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Exercise Hypotension - A Retrospective Analysis

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Thesis submitted for the requirement
of the M.Sc. Kinanthropology Program

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ABSTRACT

This retrospective study assessed the usefulness of a drop and a blunted systolic blood pressure (SBP) response to exercise testing as predictors of multiple or left main coronary artery disease (CAD) as defined by a 'Coronary Score' (CS). Three types of systolic BP response to exercise were used: 1) an increase by more than 20 mmHg (Group I, n=107), 2) an increase by 20 mmHg or less (Group II, n=84), and 3) a decrease of at least 10 mmHg (Group III, n=45). The extent of CAD was significantly greater in groups II and III than in group I (group I, 6.7±6.9; group II, 9.3±7.1; group III, 11.7±8.5, $p<0.05$). However, the difference was not statistically different between groups II and III which reinforces the value of a blunted SBP response. Treatment outcome also differed between SBP groups. Seventy percent of patients in group I received medical therapy. Over 70% of those in groups II and III underwent coronary angioplasty (PTCA) or coronary bypass surgery (CABG). It was concluded that similarly to a drop in SBP, a blunted SBP response to treadmill exercise testing in patients with known or suspected CAD is a potential indicator of multiple or left main coronary artery disease.

CHAPTER 1

Introduction

Since the first national mortality statistics were published in 1921, cardiovascular disease (CVD) has been the leading cause of death in Canada, accounting for almost half of all deaths each year (Statistics Canada 1989). In 1987, more than 77,000 Canadians (43% of all deaths) died from CVD. This represented almost 60% more than cancer, the second leading cause of death (fig 1).

In 1987 again, ischemic heart disease accounted for over 46,000 deaths. Acute myocardial infarction deaths amounted to 26,000 and thousands more bear the scar of an old myocardial infarction.

In 1984 and 1985, in Canada alone, an average of 123,000 surgical procedures were performed on the cardiovascular system: 4,000 on valves and septa, 13,000 on coronary vessels, 24,000 cardiac catheterizations, 10,000 implantations, removals or replacements of cardiac pacemakers, and 1,300 other operations on the heart and the pericardium (Statistics Canada 1986). This list did not include percutaneous transluminal coronary angioplasties (PTCA) and heart transplants which are now performed almost routinely. The cost of the aforementioned cardiovascular procedures is enormous. Excluding physician fees and costs of surgery, it runs over $3 billion each year. Furthermore, because of the incongruity between the prevalence of coronary artery disease (CAD) and the percentages of diagnosed people, new and/or better techniques of diagnosis are required. Moreover, because of the considerable risks of Left Main (LM) and multiple coronary vessel disease, early

recognition is very important (Sanmarco et al. 1980).

It is well established that the prognosis of patients with CAD rests on 3 factors: 1) the extent of the lesion (Burggraf and Parker 1975) 2) left ventricular function (Sanz et al. 1982) and 3) the number of vessels with disease (Bruschke et al. 1973). Because surgery will affect mortality only in patients with triple vessel disease or left main vessel disease (Takaro et al. 1976, European Coronary Surgery Study Group 1982), it is important to diagnose properly such lesions. So far, only one test is definitive: coronary arteriography. Unfortunately, the test is very costly, entails some risk and is uncomfortable for the patient. This makes it an unsuitable procedure to routinely perform on every patient complaining of chest pain. A non-invasive, less costly and less risky approach would be of great value provided it had high predictive accuracy.

The physiological response to the exercise treadmill test may provide such an alternative. However, exercise induced ST segment depression alone provides low predictive accuracy in discriminating between patients with mild versus those with severe coronary artery disease (Haraphongse et al. 1986).

It has been reported in a number of studies now (Irving et al. 1977, Freeman et al. 1988, Haraphongse et al. 1986, Hakki et al. 1986, Hammermeister et al. 1983, Morris et al. 1978) that the blood pressure response to exercise such as a blunted systolic

blood pressure (SBP) or a decrease in SBP, may be useful in screening patients with 1) severe coronary vascular disease and 2) those with abnormal left ventricular function due to severe ischemia or a previous infarct (as diagnosed by coronary arteriography and ventriculography). Some studies have even demonstrated the superiority of systolic blood pressure (SBP) over ST segment depression in predicting mortality from coronary heart disease (Irving et al. 1977).

The "left ventricular impairment" theory explains the importance of SBP during exercise. It states that a blunted SBP response or a drop in SBP during an exercise treadmill test is caused by left ventricular dysfunction secondary to extensive myocardial ischemia as caused by LM or multiple vessel disease (Hakki et al. 1986; Levites et al. 1978; Morris et al 1978; Weiner et al. 1982; Li et al. 1979; Thomson & Keleman 1975). Hence, a measurement of blood pressure during exercise treadmill testing may help in the early detection of multiple and/or LM vessel disease and thus lead to a treatment which may substantially alleviate the risk of cardiac events.

Statement of the problem

The purpose of the present study is to determine retrospectively the usefulness of a drop and/or a blunted systolic blood pressure response to an exercise treadmill test, in revealing severity of CAD in patients with known or suspected CAD, relative to the extent of CAD as identified by a scoring system of coronary arteriography.

The hypothesis is that the incidence of a hypotensive response will increase with the severity of CAD.

The study will also look at the possible effects of medication treatment versus non-medication treatment. Within the medically treated group, the possible effects and interactions of the different classes of cardiac medications will be looked at. Except for propanolol of the β-blocker class, literature suggests no effect of cardiac medication on the BP response to exercise.

Finally, the study will look at the post-treadmill treatments performed on the patients of the different BP groups.

Limitations

The subject population for the study is a limitation since only patients with known CAD or those suspected of having CAD are part of the sample.

The sampling of blood pressure is yet another limitation. The accuracy of BP cuff sphygmomanometry monitoring is often questioned. The fact that the BP measurements have been taken by four different technologists may also cause some irregularity. However, the staff has ample experience and is able in most cases to measure BP at or to the nearest 2 mmHg.

The study was limited to patients who underwent the Bruce exercise protocol. Although it is the most popular of all treadmill protocols, some patients would have satisfied the inclusion criteria had it not been for the exercise protocol.

Finally, the fact that this is a retrospective analysis as opposed to a prospective study, also encompasses some limitations especially in the control of the study.

Scope of the study

Severity of CAD is important because patients with multiple lesions are at a greater risk of sudden cardiac death (Freeman et al. 1988) and because surgery will impact on mortality only in those with LM or multiple disease (Takaro et al. 1976, European Coronary Surgery Study Group, 1982).

Exercise treadmill testing with electrocardiographic monitoring in patients with suspected CAD has long been used to assess presence or absence of disease. Because exercise induced ST-segment depression has limited predictive accuracy (Haraphongse et al. 1986) and because it can only assess presence and not severity of CAD, Wolthius et al. (1977) suggested that other non-invasive exercise parameters such as heart and blood pressure may help increase sensitivity and specificity of exercise testing. Two authors (Irving et al. 1977, Freeman et al. 1988) have found that patients with extensive CAD on coronary arteriography also displayed lower maximal SBP during exercise. A number of authors (Hammermeister et al. 1983, Levites et al. 1978, Li et al. 1979, Thomson and Kelemen 1975, Morris et al 1978, Weiner et al. 1982) have demonstrated that a drop in SBP during exercise correlated with severe CAD. Although using different definitions of a blunted SBP response to exercise, other authors (SanMarco et al. 1980, Logan and Bruce 1958, Dubach et al. 1988, Ben-Ari et al. 1990, Hakki et al. 1986) have demonstrated that such a response may also predict severity of CAD. Unfortunately, studies have used different definitions for normal and abnormal blood pressure responses to exercise. Furthermore, studies using coronary arteriography as the method to quantify severity of disease often relied on the common and subjective "single-double-triple vessel disease" approach. In this approach the radiologist or cardiologist summarizes the

result of the coronary arteriography simply by stating the number of diseased vessel(s). A more objective and scientific approach is necessary in order to give more rigidity to the study design, result and conclusion.

In this retrospective study, a list of all patients who underwent cardiac catheterization in 1989 was used to cross-reference those who also underwent a symptom-limited Bruce exercise treadmill test. Thus 413 patients qualified for the study and 236 were analyzed. Systolic blood pressure response to exercise was categorized according to a strict definition in order to assess the value of a blunted SBP response as well as a that of a SBP drop response. Coronary arteriography was reviewed using Leaman et al's "Coronary Score" system (1981).

The results of both procedures were compared to see if an abnormal blood pressure response to exercise (a drop or a blunted response) has good accuracy in predicting left main or multiple vessel disease as seen on the cardiac angiogram.

Glossary of terms

Angina: often termed 'angina pectoris' is the pain associated with an ischemic heart.

Blunted SBP Response:

is an abnormally slow rise in SBP resulting in a low, inadequate peak systolic blood pressure with respect to the standing pre-test value. In this study it is any rise in SBP of less than 20 mmHg as seen at peak exercise.

CABG: Coronary Artery Bypass Graft, often called bypass surgery.

Cardiac catheterization:

this consists of threading a catheter from the femoral artery to the coronary arteries, then inject an iodine dye while a frame by frame X-ray movie is performed. The end result is a precise picture of the coronary arterial tree and the identification of any lesions or narrowings.

CAD Coronary Artery Disease

Drop in SBP: is any sustained drop in SBP during exercise as confirmed by two consecutive readings, despite an initial rise or not in SBP. In this study, any drop of more than 10 mmHg was considered a drop response.

LM Left Main coronary artery.

M.I.: myocardial infarction is an area of necrosis in the heart muscle tissue resulting from obstruction of the local circulation by a thrombus or embolus.

PTCA: Percutaneous Transluminal Coronary Angioplasty often called simply "angioplasty". This intervention consists of threading a catheter from the femoral artery to the diseased coronary artery, then inflating a balloon at the site of the narrowing in order to restore normal luminal diameter.

SBP: Systolic Blood Pressure as measured by an arm cuff aneroid sphygmomanometer.

Sensitivity: is the probability of a positive test given that the disease exists. It is measured by:

(True positive)/(True positive+False negative).

Specificity: is the probability of a negative test given that the disease does not exists. It is measured by:

(True negative)/(True negative+False positive).

ST-segment depression: is the depressed level of the ST wave on the electrocardiogram as opposed to its normal isoelectric position (Fig 2).

CHAPTER 2

Review of related literature

Non-invasive predictors of severity of CAD

Resting and exercise electrocardiogram

The diagnosis of severity of CAD plays a crucial role in the prevention, prognosis, treatment decision, therapy and to some extent in the follow-up of a patient with known CAD. Over the years, many parameters during the exercise test have been used to assess the presence and extent of coronary ischemia. For example, the duration of the treadmill test, the time of onset of angina and the electrocardiographic ST-segment changes represent traditional variables physicians have relied upon to help them in their diagnosis.

The resting electrocardiogram (ECG) has been a common tool used to evaluate heart disease. Any changes on the resting electrocardiogram has prompted further investigation. Such findings have often led to the exercise ECG. Today, the exercise ECG is one of the most important and valuable non-invasive diagnostic procedures. Its use in insurance medical examinations and in epidemiological studies have shown

that exercise-induced ST-segment depression is a good predictor of future cardiac morbidity or mortality. However, the 'extent of CAD' remains the best prognosis of future cardiac events (Freeman et al. 1988). The advent of coronary arteriography has provided a standard means of assessing CAD against the results of the exercise ECG. It has demonstrated that the exercise ECG alone is not completely accurate in identifying CAD and many causes of false positive and false negative results have been identified (Fox & Ilsley, 1984).

False positive

The fact that in some patients, there is ST-segment depression during exercise while the coronary arteries are normal angiographically reflects the lack of understanding of the mechanism of ST-segment depression. The Bruce treadmill test specificity for men is reported to be 80-90% whereas for women where false positive tests are more frequent, specificity is about 70%. Conditions which cause false positive tests are listed in table 1.

The frequency of a false positive exercise ECG varies with the technique used and is directly related to the prevalence of disease in the patient population. For example, false positive responses are rare (8-10%) in males with a history of chest pain (Fox and Ilsley 1984), whereas a higher incidence is observed in women at very low risk

of coronary arteriosclerosis. Women aged 20-29 and 40-70 years have 10% and 25% chances of having false positive results respectively (Fox and Ilsley 1984).

False negative

The reason for a false negative response to exercise is not very clear. One hypothesis is that there is sufficient collateral circulation, hence preventing the development of myocardial ischemia with exercise. An insufficiently provoked heart such as achieving 80% or 85% predicted maximal heart rate instead of a near maximum level can also be a factor. Another possibility is that the combined effect of ST elevation with ST depression in the same patient may result in a normal ST-segment response at exercise.

Frequent known causes of false negative test results are listed in table 2. Moreover, the fact that the resting and the exercise ECG are not always accurate in detecting CAD let alone falsely detecting CAD, suggests that it is even less capable of identifying the severity of CAD (Freeman et al 1988). Hence, this has stimulated the use of other parameters in 1) the initial diagnosis of CAD and 2) in helping to determine the severity of CAD.

The following non-invasive variables have been proposed for that purpose:

- Exercise ECG and R-wave correction
- Sum of ST-segment depression
- Exercise ECG and Treadmill Exercise Score
- Exercise ECG and thallium scintigraphy.

Exercise ECG and R-wave correction

To improve the value of exercise testing, some researchers have examined the R-wave amplitude correction in relation to exercise-induced ST depression in multiple unipolar leads (Saito et al. 1989). This idea was based on the results of some studies which stated that the magnitude of exercise-induced ST depression was influenced by R-wave amplitude. In other words, the distribution of ST depression on the left chest wall might be changed when R-wave amplitude correction was applied. This technique utilized 20 precordial unipolar leads on the left chest wall in order to better localize coronary artery narrowings (Fig 3).

