

Graded Exercise Stress Tests in Angiographically Documented Coronary Artery Disease

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SUMMARY

Graded exercise stress tests performed on 650 consecutive patients with proven or suspected coronary disease undergoing evaluation by cardiac catheterization were correlated with clinical, hemodynamic, and angiographic findings. Among 451 patients with significant coronary stenosis, 332 (74%) had interpretable stress tests and 65% of these were positive (sensitivity). The rate of "false positives" was 8%.

The clinical syndrome of typical angina identified significant coronary disease in 89% of the patients, and 58% of that group had a positive exercise test defined by objective electrocardiographic criteria.

Patients were not eliminated from this study because of recent digitalis ingestion. Although a higher frequency of uninterpretable exercise tests was found in this group (40%), the test results reflected more severe coronary disease. None of the patients with "false positive" tests were taking digitalis. It is concluded that recent digitalis ingestion should not be considered a contraindication for exercise stress testing.

Among the patients with interpretable exercise tests, the angiographic severity of coronary artery disease correlates strongly with the frequency of positive tests (40%, 66%, and 76%, with 70% or greater occlusion of one, two or three vessels respectively). Left main coronary stenosis of 70% or greater was associated with more severe ST segment changes, inability to achieve target heart rate during stress, and a lower maximum heart rate during exercise. The angiographic occurrence of collateral vessels was related to the extent of coronary disease and was associated with a higher percentage of positive exercise tests; no protective effect of collateral circulation could be demonstrated. Patients with abnormal resting hemodynamics or left ventricular asynergy had no significant difference in the frequency of positive tests after adjustment for the angiographic severity of disease.

Additional Indexing Words:

Ischemic heart disease
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Exercise test
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Coronary collateral circulation

EXERCISE STRESS TESTING has become increasingly popular in the evaluation of patients with proven or suspected coronary artery disease. Stress electrocardiography has been especially useful clinically in patients with normal resting electrocardiograms and atypical or unusual

chest pain, and in corroborating symptoms of myocardial ischemia by objective electrocardiographic data.^{1,2} In largely asymptomatic populations, stress electrocardiography has been widely used as an adjunct to standard electrocardiography; the presence of a positive stress test has definite prognostic implications.^{3,4,5,6} In the postoperative assessment of the efficacy of aorto-coronary bypass surgery, the exercise stress test provides valuable objective data which may or may not support symptomatic responses.⁷

Until recently, the evaluation of large series of patients undergoing exercise stress testing has been limited by the lack of angiographic documentation of the presence or severity of coronary artery disease except by clinical evaluation. The addition of coronary angiography to the data base of clinical evaluation, physical examination, and standard

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electrocardiography provides more clear-cut identification of "false positives" and "true negatives" and allows for the correlation of exercise stress tests with the severity of angiographic and hemodynamic abnormalities resulting from coronary artery disease. The purpose of this paper is to examine the relationship between the results of exercise stress tests and clinical, angiographic, and hemodynamic descriptors in a large series of consecutive patients undergoing coronary angiography.

Methods

Graded treadmill exercise tests and cardiac catheterization were performed on 650 consecutive patients evaluated at Duke Medical Center between January 1970 and December 1972. These studies were performed primarily for diagnostic reasons, to confirm the clinical impression of coronary artery disease, or as part of the preoperative evaluation for aorto-coronary bypass surgery. Patients having previous cardiac surgery, congenital heart disease, rheumatic valvular disease, hypertrophic subaortic stenosis, ballooning mitral valve syndromes, cardiomyopathy, etc., were eliminated from this study. All clinical data and results of standard electrocardiograms and stress electrocardiograms were collected prospectively before cardiac catheterization and evaluated without knowledge of the results of coronary angiography.

Clinical Data

Chest pain syndromes were classified according to severity (NYHA Functional Class I-IV), frequency, and type of pain. The chest discomfort was characterized by at least three cardiologists prior to catheterization into one of three classifications: classical angina pectoris ("typical angina"), discomfort suggestive of angina but not entirely typical ("atypical angina"), or discomfort clearly not representative of the anginal syndrome ("non-anginal chest pain").

A history of previous myocardial infarction was accepted only if well documented by electrocardiographic and/or serial enzyme changes.

Exercise Stress Tests

Patients were examined in the fasting state and all medications discontinued at least twelve hours before testing. Standard 12 lead electrocardiograms were obtained prior to exercise with the electrodes for the standard limb leads placed on the upper left chest, upper right chest, and lower left and right abdominal wall in order to obtain a stable baseline during exercise. The patients were exercised according to the protocol of Bruce et al.² using the graded multi-staged treadmill test. Exercise was continued for three minutes at each treadmill stage (stage I-1.7 mph, 10% grade; stage II-2.5 mph, 12% grade; stage III-3.4 mph, 14% grade; stage IV-4.2 mph, 16% grade; stage V-5.0 mph, 18% grade). Patients were encouraged to exercise to their maximum.

