | |
| | Negative | | | | |
| | | 1 mm | 1.5 mm | 2 mm | >2 mm |
| 0 | 43 (77%) | 4 (27%) | 1 (9%) | 5 (25%) | 0 |
| 1 | 4 (7%) | 5 (33%) | 4 (37%) | 3 (15%) | 2 (15%) |
| 2 | 6 (11%) | 4 (27%) | 3 (27%) | 9 (45%) | 6 (46%) |
| 3 | 3 (5%) | 2 (13%) | 3 (27%) | 3 (15%) | 5 (39%) |
| Total | 56 (100%) | 15 (100%) | 11 (100%) | 20 (100%) | 13 (Total 59 pt) |
| SCAD = significant coronary artery disease. | | | | | |
Although there was not a significant difference, patients in the false negative group experienced exercise-induced pain less often as compared to the true positive group. The mean duration of exercise prior to discontinuing the test was 5.7 min and 3.1 min respectively.

**Significant Coronary Artery Disease**

There were no significant differences in specific vessel involvement in either the false negative or true positive groups (fig. 3). The left anterior descending artery was the most frequently involved vessel in both groups (85% vs 82%) followed by the right coronary artery (62 vs 65%). The left circumflex artery was involved in 46% of the patients with false negative responses and in 49% of the patients with true positive responses. Left main artery disease was not observed in the false negative group and seen only in 4% of the true positive group. Similarly, no significant differences were observed in the frequency of single, double, and triple vessel disease (fig. 3) nor in the severity of vascular involvement (moderate, severe or occluded categories, fig. 3). In the false negative group there were eight occluded vessels occurring in as many patients. Seven of these vessels (88%) supplied abnormally contracting ventricular segments. In the true positive group, 21 occluded vessels occurred in 18 patients. Eight of these occluded vessels (38%) supplied abnormal ventricular segments.

**Collateral Circulation**

The presence of collateral circulation was uniformly associated with severely obstructed or occluded vessels in both the false negative and true positive groups. Eight patients in the false negative group (62%) demonstrated collateral circulation while 20 patients in the true positive group (41%) showed similar findings. This difference was not significant. Of the patients with left ventricular dysfunction the incidence of collateral circulation was nearly identical for both groups (58% vs 62%).

**Left Ventricular Performance**

The incidence of ventriculographic wall motion disorders was 92% in the false negative group and 27% in the true positive group ($P < 0.0001$, fig. 4). When corrected for the extent of vascular involvement (single, double or triple vessel disease) ventriculographic abnormalities were likewise more prevalent in the false negative group at each level of vascular disease.

Table 2 presents the distribution and location of wall motion abnormalities as they occurred in the false negative (12 of 13 patients) and true positive groups (13 of 49 patients). As shown on the left panel, dyskinetic segments were significantly more prevalent in the false negative group while lesser motion disorders were more often observed in the true positive group. There was no significant difference in the specific location of these segmental abnormalities in the two groups.

An abnormally high left ventricular end-diastolic pressure (> 15 mm Hg) was noted in five patients (42%) in the false negative group and in four patients (9%) of the true positive group ($P < 0.01$, fig. 4). The left ventricular end-diastolic pressure was not determined in five patients (1 false negative, 4 true positive). All of these patients demonstrated normal ventriculographic patterns.

The ejection fraction was determined in 12 of 13 patients in the false negative group and 41 of 49 patients in the true positive (fig. 4). In the former group, the ejection fraction was abnormal in five patients (42%) and in the latter group it was abnormal in three patients (7%, $P < 0.01$). The ejection fraction could not be determined in nine patients (1 false negative, 8 true positive) as a result of catheter-induced arrhythmias or unavailability of material for review. However,
the ventriculograms of all nine patients were reported as normal. An inverse relationship was observed between the ejection fraction and the occurrence of false negative responses. Thus, in the groups with low (< 55%), normal (55% - 75%), and high (> 75%) ejection fraction, the incidence of false negative responses was 63%, 37% and 0% respectively (P < 0.001, fig. 5).

Discussion

A "false negative" electrocardiographic response to exercise may theoretically arise when myocardial ischemia is prevented, masked, mild in degree, or absent entirely. Thus, certain drugs (eg., nitroglycerin or propranolol) may prevent ischemia while certain conduction disturbances (bundle branch block) may mask its presentation on the surface electrocardiogram. The observation that false negative responses frequently occur in association with single vessel involvement has been taken to indicate that a milder and perhaps undetectable degree of ischemia exists. Likewise, it has been suggested that a negative exercise test can be demonstrated in patients with left ventricular dysfunction, usually resulting from a prior myocardial infarction. The implication here is that when occluded vessels supply infarcted tissue a nonschismic response is identified. In order to clarify this issue further, we retrospectively evaluated the relationship of several parameters as determinants of the false negative response to exercise.

Analysis of our data in general showed an overall sensitivity and specificity in keeping with the results of prior studies in symptomatic patients. As has been reported, the magnitude of ST-segment change in this study was related to more extensive vascular disease (table 1) and unrelated to the presence of collateral circulation. In those patients with significant vascular disease and no ST segmental changes on exercise (false negative group), however a spectrum of vascular involvement rather than single vessel disease was noted. Similarly, the frequency of false negative tests in patients with either single, double or triple vessel disease was nearly identical (22, 21, and 19%, respectively).

A detailed comparative analysis of the false negative and true positive groups indicated that no significant differences existed in coronary vascular disease. Specifically, the distribution, severity and extent of arterial disease were nearly identical in both groups. Accordingly, there was no specific vessel or number of vessels involved which were apt to produce either a negative or positive response to exercise; nor was the presence of collateral circulation a major determinant of the electrocardiographic responses to exercise.

