Interpretation of Diagnostic Graded Exercise Tests on the Basis of Electrocardiographic, Hemodynamic, and Symptomatic Responses

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Abstract

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The purpose of this investigation was to determine whether a quanitative approach to interpreting diagnostic graded exercise tests (DGXT) could enhance the probability of predicting presence and severity of coronary artery disease (CAD). In an attempt to supplement the traditional ST segment criterion, hemodynamic, symptomatic, and additional electrocardiographic responses were included. An empirically devised treadmill score (TMS) formula based on graded exercise test responses resulted in the calculation of a single TMS for 85 symptomatic patients who had both coronary angiography and a DGXT. The TMS method was successful in detecting coronary lesions $\geq$ 50% with a sensitivity of 95%, specificity of 63% and predictive value of a positive test 87%. The true-negative rate was 83% and correct classification rate 86%. These values represent an increase in test accuracy of 3 - 25% when compared to the standard criteria (ST segment) for DGXT interpretation.

The TMS method enhanced the ability to predict CAD severity, as supported by the statistically significant difference ($p < .05$) in TMS of three combinations of CAD severity subgroupings. Thus, quantitatively interpreting the DGXT increases the accuracy of diagnosing presence and severity of CAD.

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We recommend acceptance of this thesis in partial fulfillment of this candidate's requirements for the degree:

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CHAPTER I

INTRODUCTION

Diagnostic graded exercise testing (DGXT) is a valuable tool for the evaluation of patients suspected of having coronary artery disease (CAD). Traditionally, the DGXT has been interpreted exclusively on the basis of ST segment displacement. This is predominantly a qualitative approach to CAD detection through identification of an ischemic myocardial response from the exercise responses, and then inferring coronary obstruction from the interpreted ischemia. There has been considerable controversy regarding the value of such testing due to the significant number of false-positive and false-negative DGXTs. The prevalence of disease within the population being examined can have the greatest impact upon the number of false-positive and false-negative tests. The false-positive rate increases when the prevalence of disease decreases, as seen in asymptomatic populations having a high prevalence of disease. These types of findings lead Borer et al. (1975) to conclude that "exercise electrocardiography as currently used, is of very limited value in the diagnosis of hemodynamically important large vessel coronary artery stenosis in the individual patient." In addition, these investigators

questioned the ethics involved in informing a patient of possibly erroneous results, since many are unable to cope with the knowledge that their lives may be shortened. In a subsequent rebuttal, it was pointed out that prognostication or estimation of relative risk is an established part of clinical medicine (Sheffield et al., 1977). These authors believe that a study which used only a single parameter, ST segment--and this being only positive or negative--represented a "regressive position." Recently, an interest in including additional factors has evolved, thereby making the criteria for a positive test more stringent and increasing predictive value. These additional exercise responses are of a hemodynamic, symptomatic, or electro-cardiographic nature. Cohn et al. (1979) recently showed that by weighing and combining these responses with discriminant function analysis, the ability to predict presence and severity of CAD could be improved 10-15%.

This approach to diagnostic testing allows the results to be quantitatively interpreted. By interpreting a test as being positive or negative, the test is in effect diagnosing CAD as either "present" or "absent." By encompassing many variables based on their relative importance, the exercise test may be placed on a continuum. Therefore, some idea of severity may be interpreted. One author has suggested that the DGXT be assigned a treadmill number (Cohn et al., 1979), while another has suggested a

semi-quantitative approach, i.e., normal, mildly through severely positive test (Selzer, Cohn and Goldschlager, 1976).

Purpose

The purpose of this study was twofold. First, it was necessary to determine the extent to which interpreting DGXT's on the basis of electrocardiographic, symptomatic, and hemodynamic response can increase sensitivity, specificity, and predictive value as performed at Gundersen Clinic, Ltd., La Crosse, Wisconsin. In an attempt to supplement the traditional ST segment criterion, a treadmill score was computed which utilized the other variables just mentioned. Second, with the aid of such a Treadmill Score Formula, it was determined whether the probability of correctly predicting presence and severity could be enhanced.

Null Hypothesis

Interpreting diagnostic graded exercise tests on the basis of hemodynamic electrocardiographic and symptomatic responses, as compared to the conventional method based exclusively on the ST segment displacement, will not significantly ($p. < .05$) increase sensitivity, specificity, predictive value or correct classification rate of a diagnostic graded exercise test.

Treadmill score will not significantly ($p. < .05$)

differ among those with no CAD, single vessel disease, moderate to severe CAD, advanced CAD, and left main corony artery disease.

Delimitations

1) All subjects were referred to Gundersen Clinic, Ltd., La Crosse, Wisconsin, by their primary physician for a DGXT with suspected CAD (based on presence of symptoms).

2) Subjects consisted of 85 patients who underwent coronary angiography within three months of the DGXT.

3) Subjects were tested between February 1, 1976, and April 10, 1979.

4) No subject had clinically diagnosed CAD previous to the DGXT, i.e., no previously documented myocardial infarction.

Limitations

1) Due to the "Ex Post Facto" design of the study, the accuracy of exercise responses (i.e., blood pressure) was limited by the technicians at the Gundersen Clinic, Ltd., Cardio-Pulmonary Laboratory. There were, in the three years of testing, more than one group of laboratory technicians. These technicians had extensive experience in graded exercise testing. The retrospective nature of this study minimized the pre-test bias.

2) Coronary angiography and electrocardiographic data was limited by the technical accuracy of the equipment.

3) Angiographical interpretation was limited by inter- and intra-observer variability of the cardiologist interpreting the degree of coronary stenosis.

Definition of Terms

Coronary Angiography - (Cineanography). A 35mm X-ray type film of the heart and coronary arteries that follows the course of an opaque fluid which has been injected into the blood stream. Its purpose is to detect any stenosis or obstruction in coronary arteries of the heart.

Coronary Artery Disease - (CAD). Also known as coronary atherosclerosis, a stenosis or obstruction of the luminal diameter of the coronary arteries which conduct blood to the heart muscle. The lumen becomes narrowed and the blood supply to the heart is reduced, causing myocardial ischemia. For the purpose of this study, 50% to 90% stenosis was referred to as significant CAD, and 90% or greater stenosis was referred to as critical CAD. The four major coronary arteries are the right main (RMCA), left main (LMCA), left anterior descending (LAD), and the circumflex (CX) arteries.

Single Vessel Disease. Coronary artery disease involving any one artery (excluding LMCA) with a stenosis $\geq$ 50%.

Moderate to Severe Disease. May consist of either: 1) A $\geq$ 50% stenosis in two of the three major coronary arteries (LMCA excluded), 2) LMCA with $\geq$ 50% stenosis, or 3) triple vessel disease, provided LMCA $\geq$ 50% and LAD 90%.

Advanced Disease. May be either 1) LMCA $\geq$ 90% and right main, or 2) triple vessel disease with $\geq$ 50% LMCA and/or $\geq$ 90% stenosis of LAD.

Diagnostic Graded Exercise Test - DGXT). A continuous multi-stage treadmill exercise of increasing intensity. A tool for diagnosing CAD by identifying an ischemic myocardial response from the exercise responses and then inferring coronary obstruction from the interpreted ischemia. The exercise response may be related to electrocardiographic, hemodynamic or symptomatic changes.

Hemodynamic Responses. Included were the: 1) systolic blood pressure (SBP) responses during the DGXT, 2) maximal heart rate (HR) attained during final minute of DGXT, and 3) maximal rate pressure (RPP) product attained (Max SBP X Max HR = RPP).

ST Segment Depression. The part of the electrocardiogram between the S wave and beginning of the T wave. Depression or displacement represents the alterations in ionic fluxes at the cell membrane due to myocardial ischemia, an imbalance of oxygen supply and demand.

Electrocardiographic Responses. Related to the: 1) time of onset and duration of ST segment displacement, 2) ST segment configuration, i.e., upsloping, downsloping or horizontal, and 3) magnitude of ST segment displacement, i.e., 1.0-1.9mm, 2.0-2.9mm, 3.0-3.9mm

depression for at least .08 seconds duration.

Symptomatic Responses. Symptoms reported by the patient relating to: 1) chest pain (either typical or atypical) and/or 2) shortness of breath (SOB).

Positive Test. Abnormal, inferring that disease is present based on the interpretation of the DGXT responses as representing ischemia.

Negative Test. Normal DGXT responses inferring that disease is not present.

True Positive DGXT (TP). A positive DGXT and positive coronary angiography test. Disease is present.

False Positive DGXT (FP). A positive DGXT and negative coronary angiography test. No disease is present.

True Negative DGXT (TN). A negative DGXT and negative coronary angiography test. No disease is present.

False Negative DGXT (FN). A negative DGXT and positive coronary angiography test. Disease is present.

Prevalence of Disease: the percentage of the population having disease. Since all patients had subjectively experienced atypical or typical angina, the prevalence of disease was estimated to be 50-90% in these subjects.

Sensitivity: the probability of getting a positive exercise test in people with known CAD. It is the percentage of times the DGXT gives an abnormal result when those with disease are tested.