Chest pain was *not* included in the definition of a positive or negative test, but the presence or absence of

chest discomfort during stress was recorded. A positive test was defined as horizontal and segmental ST depression or elevation of 0.1 mV (0.08 seconds duration or greater) in any of 12 continually monitored standard electrocardiographic leads. When digitalis effect or non-specific ST-T changes were present on the resting electrocardiogram, 0.2 mV ST change from control was required for inclusion in the positive group.⁸ Exercise tests were interpreted as negative only if the patient achieved 85% of the predicted maximal heart rate at peak exercise⁹ ("target heart rate") in the absence of significant ST segment changes. The test was placed in the undetermined category if any of the following occurred: (1) the patient failed to achieve target rate in the absence of significant ST segment change; (2) the patient had resting electrocardiographic abnormalities such as bundle branch block precluding evaluation of ST segment at maximal stress; (3) multiple premature beats or unstable baseline activity at maximal heart rate obscured possible ST segment changes; or (4) inter-observer differences could not be readily resolved.

The maximum ST segment elevation or depression was recorded using the resting ST segment in the same lead as a baseline. Those changes manifested by predominantly ST depression or elevation were recorded as such even though reciprocal changes were frequently present. The measurements were made using a 1.0 mV calibration = 10 mm.

After left and right heart catheterization, cardiac output was determined by the Fick principle and left ventricular cineangiography was performed in either the single plane or biplane mode. Selective coronary arteriograms, using the Sones¹⁰ or Judkins¹¹ techniques, were obtained in multiple views after the administration of sublingual nitroglycerin and 0.5 mg atropine. A significant lesion was defined as 70% or greater stenosis in a major coronary artery or branch and was agreed upon by at least three angiographers. Lesions of lesser degree were considered "normal" for the purpose of this paper. Significant lesions were divided into total occlusion or subtotal lesions (70-99% stenosis). Significant stenosis of the main left coronary was considered equivalent to combined stenosis of the left anterior descending and circumflex coronary arteries.

Data thus obtained were verified, permanently entered, and stored on a Xerox Sigma V computer, hence available for on-line statistical analysis of subgroups.

Results

General Characteristics

Among the 650 patients in this study, 199 had no significant coronary stenosis (< 70% narrowing of a major coronary artery); their mean age was 44.4 years. Sixty-seven percent of this group had a diagnostic treadmill examination, and in 33% the exercise test was not interpretable (undetermined test—see Methods for definition). Sixty-one percent of the treadmill tested patients were male; seventy-three percent achieved target heart rate during

stress. The duration of exercise reflected by the percentage of patients discontinuing exercise in each treadmill stage is noted in figure 1.

The 451 patients with significant coronary disease consisted of 108 with disease of a single vessel, 133 with disease of 2 vessels, and 210 with disease of three vessels. The mean age in each group was 46 years, 50 years, and 51 years, respectively. Seventy-three percent of the patients with disease of one vessel achieved target heart rate during stress, as opposed to 50% of patients with disease of two vessels and 42% of the patients with disease of three vessels. The percent of undetermined exercise tests was 30%, 25%, and 26%, respectively. The percent of males with disease of one, two and three vessels was 66%, 90%, and 89%, respectively. The duration of exercise, in terms of treadmill stage in which exercise was discontinued, decreased with increasing severity of coronary disease (fig. 1).

Among those patients with significant coronary disease, 45% had a documented myocardial infarction prior to catheterization. Thirty-seven percent had electrocardiographic Q wave evidence of definite previous myocardial infarction. Four percent of the patients had no chest pain within three weeks prior to the study. Seven percent of the patients with angiographically documented coronary disease were thought to have chest pain bearing no resemblance to angina pectoris. Thirty percent had "atypical angina" as described in the methods section. Sixty-two percent of the patients had "typical angina" pectoris. Fifty-one percent of the patients with chest pain had nocturnal and/or

rest pain (NYHA Functional Class IV). Nine percent of the patients had a prior history of congestive heart failure.

Clinical Correlations

Among the 264 patients characterized as having typical angina, 234 (89%) had significant coronary disease and 30 (11%) had no significant stenosis. Fifty-eight percent of the former group had a positive stress test (17% negative and 25% undetermined), compared to 10% of the latter group. Of interest is the observation that only 83% of the patients with significant coronary disease and a positive stress test developed chest discomfort during exercise (fig. 2).