The R-wave correction was obtained by dividing the ST depression with the R-wave amplitude. The 20 leads were divided in four areas, each representing a specific coronary artery: left main, left anterior descending (LAD), right coronary artery (RCA) and circumflex (CX). A particular narrowing should be in an area where the

maximal value of exercise-induced ST-segment depression with and without R-wave correction is situated. They showed that when R-wave correction was performed, the diagnostic ability of localization improved significantly from 52% to 86%. The localization of LM narrowing was correct in 100% of the cases (5 of 5!). However, there is an obvious selection and sample size bias. The authors selected their sample specifically so that all their patients had one and only one blocked coronary artery. The sample in this study was not only too small to consider the results as truly conclusive but also, the population which is best served by such a test is only one with LM disease. Furthermore, the use of 20 precordial leads in every patient tested is time consuming and economically unwarranted.

Sum of ST-segment depression

In order to minimize false positive and false negative results, some authors looked at the sum of ST-segment depression (SUM STD) in a 12-lead ECG in relation to change in heart rate (Delta HR) during exercise (Haraphongse et al. 1986). This index (SUM STD/Delta HR) would be used to predict the extent of underlying CAD, and would separate those with either no CAD, single or double vessel disease (group I) from those with triple vessel or left main stenosis (group II). The 226 patients were initially categorized by cardiac catheterization with coronary arteriography. The

variables that were significantly different in both groups with exercise were: peak exercise SBP, duration of exercise, maximal ST depression and SUM STD/DeltaHR index. It was found that 25 mm/beat/min x 100 provided the best separation between group I and II. It yielded a sensitivity of 95%, specificity of 98% and positive predictive value of 94%. Standard exercise ECG using ST depression of more than 2 mm in aVF or V5 yielded much lower values. Sensitivity was approximately 41% and 69%, specificity 74% and 88%, and predictive values were 56% and 49% for aVF and V5 respectively.

Although this method is non-invasive and seems to have a high degree of predictive value, the evaluation and calculation of ST depression especially in all 12 leads is very subjective and may be too time consuming for many physicians and diagnostic centers.

Exercise ECG and Treadmill Exercise Score (TES)

Yet another attempt to increase the accuracy of the treadmill test is the use of the treadmill exercise score. Sheffield et al (1969) used the ST integral (the integrated area of ST depression). McHenry et al in 1972 developed the ST index (SUM of mean ST depression with J point measured at 20 msec and ST slope). Others have used ST-segment/heart rate slope. Finally, Hollenberg et al. (1980, 1985) invented

the TES. This score was calculated using the integrated area of ST depression in V5 and aVF, the integrated area of ST slope in the same leads, the wave amplitude, the exercise time and the percent maximum predicted heart rate. From such results, they found that the TES had a high sensitivity and specificity (higher than ST changes alone) not only in the detection of CAD but in predicting severity of CAD. Vergari et al (1987) modified this TES. They measured ST depression at 80 msec after the J point rather than at 20 msec, and recovery period was 4 minutes rather than 10 minutes as seen in the Hollenberg study. R-wave amplitude was measured at rest from computer-averaged complexes. ST-segment depression and ST segment slope versus time was taken from the final reports of the treadmill Marquette CASE 1 computer. The area under the curve was measured with a computerized planimetry system.

As precise as it may be, the calculation of such a score is awkward to say the least. Not only does one need to calculate a rather complex formula but a computer assisted program is needed to measure ST areas and ST slopes and a planimetry is needed. Even though this TES was significantly lower in patients with CAD than normal subjects, there was still considerable overlap between the two groups. The authors of this study identified 3 groups as a result of their TES scores. Those with scores below -1.0 (similar to the abnormal ECG positive test), those with scores -1.0 and 0

(similar to non-diagnostic or inconclusive exercise ECG test) and finally those with scores over 0 (normal negative ECG response to exercise). Hence, the added complex calculations bring us back where we started and seem unworthy of the slight specificity and sensitivity gain.

Exercise ECG and thallium scintigraphy

Some authors have claimed that the exercise ECG with thallium scintigraphy is the best non-invasive way to assess severity of CAD. One study (Freeman et al. 1988) using multiple regression analysis demonstrated that the thallium defect size was the best predictor of the extent of CAD. In this study, clinical variables discriminated well between patients with 1 vessel CAD and less with those with 3 vessel CAD. The latter exhibited significant shorter exercise duration (5.5±2.2 min versus 8.3±3.3 min), lower exercise heart rate (119 vs 149 bpm) lower maximal SBP (156±29 vs 166±33 mmHg), more frequent chest pain (76 vs 20%) and more pronounced ST depression on the ECG (-1.48±1.37 vs -0.33±0.72 mm). However, as opposed to the traditional variables, thallium defect size on exercise not only discriminated well between 1 vs 3 vessel disease, but also between 1 vs 2 and 2 vs 3 vessel disease. This increase in precision has to be weighed with respect to cost of thallium scintigraphy and the risk for this test. The increased risk includes exposure to a radioactive isotope

which may be contraindicated in some circumstances i.e. in a pregnant woman, in a patient who has recently been exposed to a radioisotope for other tests etc... The cost difference between a normal treadmill test and a thallium treadmill is major; approximately $270.00 for exercise thallium with SPECT imaging versus $84.00 for a regular treadmill as per O.H.I.P. fees for 1987.

Why use blood pressure

The ease and adequate reliability of BP measurement makes it a useful tool in diagnosis. Resting and now exercise BP are common practice. During exercise testing, BP measurement is useful in assessing the risk of oncoming life-threatening arrhythmias and the risk of future cardiac events including sudden cardiac death (Bruce et al. 1977). Some studies have reported that BP results, usually systolic BP measures, are better than the ECG's ST depression in the diagnosis of CAD and in predicting future cardiac problems. The exercise treadmill test has long been used to predict presence and severity of CAD but exercise induced ST segment depression provides only a low predictive accuracy (Haraphongse et al. 1986). However, treadmill exercise test with reliable BP monitoring may improve predictability to desired levels.

Resting blood pressure

Measuring resting BP for signs of hypertension or CAD is common practice but discrepancies from visit to visit (even within the same visit) are large for a number of reasons. Hence reproducibility and reliability are low. The environmental factors for example are not controlled, causing BP to fluctuate. The small number of recordings taken during a visit is also a cause of inaccuracy. One study on variability to BP measurement was performed by Ellestad (1989). Physicians listened to the sound and watched a manometer on a sound film of BP being recorded on a patient. When the true readings were compared to the physicians' estimation of BP, the investigators observed inter- and intraobserver variations. After practical assessment of BP recordings, Ellestad concluded that most of the error came from faulty testing methodology. This included equipment and technical problems such as inaccurate aneroid manometers, inappropriate sized air bladders and cuffs, heavy pressure on the stethoscope, rapid deflation rate, terminal digit bias, systolic recheck and others.

Exercise blood pressure

The accuracy of BP recording using a sphygmomanometer during exercise is frequently questioned. Although the environment is kept constant from test to test and there is a large number of recordings taken during the test, the accuracy of the

measurement is still disputed. Many studies found the diastolic (fourth and fifth Korotkoff sounds) more difficult to detect at higher intensities of exercise and hence discarded those values. The study of Ellestad (1989) stated that problems of resting BP readings are multiplied during exercise. According to his results, when the intensity of surrounding sounds increased, the perception of Korotkoff sounds decreased. Hence motor noise of a treadmill, footstrike, vibration, friction between objects etc... all minimized perception and accuracy, especially at high intensities when it was most critical to know the patient's blood pressure. Still according to Ellestad (1989), the sounds of Korotkoff heard through a stethoscope ranged from 18 to 26 hertz. The human ear hears best at frequencies ranging from 200 to 4,000 hertz; the lowest frequency the ideal human ear can appreciate is a sound of about 16 hertz. With systolic BP frequencies falling below 20 hertz, the human ear is basically deaf to some of those sounds it should detect. However, some will dispute the fact that the intensity of the BP sounds (decibels) at the given frequencies also increases with exercise probably making perception adequate.

Many studies also stated that highly trained personnel with extensive experience in exercise testing make BP measurement precise enough to warrant its use (Sanmarco et al. 1980; Ben-Ari et al. 1990). However they agree that the recording in stage 4 or 5 of the Bruce protocol (when patients can be jogging) may be difficult to obtain with

accuracy. Most cardiac patients however, do not go beyond the third stage of the Bruce protocol (Sanmarco et al. 1980; Thomson & Kelemen 1975).

Comparison of sphygmomanometry with intra-arterial pressure recording has shown that patients with angina, experience its onset at the same systolic pressure regardless of which method was used (Irving et al. 1977). Irving et al. (1977) indicated that on two consecutive exercise treadmill tests (same patients, same day), one using sphygmomanometry and the other using intra-arterial recordings, there was good correlation (0.721) between the two blood pressure measuring methods. Systolic blood pressures agreed within 20% over the range of 100 to 240 mmHg. Von Polnitz & Hofling (1989) compared simultaneously the recording of their SpaceLab ambulatory device with intra-arterial and mercury column sphygmomanometery. They concluded that both systolic and diastolic BP measurements correlated significantly with intra-arterial and casual measurements. Indirectly, this signifies that intra-arterial and sphygmomanometry methods correlate.

Even though they did not state any studies, Ben-Ari et al. (1990) commented that shygmomanometry has been validated with intra-arterial lines in many studies.

Finally, reproducibility of BP measurement in two consecutive exercise tests support the fact that BP recording at exercise is precise. Morris et al's study (1978) supported this fact. During a second exercise test performed 2 to 5 weeks later, blood pressure

results were reproducible in all 7 patients being retested.

Irving et al (1977) found that the reproducibility of SBP during maximal exercise was better than SBP measurements at rest in follow-up tests performed 1 to 30 months later.

Increased sensitivity and specificity of the treadmill test

As indicated earlier, many studies have tried to increase sensitivity and specificity of the traditional treadmill test for diagnosing presence and severity of CAD. Wolthius et al (1977) expressed the problem of over-rating the exercise ECG at the expense of other non-invasive valuable exercise parameters such as heart rate, blood pressure and functional capacity. Because of its extensive use, the ECG has demonstrated good reliability in detecting CAD but SanMarco et al. (1980) observed that blood pressure abnormalities were also highly specific in predicting the severity of CAD. In their cohort of 378 patients, they observed 90 patients with an abnormal BP response to exercise, defined as a drop of BP or a flat BP response with exercise. The sensitivity of such a BP response for three-vessel disease or left main disease was 38.6% which was identical to that of marked ST-segment depression on the ECG. The combined use of BP and ECG ST-segment depression to evaluate the severity of CAD increased the sensitivity substantially to 56.4%. Hence, not only is

BP itself a good criterion for CAD severity but in combination with the traditional ECG parameters, it increases the predictive value of this easily performed non-invasive test.

Hypotension: prognostic implications for sudden cardiac deaths, sudden cardiac events and arrhythmias

Exercise BP and future sudden cardiac deaths

It is well known that unstable angina has a significant one year mortality and a high incidence of myocardial infarction (M.I.). Freeman et al. (1988) report a 7 to 10% mortality within 1 year and a 12 to 14% chance of M.I.

Irving et al. (1977) assessed the prognostic value of the maximal BP with exercise for future cardiac deaths due to CAD. They observed that the annual rate of sudden cardiac deaths decreased (from 97.9 per 1,000 men to 25,3 and to 6.6) as the range of maxBP to exercise increased (less than 140 mmHg, 140 to 199 and >200 mmHg respectively). In the 115 men who had a sudden cardiac death, Bruce et al. (1977) noticed that during their symptom-limited maximal exercise treadmill test, they exhibited lower heart rates, shorter duration and most importantly lower SBP and DBP. In fact, they demonstrated that failure to increase maximal SBP above 130

mmHg was the parameter with the most prognostic significance for future sudden cardiac death. Stamler et al. (1989) also noticed a strong relation between BP and death due to heart disease. Hammermeister et al. (1983) obtained a 0.71 five year survival probability for patients displaying hypotension during exercise and a 0.88 probability for patients with normal BP response. The difference was significant to $p<0.001$. Li et al. (1979), Weiner et al. (1982), Sanmarco et al. (1980), Thomson & Keleman (1975) all related similar findings in that an inappropriate rise or a drop of SBP during exercise carried a strong prognostic implication for future sudden cardiac death.

Exercise BP and life-threatening arrhythmias

Another reason to monitor BP with exercise is that a drop of SBP may foreshadow upcoming life-threatening arrhythmias. Irving & Bruce (1977) analyzed retrospectively the case of five men who had cardiac arrest due to ventricular fibrillation immediately after a symptom-limited treadmill test. They noticed that in each case the onset of arrhythmia was preceded by a significant exertional hypotension. Other studies, Hammermeister et al. (1983), Thomson & Keleman (1975), Morris et al. (1978) also acknowledged the likelihood of the development of ventricular fibrillation if exercise is continued past the point of hypotension.

BP better than ST-segment depression

Even though the exercise ECG has been used extensively, exercise induced ST segment depression provides a poor predictive accuracy of CAD (Haraphongse et al. 1986). For example, from their study with thallium scintigraphy Freeman et al. (1988) found parameters other than ST-segment depression to be predictive of multi-vessel CAD.

Some studies suggested that blood pressure and especially systolic blood pressure (SBP) (Irving et al. 1977; Stamler et al. 1989; Miall 1982) was superior to ST segment depression in predicting mortality rates from CAD (Irving et al. 1977; Bruce et al. 1977; Weiner et al. 1982; Sanmarco et al. 1980). In Morris et al's study (1978) where 22 patients displayed exercise hypotension, no significant differences in computer-quantitated ST segment abnormalities were observed between them and the patients with normal exercise blood pressures.

Although the hypotension group was at greater risk for future cardiac events (as seen earlier), ECG findings alone would not have warned the physician of this prognosis. Hence, BP monitoring during exercise is useful as an end-point or contraindication to pursuing a symptom-limited maximal exercise test and as a prognostic tool for future cardiac events such as myocardial infarction and sudden cardiac death. As we will see in the next section, it is also useful in discriminating between single vessel

disease and multivessel disease.