In this study the sole difference observed between the false negative and true positive groups was the extraordinary incidence of myocardial dysfunction associated with infarction patterns in the former group. Angiographically, motion disorders occurred much more frequently (figs. 1 and 4) and were qualitatively more severe (table 2) in the false negative responders. Both an increased left ventricular end diastolic pressure and a reduced ejection fraction characterized the hemodynamics in the false negative group. An inverse relationship between the ejection fraction and frequency of false responses (fig. 5) was also noted.

Early in the development of exercise testing Fitzgibbon...
noted that "positive step tests in subjects with coronary artery disease are commoner in those not sustaining myocardial infarction." Kattus subsequently suggested that the vast majority of false negative responses occur in patients who have survived myocardial infarction. The Seattle Heart Watch project extended this concept by noting a 20% greater frequency of exercise-induced ST-segment deviations in their "angina only" subgroup, in comparison to their postinfarction group. These results appear comparable to ours in which a 31% greater frequency of exercise test positivity was observed in the noninfarction group.

An association between the false negative test and left ventricular hemodynamics was described by Murray et al. Thus, this type of response was noted to occur commonly in association with 1) a raised left ventricular end-diastolic pressure, 2) a larger left ventricular dimension, 3) a reduced ejection fraction, and 4) the presence of wall motion abnormalities. The above findings concur with our overall experience. Bruce postulated that the spectrum of motion disorders (akinesis, dyskinesis) resulting from extensive infarction could alter the ST-segment responses upward in a manner that would cancel the expected ischemic depression. The net result would then be that "false negative ST responses are observed with other manifestations of severe impairment of cardiac function." In this regard five of six patients (83%) with the most serious motion abnormalities in our study appeared in the false negative group (table 2).

To what then may we attribute the false negative response to exercise? From our data it would appear that similar if not identical vascular anatomy can elicit either response. Left ventricular dysfunction, however, occurred predominantly, although not exclusively, in the false negative group. On a metabolic basis, the above may be interpreted to mean that the postmyocardial infarction state possesses less potentially ischemic myocardium which is available to participate in the response to exercise. Accordingly, lactate studies performed in similar patients with combined extensive vascular and myocardial disease have shown the absence of lactate production under conditions of stress. It is conceivable that the lower incidence of exercise-induced pain, enhanced chronotropic response, and increased duration of exercise, as noted in our false negative group, was caused by a similar underlying mechanism. Occluded vessels supplying abnormal ventricular myocardial segments appeared much more frequently in the false negative than in the true positive responders (88% vs 38%), a finding which supports our hypothesis. Unfortunately, because lactate, oxygen utilization, and work determinants were not performed in this retrospective study, such a conclusion must await definitive evaluation.

While our data suggest that extensive myocardial disease is contributing to the lack of ST-segment response, other reports have not noted this association. The explanation for these observed differences may reflect patient selection, varying criteria for significant coronary disease, or variations in exercise testing methodology. It is also possible that exercise test been performed at the time of catheterization and angiography, differences between groups in myocardial performances would not have appeared.

Although the purpose of this report was to investigate the pathophysiology of the false negative exercise response, certain clinical points deserve mention. It should be apparent from our data that the surface resting electrocardiogram, by demonstrating an infarction pattern, distinguished the false negative from true negative responders in the majority of instances. Thus, a negative stress test in this context would not negate the recognition of significant coronary artery disease especially in symptomatic patients. However, such a response may provide additional information regarding the status of left ventricular performance.

**Table 2. Distribution of Ventriculographic Abnormalities in the False Negative and True Positive Groups**

|Severity of Left Ventricular (LV) Dysfunction| Location of Abnormal (LV) Wall Motion|
|---|---|---|---|
|Dyskinesis| A-Hypokinesia| Ant/Apical| Posterior| Diffuse|
|False (12)| 5 (42%)| 7 (58%)| 5 (42%)| 6 (50%)| 1 (8%)|
|Negative| 1 (8%)| 12 (92%)| 6 (46%)| 5 (30%)| 2 (15%)|
|True (13)| 4 | 9 | 1 | 2 |

P = 0.001 P < 0.05 NS NS NS

Abbreviations: A = akinesia; Ant = anterior; NS = not significant.

**Figure 5. Incidence of false negative response (%) in patients with SCAD according to their ejection fraction (< 55% = low, 55–74% = normal, and > 75% = high).**

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Therapeutic implications of our study suggest that patients in the false negative subset may respond to a lower dose of antianginal therapy and demonstrate an improved prognosis as suggested by their better exercise tolerance. Their poor left ventricular function, however, may be an offsetting factor both medically and surgically. Obviously, such conclusions must await definitive prospective studies.

In conclusion, we have evaluated the determinants of the false negative exercise test in symptomatic patients. A strong association of this response with left ventricular dysfunction rather than a lesser extent of vascular disease was observed. The mechanisms involved may relate to complex metabolic and electrocardiographic relationships resulting from extensive segmental disease.

Our data suggest that in the clinical setting of symptomatic coronary artery disease a negative electrocardiographic exercise response may not always exclude extensive coronary disease and may signal the presence of associated moderately severe myocardial dysfunction.

Acknowledgment

We would like to express our gratitude to Dr. M.S. Rosenberg for his help in the interpretation of electrocardiographic abnormalities and to Mrs. Susan Burin, Ms. Susan Adams, and Ms. Patricia Houston for their technical and secretarial assistance.

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The "false negative" treadmill exercise test and left ventricular dysfunction.
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Circulation. 1978;57:763-768
doi: 10.1161/01.CIR.57.4.763
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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