

THE QUANTITATIVE ASSESSMENT OF ISCHAEMIC HEART DISEASE:
A STUDY OF THE LEEDS EXERCISE TEST.

A thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester

by

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The Quantitative Assessment of Ischaemic Heart Disease:
A Study of the Leeds Exercise Test. Rachel Lock, B.Sc.

Abstract

Elamin, Mary, Smith & Linden, 1980 suggested that the rate of development of ST segment depression with increasing heart rate during a standardised exercise test could predict the number of coronary arteries (0, 1, 2 or 3) seen to be occluded on the coronary arteriogram. Several attempts to repeat this "Leeds exercise test" had been unsuccessful possibly through inadequate adherence to the Leeds protocol. The work described in this thesis is a further attempt to replicate the Leeds test as precisely as possible after a period of instruction at Leeds.

A Leeds test and coronary arteriography were performed on 49 patients at Groby Road Hospital, Leicester.

Results of identical exercise ECGs analysed at Leeds and Leicester were compared to ensure the same methods were used and highlight potential causes of disparate results through differences in method.

Results of arteriograms assessed at both centres and on two occasions at Leicester were compared to test the reproducibility of the arteriogram and so its value as an index of coronary disease.

A computer assisted method of measuring the exercise ECG was developed.

The results of coronary arteriography and exercise testing were correlated to assess the Leeds test for the prediction of coronary disease severity.

The following main reasons why the Leeds' results have not been repeated at any other centre are proposed:

1. There has been sufficient deviation from the described methods of performing the exercise test and assessing the arteriogram.
2. Patient variables (drug regime and cardiac complications other than coronary disease) may affect the ST/HR slope.
3. There is a large variance associated with the arteriogram result and the estimate of the ST/HR slope.
4. It is questionable that an exact correlation can occur between the results of exercise testing and coronary arteriography. Also, a 3 vessel disease terminology to quantify coronary disease is inadequate.

It is recognised that the maximal ST/HR slope is an improved index of myocardial ischaemia which has probably had limited acceptance through being assessed against arteriogram results in terms of 0, 1, 2, and 3 vessel disease.

Finally, having highlighted the limitations of exercise testing and coronary arteriography, the potential of nuclear magnetic resonance in the quantitative and qualitative assessment of ischaemic heart disease in the future is addressed.

Dedicated to my father,

J.A. Lock, B.Sc., Ph.D., F.P.S.

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THE QUANTITATIVE ASSESSMENT OF ISCHAEMIC HEART DISEASE:
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Introduction

Ischaemic Heart Disease and Coronary Atherosclerosis.

Ischaemic heart disease is the condition where myocardial function is impaired because of inadequate blood flow secondary to narrowing of the coronary arteries (World Health Organisation, 1979). It is the commonest cause of death in most industrial countries. In the United Kingdom, in 1988, it accounted for 28% of all deaths (World Health Statistics Annual, 1988).

The condition is most often caused by coronary atherosclerosis. This is a disease of the epicardial arteries and is characterised by diffuse or focal stenoses which protrude into the arterial lumen by varying degrees. The stenoses are composed of smooth muscle cells containing lipids (mainly cholesterol and its esters) surrounded by a matrix of connective tissue, collagen, elastic fibres and mucopolysaccharides in varying proportions (Velican, 1979).

The aetiology of coronary atherosclerosis has not been fully established however, the major factors believed to be involved in its pathogenesis are:

1. Mechanical stress causing damage of the endothelium.
2. A genetic predisposition to hyperlipidaemia.
3. Toxic factors which cause necrosis of the endothelial cells (eg. nicotine).
4. Factors which increase the adhesion and aggregation of platelets (eg. increased levels of catecholamines).
5. The absence of presumably protective female sex hormones in men.
6. An increased turnover of fat with resultant increase in plasma levels of free fatty acids, cholesterol and low density lipoproteins. (Shepherd & Vanhoutte, 1979).

It has been suggested that the precursors of atherosclerosis are lipid rich lesions; fatty streaks that themselves cause little or no obstruction of the affected artery. These are common in late childhood and may or may

not develop over the years into advanced lesions.

The presence of coronary artery disease is not always synonymous with the occurrence of ischaemic heart disease. For example, about 15% of males aged 30 to 39 years and of females aged 40 to 49 years have coronary stenoses and yet, ischaemic heart disease in these groups is uncommon (Oliver, 1983). Coronary artery disease only manifests as ischaemic heart disease when the coronary artery lumen, and therefore blood flow, is reduced such that myocardial oxygen supply falls short of myocardial oxygen consumption.

Myocardial Contraction, Oxygen Consumption and Oxygen Supply.

Myocardial contraction occurs with the combining of actin and myosin; a process which requires the hydrolysis of adenosine triphosphate (ATP). For continual myocardial contraction, supply of ATP must be continually replenished. In the myocardium, this occurs by aerobic metabolism: resynthesis of ATP occurs through the oxidative phosphorylation of ATP from adenosine diphosphate (ADP) by phosphocreatine (eg. Katz, 1977).

Myocardial oxygen consumption is largely a function of the heart's mechanical activity. This is described by the heart's rate, development of maximum wall tension, inotropic state and muscle fibre shortening against a load (Braunwald, Ross & Sonnenblick, 1976).

Oxygen is supplied to the myocardium by the three major epicardial arteries; the right coronary artery (RCA), the left circumflex (LCFX) and the left anterior descending (LAD). (The coronary circulation is briefly described in Appendix I). Tributaries from these arteries either form a tapering network in the subepicardium or pass through the myocardial wall and form a large plexus of vessels in the subendocardium (Estes, Entman, Dixon, Hackel & Durham, 1966). Because the intramyocardial vessels are compressed by the contracting muscle and the pressure within the ventricles during systole, myocardial perfusion (particularly of the innermost layers) is almost entirely limited to diastole. In the basal state, to obtain sufficient oxygen, extraction of this by the myocardium from the coronary

supply is nearly complete (75 to 80%). Any large increase in oxygen consumption must therefore be, and normally is, met by a corresponding increase in flow rate (Eckenhoff, Hafkenschiel, Landmesser & Harmel, 1947; Katz & Feinberg, 1958). This occurs largely by vasodilation of, in particular, the precapillary arterioles by locally produced metabolites. The most active metabolite in this is thought to be adenosine; a breakdown product of ATP, and a potent vasodilator. As myocardial oxygen consumption increases, there is an increased breakdown of ATP and liberation of adenosine. Local vasodilation increases coronary flow until the increased oxygen consumption is satisfied (Berne & Rubio, 1979; Feigle, 1983). This potential for coronary flow to increase through vasodilation is called the coronary, or vasodilator, reserve (Hoffman, 1984).

The Haemodynamic Effects of a Coronary Stenosis.

An atherosclerotic stenosis, by introducing a pressure drop across its length reduces the driving pressure for blood flow. The main components of this pressure drop are: an increase in viscosity, due to the narrowing of the vessel; and turbulence, caused by the abrupt expansion at the distal end of the stenosis. The relation between the pressure drop across a stenosis, Δp and the viscous (f) and turbulent (s) components of this may be expressed in the following quadratic equation where Q is the rate of coronary flow (Gould, 1985):

$$\Delta p = fQ + sQ^2 \dots \dots \dots (1)$$

(f) and (s) are related to the stenosis geometry:

$$f = \frac{8\pi\mu l}{A_m^2} \dots \dots \dots (2)$$

$$s = \frac{\rho}{2} \left(\frac{1}{A_m} - \frac{1}{A_n} \right)^2 \dots \dots \dots (3)$$

where:

A_n = cross section area of unstenosed vessel

A_m = cross section area of stenosed vessel

l = length of stenosis

μ = viscosity of blood

ρ = density of blood

Substituting terms (2) and (3) in (1) gives:

$$\Delta p = \frac{8\pi\mu l}{A_m^2} \cdot Q + \frac{\rho}{2} \left(\frac{1}{A_m} - \frac{1}{A_n} \right)^2 \cdot Q^2 \dots \dots \dots (4)$$

Alternatively:

$$\Delta p = \frac{128}{\pi} \cdot \frac{\mu l}{d_m^4} \cdot Q + \frac{8\rho}{\pi^2} \left(\frac{1}{d_m^2} - \frac{1}{d_n^2} \right)^2 \cdot Q^2 \dots \dots \dots (5)$$

where:

d_n = diameter of unstenosed vessel

d_m = diameter of stenosed vessel

The greatest factor determining the pressure loss across a stenosis is its minimum lumen diameter (d_m); the inverse 4th power of (d_m) occurs in both terms of equation (4).

Because of the vasodilator reserve and the autoregulatory mechanism coupling myocardial oxygen consumption and blood flow, an increasing pressure drop across a stenosis due to for example an increase in reduction of lumen diameter will have little effect on blood flow until maximum peripheral vasodilation has been reached. Thereafter, further pressure loss will result in a reduced blood flow. Equally, a stenosis, by reducing the coronary reserve to maintain adequate perfusion, compromises the capacity for an increase in blood flow during increased oxygen demand (eg. exercise). In either case, if following coronary restriction, there is a deficit of myocardial oxygen, together with an increase in carbon dioxide tension, an accumulation of lactate and potassium ions and a depletion of ATP; cell function becomes impaired. If ischaemia is severe or prolonged, the impairment may be permanent. This occurs particularly in the subendocardium where the mechanical impedance to blood flow is greatest through compression of the blood vessels by the contracting myocardium and the pressure in the left ventricle.

The Management and Diagnosis of Ischaemic Heart Disease.

Ischaemic heart disease is clinically manifest as angina pectoris, myocardial infarction, heart failure, arrhythmia and primary cardiac arrest. Once diagnosed, survival and quality of existence of a patient with this disease can be improved by:

1. Medical therapy (by either increasing the blood supply to the myocardium and/or reducing myocardial oxygen demand).
2. Percutaneous transluminal angioplasty (PTCA; dilation of the atherosclerotic stenosis).
3. Coronary artery bypass graft surgery (CABG; revascularisation of the myocardium with a vein graft bypass of the coronary stenosis). (Hurst, King, Friesinger, Walter & Morris, 1986).

Often ischaemic heart disease can be correctly diagnosed from a patient's symptoms. However, two commonly used clinical methods of either substantiating the diagnosis and/or attempting to assess the severity of the disease are coronary arteriography and exercise testing.

A. Coronary Arteriography.

Coronary arteriography is the radiographic demonstration of the coronary arteries selectively injected with radiopaque medium. It was introduced by Sones and his colleagues in 1959 and developed as a diagnostic technique for demonstrating the vessel's condition by Sones & Shirey, 1962; Ricketts & Abrams, 1962 and Gensini, 1963.

Currently, the technique involves cardiac catheterisation and the injection of a bolus of radiopaque medium separately into each of the two main coronary arteries; the left and the right. The progress of the medium through the vessels is screened with X-rays from several views and the images are photographed on cine film. The processed film is subsequently reviewed; coronary stenoses are apparent as narrowings shown by the injected bolus of radiopaque medium.

Describing Coronary Disease from the Arteriogram.

Severity of coronary disease is commonly quantified from the arteriogram in terms of 1, 2 or 3 vessel disease where the three vessels are the RCA, the LCFX and the LAD. A vessel is counted as diseased if it supports a stenosis which is thought to be a potential cause of functionally important myocardial ischaemia. This is generally taken as one which occurs in the proximal segment of the artery (before the main branches and affecting a substantial mass of myocardium) and narrows the lumen by (variably described in the literature) more than either 50% or (more commonly) 70 to 75%. These two criteria reflect approximate values of critical stenoses at rest and raised levels of coronary blood flow respectively, where a critical stenosis is one in which any further increase in severity will cause a precipitous fall in perfusion pressure and therefore coronary flow (eg. Young, Cholvin, Kirkeeidee & Roth, 1977).

That a stenosis becomes 'critical' with increasing severity is largely a consequence of the inverse 4th power relation between the pressure loss across the stenosis and the minimum diameter (Equation 5; p.4).

Reported values of critical stenosis determined by experiment (by

measuring blood flow through model arterial stenoses of variable constriction), have varied from 60 to 85% reduction in lumen diameter (Mates, Gupta, Beil & Klocke, 1978).

That such a wide range of values is reported is likely to be a consequence of:

1. The relation between the reduction in lumen diameter and perfusion pressure (and so coronary blood flow), is curvilinear (equation 5; p.4). Therefore, 'critical' more adequately refers to a range of stenosis severity rather than a single value.
2. From studies in vivo, marked reduction in blood flow only occurs when the peripheral bed is maximally vasodilated since initially, local autoregulation will alter peripheral resistance in response to the reduced perfusion pressure to maintain flow. The degree of constriction limiting blood flow will therefore be influenced by the size of the peripheral bed and its vasodilator reserve. In turn, this will be modified by the presence of collateral vessels which, by aiding perfusion of the post stenotic vascular bed, will reduce the vasodilatory stimulus (Roth, Young & Cholvin, 1976; Young, 1979).
3. The pressure drop across a stenosis is dependant on the rate of blood flow, Q , at which it is measured (equation 1; p.3; Young, Cholvin, Kirkeeidee & Roth, 1977).
4. Geometrical features of the stenosis such as (a), length; (b), asymmetry; (c), entrance and exit angles; (d), surface roughness affect, differentially, the pressure gradient across a stenosis (Feldman, Nichols, Pepine & Conti, 1978; Young and Tsai, 1973 [a];[b]; Logan, 1975).

The use of 'greater than 70% reduction in lumen diameter' to define significant coronary disease from the arteriogram can therefore can only be regarded as an approximate index of a critical stenosis. A stenosis described as being greater than this order of severity is generally accepted as one which will cause a precipitous reduction in resting blood flow

(Linden & Mary, 1982) and presumably cause myocardial ischaemia with any increase in myocardial oxygen consumption above basal levels.

The use of the less stringent criteria of '50% reduction in lumen diameter' to define a significant stenosis is related to the fact that a stenosis which may have little or no effect on blood flow at rest, by compromising the vasodilator reserve, may significantly affect the maximum flow possible (Young, 1979). For example, Gould & Lipscomb, 1974 showed in open chest dog preparations that although resting coronary flow did not decrease until the vessel diameter was reduced by about 85%, maximal flow (the coronary flow reserve), began to decrease with a restriction of 30 to 40%. Further, because the pressure loss across a stenosis increases as a function of the square of the flow rate through it, an otherwise innocent stenosis may become flow limiting when flow rate is increased such as during increased myocardial oxygen consumption. For example, by an extrapolation of the data of Young, Cholvin, Kirkeeide & Roth, 1977, presenting the effect of stenoses of varying severity implanted in dog femoral and carotid arteries, a 5 fold increase in blood flow caused a decrease in the value of a critical stenosis (arbitrarily defined as that which reduced the vasodilator reserve by 10%) from about 85% to about 55% reduction in lumen diameter.

The use of a 50% reduction in lumen diameter to describe a critical stenosis, for the same reasons that held for a 70% reduction in diameter can only be taken as a rough index of a critical stenosis. Thus, there can be no single value to distinguish a critical from a non critical stenosis; also, the critical range of stenosis severity will be modified by the size of the peripheral bed and its vasodilator reserve, the existence of collaterals, the rate of blood flow and the geometrical form of the stenosis.

Length and Multiple Stenoses in Series.

Defining the significance of a stenosis only on the basis of the reduction in lumen diameter ignores the potentially significant effect of two features of coronary atherosclerosis:

1. Stenoses are seldom point lesions and can involve variable lengths of an

artery.

2. It is not uncommon in any arterial segment for multiple stenoses to occur in series (Vonruden, Blaisdell, Hall & Thomas, 1964).

1. The length of a coronary stenosis may contribute to the pressure gradient developed across it, albeit to a less extent than that caused by the degree of narrowing. This is shown in the above equation (2; p.3).

Whereas the pressure loss induced by a stenosis is proportional to the inverse 4th power of the minimum diameter, it is directly proportional to the length. Thus, if the stenosis is of substantial length, this may contribute significantly to the pressure gradient developed across it. For example, Feldman, Nichols, Pepine & Conti, 1978 showed that a point stenosis of 40 to 60% luminal narrowing of a coronary artery in the dog had only a negligible effect on blood flow. If however, the length of the restriction was increased from 10 to 15 mm, a significant gradient developed across the stenosis with consequent reduction in blood flow.

2. Based on in vitro pressure flow experiments, if the space between 2 model stenoses is long enough, then the total pressure drop across these is equal to the sum of the pressure drops of the two independent stenoses (Seely & Young, 1976). The space between stenoses for this to apply is dictated by the degree of narrowing and Reynolds number, Re , for the unstenosed vessel (where $Re = \bar{V}dp/\mu$; \bar{V} is the mean flow velocity). With smaller spacing there is an interaction between the haemodynamic effect of the 2 stenoses, and the total pressure drop has a value between the sum of the pressure drops caused by each stenosis independently and that of a single one having the combined length of the two (Seely & Young, 1976; Sabbah & Stein, 1982). An important implication of this is that although an individual stenosis may not be critical, when multiple and in series, the total effect, may be (Sabbah & Stein, 1982). This has been demonstrated in studies involving snare occlusions of the dog coronary artery by Feldman, Nichols, Pepine & Conti, 1978. The reactive hyperaemic response after releasing a 10 second complete occlusion in an

artery with multiple stenoses of 40 to 60% reduction in lumen diameter was comparable to the effect of an approximately 80% reduction in lumen diameter. Thus, the flow effects of stenoses in series are not necessarily determined solely by the most narrow point (Gould & Lipscomb, 1974).

Difficulties in Assessing the Arteriogram.

Customarily, and for this study, assessment of coronary narrowing is based on the visual impression obtained from all arteriographic projections of the stenosis (Brown, Bolson & Dodge, 1982). Severity is described in terms of percent reduction in lumen diameter relative to an adjacent apparently normal vessel segment. Assessment of a coronary stenosis from the arteriogram is complicated by the following:

1. Most atherosclerotic plaques are eccentric rather than concentric (Vlodaver & Edwards, 1971). Thus, they may appear of different severity in different arteriographic planes. Estimation of severity of a stenosis is a translation from what is seen from more than one, 2-dimensional planes to what is thought to occur 3-dimensionally. This is considerably compounded when the lesion is not well portrayed for example because images of vessels overlap or are foreshortened (Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976).
2. Atherosclerotic plaques are frequently superimposed upon diffusely diseased vessel segments and often no portion of the vessel appears normal. There may or may not be post stenotic dilation, an occurrence attributable to turbulence induced arterial wall damage (Foreman & Hutchison, 1970).
3. Plaques may be irregular, multiple, smooth and tapering or the vessel may become suddenly narrowed and remain so in its distal course.

Thus, description of a stenosis as the maximum narrowing relative to an apparently normal segment is not always truly representative (Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976).

Further, a technically poor arteriogram, either from non optimal X-ray

or photographic techniques or inadequate filling of an artery with radiopaque medium will increase the difficulty of assessing the arteriogram.

Although clinical evaluation of stenosis severity from the arteriogram is typically described in terms of the percent reduction in lumen diameter, rather than representing an absolute measurement, it more likely provides a relative grade of severity (Paulin, 1979). For example, reports in the literature often describe using the American Heart Association system, or a modification of this, to define the severity of a stenosis (Paulin, 1979). In this system, coronary stenoses are defined on the following scale of percent reduction in lumen diameter: 0, 25, 50, 75, 90, 99 and 100%. In modified systems, one or more of the seven groups are omitted. Ascribing a grade of severity to a stenosis is likely to be in parallel with the decision as to whether the stenosis is thought significant. For example, a stenosis will be labelled as greater than either 50%, or 70 to 75% (depending on which criterion is being used), secondary to whether it is considered significant (Paulin, 1979).

Observer Variability in Arteriogram Assessment.

Not surprisingly, the visual assessment of disease severity from the arteriogram is associated with considerable inter and intra observer variability (DeRouen, Murray, & Owen, 1977; Detre, Wright, Murphy & Takaro, 1975; Fisher, Judkins, Lesperence, Cameron, Swaye, Ryan, Manyard, Bourassa, Kennedy, Gosselin, Kemp, Faxon, Wexler & Davis, 1982; Galbraith, Murphy & de Soyza, 1978; Sanmarco, Brooks & Blackenhorn, 1978; Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976).

In studies specifically designed to test this, differences in estimates of stenosis severity have been quoted as occurring between ranges as large as 0 and 90% between four independent arteriogram readers (Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976). Also, a panel of eleven observers quoted as an estimate of variation in the assessment of percent reduction in lumen diameter, an average standard deviation of 18% (range 0 to 51.32%; DeRouen, Murray, & Owen, 1977; Detre, Wright, Murphy & Takaro, 1975; Fisher,

Judkins, Lesperence, Cameron, Swaye, Ryan, Maynard, Bourassa, Kennedy, Gosselin, Kemp, Faxon, Wexler & Davis, 1982).

The Accuracy of Assessing the Coronary Arteriogram.

Studies comparing estimates of the extent of lumen narrowing from cine coronary arteriograms with post mortem specimens suggest a tendency to underestimate the severity of disease. This has largely been accounted for by the nature of atherosclerosis in that 1), it can be a diffuse process and 2), residual non occluded lumens are usually eccentric:

1. Because the arteriogram is a lumenogram, a segment of vessel which appears normal may in fact be diffusely atheromatous. Grading the severity of a stenosis against an already diseased and compromised lumen may cause an underestimate of the actual severity of a stenosis.

2. If the lesion is non concentric, there may be considerable variation in the degree of observed stenosis depending on the plane in which the X-rays were projected. The severity of such a lesion will be underestimated, or even seen as normal, unless the projection is along the minor axis of the stenosis lumen. This can also cause an overestimate of severity however, underestimation will occur for a wider range of incident X-ray beam angles. Further, if the X-ray beam is not perpendicular to the longitudinal axis of the vessel, the degree of stenosis may be underestimated through the image of an adjacent normal segment being superimposed on that of the stenosis (Thomas, Davies, Dilly, Dilly & Franc, 1986).

Overestimation of the degree of lumen narrowing has also been reported, but less frequently. This can occur by a real or apparent increase in vessel diameter adjacent to a stenosis by, for example, post stenotic dilation or the superimposition of the image by a normal coronary segment (Trask, Califf, Conley, Kong, Peter, Lee, Hackel & Wagner, 1984). Coronary vasospasm, inadequate filling with radiopaque medium and kinking of the vessel are other causes (Hutchins, Bulkley, Ridolfi, Griffith, Lohr & Piasio, 1977; Murphy, Galbraith & de Soyza, 1979; Isner, Kishel, Kent, Ronan, Ross & Roberts, 1981).

In summary, the coronary arteriogram provides an anatomical impression of the presence and severity of coronary disease by allowing an appreciation of the location and degree of atherosclerotic narrowing within the coronary tree. The assessment of ischaemic heart disease from the arteriogram is limited by the following:

1. Assessing the degree of stenosis is not always easy.
2. It does not always indicate the actual extent of disease.
3. It requires a subjective opinion of whether or not a stenosis is functionally significant. This is subjective because the functional effect of a stenosis cannot be known but only inferred from the rate and manner of flow of contrast medium through the vessel.
4. It is likely to only provide a relative grading of stenosis severity.
5. It is associated with substantial inter and intra observer variability.

B. Exercise Electrocardiography Testing.

Exercise electrocardiography testing involves the continuous recording of the electrocardiogram (ECG) during progressively strenuous exercise. The basis of the test is that the ECG of an ischaemic myocardium commonly has a characteristic depression of the ST segment (figure 1.1b).

It is not sufficient to substantiate a diagnosis of ischaemic heart disease by recording the ECG at rest, because a coronary artery while severely stenosed, may still allow adequate blood flow to meet the metabolic needs of the myocardium through the auto regulatory mechanism already described (Gould, 1978). During exercise however, myocardial oxygen consumption is increased; mostly by an increase in heart rate and inotropic state, and to a lesser extent, an increase in maximal wall tension (marked by an increased blood pressure) and isometric contraction against a load (consequent of an increased stroke volume; Ross, 1972). If the coronary reserve is compromised as in coronary disease, blood flow may not be able to increase sufficiently to meet the increased myocardial demand. The myocardium becomes ischaemic causing changes in the ECG. The principle of the exercise test therefore, is to increase the myocardial demand by exercise and detect any consequent ECG changes of ischaemia.

Exercise testing as a means of diagnosing or assessing the severity of ischaemic heart disease evolved from an empirical discovery: the ECG recorded from a patient during spontaneous attacks of angina pectoris had a typical depression of the ST segment and a lowering or inversion of the T wave (Bousfield, 1918). Further, these changes also occurred in patients in whom angina was specifically precipitated by exercise (Feil & Siegel, 1928).

By 1940, it was generally agreed that angina pectoris and the accompanying ECG changes were a result of myocardial anoxaemia caused by coronary obstruction:

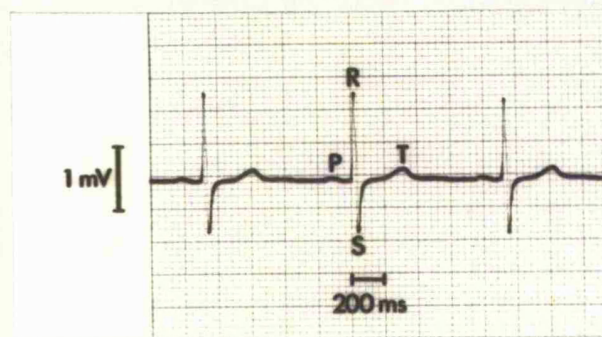
1. Patients with angina were found to have severe coronary occlusions

(Parry, 1979).

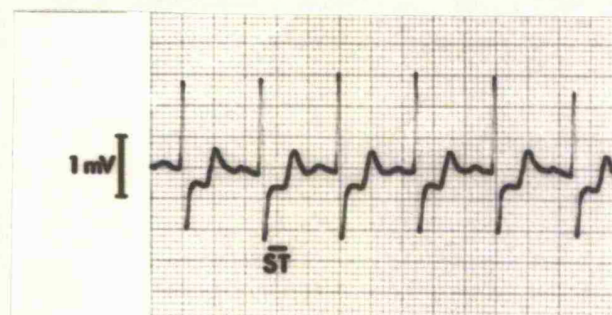
2. ECG changes during attacks of angina induced by general anoxaemia were

Figure 1.1. Depression of the ST segment in a patient with coronary artery disease.

- a). An electrocardiogram complex, PQRS_T, of normal configuration recorded at rest from a patient with coronary artery disease.



- b). The electrocardiogram from the same patient after a period of exercise showing characteristic depression of the ST segment (ST) indicative of myocardial ischaemia.



comparable to those observed in the same patients during exercise induced angina (Riseman, Waller & Brown, 1940).

3. These ECG changes were similar to those observed in dogs after ligation of the coronary arteries (Wood, Wolferth & Livezey, 1931).

That the ECG after exertion could be used to diagnose angina pectoris when this was otherwise doubtful was proposed by Goldhammer & Scherf in 1932. Since then much study has been devoted to this to try and find a means of correctly diagnosing the presence and severity of ischaemic heart disease.

Currently, in clinical practice, exercise testing is performed using various exercise protocols (eg. the Bruce, Sheffield and Balke protocols; Ellestad, 1980). Exercise is typically performed on either a bicycle or treadmill ergometer and the ECG recorded from, most usually, the standard 12 leads. Level of exertion is increased in fixed incremental stages by increasing the resistance to pedalling or the speed and incline of the treadmill. The test may be either maximal or submaximal. A submaximal test is stopped if the patient's heart rate reaches a predetermined value. This is either fixed (eg. 150 bpm.), or 75 to 90 % of the patient's predicted maximum heart rate adjusted for age and sex. In a maximal test, duration of the test is symptom limited. In both, exercise is stopped because either there are definite signs of ischaemia or continued exercise would endanger the patient (Ellestad, 1980).

The most widely used criteria indicating ischaemic heart disease (a positive test), is an ST segment depression of 1.0 mm or more measured at 80 ms after the J point. The test is negative if this level of ST depression has not occurred by the time of maximal or sub maximal exercise. The result of a test in which ST segment depression has not exceeded 1.0 mm and the target heart rate has not been reached, is indeterminant. Severity of disease is usually loosely described by the stage of exercise at which 1.0 mm of ST depression occurred.

The Generation of the Normal ECG and the Ischaemic ST Segment.

1. The Generation of the Normal ECG.

(Schamroth, 1984; West, 1985; Shepherd & Vanhoutte, 1979; Katz, 1977).

The ECG is a record of the summed action currents of all myocardial cells of the heart projected on the body surface.

A normal myocardial cell has a resting transmembrane potential of about -90 mV; with the intracellular potential negative relative to the extracellular space. During myocardial contraction and relaxation, depolarisation and repolarisation, respectively, of the cell membrane occurs through ionic fluxes (chiefly of sodium and potassium) across it. These fluxes constitute the transmembrane action currents which are reflected in the transmembrane action potential (tmap) as illustrated in figure 1.2.

The cardiac action potential is described as having four phases. During depolarisation of the membrane (phase 0), there is an abrupt reversal of polarity with the intracellular potential becoming about $+20$ mV relative to the extracellular space. This is followed by repolarisation which occurs over a longer period. It consists of, in sequence, an early rapid phase (phase 1), a relatively slow phase (phase 2) and then a faster phase (phase 3) before the resting phase (phase 4) is resumed.

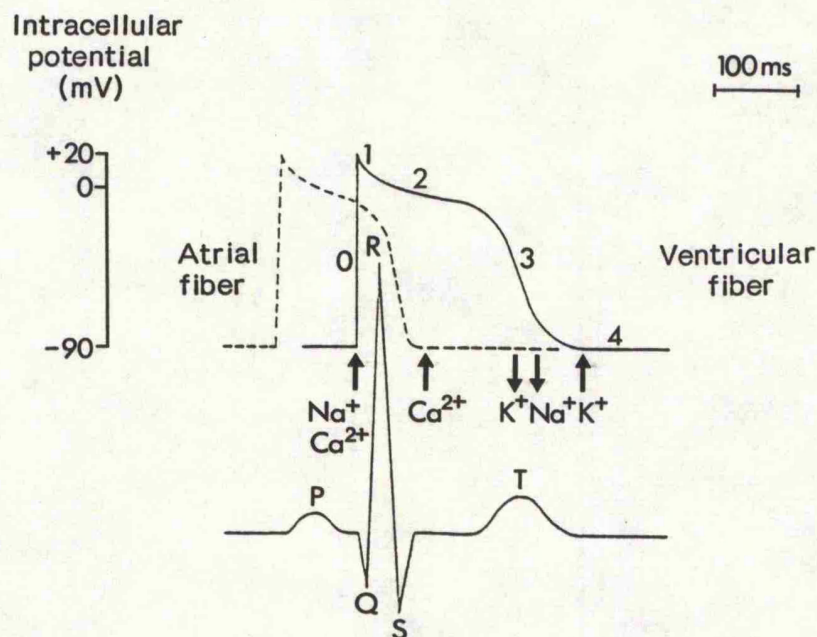
The components of the ECG corresponding to the transmembrane potential are also indicated in figure 1.2. Considering ventricular activity only, the QRS complex corresponds to phase 2; the T wave corresponds to phase 3 and the TP and PQ segments correspond to phase 4 of the action potential.

The stylised generation of the QRST complex is depicted in figure 1.3. This shows the process of depolarisation and repolarisation in a series of 4 ventricular cells hypothetically situated from the endocardium to the epicardium. When the ventricles are in a resting state, there is no difference in surface potential between the myocardial cells (figure 1.3A). No current is generated, reflected in the isoelectric PQ level on the ECG. During activation of the ventricles, depolarisation of the myocardial cells occurs transversely across the ventricular wall from the endocardium to the

Figure 1.2. A simple representation of the temporal relation between the transmembrane action potential of an atrial and ventricular fibre and the extracellular recording of the electrocardiogram (adapted from Shepherd & Vanhoutte, 1979; Goldman, 1982).

The transmembrane action potential of an atrial and ventricular fibre.

The resting membrane potential as shown, is -90 mV. Following excitation, prior to myocardial contraction, rapid depolarisation of the membrane occurs due to an influx of sodium (Na^+) and calcium (Ca^{2+}) ions; phase 0 (0). This is followed by a depolarisation of the membrane which occurs in three phases. The early rapid phase 1 (1) is followed by a relatively slow phase 2 (2) during which there is a slow influx of Ca^{2+} ions. This is then followed by a faster phase 3 of depolarisation (3) where an efflux of K^+ results in a slow return of the intracellular potential to -90 mV. At the end of phase 3, the intracellular potential is maintained by the coupled influx of K^+ and efflux of Na^+ ions.



The temporal relation of the ECG to the atrial and ventricular transmembrane potential.

The P wave on the ECG corresponds to depolarisation of the atrial fibres. The QRS complex corresponds to phase 2 of the transmembrane action potential of the ventricular fibres. The T wave corresponds to phase 3 and the TP and PQ segments correspond to phase 4 of the action potential.

Figure 1.3. Stylised generation of the normal ECG (Adapted from Schamroth, 1984).

Depolarisation and repolarisation of a series of four ventricular cells situated hypothetically from the endocardium to the epicardium is illustrated. The corresponding record obtained from an electrode facing the epicardium and connected to a capacitor coupled ECG amplifier is also shown.

(A) depicts the myocardium at rest. There is no difference in surface potential of the myocardial cells reflected in the isoelectric PQ level of the ECG.

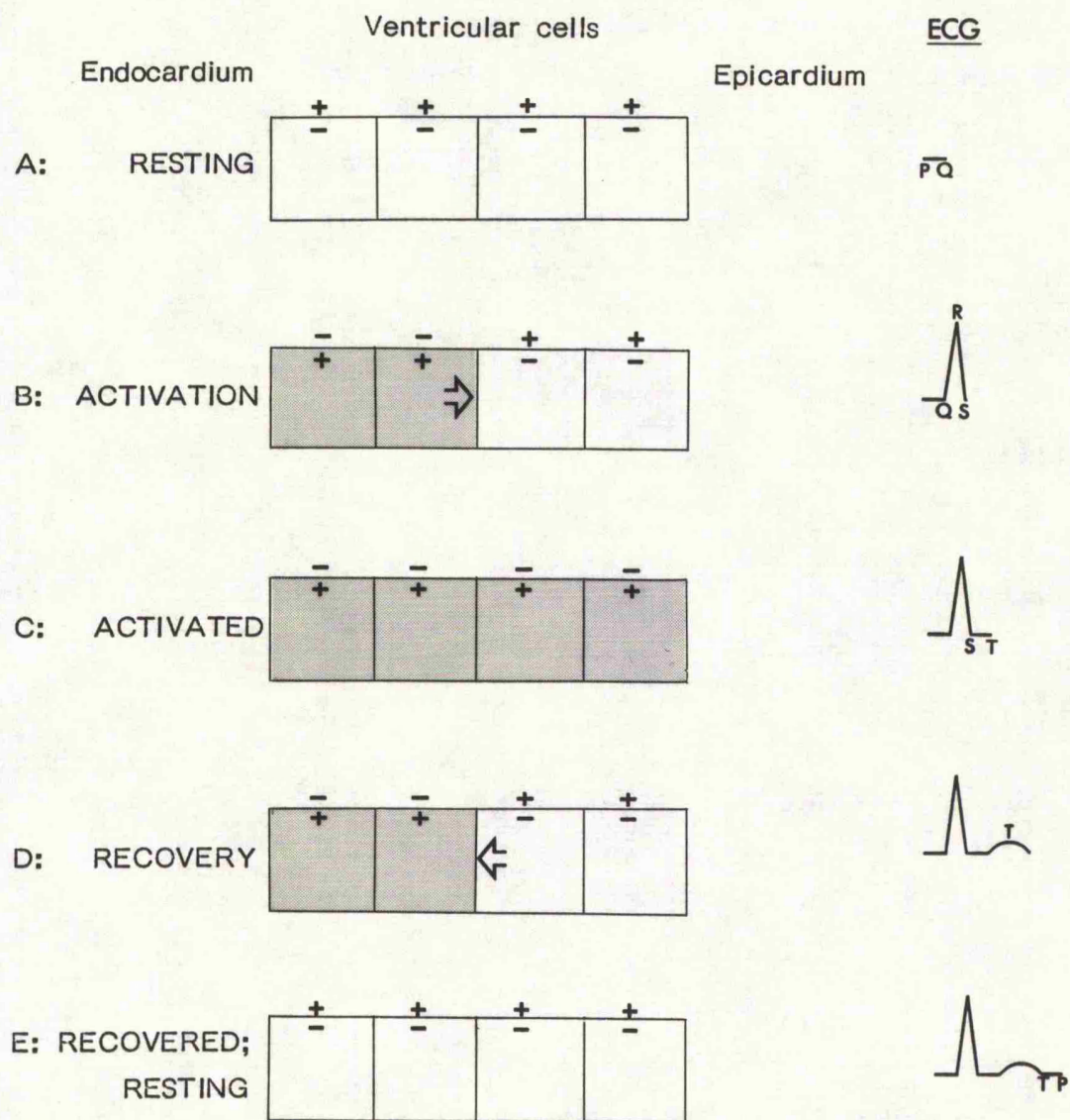
(B) depicts activation of the myocardium from endocardium to epicardium. A cardiac action potential propagated towards an epicardial electrode is reflected in the positive QRS deflection of the ECG.

(C) depicts the fully depolarised myocardial wall. The absence of any surface potential between the myocardial cells is reflected by the isoelectric ST segment of the ECG.

(D) represents repolarisation of the myocardium. This occurs in a direction from epicardium to endocardium and promotes the positively deflected T wave of the ECG.

(E) depicts the recovered myocardium and the corresponding isoelectric TP segment of the ECG.

Figure 1.3. Stylised generation of the normal ECG.



epicardium (Scher & Young, 1956). The propagation of the cardiac action potential in the direction of an epicardial electrode connected to a capacitor coupled ECG amplifier, gives rise to the positive QRS deflection (figure 1.3B). When the cells are fully depolarised (the relatively long plateau phase of the tmap), there is again no difference in surface potential between the myocardial cells. This is represented on the ECG by the isoelectric ST segment (figure 1.3C). Repolarisation occurs across the ventricular wall in the opposite direction to depolarisation; from the epicardium to the endocardium. Reversal of both the effective electrical current and the direction of repolarisation promotes a T wave deflected in the same direction as the QRS complex (figure 1.3D).

2. The Generation of the Ischaemic ST Segment.

(Schamroth, 1984; West, 1985; Shepherd & Vanhoutte, 1979; Katz, 1977; Samson & Scher, 1960; Braunwald & Maroko, 1976; Rakita, Borduas, Rothman & Prinzmetal, 1954; Holland & Brooks, 1977).

The mechanism of the ischaemic displacement of the ST segment is not fully understood. Proposed hypotheses consider it to be a consequence of:

1. During depolarisation of the myocardium, ischaemic cells do not reach the same level of depolarisation as normal cells.
2. Myocardial cells injured by ischaemia usually repolarise more rapidly than normal cells (Samson & Scher, 1960).

It is thought that this is secondary to a loss of cellular potassium by an increased efflux to the extracellular space during inadequate coronary perfusion (Weiss & Shine, 1982). This occurs partly through an outward movement of permeant anions such as lactate and phosphate which build up in the ischaemic myocardial cells and partly by changes in membrane permeability to potassium (Gaspardone, Shine, Seabrooke & Pooie-Wilson, 1986).

During activation of the myocardial cells, a potential difference therefore occurs between ischaemic and non ischaemic areas of myocardium generating a "systolic current of injury" in a direction from the normal to

the ischaemic cells. If this current is directed towards an epicardial electrode, such as in epicardial ischaemia where it is directed from the normal endocardium to the injured epicardium, elevation of the ST segment occurs. If the current of injury is directed away from an epicardial electrode, such as in the case of the more commonly occurring endocardial ischaemia where it is directed from the normal epicardium to the injured endocardium, depression of the ST segment occurs. This is depicted in figure 1.4.

Evidence that ST Segment Displacement is a Result of Myocardial Ischaemia.

That displacement of the ST segment is a consequence of myocardial ischaemia through a reduced coronary blood flow has been demonstrated in many animal studies:

ST elevation and depression has been recorded from epicardial and transmural electrodes following acute occlusion of coronary arteries by Bayley & La Due, 1944; Rakita, Borduas, Rothman & Prinzmetal, 1954; Becker, Ferreira & Thomas, 1973; Samson & Scher, 1960; Khuri, Flaherty, O'Riordan, Pitt, Brawley, Donahoo & Gott, 1975; Lekven, Ilebekk, Fønstellen & Kill, 1975; Geary, Smith & McNamara, 1981; Guyton, McClenathan, Newman & Michaelis, 1977). Further, the degree of ST segment displacement is largest in regions where the reduction in blood flow is the greatest (Rakita, Borduas, Rothman & Prinzmetal, 1954; Becker, Ferreira & Thomas, 1973; Samson & Scher, 1960; Geary, Smith & McNamara, 1981; Guyton, McClenathan, Newman & Michaelis, 1977). ST segment changes have also been shown to correlate with biochemical indices of ischaemia eg. accumulation of lactate, potassium, depletion of ATP and phosphocreatine, a reduction of oxygen tension and an increase in carbon dioxide tension (eg. Braunwald & Maroko, 1976; Lekven, Ilebekk, Fønstellen & Kill, 1975).

That the direction of the ST segment displacement (namely elevation or depression) is determined by the level within the myocardial wall at which the ischaemic region occurs and its transmural extent was demonstrated by Guyton, McClenathan, Newman & Michaelis, 1977 and Rakita, Borduas, Rothman &

Figure 1.4. Stylised generation of the ischaemic ECG (adapted from Schamroth, 1984).

Depolarisation and repolarisation of four ventricular cells situated hypothetically from the endocardium to the epicardium is illustrated where the endocardial cells are ischaemic. The corresponding record obtained from an electrode facing the epicardium and connected to a capacitor coupled ECG amplifier is also shown.

(A) and (B) depict the myocardial cells at rest and activation respectively. This is reflected in the PQRS complex on the ECG as described for figure 1.3 (A) and (B).

In the activated state, because: 1), ischaemic cells do not reach the same level of depolarisation as normal cells and 2), myocardial cells usually repolarise more rapidly than normal cells, the surface potential of the ischaemic cells is effectively more positive than of neighbouring healthy cells. A systolic current of injury therefore develops towards the ischaemic endocardium (1.4C). This is reflected on the ECG by a negative displacement of the ST segment ie. ST segment depression.

Recovery of the myocardium produces a T wave and isoelectric TP segment as described for figure 1.3 (D) and (E).

Ventricular cells

Endocardium Epicardium

A: RESTING

PQ

B: ACTIVATION

R
Q S

C: ACTIVATED

S T

D: RECOVERY

T

E: RECOVERED; RESTING

T P

Prinzmetal, 1954. For example, Rakita et al. recount that an epicardial electrode placed over a region of epicardial ischaemia shows ST elevation whereas an electrode over a region of endocardial ischaemia and separated from this by a layer of non ischaemic epicardium shows ST segment depression. (If the ischaemia becomes transmural - occurring across the whole wall of the myocardium - then ST elevation occurs. This was shown for example, by Guyton, McClenathan, Newman & Michaelis, 1977. By reducing subendocardial blood flow with a coronary constrictor and atrial pacing induced tachycardia, ST depression was recorded from epicardial electrodes. As the coronary pressure distal to the stenosis was progressively reduced, ST segment depression progressively increased until a critical level was reached at which transmural ischaemia occurred marked by a reduction in both endo and epicardial blood flow. This coincided with a rapid change of ST depression to ST elevation.)

On the basis of theoretical modelling of the electrical events in the heart, and their manifestations on the ECG, it has been postulated that the magnitude of ST segment displacement is a function of: the solid angle subtended at the electrode position by the ischaemic boundary, the transmembrane potential of the normal and ischaemic regions and a correction factor for the differences in tissue conductivity (Holland & Brooks, 1977).

Shortcomings of ST Segment Depression as an index of Ischaemic Heart Disease.

Shortcomings of ST segment depression as an index of ischaemic heart disease include:

1. ST segment depression may be caused by other factors which cause myocardial ischaemia at rest or during exercise other than coronary artery disease for example: valve disease, left ventricular hypertrophy and abnormal left ventricular loading such as chronic hypertension (Aronow & Harris, 1975; Harris, Aronow, Parker & Kaplan, 1973; Wong, Kasser & Bruce, 1969).

2. The ST segment depression response may be modified by factors which cause ST segment elevation for example, aneurysm, left ventricular dysfunction and coronary spasm which causes transmural ischaemia (Chaitman, Waters, Theroux & Hanson, 1981; Waters, Chaitman, Bourassa & Tubau, 1980; Caskey & Estes, 1964; Samson & Scher, 1960; Brown, 1981; Papietro, Niess, Paine, Mantle, Rackley, Russel & Rogers, 1980).
3. The pattern of the ST segment may be modified by conduction defects for example bundle branch block where electrical conduction through the heart is defective and the sequence of ventricular depolarisation and repolarisation is abnormal (Rowlands, 1982; Schamroth, 1984).
4. The ST segment response may be modified by various drugs for example:
 - a). Digitalis (LeWinter, Crawford, O'Rourke & Karliner, 1977; Kawai & Hultgren, 1964).
 - b). Calcium channel blockers (Stone, Muller, Turi, Geltman, Jaffe & Braunwald, 1983; Deanfield, Wright & Fox, 1983).
 - c). Beta blockers (these do not alter ST segment depression per se, but by reducing myocardial oxygen consumption for any level of workload, the magnitude of ST depression at the end of an exercise test is generally reduced in patients on this therapy; Fox, Selwyn, Oakley, Jonathan & Shillingford, 1980; DiBianco, Singh, Singh, Katz, Bortz, Gottdiener, Spodick, Laddu & Fletcher, 1980; Gianelly, Treister & Harrison, 1969; Jorgensen, Wang, Wang, Gobel, Nelson & Taylor, 1973).
5. Since the ECG is a vector, the resultant current of injury will only be reflected maximally in the ECG if it occurs in the same plane, and perpendicular to, the recording plane of the electrode.
6. A cancellation of currents of injury occurring in opposite directions may reduce the apparent degree of ST segment depression recorded by an epicardial electrode (eg. Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). This may occur for example, in endocardial ischaemia occurring on opposite walls of the heart, alternatively, where isolated segments within the myocardial wall extend to neither the epicardial nor the

endocardial surface (Holland & Brooks, 1977).

7. The same relative proportion of ischaemic myocardium can produce a larger degree of ST segment depression in a patient with a larger heart. This may cause a disparity in a comparison of absolute measures of ST displacement between subjects.
8. The same magnitude of ST segment depression produced by the same amount of ischaemic myocardium may be attenuated by different degrees in different subjects when recorded at the body surface due to differences in thoracic wall thickness or tissue composition.

The Relative Standing of Coronary Arteriography and Exercise Testing in the Diagnosis of Ischaemic Heart Disease.

As already stated, once diagnosed, survival rate and quality of existence of a patient with ischaemic heart disease can be improved by medical therapy or coronary artery bypass graft (CABG) surgery. Type of treatment, to an extent, depends on the severity of the disease. For example, CABG surgery is generally reserved for patients in whom either medical therapy has failed or there is significant left main stem (before the bifurcation into the LAD and the LCFX) or three vessel disease. (Surgery is thought to improve prognosis over medical therapy only in these subgroups; Goodwin, 1976; Rahimtoola, 1982).

Coronary arteriography is generally, considered to be the standard test for diagnosing the presence and severity of coronary disease. This is because it provides an image of the coronary vessels and any pathological narrowings of these. Coronary arteriography however is an invasive procedure; it requires cardiac catheterisation and intracoronary injection of contrast medium. Mortality rates associated with coronary arteriography have been quoted as ranging from 0.05 to 4 % although the usually accepted rate is 0.1% (Franch, King & Douglas, 1986). Exercise testing on the other hand involves less risk to the patient. Death rates as a result of exercise testing are quoted as ranging from 0.002 to 0.01% (Rochmis & Blackburn, 1971). In addition, it is cheaper by a factor of ten (Elamin, 1983) and less time consuming. Consequently, much work has centred on developing an exercise test which could indicate the presence and severity of ischaemic heart disease so that coronary arteriography could be limited to patients in whom it was essential. This refers, in the main, to patients intended for CABG surgery where arteriography is necessary to establish the location of disease and indicate whether the diseased vessel is suitable for grafting.

An exercise test which could accurately describe the severity of disease would allow the following:

1. Patients with no significant disease in spite of symptoms resembling

angina pectoris could be spared the hazard and trouble of coronary arteriography.

2. Arteriography in patients with single vessel disease could be avoided or delayed according to the patients' response to therapy.
3. Arteriography could be performed early in patients with predicted double or triple vessel disease before waiting for the conventional criteria of failed medical therapy as would be the case with patients with single vessel disease.

The means of assessing the capacity of an exercise test to detect the presence and/or severity of coronary disease has been by comparing indices obtained from the exercise test with the arteriogram result; the latter being used as the accepted standard of disease.

The clinical value of a test is described in terms of its sensitivity, specificity and predictive value (eg. Rowlands, 1982).

The sensitivity of an exercise test is defined as the percentage of patients with coronary disease (according to the arteriogram) who have a positive test result.

The specificity of an exercise test is defined as the percentage of subjects without coronary disease who have a negative test result.

The predictive value of a positive exercise test is defined as the percentage of subjects with a positive result who actually have coronary disease.

The predictive value of a negative exercise test is defined as the percentage of subjects with a negative result who do not have coronary disease.

The Predictive Accuracy of Exercise Testing.

Various types of exercise test have been devised to best predict the presence and/or severity of coronary artery disease. These have varied in terms of exercise protocol, the number and type of ECG leads and the indices used to indicate the presence of disease.

For example, indices of myocardial ischaemia have been measured at

maximal and submaximal exercise and/or at various periods (for example between 30 seconds and 10 minutes) after exercise (Martin & McConahay, 1972; Ascoop, Distelbrink & De Lang, 1977; Berman, Wayne & Cohn, 1978; Chaitman, Bourassa, Wagniart, Corbara & Ferguson, 1978; Chaitman, Waters, Bourassa, Tubau, Wagniart & Ferguson, 1979; Baron, Poole-Wilson & Rickards, 1980; Sanmarco, Pontius & Selvester, 1980 and Goldschlager, Selzer & Cohn, 1976; Ascoop, Distelbrink & De Lang, 1977; Fox, Selwyn & Shillingford, 1979; Hollenberg, Budge, Wisneski & Gertz, 1980; Rijneke, Ascoop & Talmon, 1980; Sketch, Mohiuddin, Nair, Mooss & Runco, 1980).

The types of ECG leads used have included the standard 12 leads or a selection of these (Hollenberg, Budge, Wisneski & Gertz, 1980; Sketch, Mohiuddin, Nair, Mooss & Runco, 1980; Weiner, McCabe & Ryan, 1980; McNeer, Margolis, Lee, Kisslo, Peter, Kong, Behar, Wallace, McCants & Rosati, 1978); various bipolar leads (for example CM5, CC5 and CL; eg. Chaitman & Hanson, 1981; Rijneke, Ascoop & Talmon, 1980; Ascoop, Distelbrink & De Lang, 1977) or a combination of standard and bipolar leads. Body surface mapping has also been tested using from 16 to 120 electrodes (Fox, Selwyn & Shillingford, 1979; Simoons & Block, 1981).

The most extensively studied index of ischaemia obtained from the exercise test, has been the depression of the ST segment. This has been measured at various intervals after the end of the QRS complex (eg. Ascoop, Distelbrink & De Lang, 1977; Goldschlager, Selzer & Cohn, 1976). As already said, the most widely and clinically accepted index of ischaemic heart disease from an exercise test is a depression of the ST segment by 1.0 mm, 80 ms after the J point (Amsterdam & Dressendorfer, 1982).

The Predictive Accuracy of Exercise Tests Reported Before 1980.

According to the review of the reported accuracy of exercise tests between 1971 and 1980 inclusive by Elamin, 1983, no exercise test has been accurate enough to predict, reliably, the presence and severity of coronary artery disease in an individual.

For example, figures 1.5 and 1.6 present, as histograms, the accumulated

results of 7757 reported comparisons between coronary arteriography and the results of exercise testing from 40 studies based on Elamin's review (1983). These are grouped according to whether a significant stenosis was defined as a lumen narrowing of at least 70 to 75% (figure 1.5), or at least 50% (figure 1.6), and classed according to the types of recording leads used. The index of coronary artery disease was a displacement of the ST segment at the end of the exercise test.

The averaged sensitivity in these studies ranged from 59 to 81%; the tests were unable to detect the presence of coronary disease in 19 to 41% patients shown to have coronary disease at arteriography.