A fall in blood pressure with exercise

Definition of exercise hypotension

So far, the definition of exertional hypotension in patients with CAD has been very inconsistent. In their study, Sanmarco et al. (1980) called a "flat" response when SBP failed to rise by more than 10 mmHg after the first minute of exercise or when at five minutes in exercise a fall of >20 mmHg was observed despite an initial rise. Logan & Bruce (1958) defined hypotension when SBP failed to rise by at least 10% from the resting value. As for Dubach et al. (1988), a drop of >20 mmHg without it going below standing value or any decrease below standing rest value was termed a hypotensive response. In Ben-Ari et al's study (1990) a failure of SBP to rise by more than 20 mmHg above resting value or a fall of > 10 mmHg from the previous stage despite an increase in workload was termed a hypotensive response. In Hakki et al's study (1986), three types of SBP responses to exercise were identified: an increase by more than 20 mmHg; an increase by 20 mmHg or less; and a decrease of at least 10 mmHg. Other studies (Levites et al. 1978; Li et al. 1979; Thomson & Kelemen 1975) called exercise hypotension, a drop of SBP below the preexercise standing

level. For Morris et al. (1978) and Weiner et al. (1982), any sustained drops of 10 mmHg during exercise was termed hypotensive. Table 25 summarizes these studies and their SBP response criteria.

Although inconsistently defined, exertional hypotension is now being seen by many researchers and physicians as indicative of a high number of diseased vessels and an indication for invasive evaluation.

Hypotension: a sign of multiple-vessel disease

More and more studies confirm that among patients with CAD, the occurrence of hypotension with exercise signifies the presence of severe, extensive multiple vessel disease. Irving et al. (1977) demonstrated the relationship between blood pressure and the number of stenotic coronary arteries in 22 men without CAD and 182 men with CAD. They found that CAD patients had lower maximal SBP than non-CAD patients. Lower maximal SBP was often related with 2 or 3 vessel disease or reduced ejection fraction or both. In their study, Freeman et al. (1988) found that patients with 3-vessel disease had significantly shorter exercise duration, lower maximal heart rate, more angina, more ST-depression and also lower maxSBP. When grouped by their SBP response to exercise (group 1 defined by an increase by > 20 mmHg; group 2 by an increase < 20 mmHg; group 3 by a decrease > 10 mmHg), Hakki et al. (1986)

found that multivessel CAD was significantly more frequent in group 3 than group 1 and 2 ($p<0.05$). Hammermeister et al's results of 3,000 patients were similar. Patients with a hypotensive response to exercise had more extensive CAD and more LV dysfunction than did patients with a normal increase in SBP. In fact, as per coronary arteriography, the prevalence of a hypotensive response increased from 7.4% in patients with 1-vessel disease to 10% in those with 2-vessel disease to 18% in those with 3-vessel disease. It is interesting to see in Levites et al's study (1978) that not only the incidence of significant CAD was higher in exertional hypotensive patients, but also the distribution of the coronary lesions was predominantly in the LAD artery.

Also of interest is the fact that a hypotensive response to exercise is reproducible. Morris et al. (1978) subjected 560 normal volunteers to a treadmill test and 189 patients with at least 75% stenosis of one or more of the three major coronary arteries. In the normal volunteer group, none exhibited exertional hypotension. In the CAD group, 22 (11.6%) demonstrated a drop in SBP of more than 10 mmHg. A second exercise session was performed in 7 of those 22 patients within 5 weeks and all manifested a hypotensive response to exercise. Analysis of coronary arteriography showed that 17 of the 22 patients had lesions equivalent to a left main stem stenosis. Fifteen had significant three vessel disease and the remaining 7 had 2-vessel stenosis

and four of these had a third coronary vessel artery with 50% stenosis. Of the 88 patients who had triple vessel disease, 15 (17%) had a blood pressure drop. A drop in BP was not observed in healthy subjects or in patients with single vessel CAD. The authors noted that because exertional hypotension was reproducible and because it was absent in 560 normal subjects during maximal testing, then BP can be recorded during exercise with a good degree of reliability.

Similar results were found by Weiner et al. (1982). Over 10% (47) of the 436 patients tested manifested exercise hypotension as defined by a confirmed drop of >10 mmHg. Of the forty six who had CAD, 26 (55%) had significant stenosis of either LM or three vessel CAD. As the number of stenosed arteries increased, so did the prevalence of a hypotensive response. Only 1 of 124 normal patients (<1%) had a decrease in BP compared with 10%, 11% and 21% of patients with one, two and three vessel disease respectively. During a repeat exercise test, 17 of the 22 patients retested (85%) displayed a decrease in SBP.

Other studies confirm the fact that a hypotensive response is more likely to happen in patients with a high number of stenosed vessels or those with left LM involvment. Li et al. (1979) demonstrated that in 37 patients with hypotensive responses (maximal SBP below resting levels), 73% had triple vessel disease, 23% had 2-vessel disease and 2% had only one occluded vessel. Left main involvement was present in

35% of the cases. When LM is counted as double vessel disease, the average number of diseased vessels per exercise hypotensive patients was 2.7.

In their study, Sanmarco et al. (1980) demonstrated similar results. Ninety of 378 patients awaiting catheterization displayed abnormal BP responses with exercise (failure to rise or a drop of SBP). Of those 90 patients, 63 had 3-vessel disease or LM stenosis which yields a predictive value of 70%. The sensitivity of an abnormal BP response for disease of this severity was 39% and specificity was 87%. When combined with ST-segment depression during exercise, these values were even higher. They also observed reproducibility where 16 of 23 (69%) patients retested displayed similar abnormalities. Their conclusion supported Irving et al's (1977) observation that blood pressures are highly specific in predicting severe disease and hence should be used more extensively and should be considered a critical parameter during stress testing.

One interesting and very important study was performed by Ben-Ari et al. (1990) on apparently healthy men. Of the 1347 men studied, 49 showed abnormal blood pressures with exercise as defined by failure of SBP to rise by >20 mmHg or a fall of 10 mmHg or more during exercise. When compared with an aged-matched group of 200 healthy men, upon a follow-up of 8.9 years, exercise induced ST-segment depression of >1 mm was more pronounced in the hypotensive group (11.1% vs

3.4%). From all those displaying ST-segment changes, 75% of the hypotensive group vs 60% of the control group had angina, and finally two men from the hypotensive group vs none in the control group had myocardial infarctions. Their conclusions were that a hypotensive response to exercise in seemingly healthy individuals may be an indicator of early CAD.

Hypotension not indicative of multiple cardiovascular disease ?

Although few in number, some studies or parts of studies have suggested that exertional hypotension is not a good predictor of the severity of CAD.

Even though Hammermeister et al's study (1983) reported that patients with exertional hypotension had more extensive CAD and more LV dysfunction, they failed to demonstrate that a hypotensive response was a good indicator of LM stenosis or 3-vessel disease because sensitivity was very low (15%). Some studies (Levites et al. 1978; Thomson & Keleman 1975; Baker et al. 1976) have suggested that a hypotensive response in females might not have the same prognosis as in men i.e. denote CAD or LV dysfunction. A study (Hakki et al 1986) was performed on 127 patients with known CAD. They underwent exercise thallium scintigraphy and were grouped according to their systolic BP response: increase of more than 20 mmHg (group I), increase of less than 20 mmHg (group II), decrease in BP of more

than 10 mmHg (group III). They noticed that the number of segments with perfusion defects was significantly higher in groups II and III than in group I. Multivessel CAD as well as previous M.I. was also higher in group III than in groups I and II. Stepwise multivariate analysis showed the number of thallium perfusion defects to be the most important determinant of the hypotensive responses. Along with exercise HR, a blunted BP response was also predictive of the number of perfusion defects. Why do only some patients with multi-vessel disease have a hypotensive response to exercise and why do some patients with 1 vessel disease also display a hypotensive response? Hakki et al postulated that patients with severe exercise hypotension have more thallium defects than patients with mild or no hypotension. The total number of fixed (scar) and reversible (ischemia) defects is the best predictor of SBP response since they represent the sum of insults on the left ventricular performance. They stated that hypotension is not necessarily related to the number of diseased vessels or LV dysfunction. It is the physiologic and functional consequences of CAD (location and severity of total scared and ischemic tissue) rather than the angiographic extent of disease that determine SBP response to exercise.

Importance of identifying severe CAD

Why is it so important to discriminate between one or two-vessel disease and three-vessel disease? The answer is that in most cases, the choice of treatment will differ. There is evidence that (CABG) surgery may only improve prognosis in patients with LM and those with certain combinations of triple vessel disease (European Coronary Surgery Study Group 1982).

Early recognition of LM CAD is very important (Sanmarco et al. 1980). Of the 29 patients with LM disease, 62% displayed a hypotensive response. As they stated, this response should influence the physician's approach to treatment. For example, invasive evaluations such as cardiac catheterization and possibly bypass surgery could be considered.

Conditions under which hypotension is a sign of CAD

According to Thomson and Keleman (1975) and Morris et al. (1978) the clinical implications of a decrease in SBP during an exercise treadmill test as an indicator of multiple vessel CAD are true provided that some conditions are met. Both studies suggested that: 1) the decrease in SBP is maintained during a repeat BP measurement (Morris et al. 1978; Thomson & Keleman 1975); 2) there is no sign of obstructive valvular disease and resting LV

dysfunction (Morris et al. 1978; Thomson & Keleman 1975); 3) patients are free of any combination of pharmacological agents which may significantly reduce cardiac output or increase peripheral vasodilation at exercise or both (Morris et al. 1978; Thomson & Keleman 1975); 4) there are no frequent cardiac arrhythmias at the time of BP recording (Morris et al. 1978); 5) exercise time should be at least 1 minute duration to exclude 'false positive' results of anxious patients (Morris et al. 1978); 6) there should be evidence of ischemia with ST-depression and/or symptomatic angina (Thomson & Kelemen 1975); 7) other normal expected responses such as thermoregulatory or anaerobic acidosis as well as bradycardic vasovagal response should not be a prominent feature of the observed hypotension (Thomson & Kelemen 1975). If these qualifications are fulfilled, then a significant fall in SBP during exercise is a useful, highly specific and easily ellicited sign of severe coronary artery narrowing. It is a non-invasive means of assessing from a large pool of patients with symptoms of CAD, and with severe compromise of left ventricular function those at greater risk of morbidity and mortality. This will in turn determine whose case is urgent enough to initiate therapy.

Control mechanisms of SBP - Rest and Exercise

Mean arterial pressor can be calculated from the following formula:

Pmean = R x Qc where mean arterial pressure is Pmean = Pd + 0.33(Ps - Pd),

R = resistance and Qc is cardiac output = HR x S.V. (S.V. = stroke volume).

Resistance to flow cannot be measured in humans but can be calculated by:

(R= Pmean/Qc).

At rest, the vagal (parasympathetic) tone is prominent causing HR and stroke volume to be at their low resting levels. The sympathetic tone in turn maintains a moderate resistance hence permitting good systemic flow. For a typical 125/80 blood pressure and 5 L per min cardiac output the resistance would be:

R = Pmean/Qc

R = 95 mmHg / 5 L per minute = 19 mmHg / L per min

At onset of exercise, a neural response will mediate rapid changes in Qc and R followed by a fine tuning through humoral factors. A decrease in vagal tone, an increase in venous return and an increase in sympathetic tone will drive both HR and stroke volume to easily reach a cardiac output of 30 L/min at peak exercise. Right from the start, this will increase BP, especially

systolic BP. The reason why systolic BP is more affected is because although the left ventricular pump has increased in rate and contractility, the resistance has decreased as a result of a sympathetically mediated vasodilation of the arterioles supplying blood to the active skeletal muscles. This causes more blood to go from the arteries to the arterioles and into the muscle capillaries, at the same time minimizing changes in diastolic pressure. Simply stated, Pmean increases with increasing cardiac output and decreases with decreasing resistance. For example, at peak exercise, it is common to see a Pmean of 126 mmHg and a cardiac output of 30 L per min.

This yields a 4.2 mmHg / L per min in resistance, a 4.5-fold decrease from that at rest (Fox, Bowers and Foss 1993).

Mechanisms causing exertional hypotension

There are many physiological explanations for a hypotensive response to exercise. In patients with suspected or known CAD, the "left ventricular impairment" theory explains such a phenomena. This theory states that a decrease in SBP during exercise especially in patients with multiple-vessel CAD, is caused by left ventricular dysfunction secondary to extensive

myocardial ischemia (Hakki et al. 1986; Levites et al. 1978; Morris et al. 1978; Weiner et al. 1982; Li et al. 1979; Thomson & Keleman 1975). Studies using exercise echocardiography (Ben-Ari et al. 1990), using radionuclide ventricular exercise scanning (Rerych et al. 1978; Jengo et al. 1979; Hakki et al. 1986) and studies which have looked at the effect of PTCA and CABG on reversing the hypotensive response tend to support this theory.

By means of exercise echocardiography on apparently healthy individuals displaying a lower than normal increase in SBP, Fisman et al. (1989) demonstrated that they also had an abnormal left ventricular response to exercise.

Hakki et al's study (1986), for example, looked at the determinants of exertional hypotension in patients with CAD using thallium-201 myocardial scintigraphy. They found that it is the sum of scars (infarction site) and ischemia representing the sum of insults on the left ventricular performance that is responsible for the hypotensive response.

Morris et al. (1978) looked at pre and post-bypass blood pressure response to exercise. They concluded that the initial hypotensive response was caused by "acute left ventricular pump failure secondary to extensive myocardial

ischemia". This, is supported by the fact that none of the 90 patients with single-vessel disease where less myocardium is at risk of ischemia, had this abnormal BP response. Even more conclusive is the fact that BP response was restored to normal by coronary artery bypass graft surgery in patients with multiple vessel disease. This reversal of BP with bypass surgery was also observed in Weiner et al's study (1982) where 17 of 20 medically treated patients still displayed hypotension whereas none of the 22 bypass patients did. The same results were found in Li et al's study (1979).

Other causes of exertional hypotension

Anxiety

Another main cause of hypotension during a treadmill exercise test is anxiety. Quite often, apprehensive patients with labile BP will display elevated pressures before or during the initial stage of exercise and will then drop their BP as the test progresses and anxiety abates (Irving et al. 1977; Sanmarco et al. 1980; Ben-Ari et al. 1990). However this response is known to occur *only at very low work loads* (Ben-Ari et al. 1990). This phenomena may also be

the reason for the inappropriate BP responses (flat response) in some patients with mild CAD or those with normal coronaries (Irving et al. 1977; Sanmarco et al 1980).