On the other hand, among 235 patients with "angina" during stress, 203 (86%) had significant coronary disease, while 32 (14%) had normal or insignificant coronary stenosis. Of the former group 62% had a positive stress test (11% negative and 27% undetermined), compared to 9% of the latter group (fig. 2).

Analysis of those patients with typical angina who also developed angina during stress (164 patients) revealed that 159 (97%) had significant coronary disease. Of these, 65% had disease of three vessels and 67% had a positive stress test (only 9% had a negative test) (fig. 2).

The influence of myocardial infarction on the results of the treadmill stress test was also analyzed. Among 332 patients who had significant coronary artery disease and an interpretable treadmill stress test, a history of documented myocardial infarction was present in 136 and absent in 196. The

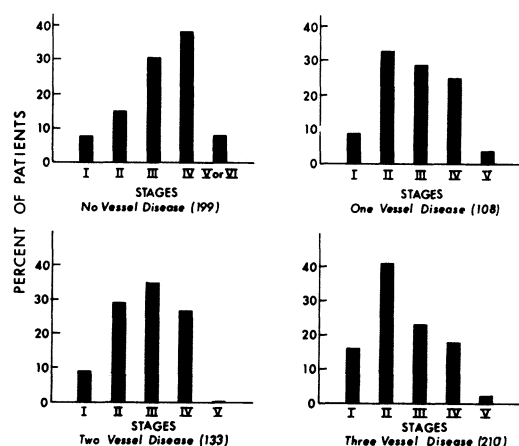


Figure 1

The maximum exercise stage attained expressed as a percent of the total group for patients with disease of 0, 1, 2, and 3 vessels.

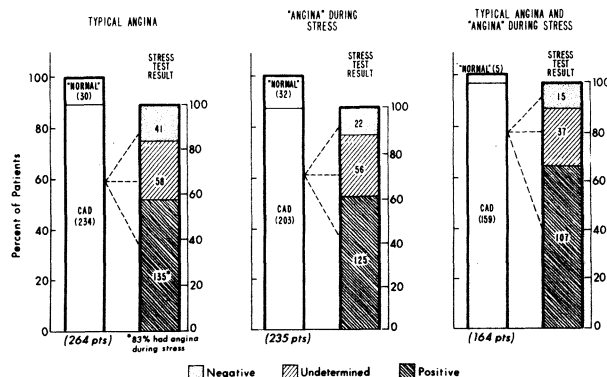


Figure 2

The relationship between typical angina pectoris and "angina" during stress, significant coronary stenosis angiographically and the stress test result. "Normal" = no area of coronary stenosis $\leq 70\%$. Note that among patients with typical angina and a positive stress test, only 83% developed angina during stress.

incidences of a positive test in these two groups were 65% and 64%, respectively.

Digitalis Therapy

Eighty-seven patients included in this study were taking oral digitalis preparations chronically and had significant coronary disease. Data obtained from this group was compared with 347 patients with significant coronary disease with no history of recent digitalis ingestion. The mean age of the digitalis group was 53 years, compared to 49 years in the no digitalis group ($P < 0.01$). The mean maximal heart rate during stress was 138 in the digitalis group, compared to 144 in the no digitalis group ($P < 0.05$). Forty-seven percent of the digitalis group achieved target heart rate, compared to 52% of the no digitalis group. In the digitalis group, the stress test results were as follows (see methods for definition of criteria): 47% were positive, 13% were negative, and 40% were undetermined. This is compared with the no digitalis group in which 47% were positive, 29% were negative, and 24% had undetermined results. Of those with diagnostic stress tests in the digitalis group, 79% were positive, compared to 62% of the no digitalis group. Sixty-one percent of the digitalis group had disease of three vessels compared to 44% of the no digitalis group. Left ventricular contraction abnormalities were more frequent in the digitalis group (67%) compared to the no digitalis group (39%). Generalized, severe hypokinesia (19%) and ventricular aneurysms (11%) were also more frequent in the former group than the latter (4% and 2% respectively). Among those patients with normally contracting left ventricles and diagnostic exercise tests, there was no significant difference in the frequency of positive exercise tests in the two groups.

None of the 11 "false positive" patients was receiving digitalis.