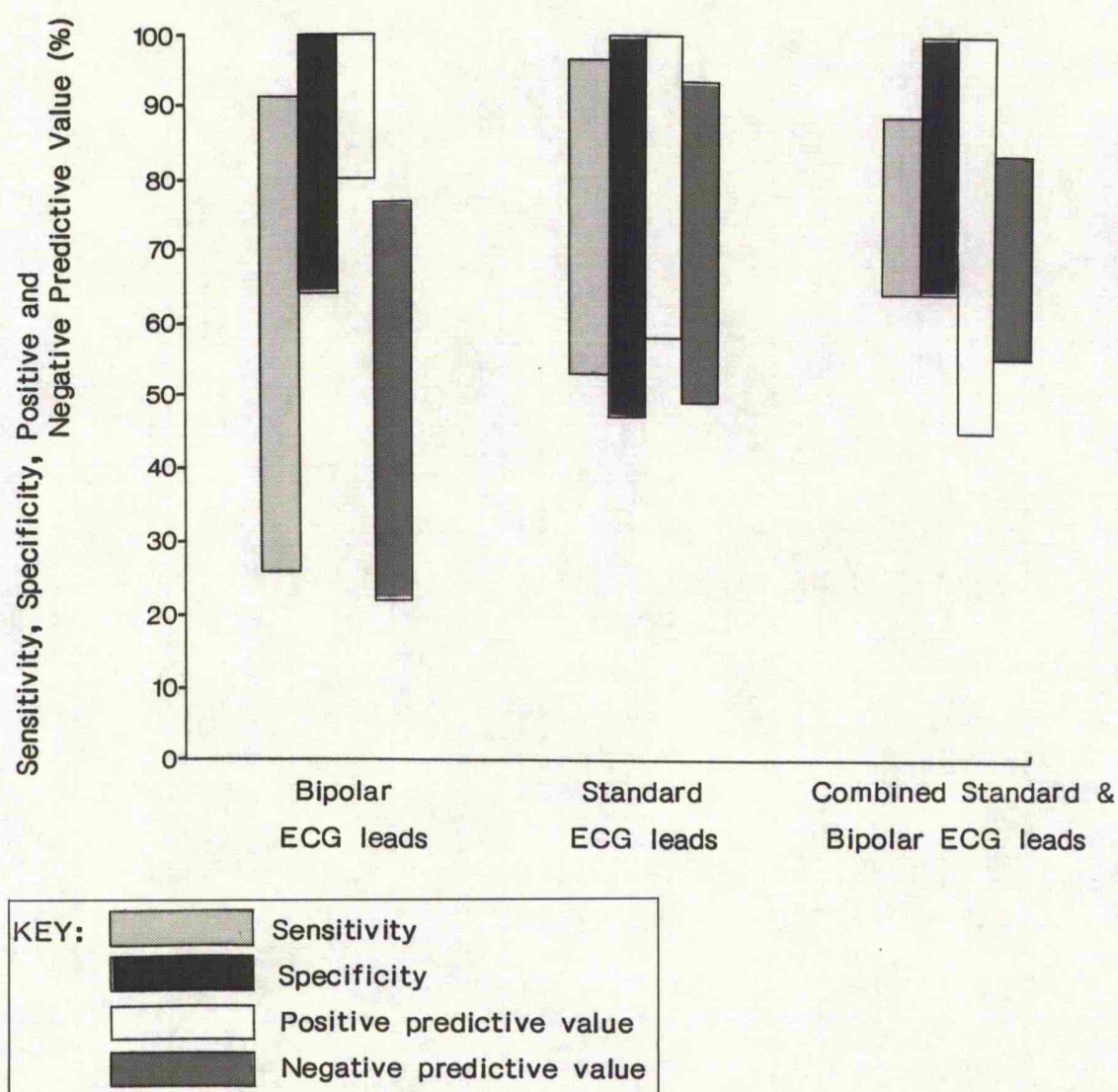
The averaged specificity of the tests ranged from 79 to 86%; the tests were unable to exclude the possibility of coronary disease in 14 to 21% of patients with no angiographically demonstrable disease.

The averaged positive predictive value of the tests ranged from 80 to 94% ie. 6 to 20% of patients with a positive exercise test did not have coronary disease. The averaged negative predictive value ranged from 53 to 72% ie. 28 to 47% of patients with a negative test had coronary disease.

Other lead systems not included in the above review include single unipolar chest leads and multiple praecordial leads. It has been shown that single unipolar chest leads reduce the diagnostic value of exercise testing in a symptomatic population (eg. Chaitman, Bourassa, Wagniart, Corbara & Ferguson, 1978). Conversely, multiple praecordial leads produce better results. For example, Fox, Selwyn & Shillingford, 1979 showed that 0.5 mm ST depression obtained from any of 16 praecordial leads as an index of coronary disease, had a sensitivity and specificity of 95 and 92% respectively. The predictive values for a positive or a negative test result were however, 97 and 85% respectively; the rate of false negative results was 15%.

Other indices used to indicate coronary disease and involving changes in the ST segment other than simply its displacement have included multivariate scores. For example, a score devised by Cohn, Kamm, Feteih, Brand & Goldschlager, 1979, combined the depth and configuration of ST segment

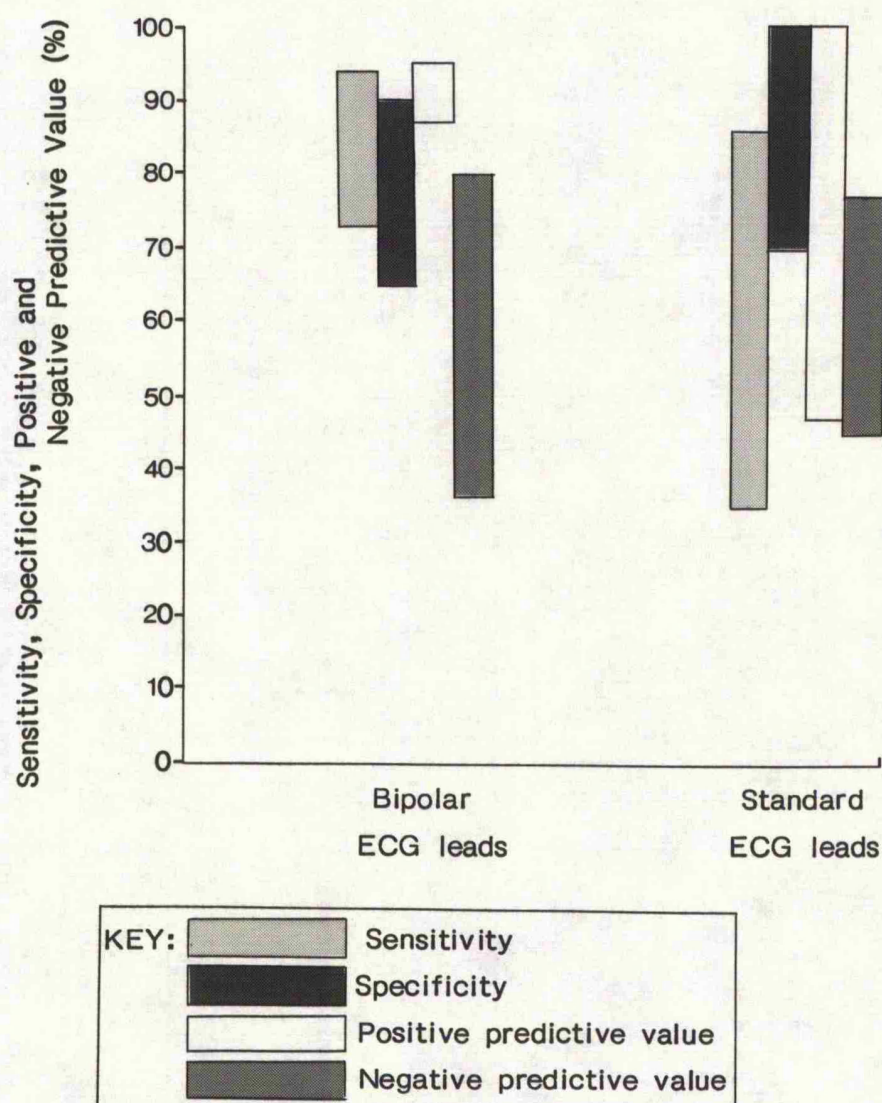
Figure 1.5. Histograms representing the cumulative predictive accuracy of exercise tests reported between 1971 and 1980 inclusive. This is presented in terms of the ranges of sensitivity, specificity and positive and negative predictive values of various indices incorporating ST segment depression for detecting coronary disease. The standard of disease was the coronary arteriogram where a significant stenosis was defined as a lumen narrowing of at least 70 to 75%. The results have been grouped according to whether bipolar, standard or combined bipolar and standard leads were used to record the ECG.



Information on Data

Lead Type:	Bipolar	Standard	Combined
Number of studies:	11	12	4
Number of patients:	1538	3572	300

Figure 1.6. Histograms representing the cumulative predictive accuracy of exercise tests reported between 1971 and 1980 inclusive. This is presented in terms of the ranges of sensitivity, specificity and positive and negative predictive values of various indices incorporating ST segment depression for detecting coronary disease. The standard of disease was the coronary arteriogram where a significant stenosis was defined as a lumen narrowing of at least 50%. The results have been grouped according to whether bipolar or standard leads were used to record the ECG.



Information on Data

Lead Type:	Bipolar	Standard
Number of studies:	5	8
Number of patients:	1517	830

depression; the time of its onset and duration of changes during exercise; the coexistence of chest pain, ventricular arrhythmias; changes in heart rate and blood pressure; and the patient's sex. By comparison with coronary arteriography, this score had a sensitivity and specificity of 94 and 65% respectively and the rate of false negative results was 20%. Another score index presented by Hollenberg, Budge, Wisneski & Gertz, 1980 was an integral of the area of the ST segment depression occurring during exercise and until recovery, in either of leads V5 and aVF. This was divided by the duration of exercise and the percent of the maximum predicted heart rate. When compared with the results of coronary arteriography this index had a sensitivity of 85% and a specificity of 91%; it had positive and negative predictive values of 98 and 50% respectively.

Further indices of exercise induced myocardial ischaemia, presented in the literature, are the area of ST segment depression (Sketch, Mohiuddin, Nair, Mooss & Runco, 1980) and a combination of the magnitude of ST segment depression and the slope of the ST segment (McHenry, Stowe & Lancaster, 1968; Ascoop, Distelbrink & De Lang, 1977). Sensitivity and specificity in these reports however ranged from 88 to 89 %, and from 85 to 92 % respectively.

The most widely used clinical index of disease (the occurrence of at least 1.0 mm ST segment depression 80 ms beyond the J point) is quoted as having a sensitivity of 70% (only 70% of patients with coronary disease tested, will produce an ST segment greater than or equal to 1.0 mm) and a specificity of 90% (only 90% of normal subjects tested will have a negative ST segment response).

Estimating the Severity of Ischaemic Heart Disease.

In most of the studies quoted above, differences could be shown between groups of patients with very severe disease and those with either mild (eg. single vessel disease) or angiographically undetectable coronary disease. None however, were able to predict, with certainty, the number of diseased coronary arteries in an individual patient.

For example, where the extent of ST depression was used at the end of the exercise test to assess the degree of severity in studies by Mason, Likar, Bierne & Ross, 1967; Martin & McConahay, 1972; Detry, Kapita, Cosyns, Sottiaux, Brasseur & Rousseau, 1977; Chaitman, Bourassa, Wagniart, Corbara & Ferguson, 1978, a variable degree of overlap occurred in the ranges of magnitude of ST depression obtained from groups of patients with different degrees of disease.

This was also the experience of: Goldschlager, Selzer & Cohn, 1976; Chaitman, Bourassa, Wagniart, Corbara & Ferguson, 1978; McNeer, Margolis, Lee, Kisslo, Peter, Kong, Behar, Wallace, McCants & Rosati, 1978; Sanmarco, Pontius & Selvester, 1980; Weiner, McCabe & Ryan, 1980 and Baron, Poole-Wilson & Rickards, 1980 who used the following indexes of disease: duration of exercise before the onset of ST depression; duration of the exercise test; the extent of ST depression; the heart rate and/or blood pressure attained at the end of the test.

Other studies attempting to assess the severity of coronary disease include those by Mason, Likar, Bierne & Ross, 1967; Chaitman, Bourassa, Wagniart, Corbara & Ferguson, 1978; Fox, Selwyn & Shillingford, 1979 and Baron, Poole-Wilson & Rickards, 1980. The indices of disease severity were the sum of ST segment depression and the number of leads demonstrating this. Although differences between the means of the indices could be shown between some groups of patients, overlap of data occurred between these groups. Similarly, an overlap of data was shown by Sketch, Mohiuddin, Nair, Mooss & Runco, 1980, using the area of the depressed ST segment. Likewise, the multivariate score of Hollenberg, Budge, Wisneski & Gertz, 1980 (the area of ST segment depression divided by the duration of exercise and the percent maximum predicted heart rate).

In conclusion, there was only a limited ability of ECG exercise tests reported before 1980 to predict the presence and severity of coronary disease in the individual patient using various indices incorporating ST segment depression.

Reasons for the Poor Predictive Accuracy of Exercise Tests Reported Before 1980.

Possible reasons for the poor predictive accuracy of the exercise tests reported before 1980 and described above are:

1. The limitations of coronary arteriography as an index of ischaemic heart disease.
2. The shortcomings of ST segment depression as an index of myocardial ischaemia.
3. Coronary arteriography and ischaemic ST segment depression represent two facets of coronary disease: the arteriogram is a purely anatomical representation of coronary disease; the exercise test indicates the cellular integrity of the myocardium. A precise correlation between the two, is questionable.
4. Some indices of myocardial ischaemia were only poorly reproducible.
5. In an exercise test in which duration is symptom limited, the time at which ST segment depression is measured may depend on subjective and variable factors, for example:
 - a). Angina pectoris; different patients may have different levels of pain threshold.
 - b). Fatigue; different patients may have different levels of exercise tolerance.
6. In several of the studies, there was a long period between performing the arteriogram and the exercise test during which, the extent of coronary disease may have altered (for example, 6 and 4 weeks; McNeer, Margolis, Lee, Kisslo, Peter, Kong, Behar, Wallace, McCants & Rosati, 1978; Sanmarco, Pontius & Seivester, 1980).

The Leeds Exercise Test.

In 1980, results obtained from an exercise test developed at Leeds suggested that it was in fact possible to establish whether coronary disease was present in an individual (Elamin, Mary, Smith & Linden, 1980). Further, it was proposed that the number (0, 1, 2 or 3) of diseased coronary arteries defined by the arteriogram could be predicted.

This proposal followed a preliminary study of 64 patients. The index of severity of disease was the maximum rate of development of ST depression relative to heart rate occurring in any of the standard 12 or the bipolar CM5 ECG leads during a continuous multistage exercise test.

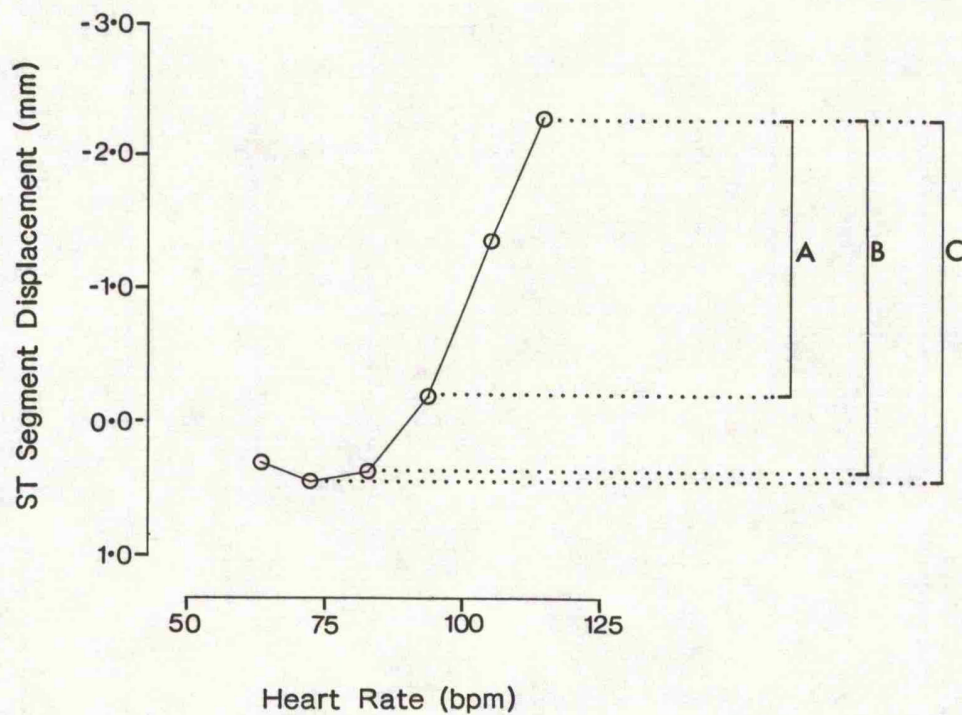
The test protocol was designed to measure the ST segment displacement during continuous exercise for as many controlled increments in heart rate as possible. The patient performed upright exercise on a bicycle ergometer against a series of incremental workloads. These were increased every three minutes so that the patient's heart rate increased by about ten beats per minute at each stage.

For each patient, in all ECG records showing ST depression at the end of the test, mean values of ST displacement (at 80 ms after the J point) and heart rate, were estimated from about 10 cardiac cycles at every stage of exercise and at rest. Slopes of linear regression of ST segment displacement on heart rate were calculated for each lead, sequentially using the data obtained from the final 3, the final 4, 5, 6 etc. stages. An example of the calculation of the ST/HR slope for one lead is shown in figure 1.7. The steepest of these slopes (from all leads) with a correlation coefficient significant at the level $p < 0.05$ was the maximal ST/HR slope.

In the initial study, maximal ST/HR slopes obtained from 64 patients occurred within 4 discrete groups defined by the ranges 3 to 11; 13 to 21; 32 to 59; 69 to 137 mm/bpm $\times 10^{-3}$. These results matched exactly the results of coronary arteriography assessed in terms of 0, 1, 2 and 3 vessel disease and performed within 7 days of the exercise test. Thus, patients in whom the maximal ST/HR slope had a value from 3 to 11 mm/bpm $\times 10^{-3}$ (or there was no

Figure 1.7. Calculation of the maximal ST/HR slope.

The relation between heart rate and ST segment displacement during a five stage exercise test is shown where there was 2.4 mm of ST segment depression at the end of the test. (Point 0 marks the resting values). Slopes of linear regression of ST displacement on heart rate are calculated with data obtained from the last 3 stages (Slope A: points 5, 4, 3); the last 4 stages (Slope B: points 5, 4, 3, 2) and the last 5 stages (Slope C: points 5, 4, 3, 2, 1). These are presented with the coefficient of linear correlation (R) and the level of significance (p) associated with it. The steepest slope calculated in this manner from data obtained from all leads with a correlation coefficient significant at the level $p < 0.05$ is the maximal ST/HR slope.



ST/HR slope \pm s.e. (mm/bpm $\times 10^{-3}$)	Correlation coefficient (R)	Level of significance (p) associated with R
A: 97 \pm 2	1.00	0.012
B: 79 \pm 9	0.99	0.012
C: 63 \pm 11	0.96	0.009

linear correlation ($p < 0.05$) between ST segment displacement and heart rate), had no significant coronary disease. Patients who had a maximal ST/HR slope from 13 to 21; 32 to 59; or 69 to 137 mm/bpm $\times 10^{-3}$ had one, two or three vessel disease respectively.

Patients were classed as having one, two or three vessel disease from the arteriogram if they had a significant stenosis in 1, 2 or 3 of the left anterior descending, (LAD), the left circumflex (LCFX) or the right coronary (RCA) arteries. A significant lesion in the left main stem was considered equivalent to significant lesions in its two major branches (the LAD and LCFX) and therefore constituted two vessel disease. A stenosis was defined as significant if it occurred in the proximal to middle sections of these three arteries narrowing it by an amount that was thought would cause ischaemia on exercise (R.M. Boyle, D.R. Smith & J.B. Stoker - personal communication; Elamin, 1983).

The severity of a stenosis was assessed from the arteriographic projection in which it looked the most severe. It was based on the degree of narrowing relative to an adjacent segment of the vessel which appeared normal. In the early reports from Leeds, it is described that for a stenosis to be significant, it should cause at least a 75% reduction in lumen diameter (Elamin, Mary, Smith & Linden, 1980; Linden & Mary, 1982; Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982). However, as shown in this study and according to a later publication, (Bishop, Adlakha, Boyle, Stoker & Mary, 1987), it was first decided whether or not the stenosis might cause ischaemia on exercise. If so, it would be labelled as 75% or more reduction in lumen diameter. Otherwise it would be labelled as less than 75% lumen reduction.

The degree of constriction of a long lesion was assessed at its narrowest point; in vessels which had more than one lesion, the degree of stenosis was that of the most severe. Neither small vessels nor the presence of collaterals influenced assessment and classification of disease was made irrespective of the dominance of the circulation. Where the arteriogram was

assessed by more than one observer, any difference of opinion was resolved by a further, joint assessment (Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982; Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982).

This method of assessment evolved from the routine clinical method of interpreting coronary arteriograms at Leeds. It was also based on their experience during a preliminary learning trial on how disease severity was reflected by the rate of development of ST depression (N.P. Silverton & G. Hart - personal communication).

The means of describing the rate of development of ST depression mathematically, was also derived during a preliminary trial. During this, in addition to the maximal ST/HR slope, two other indices of coronary disease were tested; the "steepest" ST/HR slope and the "peak" ST/HR slope (Elamin, 1983). The "steepest" ST/HR slope was the maximum slope of linear regression of ST depression on heart rate derived using data from all stages of the test. It was essentially the average rate of development of ST depression. The "peak" ST/HR slope was the steepest slope of linear regression calculated from any combination of three or more of the data points obtained. Values for the "maximal", "peak" and "steepest" ST/HR slopes were calculated for twenty patients and the results correlated with the results of arteriography. Using the "steepest" ST/HR slope as the index of coronary disease, there was an overlap between the range of slopes obtained from patients with three vessel disease and those with one and two vessel disease. This therefore did not have the potential of predicting the severity of coronary disease in an individual patient. "Peak" and "maximal" ST/HR slopes on the other hand were identical and occurred within 4 discrete ranges which matched exactly the patient's arteriogram result as already described. The maximal ST/HR slope was ultimately used as the index of coronary disease severity since it was the more easily and rapidly calculated of the two (Elamin, 1983).

The Physiological Basis of the Leeds Exercise Test.

The basis behind the rate of development of ST segment depression relative to heart rate as an index of coronary disease is that myocardial ischaemia is, in effect, a 'deficit' of myocardial oxygen required to maintain a particular level of myocardial function. The severity of myocardial ischaemia, and therefore coronary disease, is dependent upon both the delivery of oxygen to the myocardium and the level of oxygen consumption; a given degree of myocardial ischaemia may arise independently through either a reduction in oxygen supply or an increase in oxygen consumption. Since an index of ischaemic heart disease is essentially to estimate the oxygen deficit, in keeping with the preceeding argument, it is necessary to relate the measure of ischaemia with a measure of the oxygen consumption. This is accomodated in the maximal ST/HR slope where the index of myocardial ischaemia is the level of ST segment depression and the index of myocardial oxygen consumption is the heart rate.

Evidence that the level of ST segment depression is an index of endocardial myocardial ischaemia such as is precipitated by coronary occlusion (accepting its limitations) has been presented (pp.18-19). The use of the heart rate as an index of myocardial oxygen consumption is considered.

The Heart Rate as an Index of Myocardial Oxygen Consumption.

A small proportion of myocardial oxygen consumption (MVO_2) is expended in the basal metabolism of the non contracting heart and in that required for polarisation and repolarisation. The main fraction of total MVO_2 however is a function of the heart's mechanical activity (McKeever, Gregg & Canney, 1953; Braunwald, 1969; Boerth, Covell, Pool & Ross, 1969).

Factors which might determine the oxygen consumption of the heart were investigated as early as 1915. For example, Evans & Matsuoka had shown that in the canine heart lung preparation, independant increase of either the arterial pressure (by an outflow resistor) or the cardiac output (by increasing the venous return) caused an increase in the "gaseous metabolism"

of the heart. The relative effects of aortic pressure, stroke volume and heart rate on MVO_2 were later systematically studied in a more stable preparation by Sarnoff, Case, Welch, Braunwald & Stainsby in 1958. The preparation was an isolated dog heart perfused by connection to the circulation of a second intact dog. Aortic pressure, cardiac output and heart rate could be varied either alone or together. Independent variation of cardiac output, mean aortic pressure and heart rate showed that:

- a). An increase in cardiac output while mean aortic pressure and heart rate were held constant, caused only a slight increase in MVO_2 .
- b). Contrarily, when aortic pressure was increased while cardiac output and heart rate were held constant, MVO_2 increased in parallel with the increase in aortic pressure.

With further investigation, it was concluded that MVO_2 per beat was primarily determined by the product of the mean systolic pressure and the duration of systole; the tension time index. This was an index of the tension required to eject blood during systole and the duration over which this had to be maintained. The tension time index correlated well with MVO_2 regardless of which haemodynamic parameter, cardiac output or aortic pressure, was varied.

By estimating maximum wall tension developed (on the basis that the tension developed in the myocardial wall is directly related to the radius of the heart and the intraventricular pressure, and indirectly related to the left ventricular wall thickness), Rodbard, Williams & Williams, 1959, and McDonald, Taylor & Cingolani, 1966, showed that maximum wall tension per beat was a more accurate index of MVO_2 than the tension time index. There was a significantly better correlation ($p < 0.01$) between the product of peak tension developed and heart rate and MVO_2 ($r = 0.87$) than between the tension time index and the MVO_2 ($r = 0.75$; McDonald, Taylor & Cingolani, 1966). It was also suggested that fibre shortening against a load (dictated by the end diastolic volume) might also influence the level of MVO_2 however, this was of lesser importance than the maximum tension developed. (This was

confirmed by Burns & Covell, 1972 in the isolated supported canine heart preparation. The cost of myocardial fibre shortening accounted for approximately 17% of the total MVO_2 ; the development of maximal wall tension accounted for approximately 48% of it).

That ventricular pressure or more specifically, myocardial wall tension might not be the only important determinant of MVO_2 was suggested when, for example, Gregg 1963, could show only a poor correlation between the tension time index and MVO_2 in conscious dogs during either exercise or sympathetic nerve stimulation. Thus when MVO_2 increased by 50 to 300%, the tension time index usually varied by no more than 5 to 10%. Further, Krasnow, Rolett, Yurchak, Hood & Gorlin, 1964 described MVO_2 in man as increasing out of all proportion to the tension time index after administration of isoproterenol. (This has a similar haemodynamic effect to the normally occurring catecholamines adrenaline and nor adrenaline). Both these observations implicated the inotropic state of the heart (the force, velocity and extent of shortening during contraction) as another important determinant of MVO_2 . In experiments specifically designed to test this, positive inotropic stimuli (paired electrical stimulation, application of nor adrenaline, calcium, digitalis or combinations of these) to the isolated supported canine heart preparation consistently increased MVO_2 by as much as 100%; an amount generally proportional to the speed of contraction (Sonnenblick, Ross, Covell, Kaiser & Braunwald, 1965; Ross, Sonnenblick, Kaiser, Frommer & Braunwald, 1965). Conversely, pharmacological agents which depress myocardial contractility (procain hydrochloride, propranolol and pronethalol) caused a fall in MVO_2 (Graham, Ross, Covell, Sonnenblick & Clancey, 1967).

In summary, determinants of MVO_2 are:

1. The basal energy required to maintain the chemical processes of the myocardium unrelated to contraction.
2. The energy required to activate contraction i.e. polarisation and depolarisation.

3. The heart rate.
4. The maximum myocardial tension developed.
5. Myocardial fibre shortening against a load.
6. The level of the inotropic state.

Of these, the major three determinants are the heart rate, the development of ventricular wall tension and the inotropic state of the heart.

The relative contribution of these three determinants to the total MVO_2 depends on the circumstance. For example, in man at rest, total MVO_2 is chiefly determined by the heart rate and development of ventricular wall tension. During isotonic exercise however, an increase in MVO_2 largely occurs by (in descending order of importance) an increase in the heart rate, an increased myocardial inotropic state through an increased sympathetic nerve discharge and circulating catecholamines, and an increase in ventricular wall tension. During isometric exercise on the other hand, an increase in MVO_2 largely occurs by an increase in ventricular wall tension (Ross, 1972).

Accurate measurement of myocardial oxygen consumption in man can only be made by measuring myocardial blood flow and the coronary arterio-venous oxygen difference. Since this requires cardiac catheterisation, it is not very practicable during the routinely performed exercise test; a non invasive index is more apt.

By reason, the most accommodating index of MVO_2 would include all its determinants. The oxygen consumption for the basal metabolism of the myocardial cells and for their polarisation and repolarisation however, is unmeasurable in intact man. Furthermore, it is very small. Of the 3 major determinants, myocardial contractility is also unmeasurable. Heart rate on the other hand may be easily and accurately measured and myocardial tension, a function of ventricular pressure, can be estimated indirectly in terms of systolic pressure (Holmberg & Varnauskas, 1971).

The product between heart rate and systolic blood pressure has shown to

correlate well with MVO_2 ($r = 0.90$; $r = 0.86$; $r = 0.83$) in both normal subjects and patients with ischaemic heart disease during upright exercise (Nelson, Gobel, Jorgensen, Wang, Wang & Taylor, 1974; Kitamura, Jorgensen, Gobel, Taylor & Wang, 1972; Gobel, Nordstrom, Nelson, Jorgensen & Wang, 1978). These estimates have been obtained in studies where MVO_2 was calculated from estimates of myocardial blood flow (by a dye dilution method using N_2O) and the myocardial arterio-venous oxygen difference (through sampling of coronary sinus and aortic blood). Blood pressure was measured with a central aortic catheter (Nelson, Gobel, Jorgensen, Wang, Wang & Taylor, 1974; Kitamura, Jorgensen, Gobel, Taylor & Wang, 1972; Gobel, Nordstrom, Nelson, Jorgensen & Wang, 1978). Heart rate alone was shown to correlate almost as well ($r = 0.82$, $r = 0.88$, $r = 0.79$; Nelson et al., 1974; Kitamura et al., 1972; Gobel et al., 1978).

In the Leeds exercise test, heart rate alone was the index of MVO_2 . This was because the only practicable means of measuring systolic blood pressure was with a sphygmomanometer pressure cuff at the level of the brachial artery. When the maximal rate of ST segment depression was estimated relative to the rate pressure product (rather than heart rate alone), this could not, as an index, discriminate between patients with, and those without, coronary disease; a result attributed to a large error introduced by the blood pressure measurements (Elamin, 1983).

Although the use of heart rate alone might be a less representative index of MVO_2 than the rate pressure product, on the basis of the results of Nelson et al., 1974; Kitamura et al., 1972 and Gobel et al., 1978, it is a very good, easily, and in particular, accurately measured correlate of myocardial oxygen consumption.

It would be expected (as was shown by the Leeds exercise test), that patients with the more severe ischaemic heart disease would demonstrate a greater rate of development of ST segment depression with increasing heart rate as follows:

In the normal coronary circulation, increased myocardial oxygen demand

is satisfied by an equivalent increase in myocardial blood flow (Gobel, Nordstrom, Nelson, Jorgensen & Wang, 1978). In patients with coronary artery disease during exercise, adequate myocardial perfusion with oxygen is prevented and the myocardium becomes increasingly ischaemic (Amsterdam, Hughs, DeMaria, Zelis & Mason, 1974; Maseri, 1975). The rate at which the myocardium becomes ischaemic (marked by an increase in ST depression) for any reduction in blood flow, will be related to the increase in MVO_2 . That there is in fact a linear relation between the increase in myocardial ischaemia and the increase in MVO_2 , represented by the heart rate, has been shown not only in studies at Leeds, but also in earlier work by Detry, Piette & Brasseur, 1970 and Berenyi, Hajduczki & Boszormenyi, 1979.

Since the greater the extent of coronary occlusion, the greater the reduction in myocardial blood flow, it follows that the reduction of myocardial flow during exercise and so the degree of ST depression will be greater for any value of heart rate the greater the extent of disease. In other words, the same degree of ST depression will occur over a smaller increase in heart rate (and produce a steeper ST/HR slope) in patients with severe coronary disease than in those with less severe disease. Consequently, the steeper the maximal ST/HR slope obtained during the exercise test, the greater the expected extent of disease.

Patient Selection in the Leeds Trial.

The above argument holds only if myocardial ischaemia (and so ST depression), is a result of a reduction in coronary blood flow secondary to coronary obstruction. Displacement of the ST segment either at rest or during exercise may however be caused by other factors (Roitman, Jones & Sheffield, 1970); for example:

1. Valve disease (Aronow & Harris, 1975).
2. Ventricular hypertrophy (Harris, Aronow, Parker & Kaplan, 1973).
3. Hypertension (Wong, Kasser & Bruce, 1969).
4. Aneurysm and left ventricle dysfunction (Chaitman, Waters, Theroux & Hanson, 1981; Waters, Chaitman, Bourassa & Tubau, 1980).

5. Conduction defects (Orzan, Garcia, Malthur & Hall, 1978).
6. Unstable angina (Papapietro, Niess, Paine, Mantle, Rackley, Russel & Rogers, 1980; Waters, Chaitman, Bourassa & Tubau, 1980).
7. Digoxin (LeWinter, Crawford, O'Rourke & Karliner, 1977; Kawai & Hultgren, 1964).
8. Beta blockers (Froelicher & Maron, 1981; Ellestad, Cooke & Greenberg, 1979; Surawicz & Saito, 1978; Froelicher, 1980).
9. In some patients, nifedipine (Deanfield, Wright & Fox, 1983).

Patients in whom these factors applied were excluded from the preliminary study at Leeds since this might detract from any potential tally between the maximal ST/HR slope and the coronary arteriogram.

To verify the potential of the Leeds test for diagnosing the severity of coronary disease in the individual, tests were performed on further patients at Leeds (Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982; Mary, Elamin, Smith & Linden, 1982 [a]; [b]; Elamin, Mary, Smith & Linden, 1982; Mary, Silverton, Boyle, Stoker, Smith & Linden, 1985; Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982; Boyle, Elamin, Kardash, Linden, Mary, Smith & Stoker, 1982).

In all these studies, the maximal ST/HR slope accurately predicted the extent of coronary disease as previously described after slight modification of the maximal ST/HR slope ranges. Thus patients with no significant disease had maximal ST/HR slopes of less than $11 \text{ mm/bpm} \times 10^{-3}$ (rather than from 3 to $11 \text{ mm/bpm} \times 10^{-3}$) and patients with triple vessel disease had maximal ST/HR slope greater than $69 \text{ mm/bpm} \times 10^{-3}$ (rather than from 69 to $137 \text{ mm/bpm} \times 10^{-3}$; Mary, Silverton, Boyle, Stoker, Smith & Linden, 1985).

Patient selection was in the main as before although, in some of these studies a few patients had cardiac conditions other than, or including, narrowed coronaries (Mary, Elamin, Smith & Linden, 1982 [a]; [b]; Elamin, Mary, Smith & Linden, 1982; Boyle, Elamin, Kardash, Linden, Mary, Smith & Stoker, 1982). Thus in the study reporting the accumulative results of 206 patients: four had mitral valve disease; 4 had mixed aortic valve disease; 2

had hypertrophic cardiomyopathy; 1 had hypertension and left ventricular hypertrophy and 3 had left bundle branch block (LBBB; Elamin, Mary, Smith & Linden, 1982). Only 3 of these patients had significant CAD; two of the patients with LBBB and the patient with hypertension. In all 206 patients, the previously ascribed maximal ST/HR slope ranges allowed a diagnosis that agreed with the results of coronary arteriography. (This implies that the patients with valve disease, the patient with hypertension and the two with LBBB (all with no significant coronary disease) had maximal ST/HR slopes in the no significant disease range. Equally, in the two patients with LBBB and the one with hypertension, the presence of the added complication did not affect the ST/HR slope sufficient to falsify their diagnosis.)

In the later studies on the exercise test at Leeds, unlike in the first study, patients were not excluded if they were on beta blockers subsequent to the realisation and confirmation that this therapy should not, and did not, detract from the predictive results of the maximal ST/HR slope.

Beta Blockers and the Maximal ST/HR Slope.

Patients on beta blockers were not included in the initial trial at Leeds because this therapy, by reducing the level of ST segment depression at the end of an exercise test, was often associated with false negative tests when the index of myocardial ischaemia was the displacement of ST depression alone (Froelicher & Maron, 1981; Ellestad, Cooke & Greenberg, 1979; Fox, Selwyn, Oakley, Johnathan & Shillingford, 1980; DiBianco, Singh, Singh, Katz, Bortz, Gottdiener, Spodick, Laddu & Fletcher, 1980; Gianelly, Treister & Harrison, 1969). Beta blockers do not affect the ST segment per se, but by reducing the heart rate, contractile and systolic arterial response to exercise, they reduce the MVO_2 consumption for any level of exercise workload (Gianelly, Treister & Harrison, 1969; Jorgensen, Wang, Wang, Gobel, Nelson & Taylor, 1973). Based on work on anaesthetised and conscious animals, the reduction in exercise induced ST depression is considered in the main to be secondary to the reduction in myocardial work (Thomas, Gabe, Kimber, Mills & Sweeting, 1981; Vatner, Baig, Manders, Ochs &

Pagani, 1977). There is evidence that the relation between heart rate and ST segment displacement is not affected by beta blockade. For example, this was demonstrated in anaesthetised dogs by Stephan, Meesman & Sadony, 1975. Heart rate was linearly related to mean ST elevation in epicardial electrocardiographic maps whether or not the animals were treated with practolol. There was no significant difference between the linear regression coefficients of ST elevation on heart rate obtained from the two groups of animals although, the slope of regression from animals on beta blockers was displaced to the right. Thus any level of ST elevation occurred at a higher heart rate in beta blocked animals.

False negative exercise tests from patients on beta blockers (when the result is determined by the extent of terminal ST depression), has consequently been attributed to the effect of the beta blocker on myocardial oxygen demand. Since however, the Leeds test is based on the relation between changes in both heart rate and the level of ST depression, which is not affected by beta blockade, the test ought to maintain its diagnostic potential in patients on beta blockers. This was demonstrated by Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982.

Twenty one patients were studied before and after beta blockade. There was no significant difference ($p > 0.02$) in the maximal ST/HR slope before and after treatment despite large significant reductions ($p < 0.0005$) in the heart rate at rest and at the end of the exercise test.

In a parallel study, the maximal ST/HR slopes obtained from 60 patients on beta blocker therapy were compared with their arteriogram results. Using the previously observed diagnostic ranges obtained from patients not taking beta blockers, correct prediction of the patients' extent of coronary disease was possible. Beta blocker therapy therefore did not detract from the diagnostic capacity of the maximal ST/HR slope.

Reproducibility of the Leeds Exercise Test.

The exercise test at Leeds was shown to be very reproducible. There was no significant difference between the results of two consecutive exercise

tests performed within seven days of each other in 50 patients ($p > 0.05$; Linden & Mary, 1982).

On the basis of this accuracy in reproducing the maximal ST/HR slope, the Leeds test has been used to monitor changes in myocardial ischaemia by serial measurement before and after physical training, coronary artery bypass grafting and percutaneous transluminal angioplasty:

Physical Training and the Maximal ST/HR slope.

Improvement in 8 patient's coronary condition was indicated by a significantly lower maximal ST/HR slope after a 6 month physical fitness training program (The Royal Canadian Airforce 5BX/XBX plans, 1964). The difference between the mean maximal ST/HR slopes before and after training was significant at the level $p < 0.01$ (Elamin, Winter, Kardash, Silverton, Whitaker, Smith, Mary & Linden, 1983). According to the patients' arteriograms, 3 had single vessel disease 3, had double vessel disease and 2 had triple vessel disease. Although each patient produced a lower maximal ST/HR slope after training than before, this was not sufficient to change the patient's diagnosis in terms of the number of coronary vessels significantly occluded; the slope remained within the same disease range.

Coronary Artery Bypass Graft Surgery and the Maximal ST/HR Slope.

The maximal ST/HR slope and the results of coronary arteriography were compared in 46 patients before coronary artery bypass graft (CABG) surgery (Kardash, Boyle, Watson, Stoker, Mary & Linden, 1984). The number of significantly diseased coronary arteries was correctly determined by the maximal ST/HR slope on all occasions according to the prespecified ranges. During follow up exercise tests and arteriography in 26 of these patients, 6 months post-operatively, the maximal ST/HR slope accurately indicated the number of patent grafts; it was reduced by an amount sufficient to decrease the patient's grade of disease severity by the equivalent of one vessel disease for each patent graft. Similarly, the development of further significant coronary narrowing or occlusion in any graft caused an increase in the slope sufficient to increase diagnosis by an equivalent of one vessel

disease.

It is noteworthy however that two patients examined five months post operatively had maximal ST/HR slopes within the intermediate 0 to 1 vessel disease range. Unfortunately, arteriography was not performed at this time. At 6 months after the operation, when an arteriogram was performed, the maximal slope had progressed to one vessel disease corresponding to the arteriogram result.

Percutaneous Transluminal Coronary Angioplasty and the Maximal ST/HR Slope.

The effect of percutaneous transluminal coronary angioplasty (PTCA) on the maximal ST/HR slope was studied for 25 procedures in 22 patients (Silverton, Elamin, Smith, Ionescu, Kardash, Whitaker, Mary & Linden, 1984).

All successful dilations (a 30% or greater increase in the luminal diameter measured from the arteriogram with calipers) were associated with a fall in the maximal ST/HR slope. There was no significant change in the slope following the two unsuccessful attempts. In the main, after successful dilation of a stenosis, a patient's grade of disease severity according to the maximal ST/HR slope was reduced by one. Further, when followed up 6 months after angioplasty, restenosis of a dilated artery in 3 out of 12 patients was correctly indicated by an increase in the maximal ST/HR slope corresponding to an increase by the equivalent of one vessel disease. When the maximal ST/HR slope was compared with the results of arteriography, either before or after angioplasty (both immediately and six months later), there was agreement in all but 3 patients.

A Mismatch Between the Leeds Test and the Arteriogram Results in the Angioplasty Study.

In 2 of the 3 patients where the exercise test and arteriogram results did not match in the angioplasty study, although the slope before angioplasty correctly indicated one vessel disease, immediately successful dilation of the stenosis in both cases did not move the slope out of the single vessel disease range. In one of these patients, angioplasty produced only a marginal reduction in vessel diameter from 99% to 65% and at 6

months, this lesion was shown to have completely occluded the artery. It was suggested that the total occlusion may have occurred soon after angioplasty before the second exercise test, explaining why an improvement in myocardial perfusion was not detected. The other patient in whom the predicted severity of disease did not improve from the 2 vessel disease category after angioplasty was one of 2 cases included in the study who had proven variant angina (attributed to coronary artery spasm). Angioplasty had successfully dilated the coronary stenosis from 75% to 15% reduction in lumen diameter and at 6 months later, no disease was evident from the arteriogram. Following angioplasty, the maximal ST/HR slope for this patient increased from the upper to the lower region of the single vessel disease range (from 21 to 14×10^{-3} mm/bpm) however, it remained within the same range even when re-evaluated six months later when there was still no apparent stenosis. It was suggested that the patient's variant angina was responsible for the overestimation by the maximal ST/HR slope both, soon after the dilation, and six months later.

The third patient in whom there was no correlation between the arteriogram and the maximal ST/HR slope according to the arteriogram, had single vessel disease. The maximal ST/HR slope however indicated double vessel disease which reduced to single vessel disease following successful dilation. No explanation for this overestimation by the maximal ST/HR slope both before or after angioplasty could be given. Thus, of 57 comparisons between the maximal ST/HR slope and arteriogram result, there was an agreement in 52.

In summary, apart from the 5 exceptions reported above, the relief of a coronary occlusion, restenosis of a dilated artery or stenosis of a vein graft caused respectively, a decrease or increase in the maximal ST/HR slope by a magnitude representing the appropriate number of coronary arteries involved.

False Positive and Negative Results with the Maximal ST/HR Slope.

As with other exercise tests, it was shown at Leeds that the maximal ST/HR slope could produce false positive and negative results, for example in patients with either cardiac hypertrophy or after recent myocardial infarction:

Cardiac Hypertrophy and the Maximal ST/HR Slope.

Myocardial ischaemia secondary to cardiac enlargement was shown to produce false positive results when using the maximal ST/HR slope by Bishop, Boyle, Watson, Mary & Linden, 1985.

The maximal ST/HR slope was measured in 6 patients with aortic valve disease both before and 3 to 6 months after aortic valve replacement. After valve replacement, the maximal ST/HR slope reduced from a mean and standard deviation of 23.6 ± 6.6 mm/bpm $\times 10^{-3}$ (range 13 to 30 mm/bpm $\times 10^{-3}$ and equivalent to a range of single to intermediate single to double vessel disease) to 5.7 ± 4.7 mm/bpm $\times 10^{-3}$ (range 0 to 11 mm/bpm $\times 10^{-3}$); equivalent to no significant disease. The decrease in the maximal ST/HR slope occurred in tandem, with the cardiothoracic ratio, which fell from $54.2 \pm 4.0\%$ to $48.6 \pm 4.6\%$ ($p < 0.0005$) implying ischaemia caused by cardiac enlargement.

Recent Myocardial Infarction and the Maximal ST/HR Slope.

Recent myocardial infarction (MI) was shown to produce both false positive and negative results when the maximal ST/HR slope was correlated with the arteriogram result (Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987):

Of 52 patients examined between 4 and 6 weeks after myocardial infarction, although the maximal ST/HR slope agreed with the arteriogram result in 17 (33%) cases, it underestimated this in 21 (40%) and overestimated it in 14 (27%) cases.

Underestimation of disease severity by the maximal ST/HR slope was associated with the extent of myocardial scarring indicated by a higher left ventricular score (an index of ventricular dysfunction), a larger left

ventricular volume and a lower ejection fraction. In addition, ST segment elevation which can occur with aneurysm and poor left ventricle function could have masked any ST depression due to ischaemia. That these two factors might have led to the underestimation of disease severity by the maximal ST/HR slope was supported by the following:

1. Several of the patients studied had a maximal ST/HR slope of zero and most of these had either a significant narrowing of only the infarct related coronary artery.
2. The diseased vessel was often associated with poor left ventricular function and in some, aneurysm.

Overestimation of disease severity by the maximal ST/HR slope was largely attributed to cardiac enlargement occurring after infarction. This was on the basis that in 7 of 11 patients in whom the maximal ST/HR slope had overestimated the extent of disease, there was a concomitant reduction in both maximal ST/HR slope and heart size from the first examination shortly after MI to a second examination 6 months later. By contrast, this effect was seen only in 1 of 18 patients in whom the maximal ST/HR slope underestimated the extent of coronary disease.

In summary, the maximal ST/HR slope, sensitive to ischaemia caused by coronary artery narrowing can be modified by myocardial scarring and enlargement after recent infarction.

The Current Predictive Accuracy of the Leeds Exercise Test.

In 346 out of 352 (98%) tests reported so far from Leeds, the occurrence and severity of disease as determined from the maximal ST/HR slope has corresponded with the results of arteriography (Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). (This does not include results from the trials in patients after recent myocardial infarction or with cardiac hypertrophy or variant angina).

The predictive accuracy of the Leeds exercise test, for coronary disease, thus exceeds that of previously reported tests (Elamin, 1983). It was also specifically shown that the maximal ST/HR slope was a better means

of estimating the presence of coronary disease than the more conventional criteria (1.0 mm ST depression before the patient had attained 85% of his maximal heart rate; Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982). Elamin et al, 1982 present the accumulated results of the Leeds exercise test in 206 patients. Whereas the maximal ST/HR slope predicted the absence or extent of coronary disease with 100% sensitivity and 100% specificity, when the more usual criteria was applied to the same patients' data, there were 60 (29%) indeterminate results and the sensitivity and specificity of the index in the remaining patients was only 93% (120/129) and 88% (15/17) respectively.

The Advantages of the Leeds Exercise Test.

There are several advantages of the Leeds test over the exercise tests previously described in the literature and used in clinical practice:

1. Unlike previously reported exercise tests, the Leeds test was very reproducible allowing more reliance to be placed on the results.
2. Because the index of disease is derived from the continuous relation between ST segment depression and heart rate, provided that there is a significantly linear relation between these variables, then no indeterminate results are obtained.
3. Beta blockers need not be withdrawn before the test since they do not affect the relation between ST depression and heart rate. This therefore reduces an additional potential hazard to the patient since such withdrawal has been suggested to increase the risk of cardiac arrhythmias or myocardial infarction (Miller, Olson, Amsterdam & Mason, 1975). Thus patients (particularly with single or double vessel disease) may be assessed without an increased number of indeterminate or false negative results as occurs in the more usual exercise tests which depend on the extent of terminal ST depression (Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982; Froelicher & Maron, 1981).

The Implications of the Leeds Exercise Test.

The implications of the Leeds test are also multiple:

1. With the very high predictive rate of the Leeds exercise test, further investigation, including coronary arteriography in individuals with no significant coronary disease but symptoms suggestive of this could be avoided.
2. Coronary arteriography in patients with single vessel disease could also be avoided or delayed according to the patient's response to therapy.
3. Because the mortality rate of coronary disease is thought to be favourably affected by CABG surgery in patients with multiple vessel disease and not those with single vessel disease (Goodwin, 1976; Rahimtoola, 1982), arteriography need only be performed in either patients in whom significant coronary disease is predicted and medical therapy has failed or patients with predicted multiple vessel disease, that is, only patients in whom surgery is being contemplated.
4. Conversely, coronary arteriography could be performed early in those patients in whom multiple vessel disease is predicted without waiting for the conventional criteria of failed medical therapy as would be the case with patients with single vessel disease.

In effect, the Leeds exercise test could reduce the number of patients with suspected coronary disease undergoing avoidable arteriography.

Further,

5. As has been shown, the maximal ST/HR slope could be used to assess the results of coronary artery bypass graft surgery and coronary angioplasty (Kardash, Boyle, Watson, Stoker, Mary & Linden, 1984; Silverton, Elamin, Smith, Ionescu, Kardash, Whitaker, Mary & Linden, 1984).
6. Suspected improvement in coronary perfusion could be monitored in therapeutic or other trials such as physical training (Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith Mary & Linden, 1986; Elamin, Winter, Kardash, Silverton, Whitaker, Smith, Mary & Linden, 1983).
7. The progression of coronary disease could be evaluated in an individual

patient by serial exercise testing.

8. Asymptomatic subjects in an occupation where a coronary could be disastrous (for example aeroplane pilots) could be screened on the basis that it has been shown that asymptomatic subjects can have even triple vessel disease (Froelicher, Yanowitz, Thompson & Lancaster, 1973; Erikssen, Enge, Forfang & Storstein, 1976).

The Leeds exercise test is therefore potentially an extremely valuable test.

The Major Shortcoming of the Leeds Exercise Test.

The major shortcoming of this test however, is that the highly discriminative correlation between the number of occluded coronary arteries and the maximal ST/HR slope as found at Leeds has not been achieved at any other centre (Harling, 1983; Ilsley, Canepa-Anson & Rickards, 1983; Balcon, Brooks & Layton, 1984; Beattie, Seibert, Wilson, Pipberger & Blomqvist, 1984; Detre & Vanbutsele, 1984; Quyyumi, Raphael, Wright, Bealing & Fox, 1984; Way, Johnston & Sleight, 1984; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985; Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Kligfield, Okin, Miller & Borer, 1986; Finkelhor, Newhouse, Vrobel, Miron & Bahler, 1986; Okin, Ameisen & Kligfield, 1986; Thwaites, Quyyumi, Raphael, Canepa-Anson & Fox, 1986).

Although a similar trend to the Leeds' results was shown (namely an increase in maximal ST/HR slope with increasing severity of disease), there has been an extensive overlap of the ranges of ST/HR slopes obtained from patients with differing severity of disease as defined by the arteriogram.

In Leeds' opinion, their method of performing the test was critical to obtaining their results (Linden & Mary, 1984). This would seem reasonable bearing in mind the manner in which the test was developed and performed. Namely:

1. Patients were chosen in whom coronary occlusion was the only likely cause of myocardial ischaemia. This would avoid false results between a correlation of arteriography and exercise test results occurring through an ischaemic response caused by anything other than fixed coronary occlusion.
2. The protocol of the exercise test was designed to best demonstrate any linear relation between ST segment depression and increasing heart rate from which the index of myocardial ischaemia was derived.
3. The assessment and grading of the arteriogram was based on an earlier experience of how the severity of disease was reflected in the maximal ST/HR slope. Because of the inherent subjectivness of arteriogram assessment, variation in results obtained from different centres would not be surprising without some means of standardising the method (if possible), among readers.
4. Exercise testing and arteriography were performed within a short period of each other to avoid an invalid correlation between these two tests through changes in the disease.

In some of the studies attempting to reproduce the Leeds' results, the methods deviated quite markedly from those described at Leeds. The major differences are summarised:

1. The patient selection; patients in whom a false test result might occur were included in the studies.
2. There were differences in the described exercise protocol. These included:
 - a. Different modes of exercise.
 - b. The use of different and fewer ECG leads.
 - c. The latency at which ST segment displacement was measured.
 - d. The method of assessing the arteriogram.
 - e. The exercise test arteriogram interval.

The specific differences in methods used at other centres attempting to reproduce the Leeds test are presented in Table 1.1 together with the

methods used at Leeds for comparison.

It is not unreasonable that some of these differences might be responsible for the discrepancy in the relation observed between the maximal ST/HR slope and the arteriogram result at centres other than at Leeds.

For example:

1. It has been shown that a history of myocardial infarction (such as were included in the studies by Balcon, Brooks & Layton, 1984) can cause false positive and negative results when correlating the maximal ST/HR slope with the arteriogram result (Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987).

2. Differences in Protocol.

- a. Several studies used fixed treadmill exercise protocols rather than tailoring the exercise according to the patient's heart rate response (eg. Ilsley, Canepa-Anson & Rickards, 1983; Harling, 1983; Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985; Okin, Ameisen & Kligfield, 1986; Finkelhor, Newhouse, Vrobel, Miron & Bahler, 1986; Ameisen, Kligfield, Okin, Miller & Borer, 1986).