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100$$

Specificty: the probability of getting a negative test in people with no CAD. It is the percentage of times the DGXT gives a normal result when those without disease are tested.

$$\text{Specifity} = \frac{TN}{TN + FP} \times 100$$

Predictive Value of a Positive DGXT, (PV+): the probability of having CAD after having a positive DGXT. It is the percentage of those with an abnormal DGXT who have CAD.

$$PV(+) = \frac{TP}{TP + FP} \times 100$$

Predictive Value of a Negative DGXT, (PV-): also known as True Negative Rate (TNR). It is the probability of not having CAD after having a negative DGXT, or the percentage of those with a normal DGXT who do not have CAD.

$$PV(-) = \frac{TN}{TN + FN} \times 100$$

Correct Classification Rate: the percent of subjects correctly classified.

$$\text{Correct Classification Rate} = \frac{TP + TN}{\text{Total Number of Patients}}$$

CHAPTER II

REVIEW OF LITERATURE

Standard of Comparison

To determine the usefulness (sensitivity, specificity and predictive value) of the DGXT, an accurate standard of comparison is necessary. The positive or negative DGXT must be further defined as being true or false, based upon some specific criterion. Presently,three methods of assessing presence and severity of CAD are used as a criterion (Cooke and Ellestad, 1979): 1) long term follow-up studies using pathological end points, such as angina, myocardial infarction and/or death, 2) postmortem findings, and 3) coronary angiography. Follow-up studies are "non-invasive," but require years of waiting. Studies of this nature may allow the disease to progress during the elapsed time, thereby overestimating severity of disease. The most practical method, coronary angiography, offers immediate feedback for comparison with "non-invasive" diagnostic tests. Postmortem studies have been used primarily to determine the accuracy of coronary angiography.

Follow-up studies use pathological end points (i.e., angina, myocardial infarction, death) for determining those patients with CAD. Although the most common underlying disease in those suffering a myocardial infarction

is CAD, many remain asymptomatic with insignificant coronary arterial stenosis. Khan and Haywood (1974) found that nine of 78 (12%) consecutive patients with clinically diagnosed myocardial infarction had normal coronary arteries, as determined by angiography. Similar results were found in a postmortem study conducted on ten patients who died of an acute myocardial infarction within 25 days of onset of symptoms (Eliot, Buroldi and Leone, 1974). Six patients had totally patent arteries, one had a single 20% occlusion, two had a 40-50% obstruction,and the remaining patient had a 40-50% stenosis in two coronary arteries. Therefore, documented cases of typical acute myocardial infarction are seen in the absence of significant coronary arterial obstruction.

Chest pain may mistakenly be interpreted as a sign of CAD when used as a pathological endpoint. Four patients with patent arteries elicited spontaneous arterial spasm during coronary angiography (Maseri et al., 1975). The spasm caused complete occlusion with no distal filling. Therefore, a detectable and permanent narrowing of the coronary arteries may not be a prerequisite for angina. Bamrah, Bahler and Rikita (1974) found that 17 of 58 (30%) patients with suspected CAD due to chest pain had normal angiograms and intracardiac pressures. Of these 17 patients with chest pain, only one had typical angina. Therefore, if chest pain is used as a pathological endpoint for CAD,

it is important to distinguish between typical and atypical angina.

The accuracy of coronary angiography is determined by correlation with postmortem findings. In one comparison study, 134 segments of the coronary arteries were dissected from each of ten patients with CAD (Vlodaur et al., 1973). The results showed angiography had a 33% false-negative rate. Some possible explanations for the underestimation of angiography were: 1) intravascular pressure of a postmortem injection may distend a weakened sclerotic wall, and 2) the apparently normal looking arterial wall resulting from too few angled projections. In another postmortem study angiography was in agreement 79% of the time (<25% difference in cross-sectional area), overestimating 6% and underestimating 15% of the time (Schwartz et al., 1975). Angiographical findings correlated higher with anatomic findings in proximal as opposed to distal segments. Errors were presumably due to 1) vessels with elongated circumferential lesions mistakenly interpreted as "small, but otherwise normal," 2) prosthetic values obstructing view, and 3) a severe proximal lesion causing decreased accuracy of interpretation in distal vessels.

Twenty-three patients who died following coronary artery by-pass grafting had an autopsy to determine accuracy of recent angiogram (Grondin et al., 1974). In nine cases there was a 25% underestimation of severity, which

led to incomplete revascularization, a contributing factor in surgical failure. The author suggested that the discrepancy was due to postmortem shrinkage of the arterial walls, while atheromatous material remained unchanged, thereby appearing to be a more significant stenosis.

Observer variability of interpretation, as well as technical accuracy, present certain limitations for coronary angiography. A study to determine interobserver variability was conducted with four experienced observers (two radiologists, two cardiologists) (Zir et al., 1976). Independent assessment of 20 angiograms resulted in a substantial degree of variability. In only 65% (13/20) of the angiograms reviewed did all four agree on the significance of occlusion ($>$ or $<$ 50%). Inter- and intra-observer variability was determined after 22 physicians read 13 angiograms on two occasions (Detre et al., 1975). Inaccuracies between observers were similar to the errors within observers. That is, similar errors were made if the same physician interpreted the angiogram twice as when two separate physicians interpreted. The distal portion of the left anterior descending and circumflex coronary artery caused the greatest variability. The right main coronary artery and presence of ventricular aneurism was read most consistently. The usefulness of this study is limited since no measure of validation (i.e., autopsy) was used. Therefore, the observer in disagreement may have

possibly been correct. These results suggest that although uniformity of interpretation is not always present, knowledge of this fact should be taken into account.

Another limitation of accuracy occurs when an arterial spasm occurs during angiography (Chahire et al., 1975). These spasms may be spontaneous or catheter induced due to irritation. When spasms are present they appear as occlusions, and when absent they appear as normal vessels. The possibility of overlooking an occlusion exists if it occurs at the origin of the branch artery, flush with the wall of the major artery (Barresi, Manchester and Shelburne, 1973). The occluded vessel would have been presumed absent, since it would not show up on film.

To successfully investigate the ability of a "non-invasive" exercise test to diagnose CAD, there must be an accurate standard to which results can be compared. Long term follow-up studies utilizing pathological end-points are limited since clinical symptoms are not always due to CAD. Although coronary angiography allows immediate diagnosis, it tends to underestimate the severity of disease when compared to postmortem findings. Observer variability presents a minor limitation, but this can be compensated for by taking a consensus during the interpretation. Therefore, when determining the usefulness of the DGXT in predicting the presence and severity of CAD, coronary angiography is at present the most practical and accurate "gold standard" of comparison.

Diagnostic Exercise Test Responses

The positive or negative interpretation of the DGXT can be based on one or several exercise responses. Understandably, diagnostic accuracy suffers when only one variable is examined (Borer et al., 1975). Conversely, accuracy may be greatly enhanced by multivariate discriminant function analysis, incorporating as many as eleven variables (Cohn et al, 1979).

The single most highly regarded indicator has been the electrocardiographic ST segment response. Bruce and Hornsten (1969) have explained why.

> The underlying assumption is that ventricular repolarization pacer recorded in the electrocardiogram indicate a changing balance between hemodynamic and aerobic metabolic stresses imposed on the myocardium and the cellular strain resulting from a relative inadequacy of oxygen transport by the coronary circulation.

Therefore, ST segment depression represents the alteration in ionic fluxes at the cell membrane, which are caused by myocardial ischemia.

Goldman, Tselos and Cohn (1976) conducted a study to determine the reliability that significant ST segment depression had on selecting those with CAD ($\geq$50% stenosis). From the 59 subjects, subgroups were formed based upon degree of ST depression ($<$1.0mm, 1.0 - 2.9mm and $>$3.0mm depression). Fifteen had a normal ST response ($<$1mm), yet 2/15 had triple vessel disease and 10/15 had proximal lesions of the left anterior descending coronary artery (LAD). Of

those with 1.0 to 2.9 mm depression (18), six had triple vessel disease and 12 had lesions of the LAD. In the group with the most significant ST depression (26) 18 had triple vessel disease and 24/69 had LAD disease.

Significant ST segment depression has been highly correlated with disease of the main left coronary artery (Cheitlin et al., 1975). The anatomic pathologic coronary anatomy as seen by angiography were correlated with three subgroups having angina and varying severity of ST segment depression ($<$ 1mm, 1.0 to 1.9 mm, and $>$ 2mm for .08 sec.). Of the 106 patients, three-fourths with $>$ 2mm ST depression had critical lesions ($\geq$75% stenosis of left main coronary artery, $\geq$75% of left anterior descending and circumflex, or $\geq$90% of left anterior descending). All patients with left main coronary artery stenosis $\geq$75% had at least 2mm ST segment depression. Of those having ST depression of 1.0 to 1.9 mm, 76% had critical lesions; while 36.7% of those with $<$ 1mm had disease. Over 95%of those with "critical" lesions had a positive test based simply on 1mm depression. However, all patients were known to have previously had chest pain, which explains the high true-positive rate. Therefore, given the presence of marked ST segment depression with chest pain, a high probability of having left main coronary artery disease exists.