Risk Factors

Risk factors for coronary artery disease were analyzed in patients with diagnostic stress tests and significant coronary disease. The frequency of positive tests were compared for patients with and without the following risk factors: history of hypertension, history of cigarette smoking (one-half pack/day within three years prior to onset of symptoms), family history of coronary disease, a history of diabetes mellitus, and hyperlipemia. These comparisons were also made using the following data obtained during hospitalization:

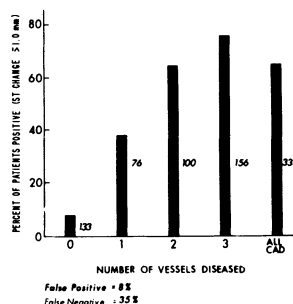


Figure 3

The correlation of severity of coronary disease with stress test result in 465 patients with diagnostic stress tests.

systolic blood pressure (≥ 160 mm Hg), diastolic blood pressure (≥ 90 mm Hg), serum cholesterol (≥ 250 mg%), serum triglycerides (≥ 150 mg), and lipid type on electrophoresis. None of the above mentioned variables was associated with significant differences in the frequency of positive stress tests.

Angiographic Correlations

Since the frequency of undetermined stress test results was similar for normal patients and those with one, two, and three vessel disease, these were eliminated in the analysis of angiographic findings. As noted in figure 3, 11 of 133 patients (8%) with no significant coronary disease had a positive response during exercise ("false positives"). Among 332 patients with significant coronary disease, 65% were positive during stress. The percentage of patients with positive tests increased with the severity of coronary disease as demonstrated in figure 3.

The degree of ST segment depression was also related to the severity of coronary disease angiographically (fig. 4). Patients having ST segment

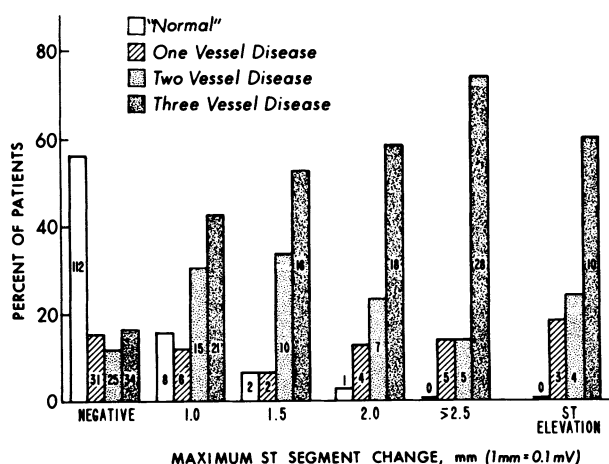


Figure 4

The maximum degree of ST change related to the severity of coronary disease. The number of patients in each subgroup is depicted in the bars.

depression greater than 2.0 mm were much more likely to have three vessel disease than those with less severe ST depression. Patients with normal angiograms were infrequently encountered.

Among patients with disease of a single vessel, the prevalence of positive exercise tests was similar for stenosis involving the left anterior descending, left circumflex, and right coronary arteries (38%, 42%, and 44%, respectively). Thirty-five percent of patients with subtotal stenosis of a single vessel had positive exercise stress tests, compared to 50% of patients with a total occlusion of a single vessel ($P = \text{NS}$).

Patients with predominantly ST segment elevation were unlikely to have normal coronary arteriograms and consisted mainly of patients with disease of three coronary vessels. Among patients with an abnormal left ventriculogram, predominant ST elevation occurred in 18% compared to 6% of patients with normal left ventriculograms ($P < 0.05$). No association was found between exercise induced ST elevation and the presence of left ventricular aneurysms.

Left Main Coronary Stenosis

Left main coronary stenosis greater than 70% occurred in 31 patients with diagnostic stress tests. This group was compared with patients having disease of three coronary vessels, but no significant stenosis of the left main coronary (125 patients). The mean age of the group with left main coronary disease was 53 years, compared to 50 years in the group with disease of three vessels but no significant left main lesion. The maximum heart rate obtained was 133 in the patients with subtotal occlusion of the left main coronary artery, compared to 142 without such a lesion. Only 33% of the patients with stenosis of the left main coronary artery achieved target heart rate, compared to 56% of those with disease of three vessels ($P < 0.05$). Eighty-seven percent of the patients with stenosis of left main coronary artery had a positive stress test, compared to 74% of those without left main lesions ($P = \text{NS}$). The degree of ST segment change among patients with stenosis of left main coronary artery was contrasted with the degree of ST change in those with disease of three vessels but no lesion in the left main coronary (fig. 5). It should be noted that there is a tendency for patients with left main coronary stenosis to have more severe ST segment changes, 30% of that group having ST change greater than 2.5 mm, compared to 22% of the patients with disease of three vessels ($P = \text{NS}$).