Since exertion in such protocols is increased by fixed increments in treadmill incline and/or speed, they do not necessarily result in discrete increases in heart rate ideal for demonstrating a potential linear relation between ST segment depression and heart rate.

- b. Because the ECG is a vector quantity, the observed polarity and magnitude of its components, including displacement of the ST segment will depend on the orientation of the ECG recording electrode. It is therefore plausible that if the number of recording electrodes are reduced from 12 to 3 (as described by Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985 and Finkelhor, Newhouse, Vrobel, Miron & Bahler, 1986), then the degree of ST

- segment depression and correspondingly the maximal ST/HR slope could be underestimated. By similar reasoning, lead systems with different orientations such as the XYZ orthogonal leads (as used by Detre & Vanbutsele, 1984 and Beattie, Seibert, Wilson, Pipberger & Blomqvist, 1984) might provide different data from the standard 12 ECG leads.
- c. If the ST segment is horizontal, measurement of its displacement at different latencies along its length will have no effect on the maximal ST/HR slope. However, the exercise induced ischaemic ST segment can vary from upsloping to horizontal to downsloping (Goldschlager, Selzer & Cohn, 1976). It should not necessarily be expected therefore that a maximal ST/HR slope derived from the ST segment displacement measured at for example, 60 or 70 ms after the J point (as by Detre & Vanbutsele, 1984 and Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985 and Ameisen, Kligfield, Okin, Miller & Borer, 1986), will be equal to one derived from the ST segment displacement measured after a latency of 80 ms.
- d. On the basis of the observer variability apparently associated with the interpretation of the arteriogram, the assessment of these at different centres may give different results and so a different correlation with the maximal ST/HR slope. Different results are particularly likely if different criteria are being used to describe a significant stenosis eg. a 50% or more reduction in lumen diameter (as quoted by Detre & Vanbutsele, 1984; Kligfield, Okin, Ameisen, Wallis & Borer, 1985) rather than a 75% or more reduction in lumen diameter quoted by the Leeds team.
- e. By allowing an interval as long as 2 to 3 months between performing the exercise test and the arteriogram (Quyyumi, Raphael, Wright, Bealing & Fox, 1984; Kligfield, Okin, Ameisen, Wallis & Borer, 1985), a mismatch between the results of arteriography and exercise testing might occur since coronary lesions can both progress and (less commonly) regress

Table 1.1. Deviations from the Leeds' protocol at other centres attempting to repeat the Leeds exercise test.

Method	At Leeds	At Other Centre	Author (first name)
Exercise	Bicycle	Treadmill	<p> Ilsley, 1983 Harling, 1983 Okin, 1985 Ameisen, 1985 Kligfield, 1985 Okin, 1986 Finkelhor, 1986 Ameisen, 1986 </p>
Increase in workload	According to heart rate	Standard/modified Bruce protocol	<p> Ilsley, 1983 Okin, 1985 Ameisen, 1985 Kligfield, 1985 Finkelhor, 1986 Ameisen, 1986 </p>
		constant workload	Harling, 1983
ECG recording leads	Standard 12 plus CM5	Standard 12	Ilsley, 1983
		XYZ	<p> Detre, 1984 Beattie, 1984 </p>
		aVF,V5,V6	<p> Okin, 1985 Ameisen, 1985 Kligfield, 1985 </p>
		II,V1,V5	Finkelhor, 1986

Table 1.1 (cont.). Deviations from the Leeds' protocol at other centres attempting to repeat the Leeds exercise test.

Method	At Leeds	At Other Centre	Author (first name)
Latency after J point at which ST displacement is measured	80 ms	60 ms 70 ms 2/8 ths distance from J point to end of T wave	Detre, 1984 Okin, 1985 Ameisen, 1985 Kligfield, 1985 Ameisen, 1986 Beattie, 1984
Arteriogram assessment	Visual	If in doubt, measured	Quyyumi, 1984
Definition of a significant stenosis (reduction in lumen diameter)	" > 75% "	$\geq 50\%$ $\geq 50\%$ (left main stem)	Thwaites, 1986 Detre, 1984 Kligfield, 1985
Arteriogram exercise test interval	1 week	Within 2 months 12 \pm 2 weeks	Quyyumi, 1984 Kligfield, 1985

(Moise, Goulet, Theroux, Taeymans, Lesperance & Bourassa, 1985).

The Purpose and Aims of this Study. Because of the potential value of the Leeds test, the sound physiological basis of it, and the possibility that it had not been repeated at another centre since neither had its methods, this study was undertaken to test the relation between the maximal ST/HR slope and the arteriographic appearance of coronary disease using, as far as possible and under their guidance, Leeds' methods.

The aims were:

1. To see if the same precise relation between the maximal ST/HR slope and the arteriogram result that was observed at Leeds could be obtained at Leicester.
2. To make a fairer assessment of whether differences in protocols used at other centres might detract from the high degree of correlation seen between the arteriogram and exercise test results at Leeds.

At the same time, the following reservations about the Leeds test were harboured:

1. The very good correlation between the exercise test and the arteriogram results at Leeds implies that the interpretation of the arteriogram is completely reliable. This however is contra-indicated by the difficulties involved in evaluating the arteriogram as described earlier, and the consequent observer variability associated with it according to the literature. In no studies from Leeds is the reproducibility of the arteriogram assessment presented and an implicit assumption was that it was accurate and repeatable.
2. The coronary arteriogram and the exercise test reflect two facets of coronary disease. Whereas the arteriogram is a purely anatomic presentation of coronary disease from which its functional effect can only be speculated, the exercise test presents a more objective functional index of disease by indicating the cellular integrity of the myocardium under conditions of increased metabolism. To what degree these two facets of the disease may be correlated is questionable particularly

since interpretation of coronary disease from the arteriogram at Leeds did not allow for the length and possible asymmetry of stenoses; distal stenoses; a possible additive effect of multiple stenoses in series; the variable dominance of the circulation and a potential influential effect of collateral vessels.

To achieve the above aims and resolve as far as possible, the above reservations, the following steps were taken with the approval of the Leicester Ethical Committee:

1. The method of performing the Leeds exercise test was observed during a period spent at Leeds so that it could be performed on patients at Leicester.
2. The method of assessing the arteriogram was described and discussed during a meeting between 2 experienced arteriogram readers from Leicester and 3 arteriogram readers from Leeds involved with the Leeds test. The purpose was to enable the arteriogram readers from Leicester to assess arteriograms in the same manner used at Leeds in a prospective comparison of arteriogram and exercise test results obtained from patients at Leicester.
3. A Leeds protocol exercise test and coronary arteriography were performed on 49 patients at Leicester who had been admitted to Groby Road Hospital, Leicester for coronary arteriography to confirm/substantiate a diagnosis of coronary disease and/or be evaluated for surgery.
4. Identical photocopies of a sample of exercise tests performed at Leicester were analysed at both Leeds and Leicester and the results compared. This was first to ensure that subsequent analysis of the exercise ECG at both centres was the same, and second, to highlight any possible causes of disparity of results between those presented at Leeds and those from other centres not having undertaken a similar learning programme.
5. Results of a sample of arteriograms performed at Leicester and assessed at both centres and on two different occasions at Leicester were

compared. This was to test the reproducibility of the arteriogram result and therefore assess the reliability of the arteriogram as an index of coronary disease in this respect.

6. Results of coronary arteriography and exercise tests (using the Leeds protocol) from the patients studied at Leicester were correlated to assess the ability for the maximal ST/HR slope to predict the presence and severity of coronary disease as defined by the arteriogram.

Following an account of the patients and general methods used in this study, the results obtained are presented in 3 chapters. Results chapter 1 concerns the analysis of the exercise test; results chapter 2 concerns the arteriogram as an index of coronary disease in terms of the reproducibility of its assessment and results chapter 3 presents the correlation between the maximal ST/HR slope and arteriogram results obtained at Leicester.

Patients and General Methods

Patients.

Forty nine patients were included in this study. The only criterion for inclusion was that they had been admitted to Groby Road Hospital for coronary arteriography to confirm/substantiate a diagnosis of coronary disease and/or be evaluated for surgery. There were 43 males and 6 females. The mean age was 54 years (range 28 to 69).

General Methods.

Each patient underwent coronary arteriography and was given an exercise test using the Leeds protocol. Informed consent was obtained from every patient prior to both exercise testing and arteriography.

The Exercise Test.

The aim of the exercise test was to obtain stable electrocardiogram (ECG) records from the standard 12 leads and the bipolar CM5 lead from which the ST segment displacement could be measured for as many controlled increments in heart rate as possible.

The exercise test was performed according to the method demonstrated at Leeds during the period spent there. It was the same as that published in the literature by those who devised the test (eg. Elamin, Mary, Smith & Linden, 1980) except that a different type of bicycle ergometer and ECG recording system was used. Also, at Leicester (and not at Leeds), the exercise ECGs were additionally recorded on magnetic tape. This was because it was anticipated that a computer assisted method of analysing the ECG would be developed. Tape recording provided a convenient method of storing the ECG which could be later digitised and fed into a computer.

The following section describes the exercise test at Leicester. The differences between the ergometer and recording systems used at Leeds and at Leicester, and the significance of these, are described and discussed at the end of this section.

The Exercise Test Room.

All exercise tests were performed in the Physiological Measurements Room at Groby Road Hospital, Leicester, under the supervision of a physician. Resuscitatory equipment and emergency drugs were always available.

The Method.

The ECG.

The ECG was recorded with pre-gelled self adhesive silver/silver chloride electrodes (Medicotest, model R-00-S). These were attached to the patient in the electrode sites given below after the skin had been prepared to minimise electrical resistance.

Preparation of the Electrode Sites.

Any hair around the electrode site was removed with a disposable razor. The skin was cleaned with methanol (Fisons), rubbed with a pumice stone to remove the superficial layer of keratinised skin and cleaned again with methanol.

The Electrode Sites.

The electrode sites for the praecordial leads of the standard 12 lead ECG were as follows (eg. Hope & Longmore, 1986):

Lead V1: in the 4th intercostal space at the right sternal edge.

Lead V2: in the 4th intercostal space at the left sternal edge.

Lead V3: at the midpoint between V2 and V4.

Lead V4: in the 5th intercostal space in the midclavicular line.

Lead V5: at the level of V4, in the left anterior axillary line.

Lead V6: at the level of V4, in the left mid axillary line.

The limb lead electrodes were placed on the torso rather than the limb extremities to minimise movement artefacts. The positions were as described by Mason & Likar, 1966, except that the electrodes were placed on the dorsal, not the ventral, surface. Thus the arm electrodes were attached between the lateral part of each scapular spine and its acromion; the leg electrodes were attached over each posterior, superior illiac spine.

An electrode was also attached over the manubrium of the sternum to

record from the CM5 position; between the praecordial V5 electrode and the manubrium electrode.

Lightweight wires were clipped onto press studs on each electrode and passed to a junction box which was fastened around the patient's waist. (All electrode/electrode wire/junction box connections were cleaned with contact cleaner lubricant (Radio Spares) prior to each exercise test session). A single cable led from the junction box to the ECG recorder.

The ECG Recorder.

The ECG Recorder was a 'Lifeline 3 Channel ECG System' (International Medical Corporation). Its frequency response was such that over the frequency range of 0.03 to 100 Hz, there was no attenuation of the signal greater than 3 dB. The input impedance was greater than 10^8 ohms.

The ECG recorded at the electrode sites was amplified such that 1 mV produced a deflection of 10 mm on the ECG recorder. This was continuously displayed on a monitor in the following groups of three leads which could be selected as required:

- Group A: standard limb leads I,II,III
- Group B: augmented limb leads aVR,aVL,aVF
- Group C: praecordial leads V1,V2,V3
- Group D: praecordial leads V4,V5,V6
- Group E: bipolar lead CM5.

The displayed ECG could be recorded simultaneously with heated styluses on thermal recording paper (Camcare ECG recording paper). The linearity of the paper record, as claimed by the manufacturers, was 0.5% over the middle 40 mm and $\pm 1\%$ over the entire 50 mm chart range. The chart speed was 25 mm s⁻¹.

Magnetic Tape Recordings.

A Racal Store 4DS magnetic tape recorder was used to store the ECG on 1/4" magnetic tape (Ampex Polyester recording tape). The ECG signals, were taken from 3 auxillary jacks on the ECG recorder, one for each lead, and input respectively into 3 FM channels of the tape recorder. The sensitivity

was set at 2V and the tape speed at $7.5'' \text{ s}^{-1}$. The tape recorder, so set, had a frequency response of DC to 2500 Hz and a signal to noise ratio of 48 dB. A voice channel was used to identify the patient, the stage of exercise and the lead group being recorded.

All recordings from the ECG recorder subsequently described were recorded simultaneously on both the paper recorder and the tape recorder.

The Exercise Test.

Before each test, the protocol and apparatus were explained to the patient.

Fifteen to 20, 1 mV calibration pulses and the resting ECG were recorded. The blood pressure was measured.
ECG recordings.

Sequential recordings were made of lead groups A to E. Duration of recording of each lead group was such that 15 to 20 complexes on a stable baseline were obtained.

Blood Pressure Measurements.

Systolic and diastolic blood pressures were measured with a wall fitted sphygmomanometer (Accoson). Diastolic pressure was taken at Phase V of the Korotkov sounds (when the snapping sound heard over the brachial artery disappears as the sphygmomanometer cuff is deflated; Korotkov, 1956).

Exercise and the Bicycle Ergometer.

During the exercise test, upright exercise was performed on a mechanically braked bicycle ergometer (Monark, Model No. 868). A variable braking force (workload) could be applied on a continuous scale. Rate of pedalling by the subject was indicated on a speedometer in revolutions per minute (rpm).

The Pretest.

To estimate the initial workload for the exercise test that would increment the patient's heart rate from rest by about 10 bpm, the patient was asked to pedal at 60 rpm against no load for 1 minute. The heart rate was monitored on the ECG recorder as the value of a running 16 beat

average. The increment in heart rate was noted, and from this, a workload anticipated to cause an increase in heart rate of 10 bpm was estimated. If the heart rate during the pretest increased by more than 10 bpm, during the exercise test the patient was asked to pedal at a slower rate (eg. 50 rpm).

Any lead that produced a signal contaminated with baseline wander or excessive muscle noise during the pretest was re-applied. The saddle and handlebar height were adjusted if necessary, to enable the patient to pedal with as little movement of the torso as possible. This was to limit baseline wander on the ECG.

When the patient's heart rate had returned to its resting value, the exercise test was begun.

The workload was set at the previously estimated level and the patient was asked to pedal continuously at constant speed. When the heart rate had become stable (after about three minutes), blood pressure and ECG records were taken as described above. The workload was then, and approximately every three minutes thereafter, increased by an amount anticipated to cause an increase in the heart rate of about 10 bpm. Then, and when the heart rate was stable at each level of exercise, further blood pressure and ECG records were taken until any of the following indicated termination of the test (Elamin, Mary, Smith & Linden, 1980; Boyle, Mary & Silverton, 1981):

1. The heart rate was 85% of its age predicted maximum.
2. Increasing angina.
3. ST segment depression of 3 or more mm.
4. Signs of vasoconstriction and inco-ordination.
5. Severe dyspnoea or fatigue.
6. Feeling of faintness.
7. Claudication and/or musculo-skeletal discomfort.
8. Excessive rise in blood pressure (sbp > 230 mm Hg).
9. A drop in heart rate or systolic blood pressure as exercise continues.
10. Progressive ST segment elevation.

11. Atrial fibrillation.
12. Supraventricular tachycardia.
13. Ventricular tachycardia.
14. Ectopic ventricular beats: >3 in 10 seconds; multiform; R on T; bigemini; >3 consecutive beats.
15. Progressive widening of the QRS complex.
16. Heart block.

After exercise was stopped, a standard 12 lead ECG and the blood pressure was recorded immediately, and after 3, 6 and 9 minutes or until the patient had recovered.

Differences Between Exercise Tests Performed at Leeds and at Leicester.

A different type of bicycle ergometer and ECG recording system from those at Leeds were used at Leicester.

1. The Bicycle Ergometer.

The bicycle ergometers used at Leeds were electrically braked models (either Elema Schonander, type 380 or Ergomed 740, Siemens). The only difference between these and the model used at Leicester was the mechanism of applying a resistance to pedalling. This is of no consequence to the test because increased exertion at both centres was solely determined by the level of heart rate caused by cycling in the upright position against a changeable load, irrespective as to how this was achieved.

2. The ECG Recording System.

At Leeds, the ECG was recorded with silver-silver chloride re-usable electrodes (Siemens exercise electrodes, Sweden). These were daubed with electrode jelly (Camjel, Cambridge Medical Instruments) and attached to the patient by double sided sticky rings (Siemens or Hewlett Packard), in the electrode sites described above after these had been cleaned; also described above. The electrodes were connected via light weight cables to the ECG recorder.

Various ECG recorders were used at Leeds. The latest recorder was a Mingograph inkjet recorder (type 62 A, Siemens: Elamin, 1983; Kardash,

Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982; Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982; Silverton, Elamin, Smith, Ionescu, Kardash, Whitaker, Mary & Linden, 1984; Kardash, Boyle, Watson, Stoker, Mary & Linden, 1984; Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986; Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). This had a frequency response such that between 0.05 and 500 Hz, there was no attenuation of the input signal greater than 3 dB (Elamin, 1983). This model was adapted to record from the CM5 bipolar lead in addition to the standard 12 leads. Six leads could be recorded at any one time.

An earlier recorder used in the Leeds studies was the Mingograph type 34 (Siemens). Because this could only record from the standard 12 leads, the CM5 lead was recorded separately on an SE Laboratories recorder (Elamin, 1983; Elamin, Mary, Smith & Linden, 1980; Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982). There is some conflict in the publications from Leeds about the exact recorder used. On the one hand, Elamin, Mary, Smith & Linden, 1980; Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982 and Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982 who describe the accumulated results of the Leeds exercise test on 64, 120 and 206 patients respectively, state that the ECG recorder was as reported by Raffo, Luksic, Kappagoda, Mary, Stoker, Whitaker & Linden, 1979. These authors describe recording the CM5 lead with an SE Laboratories amplifier and recorder (models 420/3 and 1127/01 respectively). The frequency response of the system was linear upto 40 Hz. On the other hand, in the dissertation by Elamin, 1983, which also includes the results of the Leeds exercise test on the 64 patients previously described (Elamin, Mary, Smith & Linden, 1980) it is stated that the CM5 lead was recorded with a SE Laboratories amplifier and recorder (models 420 and 427 respectively). The frequency response of this system was linear up to 100 Hz and it allowed four ECG leads to be recorded at any one time.

Two potentially significant differences of the ECG recorder used at Leicester from those used at Leeds were:

- a). The frequency responses of the recording systems.
- b). The number of ECG leads that could be recorded simultaneously.
- a). The Frequency Response of the Recording Systems.

The upper frequency limit of the recorder used at Leicester was 100 Hz whereas those at Leeds were 500 Hz and either 100 or 40 Hz. An inappropriate frequency response of the recording system may introduce errors in the ECG amplitude and duration of peaks and peak intervals (Berson & Pipberger, 1966). Analysis of the ECG in the Leeds exercise test requires measuring the ST segment displacement 80 ms after the J point. It is therefore crucial that any distortion of the ECG introduced by the recording system does not affect the duration of the QRS interval and therefore either the position of the J point or the duration of the ST interval. Spectral analysis of the ECG has shown that reducing the upper limit of the frequency band pass to below 200 Hz may alter the amplitude of the QRS components by about 0.5% (Golden, Wolthuis & Hoffler, 1973; Riggs, Isenstein & Thomas, 1979). Duration of the peaks and peak intervals however are not affected until the upper limit of the band pass is well below 100 Hz. Therefore, by using a recorder at Leicester with an upper frequency cutoff of 100 Hz rather than 500 Hz should not have introduced any errors into the test performed at Leicester.

Distortion of the ECG with respect to peak duration and interval times has been shown to occur when there is an upper frequency cutoff of less than 60 Hz. (Berson & Pipberger, 1966). This can introduce errors in the subsequent measurement of ST segment displacement. For example, errors in locating the J point can be caused by either an increase in QRS duration or the appearance or disappearance of S waves (Golden, Wolthuis & Hoffler, 1973). They can also be caused by a decrease in the QT interval through a phase shift of the QRS complex towards the T wave. This decreases the QT interval because an equivalent phase shift does not occur for the T wave

because of its lower frequency component. If an ECG recorder with an upper frequency limit of 40 Hz was used at Leeds, it can only be commented that the diagnostic ranges of maximal ST/HR slope were generated in spite of using a recorder with an upper frequency limit of either 500, 100 or 40 Hz.

b). The Number of Leads Recorded Simultaneously.

Whereas the Leeds' recorders could record either 4 or 6 ECG leads simultaneously, with the Leicester recorder, only 3 leads could be recorded at any one time. Recording the ECG at each stage of exercise at Leicester therefore occurred over a longer period. A disadvantage of this was that there was a greater chance for the heart rate to increase during recording. Although this could be controlled to a large extent by the operator of the test in the manner of loading the bicycle, the chances of having to reject a patient's data for analysis because of an unstable heart rate were potentially greater when using the Leicester recorder. This was in fact necessary in 1 of 49 cases in this study.

Procedures were otherwise similar at both centres. Above all, the objectives were the same, namely to obtain records of the ECG at progressively increased levels of heart rate.

Coronary Arteriography and Left Ventriculography.

Coronary arteriography and left ventriculography were performed in the patients in this study by the radiologists, consultant and registrar cardiologists at Groby Road Hospital, Leicester.

In all cases, the Judkins technique for coronary arteriography was used (Judkins & Judkins, 1984). With this method, radiopaque medium is injected into the left and right coronary arteries through two preshaped catheters introduced via the femoral artery. They are shaped such that the catheter shaft can be held against the inside (for the left coronary artery) and outside (for the right coronary artery) of the aortic curve while its tip is oriented into the orifice of the artery.

The following account is a description of the Judkins method of arteriography as used at Groby Road Hospital, Leicester.

The femoral artery is punctured with a needle at the level of the groin under local anaesthetic (Citanest 1%). A guide wire is passed through the needle into the artery. The needle is removed and a sheath catheter with haemostatic valve passed over the guide wire. The guide wire is then removed leaving the sheath in the artery. This acts as a conduit through which cardiac catheters can be easily passed.

For each of the left and right coronary arteries, the appropriately shaped catheter is fed through the sheath into the femoral artery. The progress of the catheter, being radiopaque, is screened on a monitor and its tip is advanced into the coronary orifice. When the tip of the catheter is in place, 2 to 10 ml radiopaque contrast medium (Niopam) is injected into the artery as a single bolus over about 5 seconds. Passage of the contrast medium through the artery is filmed with a 35 mm cine camera at a film speed of 50 frames a second. It is also recorded on video tape to enable a rerun of the injection to ensure that the display of the artery is satisfactory. Injection of contrast medium into the artery is repeated so that the artery can be filmed from the posterior aspect (PA), the left anterior oblique (LAO) and right anterior oblique (RAO) projections with cranial and caudal angulation. The catheter is then withdrawn.

Left Ventriculography.

Left ventriculography was also performed at the time of cardiac catheterisation, before coronary arteriography. A catheter is advanced into the left ventricle and 25 to 40 ml of radiopaque contrast medium injected over about 3 seconds. The left ventricle containing contrast medium is filmed from the RAO projection.

At the end of arteriography and left ventriculography, catheter and sheath are removed and haemostasis at the puncture site is induced by compression.

Coronary Arteriography at Leeds.

At Leeds, coronary arteriography was performed by either the Judkins or the Sones method (Sones & Shirey, 1962). Both are standard techniques of performing arteriography and differ only in the type of catheter used and the route by which these are introduced into the arterial system. In the Sones method, only one cardiac catheter is used for injection of radiopaque medium into both coronary arteries. It is introduced into the arterial system via the brachial, rather than the femoral, artery. These differences in technique are of no significance in that neither will affect the assessment of presence and severity of coronary disease from the arteriogram.

Results 1: The Analysis of the Exercise Test

Introduction.

It is the practice at Leeds that any newcomer to their team, involved in the analysis of their exercise test, requires a period of learning how to measure the ECG. These have taken from three to six months (Bishop, Adlakha, Boyle, Stoker & Mary, 1987).

This chapter presents a learning study of the Leeds' method of analysing the exercise ECG. The aim was to learn, through a collaboration with a member of the Leeds' team, their method of analysis with the purpose of reproducing their test at Leicester. In so doing, it was hoped to assess whether inadequate learning/reproduction of their method might limit reproducing the Leeds test at other centres.

Method.

To learn how to measure the ECG:

1. A period was spent at Leeds to observe this; a demonstration of the method was given.
2. Identical photocopies of a selection of exercise tests performed at Leicester were measured at both centres and the results compared.
1. The Leeds' Method of Measuring the ECG, Estimating the Maximal ST/HR Slope and Quantifying the Severity of Coronary Disease.

The Leeds' method of measuring the ECG, estimating the maximal ST/HR slope and quantifying the severity of coronary disease is described. This is based on the demonstration given at Leeds, correspondence with Leeds during this study and descriptions published in the literature (eg. Elamin, Mary, Smith & Linden, 1980; Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982; Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982).

A. The Leeds' Method of Measuring the Exercise ECG.

For each exercise ECG, only leads which had ST segment depression in the final stage of exercise were measured. Mean values of ST displacement and heart rate were estimated from measurements made of at least 10 cardiac

cycles at rest and at each stage of exercise.

i). Estimation of ST Segment Displacement.

ST segment displacement was measured with a 0.1 mm calibrated magnifying glass (x8; Flubacher & Co., Switzerland). It was measured relative to the PR level and at a point 80 ms from the J point; the point of flexure between the QRS complex and the ST segment which marks the end of ventricular depolarisation. The PR level was a pencil line drawn connecting the point marking the take off of the q or R wave of the complex being measured and the next one. The top of the pencil line was flush with the top of the ECG trace. If the signal was contaminated with noise, the line was drawn through the middle of the trace.

Measurement of ST segment displacement is shown in figure 1.1. PR represents the PR level of the complex PQRST being measured; J marks the J point (figure 1.1a). The left hand side of the graticule of the calibrated magnifying glass is placed on the J point (figure 1.1b). Since the width of the graticule is 2 mm, the scale on the right hand side of this, where ST segment displacement is measured, is an equivalent of 80 ms beyond the J point at a recording paper speed of 25 mm s^{-1} . In the example shown, there is 1.3 mm of ST segment depression.

As far as possible, consecutive complexes were measured to limit any variation due to changes in heart rate.

Complexes in which ST segment displacement might be masked were not measured. This included:

1. Abnormal complexes, or complexes atypical of those ultimately measured.
2. Complexes with underlying baseline wander (described by a vertical excursion of the PR segment greater than 4 mm).
3. Complexes distorted by artefacts for example noise due to muscle tremor.

Occasionally, if there was a complex with either a less well defined PR segment or less distinct J point than neighbouring complexes, this would not be measured to try and limit possible variation in measurement caused by an uncertainty of the reference points.

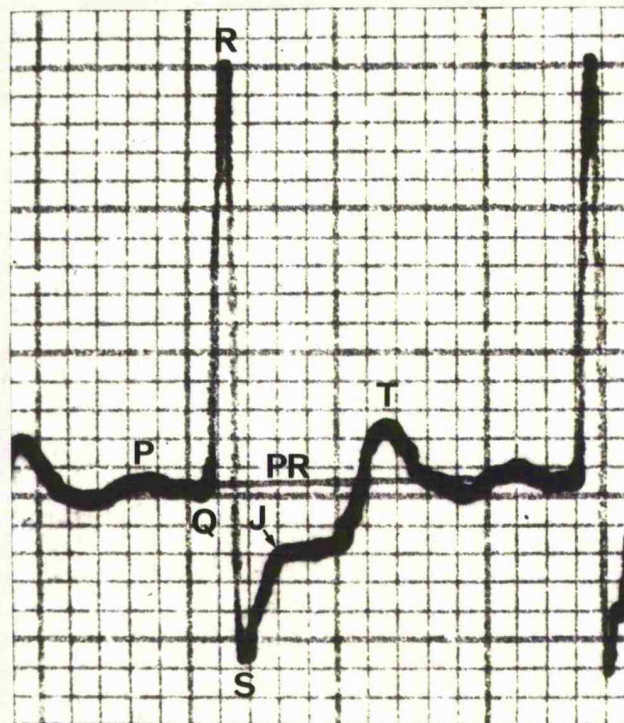
Figure 1.1. An illustration representing the measurement of ST segment displacement.

a. An ECG complex PQRS to be measured. PR is a line drawn connecting the points marking the take off of the R wave of the complex being measured and that following it. It represents the PR level against which ST segment displacement is measured. J marks the J point; the end of ventricular depolarisation.

- a. An ECG complex PQRS to be measured. PR is a line drawn connecting the points marking the take off of the R wave of the complex being measured and that following it. It represents the PR level against which ST segment displacement is measured. J marks the J point; the end of ventricular depolarisation.
- b. The measurement of ST segment displacement. The left hand side of a 0.1 mm calibrated magnifying glass (x 8; Flubacher & Co., Switzerland) is placed on the J point (J). Since the width of the graticule is 2 mm, the scale on the right hand side of this, where ST segment displacement is measured, is an equivalent of 80 ms beyond the J point where the recording paper speed is 25 mm s⁻¹. In this example, there is 1.3 mm ST segment depression.

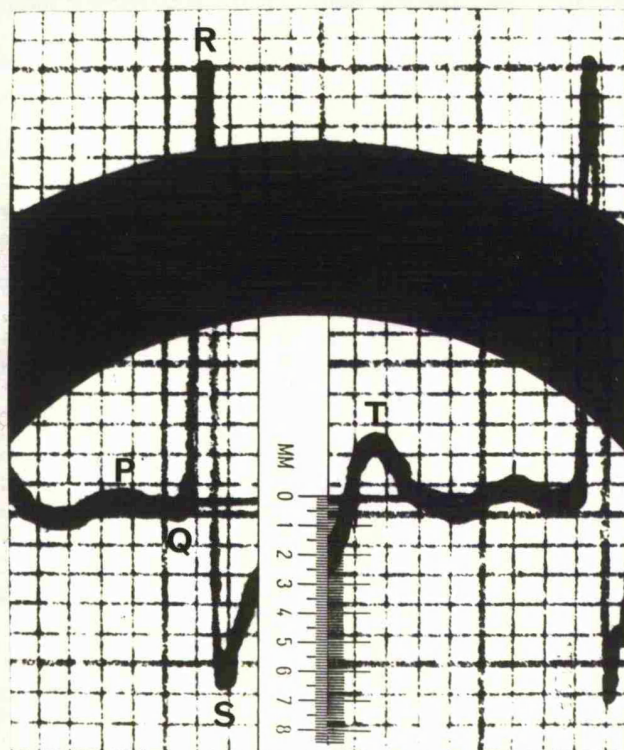
Figure 1.1. An illustration representing the measurement of ST segment displacement.

a.



(Magnification: x 4)

b.



(Magnification: x 4)

ii). Estimation of the Heart Rate.

The heart rate was estimated from the reciprocal of the R-R interval of each complex in which ST segment displacement was measured. The R-R interval was measured with a 0.5 mm graduated ruler.

B. Estimation of the Maximal ST/HR Slope.

In each patient, linear regression analysis of ST segment displacement on heart rate was performed using the mean values of ST displacement and heart rate. Slopes of regression were obtained from initially, the last three stages and then by successively including the data from each preceeding stage. Thus slopes would be derived from the final three stages, the final four, five and six stages respectively. The steepest of these slopes with a correlation coefficient significant at the level of $p < 0.05$ was the maximal ST/HR slope.

Figure 1.2 shows an example of the relation between ST segment displacement and heart rate in a patient with ST segment depression at the end of exercise in 10 leads (leads I, II, aVF, V1 to V6 and CM5). Table 1.1 shows the calculation of the maximal ST/HR slope. It presents the slopes of linear regression of ST segment displacement on heart rate obtained from the final three, four and five stages. The level of significance for each correlation is also shown. The maximal ST/HR slope, the steepest slope with a correlation coefficient significant at the level $p < 0.05$ was derived from data obtained from lead V4 in stages five, four and three. It had a value $111 \text{ mm/bpm} \times 10^{-3}$.

C. Quantifying the Severity of Coronary Disease.

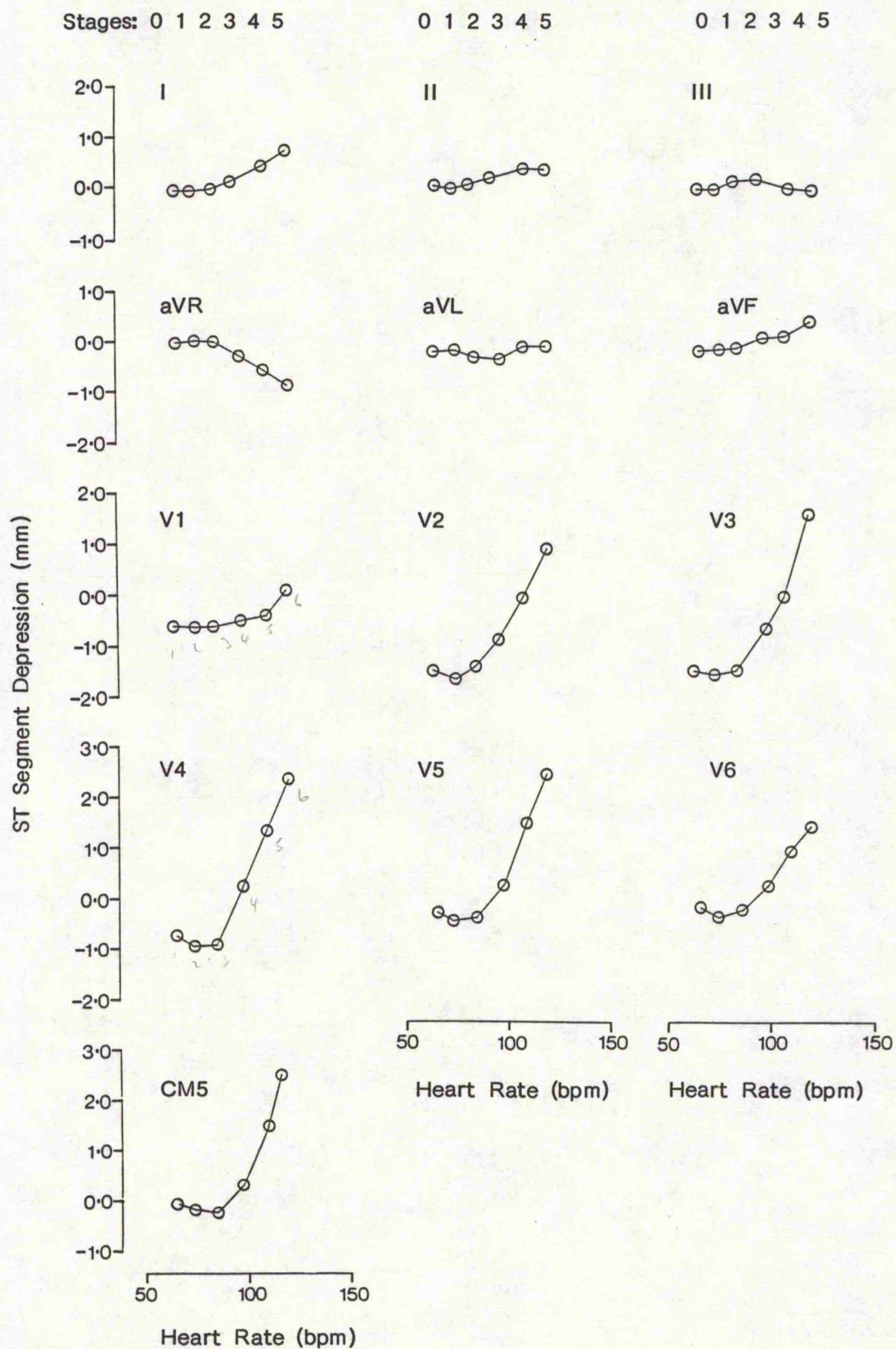
Depending on the maximal ST/HR slope obtained, the patient was classified as having either no significant disease, one, two or three vessel disease according to the disease category ranges of maximal ST/HR slope found empirically at Leeds as follows (Mary, Silverton, Boyle, Stoker, Smith & Linden, 1985):

Table 1.1. The calculation of the maximal ST/HR slope.

This represents the derivation of the maximal ST/HR slope for the patient whose exercise test data is shown in figure 1.2. Slopes of linear regression of ST segment displacement on heart rate (ST/HR slope) observed during the last 3, the last 4 and the last 5 stages of exercise in leads I, II, aVF, V1 to V6 and CM5 are presented. The level of significance (p) associated with the coefficient of linear correlation for each slope is also shown. The maximal ST/HR slope, the steepest slope with a correlation coefficient significant at the level $p < 0.05$ is obtained from lead V4; stages 5, 4 and 3 and has a value $111 \text{ mm/bpm} \times 10^{-3}$.

Stages	p	ST/HR slope (mm/bpm x 10 ⁻³)		p	Stages
Lead I			Lead II		
5,4,3	0.03	17	7	0.44	5,4,3
5,4,3,2	0.009	15	9	0.09	5,4,3,2
5,4,3,2,1	0.0006	15	10	0.01	5,4,3,2,1
Lead aVF			Lead V1		
5,4,3	0.27	15	21	0.23	5,4,3
5,4,3,2	0.05	14	16	0.07	5,4,3,2
5,4,3,2,1	0.02	12	12	0.04	5,4,3,2,1
Lead V2			Lead V3		
5,4,3	0.5	78	97	0.06	5,4,3
5,4,3,2	0.01	64	85	0.009	5,4,3,2
5,4,3,2,1	0.004	55	69	0.07	5,4,3,2,1
Lead V4			Lead V5		
5,4,3	0.004	111	97	0.01	5,4,3
5,4,3,2	0.008	94	79	0.01	5,4,3,2
5,4,3,2,1	0.007	76	3	0.009	5,4,3,2,1
Lead V6			Lead CM5		
5,4,3	0.02	61	112	0.07	5,4,3
5,4,3,2	0.01	50	84	0.03	5,4,3,2
5,4,3,2,1	0.006	41	62	0.02	5,4,3,2,1

Figure 1.2. The relation between ST segment displacement and heart rate during an exercise test in a patient with suspected coronary disease. ST segment depression was present in leads I, II, aVF, V1 to V6 and CM5.



<u>Maximal ST/HR slope</u> (mm/bpm $\times 10^{-3}$)	<u>Category of disease</u>
0 to 11	No significant disease
13 to 21	One vessel disease
32 to 59	Two vessel disease
69 and above	Three vessel disease

(The patient whose exercise test is illustrated in figure 1.2 was therefore classed as having three vessel disease).

2. A Comparison of Results of Exercise Tests Measured at Leeds and at Leicester.

Method.

Three sets of identical photocopies were taken of 8 patients' exercise ECG obtained during exercise tests performed at Leicester. One set was sent to the Department of Cardiovascular studies, Leeds, for measurement and derivation of the maximal ST/HR slope. The same ECG complexes that were measured at Leeds for each test were subsequently measured at Leicester on the second set of photocopies. This included 2072 complexes from 54 ECG leads comprising a range of all the 13 leads (the standard 12 and the CM5 lead).

Results.

The maximal ST/HR slopes obtained at both centres for the 8 tests measured are shown in table 1.2 and illustrated in figure 1.3a and 1.3b. (In figure 1.3a, the error bars represent the standard error of the slope; in figure 1.3b, the error bars represent the 95% confidence interval about the slope. The shaded areas marked NSD, 1VD, 2VD and 3VD show the ranges of maximal ST/HR slope indicating no significant coronary disease, one, two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980.)

Using Students' two tailed t-test for unpaired data, a significant difference ($p < 0.05$) between the slopes obtained at the 2 centres was demonstrated in 2 cases; 1 and 3 (table 1.2). Different diagnostic results

Table 1.2. A comparison of the maximal ST/HR slopes of 8 patients exercise ECGs measured manually at Leeds and at Leicester (Leic).

The maximal ST/HR slopes \pm the s.e, the ECG leads from which these were derived and the corresponding diagnosis according to the Leeds Test ranges obtained at both centres for each patient is shown. The level of significance of the difference between the slopes obtained at the two centres is also presented.

Case	Centre	Maximal ST/HR slope \pm s.e (mm/bpm $\times 10^{-3}$)	ECG lead	Diagnosis (vessel disease)	Level of significance of difference between slopes
1	Leic	27.8 \pm 4.0	V1	1 to 2	0.0006
	Leeds	17.1 \pm 1.7	V1	1	
2	Leic	115.2 \pm 4.3	V2	3	0.15
	Leeds	120.4 \pm 2.6	CM5	3	
3	Leic	76.4 \pm 4.0	CM5	3	0.02
	Leeds	59.7 \pm 9.4	V5	2 to 3	
4	Leic	116.4 \pm 14.8	V4	3	0.62
	Leeds	108.8 \pm 23.3	V4	3	
5	Leic	57.6 \pm 4.2	V2	2	0.36
	Leeds	54.2 \pm 5.5	V2	2	
6	Leic	13.7 \pm 1.1	V6	1	0.28
	Leeds	12.3 \pm 2.1	V6	0 to 1	
7	Leic	22.8 \pm 4.5	CM5	1 to 2	0.55
	Leeds	21.3 \pm 1.6	CM5	1	
8	Leic	53.3 \pm 1.2	V4	2	0.72
	Leeds	54.0 \pm 2.9	V4	2	

Figure 1.3a. The maximal ST/HR slopes (\pm the standard error) from 8 patients exercise tests measured manually at Leeds and Leicester. The shaded areas marked NSD, 1, 2 and 3 VD denote the ranges of maximal ST/HR slope which indicate no significant disease, one, two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980.

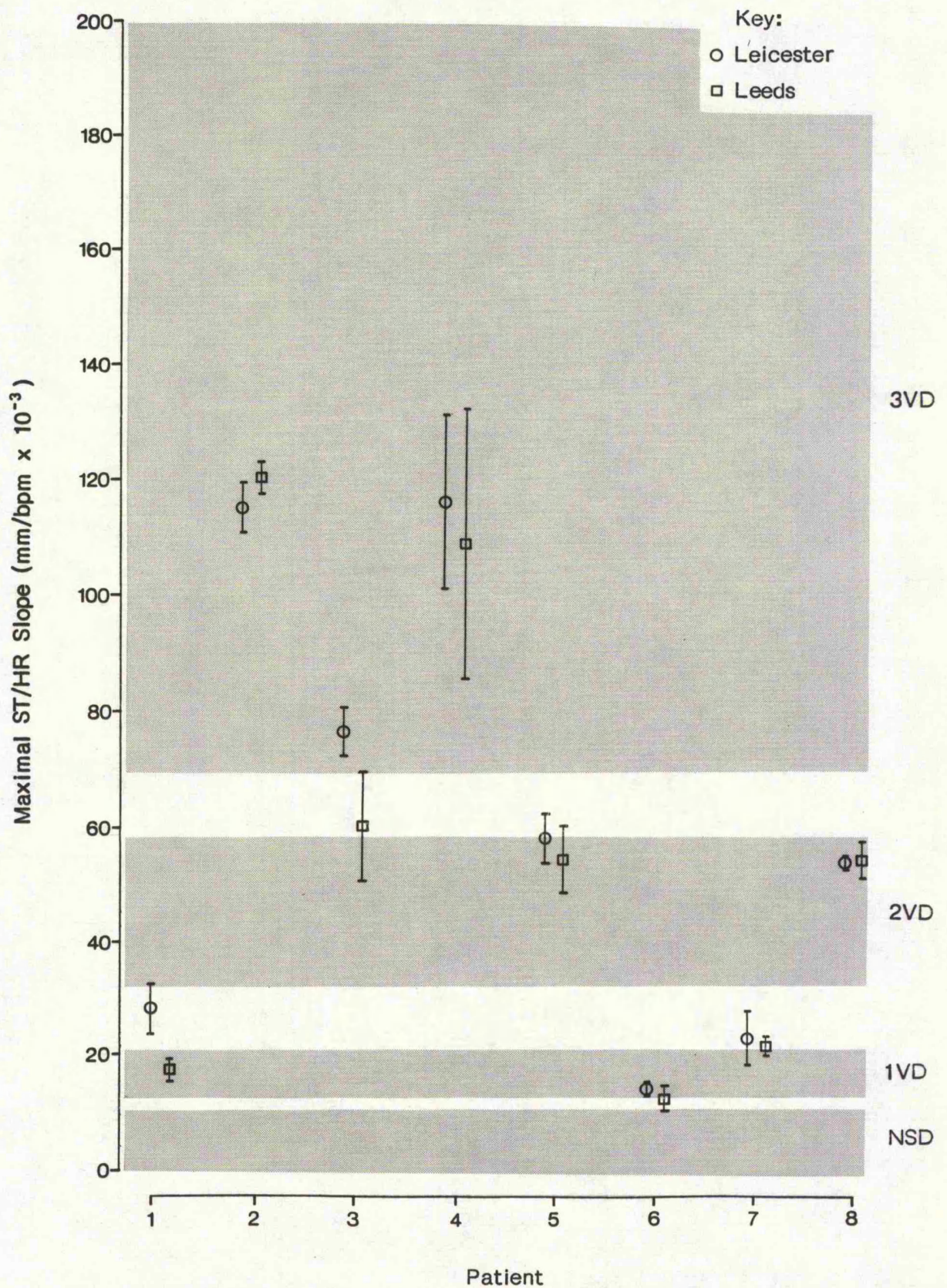
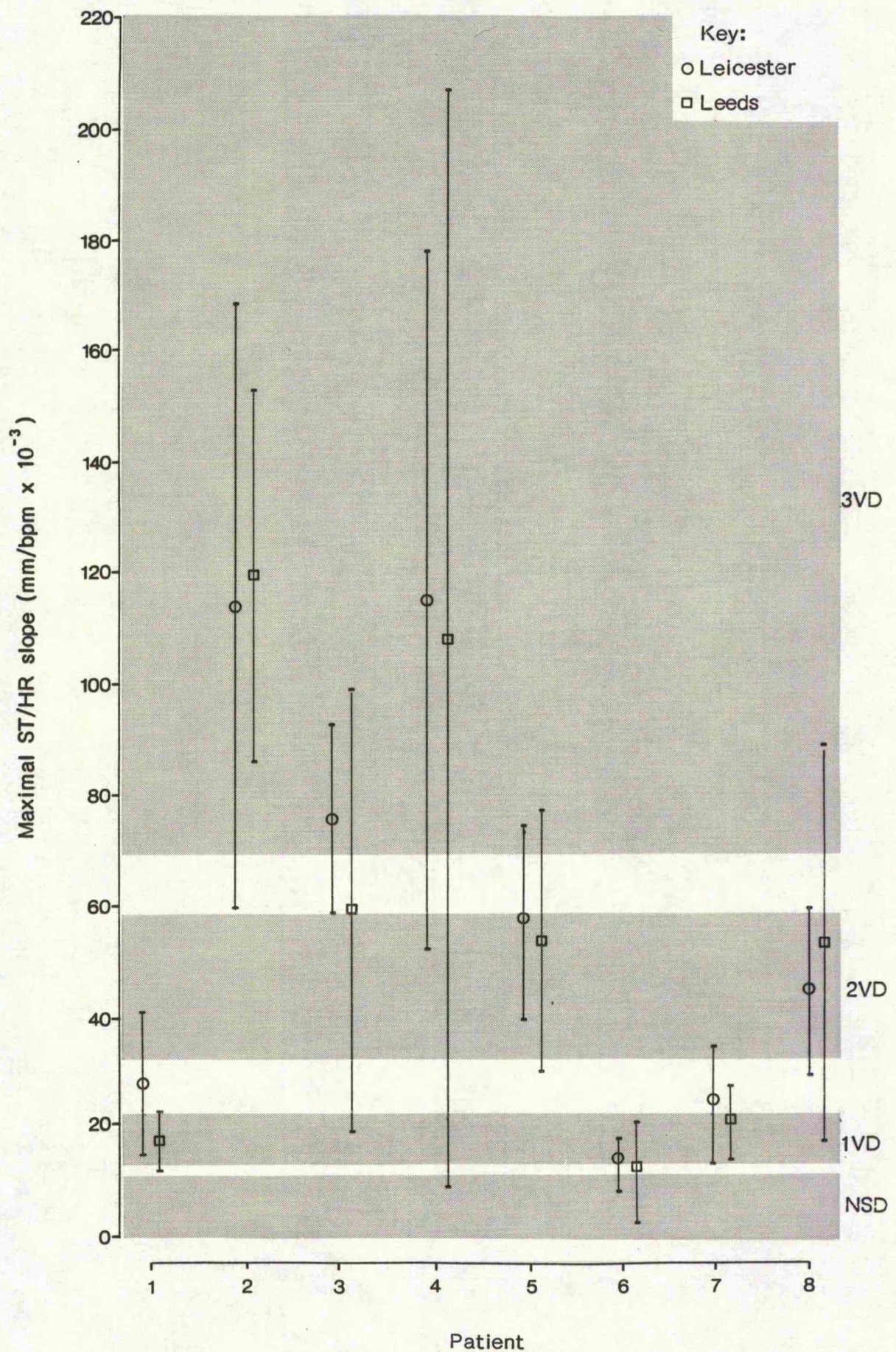


Figure 1.3b. The maximal ST/HR slopes (\pm the 95% confidence intervals) from 8 patients exercise tests measured manually at Leeds and Leicester.



however were obtained in 4 out of the 8 exercise tests measured. A different diagnostic result could be obtained by the two centres despite there being no demonstrable difference ($p < 0.05$) in the slopes since the diagnosis depends on the position of the slope relative to the Leeds' disease category ranges (eg. cases 6 and 7; figure 1.3).

The Probability of Repeating the Diagnostic Result.

To present the above results in terms of an ability to reproduce Leeds' diagnostic result, the confidence associated with each diagnostic result was calculated. These are presented in table 1.3. The probability of repeating the Leeds' diagnostic result using Leeds' data is shown in column A; that using the Leicester data is shown in column B. Column C is the probability of repeating the diagnostic result obtained at Leeds using the data obtained at Leicester. The latter was only 50%. The cause of this poor reproducibility was investigated.

The Cause of the Poor Reproduction of Leeds' Results Obtained at Leicester.

Measurements of heart rate and ST segment displacement from the two centres were compared to identify whether the measurement of either or both of these variables was a cause of the poor reproduction observed.

1. A Comparison of Heart Rate Measurements Made at Leeds and at Leicester.

Linear regression analysis of heart rate measurements from Leicester on heart rate measurements from Leeds gave the following characteristics:

correlation coefficient = 1.00

slope of linear regression = 0.99

95% confidence interval about the slope = 0.99 to 1.00.

Estimate of the y-intercept = 0.24 bpm

95% confidence interval on the y-intercept = -0.07 to 0.41 bpm.

Because a slope value of 1.00 and a y-intercept value of 0.00 bpm were within the 95% confidence interval estimates of the slope and y-intercept estimates obtained, it was assumed that there was no significant difference

Table 1.3. The probability of being able to repeat the patient's diagnostic result.

A: with measurements made at Leeds.

B: with measurements made at Leicester and

C: the probability of reproducing the diagnostic result obtained at Leeds using the measurements made at Leicester.

Case	Probability of Being Able to Repeat the Diagnostic Result		
	A	B	C
1	0.90	0.72	0.03
2	0.98	0.97	0.97
3	0.31	0.90	0.03
4	0.86	0.96	0.96
5	0.73	0.60	0.60
6	0.32	0.69	0.20
7	0.42	0.82	0.22
8	0.79	0.92	0.92
Mean Probability:	0.67	0.82	0.50

($p < 0.05$) between the heart rate measurements made at both centres.

2. A Comparison of ST Segment Displacement Measurements Made at Leeds and at Leicester.

Linear regression analysis of ST segment displacement measurements from Leicester on ST segment displacement measurements from Leeds gave the following characteristics:

correlation coefficient = 0.74

slope of linear regression = 0.74

95% confidence interval about the slope = 0.64 to 0.84

Estimate of the y-intercept = -0.11 mm

95% confidence interval on the y-intercept = -0.21 to -0.02 mm.

Because a slope value of 1.00 and a y-intercept value of 0.00 mm did not occur within the 95% confidence interval estimates of the slope and y-interval estimates obtained, it could not be assumed that there was no significant difference ($p < 0.05$) between the heart rate measurements made at the two centres.

Reasons for Differences in Measurement of the ST Segment.

To explain the differences in measurements of ST segment displacement, each ECG complex measured at both centres was examined with the magnifying eyepiece. Any queries about the Leeds' measurement was satisfied by correspondence.

In complexes where different measurements were obtained at the two centres, this occurred because:

1. Different isoelectric levels had been used.
2. There were differences in identifying the J point.

These and their effect on the maximal ST/HR slope are discussed.

Differences in Measuring ST Segment Displacement at Leeds and Leicester and their Effect on the Maximal ST/HR Slope.