A large scale study correlated ischemic ST depression and time on treadmill with coronary angiography of 1472

patients (McNeer et al., 1978). If the DGXT was positive (>1mm, .08 sec.) at stage I or II of the Bruce Protocol, there was 97% chance of significant CAD (≥50% stenosis). Sixty percent of those had triple vessel disease and 25% had significant narrowing of the left main coronary artery. If the patient went to at least stage IV with a negative or indeterminant ST response, there was less than a 15% chance of triple vessel disease and 1% chance of left main coronary artery disease. Ninety percent of all positive ECG's had significant CAD, of which 44% had triple vessel disease. The most predictive information was from 1) ST depression, 2) ST segment response, and 3) exercise duration. Although stage of exercise correlated well with those who had CAD, it failed to correlate well with those without disease since 47% of those achieving stage IV had significant CAD. Those finishing only stage I and/or having the greatest ST segment displacement had the greatest chance of having significant CAD, three vessel disease, and LMCA disease.

Robb and Marks (1967) evaluated the relationship between degree of ST segment depression and mortality on 2,224 males applying for life insurance. Following the Masters two-step test, subgroups were formed based on ST depression (<1mm, 1.0 to 1.9mm and >2mm depression). The long-term follow-up results showed that those with <1mm. ST depression had 2.5 times the mortality rate than those without ST depression.

A depression of 1.0 to 1.9mm increased mortality to 3.7 times normal, and those with > 2mm ST depression had 15.8 times the mortality rate of those with a negative response. Those with a greater ischemic response had higher mortality from coronary diseases, as well as all other causes. When mortality from CAD alone was considered, mortality rates were of even greater magnitude for ischemic responders. Therefore, the incidence of coronary events and mortality was increased proportionally to severity of positive stress test, or degree of ST segment depression.

Configuration, as opposed to magnitude of the ST segment has also been shown to correlate well with presence and severity of CAD (Goldschlager, Selzer and Cohn, 1976). Two hundred sixty-nine patients with angiographically proven CAD and 141 normals were divided into sub-groups having downsloping, horizontal, or upsloping ST segment responses, in order of decreasing severity. The resulting false-positive rates were 1%, 15% and 32%, respectively. In addition to the decreased false-positive rate, there was an increased occurrence of triple vessel disease. Of those patients who had a negative ECG response, 57% had single vessel, 34% double, and 8% triple vessel disease. This illustrated the decrease in false-positives as the severity of disease increased. A similar study showed an increased sensitivity in patients with greater severity of disease (Tonkon et al., 1977). Sensitivity for single,

double, and triple vessel disease (≥75% stenosis) was found to be 42%, 66%, and 80%, respectively. There was also a significantly increased ($p < .05$) frequency of positive DGXT's in those with stenosis of the LAD artery.

Additional studies have shown the significance that hemodynamic responses have in predicting coronary occlusive disease. Thomson and Kelemen (1975) examined the development of hypotension accompanying angina in 17 patients. Although two died before angiography, 14 of the remaining 15 had 90% stenosis of the LAD. The remaining 15 had 90% stenosis of the LAD. The remaining subject had two 75% occlusions of the LAD. All the subjects had a normal blood pressure response, as well as no angina or ST depression following revascularization. This indicated that myocardial ischemia, not valvular disease or the usual drop in peripheral resistance due to exercise, was responsible for hypotension. Exercise-induced angina, when accompanied by a fall in systolic blood pressure (below resting level), is a reliable indicator of a severe compromise in left ventricular blood supply. A similar study also concluded that a 10mm Hg or more decrease in systolic blood pressure due to acute left ventricular pump failure secondary to extensive myocardial ischemia was an indicator of multivessel CAD (Morris et al., 1978).

A recent study showed that an increased death rate due to CAD was associated with a decreased systolic blood

pressure (SBP) during maximal exercise testing (Irving, Bruce and De Rouer, 1977). Those attaining a maximum SBP of less than 140mm Hg had an annual rate of sudden death of 97.9 per 1,000 men. A maximum SBP of 140-199mm Hg was 25.3 per 1,000 and greater than 200mm Hg gave a rate of 6.6 per 1,000. It was suggested that a lower SBP is a consequence of CAD and/or abnormal left ventricular function due to myocardial ischemia or previous infarction. Maximum SBP was a better predictor of mortality due to CAD than ST depressions and arrythmias.

To determine the role that chest pain has in diagnosing CAD a follow-up study was conducted on 950 patients who had a positive treadmill test (Cole and Ellestad, 1976). If chest pain was present there was a 75% chance of suffering an MI or death within the next five years as opposed to 43% for those who were asymptomatic. Therefore, angina in addition to ST depression increases sensitivity and prognostic value of the exercise test. A similar study regarding chest pain concluded that 1) chest pain during exercise can more accurately predict presence and severity of CAD, and 2) that chest pain even without a positive ECG appears to be as predictive of CAD as the positive ECG along (Weiner et al, 1976).

Type and severity of chest pain has been directly correlated with prevalence of coronary stenosis (Chaitman et al., 1979). Typical angina, probable angina and

nonspecific chest pain resulted in an 86%, 65% and 28% prevalence of disease, respectively. Predictive value for a positive test in those with typical angina was 100%, 82% in those with probable angina, and 45% with those having nonspecific chest pain. Therefore, the diagnostic accuracy of a stress test was substantially increased in patients having typical or probable angina.

Utilizing a multivariate approach for interpreting a DGXT can greatly improve predictive value (Berman, Wynn and Cohn, 1978). The sensitivity of 237 patients with chest pain increased from .78 to .97 simply by increasing ST segment criterion from 1.0 to 1.9 mm to $>$ 2mm depression. Combining an ST depression of 1.0 to 1.9mm with two of the following: 1) a rate pressure product $\leq$ 23,000, 2) exercise duration $<$ six minutes, or 3) ST depression $>$ 3 minutes into recovery, yielded an increased sensitivity to .89. Specificity, or the predictability of a negative test increased from .60 to .86 when a rate pressure product $\geq$ 30,000 was elicited. The variable that best separated the TP from the FP was a RPP $\leq$ 23,000. Therefore, in symptomatic patients the predictive value of the DGXT was significantly ($p < .05$) increased when persistence and depth of ST depression, as well as rate pressure product were taken into consideration.

Ellestad (1977) analyzed 11 variables in an attempt to reclassify 95 false-positive stress tests. In order of

importance he found the following responses of greatest significance for men: 1) maximum heart rate, 2) maximum systolic blood pressure, 3) contour of ST segment, 4) age, 5) history of chest pain, 6) resting T waves, 7) chest pain during test, 8) ST and T waves changes post-hyperventilation, 9) resting ECG, 10) time of onset of ST depression, and 11) increased P wave negativity in V_1 with exercise. Sixty-five percent of false-positives were correctly reclassified and overall error was reduced from 44% to 21%.

Selected variables from the exercise test, angiography, and clinical examination were examined to determine those variables most predictive of survival (Hammermeister, De Rouen and Dodge, 1979). Data was collected on 746 medically treated patients and 1870 patients who underwent myocardial revascularization. Questionnaires, hospital records and death certificates were used to obtain follow-up information regarding cause of death. Regression analysis showed left ventricular ejection fraction followed by age and number of diseased vessels ($\geq$70% stenosis) were most predictive of survival in medically treated patients. Resting ventricular arrythmias, ejection fraction, heart murmur and left main coronary artery stenosis ($\geq$50%) were most predictive of survival in patients undergoing surgical intervention.

Perhaps the best example of a quantitative diagnostic interpretation is presented by Cohn et al., (1979). A

test score was quantified by weighing and combining various exercise responses through discriminant function analysis. This statistical method maximizes the separation of patients into different categories based on treadmill response. Among the variables examined were configuration and depth of ST segment, duration and onset of ischemia, chest pain, sex, heart rate, blood pressure changes, and graded ventricular arrythmias.

Results showed a predictive value of a positive test to be 87%, specificity of 80% and 94% sensitivity. Although no data was given regarding such values based on the standard criterion (ST segment) for treadmill test interpretation, it was stated that test accuracy (sensitivity, specificity, and correct classification rate) increased 10-15%. Expressing the results numerically enables the derivation of probability statements for presence and severity of CAD. Thus, the DGXT results may be quantitatively judged.

False-Positives and False-Negatives

Understanding the reason for false-positive and false-negative exercise tests is necessary if the false results are to be kept at a minimum. Decreasing the number of false exercise tests will increase sensitivity, specificity, and predictive value resulting in a diagnostic tool of greater usefulness. Incorrect interpretation of

the DGXT may be attributed to the fact that symptoms and electrocardiographic abnormalities may be absent in those with CAD, and abnormal responses may be present in those without significant CAD.