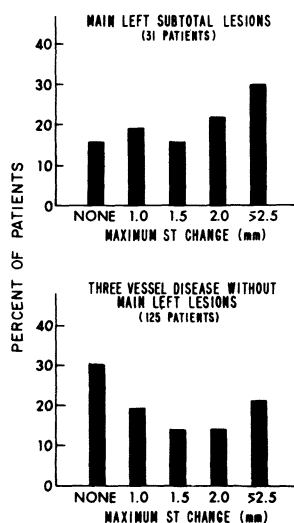


Figure 5

The maximum ST segment change during stress in 31 patients with significant main left coronary lesions (upper panel) compared to 125 patients with disease of three coronary vessels and no significant lesion of the left main coronary artery (lower panel).

The ability to predict the presence of severe stenosis of the left main coronary artery using the maximum heart rate alone was assessed. Among patients with a positive stress test and maximum heart rates ≤ 130 , 23% had lesions of the left main coronary artery. This is significantly greater than the frequency of lesions of left main coronary artery among patients with positive stress tests and maximum heart rates > 130 (9%; $P < 0.01$).

Collateral Circulation

The presence or absence of intracoronary collateral flow at the time of angiography was recorded without attempts to estimate the degree of extent of collateralization. One hundred fifty-eight patients had collateral vessels identified. Ten percent had disease of a single vessel, 22% had disease of two vessels, and 68% had disease of three vessels. Among the 118 patients in whom no collateral vessels could be identified, 40% had disease of one vessel, 36% had disease of two vessels and only 24% had disease of three vessels. The mean age of the patients with collaterals was 50 years, compared to 49 years among those without collaterals. The mean maximum heart rate obtained during exercise was 139/min for those with collaterals. Fifty-two percent of those with collaterals achieved target heart rate, compared to 78% of those without collaterals. The patients with collateral vessels had a significantly higher percentage of positive tests, compared to those patients without collaterals (75% vs 47%) ($P < 0.001$). Significant differences ($P < 0.05$) were also present after subgrouping patients for disease of one or three vessels, but not for those with two.

Correlation with Hemodynamics

Since the presence of a positive exercise stress test is related to the severity of coronary disease, attempts to correlate hemodynamics with exercise stress tests must take this factor into account. Therefore, resting hemodynamics during catheterization were compared in an angiographically homogeneous group (three vessel disease) in which a diagnostic exercise test was obtained. This included 114 patients with a positive treadmill test and 32 patients with a negative exercise test. There were no significant differences between resting right heart pressures, left ventricular end diastolic pressure, cardiac output, or biplane left ventricular ejection fraction. No hemodynamic measurements were obtained during exercise.

Ventricular Asynergy

There were 186 patients with normally contracting ventricles. Nineteen percent of these had a history of previous myocardial infarction and 14% had electrocardiographic evidence of previous infarction (67% were diaphragmatic or posterior infarctions). Sixty-three percent of these patients had a positive exercise test. The distribution of disease in one, two, and three vessels was 30%, 34%, and 36%, respectively.

One hundred thirty-one patients had ventricular asynergy. Seventy-four percent had previous myocardial infarction by history, and 64% had Q wave evidence of previous myocardial infarction. Sixty-nine percent of these patients had a positive exercise test. The distribution of disease of one, two, and three vessels was 15%, 26%, and 59%, respectively. Subgrouping patients by the location of asynergy (apical, anterior, posterior, diffuse, and left ventricular aneurysm) demonstrated a similar frequency of positive stress tests in each group.

Patients with disease of three coronary vessels with and without ventricular asynergy, were also compared. Eighty-one patients with asynergy had a 79% frequency of positive stress tests, compared to a 76% positive rate among 70 patients with normally contracting left ventricles.

"Undetermined" Test Results

The frequency of undetermined tests (see methods section for definition) in normals and in patients with disease of one, two and three vessels was 36%, 17%, 18%, and 29%, respectively. The vast majority of tests were not interpretable because target heart rate was not reached (81%). Resting ST-T abnormalities were also more common in the

undetermined group (39% vs 22%). As expected, more patients in the undetermined group were taking digitalis preparations (27% vs 13%).

False Positives

A "false positive" exercise test was defined as the presence of a positive stress test (see methods section) in a patient without significant narrowing ($\geq 70\%$) of any major coronary artery. This occurred in 11 patients among 133 (8%) who were considered to have insignificantly narrowed or normal coronary arteries. Among the 11 patients, six were female (as opposed to 23% of the entire group); five had minor, non-diagnostic resting ST segment abnormalities; however, these were not considered severe enough to interfere with the exercise test interpretation. One of the patients had left ventricular hypertrophy. Eight patients had normal coronary arteries angiographically. Three of the patients had abnormalities of the coronary arteries which were considered insignificant (one had insignificant narrowing ($< 50\%$) of all three coronary arteries; the remaining two had insignificant disease of the left anterior descending coronary only). None of the 11 patients had abnormally contracting ventricles on cineangiography. None were receiving digitalis or other drugs thought to interfere with interpretation of the exercise electrocardiogram.