1. Different Isoelectric Levels.

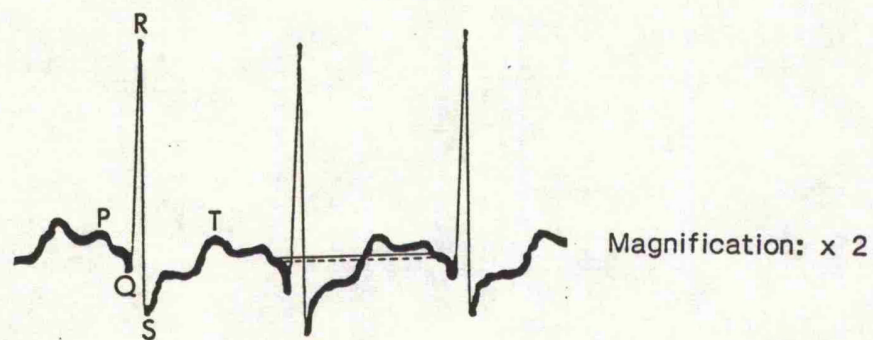
The isoelectric level drawn at Leicester was usually higher than that drawn at Leeds. This was largely because in the early stages of this study, there was some confusion about the definition of the PR level. From the demonstration given at Leeds, it was taken that the reference level used was the plateau of the PR segment. Therefore, a pencil line was drawn to pass through the PR plateaux (the top of the pencil line flush with the top of the ECG trace) rather than through the point marking the take off of the q or R wave on either side of the ST segment measured. If the signal was contaminated with noise then the line was drawn through the middle of the trace and if the PR segment was not horizontal but downsloping towards the following q or R wave, then the PR level was drawn through the mid point of the vertical excursion of the segment. This error in drawing the PR level was not helped by the Leeds' method described in the literature. The PR level is described fairly ambiguously as "the line drawn between two consecutive PR segments" (eg. Elamin, Mary, Smith & Linden, 1980; Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982; Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982).

The level as used at Leeds was because it was more easily identifiable than a representative point on the PR plateau which is not always horizontal. Using the end of the PQ segment would therefore promote more reproducible measurements.

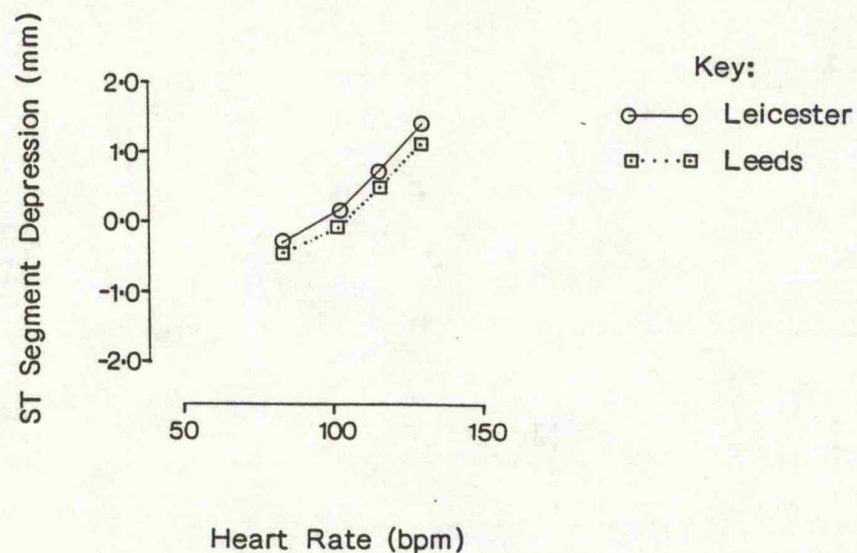
An example of a complex where different PR levels were used at the two centres because of different definitions describing these is shown in figure 1.4a. This difference in drawing the reference level from which ST displacement was measured typically caused a vertical and upward displacement of ST/HR slopes obtained at Leicester relative to those obtained at Leeds. Although it often produced a large difference between estimates of ST segment displacement, the effect on the ST/HR slope was

Figure 1.4. An illustration of the effect of using different PR reference levels on the maximal ST/HR slope.

- a. An example of a complex PQRST where different PR levels were drawn at Leeds and Leicester as a result of different definitions to define this. The continuous line represents the PR level drawn at Leicester based on the definition; 'the level of the PR segment plateau'. The broken line represents the PR level drawn at Leeds based on the definition; 'the level of the point of take off of the q wave'.



- b. The effect on the maximal ST/HR slope of using the different PR levels as illustrated in figure 1.4a is a typical vertical and upward displacement of the ST/HR slope obtained at Leicester (continuous line) relative to that obtained at Leeds (broken line).



variable. In some cases, as shown above (figure 1.4), the relative positions of the two isoelectric levels were constant throughout the exercise test; the difference between the ST segment depression was systematic. In these cases, the ST/HR slopes obtained at both centres, although separated vertically, were parallel. There was therefore little difference in their slopes (figure 1.4b). In other cases however, a PR segment which was initially horizontal (therefore promoting identical isoelectric levels according to the two definitions) would in subsequent stages become declined towards the Q (or R) wave causing a separation of the two levels of reference. As the test proceeded, the difference between displacement measurements obtained at Leeds and Leicester increased producing different ST/HR slopes.

2. Different J Points.

Slight differences in locating the J point also contributed to different values of ST segment displacement. This was particularly so when the ST segment was not horizontal in the region 80 ms after the J point. Small variations in locating the J point could cause large variations in the ST segment displacement measured.

Different points were identified as the J point when either:

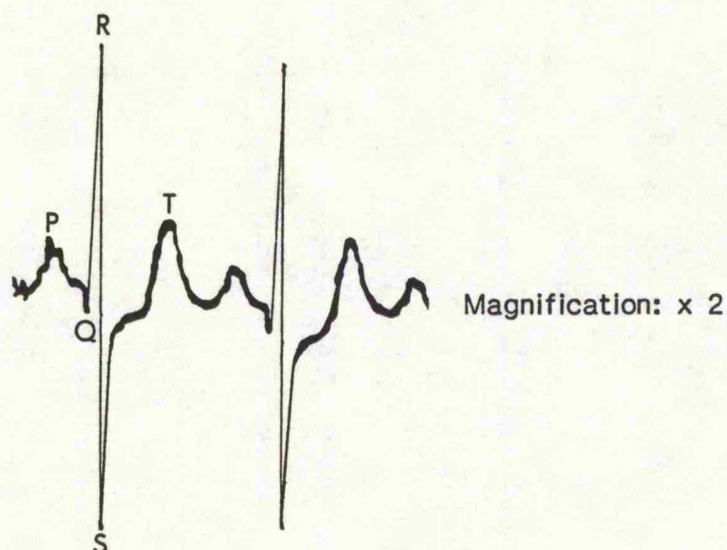
1. The QRS complex merged imperceptibly with the ST segment.
2. The curvature of the J region was such that two different positions could equally represent the J point.
3. The J point was represented by a distinctly different landmark.

These are illustrated:

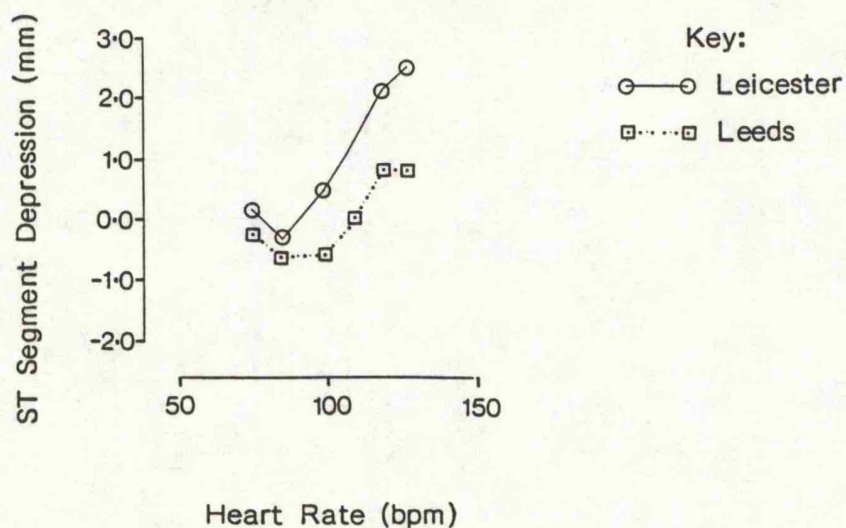
1. Figure 1.5 shows a complex where the J point, marking the end of ventricular depolarisation is not very obvious because of the gradual transition from the S wave to the ST segment. Identifying the J point is therefore subjective. Small differences in locating the J point in this example caused large differences in ST segment displacement measured because the 80 ms region from this point is coincident with the almost vertical limb of the T wave. In this example, Leeds used a J point beyond that used by

Figure 1.5. An illustration of an effect of using different J points on the maximal ST/HR slope.

- a. A typical complex PQRSST where, because of the gradual transition from the S wave to the ST segment, locating the J point is subjective. This can cause large differences in the estimate of ST segment displacement when the 80 ms region beyond the J point coincides with the steeply rising limb of the T wave.



- b. By using a point at a later latency at Leeds to mark the J point, this has caused a divergence from linearity of the maximal ST/HR slope (broken line) compared with that obtained at Leicester (continuous line) since the ascending limb of the T wave rather than the ST segment is being measured.



Leicester. This caused a marked difference in the ST segment depression measured in the final stage of exercise (heart rate = 127 bpm). The effect of this on Leeds' ST/HR slope (broken line; figure 1.5b) is a divergence from linearity in the terminal stage. (The upward shift of the Leicester ST/HR slope produced by using a different isoelectric level as described above is also apparent in this example).

2. Figure 1.6 shows an example of a complex in which different positions could be equally regarded as the J point. The points used to represent the J point at Leeds and Leicester are marked by the broken and continuous lines respectively. The effect on the maximal ST/HR slope was, as described above, dependant on the gradient of the signal in the region 80 ms beyond the J point.

3. Figure 1.7a shows an example of a complex where distinctly different locations were used to represent the J point causing different estimates of mean ST segment displacement and therefore, maximal ST/HR slope.

These complexes were obtained from lead V1 and have rSr' configurations. (r denotes a first small positive wave, S denotes a first large negative wave and r' denotes a second small positive wave). In a normal V1 complex, there is no r' wave and the J point is at the region of inflection between the S wave and the ST segment. In the above case, at Leeds, the r' wave was used to mark the J point. At Leicester however, the point of inflection between the r' wave and the ST segment was used. The level of the ST segment was consequently measured at a later latency at Leeds than at Leicester. Differences in ST depression are increasingly apparent with increasing heart rate as the gradient of the ST segment increased (figure 1.7b).

It is pertinent to note that a similar rSr' configuration also occurred in lead aVR of the same patient. In this case however, the J point used by Leeds was the same as that used by Leicester namely the point of inflection between the r' wave and the ST segment. This demonstrates an inconsistency by Leeds in the choice of J point with respect to the configuration of the complex. When Leeds were questioned about this, it was said that normally

Figure 1.6. An example of a complex, PQRSST where two different points could be equally regarded as the J point. The points that were used to represent the J point at Leeds and Leicester are indicated.

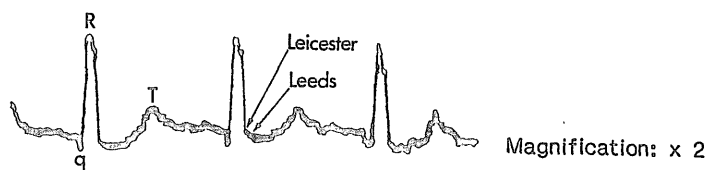
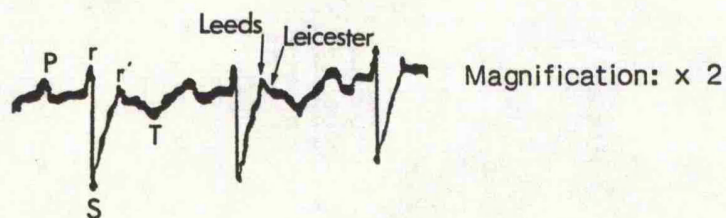
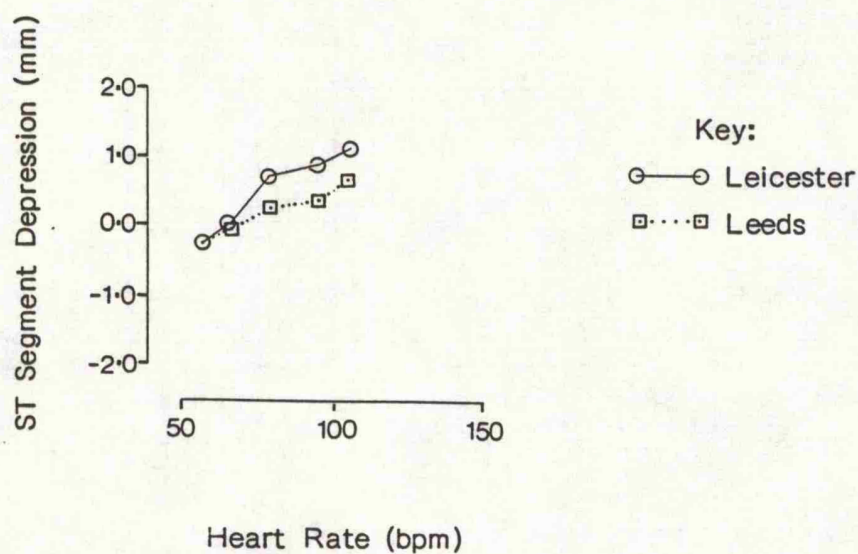


Figure 1.7. A case where the J point was represented by a distinctly different landmark at Leeds and at Leicester and the effect of this on the maximal ST/HR slopes obtained.

- a. An ECG complex PQRS_T showing the different landmarks used at each centre to represent the J point.



- b. Using the different locations to represent the J points shown in figure 1.7a, the maximal ST/HR slope obtained at Leicester (continuous line) was steeper than that obtained at Leeds (broken line). Increasing differences in the estimate of ST segment displacement occurred with increasing heart rate as the gradient of the ST segment increased.



the inflection between the r' wave and the ST segment would be used as the J point however, in the above case, it was thought that the r' wave provided a more consistently determinable reference point.

Remeasurement of the Exercise ECG by Leicester.

That observer variability in locating the J point and the use of different criteria to determine the PR level was responsible for the different diagnoses obtained at the two centres in the four of the eight patients was demonstrated by remeasurement.

The ST segments of the exercise ECGs of patients 1, 3, 6 and 7, in whom the diagnostic results obtained at both centres differed were remeasured at Leicester on the third set of photocopies of the exercise ECGs. Measurements were made in a manner more closely resembling that used at Leeds based on the examination of the complexes measured and described above.

The maximal ST/HR slopes obtained by remeasurement at Leicester for the 4 patients are presented in table 1.4. The results obtained at Leeds are also presented for comparison. A significant difference ($p < 0.05$) between pairs of slopes obtained from the two centres could not be demonstrated (Students' two tailed t-test). The same diagnostic result was obtained by both centres in all but one; case 6. In this patient however, the difference between the diagnostic results obtained by the two centres is borderline. The maximal ST/HR slope obtained by Leicester is the upper limit of the no significant disease range, the maximal ST/HR slope obtained by Leeds placed the patient just within the no significant disease to one vessel disease category.

The Probability of Repeating the Diagnostic Result After Remeasurement at Leicester.

The probability of repeating the diagnostic result after remeasurement at Leicester of the exercise ECG of patients 1, 3, 6 and 7 were calculated and are presented in table 1.5. The mean probability of repeating Leeds' diagnostic result using the data obtained by Leicester improved from 0.50 to 0.69. It reflects the same order of confidence of diagnostic results

Table 1.4. The maximal ST/HR slopes \pm the s.e after remeasurement at Leicester (Leic) in 4 cases in whom the first diagnostic result obtained at Leicester differed from that obtained at Leeds. The ECG leads from which these were derived, the corresponding diagnosis according to the Leeds Test ranges and the level of significance of the difference between the slopes obtained at the two centres is also shown.

Case	Centre	Maximal ST/HR slope \pm s.e (mm/bpm $\times 10^{-3}$)	ECG lead	Diagnosis (vessel disease)	Level of significance of difference between slopes
1	Leic	17.6 \pm 1.7	V1	1	0.65
	Leeds	17.1 \pm 1.7	V1	1	
3	Leic	62.9 \pm 8.8	V5	2 to 3	0.64
	Leeds	59.7 \pm 9.4	V5	2 to 3	
6	Leic	11.0 \pm 1.6	V6	0	0.36
	Leeds	12.3 \pm 2.1	V6	0 to 1	
7	Leic	20.9 \pm 2.7	CM5	1	0.81
	Leeds	21.3 \pm 1.6	CM5	1	

Table 1.5. The probability of being able to repeat the patient's diagnostic result after remeasurement of the ECG of patients 1, 3, 6 and 7 at Leicester.

A: with measurements made at Leeds.

B: with measurements made at Leicester and

C: the probability of reproducing the diagnostic result obtained at Leeds using the measurements made at Leicester.

Case	Probability of Being Able to Repeat the Diagnostic Result		
	A	B	C
1	0.90	0.89	0.89
2	0.98	0.97	0.97
3	0.31	0.37	0.37
4	0.86	0.96	0.96
5	0.73	0.60	0.60
6	0.32	0.49	0.33
7	0.42	0.46	0.46
8	0.79	0.92	0.92
Mean Probability:	0.67	0.71	0.69

obtained by Leeds; 0.67 (column A).

Reproducibility of Measuring the Exercise ECG at Leicester.

To test the reproducibility of measuring the ECG at Leicester, 100 complexes were chosen at random from all the exercise ECGs obtained at Leicester. Heart rate and ST segment displacement were measured on two occasions separated by a period of four weeks.

Results.

1. Heart Rate Measurements.

Linear regression analysis of heart rate measurements made on the two occasions gave the following characteristics:

correlation coefficient = 1.00

slope of linear regression = 0.99

95% confidence interval about the slope = -0.6 to 7.95

Estimate of the y-intercept = 0.14 bpm

95% confidence interval on the y-intercept = -0.01 to 0.29 bpm.

2. ST Segment Displacement Measurements.

Linear regression analysis of ST segment displacement measurements made on the two occasions gave the following characteristics:

correlation coefficient = 0.95

slope of linear regression = 0.94

95% confidence interval about the slope = 0.87 to 1.00

Estimate of the y-intercept = -0.05 mm

95% confidence interval on the y-intercept = -0.12 to 0.01 mm.

Because a slope value of 1.00 and a y-intercept value of 0.00 (bpm,mm) were within the 95% confidence interval estimates of the slope and y-intercept estimates obtained from both heart rate and ST segment displacement measurements respectively, it was assumed that there was no

significant difference ($p < 0.05$) between the two sets of measurements.

Therefore, with experience of measuring the exercise ECG, reproduction of heart rate and ST segment displacement measurements is possible.

Conclusion and Discussion.

1. The Leeds' method of analysing the exercise ECG is described.
2. It is shown that both observer variation in locating the J point and the PR level on the ECG and the use of different criteria to define these reference points can limit reproducing the maximal ST/HR slope and therefore, the Leeds' test results.
3. This however can be resolved to a large extent by an adequate learning of, and experience with, Leeds' method of measurement.

The ultimate goal when measuring a variable such as ST segment displacement is to obtain an estimate with sufficient precision to be able to test a proposed hypothesis. Measurement of ST displacement is complicated because the ECG has subtle beat to beat variations in its configuration. These are largely a result of changes of the hearts' position within the thorax during contraction and relaxation, movement of the ECG electrodes relative to the heart through respiratory movements of the chest and a contamination of the signal with electromyographic noise.

The variance of measurements of ST segment displacement can be limited by:

1. Making a large number of measurements.
2. Reducing factors which alter the real or apparent magnitude of the displacement.
3. Having a comprehensive definition of the manner of measurement which will encompass variations in ECG waveforms.
4. Measuring in a consistent manner.

Points 1 and 2 were observed by Leeds. Points 3 and 4 are to an extent inter-related and were the main cause of difference in results obtained at the two centres:

1. Each estimate of ST displacement was derived from at least 10

measurements. This is a practical number and reflects a compromise between a), measuring a number of complexes to reduce variance of measurement and b), a finite time is required to record the ECG from all leads at each stage while the patient is still exercising. The shorter the recording time (determining the number of complexes that can be measured), the less likely the heart rate will increase and change the extent of ST segment displacement. By measuring ST displacement over at least 10 complexes, changes in its magnitude due to respiratory movements are more likely to cancel than if, for example, only 2 or 3 complexes are measured. Similarly, it would reduce the effect of electromyographic noise.

2. When measuring the ECG, attempts were made by Leeds to limit factors which may alter (a), the real or (b), the apparent magnitude of ST displacement at any stage:

- a). In the ischaemic myocardium, ST segment depression increases with increasing heart rate. To limit (if any) changes in heart rate and therefore ST segment displacement, as far as possible consecutive complexes were measured.
- b). The magnitude of ST segment displacement can be masked by excessive baseline wander, electromyographic noise and abnormal and atypical complexes. Such complexes were not measured to avoid a biased estimate of ST displacement.

3. The degree to which a method can be reproduced depends largely on how well it can be/is defined. Inexplicit definition of Leeds' method concerning the reference PR level was the main cause for the initial poor reproduction of their results in this exercise. This however is easily remedied by a more descriptive definition. Because of the subtle beat to beat variations in complex configurations, a definition must consider commonly occurring variations in the ECG which could cause ambiguities in measurement. Rules could then be set to resolve these. For example, based on what was seen in this study, where a complex has two points which could equally represent the J point, it could be decided to systematically take the first point as the

point of reference.

In the case of manual ECG measurements, definition cannot entirely ensure that this will always be reproducible. For example, where the end of the QRS complex merges gradually into the ST segment, recognition of the J point is subjective and therefore potentially variable from one measurement to the next. Differences in the manual measurement of this type of complex are likely to persist regardless of any definition of method.

4. A definition of measurement unless followed, or exceptions to the rule are themselves defined, defeats its purpose. This was another source of disparity of maximal ST/HR slopes obtained from the two centres. It was the tendency for Leeds to use a consistently determinable reference point over and above what might otherwise be regarded as the defined point. Granted, this will possibly limit the variance of measurement, however, this could be at the cost of altering the value of the variable.

In summary:

1. Without any guidance on the Leeds method of measurement, different maximal ST/HR slopes may easily occur at different centres through differences in measurement of the ECG.
2. It is suggested that a more explicit definition of the method used by Leeds which considers beat to beat variation in ECG configuration would limit a disparity of results at different centres.
3. Although it was shown that measurement can be faithfully reproduced by one observer, variance in measurement particularly between observers is inevitable and unavoidable where locating the J point is subjective. This could be limited by periodic cross comparisons and discussions of measurements in attempts to standardise these.

Results 2: The Coronary Arteriogram as an Index of Coronary Disease.

Introduction.

The maximal ST/HR slope, at Leeds, has to date correctly indicated the extent of coronary disease as defined by the arteriogram in 346 out of 352 (98%) cases (Bishop, Adlakha, Boyle, Stoker & Mary, 1987). That the maximal ST/HR slope could correctly predict the severity of coronary disease according to the arteriogram to this degree implies that the arteriogram, as assessed at Leeds, is itself a reliable index of the disease. This however is at odds with the general belief, according to the literature, that arteriogram assessment can produce different results when assessed either by different observers or the same observer on different occasions (eg. Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976).

In none of the studies from Leeds is the reproducibility of arteriogram assessment presented. Inter observer variability is however suggested in the studies by Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982 and Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982. It is described that when the arteriograms were read by more than one observer, any differences in results were resolved in a further joint study. Although presenting the arteriogram result as the consensus opinion of more than one reader may limit observer variability, it is questionable that it would eliminate it altogether (Galbraith, Murphy & de Soyza, 1978).

Observer variability associated with the assessment of the arteriogram implies a limitation in its use as an index of coronary disease which might cause a mismatch between exercise test and arteriogram results. This chapter presents an assessment of the arteriogram, as assessed at Leeds, as an index of the severity of coronary disease. The aims were:

1. To find out at first hand how Leeds used the arteriogram as a quantitative index of coronary disease with an intent to reproduce their test at Leicester.
2. To test the reproducibility of assessing the arteriogram using Leeds' method.

In so doing, it was hoped to assess whether:

1. There were any features of the Leeds' method of evaluation which might reduce observer variability (as implied in the literature) that would otherwise present a flaw in the use of the arteriogram as an index of disease severity.
2. Grading the severity of coronary disease from the arteriogram could cause a discrepancy between exercise test results observed at Leeds and at other centres.

Method.

1. To find out how Leeds evaluated the arteriogram so that their method could be repeated at Leicester, a meeting was held between three readers from the Leeds' team and two readers who would prospectively assess the arteriogram at Leicester. The readers from Leeds explained and discussed their method used.

2. To test the reproducibility of the Leeds' method of assessing the arteriogram:

- a). The results of 26 arteriograms read at both Leeds and Leicester were compared.
- b). The results of 7 arteriograms read on 2 separate occasions by the 2 Leicester readers were compared.

The Arteriogram Readers.

The arteriogram readers from Leicester were consultant cardiothoracic surgeon J.S. Bailey (JSB) and consultant cardiologist V.J. Redding (VJR). Both were experienced in assessing arteriograms for the routine management of their patients.

The arteriogram readers from Leeds were consultant cardiologists R. Boyle (RB), D.R. Smith (DRS) and J.B. Stoker (JBS). All three had been involved in assessing the arteriogram for correlation with the maximal ST/HR slope at Leeds (eg. Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982).

1. The Leeds' Method of Assessing the Arteriogram.

The following account of the Leeds' method of assessing the arteriogram is based on the meeting held between the five readers.

Severity of coronary disease was graded using the 0, 1, 2, 3 vessel notation. Coronary vessel disease was defined as a significant stenosis in the proximal to middle segments of any of the 3 major coronary arteries. The arteries were the right coronary artery (RCA), the left anterior descending artery (LAD) and the left circumflex artery (LCFX); the proximal to middle segments were from the arteries' origin upto and including the junction with its first major branch (Appendix I). As a general rule, the appropriate segments were: for the LAD - from its origin upto and including the junction with the second diagonal artery; for the LCFX - from its origin upto and including the junction of the largest of either the most dominant lateral branch or the obtuse marginal artery; for the RCA - from its origin upto and including the junction of either the major right ventricular branch or the acute marginal branch. Any stenoses beyond these major branches were not assessed. The relative distribution of the arteries (either balanced or left or right dominant) was not taken into account when assessing disease. Thus, the RCA was always counted as one vessel even if it was small and non dominant. Further, if the left coronary system divided into 3 major vessels; an LAD, a LCFX and an intermediate ramus, it was still counted as two vessels: the LAD was counted as one vessel and the larger of the intermediate ramus and the LCFX was counted as the other. If the CFX, LAD and intermediate ramus were of similar calibre then only the LAD and the CFX arteries were considered.

A significant stenosis was one which was thought would reduce perfusion of the myocardium by an amount sufficient to produce ischaemia on exercise. The stenosis was assessed from the view in which it looked the most severe. The potential additive effect of length and stenoses in series did not add to the assessment of severity: the degree of a stenosis was estimated at its narrowest point and where there was more than one stenosis, only the most

severe was considered. Any potential effect of collateral vessels was also not considered.

This method of evaluating the arteriogram is essentially a more detailed account of what is described in the Leeds' publications (eg. Elamin, Mary, Smith & Linden, 1980). It is similar in all respects except for the definition of a significant stenosis. In the Leeds' publications, a significant stenosis was defined as one which reduced the lumen diameter by at least 75% whereas, in the meeting described above, it was described as one which was thought would produce myocardial ischaemia on exercise. This difference was resolved in that during assessment, a stenosis was labelled as a 75% or more restriction in lumen diameter if, first, it was thought that it would cause myocardial ischaemia on exercise.

2. The Reproducibility of Assessing the Arteriogram Using Leeds' Method.

A. A Comparison of Results of Arteriograms Read at Both Leicester and Leeds. Method.

Twenty six arteriograms were read independently by JSB and VJR at Leicester using the Leeds' method described above. The results were reported by both readers in terms of the number of coronary arteries significantly occluded (0 to 3) and included general comments on the degree and location of stenoses and the left ventricular contraction.

The same 26 arteriograms were then sent to Leeds and were read by RB, DRS and JBS. The results were reported in terms of the number of arteries significantly occluded (0 to 3) and were the consensus opinion of the 3 readers. Location and estimated degree of stenosis and the left ventricular score were also given.

Results.

The number of coronary arteries thought to be significantly occluded in each arteriogram were compared between the following:

1. JSB and the consensus of RB, DSR and JBS.
2. VJR and the consensus of RB, DSR and JBS.
3. JSB and VJR.

The arteriogram results presented at Leeds were the consensus opinion of the three readers since this was their normal practice for correlation with the maximal ST/HR slope when there was more than one reader (eg. Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982). The results from Leicester were the independent results of each reader since it was thought that the consensus opinion of only two readers was likely to reflect the result of the more dominant person.

1. A Comparison of the Arteriogram Results Obtained at Leeds and by JSB.

The results of the 26 arteriograms read at Leeds and by JSB are presented as a scattergram in figure 2.1.

The same results were obtained for 16/26 (62%) arteriograms. In 8 (31%), the result differed by one grade. In 2 (8%), the result differed by two grades. Of all these results, those of JSB were greater than those of Leeds.

2. A Comparison of the Arteriogram Results Obtained at Leeds and by VJR.

The results of the 26 arteriograms read at Leeds and by VJR are presented in figure 2.2.

The same results were obtained for 18/26 (69%) arteriograms. In the remaining 8, the result differed by one grade. Of four of these results, those of Leeds were greater than those of VJR; in the other 4, the Leeds' results were less than those of VJR.

3. A Comparison of the Arteriogram Results Between JSB and VJR.

The results of the twenty six arteriograms read by JSB and VJR are presented in figure 2.3.

The same arteriogram results were obtained for 17/26 (65%) arteriograms. In 6 (23%), the results differed by one grade and in 3 (12%), the results differed by two grades. Of all these results, those of JSB were greater than those of VJR.

In conclusion, assessment of arteriograms at Leeds and Leicester using the Leeds' method was not reproducible in all cases.

Figure 2.1. Scattergram showing the results of 26 coronary arteriograms read at Leeds (the consensus of three readers RB, DSR and JBS) and at Leicester by consultant cardiothoracic surgeon, JSB. There was an agreement of results in 16/26 (62%) cases.

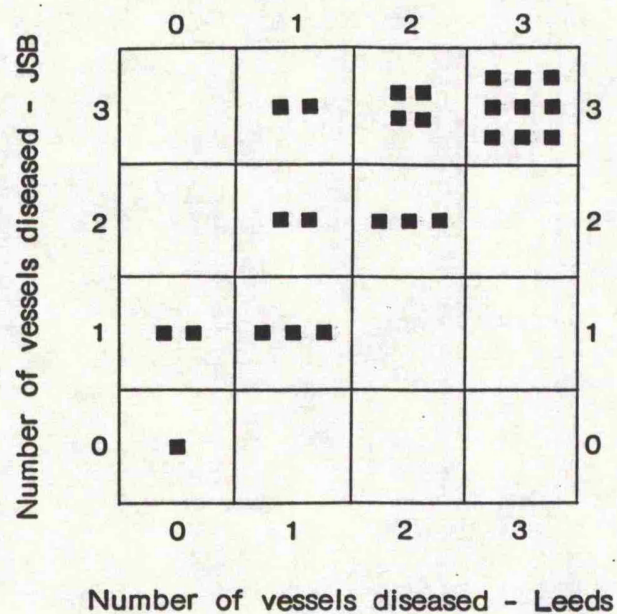


Figure 2.2. Scattergram showing the results of 26 coronary arteriograms read at Leeds (the consensus of three readers RB, DSR and JBS) and at Leicester by consultant cardiologist, VJR. There was an agreement of results in 18/26 (69%) cases.

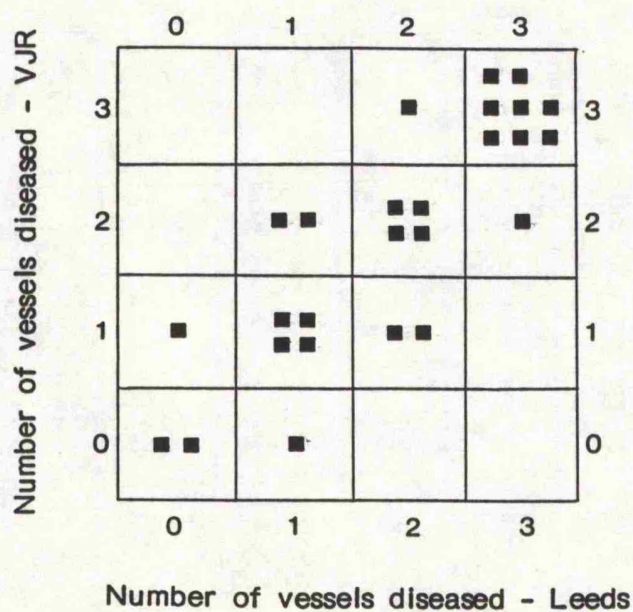
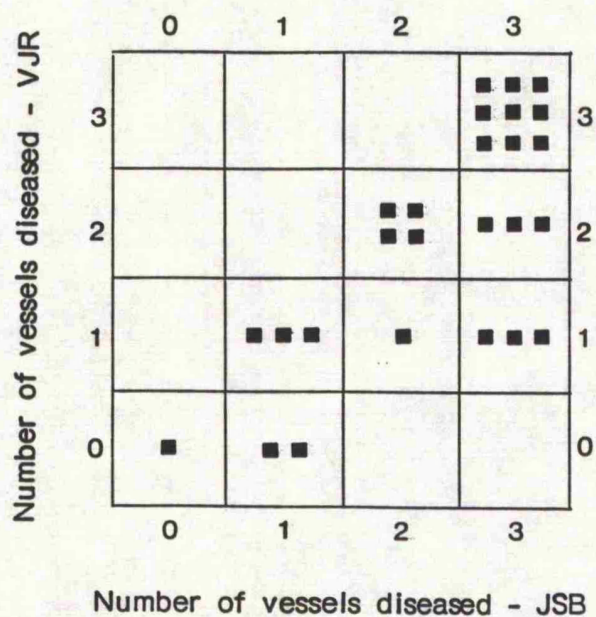


Figure 2.3. Scattergram showing the results of 26 coronary arteriograms read by consultant cardiothoracic surgeon, JSB, and consultant cardiologist, VJR, from Leicester. There was an agreement of results in 17/26 (65%) cases.



B. A Comparison of the Results of Arteriograms Read on Two Separate Occasions by the Readers at Leicester.

Method.

Seven arteriograms were re-read by both JSB and VJR at Leicester after a period of at least one month without their knowing the results of their first assessment. The seven arteriograms (not all common to both readers) were chosen for the following reasons, based on the comparison of arteriogram results described above:

1. Different results had been obtained from all readers; Leeds, JSB and VJR.
2. Although both Leicester readers gave the same result, this differed from that of Leeds.
3. The result of either JSB or VJR was different from that of Leeds.

Results.

The results of the seven arteriograms assessed on two occasions by the two readers at Leicester are presented as scattergrams in figures 2.4 (a) and (b).

The same result was obtained by JSB for the first and second assessments in 6/7 (86%) cases (figure 2.4a).

The same result was obtained by VJR for the first and second readings in 4/7 (57%) cases (figure 2.4b).

In conclusion, assessment of the same arteriogram on two occasions by two readers using Leeds' method was also not reproducible in all cases.

Reasons and Comments on Differences in the Arteriogram Results.

Different arteriogram results occurred between the readers from the two centres because of different opinions as to whether or not a stenosis was significant in terms of either the luminal narrowing or its relative position in the coronary tree.

It was also seen that the Leeds readers did not keep to their definition of a proximal stenosis on two occasions:

Figure 2.4a. Scattergram showing the results of a blind double assessment of 7 coronary arteriograms read by consultant cardiothoracic surgeon, JSB, at Leicester. There was an agreement of results in 6/7 (86%) cases.

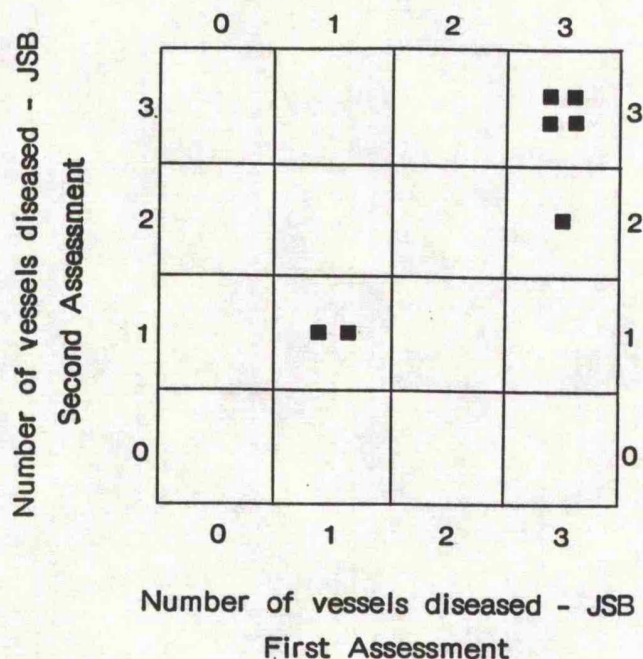
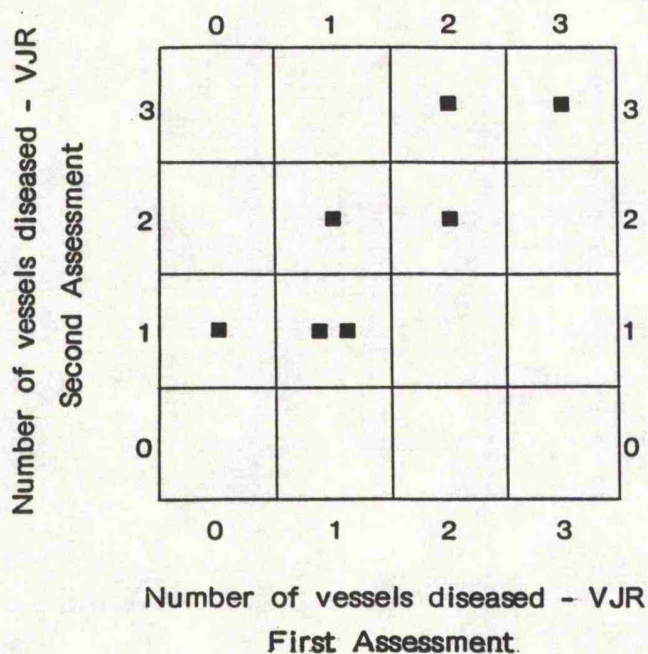


Figure 2.4b. Scattergram showing the results of a blind double assessment of 7 coronary arteriograms read by consultant cardiologist, VJR, at Leicester. There was an agreement of results in 4/7 (57%) cases.



1. In one case an 80% stenosis beyond the 1st diagonal was reported as not significant. In another case, an 85% stenosis distal to the 2nd diagonal (downstream of the 1st diagonal by definition) was reported as significant.
2. A 100% occlusion on the RCA beyond the main marginal branch was reported as significant, contrary to their stipulation that a lesion beyond the major branch of the artery would not be assessed.

Further, the constraint of a definition itself, caused different results between the two centres in two cases. In both, a stenosis was thought by a reader at Leicester to be significant, that is, it was likely to reduce myocardial perfusion sufficient to be included in the overall diagnostic result. However, because it was thought that these stenoses were "too distal" according to the Leeds' method of evaluation, they were not included in the final result. In the assessment at Leeds however, both stenoses had been counted.

To explain these reasons for differences in the arteriogram result, arteriogram assessment, both in general and for the correlation with the maximal ST/HR slope was observed at Leicester and Leeds respectively. The aim was to see why differences in opinion regarding the significance of a stenosis might arise with reference to:

1. Its structure (including the reduction in lumen diameter).
2. Its location within the coronary tree and, of particular relevance to this, how absolute Leeds' definition of the proximal to middle segment of a coronary artery was.

Method.

Separate sessions were spent with four clinicians at Leicester and two clinicians at Leeds whilst each evaluated a series of arteriograms.

The Arteriogram Readers at Leicester.

The arteriogram readers at Leicester (Groby Road Hospital) were Mr. J.S. Bailey and Dr. V.J. Redding and consultant radiologists Dr. N. Hudson and Dr. J. Walker. All were experienced in evaluating the arteriogram

for the routine management of patients with known or suspected coronary disease.

The Coronary Arteriograms Reviewed at Leicester.

The arteriograms reviewed were from patients who had been given a Leeds protocol exercise test, at Leicester, at that stage of this study.

The Arteriogram Readers at Leeds.

The arteriogram readers at Leeds (General Infirmary/ Killingbeck Hospital) were Dr. N.P. Silverton and Dr. G. Hart. Both were familiar with the method of arteriogram interpretation used for the Leeds exercise test:

Dr. Silverton had had first hand experience with the Leeds test and the appropriate interpretation of the arteriogram. He had assessed the effect of percutaneous transluminal angioplasty on the maximal ST/HR slope, and reported that the slope correctly predicted the results of coronary arteriography on 52 out of 57 occasions (Silverton, Elamin, Smith, Ionescu, Kardash, Whitaker, Mary and Linden, 1984).

Dr. Hart, although not directly involved in any such study, was familiar with the method of arteriogram assessment used and had been called upon to provide an additional opinion on unresolved arteriogram results.

The Coronary Arteriograms Reviewed at Leeds.

The arteriograms were chosen by the Leeds' readers to illustrate points pertinent to their method of interpretation.

An Evaluation of the Assessment of Arteriograms at Leicester and at Leeds.

Method.

During each session spent with the arteriogram readers a selection of cine coronary arteriograms were reviewed on a 35 mm arteriogram projector (Tagerno or Vanguard). This allowed control of speed and direction of the film projected and had a freeze frame facility to allow continuous or frame by frame examination of the arteriogram. The readers described and discussed their method of evaluating the severity of coronary disease. Each session was recorded on cassette tape recorder.

A. The Routine Assessment of the Coronary Arteriogram at Groby Road Hospital, Leicester.

Arteriogram assessment observed at Groby Road Hospital was the routine method used there; it was essentially to determine whether it could provide an explanation of symptoms presented by a patient, and thereby provide a basis for appropriate management.

Assessment of coronary disease involved 3 major steps:

1. An examination of the left ventriculogram.
2. An overall assessment of general disease by a relatively quick review of the entire arteriogram.
3. A more detailed and specific assessment of diseased arteries.

1. Examination of the Left Ventriculogram.

Left ventricular function was assessed from the ventriculogram in terms of the completeness of ejection of contrast medium during systole in about four cardiac cycles in each radiologic view presented. Normal contraction is approximately uniform and concentric. Poor contraction can occur when either a region of myocardium has infarcted or it is viable but working in a depressed state because of a reduced blood supply. It can therefore indicate the location and functional extent of coronary disease. Disease therefore, would be anticipated in coronary arteries supplying areas of myocardium with impaired contraction and would be looked for in these arteries later in the assessment of the arteriogram.

The appearance of calcium in the likely vicinity of a coronary artery was also used to anticipate coronary disease from the left ventriculogram since atheromatous plaques often become calcified.

2. Overall Assessment of General Disease.

The coronary arteriogram was initially reviewed in its entirety. Normal coronary arteries appeared as well defined vessels with smooth walls. Atherosclerotic stenoses ranged from rough irregular wall surfaces to blatant constrictions.

Filling of the left and right coronary systems with radiopaque medium

was observed in all radiographic views presented. This was to identify the major vessels, familiarise the observer with the relative distribution of the coronary arteries and see which areas of myocardium had a blood supply and which did not. It provided an overall picture of the state of the coronary circulation indicating regions which would require particular attention in a subsequent, more detailed examination.

For example:

- a). An atherosclerotic artery can appear rigid and inflexible; it does not contract or bend as much as an undiseased vessel during ventricular contraction.
- b). The presence of collaterals, indicated by retrograde flow of radiopaque medium into a non injected coronary artery, suggest a severe or complete occlusion of the non injected artery.
- c). The relative rate of filling of the artery with contrast medium can suggest the presence and extent of disease. For example, following the injection of contrast medium into an artery which divides into two networks, if one fills before the other, this may indicate disease in the latter.
- d). Filling of a diseased vessel can appear relatively slow and intermittent as the rate of flow of contrast medium through different degrees of narrowing, changes.
- e). Contrast medium appears more opaque in a diseased artery than in a normal artery; the non impeded flow through the latter has a characteristic pale appearance.
- f). Delayed clearance of contrast medium from an artery can indicate disease by suggesting either an impeded outflow or a reduced driving pressure.

3. Detailed and Specific Assessment of Disease.

Examination of diseased artery segments was restricted to views in which the image was neither foreshortened nor overlapped with the images of other vessels or radiographically dense structures. When assessing coronary disease, it was regarded simply as being either significant or not

significant. By significant was meant that it would compromise blood flow and cause important functional or symptomatic changes of ischaemia. Criteria used to assess whether a stenosis was significant were related to:

1. The potential for the stenosis to limit blood flow sufficient to cause ischaemia.
2. The amount of myocardium that was at jeopardy of this.

1. The potential for a stenosis to cause functionally important ischaemia was decided largely on the basis of its geometry - the degree of arterial narrowing and the length of this. If present, the proximity and severity of other stenoses also influenced the assessment. In terms of luminal narrowing, it was believed that a significant stenosis was one which appeared to reduce the lumen diameter by an order of 70% relative to an immediately proximal and apparently normal segment. This estimate was however confounded by:

- a). Most stenoses are asymmetric and are seen to restrict the lumen by different degrees from different views.
- b). The lumen of a stenosed vessel is often irregular and there is no clearly discernible single degree of narrowing.
- c). Stenoses (particularly the more severe) are often poorly defined because the flow of contrast medium through them is non streamline.

These complexities were resolved by approximation (all estimates of stenosis severity were made by eye).

The reference calibre against which severity of a stenosis was judged, was usually of a segment immediately proximal to the stenosis. If this was diffusely diseased (or absent if the stenosis occurred at a branch point), then the reference calibre was estimated on the basis of either or both:

- i). a normal segment somewhere remote from the stenosis,
- ii). the general size of the vessel.

The position of the reference segment could not always be defined.

Both the length of a stenosis and the occurrence of multiple stenoses in series also influenced the decision of significance. Thus the relative

significance of a stenosis was thought to increase as a function of its length. Further, stenoses in series which independently might not be considered very severe or significant, could be thought to have a significant effect, combined.

How the above features of coronary disease (degree of narrowing, length, multiple stenoses) affected the assessment could not be defined quantitatively. Describing a stenosis was a matter of opinion and probably based to a large extent on the manner of flow of contrast medium through, and its clearance from, the diseased vessel. It was described as a very subjective process.

2. The significance of a stenosis in terms of the amount of myocardium that was at jeopardy of ischaemia was decided by:

- a). The position of the stenosis along the length of the artery.
- b). The number of vessels involved by the stenosis.
- c). The presence of other vessels supplying the same area of myocardium as the diseased one.

The position of the stenosis along the length of the artery influenced the assessment of its significance by its relation to the watershed beyond. Clearly, a proximal stenosis (before the major branches) would be more important than a distal stenosis (beyond the major branches) because it affected more myocardium. For example, a 70% stenosis of a minor branch would not be rated as significant as a 70% stenosis of the left main stem. By similar reasoning, composite lesions affecting more than one vessel and jeopardising a greater amount of myocardium were thought more important than a single vessel lesion supplying less myocardium. Conversely, the considered significance of a diseased vessel was less if the watershed of the diseased artery was perfused by other vessels including collaterals.

Describing a stenosis as significant with regards the combined effect of its geometrical form and the amount of myocardium at jeopardy of ischaemia was based on clinical judgement; an experience of patients with varying disease patterns, their presentation of disease and their response to

treatment.

In conclusion, visual assessment of the coronary arteriogram for the routine management of a patient with coronary disease is subjective. Differences in opinion as to whether a coronary stenosis is significant can occur at several stages in its assessment:

1. The interpretation of a 3-dimensional form from several 2-dimensional images.
2. Approximating the degree of narrowing when this is uneven.
3. Assessing the stenosis where this is poorly defined by contrast medium.
4. Deciding the reference calibre.
5. Assessing the affect of length on the reduction in blood flow.
6. Assessing the potential additive affect of multiple stenoses in series.
7. Deciding whether or not the stenosis would reduce blood flow sufficiently to cause myocardial ischaemia.
8. Assessing whether adjacent vessels, including collaterals, could compensate for the reduced perfusion of a diseased one.
9. Deciding whether the amount of myocardium at jeopardy of ischaemia would lead to functionally important debility.

The arteriogram assessment described above was not the same as used at Leeds. In particular, severity of coronary disease was not described by the 3 vessel notation. When asked, all readers at Groby Road Hospital, normally avoided using this terminology since it did not allow for the variability of both coronary anatomy and disease:

1. The coronary circulation can not always be described solely as 3 vessels; the RCA, the LAD and the LCFX. For example, if the left coronary artery itself divides into the 3 major arteries the LAD, the LCFX and an intermediate ramus, in order to conform to the 3 vessel notation, the intermediate ramus would have to be considered with either the LAD or the LCFX. This is not always appropriate. For example, a significant stenosis on both the intermediate ramus and either the LAD or the LCFX would have to be classified as single vessel disease. This however could cause more ischaemia

than a singly stenosed LAD or LCFX in the absence (or even presence) of an intermediate ramus. Further, a dominant left coronary system can consist of three or even four major vessels each of which should be considered in its own right for example, the LAD, LCFX, a large diagonal and obtuse marginal artery. A 3 vessel notation was thought inadequate.

2. Disease of a major coronary artery can present itself in many ways.

For example, it may occur as one or a combination of:

- a). a single stenosis in a proximal coronary segment,
- b). a severe stenosis of a large branch of a main coronary artery,
- c). diffuse atherosclerosis along all or a variable length of the artery and/or its branches.

To define overall severity of disease in terms of the presence or absence of a severe stenosis in the proximal segment of any of the '3' main arteries was thought an inadequate representation of coronary disease. Rather, it required - at least - a qualifier such as severe, moderate or mild. Thus, a proximal '90%' reduction in lumen diameter could be described as a severely diseased artery; a '70%' reduction in lumen diameter, either more distal, or on a major branch could be described as a moderately diseased artery; diffuse disease along a length of an artery could be described as mild disease.

B. Assessment of the Coronary Arteriogram at Leeds for Correlation with the Maximal ST/HR Slope.

Assessment of the arteriogram in the Leeds protocol was to provide a graded index of coronary disease.

The procedure used to examine the arteriogram at Leeds was the same as at Leicester, described above. Namely, the following were assessed:

- 1. Left ventricular function.
- 2. The general distribution of disease.
- 3. The degree of specific coronary stenoses.

As has been described, a coronary stenosis was counted in the diagnostic grade of disease if:

1. It occurred in the proximal to middle segments of any of the RCA, the LCFX or the LAD.
2. It was significant, that is, it would limit blood flow sufficient to cause ECG changes of ischaemia on exercise.

Two points were at question:

1. What were the criteria used to define 'significant'.
2. How absolute was the definition of a proximal to middle segment of a coronary artery.

1. The Leeds' Criteria of Significance.

Both during the sessions observing arteriogram assessment at Leeds, and in the Leeds' publications, a significant stenosis was described as one in which there was a reduction in lumen diameter of at least 75%. The estimate of narrowing was relative to the nearest segment of the same artery that appeared normal. Estimating the extent of luminal narrowing however, was not an attempt to allocate an exact value to this, but just required its distinction into one of the following categories: completely blocked, tightly narrowed, moderately narrowed, somewhat irregular, normal or as good as normal. Dr Silverton, for example, when assessing the severity of a stenosis considered: "Is the vessel normal; 0%, or is it completely blocked; 100% ? Is the vessel irregular but not particularly badly blocked; 40 or 50% ? Is it blocked and significantly so, that is, will it reduce perfusion of the myocardium sufficient to cause ischaemic ECG changes on exercise; 75, 80 or 90%, ?". Thus, the decision to class the stenosis as significant, although based on the degree of luminal narrowing was, as at Leicester, subjective.

Unlike at Leicester, however, the manner of assessment of a stenosis was simplified in that it was based on:

- a). Only one radiographic view.
- b). The point of maximum narrowing, in the case of an irregular lesion.

Also, no account was made of:

- c). The length of the stenosis.

- d). The potential influence of nearby stenoses.
- e). The possible compensatory effect of other vessels including collaterals perfusing the same watershed as the stenosed vessel.

2. The Proximal to Middle Segment of the Coronary Arteries.

The definition of the proximal to middle segment of the coronary arteries was described as being from the arteries' origin upto and including the junction with its first major branch. This generally meant:

- a). the second diagonal artery - off the LAD.
- b). the largest of either the most dominant lateral branch or the obtuse marginal artery - off the LCFX.
- c). the largest of either the major right ventricular branch or the acute marginal - off the RCA.

Any stenoses beyond these branches did not contribute to the final diagnostic grade. This held even if it were severe enough to account for angina pectoris in the patient, promote a myocardial infarct or warrant bypassing if surgery were performed. However, it was emphasised by both readers, that the above definitions as to the coronary branches were only approximate. They were quoted purely as a guide for other readers assessing either the same or other arteriograms using the Leeds' method. In some cases, these definitions could not be rigorously held. For example, a tight stenosis in a large lateral branch of the LCFX might be classified as single vessel disease if the lateral branch perfused a larger amount of myocardium than the rest of the LCFX beyond the branch. Apparently therefore, if the stenosis affected the major watershed of the artery then it was counted in the final grade of disease severity (accepting that it was flow limiting).

This method of assessing the arteriogram at Leeds was based on their routine manner of interpreting the arteriogram in the clinical evaluation of patients but also evolved from a preliminary unpublished study. In that study, maximal ST/HR slopes from patients with coronary disease were compared with the results of their arteriograms where all coronary stenoses

were described in terms of their severity and location within the coronary tree. It turned out that the maximal ST/HR slope and the coronary arteriogram provided compatible indices of disease severity only if the method of defining the arteriogram described above was used. The observation was empirical and having provided an interpretable correlation between the arteriogram and the ST/HR slope in patients with good left ventricular function, the method of interpreting the coronary arteriogram was adopted (G.Hart - personal communication).