Although ST segment depression has been traditionally viewed as a result of myocardial ischemia, several authors have insisted that it is naive to expect that ST segment depression is due to ischemia alone (Froelicher et al, 1976). Exercise electrocardiography may give a false-positive regarding ischemia due to CAD, yet a true-positive regarding cardiomyopathies, viral myocarditis, myocardial cell membrane and oxygen-hemoglobin dissociation abnormalities, coronary artery spasms, and valvular and congenital heart disease. Abnormal ST segment depression may appear in patients free of CAD who are taking certain medication, i.e., digitalis, diuretics. Digitalis and diuretics resulting in electrolyte imbalances will alter repolorization, thereby resulting in a false-positive ECG response. A similar result will occur in anemic patients due to the imbalance between oxygen supply and demand. False-positive results have been found in subjects tested in a non-fasting state, since ST segment and T waves are altered following glucose ingestion (Riley, Oberman and Sheffield, 1972).

A major determinant in false-positive and false-negatives is the prevalence of disease within the population being tested. This is best illustrated by the following

example from Redwood, Borer and Epstein (1976).

> If 100 patients are tested from a population in which the disease prevalence is 90% (as might exist in a population referred to an institution because of symptoms of coronary disease) then 900 would have coronary disease, and 100 would be free of disease; since the test is 95% sensitive, then 855 of the 900 diseased patients have a positive test. In addition, if specificity is 95%, five of the 100 patients without disease will have a falsely-positive test result. Thus, there would be 860 patients with a positive test, of whom 855 would actually have coronary disease, yielding a predictive accuract of 99%.
>
> In contrast, if 1000 patients are tested from a population with a disease prevalence of only 2% (as might exist in an otherwise unselected group of asymptomatic individuals) then 20 would have coronary disease and 980 would be free of disease. Since the test is again 95% sensitive and 95% specific, 19 of the 20 subjects with disease will have a positive test and 40 (5%) of the 980 subjects without disease will have a falsely-positive test result. Thus, of 68 subjects with a positive test, only 19 will be true positive and the predictive accuracy will be only 28%.

In an attempt to define the limitations that a maximum exercise test has on the diagnosis of CAD, patient history, angiographical data, and sex were compared in 278 patients (Detry et al., 1977). In subjects with no previous myocardial infarction, false-positives and false-negatives were strongly influenced by sex. Males had a 7% false-positive rate and 40% false-negative rate, while women had 38% false-positives and 19% false-negative rate. The accuracy of the diagnostic test depends on the prevalence of disease; therefore, the fact that men had

a greater occurrence of CAD (based on angiography) explains the fewer false-positives and greater false-negatives.

The influence that valvular disease and left ventricular dysfunction has as determinants of false-negative responses in symptomatic patients was examined (Kramer, Susmano and Shekelle, 1978). The only difference between false-negatives and true-positives was the increased incidence of myocardial dysfunction associated with infarction patterns in the false-negatives. In addition, false-negatives were found to have an increased left ventricular end diastolic pressure and decreased ejection fraction. The authors concluded that in symptomatic patients especially, a negative GXT does not negate recognition of significant CAD, but may provide additional insight regarding the status of left ventricular performance.

Possible causes for exertional ST segment depression in the absence of CAD are discussed by Roitman, Jones and Sheffied (1970). Exercise electrocardiography was not helpful in diagnosing CAD if one of the following were present: left ventricular hypertrophy, aortic stenosis and insufficiency, mitral insufficiency, arterial hypertension, digitalis or resting ST segment depression. In patients taking digitalis glycoside, the false-positive rate became normal simply by increasing the electrocardiographic criterion for a positive test from 1mm to 2mm ST

segment depression (Bartel et al., 1974). False-negatives were found in approximately 10% of symptomatic patients having no accompanying ischemic ST response (Kattus, 1974). This was usually found to occur in patients having previously suffered a myocardial infarction. In patients with varying severities of CAD who had no previous myocardial infarction, Kramer et al.,(1978), found the frequency of false-negatives to be nearly identical. That is, patients with single, double, or triple vessel disease had a false-negative rate of 22%, 21%, and 19% respectively.

CHAPTER III

METHODS

The description of the procedures utilized in this investigation are broken down into: 1) subject selection, 2) diagnostic graded exercise testing (DGXT), 3) coronary angiography, 4) determination of DGXT usefulness based on the electrocardiographic responses, 5) derivation of DGXT treadmill score, 6) determination of test usefulness on the basis of the derived treadmill score, 7) a statistical analysis comparing treadmill score method to the standard ECG method of predicting presence and severity of CAD.

Subject Selection

The retrospective nature of this study required no additional testing or data collection. All necessary data was collected on a separate data summary sheet (Appendix A) from the patients' DGXT and coronary angiography file. All DGXT's and coronary angiography were performed at the Gundersen Clinic, Ltd., Cardio-Pulmonary Laborary and Lutheran Hospital Catheterization Laboratory, La Crosse, Wisconsin. The study group was comprised of 85 consecutive patients with chest pain of possible cardiac origin referred for diagnostic treadmill evaluation. All patients met the following criterion: 1) coronary angiography was completed within three months of the DGXT, 2) no subject had a

previously documented myocardial infarction, and 3) subjects were tested between February 1, 1976, and March 1, 1979. All data was handled confidentially and presented in an anonymous manner.

Diagnostic Graded Exercise Test (DGXT)

Patients underwent a symptom limited Sheffield Modification of the Bruce Protocol in which speed and grade were increased every three minutes (Appendix B). A few tests utilized the Naughton Protocol(Appendix C), which involved two minute stages and lower MET increments from stage to stage. Each stage of the DGXT was converted to and referred to by MET level, thereby alleviating the minor differences in protocol. Skin preparation and the method of electrode placement (Mason-Likar, 1967) are standard procedures described in detail elsewhere (Ellestad, 1975).

ECG recordings were made prior to the DGXT (supine, standing, and post-hyperventilation in the sitting position) every third minute of exercise, immediately at the conclusion while standing, and at two, four and six minutes of recovery with the patient sitting. Blood pressure was taken the first and third minute of each stage of the protocol and each minute if symptoms were present. Patients with complete bundle branch block, which would render the ECG uninterpretable regarding ischemic changes, were excluded. The exercise test was terminated for a number of

reasons: in the presence of potentially dangerous exercise-induced arrythmias (bigeminy, trigeminy, ventricular tachycardia, etc.), with a sustained drop in blood pressure (≥ 10mm Hg drop in systolic blood pressure), with severe angina-like chest pain and/or excessive ischemic ST segment displacement as judged by the attending cardiologist, or the attainment of 90 to 100% of the age predicted heart rate. Subjects regularly taking cardiac drugs did not have their medications withheld prior to the DGXT.

Coronary Angiography

Coronary Angiography, using the Seldinger percutaneous technique, was accomplished with entrance through the right femoral artery and vein. The procedure was performed under mild sedation with 100 mg. of Seconal I.M. and directly under 1% Xylocain local anesthesia. The left ventricle was opacified with 45cc of Renografin - 76 (Squibb) dye injected in a period of three seconds and the appropriate pressures monitored. Ventricular contractility was classified as normal, mild dysfunction, moderate or severe dysfunction. The ejection fraction and left ventricular end diastolic pressures were determined. Selective coronary arteriography was performed and the degree of coronary artery disease determined for the following vessels: right and left main coronary arteries, left anterior descending, circumflex, and obtuse margin arteries. All vessels were visualized

in at least two planes, which were at right angles to each other. Filming was done with 35mm cinematographic film at 45 fms.

Determination of DGXT Usefulness Based on the Electrocardiographic Responses

The DGXT's were interpreted as positive or negative, depending on whether the ST segment depression met the minimal criterion of .1mV for .08 seconds. These were then reclassified as True-Positive (TP), False-Negative (FN), or False-Positive (FP), True-Negative (TN), regarding presence or absence of coronary artery disease ($\geq$ 50% stenosis of at least one vessel), as interpreted from coronary angiography. Sensitivity, specificity, correct classification rate, and predictive value of a positive and negative test were then calculated. These values were again determined based on the severity of disease. The true-positives and false-negatives were placed in one of the following exclusive (separate, not overlapping) categories: 1) single vessel disease, 2) moderate to severe disease, or 3) advanced CAD. To avoid overlapping categories, each was placed in the subgroup of greatest CAD severity, provided the following criterion were met: 1) single vessel disease involved any one coronary artery (excluding the LMCA) with a stenosis $\geq$ 50%; 2) moderate to severe disease may consist of a) a $\geq$ 50% stenosis in two of the three (RMCA, LAD, CX) major coronary arteries (LMCA excluded), or b) LMCA

with a ≥ 50% stenosis, or c) triple vessel disease, provided LMCA ≥ 50% and LAD is ≥ 90%; 3) advanced disease may be either a) IMCA ≥ 90% and right main, or b) triple vessel disease with ≥ 50% LMCA and/or ≥ 90% stenosis of LAD. An additional subgrouping included those having ≥ 50% stenosis of the LMCA with any additional arteries.

