NONINVASIVE RISK STRATIFICATION AFTER MYOCARDIAL INFARCTION

by

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SUMMARY

In order to identify patients with severe coronary artery disease (CAD) and at a higher risk of future cardiac events after uncomplicated myocardial infarction, 105 consecutive patients were studied prospectively. There were 93 men and 12 women with a mean age of 56 ± 8.2 years. Treadmill testing, exercise radionuclide ventriculography, thallium-201 myocardial imaging and selective coronary arteriography were performed 6-8 weeks after infarction. Patients were grouped into those who had single and multiple vessel disease. Multiple regression analysis of 18 noninvasive indices was carried out using generalized linear interactive modelling (GLIM) and the results were compared with the severity of underlying CAD and the clinical outcome after a mean follow-up period of 18.8 ± 3.4 months. At the end of the follow-up period, patients were categorized into those who had no cardiac events, minor cardiac events, and major cardiac events.

Multivariate analysis produced an algorithm from three factors found to be most predictive of the severity of CAD. These included ST-segment depression on exercise, total score of rest and exercise regional wall motion and the presence of significant redistribution on thallium-201 imaging. The sensitivity of this algorithm for predicting multiple vessel disease was 42%, with a specificity of 94%, and a predictive accuracy of 69%. However, the total score of regional wall motion abnormalities was the single most predictive factor of major cardiac events with a sensitivity of 94%, a specificity of 57%, and predictive accuracy of 63%. None of the other factors produced additional prognostic information. Therefore, exercise radionuclide ventriculography appears to be the investigation of choice in assessing prognosis after myocardial infarction.
To:

Dr E B Raftery

Who taught me the real meaning of science and provided inspiration to my career.
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CHAPTER 1

INTRODUCTION
1 INTRODUCTION

1.1 HISTORICAL REVIEW

The introduction of Laennec's paper stethoscope revolutionised the practice of medicine. "I took some sheets of paper and rolling them very tightly, I applied one end to the precordial region and placing my ear at the other end, I was surprised as I was gratified to hear the beating heart much more clearly and distinctly than if I had applied my ear directly to the chest. It occurred to me that this means could become a useful method..." (R T H Laennec, 1846).

1.1.1 Graded exercise electrocardiography

Changes in the electrocardiogram during an attack of angina pectoris were first described by Bousfield G, 1918. "As I was about to photograph the first lead, patient had an attack of angina pectoris, to seizures of which he had been subject. Having hastily sent for amyl nitrate capsule, I felt justified in proceeding with the cardiogram until the remedy arrived", (Bousfield, 1918). The electrocardiographic changes were first induced by exercise in 1928 by Fiel et al. In 1920, Pardee was the first to suggest that ST-segment change in the electrocardiogram were related to myocardial ischaemia, and this was later confirmed by Wilson in his experimental model (1930, 1934). Master introduced the two-step test (1929, 1935, 1942) to quantify the cardiovascular response to exercise by measuring the changes in heart rate and blood pressure. During the following years, exercise
electrocardiography became accepted as a diagnostic test for myocardial ischaemia (Master et al, 1942; Wegria et al, 1949) and the foundations of modern exercise electrocardiography were established (Astrand, 1958; Balke 1959). The development of the treadmill and later the bicycle ergometer led to more accurate assessment and improved diagnostic ability and furthermore, offered a degree of reproducibility which was not possible with the step test (Bruce 1974, a, b) and (Ellestad et al, 1969, 1979).

1.1.2 Application of radioisotopes in cardiac patients

The introduction of Laennec's paper stethoscope revolutionised the practise of medicine. However, the technological revolution of the twentieth century has brought with it another fundamental change. This new approach to medical problems is the child of the technological revolution, and its contribution to diagnosis has paralleled the growth of technology.

Prinzmetal et al (1949) defined radiocardiography as "method of recording graphically the passage of radioactive blood through the cardiac chambers by means of a specially constructed ink-writing Geiger-Mueller counter". A carefully shielded Geiger-Mueller tube was placed over the precordium; 0.1 to 0.2 millicurie of radiosodium (Na-24) was rapidly injected into one of the antecubital veins, and the counts were recorded by means of a specially devised ink-writing counter. The curve thus represented the concentration of radiosodium in the structures underlying the tube. In earlier experiments, Prinzmetal et al (1948) performed these techniques in normal subjects and obtained both diphasic
and monophasic curves. At that time, it was difficult to understand this finding until further studies revealed that after an ordinary rapid intravenous injection, completed in half a second, it might take as long as twelve seconds before the last trace of radiosodium to leave the vein. The precordial tracings in normal subjects consisted of principal waves connected by a plateau-like transitional point. The first wave was called the R-wave which represented the passage of radiolabelled blood through the right side of the heart. The second wave, which represented the passage of blood through the left side of the heart, was termed the L-wave. This procedure was applied to patients in the succeeding years and proved to be useful in the diagnosis of several cardiac conditions, especially in differentiating heart disease from other conditions.