Discussion

The present study is based upon the correlation of data obtained during exercise testing in a large, consecutive group of patients undergoing cardiac catheterization either for diagnostic purposes or as part of the evaluation for aortocoronary bypass surgery. The patient population is obviously highly selected, and the applicability of these data to other hospital based series, and to office and community practices of general medicine and cardiology depends upon the strength of the descriptors utilized in this study with regard to the patient's final outcome. Since this patient population is extremely heterogeneous, it is obviously necessary to form relevant subgroups for various portions of the analysis. In the absence of a group of randomly allocated patients in a free living community who have been subjected to cardiac catheterization and coronary angiography, we are restricted to methods of analysis as described in this paper.

The use of exercise stress testing has achieved wide popularity and can be safely performed on large numbers of people in the office, outpatient

clinic, or hospital.¹ It is not surprising that many patients with ischemic heart disease manifest no signs of myocardial ischemia at rest, since in many cases, symptoms occur only with exertion. It therefore seems appropriate to stress the cardiovascular system in an attempt to provoke myocardial ischemia so that *objective* electrocardiographic changes may be recorded and added to the data obtained at rest. The presence of a positive exercise test has definite strong prognostic implications.³⁻⁶ Correlations of the data obtained during exercise testing with symptomatic, angiographic, hemodynamic, and prognostic descriptors form the basis of this paper.

From an over-all standpoint, the results of this paper are in keeping with several other studies demonstrating a low rate of false positive exercise tests (8%) in patients subjected to similar degrees of stress or work load.¹²⁻¹⁶ On the other hand, the percentage of patients having false negative exercise tests appears to be related to the severity of coronary artery disease. Thus, approximately 60% of patients with disease of a single coronary vessel who have an adequate exercise response have no significant electrocardiographic changes during stress. This is contrasted with a 34% and 24% frequency of negative but adequate exercise tests in patients with disease of two and three vessels, respectively. These findings are similar to those previously reported in smaller series of patients.^{13-15, 17, 18}

The relationships of chest pain syndromes with the exercise test responses and coronary angiography are important since some investigators and clinicians regard the occurrence of angina during stress as a positive test. It is of interest that 47% of our entire patient group had "classical" angina pectoris. Of these, 11% had no significant coronary artery disease angiographically. Among those patients with typical angina and significant coronary artery disease angiographically, only 58% had a positive exercise test using significant electrocardiographic changes as the end point. Even among the patients with significant coronary disease, typical angina, *and* a positive exercise test, only 83% developed angina pectoris during the exercise test. Thus, from an over-all standpoint, a patient with typical angina had an 89% chance of having a positive exercise test.

Analysis of those patients having "angina" during exercise stress testing revealed that 86% had significant coronary disease while 14% did not. Among those patients with significant coronary

artery disease who developed angina during stress, only 62% had a positive exercise test. On the other hand, among those patients with typical angina pectoris who developed angina during stress, 97% had significant coronary disease angiographically, 67% had positive stress tests, and 65% had disease of three coronary vessels. It may be concluded that utilization of "angina" as the only end point in stress testing is fraught with the hazard of including patients without significant coronary artery disease and too frequently lacks accompanying electrocardiographic signs of ischemia.

A paucity of data has been published on exercise testing in patients on chronic digitalis therapy. Kawai and Hultgren¹⁹ reported ST-T changes during a Master's test in digitalized cardiac patients and normals; however, the maximum heart rates achieved were not specified, and the ECG criteria for positivity were not rigid. Nordstrom-Ohrberg²⁰ demonstrated ST-T changes in 64 digitalized volunteers. These changes occurred in 32% at rest, 75% on standing, and 89% during bicycle exercise. Adair et al.²¹ reported normalization of ST-T changes in digitalized normal men as target heart rates were approached, suggesting that exercise induced ST-T changes in digitalized patients with significant coronary disease may indicate ischemia. A significant number of patients in this series (17%) were taking digitalis preparations prior to exercise testing. Comparison of patients with significant coronary disease with and without recent digitalis ingestion revealed a higher frequency of undetermined tests in the digitalis group due primarily to the presence of resting ST-T changes. However, among those exercise tests which were interpretable, a higher frequency of positive tests was present compared to the "no digitalis" group. This result is probably due to the fact that the digitalis group was significantly older, contained more patients with disease of three coronary vessels and had almost twice the prevalence of ventricular asynergy (including severe hypokinesis and left ventricular aneurysms).