Derivation of a DGXT Treadmill Score

Several exercise responses were examined in an attempt to identify those variables most indicative of CAD. A greater point value was awarded to those responses that appeared to be most useful in predicting presence and severity of CAD. This approach assumed that severity of CAD was a principle determinant of severity of myocardial ischemia, and this, in turn, was reflected in the DGXT response of the patient. Subsequently, a single, practical treadmill score was empirically derived. The DGXT evaluation then resulted in a single treadmill score, thereby placing each test on a quantitative continuum. Theoretically, the higher the treadmill score, the greater the probability of the presence and severity of CAD. A number along this continuum was determined, in such a manner that a treadmill score greater than or equal to five units was positive, and less than or equal to four units was negative.

Initially, each file was critically reviewed to assess those apparent differences between patients with CAD (TP and

FN), and patients without CAD (TN and FP). To determine the variables and their appropriate weight in the formula, each required variable was examined independently.

Determination of Test Usefulness On the Basis of the Derived Treadmill Score

The DGXT's were interpreted as positive or negative, depending on whether the treadmill score was greater than or equal to five units. These were then reclassified as true-positive (TP), false-negative (FN), or false-positive (FP), true-negative (TN), regarding presence and absence of CAD ($\geq$ 50% stenosis of at least one vessel) as interpreted from coronary angiography. Sensitivity, specificity, correct classification rate, and predictive value of a positive or negative test were then calculated. These values were again determined based on severity of disease. Those with disease (TP and FN) were placed in the following exclusive categories: 1) single vessel disease, 2) moderate to severe disease, and 3) advanced CAD. The additional subgrouping of those with LMCA disease was calculated as well.

Statistical Analysis Comparing Treadmill Score Method to the Standard ECG Method of Predicting Presence and Severity of CAD

Sensitivity, specificity, correct classification rate and predictive value of a positive and negative test were calculated based on treadmill score method and standard ECG method. Such values were then analyzed using a one-tailed

test for differences between proportions to determine whether a statistically significant increase ($p < .05$) occurred.

A chi square was used to determine if the various responses resulted in a statistically significant difference between those with and without disease.

To examine the treadmill score formula's ability to detect differences in severities, a non-paired student's t-test was used between the following sub-groups: single vessel disease, moderate to severe CAD, advanced CAD and LMCA disease.

CHAPTER IV

RESULTS AND DISCUSSION

Coronary Angiography

Eighty-five patients (65 males, 20 females) consecutively referred for a diagnostic graded exercise test (DGXT) underwent coronary angiography no later than three months post-DGXT. Selected characteristics of the patients are presented in Table 1. Angiography revealed that 61/75 (72%) had $\geq$ 50% stenosis of at least one coronary artery. This relatively high prevalence of disease was a reflection of the fact that all patients were referred for the DGXT because of chest pain of presumably cardiac origin (typical or atypical angina). The present prevalence value for CAD is in agreement with previous studies (Table 2) that have been completed using symptomatic populations (Berman et al., 1978, Chaitman et al., 1979, and Cohn et al., 1979).

In the present investigation, single vessel disease occurred in 16/85 (19%) of the patients, 26/85 (31%) had moderate to severe disease and 19/85 (22%) had advanced CAD as defined on page 5 of chapter 1. The left main coronary artery (LMCA) was significantly occluded ($\geq$50%) in 13/85 or 15% of the patients studied.

Table 1

Patient Characteristics

Variable	$\bar{X}$	S.D.	Range
Age (yrs.)	53.8	9.1	33-72
Height (cm.)	171.6	8.7	151-90
Weight (kg.)	81.5	14.4	52-112

S.D. = Standard Deviation

$\bar{X}$ = Mean

Table 2

Prevalence of CAD in Subjects of Previous Studies

Authors	N	CAD Criterion	Symptoms	Prevalence of Disease
Berman et al.	237	≥70%	chest pain	71%
Chaitman et al.	200	≥70%	typical angina	86%
		≥70%	probable angina	65%
Cohn et al.	405	≥50%	typical or atypical angina	72%

N = Number of Subjects

Treadmill Score Formula

In order to implement a method by which the DGXT could be diagnostically interpreted based upon several variables, a treadmill score formula was empirically devised. Each variable was quantified based on its ability to distinguish those with, from those without CAD. Intitially those with angiographic documented CAD were examined to determine which, if any, abnormal responses separated true-positives (TPs) from false-negatives (FNs). Those variables were empirically assigned a series of numbers to attempt to reclassify a FN as a TP. This was also done in an attempt to separate false-positives (FPs) from true-negatives (TNs). The variables included were symptoms (chest pain: typical and atypical angina), systolic blood pressure (SBP) changes, as well as resting and exercise ECG characteristics.

Exercise-induced chest pain results in a poorer prognosis (Cole and Ellestad, 1976) and increased probability of coronary stenosis (Weiner et al., 1976, Chaitman et al., 1979). The onset of chest pain was detected in six of the originally classified false-negatives (based on ECG). Of the 40 patients experiencing chest pain < 4 METS, 35 had CAD. Due to the significant difference ($p < .01$) between those with and without disease, chest pain <4 METS was empirically assigned a point value of 5 in the treadmill formula. Figure 1 illustrates that a greater percentage of those with CAD exhibit pain. In addition, there is a tendency

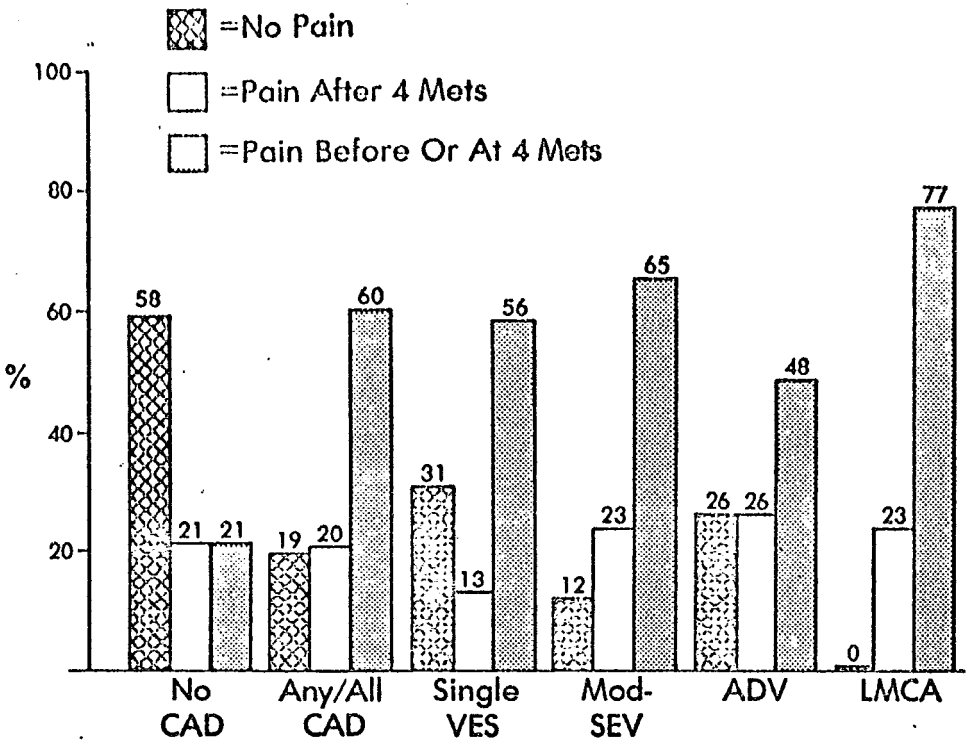

Figure 1. Relationship between the time of onset of chest pain and the severity of coronary artery disease. The number at the top of the bar is the calculated percentage of patients in each subgrouping.

for the percentage of symptomatic responses to increase as the severity of CAD increases. Thus, those with CAD constitute not only a greater percentage of those with chest pain symptoms, but the chest pain in these patients presents itself at a lower metabolic workload as well (<4 METS).