Anaerobic acidosis and thermoregulatory drift

At the other end of the spectrum, when patients are able to achieve 15 minutes (Stage 5) or more of the Bruce treadmill protocol, we may again see a drop in blood pressure (Morris et al. 1978; Sanmarco et al. 1980). This can be explained by one of two physiological mechanisms other than left ventricular pump failure. One mechanism occurs when patients exceed their usual limits of exercise and are well into the anaerobic phase (Thomson & Kelemen 1975; Levites et al. 1978). With the point of collapse approaching, severe metabolic acidosis from excessive lactate production often causes SBP to drop precipitously (Irving et al. 1977) along with marked pallor, sweating and trouble with coordination. Such drop in SBP should not be interpreted as an abnormal event.

The other mechanism seen at high levels of exercise is a thermoregulatory response. The system's response to prolonged dynamic exercise is an

increased sympathetic vasodilatation of skin vasculature in order to dissipate increased muscular heat (Morris et al. 1978, Ben-Ari et al 1990). This blood shift reduces total peripheral resistance (TPR) and since cardiac output is near or at maximal, systolic and mean arterial BP can decrease. This response also termed "cardiovascular drift" only happens with severe prolonged exercise and hence is not expected in patients with suspected or known CAD.

Neurogenic response

A neurogenic response such as a vasovagal discharge can also produce hypotension. However, this response almost always happens in association with bradycardia which is more likely to occur after, rather than during exercise (Thomson & Kelemen 1975; Levites et al. 1978; Ben-Ari et al. 1990; Sanmarco et al 1980). During a hypotensive response due to LV dysfunction, HR does not change or keeps rising making it easy to discriminate between the latter and a bradycardic vasovagal response.

Pharmacological causes

Impaired autonomic function can also occur as an effect of medication such as antihypertensive or propranolol therapy (Thomson & Kelemen 1975) and hence cause a hypotensive response during exercise. However, most studies (Irving et al. 1977; Hakki et al. 1986; Sanmarco et al. 1980; Thomson & Keleman 1975) which included patients on drug therapy in both the control group and the hypotensive group, found no increase in prevalence of BP abnormalities (hypotensive or a blunted response). The inclusion or exclusion of patients on medication from both groups did not alter the results of the statistical analysis for Sanmarco et al's study (1980). They, however, caution the interpretation of a hypotensive response in patients receiving propranolol treatment.

Using a multivariate logistic model, Hammermeister et al. (1983) did notice that a combination of propranolol and some other variables could cause the development of exertional hypotension. They recommended that in the event of a hypotensive response in patients on full doses of propranolol, the latter response should not be used as the sole indication for invasive studies.

A drug combination of propranolol, methyldopa and long lasting nitrates was

the suspected cause of the single faise positive decrease in BP in the Morris et al. study (1978). They imply that this combination has the potential to reduce maximal cardiac output while stimulating peripheral vasodilatation during exercise. These two physiological effects will obviously cause a dramatic decrease in SBP.

All in all, except for propranolol and its use in combination with some other drugs, most medication should not hamper significantly the normally operative adaptive mechanisms which maintain SBP during exercise.

Other heart diseases

Other heart diseases can also cause exertional hypotension. Such a response was observed by Morris et al. (1978) in patients with obstructive cardiomyopathy. It is suspected that the left ventricular outflow tract is obstructed by the disease and hence the LV cannot supply the increase demand of the system. Patients with fixed stroke volume such as patients with aortic or mitral stenosis or congestive cardiomyopathy may also have little increase in SBP with exercise (Sanmarco et al. 1980; Thomson & Keleman 1975).

It is obvious from these studies that when a hypotensive response is observed with exercise, it is also important to consider other clinical factors that may cause hypotension. It is also important to understand that the pathophysiological significance of the decrease in SBP at maximal exercise in healthy men who performed 15 minutes is different than the same response seen in a 60 year old man with a previous M.I. who exercised for 3 minutes.

Effect of Coronary Bypass Surgery

Finally, the hypotensive response can be reversed with coronary bypass surgery (Irving et al. 1977) or coronary angioplasty. Morris et al. (1978) noticed a return to normal BP response in 6 of 6 (100%) patients who exercised again after CABG. Similar results were observed by Weiner et al. (1982) and Thomson & Keleman (1975). Not only did exercise time and HR increase after CABG but the BP showed a normal rise. This restoration of normal BP with exercise following bypass surgery suggests that severe ischemia leading to poor LV function is the cause of the hypotension.

Although it can determine ischemia, exercise ECG cannot adequately assess

severity of CAD not only because of its relatively poor sensitivity and specificity but mainly because of the intrinsic nature of the measurement. The ECG superficially monitors the electrical activity of the heart. Blood pressure measurements monitor the hemodynamics of the left ventricle pump. A drop of the ST segment on the exercise ECG can clue physicians on possible ischemia but it cannot adequately determine the number of ischemic areas. The more leads with ST depression and the more important the extent of the ST depression points to a poorer prognosis but it does not necessarily imply multiple vessel disease. Unless a sudden and dramatic vasodilation occurs, a drop in SBP during exercise however means that the left ventricular pump is impaired and cannot cope with the demand. This failure occurs when a good part of the ventricle is deprived of oxygen due to a severe narrowing of the LM vessel or narrowings in many of the other supplying arteries.

Cardiac Angiography: "The Gold Standard"

Because cardiac angiography is considered the "Gold Standard" in the determination of CAD, data from other diagnostic tests are always compared to it. Alike many other tests, there are a number of scoring systems derived

from the coronary arteriogram.

Results of the Ad Hoc Committee on Grading of Coronary Arterial Disease of the American Heart Association is the basis of most scoring systems. It classifies obstructions as: normal lumen, 25%, 50%, 75%, 90%, 99% reduction and occlusion. See table 3 for a more detailed explanation.

By far the most simple and therefore most widely used method of qualifying severity of CAD using the above classification is the one of "Single-Double-Triple-Left Main (SDTLM)" system. Although this rating in the clinical setting may be useful and possibly sufficient, a more scientific approach may be utilized for experimental research. Another indisputable flaw of this rating is the profound difference between a 99% obstruction of the proximal left anterior descending artery (LAD) and a 75% obstruction of its distal segment. A method that assigns a different severity score depending on 1) the degree of luminal narrowing and 2) geographical importance of the location of the narrowing is much more appropriate.

The area of a circle (cross-section of an artery) is measured by $\prod r^2$, hence if the radius is divided by a factor of 2, this means a reduction in the area by a factor of 4. From this observation, clinical observations and in keeping with

Poiseuille's Law on viscosity and flow, reduction in arterial lumen diameter of 70% and more are considered pathological, and often require aggressive intervention i.e. PTCA or CABG. Although also pathological, 50-70% lesions are usually treated medically (drug therapy) if at all. Hence most coronary scoring systems will start their scores for lesions of 70% and up.

Coronary Artery Jeopardy Score

In 1985, Califf et al. designed the "Jeopardy Score" which divided the coronary circulation in six arterial segments: LAD, major anterolateral (diagonal) branch, first major septal perforator, left circumflex artery (Cx), major circumflex marginal branch and posterior descending artery. In patients with left dominant systems, the right coronary artery (RCA) had no points. Each segment with 75% narrowing or more received 2 points and so did any segment distal to the original 75% narrowing provided they too had 75% narrowing or more (see figure 4). Hence the maximal number of possible points is 12. Although this scoring system is simple to use, it still doesn't discriminate between a 75% and a 99% narrowing. Furthermore, this system does not apply to patients with previous (CABG) surgery. This last point

made this scoring system unacceptable for our study.

Coronary Artery Severity Score

Freisinger et al. (1973) developped a computerized "Severity Score (SC)" which takes into consideration the geographical location of the narrowing (proximal vs mid vs distal), the increasing severity of narrowing as per the aformentioned classification system, the cumulative effect of multiple lesions in the same artery, the significance of their location (LAD vs RCA vs Cx etc...), the influence of the collaterals, the size and quality of the distal vessel, and the importance of the status of myocardial function.

This sophisticated severity score (perhaps too intricate!) still carries the disadvantage of not being applicable to post CABG patients as no guidelines have been implemented for such patients.

Coronary Artery - Coronary Score

Finally a detailed "Coronary Score" (Leaman et al. 1981) which accounts for severity of narrowing, location of the lesion and is applicable to post CABG patients was retained. It discriminates between proximal vs mid vs distal, and

also discriminates between the different percentages of narrowing. It also identifies an artery location weighting system. For example, based on their review of literature, Leaman et al. (1981) established that the average left ventricular mass (free wall plus septum) in the average male was 155 grams. Based on other studies they established the average coronary blood flow to be approximately 96 mL/100 g of left ventricular muscle. In the right dominant coronary artery system, they established that the RCA supplies approximately 16% and that the LAD with its septal and Cx supplies 84% of the flow to the left ventricle. Hence the LAD system carries five times more flow than the RCA. The LAD system was then broken down and it was established that the actual LAD artery carries 66% vs 33% (Cx) of the flow. Hence the LAD artery carries 3.5 times and the Cx 1.5 times as much blood as the RCA. Similarly, the RCA, LAD and Cx were further subdivided and weighting factors assigned to each segment (Figure 5). As seen in figure 5, this scoring system also discriminates between the two dominant systems: Right dominance and Left dominance. Finally, in patients with previous CABG, a previously diseased vessel segment is considered normal provided its bypass graft is patent. If the bypass graft is occluded, the score derived

from its native artery prevails i.e. the score is derived as if no graft had been done.

Finally, the sum of all segmental scores establishes the total coronary score. A score of 0 indicates no lesions at all and hence no CAD. Although impossible, the highest possible score is 90, that is if all segments were occluded. The higher the coronary score, the worst the CAD scenario.

Due to its relative ease of calculation, the fact that it is one of few that is applicable to post CABG patients, and also because it recognizes and takes into account the geographical importance as well as the severity of a lesion, this coronary scoring system is the one utilized for the present study.

Since identification of severity of CAD is important, and because exercise ECG alone cannot determine severity of CAD, a number of methods using variations of the ECG with exercise have been looked at. Unfortunately these methods are often cumbersome and for the most part still do not improve the diagnostic value of the simple exercise ECG. Blood pressure response to exercise on the other hand is a simple non-invasive method which when performed correctly, may help differentiate patients with LM or multiple vessel disease from those with single or no disease.

CHAPTER 3

Methodology

In order to see if a drop or a blunted blood pressure response to exercise can indeed differentiate between multiple or LM vessel disease against those with single or no vessel disease, it was necessary to obtain a cohort of patients who had had both an exercise treadmill test and a coronary arteriography within six months of one another.

Selection of subjects:

The records of all patients who underwent both treadmill exercise testing and coronary arteriography at the University of Ottawa Heart Institute during the year 1989, were reviewed. They included patients of all age groups and of both sexes. These patients were evaluated because of known or suspected CAD. From the 4000 patients who underwent coronary arteriography that year, approximately 600 patients performed a Bruce treadmill test followed by coronary arteriography within six months of one another. Patients

excluded were those who had recent CABG, coronary angioplasty and recent infarction within 3 months of the treadmill test, patients with valvular heart disease or cardiomyopathy. Patients who underwent treadmill testing on protocols other than Bruce were also excluded. Finally, patients whose peak exercise blood pressures were not recorded for some reason were obviously also excluded. In total, 413 patients qualified for the study. All patients (n=129) displaying an abnormal SBP response to exercise (see criteria below) were analysed. Because of time constraints and difficulties in obtaining coronary angiographic results from the hospital's "Medical Records", one third or 107 of the possible 284 patients displaying normal SBP during exercise were analysed. In order to have a good representation of all patients displaying a normal SBP response, every third 'unique number' (patient's hospital number) of such patients was chosen, hence covering the full year and thus reducing seasonal variations.

Treadmill exercise testing:

All patients in this study underwent the Bruce graded treadmill exercise testing protocol. This protocol was developed by Dr. Bruce in 1979 (Bruce

& Hornsten 1979) in order to detect electrocardiographic changes suggestive of myocardial ischemia. It is used by most cardiac diagnostic centers. The characteristics of this protocol are illustrated in table 4.

After signing a written consent form, a thorough history of risk factors, previous cardiac history, medication and description of angina was performed. Cardiac medications, including beta-blockers, calcium antagonists and nitrate drugs, were routinely discontinued 3 days (flush out period) prior to the treadmill test in order to avoid any pharmacological influence on the physiological response to exercise. However, patients on medication at the time of testing were not excluded.

A 12 lead electrocardiogram (ECG) and blood pressure measurements were then performed at rest in a supine, standing and standing post-hyperventilation position. The same measurements were repeated during the final minute of each 3-minute stage, at the onset of angina, dizziness or ST-segment depression, immediately after exercise and every two minutes thereafter for at least 5 minutes. Unless any contraindications to pursue the test were encountered (see table 5), the end point of this symptom-limited test was a self-determined maximal effort. However, patients were encouraged to

achieved at least 85% of their maximal predicted heart rate (Table 6). Whenever a decrease in blood pressure was observed, a second and sometimes a third BP measurement was repeated at approximately 15 second intervals to confirm accuracy and a sustained response. If BP dropped by more than 20 mmHg, the test was stopped unless this response was thought to be caused by an anxious patient relaxing as the exercise session began.

Electrocardiography

Electrocardiograms were performed using a commercially available computer assisted system (Marquette Case 12). It provides continuous monitoring of three electrocardiographic leads (in our lab: V1, V5, and aVF), heart rate, exercise time and a digital display of ST segment depression in millimeters, 80 ms after the J point in each of the 12 leads. Electrode placements were performed according to the method of Mason and Likar (1966) using column silver/silver chloride MediTrace electrodes. Electrocardiographic changes were assessed and reported by one of four staff physicians. Marked ST segment changes are usually defined as a depression of 1 mm or more taken 80 msec after the J point with the ST segment flat or downsloping in any

monitored lead.

Blood pressure recordings

All the blood pressures were measured by any one of four trained technologists using a Tycos arm cuff adapted to a Baumanometer sphygmomanometer and a standard stethoscope with the diaphragm placed over the right brachial artery. As for resting measurements, exercise blood pressures were made with the subject's arm motionless, relaxed to his side and slightly flexed at the elbow. On the treadmill, patients were asked not to touch the railing with that arm as the treadmill's vibrations muffle the Korotkoff's sound.