Conclusion and Discussion.

1. The Leeds' method of assessing the arteriogram is described based on a discussion with members of their team. The method is essentially as reported in publications from Leeds with the exception of the definition of a significant stenosis. In publications from Leeds, a significant stenosis (one which would count towards the number of coronary vessels marked as diseased) was described as one which reduced the lumen diameter in any radiographic view by at least 75% (eg. Elamin, Mary, Smith & Linden, 1980). In the method presented in this chapter, a significant stenosis was described as one that was thought to be of sufficient constriction to cause ECG changes of myocardial ischaemia on exercise. The procedure that was in fact used resolves these differences, namely, it was first decided whether a stenosis would cause myocardial ischaemia on exercise. If so, it would be labelled as being equal to, or greater than a 75% reduction in lumen diameter. Seventy five percent reduction in lumen diameter did not represent an absolute measure of disease severity but was merely a grade, effectively to distinguish significant from non significant.

2. Leeds' method of assessing the arteriogram was shown not to be entirely reproducible:

- a). In a 3 way comparison of results of 26 arteriograms read at Leeds (the consensus of three readers) and by two readers at Leicester, the same results were obtained for a mean of 65% cases.
- b). The same results of 7 arteriograms read on two separate occasions by 2

readers at Leicester, were obtained for a mean of 72% cases.

The reasons for not being able to reproduce the arteriogram results were related to deciding whether or not a stenosis was significant in terms of both, its limiting blood flow and its location within the coronary tree. This would suggest that grading the severity of coronary disease from the arteriogram could cause a discrepancy between results obtained at other centres attempting to repeat the Leeds' test.

3. Poor reproduction of arteriogram results is well described in the literature (eg. Zir, Miller, Dinsmore, Gilbert & Harthorne, 1976) and this study would support this. By observing the routine assessment of arteriograms at Groby Road Hospital, it was apparent that this is a result of the subjective nature of deciding whether coronary disease is functionally significant. This decision is subjective in that it involves the following:

- a). The interpretation of a 3-dimensional form from several 2-dimensional images.
- b). Approximating the degree of narrowing when this is uneven.
- c). Assessing the stenosis where this is poorly defined with contrast medium.
- d). Deciding the reference calibre.
- e). Assessing the affect of length on the reduction in blood flow.
- f). Assessing the potential additive affect of multiple stenoses in series.
- g). Deciding whether the stenosis would reduce blood flow sufficiently to cause myocardial ischaemia.
- h). Assessing whether adjacent vessels, including collaterals, could compensate for the reduced perfusion of a diseased one.
- i). Deciding whether the amount of myocardium at jeopardy of ischaemia would lead to functionally important debility.

This reflects an important feature of coronary arteriography: although it can provide an anatomical definition of coronary stenoses, it offers no direct information about their haemodynamic consequences short of the manner

of flow of contrast medium through, or clearance from, the vessel.

4. Based on time spent observing arteriogram assessment at Leeds, it was seen that the variance introduced into assessment of a stenosis described above was limited in that it was based on:

- a). Only one radiographic view.
 - b). The point of maximum narrowing, in the case of an irregular lesion.
- No account was made of:
- c). The length of the stenosis.
 - d). The potential influence of nearby stenoses.
 - e). The possible compensatory effect of other vessels including collaterals perfusing the same watershed as the stenosed vessel.
 - f). For a stenosis to be included in the grade of disease severity, it must occur before, or at the level of, the major branch of the three main arteries.

Although this will minimise observer variation in arteriogram assessment as shown in the reproducibility studies presented here, it does not eliminate it because:

- i). Deciding whether a stenosis is sufficiently flow limiting to cause ischaemia on exercise is still conjectural; it can only be inferred from the arteriogram.
- ii). Defining the proximal to middle segments of a coronary artery is often defeated by the large variation in the distribution and size of coronary arteries and their branches.

It remains surprising therefore that the Leeds exercise test presented such a good correlation between the maximal ST/HR slope and the coronary arteriogram result because of the inherent variance in the assessment of the latter. Although none of the studies from Leeds present the confidence associated with the arteriogram result, as already said, interobserver variability is suggested in that when arteriograms read by more than one observer gave different results, these were resolved in a joint assessment (Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982;

Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982).

5. The good correlation between the maximal ST/HR slope and the arteriogram result is also questioned in terms of Leeds' method of assessing the latter. It was said that their method of arteriogram assessment was based on an observation of how different states of coronary disease was reflected in the maximal ST/HR slope. It is surprising that such a good correlation was observed when asymetry of a stenosis, its length, the potential additive effect of multiple stenoses in series and the presence of collaterals were not considered. Although this might limit the variance of results, these features of coronary disease have been shown to influence the haemodynamic effect of a stenosis (Young & Tsai, 1973 [a], [b]; Feldman, Nichols, Pepine & Conti, 1978; Seely & Young, 1976; Roth, Young & Cholvin, 1976, respectively). Also, the use of the 3 vessel notation is not always representative of coronary disease (Oliver, 1983).

Results 3: A Correlation Between the Leeds Exercise Test and the Coronary Arteriogram Results at Leicester.

Introduction.

The maximal ST/HR slope obtained at Leeds from their exercise test correctly indicated the presence and severity of coronary disease as defined by the arteriogram in 98% of patients studied so far (Bishop, Adlakha, Boyle, Stoker & Mary, 1987). Attempts to repeat the same predictive results of this test at other centres have failed (Balcon, Brooks & Layton, 1984; Quyyumi, Raphael, Wright, Bealing & Fox, 1984; Ilsley, Canepa-Anson & Rickards, 1983; Detre & Vanbutsele, 1984; Beattie, Seibert, Wilson, Pipberger & Blomqvist, 1984; Way, Johnston & Sleight, 1984; Thwaites, Quyyumi, Raphael, Canepa-Anson & Fox, 1986; Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985).

It was suggested that the manner of performing and analysing the exercise test at Leeds was critical to obtaining their results. Further, it was likely that these results had not yet been repeated at any other centre as neither had their exact methods (Linden & Mary, 1984).

Having studied the methods used at Leeds, an exercise test (using their protocol) and coronary arteriography were performed on 49 patients at Groby Road Hospital, Leicester. This chapter presents the results obtained from these two tests and a correlation between them where applicable. The aims were:

1. To test the relation between the maximal ST/HR slope and the arteriogram result using as far as possible, Leeds' method.
2. To gain insight as to whether differences in protocols used at other centres might detract from this relation.

The methods used in this study were essentially (and as far as possible with respect to the arteriogram assessment), the same as at Leeds:

1. Any differences in the performance of the exercise test and coronary arteriography at Leicester, as described on pp. 60-63 and p. 65

respectively, would not have affected the results obtained.

2. The evaluation of the arteriogram was based on the guidelines set by Leeds. (It has however been shown that arteriogram assessment even when based on the Leeds' method is not entirely reproducible).
3. Deriving the maximal ST/HR slope from the exercise ECG was as at Leeds except that ST segment displacement and heart rate were measured using a computer assisted method. As described below this provided essentially equivalent measurements to those made manually. The computer assisted method had the advantage of being faster and less laborious than measurements made with a magnifying eye piece. It was devised for this reason and is described below.

A Computer Assisted Method of Analysing the ECG.

This method used the ECG signal that was recorded on magnetic tape during the exercise test. The scheme was as follows:

1. The tape recorded ECG was digitised.
2. The digitised signal was fed into a block of computer memory. To spare memory, it was designed that the data, continuously input, would overwrite itself after 255 points.
3. Before being overwritten, an ECG segment, from the end of the P wave to the end of the T wave, was identified and transferred to another memory block.
4. This was programed to occur until 11 ECG segments had been stored.
5. The 11 complexes were displayed and a maximum of 10 chosen by the operator for measurement.
6. The chosen complexes were averaged after effective alignment with respect to both voltage and time.
7. The heart rate was automatically calculated from a computer estimate of the mean RR interval.
8. ST segment displacement 80 ms after the J point and relative to the level of the PR segment was estimated by the computer from the averaged ECG segment. The PR level and the J point were located by the operator.

9. The maximal ST/HR slope was derived using saved values of ST displacement and heart rate obtained from each lead at each stage of exercise.

This method of analysis was developed on a Research Machines 380Z microcomputer with an 8" floppy disc storage system. It was programed in Basic, patched with Z80 Assembler subroutines where rapid execution was either necessary (to collect and store digitised data), or desirable (to reduce computing time when handling multiple large arrays of numbers). The following presents the main features of the program.

During the exercise test, at the end of each stage the ECG from the 13 leads was recorded on FM tape in 5 successive groups of 3. In each group, the 3 ECGs were recorded simultaneously on 3 different channels.

1. & 2. Digitising and the Capture of the Tape Recorded ECG.

The 3 signals were replayed in parallel, into 3, 8-bit analogue to digital convertors (ADC; Digitimer D201). Digital conversion was simultaneous and by successive approximation. Since each ADC port had to be read before it could perform another conversion, rate of conversion was determined by the rate of sampling by the computer. This, as is described below was set at 500 Hz.

The digitised data was sampled from the 3 ADC ports and transferred respectively to 3, 0.25 K rolling memory blocks which, at a sampling rate of 500 Hz, could hold 510 ms of digitised ECG at any instant. Data sampling was an interrupt service routine supplying an assembler routine which scanned these rolling memory blocks, isolating and storing segments of successive ECG complexes from the end of the P wave to the end of the T wave. The sampling routine was set to interrupt the search and storage routine every 2 ms. As stated above, this determined the analogue to digital conversion rate of 500 Hz.

3. & 4. Recognising and Storing the Required Segment of the ECG.

To recognise the required segment of the ECG, the QRS complex was detected. A fixed number of data points before and after this, then marked the required segment. The number of data points was such as to include the section of signal from the end of the P wave to the end of the T wave for

all heart rates encountered.

Detection of the QRS Complex.

The QRS complex was detected in the rolling memory block by an amplitude threshold method. Because the 3 ECG signals were recorded simultaneously, it was only necessary to locate the required ECG segment from any one of the 3 channels digitised. Temporally identical segments would then be taken from the other 2 channels. The channel and threshold level used to detect the QRS complex was decided prior to digitising the signal. The channel chosen was that which had the largest R or S wave relative to the other deflections in the cardiac cycle; the value of the threshold selected was based on the size of this wave. This could be seen either from the chart record obtained during the exercise test or by displaying the signal to be input from the tape recorder on a cathode ray oscilloscope (Tektronix Type 502A).

During analogue to digital conversion, the ECG was converted into digits from 0 to 255. A value of 128 was arbitrarily designated as zero. Threshold values to detect positive (R) waves were therefore chosen between 0 and 128. Threshold values to detect negative (S) waves were chosen between 0 and -128. The actual values chosen depended on the excursion of the wave.

The threshold value was compared successively, by the computer, with each data point on the rolling memory block of the chosen channel. When a true comparison was made, a segment consisting of 64 data points (128 ms) before, and 191 data points (382 ms) after, this point was transferred from the rolling memory block to storage memory space. Coincident segments from the other two channels were also transferred to separate storage locations. This detection-storage process was programmed to occur until 11 complexes were acquired.

5. Selecting the ECG Complexes for Averaging.

A maximum of 10 of the 11 complexes were chosen for averaging. Each ECG segment acquired was displayed individually on a visual display monitor (Phillips Computer Monitor 80). The segment could be either accepted or rejected for averaging. Complexes were rejected for the following reasons:

- a). It was not of sinus origin.
- b). It was not the required segment, for example, it was obtained by incorrect triggering on either a T wave or a bifid R wave.
- c). It was distorted by excessive baseline wander.
- d). It was excessively contaminated with noise.

As each ECG segment was displayed, the position of the isoelectric PR segment was defined. (This was to enable aligning each complex so that the isoelectric PR level occurred at a common voltage; necessary before averaging and described below).

Defining the PR Segment.

On the first accepted ECG segment, a pair of vertical parallel lines were programmed to appear over the ECG segment where the isoelectric PR segment was anticipated. The average of the digitised signal within this window was taken to be the isoelectric level. The window was initially set at a width of 20 ms however if necessary, it could be expanded/reduced or moved to any position along the complex to allow correct alignment over the PR segment.

6. Averaging the ECG Segments Following their Temporal and Voltage Alignment.

The ECG segments accepted for averaging were transferred to another memory array where each segment was aligned both temporally and with respect to their isoelectric voltage level.

The common reference for voltage alignment was the isoelectric PR segment. The voltage of each complex was corrected such that the PR segment, contained within the PR window described above, resided at a voltage level designated by a value of 128.

The common reference point used for temporal alignment was the point of maximum displacement from the isoelectric level; the true peak or nadir. For every ECG segment, the maximum peak or nadir was found with an Assembler subroutine. The segment was shifted in memory so that the peak or nadir resided at a fixed and known address. The ECG segments were summed coherently in that the peaks/nadirs were aligned and the mean signal was

calculated. This was done for each of the 3 channels and the resultant complexes were displayed on the visual display monitor. These were optionally stored on floppy disc for later measurement of the ST segment displacement.

7. Heart Rate Estimation.

The heart rate was estimated as the arithmetic mean of heart rate values corresponding to the R-R interval between each of the complexes chosen for averaging. The R-R interval was estimated by counting the number of interrupt service routines (each of 2 ms duration) that occurred between each threshold defined peak/nadir. Occasionally due to baseline wander or atypically small complexes, the machine code subroutine would not detect consecutive beats. This could produce an estimated heart rate much lower than the true value. A small routine was therefore included in the program to inspect all the values of heart rate accepted, and reject any whose value was less than 2 standard deviations from the median. This successfully excluded heart rates estimated from non consecutive RR intervals.

For each patient, an averaged ECG and corresponding heart rate was obtained and stored for all 13 leads, at rest and for each stage of exercise. For every patient, 10 calibration pulses (10 mV/mm) also recorded on tape at the time of the exercise test were similarly digitised, averaged and stored.

The main features of the computer program are presented as a block diagram in figure 3.1. Figure 3.2 illustrates 10 digitised ECG complexes accepted for averaging and the resultant mean complex.

The Assembler routines, the core of the computer program, is presented in Appendix II. It includes the following routines:

- a). Sampling of digitised data from the ADC ports.
- b). Identification of threshold determined peaks/nadirs.
- c). Acquisition of 11 ECG segments from the end of the P wave to the end of the T wave.
- d). Locating the true peaks/nadirs and subsequent temporal alignment of the

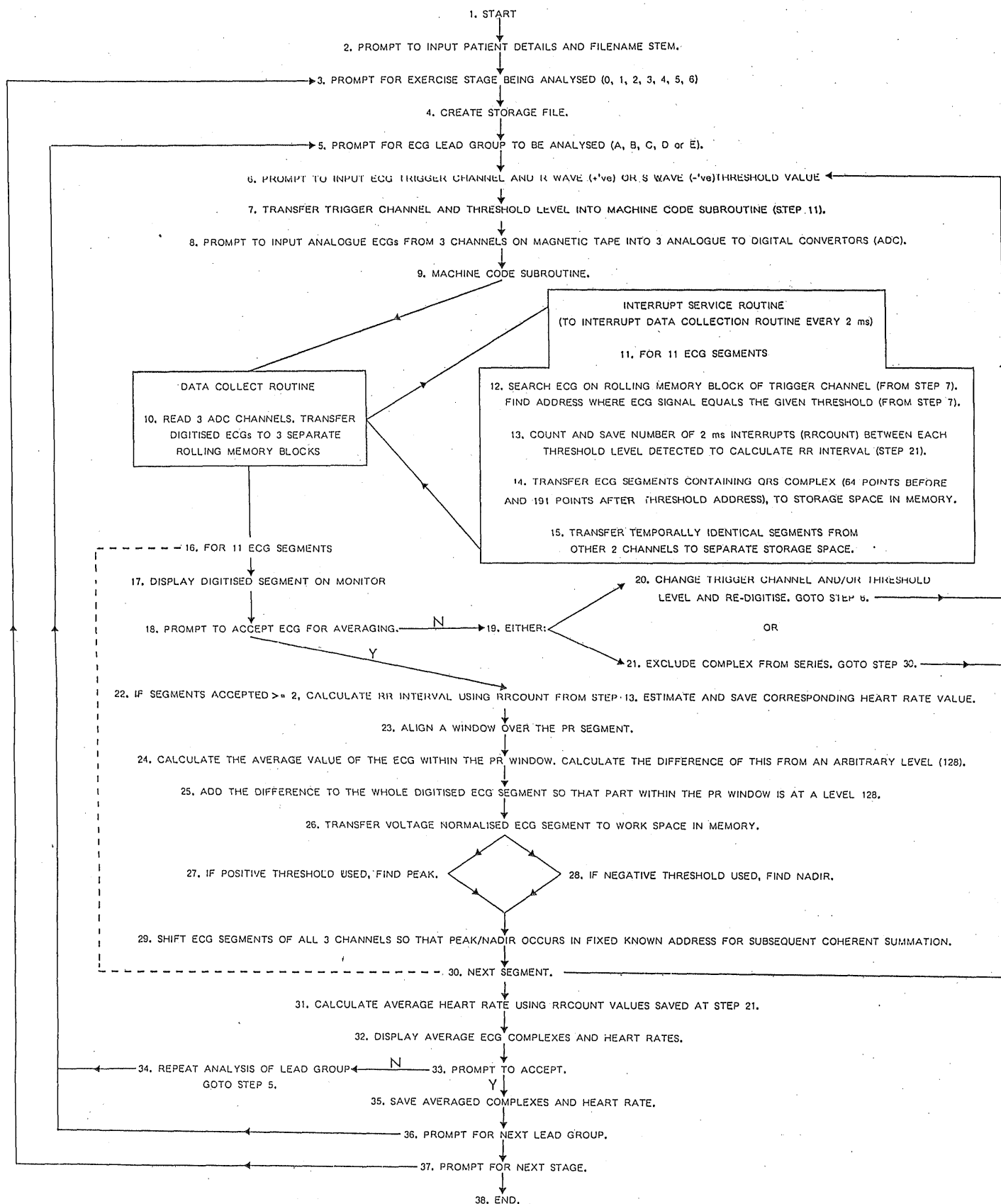
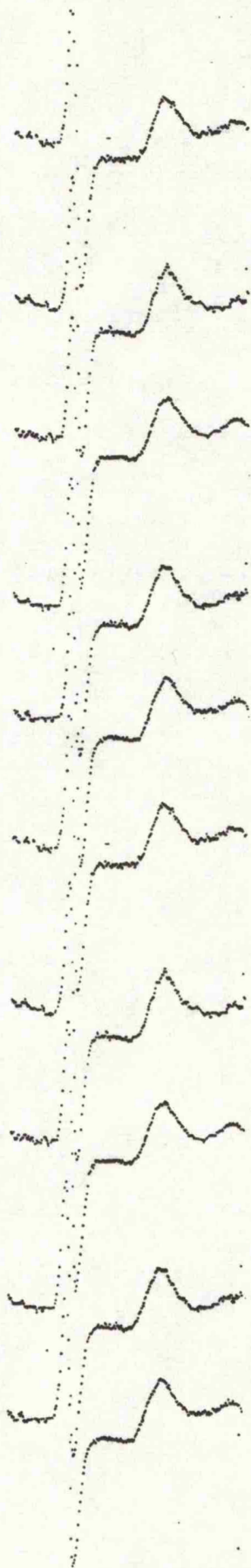


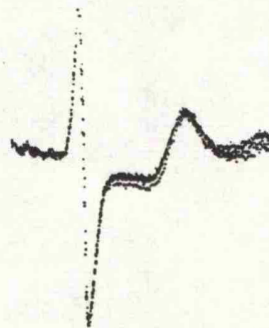
Figure 3.1. Flow diagram of computer program developed to facilitate measurement of the exercise ECG. A full explanation is given in the text (pp. 101-105).

Figure 3.2. Ten digitised ECG complexes accepted for averaging.

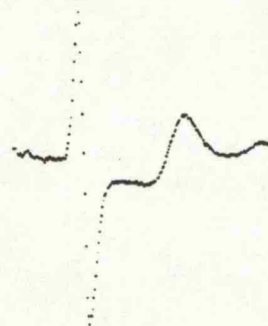
a). The individual complexes.



b). The ECG complexes aligned with respect to time and voltage for coherent summation.



c). The mean ECG complex.



QRS complexes.

e). Voltage alignment of the QRS complexes relative to their isoelectric level.

f). Determination of the R-R interval for estimation of the heart rate.

8. Estimation of ST Segment Displacement.

To estimate the ST segment displacement 80 ms after the J point and relative to the isoelectric level, a further program was written in Basic.

The mean ECG complex to be measured was recalled from floppy disc and plotted on the visual display monitor. By highlighting each data point in succession gave the appearance of a cursor moving along it. This was programmed to 'move' either forwards or backwards along the displayed ECG, continuously or in single steps by depressing appropriate keys on the keyboard. With this cursor, positions thought to represent the level of the PR segment and the J point were marked. The difference between the mean of 5 data points about both the point marking the PR level and a point 80 ms from the J point was calculated to represent the ST segment displacement. The mean of 5 points was used rather than the value of a single point to minimise any aberrant values due to a noisy signal.

Calibration of the Signal.

The value of ST segment displacement was calibrated using the averaged calibration square wave pulse created and saved for each patient. Using the 'cursor', the difference between the maximum and minimum of the square wave pulse was determined. Since this represented 1.0 mV, the voltage equivalent of the ST segment displacement was calculated.

9. Derivation of the Maximal ST/HR Slope.

The estimated ST segment displacement and the previously stored heart rate were stored on another floppy disc. These were used in a further program to determine the maximal ST/HR slope as described by Elamin, Mary, Smith & Linden, 1980 and on p. 68 in this presentation.

Repeatability of the Computer Assisted Measurements of ST Segment Displacement.

To test the repeatability of the computer assisted measurement, the ST segment displacement of 100 complexes chosen at random was measured twice. The results are presented as a scattergram in figure 3.3. Linear regression analysis of the two sets of measurements gave a slope and standard error, $m \pm \text{s.e.}$, of 0.97 ± 0.01 . The 95% confidence interval on the slope was from 0.95 to 0.99. The estimate of the intercept on the y axis was 0.01 mm. The 95% confidence interval on the y-intercept was from -0.01 to 0.03. The coefficient of linear correlation was 0.99. This was significant at the level $p < 0.0001$.

A Correlation of ST Segment Displacement Measured Manually and with the Computer Assisted Method.

To test how the manual measurements of ST segment displacement compared with the computer assisted measurements, values of ST segment displacement obtained by both methods from 8 patients were correlated. There were 273 measurements. The results are presented as a scattergram in figure 3.4. Linear regression analysis of measurements by the computer assisted method on manual measurements gave a slope and standard error, $m \pm \text{s.e.}$, of 0.98 ± 0.01 . The 95% confidence interval on the slope was from 0.96 to 1.00. The estimate of the y intercept was 0.98 mm. The 95% confidence interval on the slope was from -0.02 to 0.02. The coefficient of linear correlation was 0.98. This was significant at the level $p < 0.0001$.

A Correlation of the Maximal ST/HR Slopes Estimated Using Manual and Computer Assisted Measurements of the Exercise ECG.

To test how the maximal ST/HR slope estimated using the computer assisted method and manual measurements compared, these were derived for 20 patients' exercise tests and correlated. The results are presented as a scattergram in figure 3.5. Linear regression analysis of the computer assisted estimates on the estimates made from manual measurements gave a slope and standard error, $m \pm \text{s.e.}$, of 1.04 ± 0.03 . The 95% confidence

Figure 3.3. Scattergram representing the repeatability of measurements of ST segment displacement using a computer assisted method. Linear regression analysis of measurements made on two occasions gave a slope \pm standard error of 0.97 ± 0.01 . The correlation coefficient was 0.99; significant at the level $p < 0.0001$.

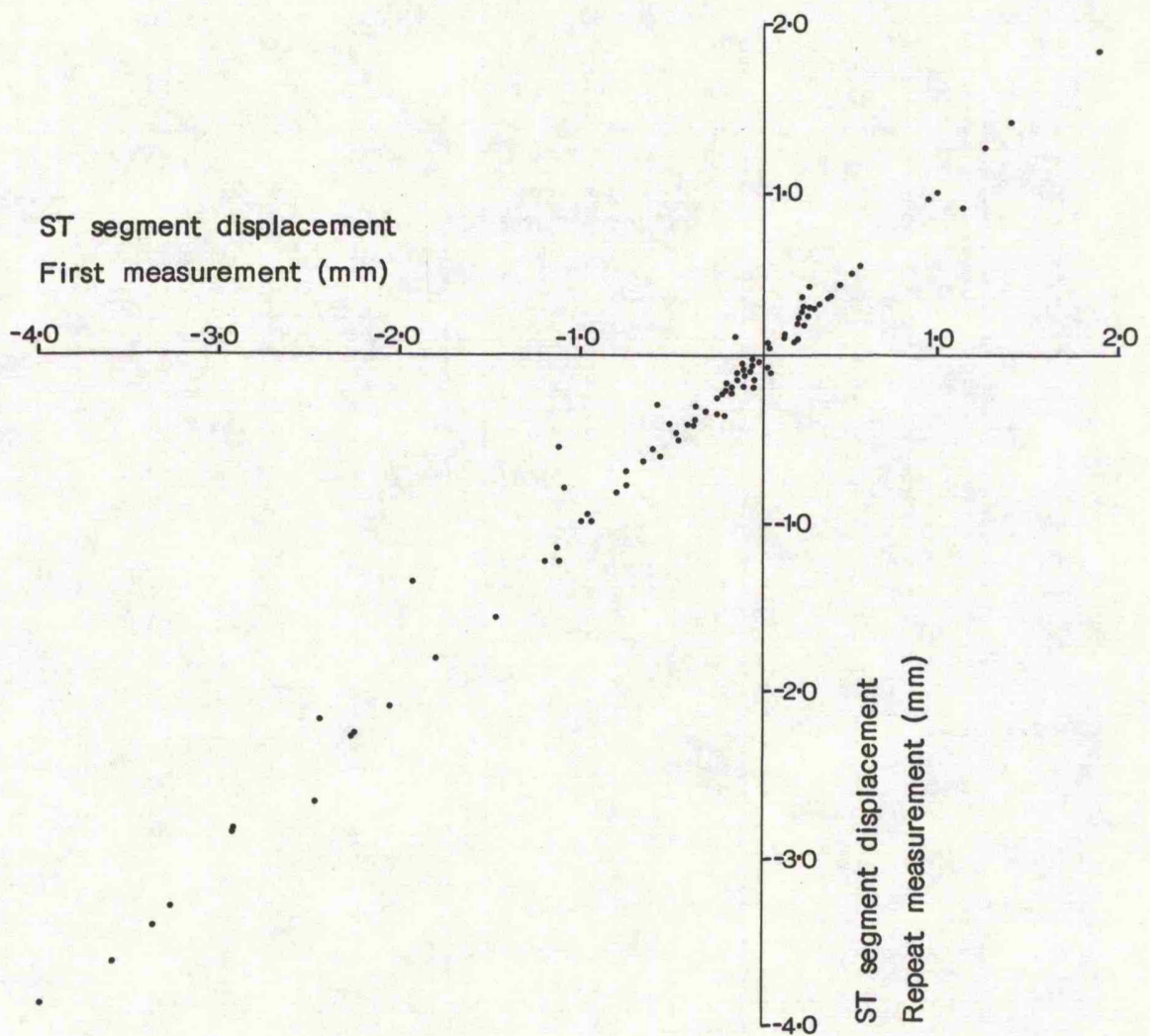


Figure 3.4. Scattergram representing the linear correlation between measurement of ST segment displacement made by hand and with a computer assisted method. Linear regression analysis of measurements made by hand on measurements made with the help of the computer gave a slope \pm standard error of 0.98 ± 0.01 . The correlation coefficient was 0.98; significant at the level $p < 0.0001$.

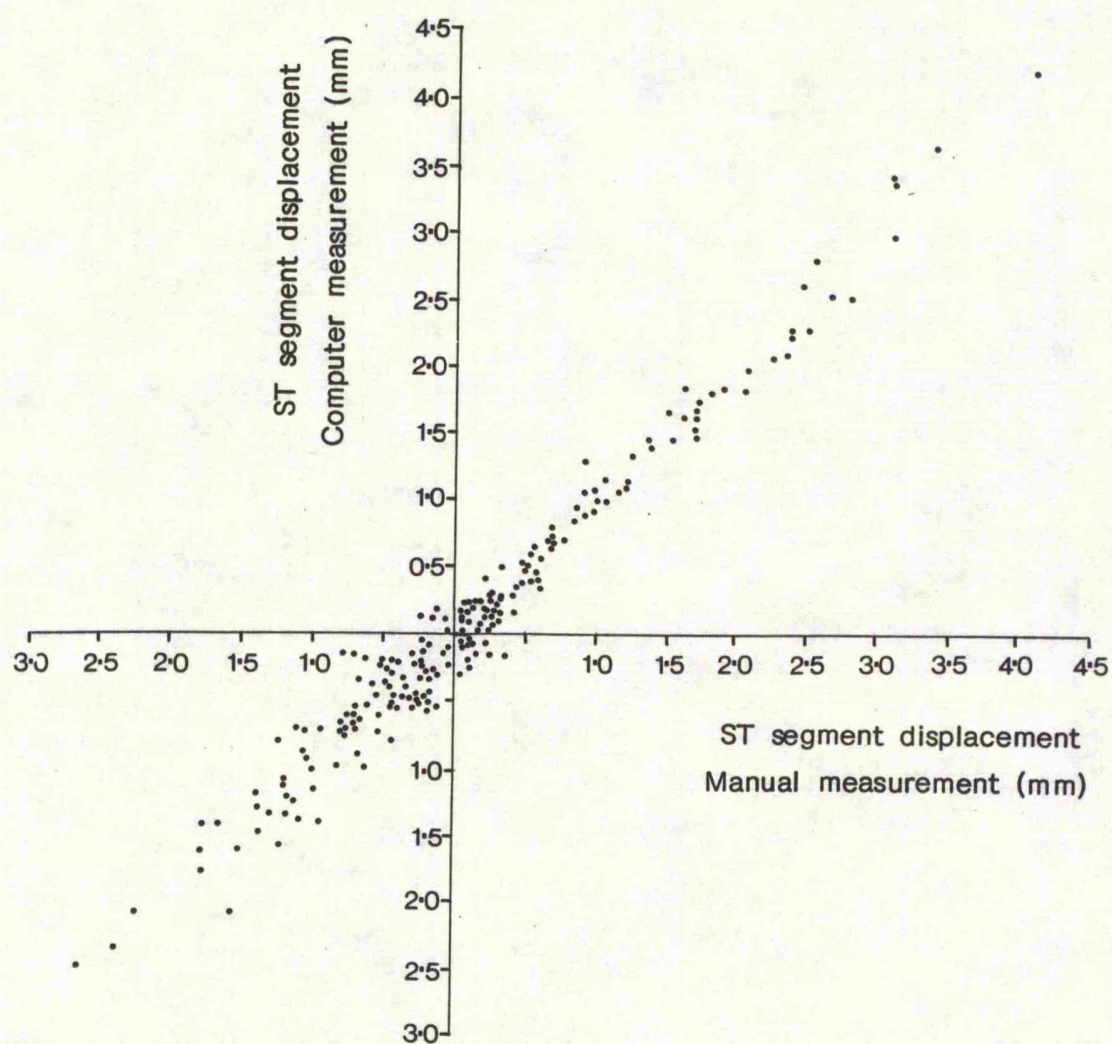
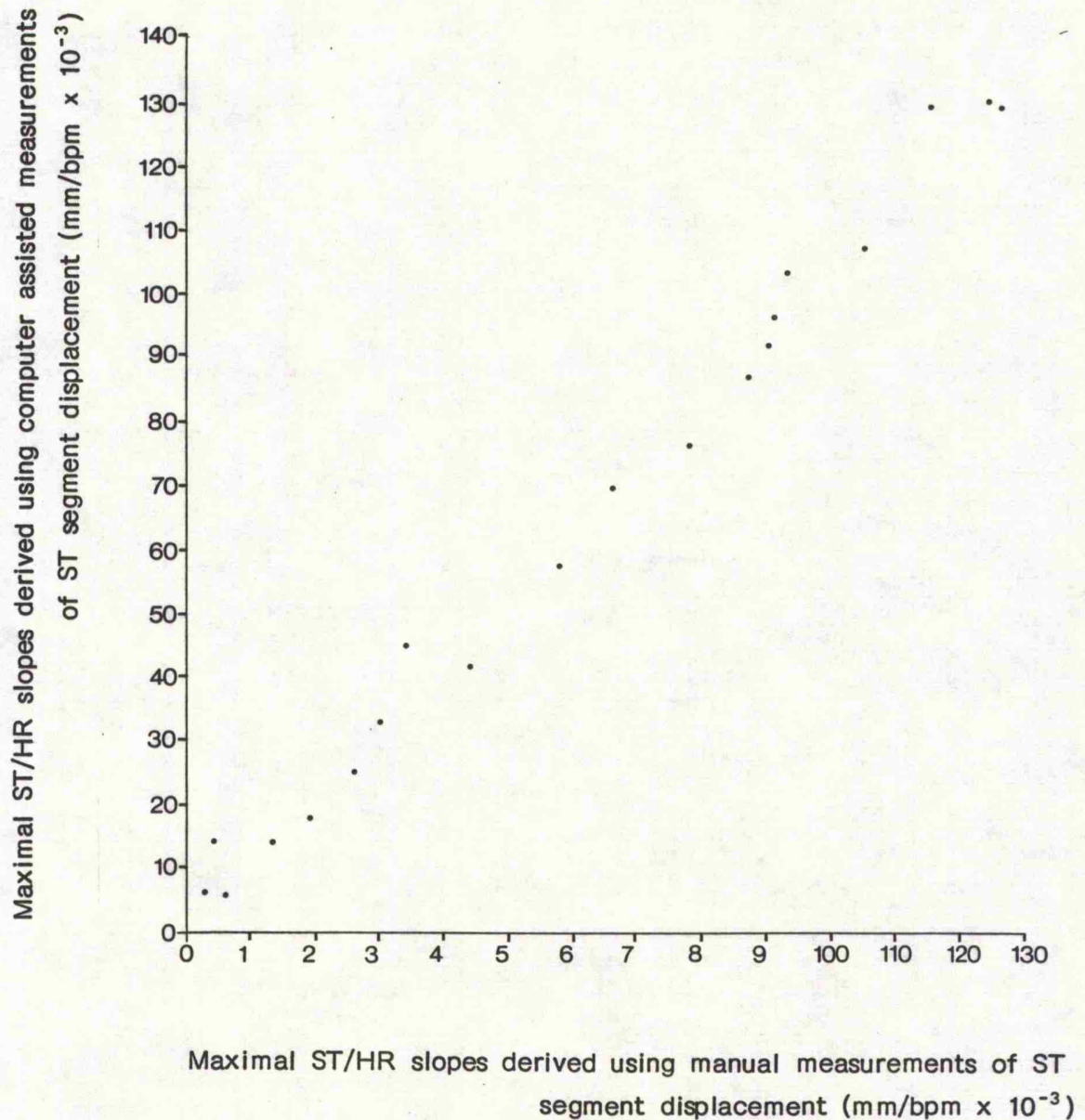


Figure 3.5. Scattergram showing the correlation of maximal ST/HR slopes obtained from estimates of ST segment displacement made by hand and with a computer assisted method. Linear regression analysis of slopes using measurements made with the help of the computer on slopes using measurements made by hand gave a slope \pm standard error of 1.04 ± 0.03 . The correlation coefficient was 0.99; significant at the level $p < 0.0001$.



interval on the slope was from 0.98 to 1.09. The estimate of the intercept on the y axis was 0.01 mm/bpm $\times 10^{-3}$. The 95% confidence interval on the slope was from -0.01 to 0.03. The coefficient of linear correlation was 0.99. This was significant at the level $p < 0.0001$.

On the basis of the repeatability of the computer assisted measurements and the high correlation of these with manual measurements, the computer assisted method was used to analyse the exercise tests of the patients studied at Leicester.

The Results of Exercise Testing and Coronary Arteriography.

The following account presents the results of the Leeds protocol exercise test and coronary arteriography obtained from the 49 patients studied at Leicester. A correlation of these results where applicable is also presented.

The patients and general methods (exercise testing and coronary arteriography) have been described on pp. 55-65.

A. Exercise Test Results.

During the exercise test, the patients performed a mean of 4 stages of exercise. Workload was increased by a mean of 1.72 kp. There was an increase in mean heart rate of 48 bpm; the mean increase in heart rate per stage was 12 bpm. This was associated with a mean maximum depression of the ST segment of 1.43 mm. The exercise test was terminated in the following proportion of patients for the following reasons:

- 57% (28/49) : Severe ST segment depression (≥ 3 mm) and/or increasing angina.
- 24% (12/49) : Fatigue.
- 14% (7/49) : Completion of 6 stages of exercise.
- 2% (1/49) : Shortness of breath.
- 2% (1/49) : An inability to cycle.

Analysis of the Exercise ECG.

In 6 of the 49 patients, a maximal ST/HR slope either could not be, or was not, calculated:

1. The maximal ST/HR slope could not be calculated in 2 patients who performed only one stage of exercise and there was therefore insufficient data. Both patients' test was stopped because of the development of 2.5 mm ST depression.
2. The maximal ST/HR slope was not calculated in 4 patients because the heart rate response did not conform to the Leeds' test criteria in the following respects:

- a). It was very erratic - the patient was unable to pedal continuously.
- b). It did not increase progressively despite constant increases in workload.
- c). It did not increase by more than 15 bpm over 5 stages of exercise.
- d). It was not stable during recording.

In the remaining 43 patients, slopes of linear regression of ST depression on heart rate obtained at each stage of exercise were calculated for each ECG lead.

No Significant Relation Between ST Displacement and Heart Rate and Non Conclusive Tests.

In 8 patients, there was no significant relation ($p < 0.05$) between ST segment depression and heart rate in any lead. In the initial study at Leeds, (Elamin, Mary, Smith & Linden, 1980), this was found only in patients with no significant disease; it was therefore subsequently used as an index of this (eg. Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982).

The absence of a significant correlation between ST depression and heart rate found in the 8 patients here was thought to indicate no significant disease in only one case. This patient performed 5 stages of exercise producing an increase in heart rate of 65 bpm (from 80 to 145 bpm). ST depression at the end of the test occurred in only 2 ECG leads and was less than 0.2 mm.

A similar conclusion was less likely in the other 7 cases:

- a). In 4, only 2 stages of exercise were performed; these patients' tests were stopped because they had developed 2.5 and 3.0 mm of ST depression respectively. In light of the severity of ST depression, the absence of a significant relation between this and the heart rate was thought to be a consequence of the limited number of data points, rather than reflect an absence of coronary disease. The results were interpreted as inconclusive, however suggestive of disease.

b). The same conclusion as (a), above, was indicated in 2 other cases despite their performing 3 and 4 stages of exercise respectively. The relation between ST depression and heart rate observed in these patients from ECG leads with more than 0.5 mm ST depression is shown in figure 3.6.

In both patients, there was a clear increase in ST depression with increasing heart rate during exercise. The relation between these variables however, is curvilinear; it could not be expressed by a slope of linear regression significant at the level $p < 0.05$. This might have been achieved had a further stage been performed in case (1), or alternatively, in both cases, had additional data been acquired intermediate to that presented. For example, in case (1), the average increment in heart rate per stage was 20 bpm (individual increments: 22, 15, 23 bpm) despite relatively moderate increases in workload (stage 1: 0 kp; stage 2: 0.5 kp; stage 3: 0.75 kp). With hindsight, less workload (eg. 0 kp, 0.25 kp, 0.5 kp, 0.75 kp etc.) might have allowed a conclusive result.

c). In the 7th patient, terminal ST segment depression after 3 stages of exercise occurred in one lead and was only 0.2 mm. The patient was unable to continue exercise because of shortness of breath and exhaustion. He described the onset of angina. Had further stages been performed, a definite ischaemic response and maximal ST/HR slope might have been observed. The result was therefore inconclusive.

In summary, 13 of the 49 exercise tests were either invalid or did not show a significant ($p < 0.05$) relation between ST depression and heart rate (although coronary disease was strongly suspected).

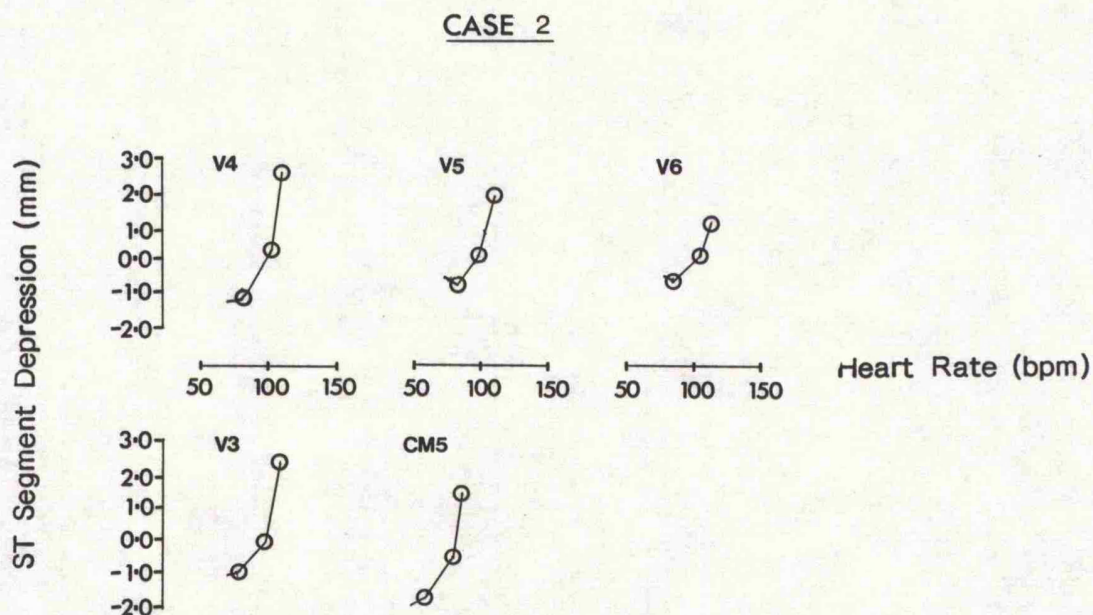
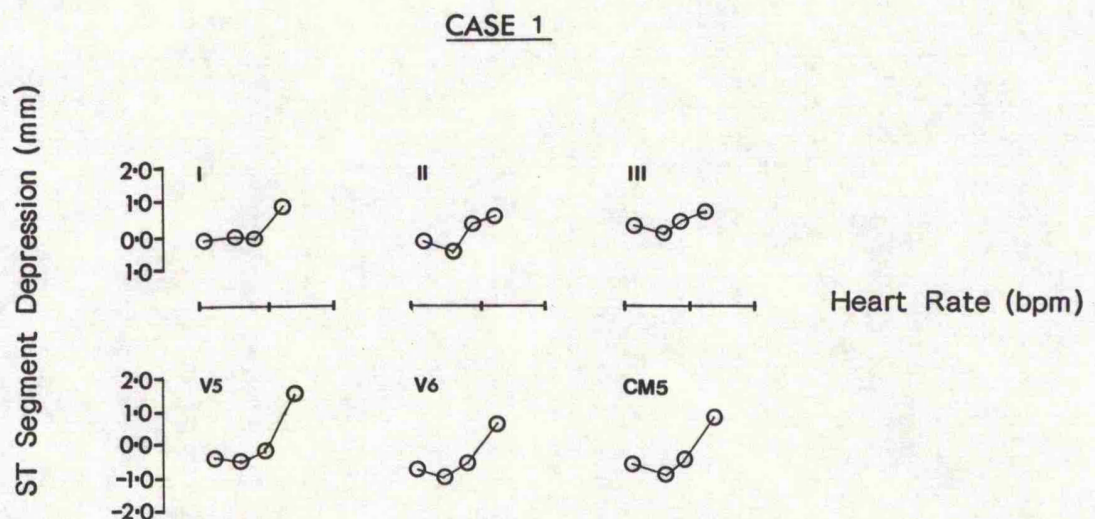
Conclusive Maximal ST/HR Slopes.

In 35 cases, a conclusive maximal ST/HR slope was obtained. Four, were from patients in whom a mismatch between the arteriogram result and the exercise test might occur (Elamin, Mary, Smith & Linden, 1980); the patients presented with:

[a]: Aortic stenosis with regurgitation.

[b]: Hypertension (resting systolic blood pressure was 200 mmHg.)

Figure 3.6. Two examples where there was no significant ($p < 0.05$) linear relation between ST segment displacement and heart rate during exercise testing. Because of the severe ST segment depression, (case 1: 2.5 mm; case 2: 3.0 mm), the non linear relation was taken as a consequence of the limited number of data points rather than an indication of no significant coronary disease.



[c]: Left ventricular aneurysm.

[d]: Myocardial infarct within less than 6 weeks.

These patients' results are discussed separately in Appendix III.

The Maximal ST/HR Slopes.

For the remaining 31 patients, the maximal ST/HR slope, the standard error of the slope and the ECG leads from which they were derived are presented in table 3.1. The frequency distribution of this data is illustrated in figures 3.7 (a) and 3.7 (b).

a). Frequency Distribution of the Maximal ST/HR Slope (figure 3.7a).

There were 3 clusters of maximal ST/HR slopes. These occurred in the ranges: 0 to 49, 70 to 109 and 130 to 139 mm/bpm $\times 10^{-3}$. There is a possible bimodal spread in the first cluster with peaks in the ranges 10 to 19 and 40 to 49 mm/bpm $\times 10^{-3}$.

b). Frequency Distribution of the ECG Leads from which the Maximal ST/HR was Derived (figure 3.7b).

The maximal ST/HR slope was most frequently obtained from lead V4 (in 8/31; 26% cases). It was also commonly obtained from leads V1 (in 5/31; 16% cases) and V6 and CM5 (in 4/31; 13% cases).

The Severity of Coronary Disease from the Maximal ST/HR Slopes Using the Leeds Disease Category Ranges.

It was shown at Leeds that the following ranges of maximal ST/HR slope (for 98% cases studied) indicated the corresponding grade of disease severity as defined by the arteriogram (Elamin, Mary, Smith & Linden, 1980):

<u>Maximal ST/HR slope</u>	<u>Grade of Disease Severity</u>
(mm/bpm $\times 10^{-3}$)	
0 to 11	No significant disease
13 to 21	One vessel disease
32 to 59	Two vessel disease
69 and above	Three vessel disease

The severity of coronary disease of the patients studied at Leicester according to the above is presented in table 3.2.

Table 3.1. The maximal ST/HR slope, the standard error (s.e) of the slope and the ECG lead from which these were derived in 31 patients studied at Leicester.

Patient	Maximal ST/HR Slope (\pm s.e) (mm/bpm $\times 10^{-3}$)	ECG Lead
1	30 \pm 1	V1
2	130 \pm 24	V4
3	25 \pm 4	V5
4	130 \pm 27	V4
5	97 \pm 1	V4
6	88 \pm 5	V5
7	93 \pm 6	V4
8	14 \pm 1	V6
9	70 \pm 13	CM5
10	25 \pm 2	V6
11	76 \pm 17	V5
12	131 \pm 26	V2
13	33 \pm 3	aVF
14	18 \pm 2	V1
15	46 \pm 5	CM5
16	6 \pm 2	III
17	44 \pm 0	V6
18	15 \pm 2	II
19	14 \pm 2	aVF
20	11 \pm 1	aVF
21	14 \pm 1	V1
22	37 \pm 4	V6
23	77 \pm 7	V4
24	6 \pm 2	V1
25	45 \pm 5	CM5
26	70 \pm 3	V4
27	13 \pm 4	aVL
28	104 \pm 5	CM5
29	108 \pm 1	V4
30	14 \pm 3	V1
31	42 \pm 8	V4

Figure 3.7a. The frequency distribution of the maximal ST/HR slopes obtained in 31 patients studied at Leicester.

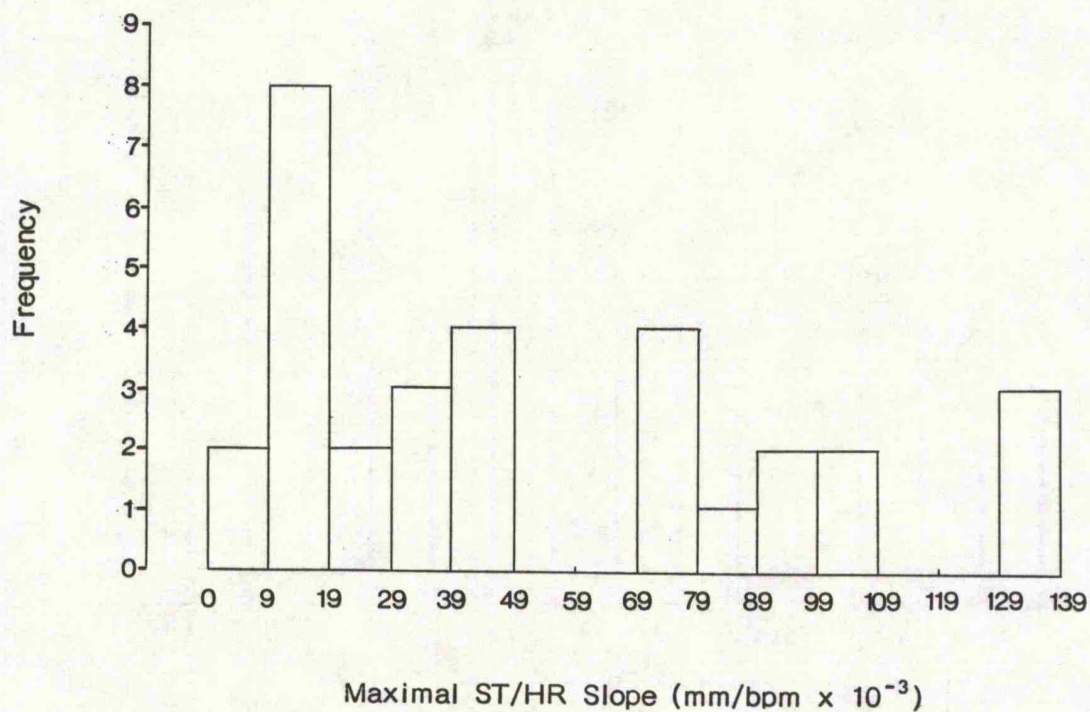


Figure 3.7b. The frequency distribution of the ECG leads from which the maximal ST/HR slope was obtained in 31 patients studied at Leicester.

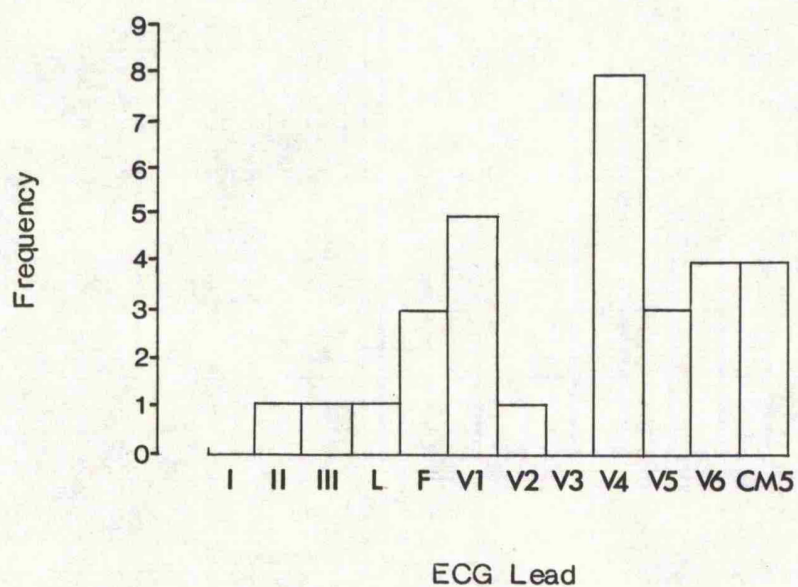


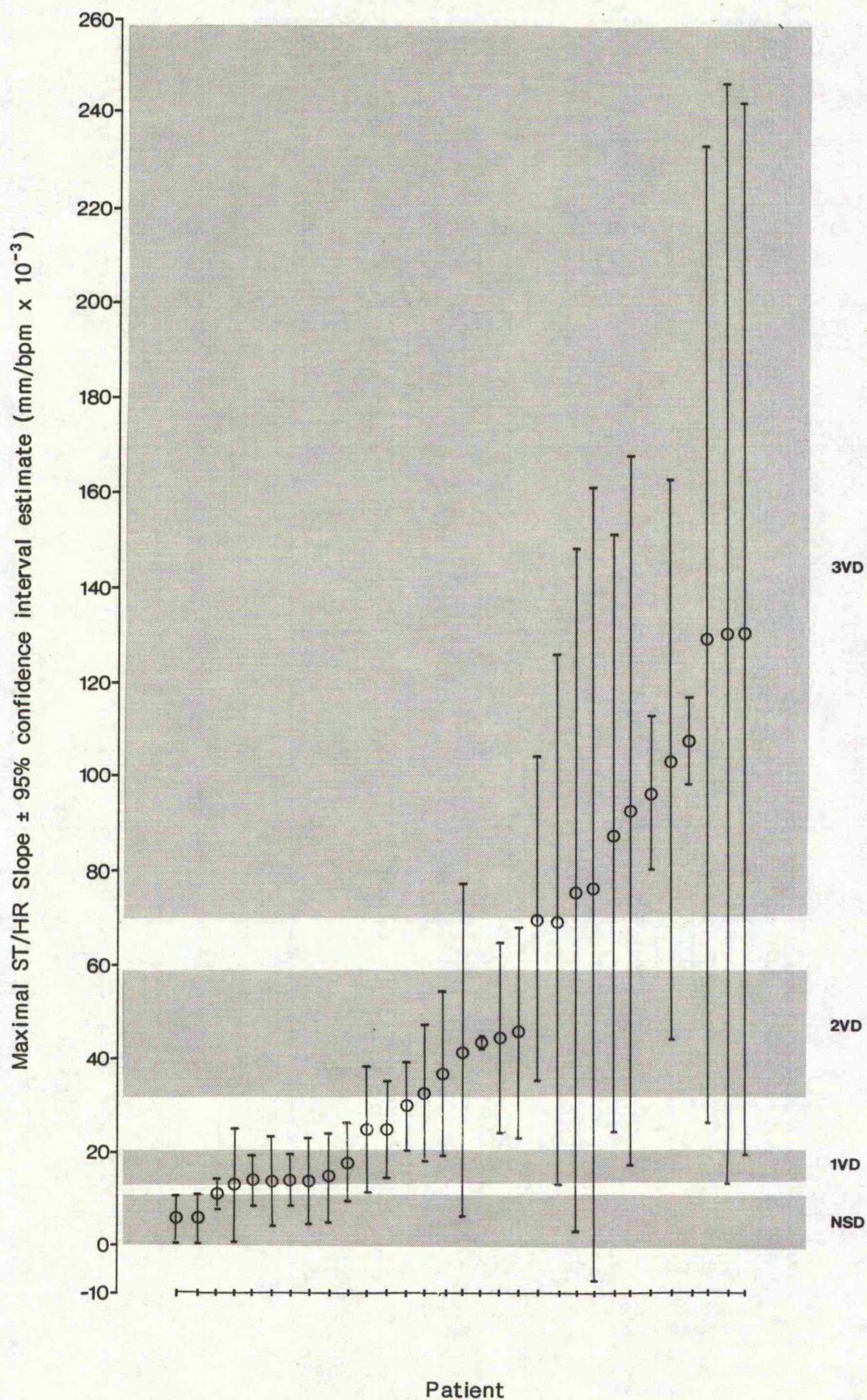
Table 3.2. The maximal ST/HR slope and the corresponding degree of disease (number of coronary arteries significantly occluded) according to the Leeds' diagnostic ranges of maximal ST/HR slope in 31 patients studied at Leicester.