The type of systolic blood pressure (SBP) response also significantly ($p < .02$) distinguished between those with and those without CAD, thereby helping to reclassify FNs as TPs. This finding was in agreement with Morris et al. (1978), who concluded that a 10mm Hg or more decrease in systolic blood pressure was an indicator of CAD, since acute left ventricular pump failure is secondary to extensive myocardial ischemia. Results showed that 10/12 patients (83%) with exercise induced hypotension (>10mmHg decrease in SBP) had CAD. Of the 18 patients eliciting a flattened SBP (<10mmHg decrease in SBP during the last three readings), 17 (94%) had CAD. Similar studies have concluded that the drop in SBP with exercise is due to a compromise in left ventricular blood supply (Thomson and Keleman, 1976, Irving et al., 1977). Five points were assigned to those with a drop in SBP, and three points to those with a flattened SBP response. Figure 2 illustrates that as severity of disease increases, the percentage of those eliciting a flattened or hypotensive SBP response with exercise tends to increase. There was approximately a four-fold increase in the percentage of

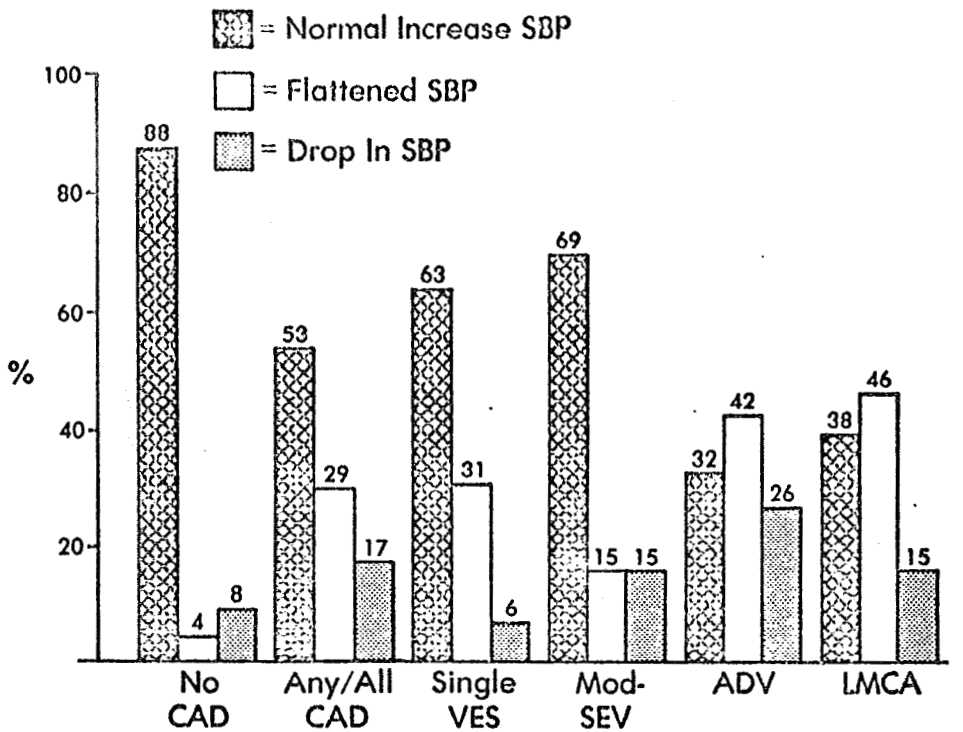

Figure 2. Relationship between the type of systolic blood pressure response to graded exercise testing and the severity of coronary artery disease. The number at the top of the bar is the calculated percentage of patients in each subgrouping/

flattened-hypotensive responses in those with CAD than those without.

As had been anticipated, the ECG provided the most information regarding presence and severity of CAD. Specifically, ST segment configuration, degree and onset of ST segment depression, exercise induced arrythmias, and resting inverted T waves were studied. The degree of ST segment depression and configuration significantly ($p < .01$) differentiated between the CAD and non-CAD groups. The scoring scale developed for ST segment displacement (Table 3) incorporated degree of depression and time of onset, resulting in a maximal point value of 6. Other point values can be seen in Table 3. Of those patients scoring 5 points in this individual category, 100% had CAD. These results were in agreement with Goldman et al., (1976), who concluded that depth of ischemic ST depression helps identify those with CAD, and McNeer et al., (1978), who, because of his test termination based on ST segment, concluded that those finishing only stage I or II of the Bruce Protocol had the greatest chance of having CAD. Thirteen patients had $\geq$ 50% stenosis of the LMCA, of which 85% (11/13) had $>$ 2mm ST segment depression before the 4 MET level was reached. Cheitlin et al., (1975) found that all patients (11/11) with LMCA disease $\geq$ 75% had at least 2mm ST segment depression.

ST segment configuration was also useful in correctly differentiating a positive from negative DGXT. Of the 44

Table 3

Scoring Scale for Degree and Onset of ST Depression as Related to Presence and Severity of CAD

Score	No CAD	Single Vessel	Moderate to Severe	Advanced CAD	LMCA
0 - Normal	14	3	3	1	0
1 - 1-1.9mm after 4 METS	5	2	3	1	0
3 - 1-1.9mm before 4 METS	3	4	7	3	1
4 - -2mm after 4 METS	2	1	1	3	0
5 - 1-1.9mm before 4 METS, -2mm after	0	2	2	2	1
6 - >2mm before 4 METS	0	1	10	9	11
TOTAL	24	13	26	19	13

LMCA = Left Main Coronary Artery

subjects with a horizontal or upsloping ST segment depression, 34 (77%) had CAD. In contrast, 58% without CAD had no ST segment depression, and 0% had a downsloping segment. Figure 3 illustrates an inverse relationship between severity of disease and the percentage of patients without ST segment depression. There was a resulting 23% and 0% false-positive rate for upsloping-horizontal and downsloping configuration respectively. Goldschlager et al., (1976) reported a 47% and 1% false-positive rate respectively. A horizontal or upsloping ST segment was awarded 1 point, and a downsloping configuration 3 points.

Frequency of exercise induced premature ventricular contractions (PVCs) also helped separate CAD from non-CAD patients (Cohn et al., 1979). Results showed that 15% of those with CAD had frequent PVCs (>8 per minute, bigeminy, trigeminy) as opposed to only 4% in those without CAD. Therefore, the presence of frequent PVCs increases the probability of CAD four times. The absence of PVCs was seen in 79% of those with CAD and 83% for those without. Thus, including frequency of exercise induced PVCs is more useful in increasing sensitivity than in increasing specificity.

Resting inverted T waves were given a point value of 2 in the treadmill score formula. Ellestad (1977) found that this variable was more indicative of CAD than exercise induced chest pain and time of onset for ST segment

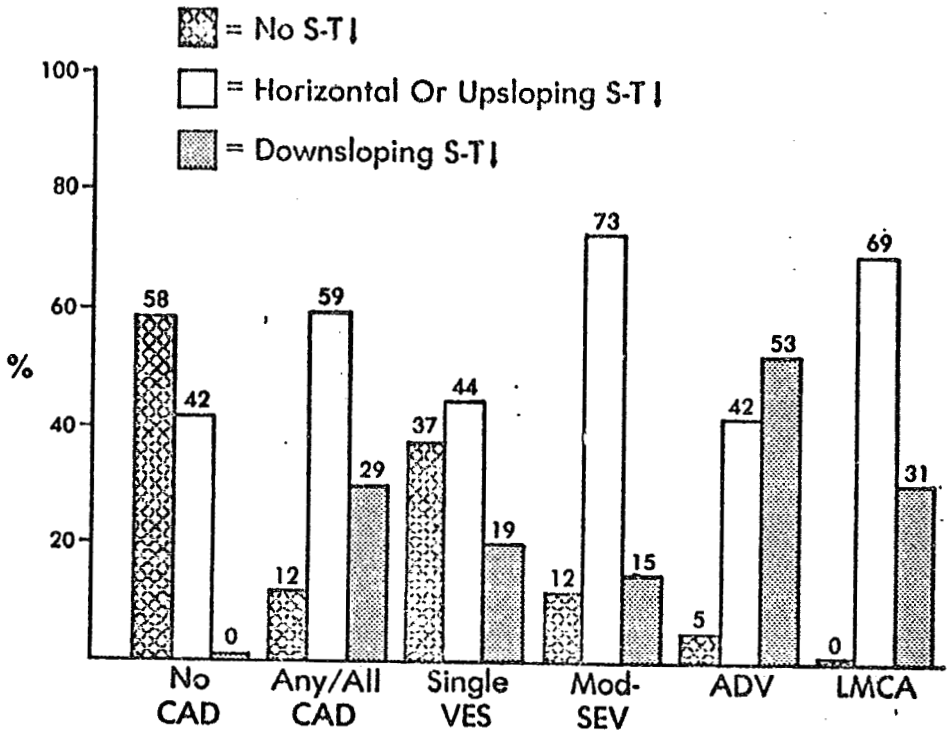

Figure 3. Relationship between the configuration of the ST segment depression and the severity of coronary artery disease. The number at the top of the bar is the calculated percentage of patients in each sub-grouping.

depression. Again, inclusion of this variable improved sensitivity more than specificity since almost twice as many with inverted T waves had CAD (15%) than those free of disease (8%).

Hemodynamic variables such as maximum heart rate and rate pressure product were not included since a beta adrenergic blocking drug would not permit true maximal values. Although including such variables has shown to increase sensitivity (Berman et al., 1979), CAD in the present study was not disguised by those on medication. This was illustrated by the fact that no false-negative had taken any drug prior to the DGXT (Table 4).

The resulting formula scored the DGXT from 0-24 (Table5), the higher score increasing probability of presence and severity of CAD. The new criterion for interpreting the DGXT was such that a treadmill score 4 units was considered negative for CAD.