A normal SBP response to exercise is any sustained increase of more than 20 mmHg from standing baseline.

An abnormal SBP response to exercise was defined as 1) failure of SBP to rise by more than 20 mmHg from initial standing pre-exercise level (blunted response) and 2) a sustained decrease of at least 10 mmHg when compared with the previous workload regardless of an initial rise or not.

Hence, patients were categorized in one of three groups depending on their SBP response.

Group I	increase in SBP > 20 mmHg
Group II	increase in SBP ≤ 20 mmHg
Group III	decrease in SBP > 10 mmHg

The normal physiological response to graded exercise is an increase in SBP. This increase is in the order of >20 mmHg between the standing rest value and the one obtained in the first stage of the Bruce protocol. After the second and third stages, the increases are approximately 40 mmHg and 50 mmHg or more respectively (Wolthius et al. 1977). Regardless of beta-blockade or not, the increase should be at least 20 mmHg or more between rest standing and peak exercise. Hence the criteria of 20 mmHg SBP or more characterized the group with normal SBP responses to exercise.

While few studies have addressed the implications of abnormal SBP responses to exercise (Irving et al. 1977; Freeman et al. 1988; Morris et al. 1978; Li et al. 1979; Thomson & Keleman 1975), fewer studies have dealt

with the effect of a flat or blunted SBP responses (Hakki et al. 1986; Sanmarco et al. 1980; Ben-Ari et al. 1990). Table 25 demonstrates the lack of consensus in the definition of a blunted SBP response to exercise. In our study, any SBP recorded between rest-standing and rest-standing + 20 mmHg at peak exercise was termed a blunted response and hence fell in group II. Group III were all those whose SBP dropped by more than 10 mmHg regardless of an initial rise in blood pressure or not. This figure is supported by the American College of Sports Medicine as a contraindication to continue the exercise.

Cardiac catheterization

Coronary arteriography by the Judkins (1968) percutaneous femoral approach or Sones and Shirey (1962) techniques were usually performed in multiple projections. Left ventricular cineangiography and selective coronary arteriography were recorded on 35-mm film at 60 frames/sec using a cesium iodide image intensifier system. Significant CAD was defined as obstruction of ≥75% in one or more of the major vessels.

Data collection

Data collected for this study was categorized into three groups: 1) Personal Data 2) Catheterization Results 3) Treadmill Test Results.

Statistics:

1- Using descriptive statistics, the study looked at differences between SBP groups for the following indepedent variables: age, gender, medications, previous history of M.I. and PTCA/CABG, resting HR and SBP, exercise HR and SBP, exercise time, ST segment depression, angina, LV class, artery involved, BP category and coronary score.

2- Correlation and a stepwise multiple linear regression analysis were used to see which of the independent variables was the best predictor of severity of CAD as identified by the coronary score of the angiogram.

3- One way ANOVA with Tukey-B post hoc test was used to assess significant differences in CAD severity as described by the Coronary Score (dependent variable) between the 3 SBP groups (independent variable).

The same was done but using the more traditional angiogram scoring system of Single-Double-Triple-Vessel Disease (SDTVD) as the depend variable.

4- Chi-square was performed to evaluate differences between the categorized number of diseased vessels versus the different SBP groups.

5- Two way ANOVA with post hoc parameter estimation test was performed to see if there were any interactions between presence or absence of cardiac medications AND SBP groups in identifying severity of coronary disease.

6- Finally, Chi-square was performed to evaluate differences in post-treadmill treatment patients of the different SBP groups received.

CHAPTER 4

RESULTS

The study population was comprised of 236 patients (173 men and 63 women) with known or suspected CAD. Mean age was 58.7±9.7 years (range 27 to 80). Of the 413 possible patients, 284 (69%) displayed a normal SBP response to exercise (Group I, SBP >20 mmHg), 84 (20%) displayed a blunted response (Group II, SBP ≤20 mmHg) and 45 (11%) displayed a drop in SBP (Group III, SBP < 20 mmHg). The clinical features of the patients according to their SBP response to exercise are shown in Table 7.

Predictors of CAD

Correlation and stepwise multiple linear regression were performed on variables that could potentially predict severity of CAD as described by coronary arteriography. Table 8 illustrates correlations with Coronary Score and Table 9 summarizes results of regression (variables entered stepwise while P In value ≤ 0.05) with the coronary score and SDTVD as the

dependent variables. Correlation of SBP groups was not high (-0.25) but is regularly higher than ST depression (-0.22). Again, although R-square values are low, SBP group is atop the list in the regression analysis. Undoubtedly grouping of SBP response during exercise (SBP group) is better than presence of ST depression in predicting severity of CAD.

CAD severity between BPgroups

One way analysis of variance (ANOVA) performed on the Coronary Score (dependent variable) and the categorized systolic blood pressure response (independent variable) followed by post hoc Tukey-B test with significant level of $p<0.05$ demonstrated significant differences in CAD severity between individuals displaying normal SBP responses during exercise (Group I) and those displaying abnormal SBP responses (Group II & III)(Table 10 and 11 and 22). However no significant differences were observed between the two abnormal SBP response categories.

Effect of medication

Two way ANOVA was performed to evaluate the combined effect of medication and SBP groups in explaining Coronary Score (Tables 12, 13, 14 and 15). For categories of β-blockers and Calcium channel blockers, there were no significant differences between patients on or off these drugs in explaining Coronary Score. There were also no interactions between drugs and SBP groups in explaining Coronary Score. The only significant effect was between the SBP groups as already identified by the one-way ANOVA. However, interaction was observed in patients taking nitrates versus those not on nitrate therapy. In patients ***on*** nitrates, there was a significant difference in Coronary Score between SBP Group I(normal SBP)and SBP Group III (SBP drop), and also between the two abnormal SBP Groups II and III.

In those ***not*** taking nitrates, there was significant differences in Coronary Score between all SBP Groups.

Finally, in all patients displaying a drop in BP during exercise (Group III), there was a significant difference in Coronary Score between those taking nitrates (mean Coronary Score = 18) and those not taking nitrates (mean score = 10).

Two-way ANOVA (Tables 16, 17 and 18) were also performed using age, gender and ST segment depression along with SBP groups with Coronary Score as the dependent variable. These variables were selected for this analysis as they were the first four factors to appear in the stepwise multiple linear regression. None of these varibles displayed interactions with SBP groups. There was, however, an overall significant difference in Coronary Score between men (mean CORSCORE =9.96) and women (mean CORSCORE =7.00) and between patients displaying ST segment depression on ECG (mean CORSCORE =9.8±7.9) and those with a negative ECG during exercise (mean CORSCORE =6.4±5.9). No differences were observed between age groups (by decades) for the coronary scores.

Coronary lesion distribution

Results of a the Chi-square analysis between SBP groups and the number of vessels diseased (1 vs 2 vs 3 vs 4) revealed significant differences between groups (Table 19). Group III (drop in SBP) had a higher percentage of 4 vessel disease (53.3%) than did group II and I with 33.3% and 13.3% respectively. Patients in group II had the highest percentage of 3 vessel

disease (42.9%) as compared with groups III and I (28.6%). Finally, group I had the highest percentage of 1 and 2 vessel disease with 53.8% and 48.6% respectively. The mean number of diseased vessels for groups I-III are: 1.7±0.8, 2.1±0.9, 2.5±1.1, respectively.

Subsequent therapy of the different BP groups

Again a Chi-square analysis between SBP groups and the different therapy groups demonstrated a significant difference between groups (Table 20). Over 70% of patients displaying normal BP response during exercise did not receive treatment within 6 months of their tests. Groups II and III received more PTCA (45.5% and 33.3%) than did group I(21.2%). More patients in group III (37.8%) necessitated CABG than those in group II (35.1%) and group I (27%). Finally, no deaths were observed in group I but there was one death in each of groups II and III within 6 months of their treadmill and angiogram tests.

CHAPTER 5

DISCUSSION

In 1977, Morris et al reported that 12% of 189 CAD patients displayed a drop of SBP of more than 10 mmHg during exercise. Weiner et al. (1982) observed 10% of 456 patients to drop their pressure by more than 10 mmHg. The present study indicates that 11% of 413 patients displayed a similar drop in SBP and 20% displayed a blunted SBP response for a total of 31% with abnormal SBP response to exercise (Table 23). These combined figures are slightly higher than reported in previous studies. SanMarco et al. (1980) reported 90 of 378 patients (24%) had an abnormal SBP response to exercise characterized by either a blunted response or a drop in SBP. Certainly the population being tested has an impact on these findings. In this study, the prevalence of CAD in the tested population (mostly men with a mean age 58.7) is much higher than in young asymptomatic subjects with no risk factors.

A number of authors have found parameters other than ST segment depression (i.e. left ventricular ejection fraction, systolic blood pressure etc.) to be predictive of multivessel CAD (SanMarco et al. 1980, Freeman et al. 1988, and Morris et al. 1978). Results of the present study confirm these findings. Regardless of the system used to quantify the angiogram results i.e. Coronary Score or SDTVD, the best predictor of any of these scores is systolic blood pressure. SBP response as grouped according to the study design was consistently the main predictor of severity of CAD. Electrocardiographic ST segment changes was the last variable entered at a "p IN value" of 0.05 in both coronary scores. Although SBP alone may be a predictor of severity of CAD, results of the percent of variance value of 8 to 12% demonstrate that it may not be as good a predictor as the previous studies might imply. SanMarco et al (1980) observed a sensitivity of an abnormal SBP response to exercise for 3 vessel disease of 38.6%, barely superior to the traditional marked ST depression. However, combining SBP and ST depression increased sensitivity to 56.4%. In our study, when ST depression was included in the regression, R-squares of 19 to 27% were obtained, demonstrating an effect similar to SanMarco's study.

There is a significant difference in CAD severity between groups II and III when compared with group I. This demonstrates the importance of a blunted (not only a drop) SBP response to exercise in predicting severity of CAD. With similar grouping of SBP during exercise, Hakki et al. (1986) stated that adding a blunted SBP response to a drop of SBP increased sensitivity. While using a drop in SBP as the only criteria for an abnormal SBP response to exercise, Hammermeister et al. (1983) reported a sensitivity of 15% whereas combining a blunted and a drop in SBP response to exercise SanMarco et al. (1980) obtained a sensitivity of 39%. In the present study, sensitivity to Coronary Score of a drop in SBP alone was 31%, that of a blunted SBP was 46%. When combined, a blunted and a drop in SBP yielded a sensitivity of 56.9%. Even though sensitivity of a drop in SBP is quite high, adding the blunted SBP group increases significantly the sensitivity as observed by SanMarco et al. and as anticipated by Hakki et al. Specificity of this study was 80%, 67% and 57% for group III, group II and groups III and II combined respectively (Table 21).

The Hammermeister et al.'s study also reported an increased prevalence of abnormal SBP with exercise with the number of diseased vessels: 7.4% to

10% to 18% with 1 to 2 to 3 diseased vessels, respectively. Figure 6 shows the distribution of coronary lesions in the different SBP groups of the present study. These data further demonstrates the difference and importance of the blunted SBP response with respect to the normal response. Incidence of 3 vessel disease progresses from 17% to 35% then to 53% from group I to III while at the same time incidence of single vessel disease decreases from 51% to 33% to 29%.

Furthermore, the outcome of procedures performed within 6 months following the treadmill test significantly differs between the SBP groups (Figure 7). From the 97 cases where outcome was known, approximately one third had no procedures performed following their tests (except for possible medical therapy), one third underwent PTCA and the last third underwent CABG. However, 70% of those who had no interventions had normal SBP during the exercise test (group I) and over 70% of those who underwent PTCA or CABG exhibited abnormal SBP responses during their treadmill tests (groups II and III).

Most studies agree that there is no effect from medication on the SBP response to exercise, except possibly for propanolol (Irving et al. 1977; Hakki

et al. 1986; SanMarco et al 1980; Thomson and Keleman 1975). This study reports the same findings for β-blockers and Ca-antagonists. However a difference was observed between patients taking nitrates and those not taking nitrates.

Nitrate drugs are good peripheral vasodilators. In patients receiving nitrate therapy, at rest, the decreased total peripheral resistance (TPR) creates a lowered blood pressure. At onset of exercise, because the peripheral musculature is already vasodilated, the increasing cardiac output may not be sufficient to increase systolic BP as would be expected normally. As exercise progresses and cardiac output further increases, more normal SBP responses are usually observed. Our study did, however, demonstrate an abnormal effect of peak SBP response due to nitrate therapy. Firstly, although all patients displaying a drop in SBP had worse coronary scores, hencc more extensive disease, there was a sighificant difference in coronary score if patients were receiving nitrate therapy or not. Those on therapy had worst coronary scores than those not receiving therapy. This may simply be explained by the fact that patients receiving nitrates had worse vessel disease and more symptoms thus needed enhanced therapy. Secondly, within patients

receiving nitrate therapy, the absence of difference in severity of CAD between group I and group II may be explained by the decreased TPR from therapy. Nitrate therapy may potentially cause an abnormal increase in SBP (blunted response) with exercise which does not necessarily indicate severity of CAD. This would then be viewed as an artificial pharmacologically mediated response as oppose to a pathophysiologic response. Still in the nitrate treated group, a drop in SBP however still carries a strong diagnosis for severe CAD. Lastly, when patients are not on nitrate therapy, the blunted SBP group (group II) is then indicative of severity of CAD as is a drop in SBP.

Hence, the peripheral vasodilatory effect of nitrates may prevent SBP from rising appropriately with exercise and thus explain why a blunted SBP response can occur despite a normal coronary score.

CONCLUSION

As with a definite drop of the BP with exercise, an abnormally low increase of the SBP may indicate severe CAD. Of the 180 patients with 3-vessel disease in Irving et al's study (1977), the mean increase in SBP with exercise was about 20 mmHg, less than half of what was observed in the 85 patients with normal coronaries. They suggested that perhaps the criterion for abnormal BP to exercise (decrease of BP below resting level) is too stringent for the detection of multiple-vessel disease. Using a broader definition of exertional hypotension such as adding failure to increase SBP by ≥10 mmHg (Sanmarco et al. 1980) as opposed to consider strictly a drop in SBP (Hammermeister et al. 1983), may yield higher sensitivity. Sanmarco et al. obtained a sensitivity of 39% whereas Hammermeister et al. obtained 15% (table 21).