Patient	Maximal ST/HR Slope (mm/bpm x 10 ⁻³)	Degree of Disease (vessel disease)
1	30	1 to 2
2	130	3
3	25	1 to 2
4	130	3
5	97	3
6	88	3
7	93	3
8	14	1
9	70	3
10	25	1 to 2
11	76	3
12	131	3
13	33	2
14	18	1
15	46	2
16	6	0
17	44	2
18	15	1
19	14	1
20	11	0 to 1
21	14	1
22	37	2
23	77	3
24	6	0
25	45	2
26	70	3
27	13	1
28	104	3
29	108	3
30	14	1
31	42	2

Table 3.3. The 95% confidence interval estimates of the maximal ST/HR slope, the range of diagnosis described by this (the number of coronary arteries significantly occluded) and the probability of repeating the diagnostic result in 31 patients studied at Leicester.

Patient	95% confidence interval estimate (mm/bpm $\times 10^{-3}$)	Range of diagnosis described by 95% interval estimate (vessel disease)	Probability of repeating diagnosis
1	9	1 to 2	0.82
2	103	1-2 to 3	0.94
3	13	0-1 to 2	0.72
4	116	1 to 3	0.92
5	16	3 to 3	0.99
6	63	1-2 to 3	0.92
7	75	1 to 3	0.92
8	5	0 to 1	0.78
9	56	1 to 3	0.53
10	10	1 to 2	0.87
11	72	0 to 3	0.64
12	111	1 to 3	0.93
13	14	1 to 2	0.61
14	8	0 to 1-2	0.86
15	22	1-2 to 3	0.80
16	5	0 to 0	0.96
17	1	2 to 2	1.00
18	9	0-1 to 2	0.74
19	9	0-1 to 2	0.63
20	3	0 to 1	0.41
21	5	0 to 1	0.79
22	17	1 to 2	0.82
23	84	0 to 3	0.77
24	5	0 to 0	0.95
25	20	1-2 to 2-3	0.89
26	34	2 to 3	0.60
27	12	0-1 to 2	0.43
28	59	2 to 3	0.95
29	9	3 to 3	0.99
30	9	0-1 to 2	0.57
31	35	0 to 3	0.74
Mean probability of repeating diagnostic result:			0.79

Figure 3.8. The maximal ST/HR slopes \pm the 95% confidence interval estimates on the slope of 31 patients studied at Leicester.



Using Leeds' criteria, 12 patients were classed as having 3 vessel disease, 6 patients were classed as having 2 vessel disease, 7 patients were classed as having 1 vessel disease and 2 patients were classed as having no significant disease. The maximal ST/HR slopes of 4 patients did not occur within the defined boundaries of disease severity: the slope of one patient occurred in the 0 to 1 vessel disease range and the slopes of 3, occurred in the 1 to 2 vessel disease range.

The 95% Confidence Intervals of the Maximal ST/HR Slopes and the Probability of Repeating the Diagnostic Result.

The 95% confidence interval on the maximal ST/HR slope, the range of diagnoses described by these and the probability of repeating each diagnostic result were calculated. (The 95% confidence interval (CI (95%)) on the slope was estimated from the expression:

$$CI (95\%) = t_{0.05} \times s.e \dots\dots\dots(3.1)$$

where $t_{0.05}$ is Students' value of t associated with a probability of 0.05 and $(n-2)$ degrees of freedom. $s.e$ is the standard error of the slope.) These are presented in table 3.3; the range of diagnoses described by the 95% confidence intervals on the slope are illustrated in figure 3.8.

Corresponding to the wide range of standard errors on the maximal ST/HR slope (0 to 27 mm/bpm $\times 10^{-3}$; table 3.1), there was a wide range of 95% confidence intervals (1 to 116 mm/bpm $\times 10^{-3}$; table 3.3). The range of diagnosis described by the 95% confidence interval occurred within 1 disease range in 5 patients, but extended over:

- 3 disease ranges in 11 patients;
- 4 disease ranges in 8 patients;
- 5 disease ranges in 4 patients and
- 7 disease ranges in 3 patients

where the disease ranges are 0 VD (vessel disease); 0 to 1 VD; 1VD; 1 to 2 VD; 2VD; 2 to 3 VD and 3VD (table 3.3; figure 3.8). In 3 cases for example, the diagnosis described by the 95% confidence interval extended from no significant disease to 3 vessel disease (7 disease ranges).

The 95% confidence interval on the slope increased with increasing maximal ST/HR slope. This was because steeper maximal ST/HR slopes were obtained from patients with more severe disease and there was a tendency for increased values of the standard error of the slope and $t_{0.05}$ (the determinants of the 95% confidence interval) in these patients:

1. Exercise in patients with more severe disease was more often limited by their symptoms: fewer stages could be managed and so a lesser number of data points (n) were available to represent the relation between heart rate and ST depression. The value of t in expression (3.1) increases with decreasing degrees of freedom ($n-2$).
2. The relation between heart rate and ST depression in patients with severe disease was more often curvilinear, resulting in larger standard errors on the slope of linear regression.

The Mean Probability of Repeating the Diagnostic Result.

The mean probability of repeating the diagnostic result was 0.79 (range 0.41 to 1.00).

B. Coronary Arteriogram Results.

The coronary arteriograms of 46 of the 49 patients studied were read by either one or both of JSB and VJR from Groby Road Hospital, Leicester using the guidelines set by Leeds;

1. Arteriogram results were not presented from both readers in 4 cases because:
 - a). The arteriogram was of inadequate technical quality to allow a sure diagnosis (1 case).
 - b). The exercise test did not yield any results: only one stage was performed (2 cases); the patient was unable to pedal continuously (1 case).
2. Arteriogram results were not presented from one of the 2 readers in 7 cases because:
 - a). The arteriogram was of inadequate technical quality to allow a sure diagnosis (1 case).

b). The arteriogram was lost from the X-ray department before it could be read (2 cases).

c). The patient's exercise test was either invalid or there was no significant linear relation between ST depression and heart rate (4 cases).

In summary, arteriogram results were available for 35 cases from JSB and 33 cases from VJR. Thirteen of these arteriograms had been read at Leeds.

As previous, in some cases, different results were obtained from the three readers; VJR, JSB and Leeds. The results were compared.

A Comparison of the Results of Coronary Arteriograms Read by JSB, VJR and Leeds.

The results of arteriograms read by VJR, JSB and Leeds (the concensus of RB, DSR and JBS) are presented as scattergrams in figures 3.9 (a), 3.9 (b) and 3.9 (c). The number of cases in which there was an agreement of results is summarised in table 3.4.

The same results were obtained in:

1. 69% of cases read by JSB and Leeds.
2. 77% of cases read by VJR and Leeds.
3. 64% of cases read by JSB and VJR.

In each case of disagreement between JSB and either Leeds or VJR, the result of JSB was greater (by either 1 or 2 grades) than the results of the other two readers. In the 3 cases of disagreement between VJR and Leeds, the result obtained by VJR was greater than that obtained by Leeds in one case and less, in two.

C. A Correlation of the Maximal ST/HR Slope and the Arteriogram Result of JSB, VJR and Leeds.

Because of the disparity in arteriogram results obtained from the 'three' readers, the maximal ST/HR slopes were correlated with the arteriogram results obtained by each 'reader'.

Figures 3.10 (a) and 3.10 (b) show the relation between the maximal ST/HR slope and the coronary arteriogram results obtained by JSB and VJR

Figure 3.9a. Scattergram presenting the results of 13 coronary arteriograms read at Leeds (the concensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiothoracic surgeon, JSB. There was an agreement of results in 9/13 (69%) cases.

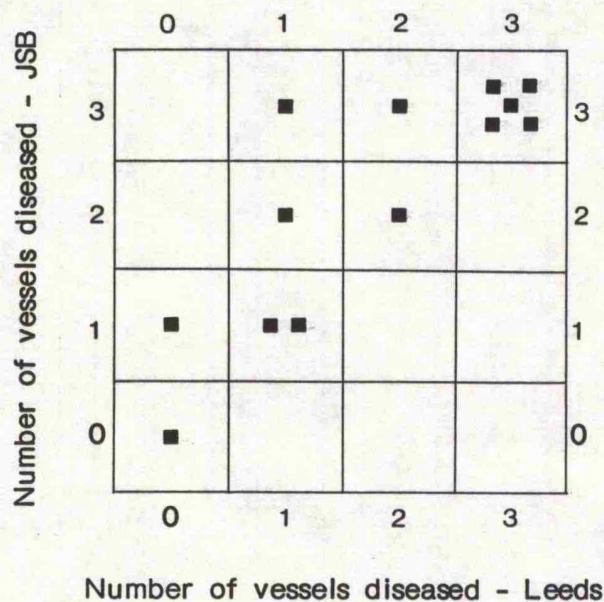


Figure 3.9b. Scattergram presenting the results of 13 coronary arteriograms read at Leeds (the concensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiologist, VJR. There was an agreement of results in 10/13 (77%) cases.

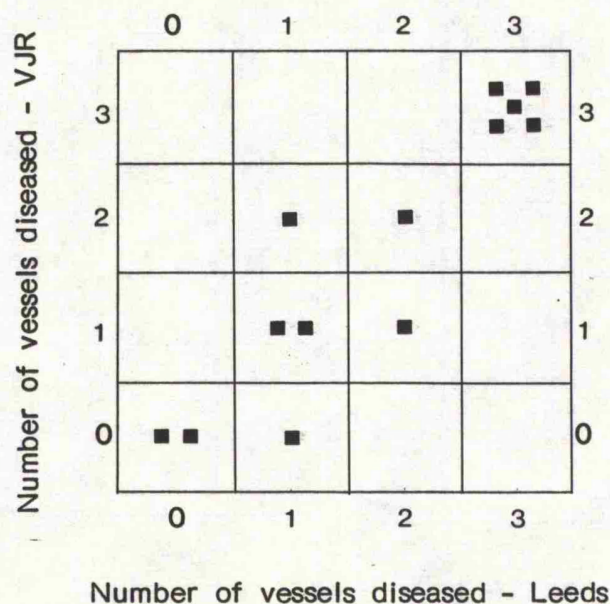


Figure 3.9c. Scattergram presenting the results of 33 coronary arteriograms read at at Leicester by consultant cardiothoracic surgeon, JSB, and consultant cardiologist, VJR. There was an agreement of results in 21/33 (64%) cases.

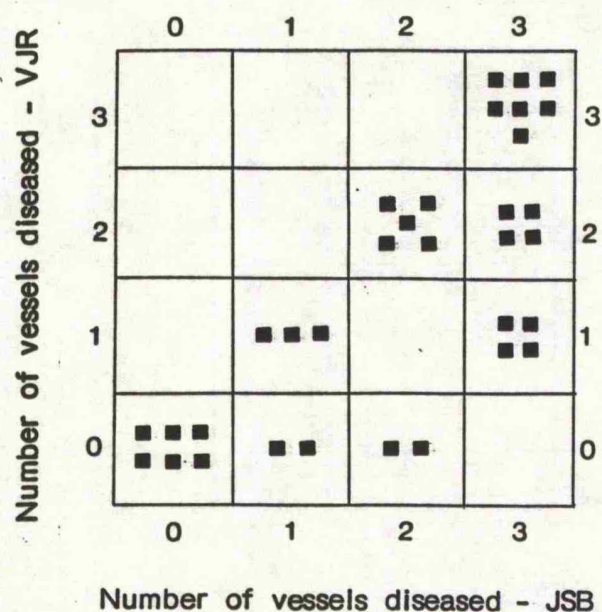


Table 3.4. Summary of the percent agreement of results of coronary arteriograms read at Leeds (the consensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiothoracic surgeon, JSB, and consultant cardiologist, VJR.

Arteriogram readers compared [figure]	Number of arteriograms	Percent agreement
JSB/Leeds [3.9a]	13	69
VJR/Leeds [3.9b]	13	77
JSB/VJR [3.9c]	33	64

Figure 3.10a. The relation between the maximal ST/HR slope and the arteriogram result according to consultant cardiothoracic surgeon, JSB (Leicester) for 31 patients studied at Leicester. The vertical bars NSD, 1, 2 and 3 VD mark the ranges of maximal ST/HR slope indicating no significant disease, one, two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980.

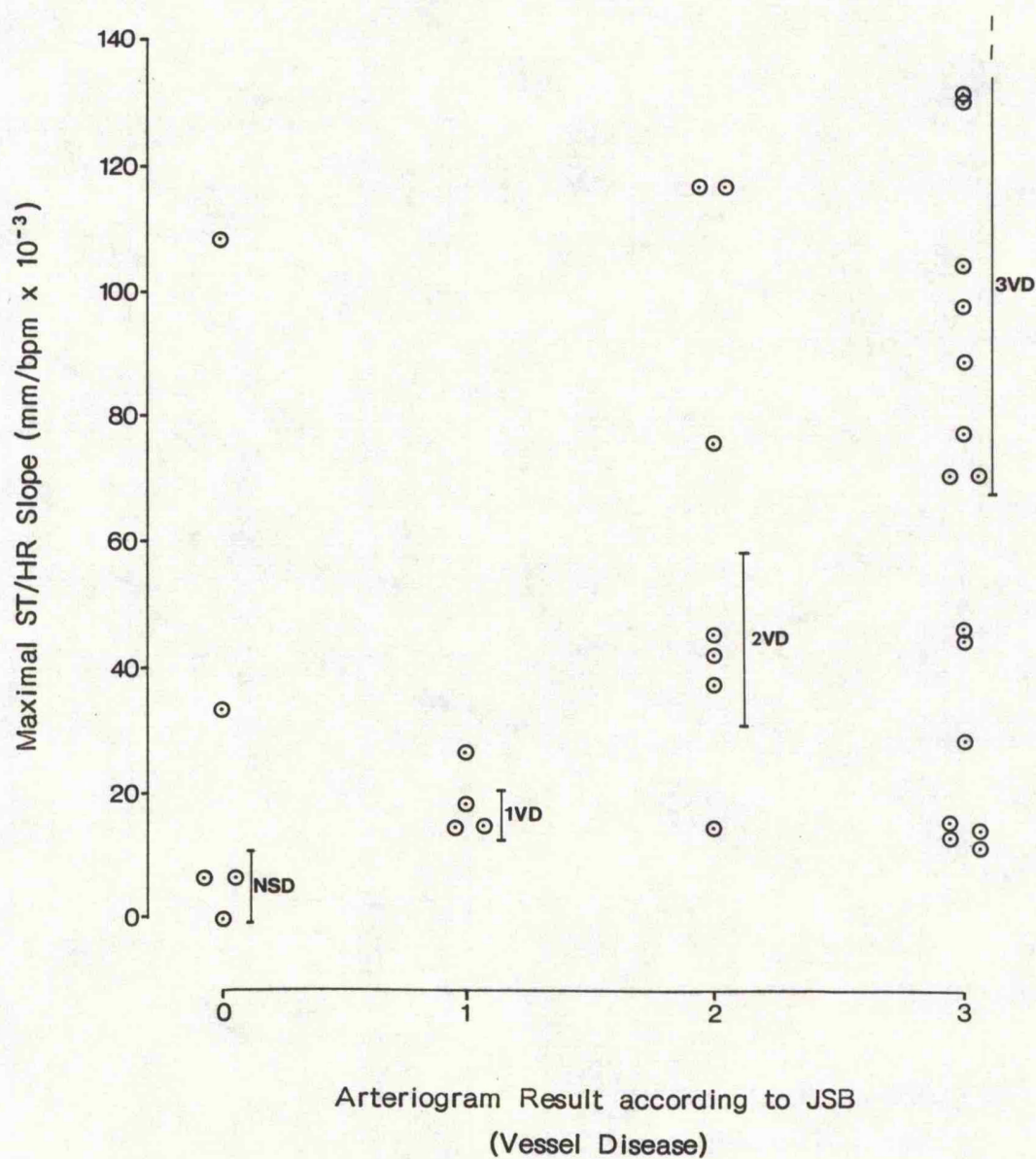
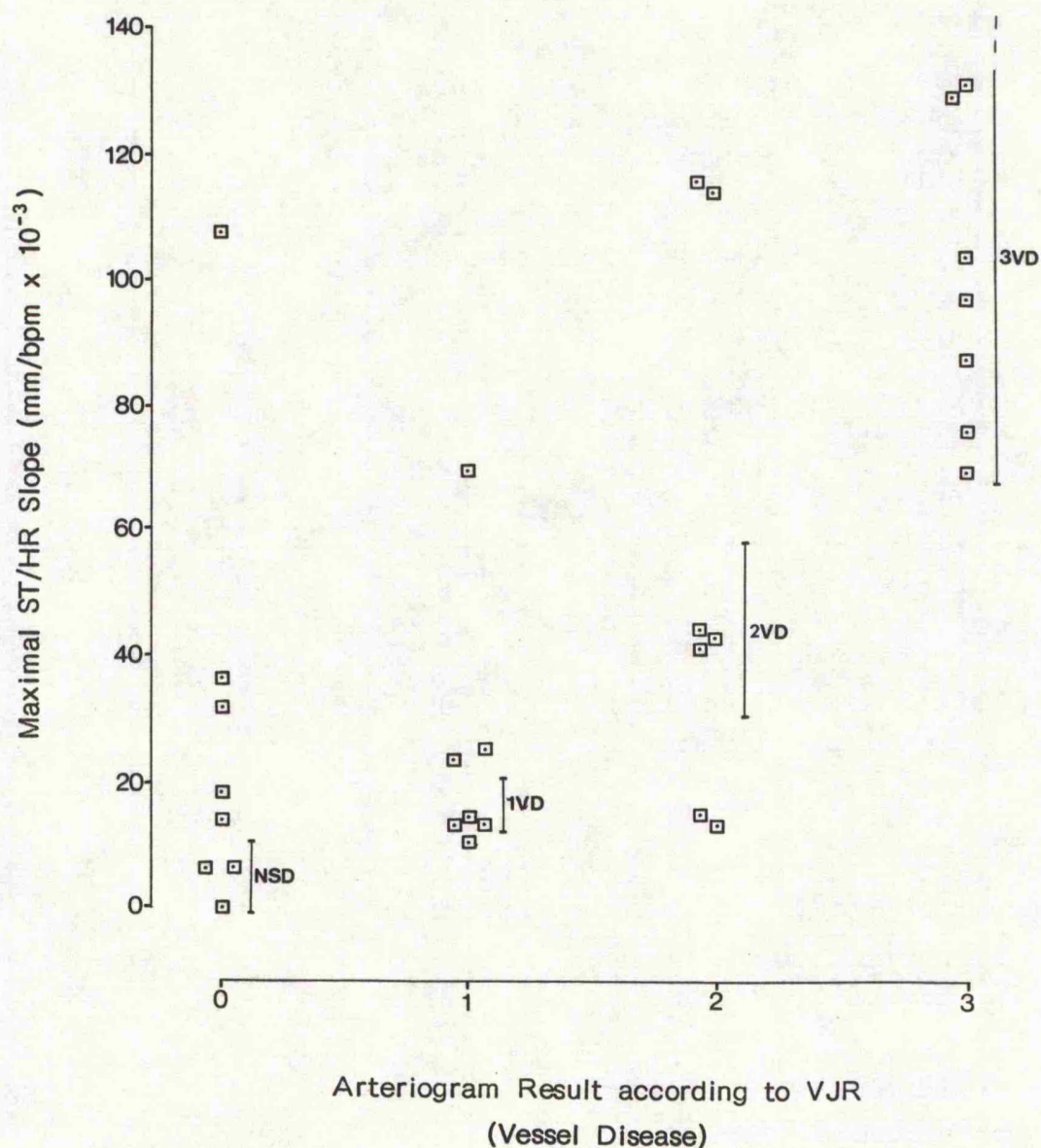


Figure 3.10b. The relation between the maximal ST/HR slope and the arteriogram result according to consultant cardiologist, VJR (Leicester) for 29 patients studied at Leicester. The vertical bars NSD, 1, 2 and 3 VD mark the ranges of maximal ST/HR slope indicating no significant disease, one, two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980.



respectively. Figure 3.10 (c) shows the relation between the maximal ST/HR slope and the arteriogram result obtained at Leeds. The percent agreement between the exercise test and arteriogram results are summarised in table 3.5a. Table 3.5b summarises the proportion of exercise tests whose diagnostic result was greater than, or less than, that of the arteriogram according to the three readers.

The Relation Between the Results of Exercise Testing (using the Leeds' diagnostic ranges of maximal ST/HR slope) and Coronary Arteriography.

The relation between the results of exercise testing and coronary arteriography are described for the results of each of the three arteriogram readers:

A. A Correlation of the Results of Exercise Testing and Arteriography as Read by JSB.

The results of exercise testing and arteriography as read by JSB were the same in 17/31 (55%) cases. The exercise test predicted a higher grade of disease than was assessed from the arteriogram in 6 cases and a lower grade in 8.

B. A Correlation of the Results of Exercise Testing and Arteriography as Read by VJR.

The results of exercise testing and arteriography as read by VJR were the same in 16/29 (55%) cases. The exercise test predicted a higher grade of disease than was assessed from the arteriogram in 10 cases and a lower grade in 3.

C. A Correlation of the Results of Exercise Testing and Arteriography as Read at Leeds.

The results of exercise testing and arteriography as read at Leeds were the same in 6/12 (50%) cases. The exercise test predicted a higher grade of disease than was assessed from the arteriogram in 3 cases and a lower grade in 2.

In summary, there was a 55, 55 and 50% agreement between the results of exercise testing and arteriography as read by JSB, VJR and Leeds

Figure 3.10c. The relation between the maximal ST/HR slope and the consensus arteriogram result according to consultant cardiologists RB, DSR and JBS (Leeds) for 12 patients studied at Leicester. The vertical bars NSD, 1, 2 and 3 VD denote the ranges of maximal ST/HR slope indicating no significant disease, one, two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980.

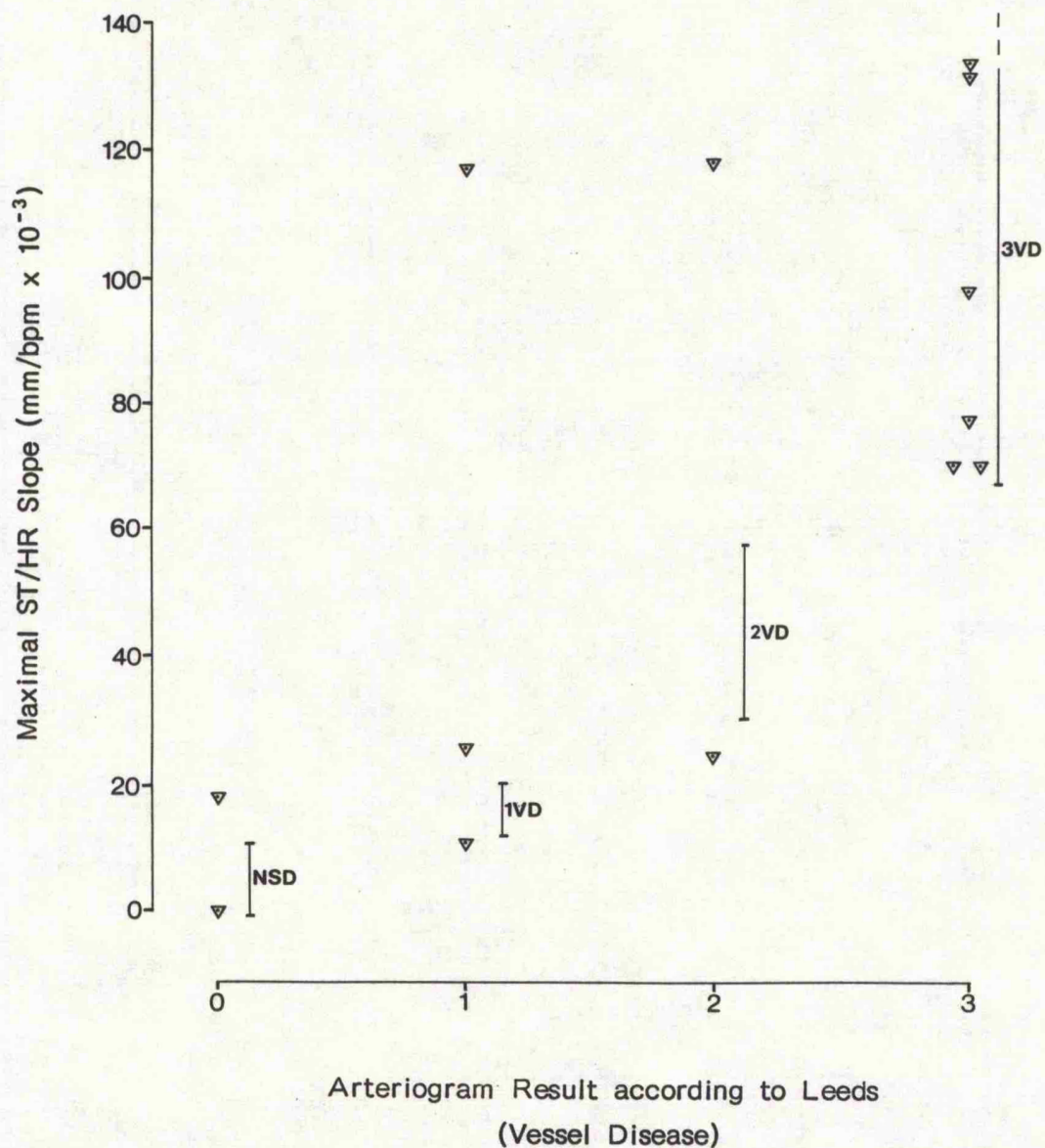


Table 3.5a. Summary of the percent agreement between the exercise test and coronary arteriogram results as read at Leeds (the concensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiothoracic surgeon, JSB, and consultant cardiologist, VJR, for 31 patients studied at Leicester.

Arteriogram Reader	Percent agreement between results of exercise testing and arteriography
JSB	55
VJR	55
Leeds	50

Table 3.5b. Summary of the proportion of exercise tests whose diagnostic result was greater than, or less than, that of the coronary arteriogram as read at Leeds (the concensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiothoracic surgeon, JSB, and consultant cardiologist, VJR, for 31 patients studied at Leicester.

Arteriogram Reader	Proportion of exercise tests whose diagnostic result was:	
	Greater than the Arteriogram Result	Less than the Arteriogram Result
JSB	19%	26%
VJR	34%	10%
Leeds	25%	17%

respectively.

In each of the correlations above, there was an overlap of the ranges of maximal ST/HR slopes obtained from patients classed as having either no significant disease, one, two or three vessel disease from their arteriogram.

The Effect of Medical Therapy on the Maximal ST/HR Slope.

The effect of beta blocker, calcium channel blocker and nitrate therapy on the maximal ST/HR slope has been studied at Leeds with the following results:

1. Beta blockers have no effect on the maximal ST/HR slope (Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982).
2. The calcium channel blocker, nifedipine, can cause either an increase, no change or a decrease in the maximal ST/HR slope (Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986).
3. Isosorbide di nitrate can increase the maximal ST/HR slope (Bishop, Linden, Mary & Stoker, 1986).

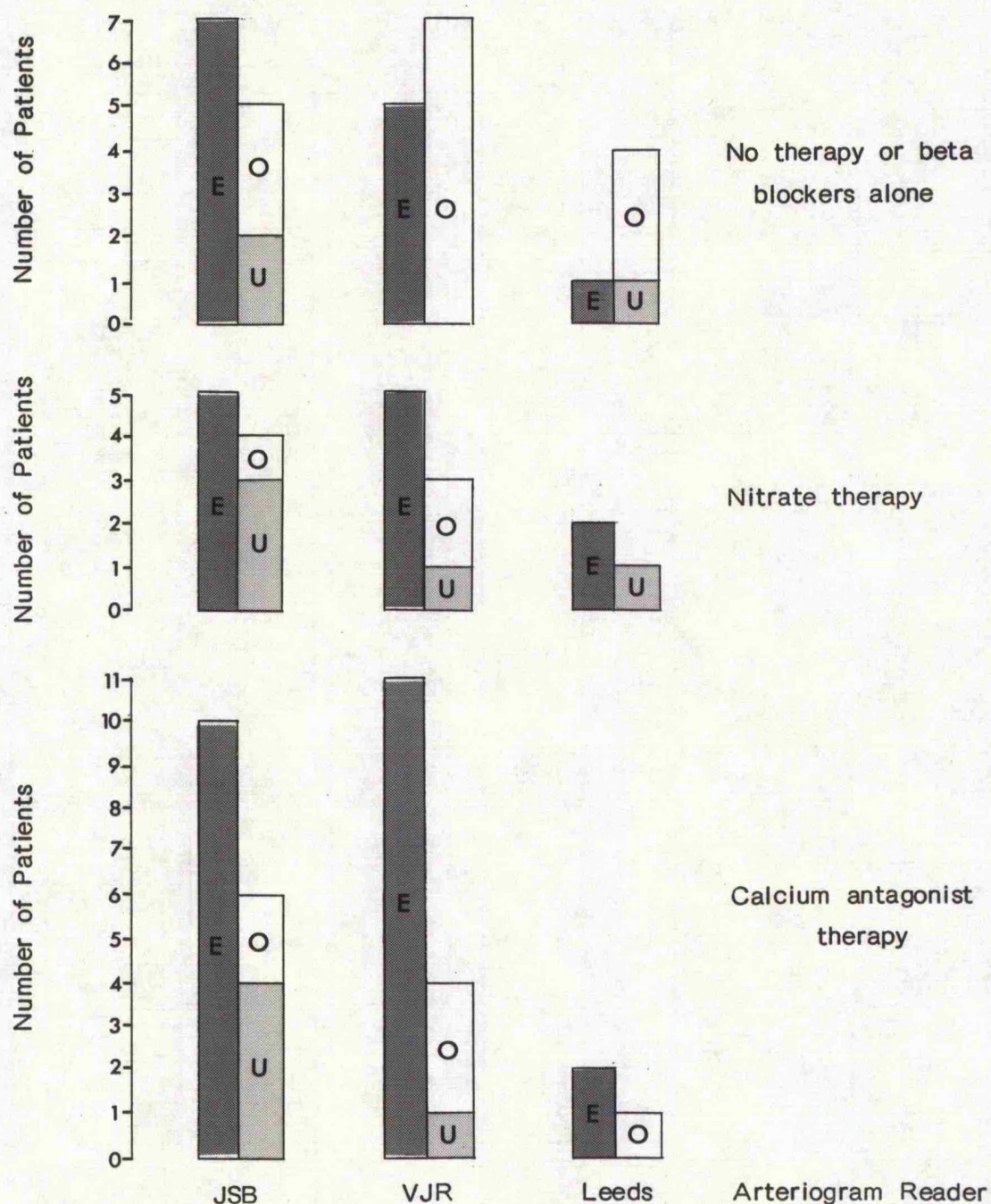
Of the patients in this study 12 were either on no medical treatment or were taking beta blockers alone. Nineteen were taking calcium channel blockers and/or nitrates, either with or without beta blockers. (Beta blocking agents included Atenolol, Propranolol, Metoprolol, Acebutalol and Oxeprenolol. Nitrates included isosorbide mono nitrate and Isosorbide di-nitrate. Calcium channel blockers included Nifedipine and Verapamil.

It was possible therefore that some of the patients' drug regime may have adversely affected the relation between the maximal ST/HR slope and the arteriogram result seen in this study. The number of patients on each drug regime and the number of occasions the maximal ST/HR slope underestimated, (U), gave an equivalent result, (E), or overestimated, (O), the arteriogram result according to the 3 readers are presented as histograms in figure 3.11.

Although a drug effect cannot be excluded, a greater number of equivalent exercise test and arteriogram results were obtained from patients

Figure 3.11. The relation between patient drug therapy and whether the maximal ST/HR slope produced an underestimate (U), an equivalent result (E) or an overestimate (O), of the coronary arteriogram result as read at Leeds (the consensus of consultant cardiologists RB, DSR and JBS) and at Leicester by consultant cardiologist (VJR) and consultant cardiothoracic surgeon (JSB) for 31 patients studied at Leicester.

Key: **E** : Equivalent exercise test and arteriogram result.
O : Overestimate of arteriogram result by exercise test.
U : Underestimate of arteriogram result by exercise test.



on calcium channel blocker and/or nitrate therapy. This was irrespective of the arteriogram reader. Conversely, there was a greater number of false predictions in patients not on medical therapy (or on beta blockers alone), than in patients who were taking calcium channel blockers or nitrates according to the arteriogram results of VJR and Leeds. Calcium channel blockers and nitrate therapy therefore had no systematic influence on the maximal ST/HR slope.

The Relation Between the Maximal ST/HR Slope and the 'Majority Opinion' Arteriogram Result.

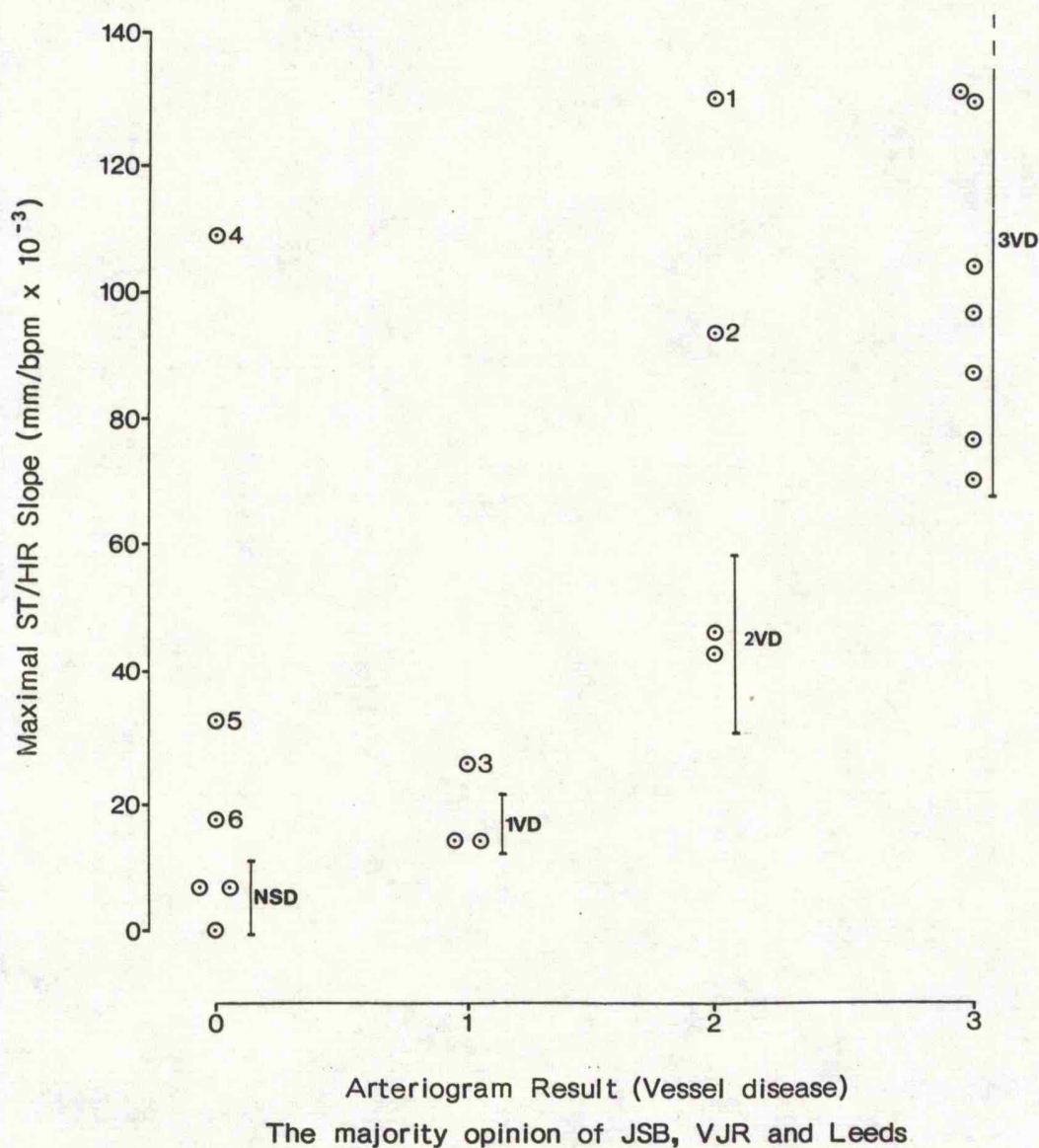
To partially resolve the differences in the arteriogram results obtained by the 3 readers, the 'majority opinion' arteriogram result was found. This was taken as that result where at least 2 of the 3 readers had reached the same conclusion. This limited the number of arteriogram results to 20; 11 were rejected because:

- a). 3 were read by only one reader. (In each, the exercise test result did not tally with the arteriogram result).
- b). In 8, different results were obtained by each reader. (In 4, there was no tally between any reading of the arteriogram - there were 9 readings - and the exercise test result. In the other 4, the arteriogram result of only 1 of the readers agreed with the exercise test result; 4 of 8 readings.

In summary, by using the majority opinion arteriogram result, 4 true and 16 false comparisons were excluded.

The relation between the maximal ST/HR slope and the majority opinion arteriogram result is presented in figure 3.12. The predictive accuracy of the exercise test was 70% (14/20). This result cannot be taken to truly represent the predictive accuracy of the test since the arteriogram results have in effect been selected and more false than true comparisons were rejected from the correlation. The purpose of presenting these results was to see the relation between the maximal ST/HR slope and the arteriogram result using only those results of arteriography associated with some degree

Figure 3.12. The relation between the maximal ST/HR slope and the coronary arteriogram result presented as the majority opinion of the five readers from Leeds and Leicester (RB, DSR, JBS, JSB and VJR). The shaded areas marked NSD, 1, 2 and 3 VD denote the ranges of maximal ST/HR slope which indicate no significant disease, one two and three vessel disease respectively, as proposed by Elamin, Mary, Smith & Linden, 1980. Cases marked 1 to 6 where there was a mismatch between the exercise test and arteriogram result according to the Leeds' diagnostic ranges of maximal ST/HR slope are discussed in Appendix V.



of confidence (namely that two readers came to the same conclusion). In 6 cases, there was a mismatch between the arteriogram result and the diagnosis based on the maximal ST/HR slope. These six cases marked 1 to 6 are discussed individually in Appendix V to try and offer, if possible, some explanation for the discrepancy of results obtained from the two tests. As is described there, if the Leeds proposal is to be accepted:

A: There was no obvious reason for the mismatch in the exercise test and arteriogram results of cases 3 and 5.

B: Possible reasons for the mismatch in the test results of the other 4 cases were:

1. An inadequacy of the 3 vessel disease notation to describe the extent of myocardial ischaemia in cases 1 and 2.
2. An underestimation of the degree of arterial narrowing as seen on the arteriogram in cases 2, 4 and 6.
3. An increase in the maximal ST/HR slope by Nifedipine in case 1.
4. A reduced coronary reserve caused by iron deficient anaemia may have aggravated the ischaemic response due to coronary occlusion.

Conclusion and Discussion.

This chapter presents:

1. The results of exercise testing (using the Leeds protocol) and coronary arteriography obtained from 49 patients studied at Leicester.
2. A correlation of these results where applicable.

It has been suggested that the manner of performing and analysing the exercise ECG and assessing the arteriogram at Leeds was critical to their obtaining the very good correlation between the results of these two tests (Linden & Mary, 1984). To all intents and purposes, the methods used at Leeds were repeated at Leicester in 49 patients with known or suspected coronary disease. Based on this, the following observations on the Leeds exercise test were made:

1. A conclusive result cannot always be obtained.
- a). A maximal ST/HR slope cannot be derived from patients unable to perform

more than one stage of exercise. This occurred in 4% (2/49) of patients in this study.

- b). Derivation of the maximal ST/HR slope requires the demonstration of a potential linear relation between ST segment depression and heart rate. Further, obtaining a reliable slope depends on achieving, during exercise, sufficient small increments in heart rate which are stable during recording.

In summary, a conclusive result cannot be obtained if:

- i). The heart rate response as described is not achieved. This occurred in 8% (4/49) of the patients in this study.
- ii). The relation between ST depression and heart rate is not linear ($p \geq 0.05$). This occurred in 14% (7/49) of the patients.

In this study, the exercise test was either invalid or inconclusive in 27% (13/49) of patients. This result contradicts one of the advantages originally proposed to be held by the Leeds test namely, indeterminate results do not occur.

2. Values of maximal ST/HR slope obtained from the patients studied here did not occur within three distinct ranges as found at Leeds and marked by the ranges: 0 to 11; 13 to 21; 32 to 59; 69 and above $\text{mm/bpm} \times 10^{-3}$. Rather, the maximal ST/HR slopes were distributed as three clusters marked by the ranges: 0 to 49; 70 to 109; and 130 to 139 $\text{mm/bpm} \times 10^{-3}$.

3. The maximal ST/HR slopes of 13% (4/31) of the patients in this study occurred outside the Leeds¹ defined boundaries of disease severity.

4. The range of 95% confidence limits on the maximal ST/HR slope had an upper limit of 116 $\text{mm/bpm} \times 10^{-3}$. Correspondingly, it extended over more than one disease category in 89% (26/31) of cases. This would suggest a limited confidence associated with the diagnosis derived from the slope.

5. As shown previously, inter observer variability occurred in the assessment of the arteriogram. In a 3-way comparison of arteriogram results of the three readers in this study, agreement of results occurred in only 69, 77 and 64 % of cases. This suggests:

- a). The arteriogram is not an ideal index of coronary disease.
- b). Any assessment of the predictive accuracy of the maximal ST/HR slope will vary according to the arteriogram reader.

6. In a comparison of arteriogram and exercise test results, there was an agreement in 55, 55 and 50 % of cases depending on the arteriogram reader. Further in each of these correlations, there was an overlap of the ranges of maximal ST/HR slopes obtained from patients classed as having either no significant disease, one, two or three vessel disease. This is in poor contrast with the predictive accuracy of the maximal ST/HR slope reported at Leeds (98%; Bishop, Adlakha, Boyle, Stoker and Mary, 1987). It is, however of a similar, and a greater, order of magnitude of the predictive accuracy of the maximal ST/HR slope reported by Quyyumi, Raphael, Wright, Bealing & Fox, 1984 and Balcon, Brooks & Layton, 1984 (42 and 24%, respectively) whose methods most closely resembled those at Leeds.

Potential Causes of the Low Predictive Accuracy of the Leeds Exercise Test at Leicester.

Potential causes of the low predictive accuracy of the Leeds test at Leicester are: the patient selection; the methods used; the patients' drug therapy and the variance associated with the maximal ST/HR slope.

1. The Patient Selection.

Patients in whom a mismatch between the maximal ST/HR slope and the arteriogram result might occur (Elamin, Mary, Smith & Linden, 1980) were excluded from the calculation of the predictive accuracy of the Leeds test in this study. It is therefore unlikely, that patient selection contributed to the poor correlation between the maximal ST/HR slope and the arteriogram result obtained.

2. The Methods Used.

During this study, emphasis was placed on reproducing the Leeds' methods and this was met as far as possible. Reservation is held concerning reproducing, exactly, the arteriogram result since, by the nature of its assessment, different observers can derive different results. This caused

differences in the correlation between the maximal ST/HR slope and the arteriogram result for different arteriogram readers.

3. The Patients' Drug Therapy.

It is possible that the relation between the arteriogram result and the maximal ST/HR slope might have been adversely affected by some of the patient's drug regime. Nineteen of the 31 (61%) patients studied were on calcium channel blocker and/or nitrate therapy. Both of these have been shown, at Leeds, to affect the maximal ST/HR slope (Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986 and Bishop, Linden, Mary & Stoker, 1986 respectively):

a). The Calcium Channel Blocker, Nifedipine, and the Maximal ST/HR Slope.

The effect of the calcium channel blocker, nifedipine, on the maximal ST/HR slope obtained from 23 patients was described in 28 comparisons before and after 2 weeks of therapy (10 mg twice daily; Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986). There was an increase in the slope in 24 comparisons, no change in 3 and a decrease in 1. The mean increase in maximal ST/HR slope (\pm the standard error) was $5.78 \pm 1.63 \times 10^{-3}$ mm/bpm, significant at the level $p < 0.005$. In 11 patients, the increase was greater than 10% although there was no effect on the resting level of ST depression either at rest or at the end of the test. Increasing the dose to 20 mg twice daily for two weeks caused a further increase in the maximal ST/HR slope in 2 out of 3 patients. There was no change in the third. The largest increases in the maximal ST/HR slope due to nifedipine occurred in patients with double and triple vessel disease; in one, the increase placed the patient into the next higher disease category.

Only 15 patients in that study underwent coronary arteriography and the results of these were compatible with the diagnosis derived from the exercise test.

b). Nitrates and the Maximal ST/HR Slope.

The effect of nitrates on the maximal ST/HR slope is only briefly reported (Bishop, Linden, Mary & Stoker, 1986). Eight patients were examined

after treatment with, and then withdrawal from, isosorbide di-nitrate. In 12 comparisons of the maximal ST/HR slope before and after nitrate therapy, the slope increased in 11. The mean increase (\pm s.e) was 15.5 ± 4.7 mm/bpm $\times 10^{-3}$.

A drug effect on the maximal ST/HR slope and therefore its accuracy in predicting the results of arteriography can not be entirely dismissed in this study. However, a greater number of correct predictions were obtained from patients who were on medical therapy than from patients who were not. Conversely, according to the results of 2 arteriogram readers, a greater number of false predictions occurred in patients who were on no therapy or beta blockers alone.

4. The Variance Associated with the Maximal ST/HR Slope.

In the majority of patients (87%; 27/31), the range of disease described by the 95% confidence interval estimate extended more than one disease range category. This is collectively reflected in the mean probability of repeating the diagnostic result; 0.79 (range 0.41 to 1.00). Therefore at best, and in terms of estimating the maximal ST/HR slope, the predictive accuracy of the Leeds exercise test would be expected to be of the order of 79%. This excludes any limitation in arteriogram interpretation or any theoretical consideration as to why a precise relation between the maximal ST/HR slope and arteriogram result might not exist.

In summary therefore:

1. The Leeds protocol exercise test does not always produce a conclusive result.
2. Assessment of the maximal ST/HR slope as an index of coronary disease is limited when using the arteriogram as a standard of disease - this being prone to observer variability.
3. The standard error associated with the maximal ST/HR slope would suggest (in this study), a predictive accuracy of the test of no more than about 79%.
4. The mean predictive accuracy of the maximal ST/HR slope was only 53%

reflecting a potential drug effect on the slope and/or a discrepancy between the indices from the two tests; exercise testing and arteriography.

Three points warrant further comment:

1. In 2 of the 13 inconclusive tests, the patient was unable to perform more than 1 stage of exercise because of symptoms of severe myocardial ischaemia. In such patients, although a Leeds test might prove inconclusive, common sense would suggest further investigation of the patient was required.

2. In 4 of the 13 inconclusive tests, a controlled graded increase in heart rate was not obtained. It is conceivable that in some cases (for example, the patient who was unfamiliar with cycling), training or a rehearsal of the test might have allowed a conclusive result.

3. In 6 of the 13 inconclusive tests, no significant relation ($p < 0.05$) could be demonstrated between ST depression and heart rate although the presence of coronary disease was strongly suspected by, for example, severe ST depression. The inability to demonstrate a linear relation between the 2 variables was a consequence of:

- a). There are, by the nature of the test, only a limited number of data points available to represent the relation between ST depression and heart rate.
- b). The relation between ST depression and heart rate (particularly in patients with more severe disease), tended towards the curvilinear, with greater increases in ST depression occurring at increased heart rates. These 2 factors were also largely responsible for the large 95% confidence intervals about the slope undermining the confidence associated with the maximal ST/HR slope.

It is suggested that for one case in this study, more data points might have been obtained had less workload been applied during the exercise test. There is the chance that this would have produced a conclusive result. An alternative approach, applicable to all patients might be to measure the

continuous relation between ST depression and heart rate. This could be done using a running computer average of a set number of complexes and an exercise protocol designed to cause a gradual increase in heart rate. This might show more clearly the relation between heart rate and ST depression and indicate an alternative and suitable means of quantifying it.

Discussion and Conclusion.

Because of the potential value of the Leeds exercise test, its sound physiological basis, and the possibility that it had not been repeated at another centre since neither had its methods, the purpose of this study was to test the relation between the maximal ST/HR slope and the arteriographic appearance of coronary disease using, as far as possible, and under their guidance, Leeds' methods.

As was described in the introduction to this study, the results obtained at Leeds were probably highly influenced by their protocol design. Thus: patients were chosen in whom coronary occlusion was the only likely cause of myocardial ischaemia; the exercise protocol was designed to best demonstrate any linear relation between ST segment depression and heart rate from which their index of disease was derived; the manner of assessing the arteriogram was based on earlier experience as to how severity of disease according to the arteriogram was reflected in the maximal ST/HR slope and exercise testing and arteriography were performed within a short period of each other to avoid an invalid correlation between these two tests through changes in the disease.

Attempts to Repeat the Leeds Exercise Test at Other Centres.

In several attempts at other centres the protocol used deviated (sometimes quite markedly) from those described at Leeds. It was suggested in the introduction that this might reasonably cause differences in the observed predictive capacity of the maximal ST/HR slope:

1. It was shown at Leeds that myocardial infarction (MI) less than 6 weeks before an exercise test can cause false positive and negative results when correlating the maximal ST/HR slope with the arteriogram result (Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). It is possible that the inclusion of patients with a past myocardial infarction in the study of Balcon, Brooks & Layton, 1984, might have contributed to their poor predictive accuracy of the maximal ST/HR slope (29%). Nineteen (39%) of their 49 patients studied had had a previous infarction, although the

interval between the this and the exercise test is not reported. That this might have adversely affected their results is indicated in that for a large proportion (16/19; 84%) of their patients with a history of infarction, there was a mismatch between the maximal ST/HR slope and the arteriogram result. Conversely, a similar proportion of patients (10/12; 83%) in whom there was a tally between the maximal ST/HR slope had not had an infarct.

It is only fair to note, however, that a history of MI was not specified as an exclusion criterion by Leeds in their early publications. Further, in the report presenting the accumulated results of 206 patients, 37 (18%) had a history of MI, with apparently no detracting from the accuracy of their test (Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982). Again however, the time interval between infarction and the exercise test is not given and so no firm conclusion can be made.