1.1.2.1 Ventricular function

Following direct injection of technetium-99m pertechnetate into a dog's left ventricle, Mullins et al (1968) used a triggering signal to obtain an isolated image of the heart in one phase of the cardiac cycle. The nuclear data were videotaped from the scintillation camera's oscilloscope screen while the audio channel recorded the R-wave signal. On replay of the videotape information, the film recording was gated using the R-wave as a marker of the onset of each cardiac cycle. In that manner, an end-diastolic image of the left ventricle was recorded and the volume was calculated from an outline of this chamber correlated with the measurement of volumes made by contrast angiography. The high correlation spurred the development of other noninvasive approaches to the measurement of ventricular function; first transit bolus
measurement, which did not employ a physiological marker (Mason et al, 1969), and equilibrium gated blood pool measurements which did. The latter technique differs fundamentally from first transit methods in that each cardiac cycle does not stand on its own. Instead it is used in combination with other beats to define the patient's cardiac function. Thus, all measurements utilize an average of several cardiac cycles. This approach may result in a loss of some high frequency information that is contained in first transit studies, but provides information of a much greater statistical certainty.

Blood pool scans initially employed labelled albumin as the radiopharmaceutical for blood pool imaging (Strauss et al, 1971; Zaret et al, 1971). Data were recorded only during end-systole (corresponding to the downslope of the T wave on the electrocardiogram) and at end-diastole (corresponding to the P-R interval). These recordings required up to 20 minutes per image, and the results were of relatively poor quality. Images were recorded in only one position - the right anterior oblique (RAO). Although the RAO projection is used with contrast ventriculography to observe the long axis of the left ventricle, it is not optimal for blood pool imaging with a parallel hole collimator because there is a maximum superimposition of the right ventricular silhouette on that of the left and there is a large gap between the collimator and the left ventricle. These two factors reduce the resolution of the left ventricular borders. Analysis of the images was completed by drawing the borders of the left ventricle from a life-size projection and applying the area/length method of Sandler and Dodge (1960) to calculate the volume of the chamber at end-diastole and end-systole. The measurements were found to correlate with contrast
angiography for both the ejection fraction and ventricular volume (Kasser et al, 1969).

Despite the difficulties with resolution, Zaret et al (1971) were able to apply these techniques to define regional wall motion abnormalities by percent change in hemi-axis. In additional clinical studies, it became apparent that the right ventricle could enlarge to a point where the left ventricle was obscured or that an aneurysm in the anterior segment could obscure motion of uninvolved segments. This lead Rigo et al (1974a) to employ both right and left anterior oblique views to assess cardiac performance in patients with suspected left ventricular aneurysm.

Initial clinical applications of the gated blood pool technique were then employed to define right ventricular function in patients with cardiogenic shock (Rigo et al, 1974b). The dilatation and poor contraction of the right ventricle were found to be a cause of a low output state in some patients with inferior wall infarction. Equilibrium blood pool ventriculography was used to evaluate the prognosis of patients with acute myocardial infarction (Rigo et al, 1975a) and to measure ventricular dysfunction in those with transmural as opposed to nontransmural infarction (Rigo et al, 1975b). The ejection fraction was found to be a major predictor of survival, regardless of the presence of arrhythmia following myocardial infarction (Schulze et al, 1975).

Computer systems permit both recording of multiple points in the cardiac cycle and the display of the data in real time as an average cardiac
cycle cineangiogram (Burow et al, 1977). This allows the application of objective computer algorithms for analysis, in addition to a simple inspection and interpretation of the data.

In-vivo labelling of red blood cells provides a means of recording data with a higher target-to-background ratio than that obtained with technetium-99m albumin (Ravel et al, 1977 and Thrall et al, 1978). The collimator-object relationship was optimized by selecting high resolution collimators and positioning the heart as close to the collimator as possible.

At a later stage, equilibrium blood pool imaging was used in intervention studies. The intervention scan can detect changes in regional and/or global ventricular function in comparison to a baseline recording while the patient is at rest. Initially, pharmacological interventions were employed (Saler et al, 1976) to define changes in ventricular function in patients with myocardial infarction who were treated with nitroglycerine (Ritchie et al, 1979). Regional wall motion improvement was apparent in those with unstable angina as opposed to those with infarction who displayed no change in akinesis, while haemodynamic measurements in both groups were similar.