Since none of the "false positive" stress tests was attributed to digitalis ingestion and the majority of patients in the digitalis group had diagnostic stress tests as well as more severe coronary disease, the authors emphasized the value of stress testing these patients.

The findings of this study are in agreement with other reports demonstrating increasing frequency of positive stress tests with more severe coronary disease angiographically.^{15-17, 22-24} In addition, the

presence of deeper ST segment depression (2.0 mm) and predominant ST elevation were associated with more severe coronary disease, and few "false positives." Similar findings have been reported by Mason,¹⁷ Cohn,²⁴ Kaplan¹⁶ and others.^{15, 22, 23} Analysis of patients with disease of a single vessel revealed no difference in the prevalence of positive tests with respect to which coronary artery was involved. This agrees with the findings of Kaplan et al.¹⁶ but differs from data published by McHenry et al.²³ who demonstrated a higher frequency of positive tests in patients with isolated lesions of left anterior descending coronary artery. The reasons for this discrepancy are not apparent but may be related to patient selection.

Lavine et al.²⁵ stated that severe stenosis of the left main coronary artery is associated with a markedly positive stress test but only six patients had pacing studies and only four underwent exercise testing. Among the 32 patients with disease of the left main coronary artery studied by Cohen et al.,²⁶ 20 had a double Master's test, 17 were positive, and 14 of the latter had ST change ≥ 2 mm. Data from the present study confirm this finding. In addition, this group is characterized by lower maximum heart rates during stress and inability to achieve target heart rate during stress, emphasizing a particularly critical anatomic-physiologic relationship.

Several investigators have recently questioned the "protective effect" of coronary collateral flow. Helfant et al.²⁷ found no significant difference in the occurrence of myocardial infarction or sudden death comparing patients with and without collateral flow determined by coronary angiography. Data from the present study are similar to the findings of Harris et al.²⁸ and support the impression that collateral vessels appear to be related to the severity of coronary disease since almost three times as many patients with disease of three vessels were present among patients with collateral vessels. Furthermore, a higher rather than lower frequency of positive stress tests occurred in the presence of collateral vessels in the entire group, or after separation into one, two, or three vessel disease subgroups. Although future analysis of the type, extent and size of collaterals and the associated anatomical lesions may reveal other subgroups in which collaterals provide "protection," no such effect could be demonstrated in the present series.

Data from the present study as well as previous reports, demonstrate a strong relationship between

the frequency of positive stress tests and the anatomical severity of coronary disease. In addition, the marked heterogeneity of the population selected for angiography requires both analysis of large numbers of patients and comparison of reasonably homogeneous subgroups in order that valid conclusions can be drawn. This concept is relevant to analysis of stress tests in patients with normal versus abnormal ventricular function. Patients with abnormal ventricular function are much more likely to have disease of three coronary vessels than patients with normal ventricular function; thus, the former group may be expected to have a higher frequency of positive stress tests than the latter. Indeed, after eliminating patients with disease of one or two vessels from the analysis, there is essentially no difference between patients with positive or negative stress tests with respect to right heart pressures or left ventricular end diastolic pressure, cardiac output, ejection fraction, history of previous myocardial infarction, electrocardiographic evidence of infarction, or ventricular asynergy by cineangiography. Unfortunately, hemodynamic measurements were not obtained during exercise.

The rate of false positives in the present study was 8% which compares favorably with other authors.^{15-17, 22-24} False positives occurred more frequently in females and, as expected, in the presence of "minor" ST segment abnormalities. Perhaps more stringent attention to the baseline ST segment might have eliminated several patients from this category; however, such restrictions would likely change the interpretation of many "true positive" tests to "undetermined" tests. None of the false positive tests was secondary to recent ingestion of digitalis or other drugs. The possibility that a significant coronary lesion went undetected cannot be dismissed, nor could we eliminate the possible protective effect of the routine use of nitroglycerine on coronary spasm during coronary arteriography.

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References

1. Measurement in Exercise Electrocardiography. The Ernst Simonson Conference, edited by BLACKBURN H. Springfield, Charles C Thomas, 1969
2. BRUCE RA, HORNSTEN TR: Exercise stress testing in evaluation of patients with ischemic heart disease. *Progr Cardiovasc Dis* 11: 371, 1969