2. In 8 attempts to reproduce the Leeds' results, a treadmill ergometer was used (Ilsley, Canepa-Anson & Rickards, 1983; Harling, 1983; Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985; Okin, Ameisen & Kligfield, 1986; Finkelhor, Newhouse, Vrobel, Miron & Bahler, 1986; Ameisen, Kligfield, Okin, Miller & Borer, 1986). Six specifically used either the standard or modified Bruce protocols. In both of these protocols, increases in work load (an increase in the treadmill incline, either alone or with an increase in speed), are fixed for each stage. They do not necessarily promote discrete small increments in heart rate in the individual patient. In the Bruce protocol particularly, increments in heart rate between stages are large (for example 27 bpm) and often the heart rate at the end of each stage is not stable (Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Pollock, Bohannon, Cooper, Ayres, Ward, White & Linnerud, 1976; Pollock, Foster, Schmidt, Heilman, Linnerud & Ward, 1982). This can limit the number of data points obtained during the test particularly in patients limited by a poor exercise tolerance or symptoms. The likelihood of obtaining sufficient data with a

fixed treadmill protocol rather than an exercise protocol adjusted according to the patient's heart rate, is therefore reduced. Also, an exercise protocol which gives few data points with large increments in heart rate reduces the chances of being able to demonstrate a significantly linear relation between ST segment displacement and heart rate as was also seen in this study and may underestimate the slope of this relation.

3. As argued in the introduction, because the ECG is a vector, and because ischaemia and attendant changes in the ECG can be regional, it is possible that if the number of recording electrodes are limited, the chances of underestimating the degree of ST segment depression and correspondingly the maximal ST/HR slope are increased. Equally, lead systems with different orientations are likely to give different data.

In the Leeds test, the standard 12 and the bipolar CM5 recording electrodes were used. Different and fewer recording electrodes were used at other centres as listed:

- i). The standard 12 leads only (Ilsley, Canepa-Anson & Rickards, 1983);
- ii). The three leads; aVF, V5 and V6 (Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985).
- iii). The three leads II, V1 and V5 (Finkelhor, Newhouse, Vrobel, Miron & Borer, 1986);
- iv). Lead V5 only (Harling, 1983);
- v). The orthogonal leads X, Y and Z (Beattie, Seibert, Wilson, Pipberger & Blomqvist, 1984; Detre & Vanbutsele, 1984).

The use of fewer or different leads as a cause of reduced predictive accuracy of the maximal ST/HR slope was pointed out by Linden & Mary, 1984. This was in response to an article by Ilsley, Canepa-Anson & Rickards, 1983, who questioned the clinical use of the Leeds test on the basis that they could only show a predictive rate of disease severity of 70% in 30 patients. Among other things, Ilsley and coworkers used the standard 12 recording electrodes only. It was believed by the Leeds team that omission of lead CM5

was a significant digression from their method since by retrospectively excluding the data obtained from lead CM5 in their study of 230 patients, the predictive accuracy of the maximal ST/HR slope decreased from 100 to 89% (Linden & Mary, 1984).

If the data obtained from lead CM5 is similarly excluded in this study, the maximal ST/HR slope is underestimated in 3/35 (9%) patients. As shown in table D.1, the predictive accuracy of the maximal ST/HR slope obtained in this study according to the arteriogram result of JSB, VJR, Leeds and the majority opinion is reduced respectively from 55, 55, 50 and 70 % to 45, 45, 43 and 55 %; a mean reduction of 11%.

A similar reduction of the predictive accuracy of the maximal ST/HR slope is obtained if data from the leads groups aVF, V5 and V6; II, V1 and V5 or V5 only as used at other centres. This is shown in tables D.2 to D.4. The average mean reduction in predictive accuracy was 17%. Thus, as anticipated, a reduced number of ECG leads can adversely affect the relation between the arteriogram result and the maximal ST/HR slope.

As regards the orthogonal X, Y or Z leads, these generally show an ST segment displacement of magnitude $\frac{1}{2}$ or less that seen in the standard 12 lead system (Mankin, 1980). Thus a change may be seen in one lead system and not the other (Macfarlane, Melville, Horton & Bailey, 1981). Because these two lead sets present different data, it would not be surprising if exercise tests using them produced different maximal ST/HR slopes.

4. In the Leeds test, ST segment displacement was measured at 80ms after the J point. Six studies attempting to reproduce Leeds' results measured the ST segment at latencies other than 80ms. It was measured at:

- i). 60 ms after the J point (Detre & Vanbutsele, 1984).
- ii). 70 ms after the J point (Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985; Ameisen, Kligfield, Okin, Miller & Borer, 1986).
- iii). A point $\frac{2}{8}$ th of the distance between the J point and the end of

Table D.1. The effect of excluding data obtained from lead CM5 on the predictive accuracy of the Leeds exercise test at Leicester.

Arteriogram Reader	Predictive Accuracy	
	All leads	All leads bar CM5
JSB	55%	45%
VJR	55%	45%
Leeds	50%	43%
Majority Opinion	70%	55%
Mean Difference:	11%	

Table D.2. The effect of using data from leads aVF, V5 and V6 only on the predictive accuracy of the Leeds exercise test at Leicester.

Arteriogram Reader	Predictive Accuracy	
	All leads	Leads aVF, V5 and V6 only
JSB	55%	31%
VJR	55%	41%
Leeds	50%	33%
Majority Opinion	70%	53%
Mean Difference:	18%	

Table D.3. The effect of using data from leads II, V1 and V5 only on the predictive accuracy of the Leeds exercise test at Leicester.

Arteriogram Reader	Predictive Accuracy	
	All leads	Leads II, V1 and V5 only
JSB	55%	37%
VJR	55%	46%
Leeds	50%	31%
Majority Opinion	70%	47%
Mean Difference:	17%	

Table D.4. The effect of using data from lead V5 only on the predictive accuracy of the Leeds exercise test at Leicester.

Arteriogram Reader	Predictive Accuracy	
	All leads	Leads V5 only
JSB	55%	32%
VJR	55%	35%
Leeds	50%	42%
Majority Opinion	70%	42%
Mean Difference:	20%	

the T wave (Beattie, Seibert, Wilson, Pipberger & Blomqvist, 1984).

Variable maximal ST/HR slopes may be obtained depending on the latency at which ST segment displacement is measured since the ST segment during an exercise test can vary in its inclination (Goldschlager, Selzer & Cohn, 1976). Further, as the heart rate increases, the duration of the ST segment decreases and therefore measurement at a fixed latency from the J point may progressively encroach on the T wave.

This has been demonstrated quantitatively in this department by Sutcliffe, 1984. Using a computer assisted method of analysing exercise ECGs from patients with coronary disease, maximal ST/HR slopes were derived using the ST displacement at 10, 20, 40, 60, 80 ms and a heart rate dependant interval after the J point. The diagnostic result using the ST displacement measured at these latencies differed from that using the displacement at 80 ms after the J point in 3/8 (38%); 3/8 (38%); 4/8 (50%); 4/8 (50%) and 5/8 (63%) patients respectively.

This effect may have added to the absence of an absolute tally between the exercise test and arteriogram results obtained by Detre & Vanbutsele, 1984; Okin, Kligfield, Ameisen, Goldberg & Borer, 1985; Ameisen, Okin, Devereux, Hochreiter, Miller, Zullo, Borer & Kligfield, 1985; Kligfield, Okin, Ameisen, Wallis & Borer, 1985; Ameisen, Kligfield, Okin, Miller & Borer, 1986.

5. Where it has been disclosed, most studies attempting to repeat Leeds' results, have said to have assessed the arteriograms in a manner similar to that published at Leeds. From attempts to reproduce the Leeds' arteriogram results described in this study, it is doubtful that, even with a claim to assess the arteriogram as described by Leeds, similar results will necessarily be obtained largely because of the subjective nature of arteriogram assessment. Further, it became apparent during this study that although publications from Leeds describe a significant stenosis as being one of at least 75% reduction in lumen diameter, a stenosis was labelled such only secondary to whether it was thought to cause ischaemia on

exercise. Thus 75% was more a grade of severity than an absolute measure. Some authors attempting to reproduce Leeds' results appear to have taken the definition of a significant stenosis more literally. For example, Balcon, Brooks & Layton, 1984 question that a 75% reduction in lumen diameter should be so critical and suggest that, for example, a 70% lesion might also cause sufficient ischaemia to be reflected in a maximal ST/HR slope indicative of significant disease. Similarly, Quyyumi, Raphael, Wright, Bealing & Fox, 1984 quote "in some patients it was extremely difficult to decide whether or not a stenosis was greater or less than 75% luminal narrowing". Further, in that study, and also that of Thwaites, Quyyumi, Raphael, Canepa-Anson & Fox, 1986, when the authors were unsure of the extent of narrowing, it was measured. It is easily possible that a stenosis may appear significant and yet on measurement be less than a 75% reduction in lumen diameter. The converse is probably also true for some lesions. Thus, such attempts to define stenoses in absolute terms may have caused differences in arteriogram results which if the Leeds test holds, could contribute to a poor correlation between the arteriogram result and the maximal ST/HR slope.

Different arteriogram results may also have arisen in studies where a significant stenosis was defined as a 50% or more reduction in lumen diameter of the left main stem (Kligfield, Okin, Ameisen, Wallis & Borer, 1985), or any of the 3 main coronary arteries (Detre & Vanbutsele, 1984). Even if assessment of a stenosis is by visual impression and based on an arbitrary grading system, a 50% rather than 75% reduction in lumen diameter implies a less stringent criteria of significance which could lead to an apparent underestimation of disease severity by the maximal ST/HR slope.

6. It is possible that, by their allowing an interval of as long as 2 to 3 months between performing the exercise test and arteriography, a mismatch between the results of these tests might have occurred in the studies of Quyyumi, Raphael, Wright, Bealing & Fox, 1984 and Kligfield, Okin, Ameisen, Wallis & Borer, 1985.

In addition to the above general causes for an inability to reproduce

the Leeds test, it was shown in Results chapter 1 of this study that different maximal ST/HR slopes can be obtained at the level of measuring the exercise ECG. It was shown that without collaboration with members of the Leeds' team who were experienced in measuring the ECG, different maximal ST/HR slopes could be obtained. Most of these differences could be resolved by practice and cross checking with Leeds however, some variance in measurement was unavoidable where locating the J point was subjective.

In conclusion, in agreement with Linden & Mary, 1984, deviation from their protocol could adversely influence the predictive accuracy of the maximal ST/HR slope as seen at other centres.

Attempts to Repeat the Leeds Exercise Test at Leicester.

During this study, emphasis was placed on repeating as far as possible, and under their guidance, the methods used at Leeds. The only differences in performing the exercise test at the two centres were the types of bicycle ergometer and the ECG recording systems used. These, as discussed in the methods section of this report, should not have detracted from the results obtained in this study. In spite of this, the mean predictive accuracy of the Leeds test performed at Leicester was only 55%. This compares quite markedly with the value of 98% reported at Leeds.

A Patient Drug Effect.

Some allowance must be made for the possibility of a drug effect on the maximal ST/HR slope. Nineteen (61%) of the 31 patients studied here were on calcium channel blocker and/or nitrate therapy. Both calcium channel blockers and nitrates have been shown at Leeds to increase the maximal ST/HR slope in some patients; in other patients, calcium channel blockers have caused a decrease in the slope (Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986; Bishop, Linden, Mary & Stoker, 1986).

This could not account entirely for the relatively poor correlation between the results of arteriography and exercise testing at Leicester since:

1. A greater number of correct predictions were obtained from patients who

were on medical therapy than from patients who were not.

2. According to the results of two arteriogram readers, a greater number of false predictions occurred in patients who were on no therapy (or beta blockers alone which does not affect the maximal ST/HR slope) than patients who were on either calcium channel blockers or nitrates.

The Variance in the Estimate of the Maximal ST/HR Slope and in the Arteriogram Result.

Another potential¹⁶ cause of the poor correlation between the arteriogram and exercise test results obtained at Leicester was the variance in the estimate of the maximal ST/HR slope and (as already suggested), the arteriogram result:

The Variance in the Estimate of the Maximal ST/HR Slope.

When analysing the exercise ECGs large standard errors, and therefore the 95% confidence limits, on the maximal ST/HR slopes were seen. The range of diagnoses described by the 95% confidence intervals extended over 2 or more grades of coronary vessel disease (eg. over 1 and 2 vessel disease; over 2 and 3 vessel disease or over 1 and 3 vessel disease) in 25/31 (81%) cases. The mean probability of repeating the diagnostic result in 31 patients from whom a conclusive maximal ST/HR slope was obtained was 0.79. This was at odds with the expectation that the maximal ST/HR slopes would occur within the discrete ranges described at Leeds. It is likely that this has contributed to the inability to reproduce Leeds' results.

There was no reason to suspect that the standard error of the measurements of heart rate and ST segment displacement were responsible for the large standard errors on the slope for the following reasons:

1. Heart rate measurements were very reproducible.
2. There was no correlation between the standard error of the ST segment displacement measurements and the standard error on the maximal ST/HR slope.

The large standard errors on the maximal ST/HR slopes were subsequently attributed to the variance in the correlation between ST segment

displacement and heart rate.

None of the Leeds publications present the standard errors of their maximal ST/HR slopes. However, contrary to what might be expected from this study, the maximal ST/HR slope was shown to be extremely reproducible. The difference between maximal ST/HR slopes obtained from two successive tests in 19 patients ranged from as little as -0.05 to $+0.4$ mm/bpm $\times 10^{-3}$; the mean was $+0.03$ mm/bpm $\times 10^{-3}$. Unfortunately, the reproducibility of the maximal ST/HR slope in the individual patient could not be tested in this study. However, the variance in the maximal ST/HR slope observed in this study would suggest that the poor predictive accuracy of the ST/HR slope seen was related to the relation between ST depression and heart rate recorded during the exercise test. The Leeds protocol was specifically designed to demonstrate this relation; it required that a sufficient number of stages of exercise were performed that would precipitate small increments in heart rate (about 10 bpm) from which a slope of regression of ST depression on heart rate could be calculated. In terms of the number of stages of exercise, this criterion was satisfied at Leicester; the mean number of stages of all exercise tests was 4 and of those from which a maximal slope was estimated, it was 5. Further, the mean increase in heart rate per stage was 12 bpm. This suggests that a dependence of the result on linear regression analysis is a limitation of the test. It was particularly apparent in patients with more severe coronary disease that greater increases in ST depression occurred for increasing changes in heart rate; the relation between ST depression and heart rate may well have been better represented in these patients by some form of quadratic analysis.

The Variance of the Arteriogram Result.

Implicit in the close correlation between exercise test and arteriogram results presented at Leeds, is that there is a high degree of certainty associated with the latter. The visual assessment of disease severity from the arteriogram however, is known to be associated with considerable inter and intra observer variability (Detre, Wright, Murphy & Takaro, 1975; Zir,

Miller, Dinsmore, Gilbert & Harthorne, 1976; DeRouen, Murray & Owen, 1977; Galbraith, Murphy & de Soyza, 1978; Sanmarco, Brooks & Blackenhorn, 1978; Fisher, Judkins, Lesperence, Cameron, Swaye, Ryan, Maynard, Bourassa, Kennedy, Gosselin, Kemp, Faxon, Wexler & Davis, 1982). This, as presented in Results chapter 2, was confirmed in this study and applied even when using the Leeds method which by defining several criteria of assessment may have limited the variation in the results (assessment was made in only one radiographic view; it was the point of maximal narrowing; the stenosis had to occur in the proximal segment of an artery to be counted in the overall diagnostic result and no account was made of the stenosis length or the possible compensatory effect of other vessels including collaterals).

As was described in Results chapter 2, variation in arteriogram results was because assessment of disease requires the extrapolation of an impression of the 3-dimensional form of a stenosis from 2-dimensional images and it invariably involves the conjectural opinion of whether or not the stenosis is functionally significant.

In none of the studies from Leeds is the reproducibility of arteriogram assessment presented. Interobserver variability is however suggested in the studies by Kardash, Elamin, Mary, Whitaker, Smith, Boyle, Stoker & Linden, 1982 and Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982. It is described that when the arteriograms were read by more than one observer, any differences were resolved in a further joint assessment. It remains surprising therefore that a very good correlation between the exercise test and the arteriogram result can be obtained in respect of the subjective nature of arteriogram assessment. This was supported in this study in that the arteriogram results obtained from members of the Leeds team, could not be reproduced by experienced readers at Leicester despite receiving careful explanation of their method prior to the study. In a three way comparison of arteriogram results obtained from Leeds and the readers at Leicester, the same result was obtained in only 62, 69 and 65 % of cases respectively. Further, the results of arteriograms assessed on two separate occasions by

the two readers at Leicester were the same in only 86 and 57% of cases respectively.

An Exact Relation Between the Results of Exercise Testing and Arteriography Questioned.

It is further surprising that the Leeds test was able to show such a precise tally between results of exercise testing and arteriography (the variance in the ST/HR slope and the arteriogram result apart) because:

1. As described in the Introduction, ST segment depression occurs through the loss of intracellular potassium corresponding to an inadequate myocardial perfusion. It thereby allows an objective physiological measure of this (Samson & Scher, 1960; Braunwald & Maroko, 1976; Rakita, Borduas, Rothman & Prinzmetal, 1954; Weiss & Shine, 1982). Coronary arteriography on the other hand (as described in the Introduction and Results chapter 2), although allowing an impression of the presence, topography and degree of narrowing of the coronary arteries, it provides no information about the haemodynamic consequences of the stenosis save the manner of flow of contrast medium through, or clearance from, a diseased vessel, unless ventricular contraction is obviously impaired. Thus assessment of the functional effect of a coronary stenosis is highly speculative and precise correlation between these two tests is not necessarily expected.

2. Assessment of the severity of ischaemic heart disease from both the exercise ECG and the arteriogram has its limitations. Already described in the introduction, briefly:

Limitations of the exercise ECG in the quantitative assessment of ischaemic heart disease include:

- i). A cancellation of currents of injury may reduce the apparent degree of ST depression recorded and so the estimated severity of disease (Holland & Brooks, 1977; Bishop, Adlakha, Boyle, Stoker, Smith & Mary, 1987).
- ii). If the effective recording position of an electrode is not perpendicular to the maximum current of injury, the degree of ST depression and therefore the estimated severity of disease may be underestimated.

Limitations of the arteriogram in the quantitative assessment of ischaemic heart disease include:

- i). The arteriogram can only present 2-dimensional views of a stenosis from which a 3-dimensional form must be extrapolated.
- ii). It does not always allow an accurate description of the degree of luminal narrowing; this may be both over- or, more commonly, under-estimated.

3. The results obtained from each test were described in terms of discrete categories of disease severity (0, 1, 2 and 3 vessel disease) which is not necessarily appropriate in either case of the maximal ST/HR slope or the arteriogram result:

a). Disease Severity in Terms of Discrete Categories According to the Maximal ST/HR Slope.

The proposed predictive capacity of the Leeds test was derived from the observation that the maximal ST/HR slope obtained from patients with varying severity of disease occurred within 4 distinct groups. Patients within these groups were identified by arteriography to have no significant disease, one, two and three vessel disease respectively.

It was suggested at Leeds that this observation was a consequence of the "very sharp sudden inflection" in the relation between coronary flow and minimum stenosis diameter (Elamin, Boyle, Kardash, Smith, Stoker, Whitaker, Mary & Linden, 1982). It was said that during the pathological progression of a coronary stenosis, the period spent at the "inflection point", that is, when it changes from being non flow limiting to flow limiting is very short. Thus the chances of performing an exercise test on a patient at such a critical moment was very small thereby giving the impression of an 'all or none' graded type of response.

That values of maximal ST/HR slope should occur within such discrete ranges is surprising as follows:

If the reason for the discrete ranges proposed above is to be accepted, then on the basis of the high correlation between the ST/HR slope

and the arteriogram result, it must be assumed that an observer can recognise a critical from a non critical stenosis. From what has been said about the difficulties involved in arteriogram assessment, such discrimination is unlikely.

Further, according to Elamin, Mary, Smith & Linden, 1980, patients described at arteriography as having no significant disease can generate maximal ST/HR slopes from 0 to 11 mm/bpm $\times 10^{-3}$. (This could understandably arise through the presence of a stenosis which was considered either too distal or, proximal but not sufficiently severe for inclusion in the diagnostic result). It is conceivable that if such a stenosis occurred in addition to stenoses which promoted an ST/HR slope indicative of "1" or "2" vessel disease, then the overall slope could occur between the zones marking 1 and 2 vessel disease and 2 and 3 vessel disease respectively.

b). Disease Severity in Terms of Discrete Categories According to the Arteriogram.

Quantifying coronary disease severity from the arteriogram using the 3 vessel notation at first sight may seem a convenient method, there typically being three main coronary arteries. This terminology however is not always accommodating for example where the left coronary artery itself consists of 3 or 4 major arteries. This notation further ignores the dominance of the circulation which may result in a poor reflection of the extent of disease. For example, severe disease in a dominant left coronary artery may result in a greater extent of ischaemia than equivalent disease in a non dominant left artery because it serves more myocardium.

Further, the Leeds method of assessing the arteriogram might be considered limited in quantifying ischaemic heart disease in that the following were not considered:

- i). Severe occlusions of a major artery's branch.
- ii). Diffuse atherosclerosis along all or a variable portion of the vessel.
- iii). The length and asymmetry of a stenosis.
- iv). The occurrence of multiple stenoses in series.

- v). Collateral vessels.
- vi). The dominance of the circulation (as described above).
- vii). Distal stenoses.

All these, as described in the introduction, may contribute to the severity of myocardial ischaemia. It would follow that the degree of ischaemic heart disease more reasonably occurs on a continuous rather than a quantal scale. This in turn would be reflected in the maximal ST/HR slopes which would also be expected to occur as a continuum.

The Current Standing of the Leeds Exercise Test.

The Leeds exercise test has received much criticism on the grounds that other centres have been unable to show an exact correlation between the maximal ST/HR slope and the results of coronary arteriography expressed in terms of no significant disease, 1, 2, or 3 vessel disease.

It is concluded from this study that the failure to demonstrate such an exact relation is not surprising for the following reasons:

1. Inappropriate patients have been studied.
2. There were variations in exercise protocol and methods of analysis.
3. There is a large variance in the estimate of the maximal ST/HR slope and the severity of disease as depicted by the arteriogram.
4. An absolute correlation between the tests which reflect different facets of coronary disease is unlikely.
5. Quantifying severity of ischaemic heart disease in terms of 0, 1, 2 and 3 vessel disease whether by the arteriogram or by the maximal ST/HR slope is not entirely accommodating.

This however should not detract from the potential improvement of the maximal ST/HR slope over the more conventional index of coronary disease namely the isolated measure of ST segment depression at the end of a period of exercise. By normalising the index of oxygen deficit (ST depression) with the index of oxygen consumption (heart rate), this provides a more objective and apt relative index of myocardial ischaemia.

Illustrating the superiority of the Leeds test, Okin, Kligfield,

Ameisen, Goldberg & Borer, 1985 have shown that heart rate related changes in ST depression is a more accurate test for identifying patients with 3 vessel coronary disease than the conventional criteria of ST depression alone. Thus the occurrence of a maximal ST/HR slope (observed in leads aVF, V5 and V6 with ST depression measured 70 ms after the J point) of at least $60 \text{ mm/bpm} \times 10^{-3}$ had a predictive accuracy of 90%. This contrasted with a test accuracy of 64% using an index of at least 1 mm of ST depression.

In retrospect, it is probably unfortunate that the maximal ST/HR slope was correlated against results of arteriography in terms of one, two and three vessel disease since the shortcomings of the latter have undoubtedly limited the acceptance of the Leeds test as a potentially valuable tool in the diagnosis of ischaemic heart disease. As already described, the arteriogram has been generally accepted as the standard test for coronary disease since it provides an image of the coronary and any narrowings of them. Unlike exercise induced ST segment depression, the arteriogram reflects more an anatomical rather than a (more pertinent) functional index of coronary disease; assessment of the functional effect of coronary disease from the arteriogram is only inferential. Evaluation of the arteriogram, like that of all other indices of ischaemia, is limited by the lack of an ultimate standard.

That the maximal ST/HR slope is a potential index of the functional extent of coronary disease is suggested in the work of Kligfield, Okin, Ameisen, Wallis & Borer, 1985. Functional effect of ischaemia was assessed by the extent of exercise related reduction in left ventricular ejection fraction (LVEF) due to abnormalities of left ventricular contraction. This was estimated by radiocineangiography which measured changes in ventricular blood volume traced with radioactive Technicium (Borer, Bacharach, Green, Kent, Epstein & Johnston, 1977). It was shown that the ST/HR slope correlated linearly with the exercise related change in LVEF ($r = -0.55$; $p < 0.001$); a higher ST/HR slope was associated with a greater decrease in LVEF). It was also noted that an ST/HR slope of $4.5 \text{ } \mu\text{V/bpm}$ delineated

between patients with and without large exercise induced reductions in left ventricular function. The mean fall in exercise EF for patients with ST/HR slopes greater than 4.5 was significantly greater than for patients with lower ST/HR slopes ($-12 \pm 1\%$ and $+2 \pm 2\%$, $p < 0.0001$, respectively), regardless of the underlying distribution of disease. It was suggested therefore that this might be used to distinguish patients with, from those without, functionally significant ischaemia. Thus, the ST/HR slope significantly correlated with the functional extent of myocardial ischaemia; related to, but not necessarily totally dependant on, the anatomic extent of disease.

Further, it has been shown that there is a significant correlation ($r = -0.61$, $p < 0.001$) between the heart rate related progression of ST depression and the arteriographically determined extent of disease described by the Gensini score (Finkelhor, Newhouse, Vrobel, Miron & Bahler, 1986). This score not only considers the extent of luminal narrowing in coronary disease but also the accumulative effects of multiple obstructions, the significance of their location, the modifying influence of collateral vessels and left ventricular function (Gensini, 1983). It thus allows a more realistic quantitative description of coronary disease than simple division of patients into 1, 2 and 3 vessel disease.

Therefore, although the maximal ST/HR slope has not yet been able to discriminate patients (with a high degree of accuracy) with 0, 1, 2 or 3 vessel disease defined by the arteriogram other than at Leeds, it does appear to have some advantage over the more traditional methods of assessing ischaemic heart disease. It is conceivable, further, that rate normalising ST depression in previously tested indices of ischaemic heart disease (eg. the area of ST segment depression, the sum of ST depression measured in several leads, or even the latency at which depression is measured) may lead to an improvement in their predictive capacity.

At present, the maximal ST/HR slope as an index of ischaemic heart disease does have its limitations:

1. Considerable time is required for its estimation.
2. Inconclusive results can occur through not being able to demonstrate a significant relation between ST segment depression and heart rate.

Both these could be resolved by computer analysis:

1. It has been shown in this study that manual ST depression measurements are comparable to computer measurements made on a computer averaged complex where the J point is located manually. It is imaginable that a succinct algorithm could be composed to detect the J point thereby completely automating analysis. This would reduce the time required to analyse an exercise ECG and at the same time, limit the subjectiveness of this.

2. The occurrence of non significant slopes could be avoided by obtaining a continuous plot of the relation between ST depression and heart rate and if necessary representing this relation by some means other than linear regression.

In conclusion, the highly predictive capacity of the maximal ST/HR slope demonstrated at Leeds was not shown at Leicester. This is likely to be a consequence of the large variance associated with both the maximal ST/HR slope and arteriogram results. This, and the application of the test to inappropriate patients and deviations in the method from those described at Leeds may explain why the test has not been reproduced exactly, at other centres.

The Quantitative Assessment of Ischaemic Heart Disease in the Future.

It is clear from this study that both coronary arteriography and exercise testing are limited in the quantitative assessment of ischaemic heart disease. A relatively new application which has the potential of superceeding these tests is nuclear magnetic resonance (NMR) spectroscopy and imaging.

Nuclear Magnetic Resonance in Ischaemic Heart Disease.

The basis of nuclear magnetic resonance (NMR) is that atomic nuclei with an odd number of either or both protons and neutrons have a magnetic moment.

When these nuclei are placed in a magnetic field, their net magnetic moment becomes aligned with that of the field. Alignment is either in an anti-parallel or, with slight preponderance, parallel direction relative to the field. If such nuclei are subject to a pulse of radiowaves of frequency specific to the atom concerned, the nuclei parallel to the magnetic field become re-oriented into the less energetically favourable anti-parallel direction (excitation). After such a pulse, these nuclei tend to relax back to their initial preferred parallel alignment (relaxation) and in doing so emit a radio-frequency signal. The frequency of this signal is determined by the nucleus from which it originated, its density, the magnetic field which it experiences and relaxation parameters of the molecules containing the nucleus considered. The signal may be captured and recorded as a spectrum or an image of the object analysed (eg. Barrett, Alger & Zaret, 1985; Gutierrez & Andry, 1989).

In NMR spectroscopy, a frequency spectrum of the emitted radio-frequencies is obtained. For a heterogenous sample, this contains peaks corresponding to the frequencies of chemical groups containing the particular isotope nucleus. (Signals emitted by the nuclei being excited will vary according to the molecule it forms part of, since the surrounding electrons also impart an additional small magnetic field to the nucleus).

Of relevance to ischaemic heart disease, is the ^{31}P NMR spectrum. ^{31}P is a naturally occurring isotope and the spectrum of this presents peaks corresponding to adenosine triphosphate (ATP), phosphocreatine (PCr) and inorganic phosphate (Pi). The relative concentrations of these metabolites may be estimated from the areas beneath the spectrum peaks and the relative concentration of adenosine diphosphate (ADP) can be calculated from the following expression representing the biochemical energetics in cardiac (as well as other) muscle:



Further, the relative position of the Pi peak, sensitive to pH can provide an estimate of pH within the cytoplasm (Moon & Richards, 1973). The ^{31}P

spectrum provides a potential means of monitoring the metabolic state of the myocardium and could be used to mark the development of myocardial ischaemia.

This technique has been successful in isolated and in-vivo skeletal muscle and in-vivo, perfused small animal heart preparations (reviewed by: Gutierrez & Andry, 1989; Avison, Hetherington & Schulman, 1986; Radda & Taylor, 1985). The technique is currently being developed to allow in-vivo measurements of myocardial metabolism in man. Problems that are having to be overcome are:

- a), the loss of signals through cardiac and respiratory movement,
- b), the poor spatially resolution and,
- c), interference obtained from overlying skeletal muscle (Willis & Clarke, 1987).

In NMR imaging, the isotope is the proton. In this technique, unlike magnetic resonance spectroscopy, a magnetic gradient is applied over the area screened. Since the radiofrequency emitted by relaxing nuclei is related to the magnetic field they experience, the magnitude of the radio frequencies emitted by the protons in any sample, will depend on their relative position in the applied gradient field (Lauterbur, 1973). This provides spatial information from which an image may be reconstructed by a computer. In addition, since different tissues emit different signals according to their proton content and the distribution of these in the various molecules, this allows, in the image, a good delineation of different structures (eg. Kneeland, Lee, Whalen, Knowles & Cahill, 1984; Andrew, 1985).

Magnetic resonance imaging can therefore provide a non invasive means of observing any reduction in vessel lumens. Atherosclerotic lesions may additionally be identified on the basis of their high-fat content. Furthermore, since the magnetic resonance image signal from hydrogen nuclei in blood is flow dependant, abnormal flow patterns can be seen including possible turbulence in the vicinity of an atherosclerotic plaque. Although

these features have been used to indicate atherosclerotic lesions in large vessels, so far, images from only the proximal segments of the coronary arteries have been obtained with sufficient clarity for diagnosis. This is largely because of the tortuous nature of these vessels and their movement. It is conceivable however that with improved technology, this limitation may be overcome (Higgins, Kaufman & Crooks, 1985).

Thus, advantages of NMR in the diagnosis of ischaemic heart disease include: ^{31}P spectroscopy can enable the analysis of high energy phosphate metabolism in vivo; magnetic resonance imaging can enable images of the vascular system and estimations of rate of blood flow to be obtained non invasively and without the need for contrast medium or ionising radiation (Guttierrez & Andry, 1989; Higgins, Kaufman & Crooks, 1985). The major limitations are the, as yet, fairly poor spatial resolution in magnetic resonance spectroscopy, the cost of the equipment and the scanning times, particularly since gating is required (Barrett, Alger & Zaret, 1985).

With improved technology to overcome these limitations, NMR promises a powerful tool in the future quantitative, as well as qualitative assessment of ischaemic heart disease.

Appendix I

The Coronary Arteries.

There are two major coronary arteries; the left and the right (figure A1.1).

The Left Coronary Artery.

The left coronary artery (LCA), originates from the anterolateral (left facing) aortic sinus. It occurs as a single vessel, the left main stem, for a variable length of 6 to 26 mm in adults (Allwork, 1980). It then typically divides into two main branches; the left anterior descending (LAD) and the left circumflex (LCFX) arteries (figure A1.2).

The LAD lies in the anterior interventricular sulcus. It extends to the apex where it either ends or more commonly follows around the apex into the posterior interventricular sulcus. On the arteriogram, it is characterised by its forked terminal segment and its length and curvature which defines the anterior aspect of the left ventricle (figure A1.5). Two sets of branches stem from the LAD. These are the diagonal arteries and the anterior septal arteries. The diagonal arteries extend diagonally over the free wall of the left ventricle. The septal arteries descend vertically into the intraventricular septum (figure A1.2).

The LCFX artery passes to the left border of the heart in the atrioventricular sulcus. It is usually easily identified on the arteriogram since it occupies the same sulcus as the coronary sinus which drains most of the cardiac veins. At arteriography, after a short delay, the image of the LCFX is followed by the much wider image of the coronary sinus in approximately the same place. The LCFX continues from the anterior atrioventricular sulcus to the posterior atrioventricular sulcus. If the coronary anatomy is, what is termed, left dominant, the LCFX continues towards the apex in the posterior interventricular sulcus. (The dominant artery is defined as that which gives rise to the posterior descending artery). A number of lateral branches stem from the CFX and cross the free wall of the ventricle over a similar territory to that of the diagonal

Figure A1.1. The general course and distribution of the epicardial coronary arteries. The vessels with broken outlines indicate the vessels which would otherwise be obscured by the myocardium in the view presented. (Adapted from Warwick & Williams, 1975).

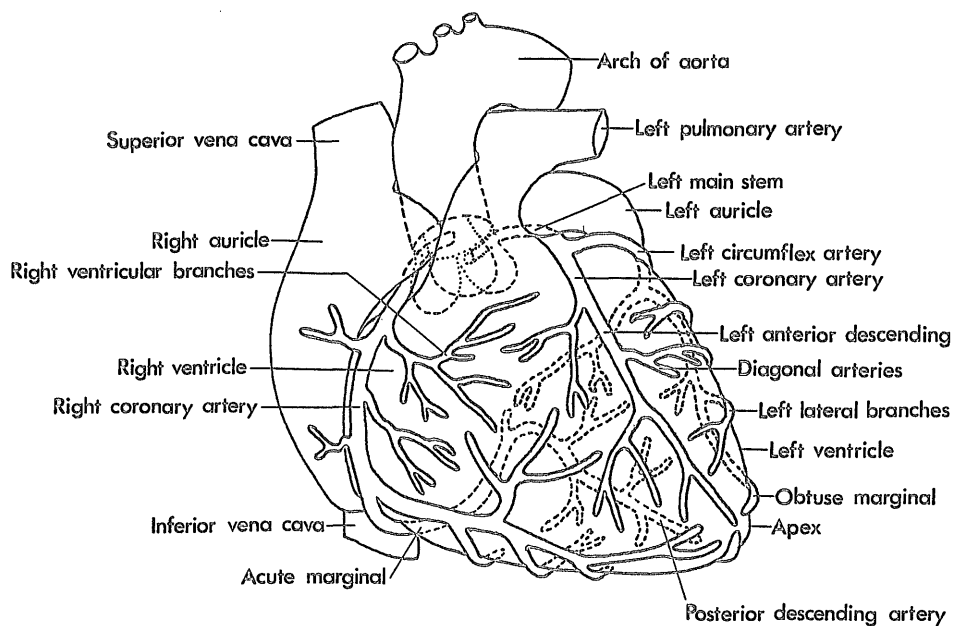


Figure A1.2. A coronary arteriogram showing the left coronary artery from the right anterior oblique (RAO) projection. The left main stem (LMS), the left anterior descending artery (LAD), the diagonal arteries (D); the anterior septal arteries (AS); the left circumflex (LCFX) and the obtuse marginal arteries (OM) are indicated. Three severe stenoses are marked by the three arrows (Adapted from Boucek, Morales, Romanelli & Judkins, 1984).

Figure A1.3. A coronary arteriogram taken from the right anterior oblique (RAO) projection in a case where the left main stem (LMS) divides into a left anterior descending artery (LAD), a left circumflex artery (LCFX) and an intermediate ramus (IR). The characteristic forked terminal of the LAD is clearly seen (arrows). (Adapted from Boucek, Morales, Romanelli & Judkins, 1984).

Figure A1.2

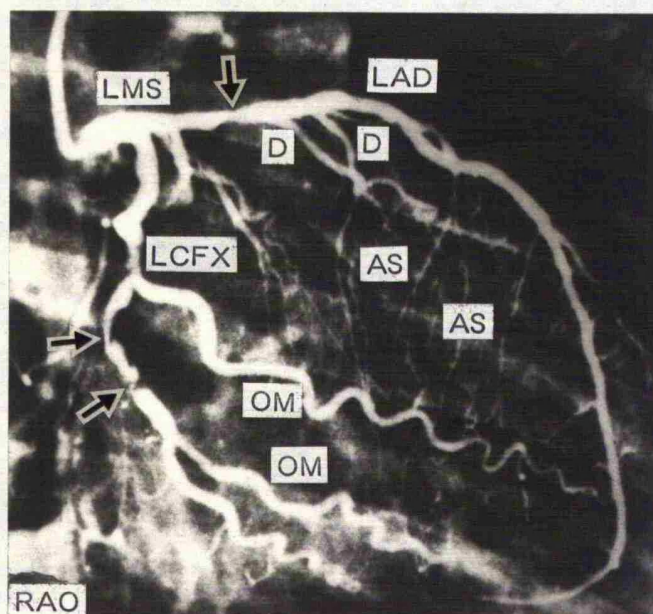
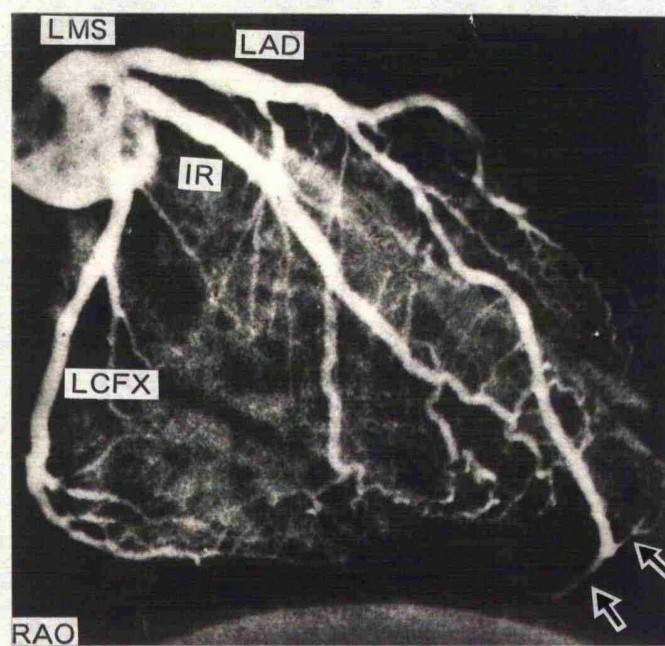


Figure A1.3



arteries from the LAD. One lateral branch is usually predominate and extends to the apex of the heart. This is the obtuse marginal artery.

The Intermediate Ramus.

In approximately 30% of cases, the left main stem divides into three major branches namely the LAD, the CFX and the intermediate ramus (Allwork, 1980). The intermediate ramus passes over the surface of the left ventricle between the LAD and the LCFX (figure A1.3). It largely replaces the diagonal arteries of the LAD and the lateral branches of the CFX.

The Right Coronary Artery.

The right coronary artery (RCA) originates in the anteromedial (right facing) aortic sinus. It extends in the right atrioventricular sulcus to the crux of the heart. If the anatomy is right dominant, the right artery extends as the posterior descending branch. This occupies the posterior intraventricular sulcus and supplies the posterior ventricular septum. The major branches of the proximal segment of the RCA supply the right ventricle. These are the right ventricular branches and are variable in size. The largest extends as far as the apex of the heart. This is the acute marginal artery (figure A1.4).

The Relative Distribution of the Coronary Arteries.

Figure A1.5 shows the relative distribution of the left and right coronary arteries in a case where the LCFX is completely occluded.

As described above, a left dominant coronary circulation is one in which the LCFX continues as the posterior descending artery. It has an estimated incidence of about 48%. A right dominant coronary circulation is one in which the RCA continues as the posterior descending artery. It has an estimated incidence of about 18%. A balanced circulation, where the left and right coronary arteries contribute equally to the perfusion of the posterior myocardium has an estimated incidence of 34% (Schlesinger, 1940).

Figure A1.4. A coronary arteriogram showing a small right coronary artery (RCA) from the left lateral (LL) projection. The artery extends as the posterior descending artery (PD) in the posterior interventricular sulcus. The right ventricular branches (V) and the acute marginal artery (AM) are indicated. (Adapted from Boucek, Morales, Romanelli & Judkins, 1984).

Figure A1.5. A coronary arteriogram showing the relative distribution of the left anterior descending (LAD) and the right coronary artery (RCA) from the right anterior oblique (RAO) projection. This was obtained from the injection of contrast medium into the RCA. The LAD has filled retrogradely through collateral anastomoses (arrow A) between the posterior descending artery (PD) of the RCA and the LAD. The LAD is completely occluded in its proximal third segment (arrow O) beyond the take off of the left circumflex which is therefore not seen. (Adapted from Boucek, Morales, Romanelli & Judkins, 1984).

Figure A1.4

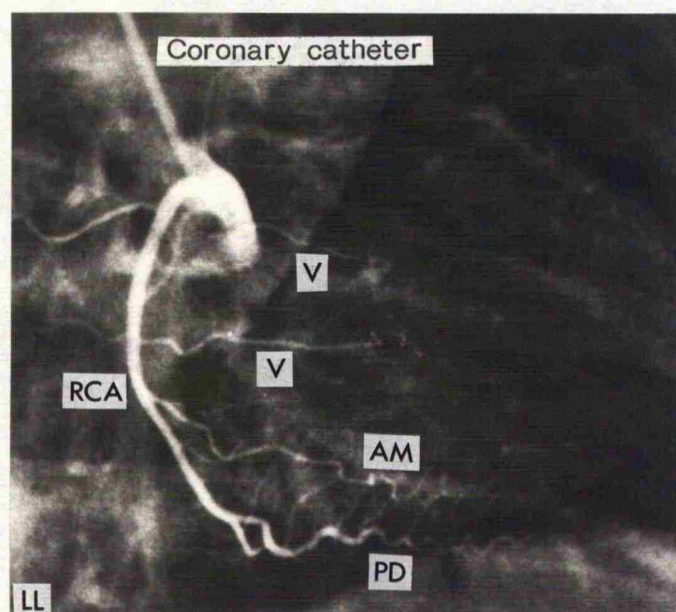
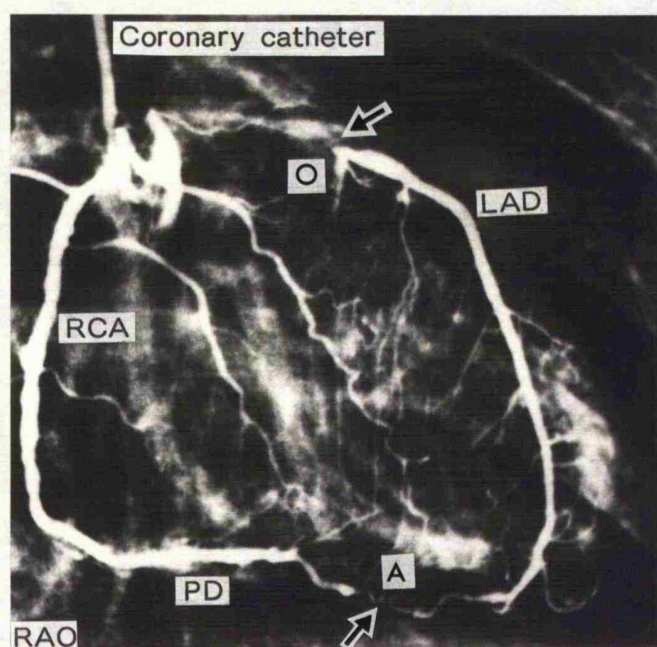


Figure A1.5



Appendix II

The Assembler Routines used in the Computer Program Developed to Assist in the Measurement of the Exercise Electrocardiogram.

```

                                ;STORECG

;PROGRAM TO STORE DIGITISED ECG SIGNALS FROM 3 SIMULTANEOUS ANALOGUE TO DIGITAL
;CONVERTOR (ADC) PORTS INTO 3 ROLLING MEMORY STACKS.COLLECTION OF DATA IS
;INTERRUPT SERVICE ROUTINE SUPPLYING ROUTINE SEARCHING FOR AND STORING 11 ECG
;SEGMENTS CONSISTING OF 64 POINTS BEFORE AND 191 POINTS AFTER THRESHOLD
;DETERMINED PEAK.
;INTERRUPT FREQUENCY ie. SAMPLING FREQUENCY=500Hz.
;RR INTERVALS ARE DETERMINED BY THE NUMBER OF INTERRUPTS (ie. 2ms) BETWEEN
;DETECTED PEAKS.

USRTV EQU 0107H                ;DEFINE MEMORY LOCATION OF USRTV
BBUFV EQU 0118H                ;DEFINE MEMORY LOCATION OF BBUFV
ADCECG EQU 3FFFH               ;DEFINE MEMORY LOCATION OF ADCECG

;CTC CONTROL BITS
CIE EQU 10000000B              ;ENABLE INTERRUPTS
CM EQU 01000000B               ;COUNTER MODE
PS EQU 00100000B               ;PRESCALE BY 256,TIMER MODE ONLY
POS EQU 00010000B              ;TRIGGER ON POSITIVE EDGE
HOLD EQU 00001000B             ;DELAY START,TIMER MODE ONLY
TC EQU 00000100B               ;TIME CONSTANT TO FOLLOW
STOP EQU 00000010B             ;STOP COUNTING
OP EQU 00000001B               ;SELECT OPERATING MODE

;CTC PORT ASSIGNMENTS
CHAN0 EQU 30H                  ;SETS VALUE OF LABELS CHAN0 etc.
CHAN1 EQU 31H                  ;
CHAN2 EQU 32H                  ;
CHAN3 EQU 33H                  ;

;ADC PORT ASSIGNMENTS
STADC EQU 39                   ;FOR SIMULTANEOUS ADC
CH1 EQU 40
CH2 EQU 41
CH3 EQU 42

ORG USRTV                      ;SETS ADDRESS REFERENCE COUNTER TO 0107
DEFW USR

ORG BBUFV                      ;SETS ADDRESS REFERENCE COUNTER TO 0118
DEFW B400H                     ;DEFINE MEMORY SIZE FOR PROGRAM AND DATA

ORG ADCECG                     ;ADCECG ORIGIN

POINT: DEFB 255                 ;DEFINE POINT=255

;INTERRUPT SUBROUTINE TABLE.
;NB.STARTS AT LOCATION DIVISIBLE BY 8.
INTBL: DEFW NULL                ;NULL INTERRUPT ROUTINE
        DEFW NULL
        DEFW NULL
        DEFW INT2               ;MODE 2 INTERRUPT ROUTINE

CLKTBL: DEFB POS OR TC OR STOP OR OP
        DEFB 250                 ;VALUE IN DOWNCOUNTER
        DEFB CM OR POS OR TC OR STOP OR OP
        DEFB 2
        DEFB CM OR POS OR TC OR STOP OR OP
        DEFB 1
        DEFB CIE OR CM OR POS OR TC OR STOP OR OP
        DEFB 1

;PRESERVE SPECIFIC MEMORY LOCATIONS FOR STORING SPECIFIC DATA.
STACK1: DEFW 0000H              ;ECG DATA STORE ADDRESSES TO
STACK2: DEFW 0000H              ;ALLOW SEQUENTIAL STORING
STACK3: DEFW 0000H              ;OF ECG SEGMENTS

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A2.2

```

RRCOUNT: DEFW 0000H          ;NUMBER OF INTERRUPTS DURING DATA COLLECTION
INTVLA:  DEFW 0000H          ;
INTVL9:  DEFW 0000H          ;
INTVL8:  DEFW 0000H          ;
INTVL7:  DEFW 0000H          ;
INTVL6:  DEFW 0000H          ;NUMBER OF INTERRUPTS (ie. 2ms) BETWEEN
INTVL5:  DEFW 0000H          ;DESIGNATED RR INTERVALS
INTVL4:  DEFW 0000H          ;
INTVL3:  DEFW 0000H          ;
INTVL2:  DEFW 0000H          ;
INTVL1:  DEFW 0000H          ;
INTVL0:  DEFW 0000H          ;

NEXTX:   DEFW 0000H          ;TO ALLOW SEQUENTIAL TRANSFER OF ECG
NEXTY:   DEFW 0000H          ;SEGMENTS FROM STORE SPACE TO WORK SPACE
NEXTZ:   DEFW 0000H          ;

RETX:    DEFW 0000H          ;TO ALLOW SEQUENTIAL RETURN OF LEVELLED
RETY:    DEFW 0000H          ;AND PEAK SYNCHRONISED ECG SEGMENTS TO
RETZ:    DEFW 0000H          ;ORIGINAL STORE SPACE FROM WORK SPACE

CHADR:   DEFW 0000H          ;TRIGGER CHANNEL ADDRESS (from Basic)
PKADR:   DEFW 0000H          ;PEAK ADDRESS

;TO ALLOW INTERRUPTION.

USR:     LD A,255            ;NUMBER OF DATA POINTS
          LD (POINT),A
          IM2                ;INTERRUPT MODE 2
          LD A,INTBL/256      ;MSBYTE OF INTERRUPT VECTOR
          LD I,A              ;SENT TO INTERRUPT REGISTER
          LD A,INTBL MOD 256   ;LSBYTE OF INTERRUPT VECTOR
          OUT (CHANO),A        ;SENT TO O/P DEVICE
          LD C,CHANO           ;SEND INTERRUPT VECTOR
                                ;TO 1st CTC PORT
          LD HL,CLKTBL         ;LOAD HL WITH CLOCKTABLE
          LD A,4               ;NUMBER OF CTC PORTS
CLOCK:   OUTI                 ;LOAD CTC PORT WITH CLOCK TABLE
          OUTI
          INC C                ;NEXT PORT
          DEC A
          JP NZ,CLOCK         ;OTHER PORTS

;CLEAR SPACE IN MEMORY FOR DATA.

LD BC,2FFH
LD HL,5000H
LD (HL),00
LD DE,5001H
LDIR

LD IX,6000H          ;
LD (STACK1),IX       ;DEFINE MEMORY LOCATIONS FOR STORING
LD IX,6C00H          ;ECG SEGMENTS OF 11 COMPLEXES
LD (STACK2),IX       ;FROM CH1,CH2,CH3
LD IX,7800H          ;
LD (STACK3),IX       ;

;TO SEARCH FOR AND STORE 64 POINTS BEFORE AND 191 POINTS AFTER
;A THRESHOLD DEFINED PEAK FOR 11 PEAKS.THIS WILL BE INTERRUPTED
;EVERY 2ms BY INTERRUPT SERVICE ROUTINE COLLECTING DATA FROM
;ADC PORTS CH1,CH2,CH3.

EI                ;ENABLE INTERRUPT

;ALLOW MEMORY TO FILL WITH DATA.

LD B,2
WAIT:    LD HL,64000
DATAFIL: DEC HL
          LD A,H
          ADD A,00H
          JP NZ,DATAFIL
          DJNZ WAIT

```

A2.3

```

;FIND THRESHOLD DEFINED PEAK BY TESTING POINT 64 POINTS BEHIND DATA
;POINT. IF POINT IS > "128" THEN COMPARE WITH POSITIVE THRESHOLD
;ELSE COMPARE WITH NEGATIVE THRESHOLD.
;NB. VALUE OF (POINT) WILL CHANGE EVERY 2ms BY INTERRUPT SERVICE
;ROUTINE.

PEAKS:  LD B,11          ;FOR 11 PEAKS
        LD A,(POINT)    ;DATA POINTER ADDRESS
        ADD A,64         ;TEST POINTER-64 POINTS BEHIND DATA POINTER

        LD L,A          ;SAVE TEST POINTER ADDRESS
        LD E,A          ;(ULTIMATELY THE PEAK ADDRESS)
        LD H,00
        LD A,(HL)
        ADD A,00H        ;TEST IF POINT IS ABOVE OR BELOW "128"
        JP P,NEGPK
        AND 7FH

POSPK:  CP 00            ;COMPARE WITH +ve THRESHOLD (from Basic)
        JP M,PEAKS      ;IF NOT REACHED THEN NEXT POINT
        JP H,RATE        ;ELSE SAVE RR COUNT TO ESTIMATE RR INTERVAL

NEGPK:  CP 00            ;COMPARE WITH -ve THRESHOLD (from Basic)
        JP P,PEAKS      ;IF NOT REACHED THEN NEXT POINT

        ;SAVE NUMBER OF INTERRUPTS BETWEEN THRESHOLD DEFINED PEAKS FOR HR
        ;CALCULATION.

HRATE:  LD H,40H         ;
        LD A,16H         ;SELECT APPROPRIATE
        ADD B            ;RR INTERVAL STORE
        ADD B            ;
        LD L,A
        LD A,(4016H)     ;ENTER MSB
        LD (HL),A
        INC L
        LD A,(4017H)     ;AND LSB
        LD (HL),A
        LD IX,00H        ;OF RR COUNT
        LD (RRCOUNT),IX ;CLEAR RR COUNT FOR NEXT RR INTERVAL COUNT

        ;STORE ECG 64 POINTS BEFORE THRESHOLD DEFINED PEAK.