Treadmill Score vs. Standard ECG Method for Determining Presence of CAD

The treadmill score (TMS) method of interpreting the DGXT resulted in 18 negative and 67 positive tests. Fifty-eight of the 67 positive tests were true-positives for CAD (See Figure 4). The ECG method resulted in 24 negative tests, of which only 14 were true-negative. All three of the negative tests actually had single vessel CAD. Ten of

Table 4

Medications of Subgroups Based on Treadmill Score

False-Positives	True-Negatives	False-Negatives	True-Positives
1- Inderal 1- Lanoxin	1-Inderal and Nitropaste 4- Inderal 1- Inderal and Isordil 1- Dyazide	No Medications	Single Vessel Disease 3- Dyazide 1- Isordil 4- Inderal and Isordil Moderate to Severe Disease 1- Inderal and Isordil 1- Lanoxin 1- Inderal and Hct 1- Inderal and Pronestyl 2- Inderal 1- Aldomet and Apresoline 1- Hct 1- Isordil Advanced CAD 5- Inderal 4- Inderal and Isordil 1- Inderal and Dyazide

Hct = Hydrochloathiazide

Table 5

Treadmill Score Formula *

ST Segment

0- normal
1- 1-1.9mm after 4 METS
3- 1-1.9mm before 4 METS
4- ≥2mm after 4 METS
5- 1-1.9mm before 4 METS, =2mm after 4 METS
6- ≥2mm before 4 METS

ST Segment Configuration

1- horizontal or upsloping
3- downsloping

Chest Pain

0- no pain
2- chest pain after 4 METS
5- chest pain on or before 4 METS

Systolic Blood Pressure

0- normal increase iwth exercise
3- flattened or plateaued
5- drop (≥10mmHg)

Premature Ventricular Contractions

0- none
1- occasional
3- significant (>8 per minute, bigeminy, trigeminy)

Resting Electrocardiogram

0- normal
2- inverted T waves

A total score of ≤4 is negative for CAD, ≥5 is positive for CAD.

* Treadmill Score = the total points received by summing the point values given for each variable.

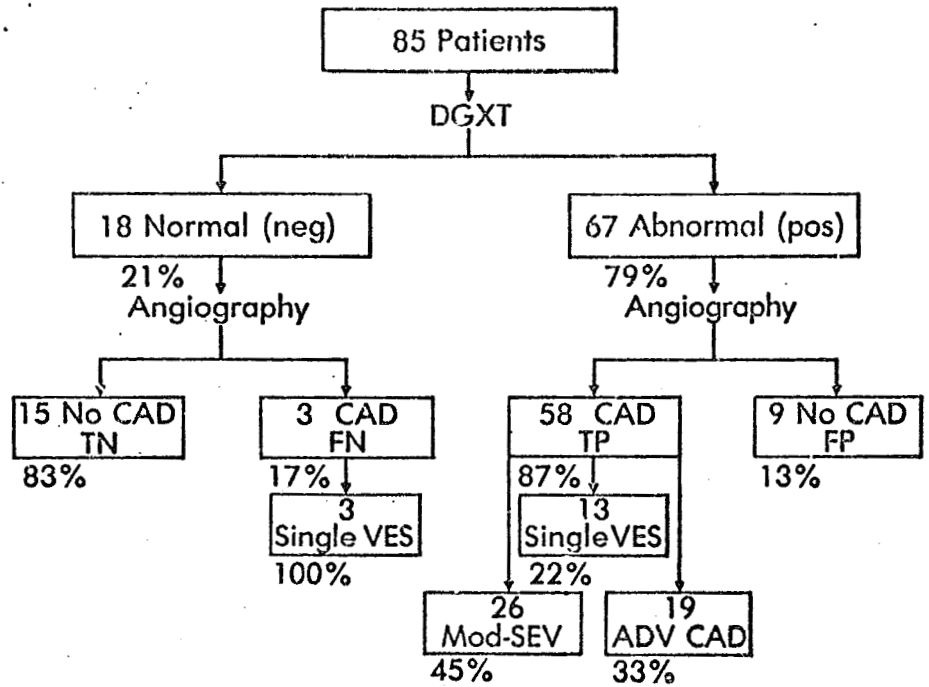

Figure 4. The study group, illustrating the separation of patients on the basis of the treadmill score and angiography. Comparison of the treadmill interpretation and the angiographic interpretation results in the classification of the patients as true-negative, false-negative, true-positive, or false-positive. Those with coronary artery disease are grouped into single vessel disease, moderate to severe disease and advanced disease. Percentages are the number of patients in a given category divided by the number of patients in the previous category.

the 61 patients with positive DGXTs were free of CAD.

Based on the ECG response alone, sensitivity, specificity, and correct classification rate (CCR) were 84%, 58% and 76%, respectively. Predictive value of a positive and negative test were 84% and 58% respectively. Following reclassification of the interpretation of the DGXT based on the treadmill score method (Figure 5), sensitivity, specificity, and CCR increased to 95%, 63% and 86%, respectively. This resulted in a substantial reduction in error when attempting to distinguish those with CAD from those without CAD (Figure 6). Predictive value of a positive and negative DGXT was 87% and 83%, respectively. These values are very similar to those reported by Cohn et al., (1979), who used discriminant function analysis of treadmill results to predict those patients who might have CAD. Table 6 illustrates that the TMS method was most successful at reclassifying FNs as TPs.

False-Positives

The DGXT may be a false-positive for coronary artery disease, yet a true-positive for other types of coronary heart disease (CHD). Upon close examination of the 9 false positives, 2 had clinically diagnosed aortic stenosis and 1 had dextrocardia. In addition, 2 subjects had abnormally elevated left ventricular end diastolic pressures, possibly indicative of cardiomyopathy. If these 5 false-positives

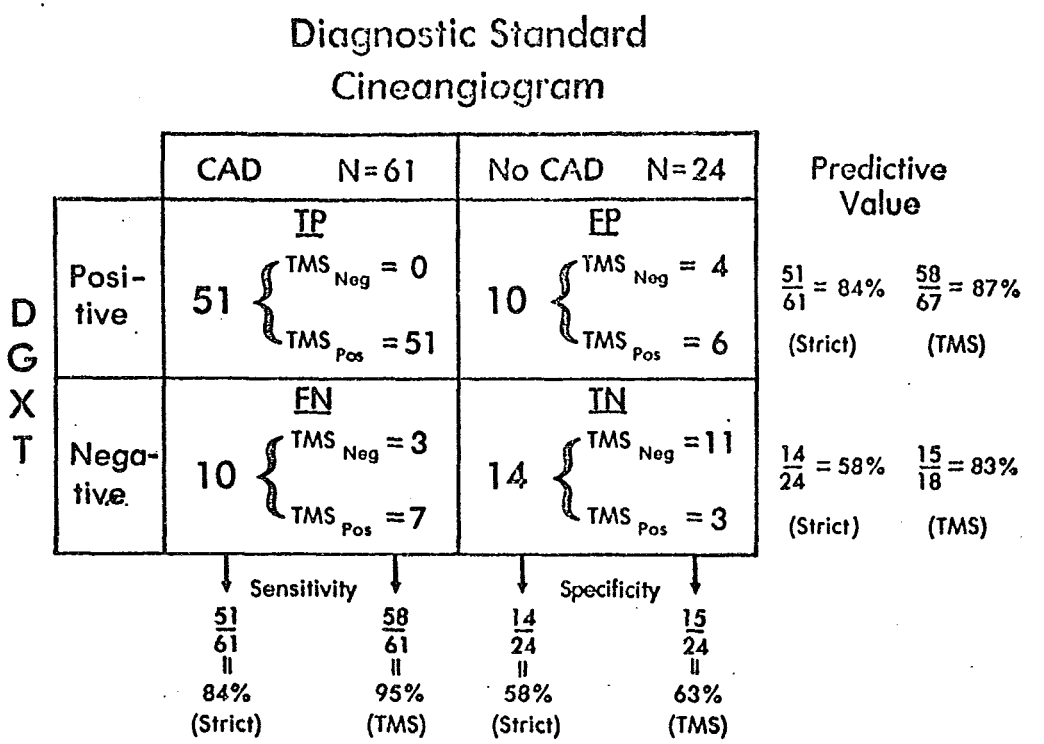

Figure 5. Latin square diagram illustrating the calculated sensitivity, specificity and predictive value when the ST segment criterion is compared to the treadmill score method. The large numerals in the blocks are the number of patients classified on the basis of the ST segment only. The smaller numerals in the blocks are the number of patients classified on the basis of the treadmill score method. Strict = calculation based on the ST segment only.