3. ROBB GP, MARKS HH: Postexercise electrocardiogram in arteriosclerotic heart disease: Its value in diagnosis and prognosis. *JAMA* **200**: 918, 1967
4. MATTINGLY TW: The postexercise electrocardiogram: Its value in the diagnosis and prognosis of coronary arterial disease. *Am J Cardiol* **9**: 395, 1962
5. DOYLE JT, KINCH SH: The prognosis of an abnormal electrocardiographic stress test. *Circulation* **41**: 545, 1970
6. BLACKBURN HW, TAYLOR HL, KEYS A: Prognostic significance of the post-exercise electrocardiogram: Risk factors held constant. *Am J Cardiol* **25**: 85, 1970
7. BARTEL AG, BEHAR VS, PETER RH, ORGAIN ES, KONG Y: Exercise stress testing in evaluation of aorto-coronary bypass surgery. Report of 123 patients. *Circulation* **48**: 141, 1973
8. COHN PF, VOKONAS PS, HERMAN MV, GORLIN R: Postexercise electrocardiogram in patients with abnormal resting electrocardiograms. *Circulation* **43**: 648, 1971
9. ROBINSON S: Experimental studies of physical fitness. *Arbeitsphysiologie* **10**: 251, 1938
10. SONES FM JR, SHIREY ED: Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* **31**: 735, 1962
11. JUDKINS MP: Selective coronary arteriography. *Radiology* **89**: 815, 1967
12. MASON RE, LIKAR I, BIERN RO, ROSS RS: Multiple-lead exercise electrocardiography. *Circulation* **36**: 517, 1967
13. ROITMAN D, JONES WB, SHEFFIELD LT: Comparison of submaximal exercise ECG test with coronary cineangiogram. *Ann Intern Med* **72**: 641, 1970
14. ASCOOP CA, SIMOONS ML, EGMOND WG, BRUSCHKE AVG: Exercise test, history, and serum lipid levels in patients with chest pain and normal electrocardiogram at rest: Comparison to findings at coronary arteriography. *Am Heart J* **82**: 609, 1971
15. MARTIN CM, MCCONAHAY DR: Maximal treadmill exercise electrocardiography. Correlations with coronary arteriography and cardiac hemodynamics. *Circulation* **46**: 956, 1972
16. KAPLAN MA, HARRIS CN, ARONOW WS, PARKER DP, ELLESTAD MH: Inability of the submaximal treadmill stress test to predict the location of coronary disease. *Circulation* **47**: 250, 1973
17. MASON RE, LIKAR I, BIERN RO, ROSS RS: Correlation of graded exercise electrocardiographic response with clinical and coronary cinearteriographic findings. In *Measurement in Exercise Electrocardiography*. The Ernst Simonson Conference, edited by BLACKBURN H. Springfield, Charles C Thomas, 1969
18. MCCONAHAY DR, MCCALLISTER BD, SMITH RE: Postexercise electrocardiography: Correlations with coronary arteriography and left ventricular hemodynamics. *Am J Cardiol* **28**: 1, 1971
19. KAWAI C, HULTGREN HN: The effect of digitalis upon the electrocardiogram. *Am Heart J* **68**: 409, 1964
20. NORDSTROM-OHRBERG G: Effect of digitalis glucosides on electrocardiogram and exercise test in healthy subjects. *Acta Med Scand* **176** (suppl 420):1, 1964
21. ADAIR RF, HELLERSTEIN HK, WHITE LW: Digoxin induced exercise ECG changes in young men: ST-T walk through phenomenon above 80% max heart rate. *Circulation* **45** (suppl II):II-11, 1972
22. FITZGIBBON GM, BURGGRAF GW, GROVES TD, PARKER JO: A double Master's two-step test: Clinical, angiographic, and hemodynamic correlations. *Ann Intern Med* **74**: 509, 1971
23. MCHENRY PL, PHILLIPS JF, KNOEBEL SB: Correlation of computer-quantitated treadmill exercise electrocardiogram with arteriographic location of coronary artery disease. *Am J Cardiol* **30**: 747, 1972
24. COHN PF, VOKONAS PS, MOST AS, HERMAN MV, GORLIN R: Diagnostic accuracy of two-step postexercise ECG. Results in 305 subjects studied by coronary arteriography. *JAMA* **220**: 501, 1972
25. LAVINE P, KIMBIRIS D, SEGAL BL, LINHART JW: Left main coronary artery disease. Clinical, arteriographic and hemodynamic appraisal. *Am J Cardiol* **30**: 791, 1972
26. COHEN MV, COHN PF, HERMAN MV, GORLIN R: Diagnosis and prognosis of main left coronary artery obstruction. *Circulation* **45** (suppl I):I-57, 1972
27. HELFANT RH, VOKONAS PS, GORLIN R: Functional importance of the human coronary collateral circulation. *N Engl J Med* **284**: 1277, 1971
28. HARRIS CN, KAPLAN MA, PARKER DP, ARONOW WS, ELLESTAD MH: Anatomic and functional correlates of intercoronary collateral vessels. *Am J Cardiol* **30**: 611, 1972