In this study, patients demonstrating abnormal SBP responses to exercise (blunted and drop) did undergo more invasive procedures such as PTCA and CABG. This helps support the finding that a blunted SBP response to exercise is a good indicator of severe CAD. It is important to caution

however that this is only true if the patient is not on nitrate therapy.

The prevalence and distribution of CAD in our study population is obviously different than that of a cohort of asymptomatic young men. It is, however, probably similar to that of other major cardiac referral centers. This makes the value of an abnormal systolic blood pressure to exercise highly suggestive of advanced CAD. The present study suggests that adding a blunted SBP response to the more traditional SBP drop with exercise, may uncover greater underlying CAD severity than previously expected. Patients who fall in this blunted SBP category could probably benefit from more intensive diagnostic interventions.

Reference List

Baker, T., Levites, R., & Anderson, G. J. (1976). The Significance of Hypotension During Treadmill Exercise Testing. Circulation, 54,(abstr. Suppl II), II-11.

Ben-Ari, E., Fisman, E. Z., Pines, A., Dlin, R., Kessler, G., & Kellermann, J. J. (1990). Significance of Exertional Hypotension in Apparently Healthy Men: An 8.9-Year Follow-Up. Journal of Cardiopulmonary Rehabilitation, 10, 92-97.

Blair, S. N., Gibbons, L. W., Painter, P., Pate, R. R., Taylor, C. B. & Will, J. (1986). Indication for Stopping an Exercise Test. In Lea and Febiger (Ed.), Guidelines for Exercise Testing and Prescription (p. 21). Philadelphia: American College of Sports Medicine.

Bruce, R. A., DeRouen, T. A., Peterson, D. R., Irving, J. B., Chinn, N., Blake, B., & Hofer, V. (1977). Noninvasive Predictors of Sudden Cardiac Death In Men With Coronary Heart Disease. American Journal of Cardiology, 39, 833-840.

Bruce, R. A., & Hornsten, T. R. (1979). Exercise Stress Testing in Evaluation of Patients With Ischemic Heart Disease. Progressive Cardiovascular Disease, 11, 371-390.

Bruschke, A. V. G., Proudfit, N. L., & Sones, F. M. (1973). Progress Study of 590 Consecutive Nonsurgical Cases of Coronary Disease Followed 5-9 Years. Circulation, 47, 1147-1153.

Burggraf, G. W., & Parker, J. O. (1975). Prognosis in coronary artery disease: Angiographic, hemodynamic, and clinical factors. Circulation, 51, 146-156.

Califf, R. M., Phillips, H.R., Hindman, M. C., Mark, D. B., Lee, K. L., Behar, V. S., Johnson, R. A., Pryor, D. B., Rosati, R. A., Wagner, D. S., & Harrell, F. E. (1985). Prognostic Value of a Coronary Artery Jeopardy Score. Journal of American College of Cardiology, 5, 1055-63.

Canadian Centre for Health Info (Formely Health Division) (1989). Statistics Canada Health Reports, 1(1).

Dubach, P, Froelicher, V. F., Klein, J., Oakes, D., Grover-McKay, M., & Fris, R. (1988). Exercise Induced Hypotension In a Male Population. Circulation, 78, 1380-1387.

Ellestad, M. H. (1989). Reliability of Blood Pressure Recordings. American Journal of Cardiology, 63, 983-985.

European Coronary Surgery Study Group. (1982). Long-term Results of Prospective Randomised Study of Coronary Artery Bypass Surgery in Stable Angina Pectoris. Lancet, 2, 1173-1180.

Fisman, E. Z., Pines, A., Ben-Ari, E., Shiner, R. J., Shae, J., & Kellermen, J. J. (1989). Left Ventricular Exercise Echocardiographic Abnormalities in Apparently Healthy Men With Exertional Hypotension. American Journal of Cardiology, 63, 81-85.

Fox, E., Bowers, R. and Foss, M. (1993). Blood Flow and Gas Transport - Circulatory Mehanics and Hemodynamics. In C. Roger (Ed.), The Physiological Basis for Exercise and Sport. (pp. 261-263). Madison, Wisconsin - Dubuque, Iowa: Brown & Benchmark Publishers.

Fox, K., Ilsley, C. (1984). The Essentials of Exercise Electrocardiography. [Monograph] Current Medical Literature

Freeman, M. R., Chisholm, R. J., & Armstrong, P. W. (1988). Usefulness of Exercise Electrocardiography and Thallium Scintigraphy in Unstable Angina Pectoris in Predicting the Extent and Severity of Coronary Artery Disease. American Journal of Cardiology, 62, 1164-1170.

Friesinger, G.C., Humphries, J.O. and Ross, R.C. (1973). Prognostic significance of coronary arteriography. In Kaltembach, M., Lichtlen, P. and Friesinger, G.C. (eds): Coronary Heart Disease. Stuttgart, George Thieme Verlag.

Gordon, D. J., Ekelund, L, Karon, J. M., Probstfield, J. L., Rubenstein, C., Sheffield, T. L., & Weissfeld, L. (1986). Predictive value of the exercise tolerance test for mortality in North American men: The Lipid Research Clinics Mortality Follow-up Study. Circulation, 74(2), 252-261.

Hakki, A., Munley, B. M., Hadjimiltiades, S., Meissner, M. D., & Iskandrian, A. S. (1986). Determinants of Abnormal Blood Pressure Response to Exercise in Coronary Artery Disease. American Journal of Cardiology, 57, 71-75.

Hammermeister, K. E., DeRouen, T. A., Dodge, H. T., & Zia, M. (1983). Prognostic and Predictive Value of Exertional Hypotension In Suspected Coronary Heart Disease. American Journal of Cardiology, 51, 1261-1266.

Haraphongse, M., Kappagoda, T., Tymchak, W., & Rossall, R. E. (1986). The value of sum of ST segment depression in 12-lead electrocardiogram in relation to change in heart rate during exercise to predict the extent of coronary artery disease. Canadian Journal of Cardiology, 2(2), 64-67.

Hollenberg, M., Budge, W. R., Wisneski, J. A., & Gertz, E. W. (1980). Treadmill Score Quantifies Electrocardiographic Response to Exercise and Improves Test Accuracy and Reproducibility. Circulation, 61, 276-285.

Hollenberg, M., Zoltick, J. M., Go, M., Yaney, S. F., Daniels, W., Davis, R. C., & Bedynek, J. L. (1985). Comparison of a Quantitative Treadmill Exercise Score With Standard Electrocardiographic Criteria In Screening Asymptomatic Young Men For Coroanry Artery Disease. New England Journal of Medicine, 313, 600-606.

Irving, J. B., & Bruce, R. A. (1977). Exertional Hypotension and Postexertional Ventricular Fibrillation. American Journal of Cardiology, 39, 849-851.

Irving, J. B., Bruce, R. A., & DeRouen, T. A. (1977). Variations in and Significance of Systolic Pressure During Maximal Exercise (Treadmill) Testing. American Journal of Cardiology, 39, 841-848.

Jengo, J. A., Oren, V., Conant, R., Brizendine, M., Nelson, T., Uszler, J. M., & Mena, I. (1979). Effects of Maximal Exercise Stress On Left Ventricular Function In Patients With Coronary Artery Disease Using First Pass Radionuclide Angiocardiography. Circulation, 59, 60-65.

Leaman, D. M., Brower, R. W., Meester, G. T., Serruys, P., & Van Den Brand, M. (1981). Coronary Artery Atherosclerosis: Severity of the Disease, Severity of Angina Pectoris and Compromised Left Ventricular Function. Circulation, 2, 285-292.

Lester, F. M., Shefield, L. T., Trammel, P., & Reeves, T. J. (1968). The Effect of Age Athletic Training on the Maximal Heart Rate During Muscular Exercise. American Heart Journal, 76, 370-376.

Levitas, R., Baker, T., & Anderson, G. J. (1978). The significance of hypotension developing during treadmill exercise testing. American Heart Journal, 95(6), 747-753.

Li, W., Riggins, R. C., & Anderson, R. P. (1979). Reversal of Exertional Hypotension After Coronary Bypass Grafting. American Journal of Cardiology, 44, 607-611.

Logan, G. A., & Bruce, R. A. (1958). Atypical Pressor Response to Upright Posture and Exercise in Patients With Mitral or Aortic Stenosis. American Journal of Medical Science, 236, 168-174.

Mason, R. E., & Likar, I. (1966) A New System of Multiple Lead Exercise Electrocardiography. American Heart Journal, 71, 196-205.

Miall, W. E. (1982). Systolic or Diastolic Hypertension - Which Matters Most? Clinical and Experimental Hypertesnion - Theory and Practice, A4(7), 1121-1131.

Morris, S. N., Phillips, J. F., Jordan, J. W., & McHenry, P. L. (1978). Incidence and Significance of Decreases in Systolic Blood Pressure During Graded Treadmill Exercise Testing. American Journal of Cardiology, 41, 221-226.

Peterson, R. J., King III, S. B., Fajman, W. A., Douglas, J. S., Gruntzig, A. R., Orias, D. W., & Jones, R. H. (1987). Relation of Coronary Artery Stenosis and Pressure Gradient to Exercise-Induced Ischemia Before and After Coronary Angioplasty. Journal of American College of Cardiology, 10, 253-260.

Rerych, S. K., Scholz, P. M., Newman, G. E., Sabiston, D. C., & Jones, R. H. (1978). Cardiac Function at Rest and During Exercise in Normals and In Patients With Coronary Heart Disease. Annals of Surgery, 187, 449-464.

Saito, F., Kato, K., Hatano, K., Noda, S., Yokota, M., Hayashi, H., & Sotobata, I. (1989). Localization of Coronary Artery Narrowings by Applying R-Wave Amplitude Correction to Exercise-Induced ST Depression in Angina Pectoris and Single-Vessel Coronary Artery Narrowing. American Journal of Cardiology, 63, 807-811.

Sanmarco, M. E., Pontius, S., & Selvester, R. H. (1980). Abnormal Blood Pressure Response and Marked Ischemic ST-segment Depression as Predictors of Severe Coronary Artery Disease. Circulation, 61(3), 572-578.

Sanz, G., Castaner, A., Bertriu, A., Magrina, J., Roig, E., Coll, S., Pare, J. C., & Narro-Lopez, F. (1982). Determinates of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. New England Journal of Medicine, 306, 1065-1070.

Stamler, J., Neaton, J. D., & Wentworth, D. N. (1989). Blood Pressure (Systolic and Diastolic) and Risk of Fatal Coronary Heart Disease. Hypertension, 13(suppl I), I-2-I-12.

Takaro, T., Hultgren, H. N., Lipton, J. J., & Detre, K. M. (1976). The VA Cooperative Randomized Study of Surgery for Coronary Occlusive Disease. Circulation, 54(Suppl III), III-107.

Thomson, P. D. & Kelemen, M. H. (1975). Hypotension Accompanying the Onset of Exertional Angina. Circulation, 52, 28-32.

Vergary, J., Hakki, A. H., Heo, J., & Iskandrian, A. S. (1987). Merits and limitations of quantitative treadmill exercise score. American Heart Journal, 114(4), 819-826.

Von Polnitz, A. & Hofling, B. (1989). Validation of the SpaceLabs Model 90202, a non-invasive, ambulatory blood-pressure monitoring device: intra-arterial and mercury column comparison study. Journal of Ambulatory Monitoring, 2(3), 169-173.

Weiner, D. A., McCabe, C. H., Cutler, S. S., & Ryan, T. J. (1982). Decrease in Systolic Blood Pressure During Exercise Testing: Reproducibility, Response to Coronary Bypass Surgery and Prognostic Significance. American Journal of Cardiology, 49, 1627-1631.

Wolthius, R. A., Froelicher, V. F., Fischer, J., & Triebwasser, J. H. (1977). The Response of Healthy Men to Treadmill Exercise. Circulation, 55(1), 153-157.

Table 1: Causes of false positive exercise treadmill tests
1. Vasoregulatory asthenia
2. Reynold's syndrome
3. Syndrome X
4. Hyperventilation and posture
5. Respiration
6. Pre-existing abnormal resting ECG
7. Cardiac hypertrophy
8. Wolff-Parkinson-White syndrome
9. Drugs (i.e. digitalis)
10. Cardiomyopathy
11. Mitral valve prolapse
12. Sudden intense exercise
13. Pericardial disorder
14. Technical or observer error

Table 2:	Causes of false negative exercise treadmill tests
1. Failure to reach an adequate exercise workload	
2. Insufficient number of leads to detect ECG changes	
3. Failure to use other information such as SBP drop, symptoms HR response etc..., in test interpretation	
4. Single vessel disease	
5. Good collateral circulation	
6. Musculoskeletal limitations before cardiac abnormalities occur	
7. Technical or observer error	

Table3:	Classification on grading of coronary arterial disease by angiography (American Heart Association)
Normal Lumen	lumen appears perfectly smooth and even; no restriction, indentation, loss of density or sudden bulging.
25%	lumen diameter is reduced by one fourth its former width.
50%	lumen diameter is reduced to one half its former width.
75%	lumen diameter is reduced to one fourth its former width.
90%	lumen appears to be reduced to about one tenth its former diameter.
99%	lumen appears to be almost totally bliterated but some contrast still passes through the obstruction.
100% (occlusion)	total obstruction of a vessel without any filling of the distal segment from the proximal portion.