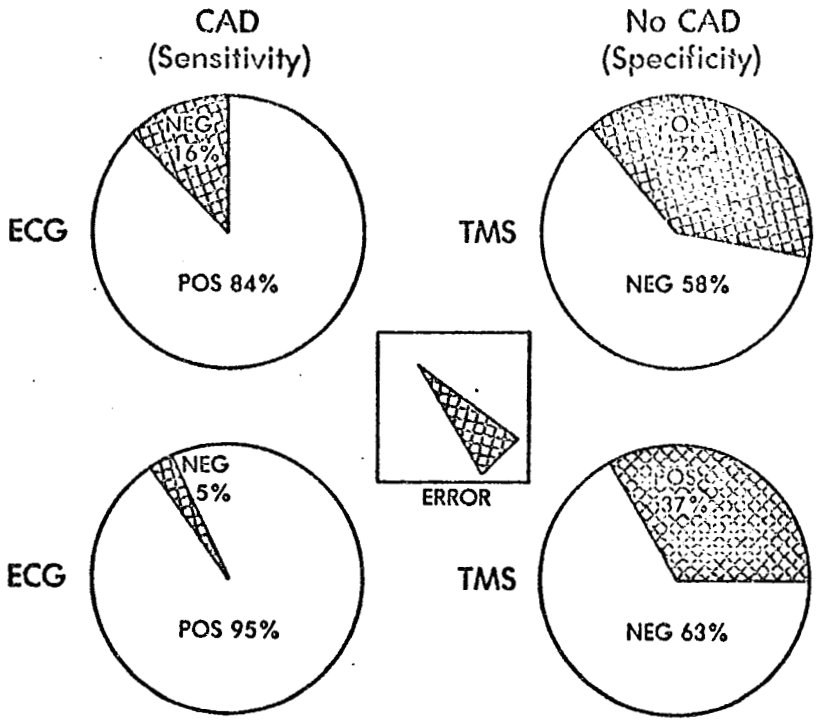

Figure 6. Pie diagrams illustrating the increase in sensitivity and specificity of Treadmill Score Method vs. ECG Method.

Table 6

Improvements in Diagnostic Accuracy

as a Result of Using the TMC Concept

Values	ECG Method	TMS Method	Discriminant Function Analysis (Cohn et al., 1979)
True Positives	51	58	-
True Negatives	14	15	-
False Postives	10	9	-
False Negatives	10	3	-
Sensitivity	84%	95% *	94%
Specificity	58%	63%	65%
Predictive Value (+)	84%	87%	87%
Predictive Value (-)	58%	83% *	80%
Corrective Classification Rate	76%	86%	85%

* $p < .05$ when compared to ECG method.

were reclassified as true positives for CHD, then specificity, predictive value of a positive test and correct classification rate would be further increased from 63%, 75% and 86% to 79%, 94% and 91%, respectively.

Treadmill Score and Determination of CAD Severity

In this study a quantitative approach to CAD detection was implemented through the use of a treadmill formula based on exercise responses. Since the resulting DGXT scores are on a continuum, it must be determined whether there is an increase in the probability of correctly assessing CAD severity. Figure 7 illustrates the differences between treadmill scores of those patients with and without CAD. A continual increase in TMS is seen with the increased severity of CAD. Those patients with LMCA disease are believed to have the poorest prognosis, which would agree with the fact that this group received the highest mean treadmill score. A non-paired student's t-test found that the treadmill scores were significantly different between single vessel disease and advanced disease ($p < .02$), single vessel disease and LMCA ($p < .01$), and between moderate to severe disease (excluding those with LMCA) and LMCA ($p < .01$). All other combinations resulted in a non-significant difference in treadmill scores between the various subgroups (Table 7).

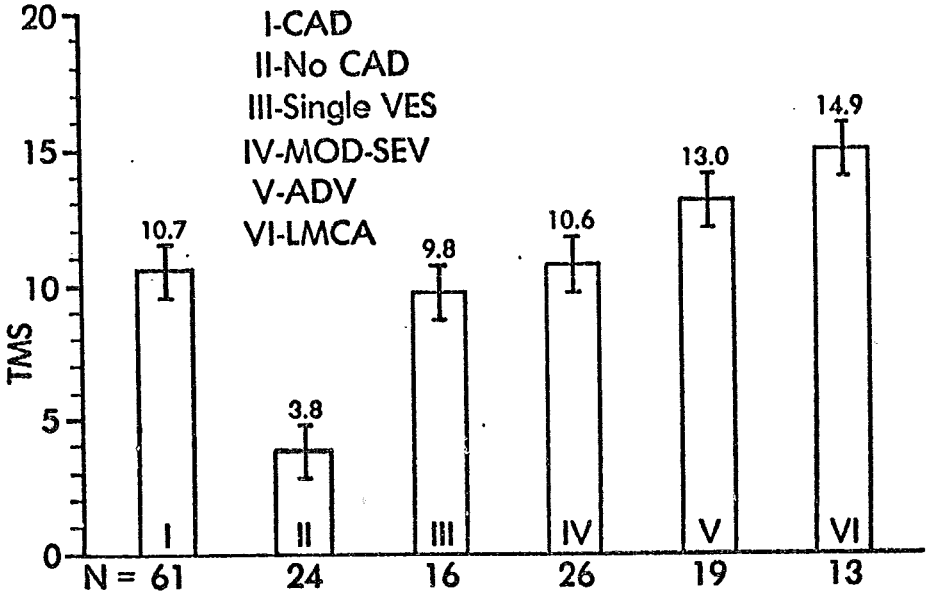

Figure 7. Relationship among the calculated mean treadmill scores and the severity of coronary artery disease. The values at the top of the bars are the group means (± SEM). N= number of patients in each category.

Table 7

Differences in Treadmill Scores of the Various CAD Severities

CAD Severity	Single Vessel Disease	Moderate-Severe Disease	Advanced Disease
Single Vessel Disease	X	-	-
Moderate-Severe Disease	$p>.05$	X	-
Advanced Disease	$p<.02$	$p>.05$	X
LMCA Disease	$p<.002$	$p<.01$	$p>.05$

LMCA = Left Main Coronary Artery

CHAPTER V

CONCLUSIONS

Summary

The purpose of this investigation was to determine whether a quantitative approach to interpreting diagnostic graded exercise tests (DGXT) could enhance the probability of predicting presence and severity of coronary artery disease (CAD). In an attempt to supplement the traditional ST segment criterion, hemodynamic, symptomatic, and additional electrocardiographic responses were included. An empirically devised treadmill score formula (TMS) based on graded exercise test responses resulted in the calculation of a single treadmill score for 85 symptomatic patients who had both coronary angiography and a DGXT. The TMS method was successful in detecting coronary lesions $\geq$ 50% with a sensitivity of 95%, specificity of 63% and predictive value of a positive test 87%. The true-negative rate (predictive value of a negative test) was 83% and correct classification rate 86%. These values were similar to those reported by Cohn et al. (1979), and represent an increase in test accuracy of 10-15% when compared with the standard criteria (ST segment) for DGXT interpretation.

Conclusions

Based on the results of this investigation the following conclustions seemed appropriate:

1. The TMS score calculation was a practical and useful method of predicting the presence of CAD. This was supported by the substantial increase in sensitivity, predictive value of a positive and negative test, and correct classification rate of the DGXT when these indices were compared to those calculated from only ST segment data.

2. The TMS calculation enhanced the ability to predict the degree of severity of CAD. This was supported by the statistically significant difference in treadmill scores of single vessel disease vs. advanced disease ($p<.02$), single vessel disease vs. LMCA disease ($p<.01$), and moderate to severe disease vs. LMCA disease ($p<.01$). Therefore, the higher the treadmill score, the more likely the DGXT was a true-positive, and the higher the probability that the patient had more severe CAD.

3. Including patients on cardiac medications did not result in a false-negative test when the TMS method of interpretation was utilized. In addition, only 2 of the 36 patients on medication were classified as false-positives. Thus, including symptomatic patients on medication did not reduce the accuracy of TMS method of interpretation.

4. A false-positive, as determined by a TMS method, may be a false-positive for CAD, yet a true-positive for coronary heart disease (CHD). Therefore, a positive treadmill score ($\geq$5 points) may indicate CHD as well as CAD.

Recommendations

Based on the conclusion of this investigation, the following recommendations were made:

1. To better calculate a treadmill score formula, discriminant function analysis might be utilized.

2. The TMS method of interpretation should be implemented at the Gundersen Clinic, Ltd., La Crosse, Wisconsin, for the purpose of cross validation.

3. The TMS could provide an objective method by which improvements following surgery and/or rehabilitation could be evaluated.

4. All results were dependent on: 1) the population studied, 2) DGXT protocol, 3) use of medications by the patients, 4) interpretation of the coronary angiograms, and 5) any other methods and procedures which might influence the specific data being collected. Thus, the derived TMS formula may only be useful in the Gundersen Clinic, Ltd., exercise testing laboratory. The TMS approach seems to have merit, and others are encouraged to apply this type of approach in their diagnostic graded exercise testing.

Appendix A

DATA SUMMARY SHEET

Name: _____ Clinic number: _____

Sex: M / F Age: _____ Height: _____ Weight: _____

Max predicted heart rate: _____ Status: _____

Medications: _____ _____mg.

_____ _____mg.

_____ _____mg.

Resting ECG: _____

_____

ANGIOGRAPHY DATA:

Ejection Fraction: _____

Cardiac Index: _____

Lt. Vent. End Diastolic Pressure: _____

Number of diseased vessels: _____

Right Coronary Artery: _____%

Left Coronary ARtery: _____%

Left Anterior Descending: _____%

Diagonal Branch: _____%

Circumflex: _____%

Obtuse Margin: _____%

Other: _____ _____%

State of Ventricle _____

SYMPTOMS:

Chest Pain: _____ yes, onset was seen at _____mph _____ grade

_____ no _____ METS

Shortness of Breath: _____ yes Reason for stopping GXT: _____

_____ no _____

Comments: _____

_____