        LD C,63          ;FOR 63 POINTS
        LD A,E           ;SAVED THRESHOLD DEFINED PEAK ADDRESS
        ADD 63           ;ADDRESS OF POINT 63 POINTS BEFORE
        LD L,A           ;SAVE POSITION FOR COMMON TIME STORING OF
        LD D,L           ;OTHER CHANNEL ECG SEGMENTS
        LD H,50H         ;MEMORY ADDRESS FOR STORING
        LD IX,(STACK1)   ;CH1 ECG SEGMENT
        LD A,(HL)
        LD (IX+0),A      ;SAVE DATA IN STORE
        INC IX           ;NEXT STORE ADDRESS
        DEC L            ;NEXT DATA ADDRESS
        DEC C            ;NEXT POINT
        JP NZ,PREP1      ;FOR 63 POINTS
        LD (STACK1),IX   ;PRESERVE STORE ADDRESS FOR NEXT CH1 ECG SEGMENT

        LD C,63          ;DITTO FOR CH2
        LD L,D
        LD H,51H
        LD IX,(STACK2)
        LD A,(HL)
        LD (IX+0),A
        INC IX
        DEC L
        DEC C
        JP NZ,PREP2      ;FOR 63 POINTS
        LD (STACK2),IX

        LD C,63          ;DITTO FOR CH3
        LD L,D
        LD H,52H
        LD IX,(STACK3)
        LD A,(HL)
        LD (IX+0),A
        INC IX
        DEC L
        DEC C
        JP NZ,PREP3      ;FOR 63 POINTS
        LD (STACK3),IX

```

```

;TO STORE 191 POINTS AFTER THRESHOLD DEFINED PEAK.
;NB.WHILE STORING PREPEAK SEGMENTS DATA POINTER WILL HAVE GAINED.
;THEREFORE STORE DATA RAPIDLY UNTIL REACH DATA COLLECTION
;ADDRESS,THEN STORE DATA AS IT IS UPDATED.

LD A,E          ;SAVED THRESHOLD DEFINED PEAK ADDRESS
ADD 65          ;65 POINTS BEHIND = 191 POINTS INFRONT
LD C,A          ;WHICH = END OF REQUIRED ECG SEGMENT
LD D,0
CONT:           ;TO TEST WHETHER STORE ADDRESS = DATA ADDRESS
JP NZ,CATCHUP   ;IF SET THEN SLOW DATA AQUISITION
LD A,(POINT)     ;RAPID DATA AQUISITION
CP E            ;TEST DATA POINTER AGAINST SAMPLE POINTER
JP Z,CAUGHT      ;IF SAME COLLECT DATA AS IS UPDATED
LD L,E          ;ADDRESS OF SAMPLE TO STORE
DEC E           ;NEXT POINT POST PEAK
JP STORE         ;STORE SAMPLE
CATCHUP:         ;NEXT POINT POST PEAK
DEC E
LD A,E
CAUGHT:          ;DATA AQUISITION ON UPDATE
LD D,1          ;TO PROMOTE SLOW DATA AQUISITION
LD A,(POINT)     ;
CP E            ;TEST FOR CHANGE IN VALUE OF (POINT)
JP Z,CAUGHT      ;WAIT UNTIL DATA POINT CHANGES
LD L,E
STORE:          ;STORE ADDRESS FOR POST PEAK SEGMENT
LD H,50H        ;FROM CH1
LD IX,(STACK1)
LD A,(HL)
LD (IX+0),A      ;STORE POST PEAK SAMPLE DATA
INC IX          ;NEXT STORE ADDRESS
LD (STACK1),IX   ;PRESERVE
LD H,51H        ;DITTO FOR CH2
LD IX,(STACK2)
LD A,(HL)
LD (IX+0),A
INC IX
LD (STACK2),IX
LD H,52H        ;DITTO FOR CH3
LD IX,(STACK3)
LD A,(HL)
LD (IX+0),A
INC IX
LD (STACK3),IX
LD A,C
CP L            ;TEST FOR END OF SAMPLE
JP NZ,CONT
DEC B
JP NZ,PEAKS     ;FOR 11 PEAKS

DI             ;DISABLE INTERRUPT

STPCLK:         ;STOP CLOCK
LD A,STOP OR OP
OUT (CHAN0),A
OUT (CHAN1),A
OUT (CHAN2),A
OUT (CHAN3),A

RET            ;RETURN TO BASIC

;MACHINE CODE SUBROUTINES TO ALIGN EACH PEAK TO X=64.

ADDRESS: LD IX,403AH
LD(CHADR),IX    ;TRIGGER CHANNEL ADDRESS (from Basic)

LD IX,403CH
LD(PKADR),IX    ;PEAK ADDRESS

LD IX,6000H     ;INITIALISE ADDRESSES FOR SEQUENTIAL RETURN OF ECG
LD (RETX),IX    ;SEGMENTS FROM WORKSPACE TO ORIGINAL STORESPACE
LD IX,6C00H     ;
LD (RETY),IX    ;
LD IX,7800H     ;
LD (RETZ),IX    ;

LD IX,6000H     ;
LD (NEXTX),IX   ;
LD IX,6C00H     ;INITIALISE START ADDRESSES FOR BLOCK
LD (NEXTY),IX   ;TRANSFER OF INDIVIDUAL ECG SEGMENTS
LD IX,7800H     ;
LD (NEXTZ),IX   ;

```

A2.5

```

;MOVE INDIVIDUAL 11 ECG SEGMENTS TO WORKSPACE TO FIND AND SHIFT
;PEAK TO X=64 AND LEVEL TO ISOELECTRIC="128".

MOVE:   LD HL,(NEXTX)      ;MOVE INDIVIDUAL CH1 SEGMENTS
        LD DE,5500H        ;TO 5500H
        LD BC,255
        LDIR
        LD (NEXTX),HL      ;PRESERVE ADDRESS FOR NEXT SEGMENT MOVE

        LD HL,(NEXTY)      ;SIMILARLY CH2
        LD DE,5700H
        LD BC,255
        LDIR
        LD (NEXTY),HL

        LD HL,(NEXTZ)      ;SIMILARLY CH3
        LD DE,5900H
        LD BC,255
        LDIR
        LD (NEXTZ),HL

        RET

;FIND ACCURATE POSITIVE PEAK ADDRESS OF TRIGGER CHANNEL.

PPKFIND: LD IY,5410H        ;MARKER ADDRESS
         RES 3,(IY+0)        ;INDICATE POINT WHEN THRESHOLD 1st CROSSES ECG
         LD BC,255
         LD A,(5412H)        ;THRESHOLD VALUE STORE
         LD HL,(CHADR)       ;TRIGGER CHANNEL ADDRESS
BELOWO:  BIT 7,(HL)          ;ONLY CONSIDER POINTS > "128" TO
         JP Z,NEXTPT        ;PREVENT OVERFLOW PROBLEMS
POSCMPR: CP(HL)
         JP P,TESTBT
         SET 3,(IY+0)        ;INDICATE HAVE REACHED THRESHOLD LEVEL
         LD (5412H),HL      ;NEW TEST ADDRESS
         LD DE,(5412H)
         DEC DE              ;POINT BEFORE LAST
         LD A,(DE)           ;TO BE COMPARED WITH NEXT POINT
         JP NEXTPT
TESTBT:  BIT 3,(IY+0)        ;IF NEXT POINT < LAST BUT ONE AND THRESHOLD
         JP NZ,PKADRES      ;PASSED,HAVE REACHED PEAK

NEXTPT:  INC HL              ;
         DEC BC              ;NEXT POINT
         JP BELOWO          ;

PKADRES: LD(PKADR),HL        ;SAVE ACTUAL PEAK ADDRESS

         LD A,L              ;
         ADD 191             ;SAVE ADDRESS OF POINT 64 POINTS BEFORE PEAK
         LD L,A              ;TO MARK START OF ECG WITH PEAK AT X=64
         LD(PKADR),HL
         JP SHIFT            ;

;FIND ACTUAL NEGATIVE PEAK ADDRESS.
;ANALOGOUS APPROACH TO ABOVE BUT FOR NEGATIVE PEAK.

NPKFIND: LD IY,5410H
         RES 3,(IY+0)
         LD BC,255
         LD A,(5412H)
         LD HL,(CHADR)
ABOVEO:  BIT 7,(HL)
         JP NZ,NEXT
NEGCMR:  CP(HL)
         JP M,TSTBIT
         SET 3,(IY+0)
         LD(5412H),HL
         LD DE,(5412H)
         DEC DE
         LD A,(DE)
         JP NEXT
TSTBIT:  BIT 3,(IY+0)
         JP NZ,PEAKAD
         LD(PKADR),HL

NEXT:    INC HL
         DEC BC
         JP ABOVEO

PEAKAD:  LD(PKADR),HL

         LD A,L
         ADD 191
         LD L,A
         LD(PKADR),HL

```

A2.6

```

;SHIFT SEGMENT SO PEAK OCCURS AT X=64.
SHIFT: LD HL,(PKADR)
        LD H,55H
        LD DE,5600H
        LD BC,255
        LDIR

        LD HL,(PKADR)
        LD H,57H
        LD DE,5800H
        LD BC,255
        LDIR

        LD HL,(PKADR)
        LD H,59H
        LD DE,5A00H
        LD BC,255
        LDIR

RET      ;RETURN TO BASIC FOR ESTIMATE OF ISOELECTRIC LEVELS
        ;AND THEIR DIFFERENCES FROM "128"

;LEVEL TO ISOELECTRIC="128".

LD HL,5600H      ;FOR INDIVIDUAL CH1 SEGMENTS
LD E,255
;
XLEVEL: LD BC,(5400H)      ;DIFFERENCE BETWEEN ISOELECTRIC LEVEL AND "128"
        LD A,(5401H)      ;ISOELECTRIC LEVEL DERIVED FROM Basic
        ADD A,00H
        JP P,XGRATER      ;IF ACTUAL LEVEL > "128" THEN..
XLESSER: LD A,(HL)        ;DECREMENT BY DIFFERENCE
        CP 0
        JP Z,XCONT
        CP 255
        JP Z,XCONT
        DEC (HL)
        DEC C
        JP NZ,XLESSER
        JP XCONT
XGRATER: LD A,(HL)        ;ELSE INCREMENT BY DIFFERENCE
        CP 0
        JP Z,XCONT
        CP 255
        JP Z,XCONT
        INC (HL)
        DEC C
        JP NZ,XGRATER
XCONT:   INC HL
        DEC E
        JP NZ,XLEVEL      ;FOR WHOLE SEGMENT

RET

LD HL,5800H      ;DITTO FOR INDIVIDUAL CH2 SEGMENTS
LD E,255
;
YLEVEL: LD BC,(5402H)
        LD A,(5403H)
        ADD A,00H
        JP P,YGRATER
YLESSER: LD A,(HL)
        CP 0
        JP Z,YCONT
        CP 255
        JP Z,YCONT
        DEC (HL)
        DEC C
        JP NZ,YLESSER
        JP YCONT
YGRATER: LD A,(HL)
        CP 0
        JP Z,YCONT
        CP 255
        JP Z,YCONT
        INC (HL)
        DEC C
        JP NZ,YGRATER
YCONT:   INC HL
        DEC E
        JP NZ,YLEVEL

RET

LD HL,5A00H      ;DITTO FOR INDIVIDUAL CH3 SEGMENTS
LD E,255

```

```

ZLEVEL: LD BC, (5404H)
        LD A, (5405H)
        ADD A, 00H
        JP P, ZGRATER
ZLESSER: LD A, (HL)
        CP 0
        JP Z, ZCONT
        CP 255
        JP Z, ZCONT
        DEC (HL)
        DEC C
        JP NZ, ZLESSER
        JP ZCONT
ZGRATER: LD A, (HL)
        CP 0
        JP Z, ZCONT
        CP 255
        JP Z, ZCONT
        INC (HL)
        DEC C
        JP NZ, ZGRATER
ZCONT:  INC HL
        DEC E
        JP NZ, ZLEVEL

RET

;NB. ABOVE ROUTINES FOR LEVELLING ECG TO ISOELECTRIC="128" ARE
;ISOLATED BY RETURNS TO BASIC INCASE ANYONE IS ALREADY AT "128".
;THE RELEVANT ROUTINE MAY THEREFORE BE AVOIDED.

;RETURN SYNCHRONISED AND NORMALISED ECG SEGMENTS TO ORIGINAL
;STORESPACE FROM WORKSPACE.

RETURN: LD HL, 5600H
        LD DE, (RETX)
        LD BC, 255
        LDIR
        LD (RETX), DE

        LD HL, 5800H
        LD DE, (RETY)
        LD BC, 255
        LDIR
        LD (RETY), DE

        LD HL, 5A00H
        LD DE, (RETZ)
        LD BC, 255
        LDIR
        LD (RETZ), DE

RET

INT2:   DI                                ;DISABLE INTERRUPT

;INTERRUPT SERVICE ROUTINE
;TO COLLECT DATA FROM ADC PORTS CH1,CH2,CH3 INTO
;3 ROLLING MEMORY PAGES FROM TOP TO BOTTOM.

        PUSH HL                          ;
        PUSH BC                          ;RESTORE REGISTER
        PUSH AF                          ;CONTENTS
        PUSH IX                          ;

        IN A, (CH1)                      ;DUMMY READS TO CLEAR DATA AND
        IN A, (CH2)                      ;RESET INTERNAL REGISTERS
        IN A, (CH3)                      ;

COLLECT: OUT (STADC), A                  ;INITIATE ADC
DATA:   LD A, (POINT)                    ;NUMBER OF POINTS
        LD L, A
        LD (B), 10

DELAY:  NOP                              ;WAIT FOR CONVERSION
        DJNZ DELAY                      ;
        LD H, 50H                        ;ASSIGN PAGE FOR CH1 DATA
        IN A, (CH1)                      ;READ TO CH1
        LD (HL), A                       ;CH1 DATA INTO ADDRESS 50(POINT)
        INC H                             ;NEXT PAGE FOR CH2
        IN A, (CH2)                      ;READ TO CH2
        LD (HL), A                       ;CH2 DATA INTO 51(POINT)
        INC H                             ;NEXT PAGE FOR CH3
        IN A, (CH3)                      ;READ TO CH3
        LD (HL), A                       ;CH3 DATA INTO ADDRESS 52(POINT)
        DEC L                             ;NEXT POINT
        LD A, L
        LD (POINT), A

```

A2.8

```

LD IX, (RRCOUNT)    ;SAVE THE NUMBER OF INTERRUPT
INC IX               ;ROUTINES BETWEEN PEAKS
LD (RRCOUNT), IX    ;TO CALCULATE HR

NULLI: POP IX         ;
        POP AF        ;STORE REGISTER CONTENTS
        POP BC        ;
        POP HL        ;

NULL:  EI            ;NULL INTERRUPT ROUTINE
        RETI         ;

FWAM:  DEFB 0        ;END OF INSTRUCTIONS

```

Appendix III

Patients Studied at Leicester in Whom a Mismatch Between the Exercise Test and Arteriogram Results Might Occur (Elamin, Mary, Smith & Linden, 1980).

There were 4 cases ([a],[b],[c],[d]) in this study in whom a false positive or negative result might occur for the following reasons:

1. Case [a] had an aortic stenosis with mild regurgitation.
2. Case [b] was hypertensive with a resting systolic blood pressure of 200 mmHg.
3. Case [c] had a left ventricular aneurysm.
4. Case [d] had had a myocardial infarct within 6 weeks of the exercise test.

False results may occur in these patients since ST segment displacement can occur in such, either at rest or during exercise, in the absence of coronary obstruction (Aronow & Harris, 1975; Bishop, Boyle, Watson, Mary & Linden, 1985; Wong, Kasser & Bruce, 1969; Chaitman, Waters, Theroux & Hanson, 1981; Waters, Chaitman, Bourassa & Tabau, 1980; Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). This may therefore obscure a correlation between the maximal ST/HR slope and an estimate of the number of coronary arteries occluded as determined from the arteriogram.

Cases [a] and [b]: Aortic Valve Disease and Systemic Hypertension.

ST segment depression has been demonstrated in patients with aortic valve disease and systemic hypertension during exercise tests in the absence of significant coronary disease (Aronow & Harris, 1975; Harris, Aronow, Parker & Kaplan, 1973; Wong, Kasser & Bruce, 1969).

In aortic stenosis and systemic hypertension, there is an increased resistance to left ventricular ejection. To counteract this and thereby maintain cardiac output, force of contraction is increased. This typically results in an increase in the left ventricle wall thickness with little or no increase in ventricle diameter; concentric hypertrophy (Grossman, Jones & McLaurin, 1975). If severe aortic regurgitation is present, this can result in an increased left ventricular filling and myocardial contraction has to

accommodate an increased flow. Adaptation is eccentric hypertrophy; a proportionate increase in the thickness of the left ventricle wall and internal diameter to enable the increased stroke volume (Grossman, Jones & McLaurin, 1975).

Myocardial ischaemia can occur in eccentric and concentric hypertrophy as a result of both an increase in myocardial oxygen demand and an inadequate myocardial perfusion.

Myocardial oxygen demand increases in response to the increased work done during contraction. It is greater when contraction is against an increased pressure (aortic stenosis and systemic hypertension) than for an increased flow (aortic regurgitation) since the energy required for the development of muscle tension is greater than that for muscle shortening (Sarnoff, Braunwald, Welch, Case, Stainsby & Macruz, 1958). Also, in myocardial hypertrophy, whether through valve disease or hypertension, myocardial oxygen demand is increased because of the increased ventricular mass (Aronow & Harris, 1975).

Impairment of myocardial perfusion occurs in these conditions since there is a greater diffusion distance between the myocardial capillaries and the centre of the enlarged or elongated myocardial fibres (Rushmer, 1968). Further, in concentric hypertrophy, ventricular compliance is reduced therefore impairing diastolic relaxation. This impedes diastolic filling of the coronary arteries (Opherk, Mall, Zebe, Schwarz, Weihe, Manthey & Kubler, 1984). Also, where there is an increase in left ventricular end diastolic pressure as in aortic stenosis and hypertensive hypertrophy, subendocardial perfusion is impaired through the increased compression of the endocardial vessels from within the left ventricle (Opherk, Mall, Zebe, Schwarz, Weihe, Manthey & Kubler, 1984).

All these factors are aggravated during the increased heart rate of exercise (increased myocardial oxygen consumption and reduced diastolic filling time of the coronary arteries) and can cause ischaemic ST-T wave changes.

Case [a], was described during the routine examination of the arteriogram as having a tight, heavily calcified aortic stenosis and mild aortic regurgitation. Further, the heart was slightly enlarged indicated by a cardiothoracic ratio of 57% (50% is typically taken as the maximum normal limit; Hope & Longmore, 1986). Left ventricular hypertrophy was also demonstrated from the patients' echocardiogram but it was not dilated. As might be expected from the account above, the maximal ST/HR slope, $57 \text{ mm/bpm} \times 10^{-3}$, equivalent to two vessel disease overestimated the arteriogram result (no significant disease) as read by both readers at Leicester.

This patient had an aortic valve replacement and a second exercise test 6 months after the operation. There was only a small decrease in the maximal ST/HR slope to $46 \text{ mm/bpm} \times 10^{-3}$; still indicative of two vessel disease. An X-ray was not performed at that time so it cannot be said that this was because there was no reduction in hypertrophy.

Case [b], with systemic hypertension, had a history of high blood pressure which at the time of the exercise test was 200/80 mmHg. From the above account, it would not have been unexpected had the maximal ST/HR slope overestimated the arteriographic estimate of disease. However, the converse occurred; although the exercise test predicted single vessel disease (maximal ST/HR slope = $15 \text{ mm/bpm} \times 10^{-3}$), the arteriogram was read as showing two and three vessel disease respectively by the 2 readers at Leicester.

Case [c]: Left Ventricular Aneurysm.

Aneurysm and left ventricular dysfunction often causes ST segment elevation during exercise (Chaitman, Waters, Theroux & Hanson, 1981; Waters, Chaitman, Bourassa & Tubau, 1980). The mechanism for this has not been fully established however, it may result from the early repolarisation of viable but injured tissue of either the dyskinetic segment or the region surrounding the aneurysm (Caskey & Estes, 1964; Samson & Scher, 1960).

Case [c] was described by the Leeds arteriogram readers and one of the readers at Leicester as having no significant disease. Also, the left

ventricle was described as showing an inferior aneurysm and inferior akinesia. It was thought by Leeds that the former might be sufficient to cause an underestimate of the diagnosis by the slope when compared with the arteriogram result. It was recommended that this patient should not be included in any correlation to assess the predictive accuracy of the test.

The maximal ST/HR slope obtained from this patient was $18 \text{ mm/bpm} \times 10^{-3}$, indicative of single vessel disease; the arteriogram result obtained by one of the Leicester readers.

Case [d]: Recent Myocardial Infarction.

Sensitivity of exercise tests for the detection of coronary disease where this depends on the extent of terminal ST segment displacement is reduced in patients shortly after myocardial infarction (Theroux, Waters, Halphen, Debaisieux & Mizgala, 1979; Paine, Dye, Roitman, Sheffield, Rackley, Russell & Rogers, 1978; Castellagnet, Greenberg & Ellestad, 1978; Ellestad & Wan, 1975). The mechanism for this decrease has not been established however may be in part a result of persistent ST segment elevation associated with recent injury or aneurysm (Castellagnet, Greenberg & Ellestad, 1978; Ellestad & Wan, 1975; Manvi & Ellestad, 1972). Also, patients early after myocardial infarction may develop cardiac enlargement and scarring. These can affect the estimate of the severity of myocardial ischaemia according to the ECG in that scarred and dead tissue (effectively a loss of myocardium) may limit myocardial ischaemia whereas cardiac enlargement may predispose to it (Hoffman, 1981; Ellestad, 1980; Castellagnet, Greenberg & Ellestad, 1978). That these can influence the maximal ST/HR slope was demonstrated by Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987. The maximal ST/HR slope was estimated in 52 patients, 4 to 6 weeks after infarction. In 21 (40%) patients, the diagnosis according to the maximal ST/HR slope underestimated the arteriogram result and the slope was significantly associated with an index of myocardial scarring; higher left ventricular scores, larger left ventricle volumes and lower ejection fractions.

In 14 (27%) patients, the diagnosis according to the maximal ST/HR slope overestimated the arteriogram result. In most of these patients there was a reduction in both the cardiothoracic ratio, an estimate of heart size, and the maximal ST/HR slope estimated from a repeat exercise test 6 months after the infarction implying overestimation by the slope secondary to myocardial enlargement.

In the remaining 17 (33%) patients, the exercise test and arteriogram results were compatible. Cardiac enlargement or scarring might also have influenced the maximal ST/HR slope but not to an extent to alter the slope outside of the disease category range demonstrated by the arteriogram. This is a possible explanation for the result of case [d]. Although this patient had had an infarct within six months of the exercise test, there was an agreement between the exercise test (maximal ST/HR slope = $58 \text{ mm/bpm} \times 10^{-3}$) and arteriogram results (2 vessel disease).

In summary, there was a mismatch between the exercise test and arteriogram result in 3 of the 4 cases in this study from whom a false result would not have been unexpected (Elamin, Mary, Smith & Linden, 1980). This occurred in:

1. The patient with aortic stenosis and regurgitation (case [a]); the maximal ST/HR slope overestimated the degree of disease as determined by the arteriogram.
2. The patient with systemic hypertension (case [b]), and contrary to expectation, the exercise test result underestimated the degree of disease as shown on the arteriogram.
3. The patient with left ventricular aneurysm; the maximal ST/HR slope, again contrary to expectation, caused an overestimation of the degree of disease as determined by the arteriogram according to 2 of the 3 arteriogram readers.

For the patient with recent myocardial infarction, there was a correct prediction of the arteriogram result by the maximal ST/HR slope.

Appendix IV

The Routine Hospital Arteriogram Report at Leicester.

A routine report was prepared by the consultant radiologists at Groby Road Hospital for all arteriograms performed there. Their method was adapted from the Green Lane Hospital system, New Zealand (Brandt, Partridge & Wattle, 1977). This is described here since it is used to illustrate the coronary anatomy of patients described in Appendix V.

In each patient, the coronary anatomy was drawn on a reporting sheet which includes a diagram depicting the left and right ventricles and the interventricular septum. These are divided into segments; each with a fixed number of myocardial units (figure A4.1). The location of a stenosis was indicated on the drawn arteries and assigned a value of severity. This was then graded on an alphabetical scale from (a) to (e) depending on the percent reduction in lumen diameter. Each grade of occlusion is associated with a multiplication factor (1.0 to 0.2; Brandt, Partridge & Wattle, 1977). This is multiplied by the total number of units of myocardium supplied by that artery distal to the stenosis. This gives a myocardial score for each artery which when summed gives an overall myocardial score. The myocardial score is a numerical indication of how severe the disease is and takes into account the importance of the stenosis in terms of the amount of myocardium affected. An example is shown in figure A4.2.

An Example of a Routine Arteriogram Report.

In this example, the coronary circulation is right dominant (the right coronary artery, RCA, supplies the inferior aspect of the heart). There is a major stenosis (75% reduction in cross section diameter) in the left main stem (LMS) and a minor lesion (30% reduction in cross section diameter) in the RCA beyond the conus branch. The diagonal area has a myocardial value of 2 units, the obtuse marginal area has a value of 3 units and the inferior area has a total value of 3 units. The latter has been subdivided to discriminate the two areas supplied by the RCA and the left circumflex artery (LCFX). The interventricular septum has also been divided into 2

Figure A4.1. Arteriogram report sheet used by the consultant radiologists at Groby Road Hospital, Leicester based on the reporting system used at the Green Lane Hospital, New Zealand (Brandt, Partridge & Wattie, 1977). Diagram (A) depicts the left and right ventricles (LV and RV, respectively) and the interventricular septum (IS). These are divided into segments, described in Keys 1 and 2, each of which is assigned a fixed number of myocardial units as shown. Chart (B) is used to indicate the units of myocardium supplied by the main branches of the left anterior descending artery (LAD), the left circumflex and the right coronary artery (RCA) plus the grade of severity of any stenoses present on these vessels. From this, the myocardial score is calculated as described in the text. Diagram (C) represents the left ventricle (LV) and is used to report left ventricular contraction according to Key 3 and, if available, estimates of systolic and diastolic volumes and the ejection fraction.

Figure A4.1. Arteriogram report sheet used by the consultant radiologists at Groby Road Hospital, Leicester.

GROBY ROAD HOSPITAL
DEPARTMENT OF CARDIOLOGY

Name Age.....yrs Unit No.....

Ward Cine No. Date.....

Key 1
C - Conus
RV A - Anterior
I - Inferior

7 units

Key 2
A - Apex
D - Diagonal Area
O - Obtuse Marginal Area
I - Inferior (Diaphragmatic)Area

2 units
3 units
3 units

Key 3
Normal 0
Hypokinetic 1
Akinetic 2
Dyskinetic 3

LV ANGIO RAO

ARTERY	Myoc. Value	GRADE	Coll.	SCORE
L.A.D.	M			
	D			
	P			
L.C.A.	OM1			
	OM2			
Circ	M			
R.C.A.	M			
	PM			
TOTAL				

DIASTOLIC VOLUME ml

SYSTOLIC VOLUME ml

EJECTION FRACTION %

(After Green Lane Hospital, Auckland, New Zealand)

Figure A4.2. An example of a completed arteriogram report for a patient from Groby Road Hospital with an estimated myocardial score of 6.0. A full description of this is presented in the text. The left ventricle (LV) is normal.

**GROBY ROAD HOSPITAL
DEPARTMENT OF CARDIOLOGY**

Name Age.....yrs Unit No.....

Ward Cine No. Date.....

C - Conus
RV A - Anterior
I - Inferior

LCA

LV
A - Apex
D - Diagonal Area
O - Obtuse Marginal Area
I - Inferior (Diaphragmatic) Area

X = stenosis

ARTERY	Myoc. Value	GRADE	Coll.	SCORE
L.A.D.	M			
	D			
	P			
L.C.A.	OM1			
	OM2			
Circ	M			
R.C.A.	M			
	PM			
TOTAL				

LV ANGIO RAO

Normal 0
Hypokinetic 1
Akinetic 2
Dyskinetic 3

DIASTOLIC VOLUME ml

SYSTOLIC VOLUME ml

EJECTION FRACTION %

(After Green Lane Hospital, Auckland, New Zealand)

sections; that supplied by the left anterior descending artery (LAD) and that supplied by the RCA. These have been given myocardial values of 4 and 3 units respectively; proportionate to the amount of myocardium supplied by each artery.

Using the nomenclature of this reporting system, the 75% left main stem lesion is described as a grade (c) stenosis; this is associated with a multiplication factor of 0.6. The area beyond this lesion subtends 6 units of the left ventricular myocardium by the circumflex artery and 4 units by the anterior septal perforator. The myocardial score for the circumflex and left anterior descending are therefore 3.6 (0.6×6) and 2.4 (0.6×4) respectively. Because the lesion on the right coronary artery is considered to be less than a 50% reduction in cross section diameter, according to the scoring system, it is not given a grade and does not contribute to the myocardial score. The myocardial score is therefore the sum of the scores for the LAD and CFX ($3.6 + 2.4$); 6.0.

Appendix V

The Relation Between the Maximal ST/HR Slope and the Majority Opinion Arteriogram Result.

When the maximal ST/HR slope was correlated with the majority opinion arteriogram result, there was a mismatch between these tests in 6 cases. A greater severity of disease was diagnosed from the exercise test than the coronary arteriogram. These cases are discussed individually to try and offer, if possible, some explanation for the discrepancy of results obtained from the two tests. This discussion is confined to the results of the correlation between the maximal ST/HR slope and the majority opinion arteriogram result since there is some degree of confidence associated with the latter, namely two readers agreed on the arteriogram result.

In this discussion, reference is made to the routine hospital arteriogram report. This is described in Appendix IV.

Case 1.

Summary of Patient's Results.

Exercise test - arteriogram interval = 3 days.

<u>Leeds Exercise Test</u>	ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis:	115 \pm 4	V2	3
Leeds manual analysis:	120 \pm 3	CM5	3

Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	CFX,LAD	2
VJR	CFX,LAD	2
Leeds	CFX	1

Reasons for the Investigation of the Patient.

This patient was investigated having experienced a 45 minute episode of burning retrosternal pain while lifting heavy weights and which was relieved by rest. He later had a 30 minute episode of severe chest pain at rest which

on admission to hospital was found not to be associated with enzyme or ECG changes consistent with a myocardial infarction (MI). A routine Sheffield protocol exercise test was performed. (The Sheffield protocol exercise test is a symptom limited treadmill test. Level of exertion is progressively increased in stages of three minutes by increasing the speed and/or the incline of the treadmill as indicated below.

Stage	1	2	3	4	5	6
Speed (mph)	1.7	1.7	1.7	2.5	3.4	4.2
Gradient (%)	0.0	5.0	10.0	12.0	14.0	16.0

The ECG is recorded from the 12 standard leads.)

The exercise test was positive at stage 3; there was 1 mm of ST segment depression at a heart rate of 112 bpm. During stage 4 of the test, the patients' ST depression progressed to 3 mm (heart rate, 140). The patient was therefore accepted for coronary arteriography.

Results of Coronary Arteriography and the Leeds Exercise Test.

According to the coronary arteriogram, the patient had either two vessel disease (by JSB and VJR) or one vessel disease (by Leeds). (All three readers considered the CFX and LAD to be diseased however, unlike JSB and VJR, Leeds did not consider the lesion on the LAD to be significant. It was labelled a 60% stenosis).

According to the Leeds exercise test, the patient had three vessel disease. This was regardless of whether the exercise ECG was measured at Leeds (maximal ST/HR slope = 115 ± 4 mm/bpm $\times 10^{-3}$) or at Leicester (maximal ST/HR slope = 120 ± 4 mm/bpm $\times 10^{-3}$).

The discrepancy between the arteriogram and exercise test results cannot be due to the methods used at Leicester since both centres derived the same result from the exercise ECG and the arteriogram result from Leicester was closer to the exercise test result than was that from Leeds.

Suggestions given by Leeds that might account for the mismatch in results were:

1. A delay between the exercise test and arteriography during which

coronary disease might progress.

2. Small vessel disease undetectable at arteriography eg. diabetic small vessel disease.
3. Hypertension.
4. A history of MI.
5. Myocarditis.
6. Valve disease.
7. Akinesis of the left ventricle.

These however did not apply in this case:

1. The time interval between the exercise test and arteriography was three days.
2. & 3. There was no evidence of diabetes or hypertension.
4. There was no history of MI.
5. There was no evidence of myocarditis; there was no arrhythmia and a chest X-ray showed a normal heart size.
6. The aortic and mitral valves appeared competent at left ventriculography, the heart sounds were normal and the jugular venous pressure was not raised.
7. There was good left ventricular contraction with no akinesia.

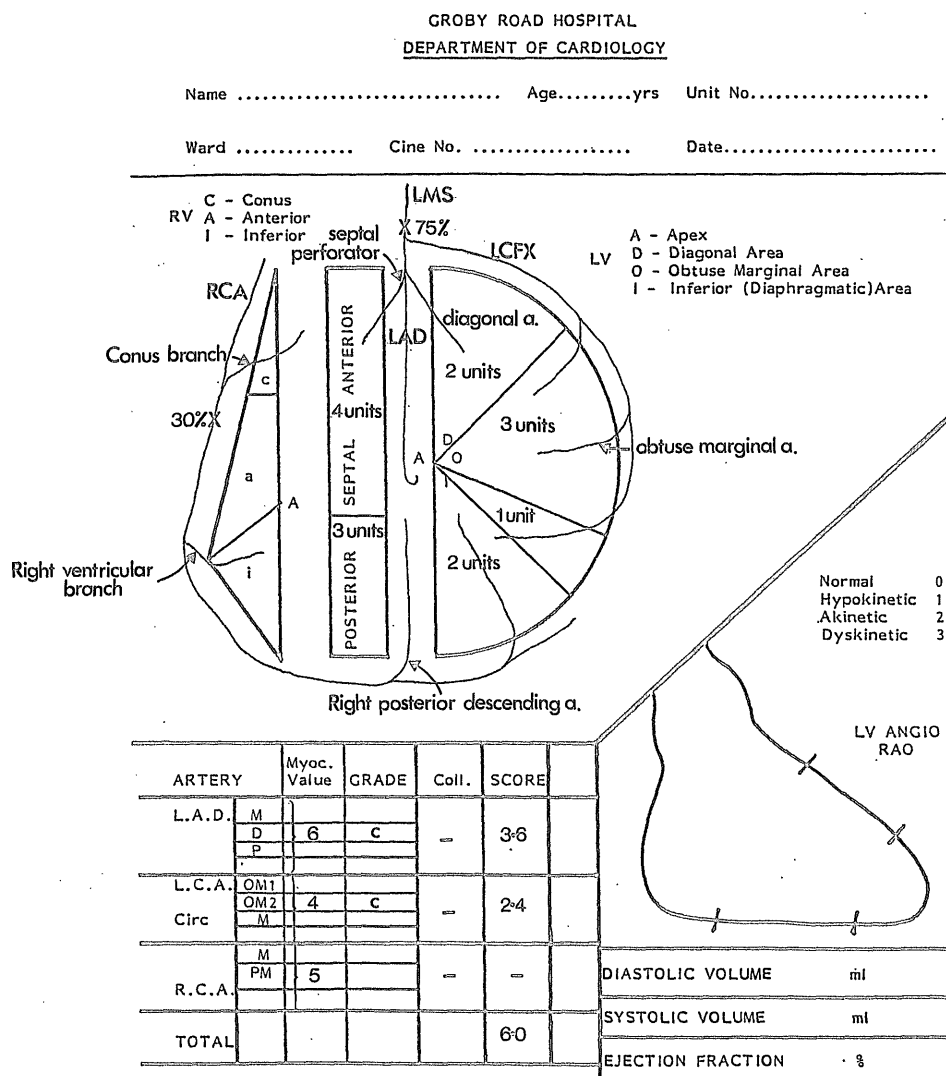
An alternative explanation for the disproportionately high ST/HR slope might be that the patient was on nifedipine therapy. As has already been described, nifedipine can cause an increase in the maximal ST/HR slope (Elamin, Hart, Silverton, Smith, Stoker, Whitaker, Mary & Linden, 1984 and Bishop, Hart, Elamin, Silverton, Boyle, Stoker, Smith, Mary & Linden, 1986). For example, in the study by Bishop et al., 1986, of 28 comparisons of the maximal ST/HR slope in 23 patients before and after nifedipine therapy, there was a significant increase ($p < 0.005$) in the slope. In only one of these comparisons however was the change in maximal ST/HR slope sufficient to increment the diagnosis of the patient by one grade. That nifedipine itself could cause a discrepancy of two grades is uncertain.

Another possible explanation for the disproportionately severe maximal

ST/HR relative to the arteriogram result may be related to the patients coronary anatomy. As shown in the patient's coronary map (figure A5.1), coronary disease was confined to a dominant left artery. The right coronary artery and its branches were very small, but normal. The patient was accepted for coronary artery bypass grafting; saphenous vein grafts were inserted from the aorta to the LCFX and LAD respectively, distal to the described stenoses. A Leeds exercise test performed 5 months post operatively produced a maximal ST/HR slope of 0 mm/bpm. Coronary arteriograms performed 5 months after this exercise test confirmed patent grafts. The implication of this is that disease of the left coronary system accounted entirely for the myocardial ischaemia reflected in the maximal ST/HR slope.

Since there is no obvious explanation for the discrepancy between the results of arteriography and exercise testing, this suggests that classification by 3 vessel categories is not appropriate in this case in which disease is confined to a dominant left circulation.

Figure A5.1. The coronary arteriogram map of case 1 in whom there was a discrepancy of the diagnosis obtained from the maximal ST/HR slope and the arteriogram.



(After Green Lane Hospital, Auckland, New Zealand)

Case 2.Summary of Patient's Results.

Exercise test - arteriogram interval = 3 days.

<u>Leeds Exercise Test</u>	ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis:	116 \pm 4	V4	3
Leeds manual analysis:	109 \pm 23	CM5	3

Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	CFX,LAD	2
VJR	CFX,LAD	2
Leeds	CFX,LAD	2

Reasons for the Investigation of the Patient.

The patient, complaining of a painful left elbow after a fall, described occasional left sided chest pain radiating to his left arm. A standard 12 lead resting ECG was reported as being severely ischaemic (Inverted T waves in ECG leads I, aVL, V5, V6). On a later recording, the ECG had progressed towards normal, however, a mild lateral infarct could not be excluded. A routine Sheffield protocol exercise test was performed. This was positive at stage 2 (1 mm ST depression after an increase in heart rate from 55 to 80 bpm). By stage 4, (heart rate, 99 bpm) the ST segment had depressed to 4 mm. The patient was therefore accepted for arteriography.

Results of Arteriography and the Leeds Exercise Test.

According to the arteriogram result of all three readers (JSB, VJR and Leeds), the patient had two vessel disease; disease of the CFX and LAD. According to the Leeds exercise test however, the patient had three vessel diseasee regardless of whether this was analysed at Leeds (maximal ST/HR slope = 116 \pm 15 mm/bpm $\times 10^{-3}$) or at Leicester (maximal ST/HR slope = 109 \pm 23 mm/bpm $\times 10^{-3}$).

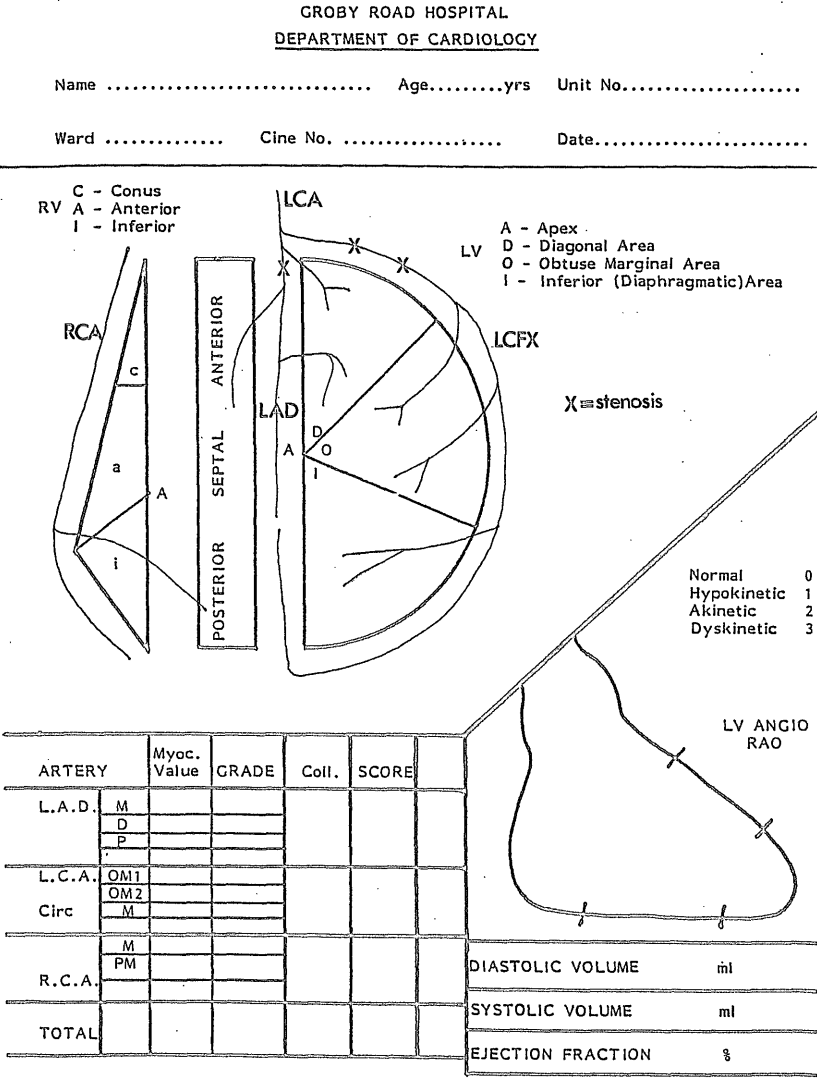
Again, the discrepancy between the arteriogram and exercise test results

could not be due to the methods used at Leicester. There were no obvious clinical reasons for the difference in these two results, as described for the preceeding case: The time interval between exercise testing and arteriography was 3 days; there was no evidence of diabetes, myocarditis, hypertension or valve disease. The patient was on beta blocker therapy only, which should not affect the maximal ST/HR slope (Kardash, Boyle, Elamin, Stoker, Mary & Linden, 1982).

It was suggested that this patient had had a mild lateral infarct about 4 months before the exercise test. It has been reported that a myocardial infarction within 4 to 6 weeks of a Leeds test may result in an overestimate of the severity of coronary disease by the maximal ST/HR slope relative to the arteriogram result (Bishop, Hart, Boyle, Stoker, Smith & Mary, 1987). This has been attributed to cardiac enlargement secondary to infarction. That this caused an overestimate of disease severity by the ST/HR slope is unlikely since the time interval between infarction and exercise testing was substantially greater than 6 weeks. Further, there was no cardiac enlargement indicated by a cardiothoracic ratio (CTR) of 43% (Cardiac enlargement is usually described as a CTR greater than 50%; Hope & Longmore, 1986).

As shown in the patient's coronary map (figure A5.2), the circulation is right dominant. In addition to severe disease of the left artery, the right coronary had severe lesions (graded 80 to 90%) in its distal branches and a less severe lesion (50%), proximally, beyond the right ventricular branch. The proximal lesion was considered not to be sufficiently severe for a diagnosis of three vessel disease. It is plausible that the lesion had a more deleterious effect than as depicted by arteriography. In addition, perfusion to the left ventricle is limited by the distal severe lesions of the dominant right artery. This again raises the question of classifying the coronary circulation into 1, 2 and 3 vessel disease without considering the watershed of each vessel.

Figure A5.2. The coronary arteriogram map of case 2 in whom there was a discrepancy of the diagnosis obtained from the maximal ST/HR slope and the arteriogram.



(After Green Lane Hospital, Auckland, New Zealand)

Case 3.Summary of Patient's Results.

Exercise test - arteriogram interval = 6 days.

<u>Leeds Exercise Test</u>	ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis:	26 ± 3	V4	1-2

Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	LAD	1
VJR	LAD	1
Leeds	LAD	1

Reasons for the Investigation of the Patient.

This patient had developed chest pain which accumulated in a myocardial infarction within the same month. A routine Sheffield protocol exercise test provoked 1 mm depression of the ST segment followed by an ST segment elevation. Since his MI, the patient had been asymptomatic. He was placed on the waiting list for coronary arteriography on a non urgent basis because of his positive exercise test, his young age (50 years) and known raised fasting serum cholesterol (level 7.9 mmol/l; normal range: 4.6 to 7.2 mmol/l) and serum triglyceride (level 3.2 mmol/l; normal range 0.8 to 1.9 mmol/l).

Results of Arteriography and the Leeds Exercise Test.

From the patient's arteriogram, all three readers diagnosed single vessel disease; there was a 75 to 90% lesion just proximal to the first septal perforator on the LAD. The CFX appeared normal; the RCA appeared only mildly irregular. According to the Leeds exercise test, the maximal ST/HR slope (26 ± 3 mm/bpm $\times 10^{-3}$) placed the patient in the mid intermediate single to double vessel disease category. Accepting the Leeds exercise test and the interpretation thereof, there were no obvious clinical reasons for the disparity of test results.

Case 4.Summary of Patient's Results.

Exercise test - arteriogram interval = 3 days.

<u>Leeds Exercise Test</u>	ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis:	108 \pm 1	V4	3

Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	NII	0
VJR	NII	0

Reasons for the Investigation of the Patient.

While being investigated because of retrosternal pain associated with acid reflux, it was noted that the patient also had a tight central chest pain precipitated by exercise. This increased markedly in the cold and after meals. A routine Sheffield protocol treadmill exercise test was positive at stage 4 with 2 mm of ST segment depression (the heart rate was 153 bpm). The patient was admitted for coronary arteriography. Routine examination of this indicated a completely occluded branch of the CFX supplying the left marginal aspect of the heart. All other vessels appeared normal and left ventricular function was good. A Leeds exercise test was performed however, since at that time a CM5 lead was not available, the result of the test (no significant disease) was not included in this study. The patient was successfully managed on antianginal therapy. After 2 years, because of persistent angina, a further Sheffield protocol exercise test was performed. This was positive at stage 2 with a ST depression of 1.5 mm (heart rate, 120 bpm). The patient was accepted for a second arteriogram to see if the coronary disease had progressed. Another Leeds exercise test was performed; this did include a CM5 lead.

Results of Arteriography and the Leeds Exercise Test.

Based on the arteriogram, the patient was thought to have no significant

disease by both readers, JSB and VJR. This result contrasted with the routine hospital report which described a totally occluded LAD which was retrogradely perfused by a large dominant RCA. (The presence of a stenosed LCFX branch reported earlier was also confirmed). The patient was accepted for surgery on symptomatic grounds 4 months after the Leeds exercise test. The LAD was found to be a very small fibrotic vessel completely blocked proximally and of only 1 mm diameter distally. It is suggested therefore that the discrepancy between the exercise test and the arteriogram result is due to, at least in part, a poor interpretation of the arteriogram. This is not uncommon and reflects a limitation of the arteriogram as an index of coronary disease.

An added cause for the mismatch of exercise test and arteriogram results may be that the patient had iron deficient anaemia. The patient's haemoglobin level was 9.3 g/dl on the day of the exercise test. (Quoted normal (♂) range is 13.5 to 18.0 g/dl; Hope & Longmore, 1986). Anaemia may aggravate myocardial ischaemia through the reduced oxygen carrying capacity of the blood. This is particularly important in patients with occlusive coronary disease where the coronary reserve is already compromised (Crawford, 1977; Marcus, 1983; Crean, 1987).

Case 5.Summary of Patient's Results.

Exercise test - arteriogram interval = 2 days.

<u>Leeds Exercise Test</u>	ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis:	30 \pm 1	V5	1-2

Repeat Leeds Exercise Test

Leicester manual analysis:	6 \pm 2	III	0
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Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	Nil	0
VJR	Nil	0

Reasons for the Investigation of the Patient.

This patient was investigated after describing muscular type pains in the central sternal and left inframammary regions with shooting pains to the throat. They were not effort related, could occur at rest, and were predictably relieved by analgaesics. The patient had earlier been admitted to hospital believed to have suffered from either a mild MI or severe angina. There were some abnormal changes in his ECG however these were not of the usual infarct pattern. They reverted to normal within a day and his cardiac enzymes were not raised. A routine Sheffield protocol exercise test was positive however only in stage 6 with 1.5 mm of ST depression at a heart rate of 178 bpm implying minimal disease. None the less, coronary arteriography was performed in view of his young age (43 years).

Results of Arteriography and the Leeds Exercise Test.

Based on the arteriogram, there was no evidence of significant coronary disease (results of both JSB and VJR). The only indication of disease was a lesion on the LAD, distal to the first large septal perforator and involving the first diagonal artery. This was described as not significant; a 50% reduction in lumen diameter.

From the Leeds exercise test, the maximal ST/HR slope ($30 \pm 1 \text{ mm/bpm} \times 10^{-3}$) indicated a diagnosis of intermediate single to double vessel disease.

An exercise thallium scan performed 3 months after the Leeds exercise test showed a normal myocardial perfusion. There was however, 2 mm ST depression on the ECG at a heart rate of 172 bpm during which the patient complained of a mild burning feeling in his chest and shortness of breath.

From the patient's clinical details, there is no apparent reason why the ST/HR slope might have predicted a greater degree of severity of ischaemia than the coronary arteriogram. The extent of disease apparent on the arteriogram was considered not sufficient to account for the patient's chest pain which was ultimately attributed to tender costochondral junctions. A Leeds exercise test was repeated 6 months after the first test. The maximal ST/HR slope was $6 \pm 2 \text{ mm/bpm} \times 10^{-3}$ in ECG lead III indicating no significant disease. The patient's symptoms at this stage had not improved possibly substantiating the diagnosis of chest pain due to a cause other than myocardial ischaemia.

Case 6.Summary of Patient's Results.

Exercise test - arteriogram interval = 3 days.

Leeds Exercise Test

ST/HR Slope \pm s.e (mm/bpm $\times 10^{-3}$)	Lead	Diagnosis (vessel disease)
Leicester manual analysis: 21 \pm 2	V1	1

Repeat Leeds Exercise Test

Leicester manual analysis: 20 \pm 0	V1	1
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Coronary Arteriography

Reader	Arteries occluded	Diagnosis (vessel disease)
JSB	LAD	1
VJR	Nil	0

Reasons for the Investigation of the Patient.

This patient was investigated with a 6 month history of chest pain :- chest tightening radiating to his left shoulder and arm and associated shortness of breath. During a routine Sheffield protocol exercise test, the patient reached stage 5 with a heart rate of 161 bpm, no ECG changes but mild chest pain during stages 4 and 5. Despite the negative exercise test, because of the occurrence of chest pain, a diagnosis of coronary disease was uncertain. Arteriography was performed because the patient held a PSV licence.

Results of Arteriography and the Leeds Exercise Test.

From the arteriogram, a diagnosis of no significant disease was given by VJR and Leeds and one of single vessel disease was given by JSB. All readers reported a lesion on the LAD just beyond the main diagonal. Although JSB thought this to be significant, it was described as being non significant by VJR and Leeds (only a 40 and 50% reduction in cross sectional diameter respectively). According to the Leeds exercise test, a diagnosis of single vessel disease was obtained (maximal ST/HR slope = 21 \pm 2 mm/bpm $\times 10^{-3}$).

It is possible that describing the patient as having no significant

disease might have occurred through underestimating the severity of the LAD lesion seen on the arteriogram; a known limitation of arteriography.

An alternative/additional reason for the overestimate of ischaemia relative to the arteriogram is that the patient was described as having iron deficient anaemia 21 days before the exercise test. The patient's haemoglobin (Hb) level at that stage was 10.8 g/dl (Quoted normal (d') range is 13.5 to 18.0 g/dl; Hope & Longmore, 1986). Following treatment with iron sulphate, a repeat Hb test 14 days later showed an increase of Hb to 11.8 g/dl. Assuming a constant increase in Hb levels estimated from these 2 results of 0.14 g/dl/day, the Hb concentration of the patient is estimated at 13.8 g/dl at the time of the test (the estimated increase in Hb is consistent with a typical therapeutic response of a 0.1 to 0.2 g/dl/day increase; British National Formulary, 1988). Since this is borderline of the normal range, it cannot be completely dismissed that a disproportionately severe ischaemic response was, at least in part, due to the patient's low level of Hb except that another Leeds exercise test, 6 months later, gave the same diagnosis of single vessel disease (maximal ST/HR slope = 20 ± 0 mm/bpm $\times 10^{-3}$).

In summary, in two cases (3 and 5), no explanation could be offered for the mismatch between the patient's diagnosis based on the arteriogram and maximal ST/HR slope.

Possible reasons for the discrepancy in results in the other four patients are:

1. The 3 vessel notation is an inadequate means of quantifying the extent of myocardial ischaemia particularly in cases with an extremely dominant left or right artery (cases 1 and 2).
2. The degree of arterial narrowing may be underestimated from its appearance on the arteriogram (cases 2, 4 and 6).
3. Nifedipine therapy may have increased the maximal ST/HR slope (case 1).
4. A reduced coronary reserve caused by iron deficient anaemia may have aggravated the myocardial ischaemia secondary to coronary occlusion,

A5.14

reflected only in the maximal ST/HR slope (case 4 and possibly case 6).

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