Pacing is known to increase myocardial oxygen consumption and areas of occult ischaemia will appear as areas of decreased wall motion. However, pacing is inferior to exercise as a means of bringing out occult myocardial ischaemia since it causes the end-diastolic dimension to decrease, thus reducing wall tension and myocardial oxygen requirements, in comparison to exercise which causes little change in

1.1.2.2 Myocardial perfusion imaging

The possibility of using radiotracers to detect regions of reduced myocardial perfusion was first explored by Yates in 1952 using phosphorus-32. Radionuclide methods for noninvasive evaluation of regional myocardial blood flow are based on the observations of Sapirstein (1956) who showed that the total extraction of any tracer that has a high extraction rate during the initial capillary transit is primarily determined by blood flow. This principle applies to particulate indicators that do not recirculate and to recirculating indicators with high extraction rates in tissue, such as potassium and the similar cationic tracers cesium, rubidium and thallium. In 1957, Love first reported the use of rubidium-86 (Rb-86) in dogs and humans for estimation of myocardial perfusion. The application of rubidium-81 (Rb-81) for the evaluation of regional myocardial perfusion was reported by Berman et al, (1975). Radio-potassium (K-43) was used to detect and evaluate transiently ischaemic myocardium by imaging patients after exercise (Zaret et al, 1973). Thallium-199 was suggested as a perfusion imaging agent on the basis of its biological similarity to potassium (Kawana et al, 1970). Subsequently thallium-201 (Tl-201) was used to obtain myocardial scintiscans in the goat (Bradley-Moore et al, 1975) and this demonstrated peak myocardial concentration at 10 to 25 minutes after injection. Thallium-201 has the advantages of lower photon energy
(69 and 83 KeV) and greater myocardial concentration (1.7 to 3.7% of the administrated dose) compared with potassium-43, rubidium-81 and cesium-129 (Lebowitz et al, 1975; Strauss et al, 1975). Exercise thallium-201 scintigraphy was first described in 1976 as a noninvasive test for detecting coronary artery disease (Ritchie et al, 1976; Shames et al, 1976). Early experiences with exercise thallium-201 imaging utilized two separate injections of the tracer during exercise and at rest. In 1977, Pohost et al reported the disappearance of thallium-201 myocardial defects present on initial images in experimental dogs over a 2 hour period after transient ischaemia. This phenomenon, which was called thallium-201 redistribution, was subsequently observed in patients with coronary artery disease (Pohost et al, 1977). The use of thallium-201 in the acute phase of myocardial infarction was reported by Wackers et al (1976) who documented the value and limitation of thallium-201 scintigraphy for the diagnosis of acute myocardial infarction. A scintigraphic perfusion defect at rest in a patient with a clinical course suggestive of myocardial infarction localized the area of infarction. However, the technique is unable to differentiate acute infarction from chronic scar due to an old infarction as both lesions cause a perfusion defect on thallium-201 scan. The application of infarct-seeking tracers was suggested in 1974 by Parkey et al who used technetium-99m stannous pyrophosphate (Tc-PYP), an agent commonly used for bone scanning. Other tracers that have been used include labelled tetracycline (Holman et al, 1974) and labelled antimyosin antibody (Beller et al, 1977). These agents have been shown to localize in infarcted myocardium with sufficient specificity to be of clinical use in the diagnosis of myocardial infarction. Experiments with animals with induced infarction and reperfusion have shown good correlation
between the extent of Tc-PYP deposition and the extent of infarction (Bruno et al, 1976). Moreover, induced infarcts in dogs without reperfusion typically demonstrated a rim of increased tracer about the border of the infarct that permits localization of the infarct (Botvinick et al, 1975). However, no consistent correlation has been found between the extent of infarction and estimation of infarct size by myocardial scintigrams using Tc-PYP. A fairly accurate estimation of infarct size is possible in patients with transmural infarction on the anterior or lateral left ventricular wall, but infarcts located on the diaphragmatic wall of the heart are less well defined (Parkey et al, 1976).

1.1.3 Cardiac catheterization

Cardiac catheterization was first performed (and so named) by Claude Bernard in 1844 (Cournand, 1975). The subject was a horse, and both the right and left ventricle were entered by a retrograde approach from the jugular vein and carotid artery. An era of investigation of cardiovascular physiology in animals then followed, resulting in the development of many important techniques and principles (eg. pressure manometry, the Fick cardiac output method), which awaited direct application to the patient with heart disease. Although others had previously passed catheters into great veins, Werner Forssmann is generally credited with being the first person to pass a catheter into the heart of a living person - himself (Barry and Grossman, 1984). He passed a catheter 65 cm through his left antecubital vein, guiding it by fluoroscopy. He looked through a mirror held by his nurse in front of the fluoroscopic screen, until it entered his right atrium. He then
walked to the Radiology Department, where the catheter position was documented by a chest roentgenogram. During the following two years, Forssmann continued to perform catheterization studies, including six attempts to catheterize himself. Forssmann's primary goal in his catheterization studies was to develop a therapeutic technique for the direct delivery of drugs into the heart.