Table 4: Characteristics of the Bruce Treadmill Protocol

Time (min)	Stage	Speed (mph)	Grade (%)	KPM
3	1	1.7	10	450
3	2	2.5	12	740
3	3	3.4	14	1,000
3	4	4.2	16	1,450
3	5	5	18	

Table 5:	Contraindications to pursue the treadmill Exercise Test

1. Fatigue
2. Failure of monitoring equipment
3. Any peripheral circulatory insufficiency
   - dyspnea
   - cyanosis
   - pallor
   - confusion
   - nausea
   - light-headedness
4. Onset of angina with exercise
5. Symptomatic supraventricular tachycardia
6. ST displacement (> than 3 mm horizontal or downsloping from rest)
7. Ventricular tachycardia (3 or more consecutive PVC's)
8. Exercise induced LBBB or RBBB
9. Onset of second and/or third degree heart block
10. R on T PVCs
11. Frequent unifocal PVCs (Greater than 30% of the complexes)
12. Frequent multifocal PVCs (Greater than 30% of the complexes)
13. Couplets (greater than 2/min)
14. Increase in HR over 20 bpm above standing resting heart rate for MI patients
15. Drop of 10 mmHg or more in SBP
16. Excessive BP rise: SBP > 250, DBP > 120
17. Inappropriate bradycardia (drop of 10 bpm)

Table 6: Predicted Maximal Heart Rates by Age and Recommended Target Heart Rates for Submaximal Exercise Testing

Age (yrs)	20	25	30	35	40	45	50	55	60	65	70	75	80
Maximal HR	197	195	193	191	189	187	184	182	180	178	176	174	172
90% of MaxHR	177	175	173	172	170	168	166	164	162	160	158	157	155
85% of MaxHR	167	166	164	162	161	156	156	155	153	151	150	148	146

Table 7: Characteristics of Patients According to SBP Response to Exercise

	Group I (n=107)	Group II (n=84)	Group III (n=45)	All Groups (n=236)
Age (yrs)	57	59	60	58.7
Men	81 (76)	55 (66)	37 (82)	173 (73)
Height (cm)	179	168	170	169
Weight (kg)	77	76	78	77
BSA (m2)	1.86	1.84	1.87	1.85
Cardiac medications				
On beta-blockers	21 (20)	27 (40)	15 (33)	63 (27)
On calcium-blockers	38 (36)	22 (32)	12 (27)	72 (31)
On nitrates	16 (15)	7 (10)	8 (18)	31 (13)

Number in parentheses are percents of patients.

Table 8: Results of correlation between Coronary Score and the studied independent variables

Variable	Correlation	P (1-tailed)
Delta SBP	-0.2581	0.000
SBP group	-0.2518	0.000
ST dep	-0.2292	0.000
SBP peak	-0.2184	0.000
Delta HR	-0.1753	0.004
Sex	-0.1616	0.007
Ex. Time	-0.1285	0.025
Age	0.1271	0.026
HR peak	-0.1241	0.029
Angina	-0.0961	0.071
LV class	-0.0319	0.339

Table 9: Results of the Stepwise Multiple Linear Regression for Angiographic Scores (dependent variables) and All the Independent Variables

Coronary Score			SDT Vessel Disease Score		
Step	Variable	R-square	Step	Variable	R-square
1	SBP Group	0.08	1	SBP Group	0.12
2	Sex	0.17	2	Sex	0.17
3	ST dep	0.2	3	Ex. Time	0.25
-			4	ST dep	0.27

data entered at a p 'IN' value < 0.05

Table 10: One Way ANOVA of Coronary Score (dependent variable) with SBP Groups (independent variable)

Source	SS	df	MS	F obs	F prob
Between Groups	842	2	421	7.86	* 0.0005
Within Groups	12434	232	53		
Total	13276	234			

* $p < 0.05$

Table 11: Tukey Post Hoc Analysis of the ANOVA Between Coronary Score and SBP Groups

SBP Group	Group I	Group II	Group III
Group I			
Group II	*		
Group III	*		

* $p < 0.05$

Table 12: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and Beta-blocker Drug (independent variables)

Source of Variation	SS	df	MS	F obs	F prob
Main Effects	742	3	247	4.594	0.004
SBP Groups	728	2	364	6.764	0.001 *
Beta-blocker	9	1	9	0.172	0.679
Two-way Interactions					
SBP Groups - Beta-blockers	101	2	50	0.942	0.391
Explained	944	5	188	3.505	0.005
Residual	12332	229	54		
Total	13276	234	57		

* $p < 0.05$

Table 13: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and Calcium Channel Blocker Drug (independent variables)

Source of Variation	SS	df	MS	F obs	F prob
Main Effects	980	3	327	6.129	0.001
SBP Groups	976	2	488	9.156	0.000 *
Calcium blocker	27	1	27	0.511	0.475
Two-way Interactions					
SBP Groups - Calcium blocker	233	2	116	2.182	0.115
Explained	1075	5	215	4.034	0.002
Residual	12201	229	53		
Total	13276	234	57		

* $p < 0.05$

Table 14: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and Nitrate Drugs (independent variables)

Source of Variation	SS	df	MS	F obs	F prob	
Main Effects	1146	3	382	7.307	0.000	
SBP Groups	1129	2	564	10.798	0.000	*
Nitrates	83	1	83	1.596	0.208	
Two-way Interactions						
SBP Groups - Nitrates	431	2	216	4.127	0.017	*
Explained	1305	5	261	4.994	0.000	
Residual	11971	229	52			
Total	13276	234	57			

* $p < 0.05$

Table 15: General Factorial ANOVA to Assess Post Hoc Interaction between SBP Groups and Nitrate Drugs

Source of Variation	SS	df	MS	F obs	F prob	
SBP Groups	1128.9	1	1129	21.59	3.000	*
A at B1	867.3	1	867.3	16.59	3.000	*
A at B2	432.6	1	432.6	8.27	3.000	*
Nitrate Drugs	83.4	2	41.7	0.797	3.840	
B at A1	18.9	2	9.47	0.18	3.840	
B at A2	10.8	2	5.41	0.1	3.840	
B at A3	432.6	2	216	4.13	3.840	*
AB	431.5	2	215.8	4.12		*
Residual	11970.8	229	52.27			

* $p < 0.05$

Table 16: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and Age (independent variables)

Source of Variation	SS	df	MS	F obs	F prob
Within+Residual	11590	218	53.17		
SBP Groups	810	2	404.95	7.62	0.001 *
Age	435	5	87.06	1.64	0.151
SBP Groups by Age	346	7	49.37	0.93	0.485
Model	1591	14	113.63	2.14	0.011
Total	13181	232	56.81		

* $p < 0.05$

Table 17: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and Gender (independent variables)

Source of Variation	SS	df	MS	F obs	F prob	
Within+Residual	12057	229	52.65			
SBP Groups	606	2	303.22	5.76	0.004	*
Sex	306	1	305.99	5.81	0.017	*
SBP Groups by Sex	37	2	18.70	0.36	0.701	
Model	1219	5	243.79	4.63	0.000	
Total	13276	234	56.74			

* $p < 0.05$

Table 18: Two Way ANOVA of Coronary Score (dependent variable) with SBP Groups and ST Segment Depression (independent variables)

Source of Variation	SS	df	MS	F obs	F prob	
Main Effects	1186	3	395	7.999	0.000	
SBP Groups	368	2	184	3.725	0.026	*
ST depression	407	1	407	8.224	0.005	*
Two-way Interactions						
SBP Groups - ST depression	45	2	22	0.457	0.634	
Explained	1197	5	239	4.842	0.000	
Residual	11225	227	49			
Total	12422	232	54			

* $p < 0.05$

Table 19: Chi-square Analysis of SBP Groups with Number of Vessels Diseased

SBP Group	No. Diseased Vessels 1	2	3	4
I	42 (45)	34 (36)	16 (17)	2 (2)
II	26 (32)	27 (33)	24 (29)	5 (6)
III	10 (23)	9 (21)	16 (37)	8 (19)

Numbers in parentheses are percents of patients

Chi-square	Value	df	Significance	
Pearson	23.75	6	0.00058	*

* $p < 0.05$

Table 20: Chi-square Analysis of the Treatment Outcome for Patients in the Different SBP Groups

Treatment	SBP Group I	II	III
None	19 (70)	5 (18)	3 (11)
PTCA	7 (21)	15 (46)	11 (33)
CABG	10 (27)	13 (35)	14 (39)
Transplant	1	0	0
Death	0	1	1

Numbers in parentheses are percents of patients

Chi-square	Value	df	Significance	
Pearson	21.62	8	0.00567	*

* $p < 0.05$

Table 21: Comparison of Reported Sensitivity of SBP Response to Exercise

Authors	Sensitivity	Specificity
SanMarco et al. (1980)(+)	39%	
combined with ST depression	56.40%	
Hammermeister et al. (1983)(*)	15%	
Current study (+)	drop = 31% blunted = 46% combined = 56.9%	drop = 80% blunted = 67% combined = 57%

(*) only patients with exertional SBP drop were studied.

(+) patients with blunted SBP response were included.

Table 21b Table Showing Sensitivity and Specificity of the Present Study

	Blunted SBP	SBP Drop	Total
True Positive	69	38	107
True Negative	n/a	n/a	20
False Positive	10	5	15
False Negative	n/a	n/a	81
Sensitivity	31.5	31.9	56.9
Specificity	87	80	57

All values are percentages

Table 22: Summary of Exercise and Angiographic Results According to SBP Response to Exercise

		Group I n=107	Group II n=84	Group III n=64	Total n=236
Peak Ex HR	(bpm) ***	150 (22)	142 (27)	132 (27)	144 (24)
Rest Stand SBP	(mmHg) **	142 (22)	152 (26)	153 (24)	148 (24)
Peak Ex SBP	(mmHg) **	183 (27)	162 (62)	161 (29)	171 (29)
Ex Duration	(sec) **	414 (116)	370 (108)	360 (113)	388 (115)
Angina	*	44 (41%)	44 (52%)	29 (66%)	117 (50%)
ST Depression	*	51 (48%)	53 (63%)	35 (80%)	139 (59%)
No. Diseased Vessels	*	1.6 (1.2)	2.3 (1.6)	3.0 (2.2)	2.1 (1.6)
Coronary Score	**	6.7 (6.6)	9.3 (7.1)	11.7 (8.5)	8.6 (7.5)

* Chi-square between groups at $p<0.05$

** $p<0.05$, Group I vs Groups II or III

*** $p<0.05$, Between all Groups

Ex. stands for exercise

Unless stated otherwise, numbers in parentheses are standard deviations

Table 23: Percentages of Patients with a Drop or Blunted SBP Response in Previous Studies

Authors	Percent Patients		
	Blunted SBP	Drop in SBP	(n)
Morris et al. (1977)	n/a	12	n=189
Weiner et al. (1982)	n/a	10	n=456
Hammermeister et al. (1983)	n/a	7.5	n=1241
Levites et al. (1978)	n/a	2.7	n=1105
SanMarco et al. (1980)	6.6	17	n=378
Ben-Ari et al. (1990)	3	n/a	n=1347 *
Hakki et al. (1986)	28	13	n=127
Present study	19	10	n=436

* Author studied only non-CAD candidates

Table 24: Mean Coronary Score for Patients ON and OFF Nitrate Therapy for the 3 SBP Groups

Nitrate Therapy	Group I	Group II	Group III ***
ON *	5.75	8.14	18.37
OFF **	6.93	9.44	10.26

* $p<0.05$ Group III vs Group II or I

** $p<0.05$ Between all Groups

*** $p<0.05$ Between patients On & Off Nitrates for SBP Group III

Table25: Summary of Criteria Used to Study Exercise Response to Exercise

Author	Year	BP Criteria	Severity of CAD Criteria
Observation			
1. Irving et al	1977	More CAD if lower max BP	Angiogram (SDT-VD)
2. Freeman et al	1988	same	Angiogram (SDT-VD) + TL Scintigraphy
Exercise Drop ONLY			
1. Hammermeister et al	1983	SBP Drop Below Resting Value	Angiogram (SDT-VD @ 70%)
2. Levites et al	1978	same	Angiogram (SDT-VD @ 75%)
3. Li et al	1979	same	Angiogram (SDT-VD @ 50%)
4. Thomson & Keleman	1975	same	Angiogram (SDT-VD @ 75%)
5. Morris et al	1978	Any Drop > 10 mmHg	Angiogram (SDT-VD @ 75%)
6. Weiner et al	1982	same	Angiogram (SDT-VD @ 70%)
7. Dubach et al	1988	Drop > 20 mmHg or any Drop Below Rest	Angiogram (SDT-VD)
Exercise Flat Responses			
1. SanMarco et al	1980	Flat < 10 mmHg Drop > 20 mmHg	Angiogram (SDT-VD @ 70%)
2. Logan et Bruce	1958	Flat if maxSBP < 10% from rest	
3. Ben-Ari et al (Normals)	1990	Flat < 20 mmHg Drop > 10 mmHg	Angiogram (SDT-VD @ 70%)
4. Hakki et al	1986	Flat < 20 mmHg Drop > 10 mmHg	TL Scintigraphy

Figure 1: Leading causes of deaths in Canada (1987)