The potentials of Forssmann's technique as a diagnostic tool were appreciated by others. In 1930, Klein reported 11 right heart catheterizations, including passage to the right ventricle and measurement of cardiac output using Fick's principle. In 1932, Padillo and co-workers reported right heart catheterization and measurement of cardiac output in two subjects (Cournand, 1975).

Andre Cournand (1941) and Dickenson Richards (1945) produced a remarkable series of investigations of right heart physiology in man. The application of cardiac catheterization to study the circulation in normal and diseased states was described by Cournand et al, 1945.

Congenital heart disease was first studied by Dexter et al 1947. They went further than their predecessors by passing the catheter to the pulmonary artery, and in addition they mentioned some observations on the 'oxygen saturation' and the source of pulmonary capillary blood obtained from the pulmonary artery 'wedge' position (Dexter et al, 1946). Problems in cardiovascular physiology and the effect of drugs were investigated using cardiac catheterization by McMichael et al (1944) in England.
Further developments came rapidly such as retrograde left heart catheterization which was first reported by Zimmerman (1950) and Limon-Lason (1950) (Barry and Grossman, 1984). The percutaneous technique developed by Seldinger in 1953 was soon applied to cardiac catheterization of both the left and right heart chambers. Transseptal catheterization was first developed by Ross (1959) and Cope (1959) and quickly became accepted as a standard technique. Selective coronary arteriography was developed by Sones in 1959 and modified for percutaneous approach by Richetts et al (1962) and Judkins (1967). A balloon-tipped flow-guided catheter was developed by Swan and Ganz (1970), which allowed for catheterization outside a specialised laboratory.


1.2 REVIEW OF LITERATURE

1.2.1 Exercise electrocardiographic testing

The management of patients who survive an acute myocardial infarction has undergone vast changes over the last three decades. Surviving myocardial infarction is the first step in a long term process which includes stratification and identification of patients who are at greatest risk from recurrent infarction, cardiac death, refractory
angina, and those most suitable for medical treatment, angioplasty or surgical revascularization.

Several clinical and haemodynamic methods have been used in an attempt to identify the 'high risk' group. The natural history of myocardial infarction has been studied in several longitudinal surveys of patients admitted to hospital (Beard et al, 1960), but accurate information is obscured by the variable indications for hospital admission. Based on several reports, accepted statistics for the outcome after myocardial infarction are a 10% six-month mortality rate (5% in the first three weeks), and about 40% of patients developing angina, a second myocardial infarction or dying within a year (Bland and White, 1941; Cole et al, 1954; Granath et al, 1977; Theroux et al, 1979; Handler et al, 1983).

The introduction of exercise tests early after myocardial infarction and their use as a diagnostic and prognostic guide had to await confirmation of their safety. There was a great concern about the possible lethal sequelae of stressing a recently infarcted myocardium. Exercise testing was thought to put the patients at risk from extension of the infarction, serious arrhythmias, aneurysm formation or a catastrophic myocardial rupture. Therefore, patients were kept bed-bound in hospital for six to eight weeks with higher risk of deep vein thrombosis and pulmonary emboli. Levine and Lown (1952) challenged these principles in their revolutionary ideas of armchair treatment. They showed that early mobilization and discharge at four weeks was quite safe. Further reports supported the view that uncomplicated cases could be discharged safely two to three weeks after infarction (Lown and Sidel, 1969; Harper et al, 1971; Wenger et al, 1973). The common practice nowadays,
including our hospital, is to discharge these patients within a week of the acute episode. The selection of low-risk patients for early hospital discharge is based on simple criteria such as the absence of diabetes, pulmonary oedema, serious arrhythmias or recurrent chest pain (Lau et al, 1980).

In animal studies, it has been shown by exercise testing within two days of induced infarction, that serious arrhythmias occur only when exercise was performed simultaneously with induction of infarction, and even then only at certain heart rates (Kaplinsky et al, 1968; Thompson and Lown, 1976).