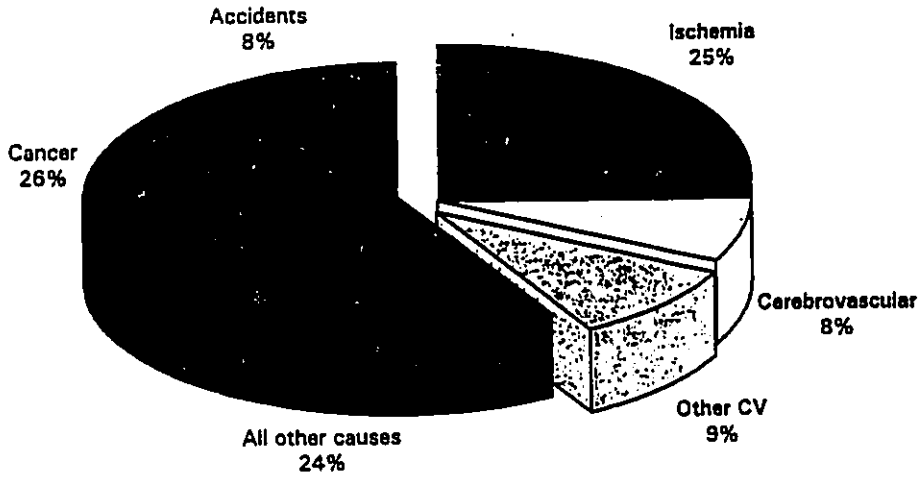
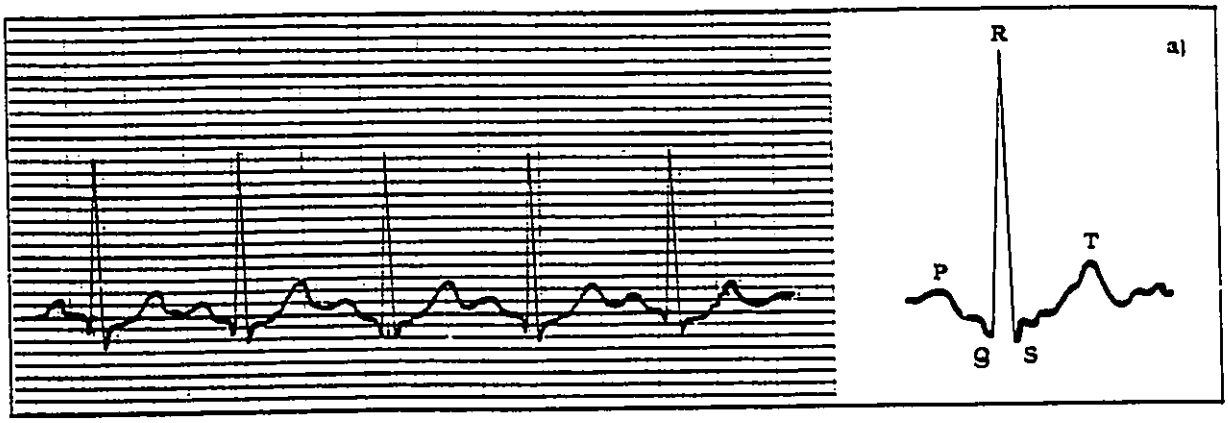


Figure 2: Example of isoelectric ST segment and ST segment depression in lead V5

Isoelectric ST segment



Depressed ST Segment

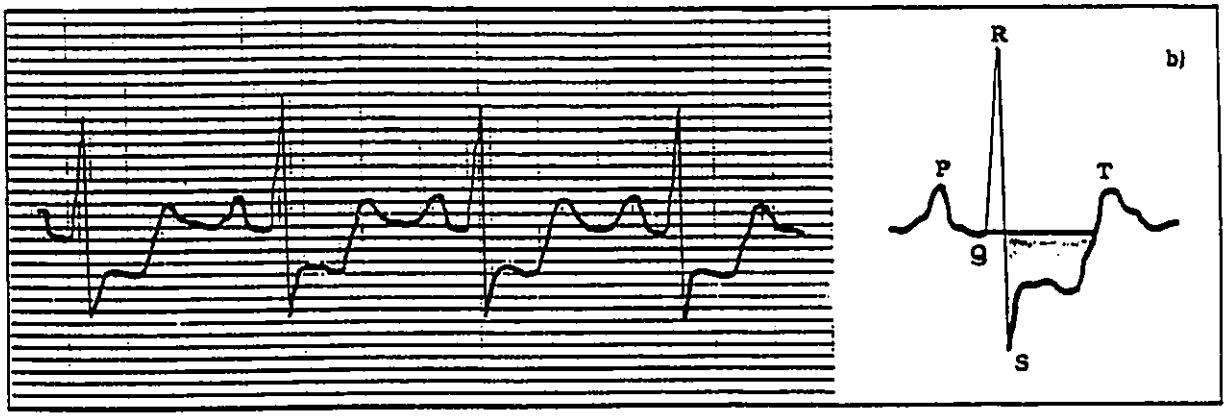


Figure 3: Schematic drawing of the 20 precordial unipolar lead as used in Saito et al's study

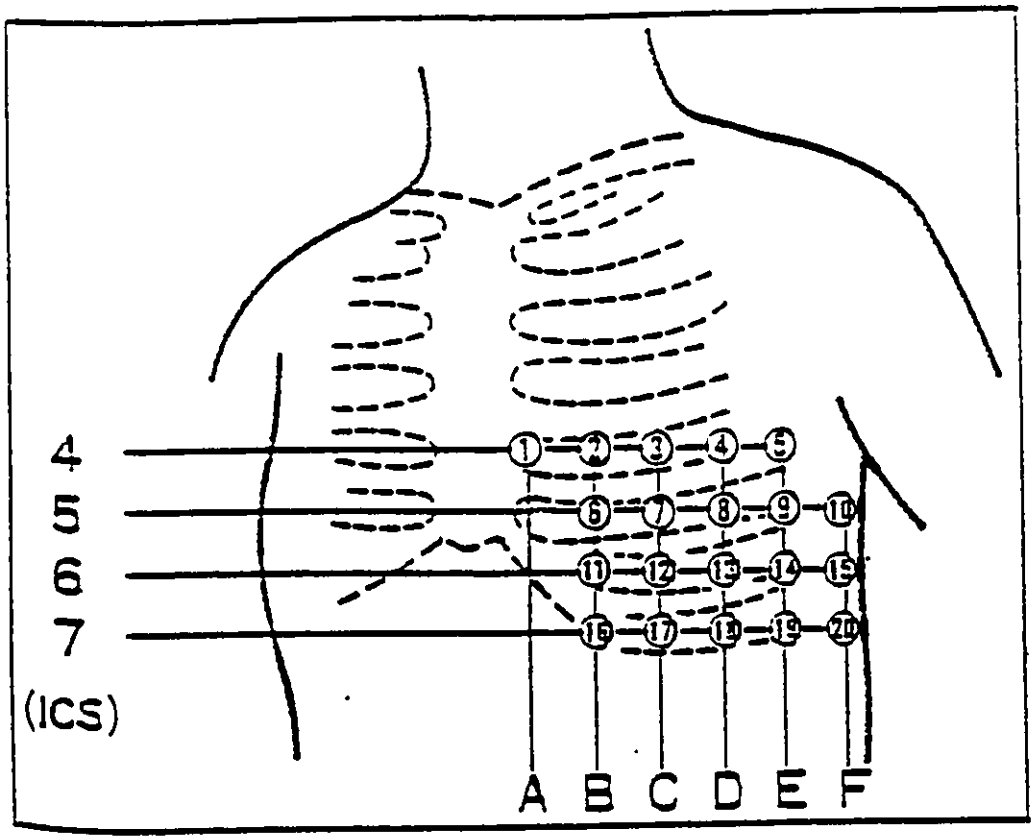


Figure 4: Diagram showing the Jeopardy Score system

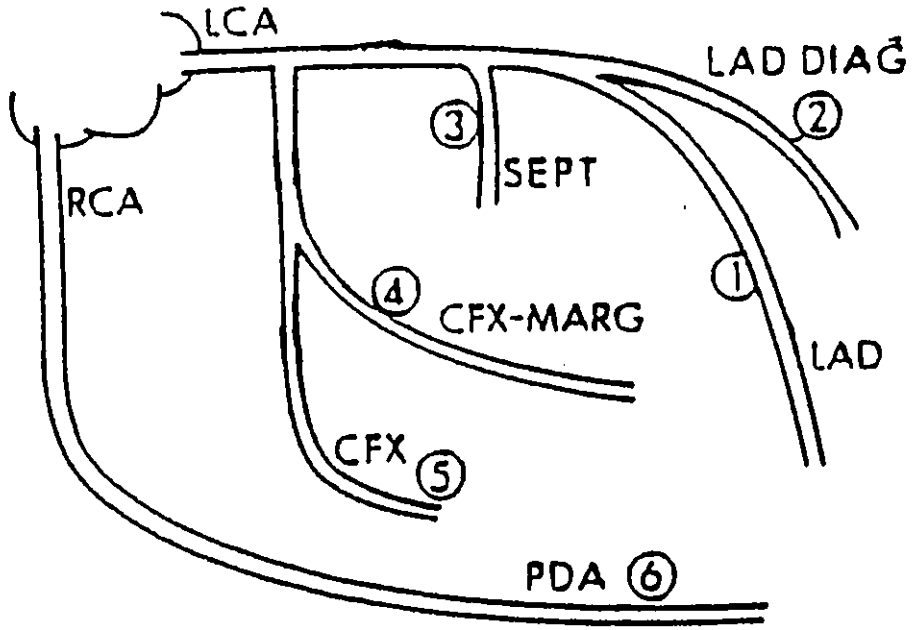
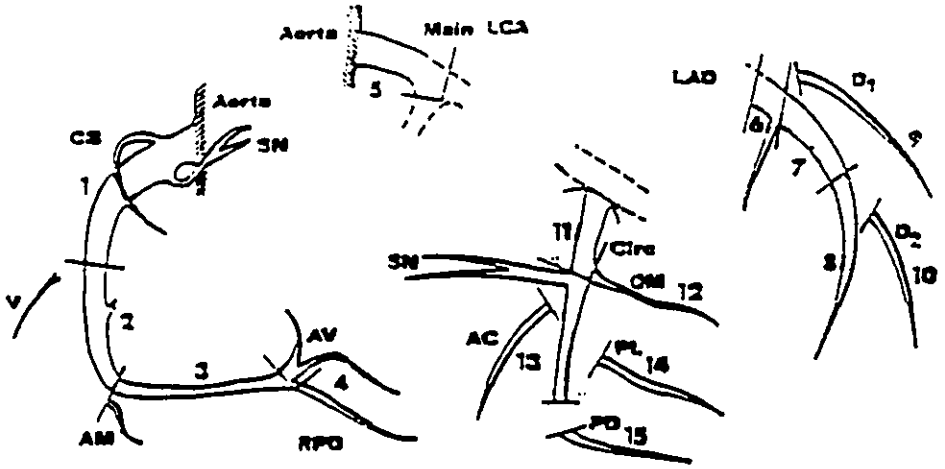


Figure 5: Diagram showing the Coronary Score system



SEGMENT	RIGHT DOMINANT	LEFT DOMINANT
1	1.0	0.0
2		
3		
4		
5	5.0	6.0
6	3.5	3.5
7	2.5	2.5
8	1.0	1.0
9	1.0	1.0
10	0.5	0.5
11	1.5	2.5
12	1.0	1.0
13	0.5	1.5
14	0.5	1.0
15	0.0	1.0

% LUMINAL DIAM. REDUCTION	WEIGHTING FACTOR
70-89	1
90-99	3
100	5

Figure 6: Distribution of Vessels Diseased per SBP Group

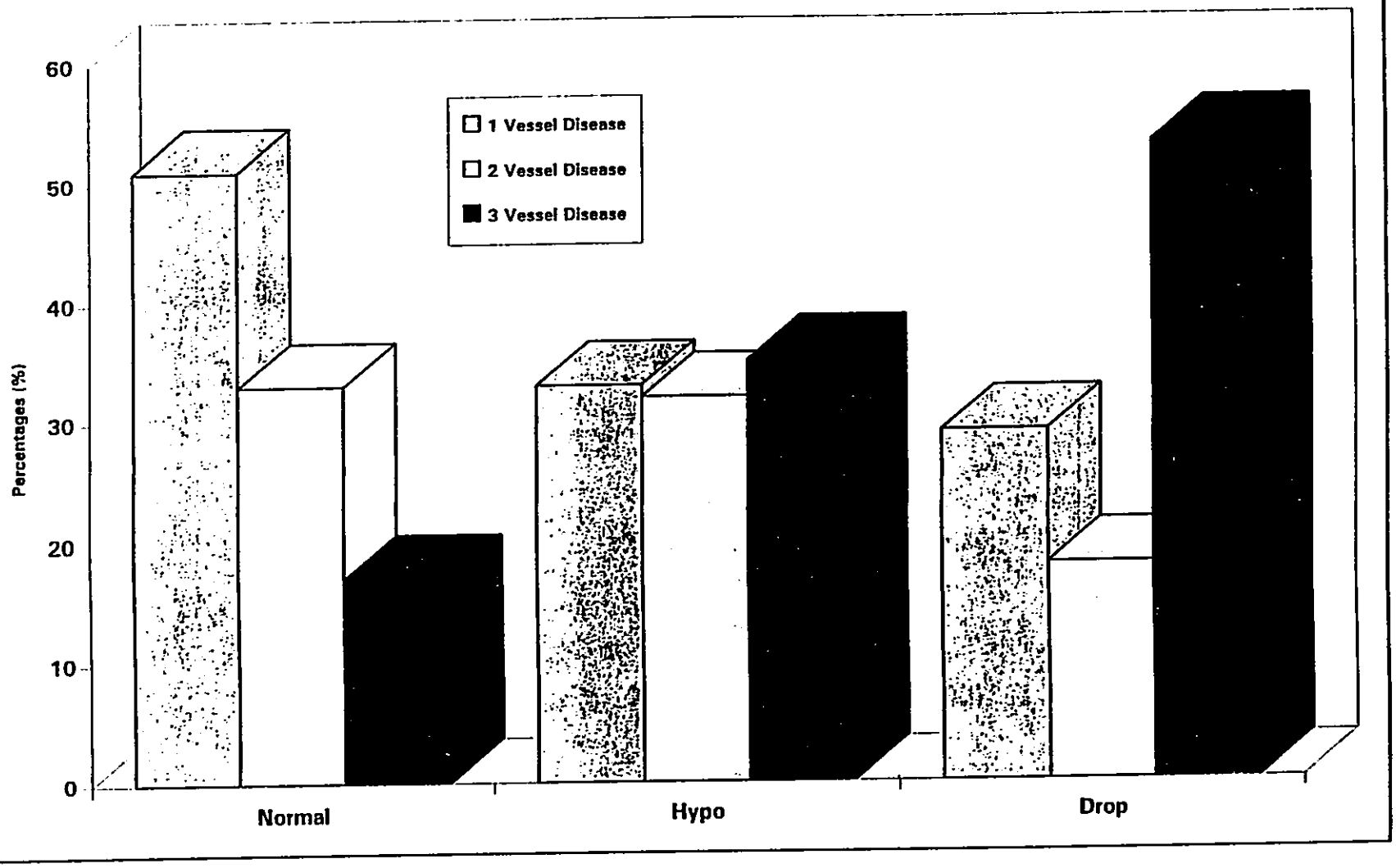


Figure 7: Distribution of therapeutic interventions performed within 6 months of the Treadmill Test for the three SBP groups