The electrocardiographic abnormalities during exercise testing were studied in 12 patients at three weeks and 18 months after the acute event (Atterhog et al, 1971). These tests were found to be safe and of possible prognostic value. The safety of exercise tests was confirmed by other studies using submaximal stress three weeks after infarction (Ericsson et al, 1973). Since the early 70's there have been several reports confirming the safety of exercise testing and evaluating it as a prognostic indicator (Granath et al, 1979; Markiewicz et al, 1977; Haskell and DeBusk, 1979; Davidson and DeBusk, 1980). The value of early exercise testing as a prognostic parameter must be considered with caution because investigators have used different exercise protocols and timing of the tests after the acute infarction. This appears to be important as exercise capacity is known to improve during recovery. In addition, patient selection is critical, particularly when patients with left ventricular failure, hypertension, unstable angina, conduction abnormalities or musculoskeletal disabilities have been excluded,
leaving up to half of all the potential subjects untested.

Symptoms of dyspnoea and fatigue combined with an inappropriate tachycardia at rest or at low work loads, and inadequate systolic blood pressure response to exercise, imply left ventricular impairment. Exercise-induced angina, ST-segment changes and ventricular arrhythmias are indicators of reversible myocardial ischaemia.

All these features have been associated with a poor prognosis (Granath et al, 1977; Sami et al, 1981; Theroux et al, 1979; Starling et al, 1981a; Schwartz et al, 1981; Fuller et al 1981). These features vary in their prognostic importance (Miller and Borer, 1982) e.g dyspnoea and fatigue alone are poorly reproducible and are of limited prognostic significance. In the year after myocardial infarction, angina was nearly twice as common in patients who complained of angina during the predischarge treadmill test than in those who did not Theroux et al, 1979). Other investigators have found angina to be reliably predictive only of future coronary bypass surgery and not of sudden death, ventricular fibrillation or recurrent infarction (Davidson and DeBusk, 1980; Koppes et al, 1980).

Exercise-induced ventricular arrhythmias have been thought to increase the risk of sudden death by two to four times (Ericsson et al, 1973; Theroux et al, 1979). More recently it has been reported that ventricular arrhythmias have no prognostic value except in combination with workload and ST segment depression (Sami et al, 1979, DeBusk et al, 1980a).
The single most reproducible prognostic index is probably ST-segment depression on exercise. This has been correlated with subsequent cardiac events, including death, and also of multiple vessel coronary disease (DeBusk et al, 1980b; Schwartz et al, 1981; Fuller et al; 1981; Akhras et al, 1982).

ST-segment depression of more than 0.2 mV during exercise was almost twice as common in patients who were subsequently treated with coronary artery bypass surgery or who had a cardiac arrest than in those with an uneventful two-year follow-up (Sami et al, 1979). In 210 selected patients exercised prior to hospital discharge, Theroux et al (1979) found that ST-segment depression increased the risk of death at one year by ten times, but was not predictive of non-fatal myocardial infarction, nor of the development of either stable or unstable angina.

It has been suggested that exercise-induced ST-segment elevation in patients recovering from myocardial infarction is related to dyskinetic left ventricular wall motion associated with an underlying ventricular aneurysm rather than to myocardial ischaemia (Chahine et al, 1976; Castellanet et al, 1978). Its mechanism and prognostic value is obscure, but when occurring alone it has been found to predict single vessel rather than multivessel disease (Weiner et al, 1978). It is also more commonly found after anterior transmural infarction (Schwartz et al, 1981).

More evidence for an association of ST-segment elevation during exercise with severe left ventricular dyskinesis was demonstrated by DeFeyter et al, 1981. Furthermore, it has been associated with a larger post-
infarction scar size and lower ejection fraction (Paine et al, 1978; Schwartz et al, 1981) and hence a poor prognosis (Borer et al, 1980; Sullivan et al, 1984). Fox et al (1983) studied 156 patients who underwent 16-lead precordial electrocardiographic mapping and suggested that exercise-induced ST-segment elevation should be considered as important as ST-segment depression in terms of myocardial ischaemia, coronary anatomy and left ventricular function.

There has been a wide variation in the recommended timing of exercise testing following myocardial infarction. Theroux et al (1979) performed limited treadmill testing one day before hospital discharge after acute myocardial infarction. The one-year mortality rates were 2.1% in patients without ST-segment depression. Sudden death occurred in 0.7% of patients who showed no ST-segment changes and in 16% of patients with ST-segment depression.

Single and multiple exercise testing were compared in 200 men during one-year follow-up after acute myocardial infarction (Sami et al, 1979). Exercise induced ST-segment depression equal to or greater than 0.2 mV 3 weeks after the event was significantly more prevalent in patients with subsequent cardiac arrest or coronary artery bypass graft surgery than in patients without subsequent events within 2 years of infarction. Ventricular arrhythmias during multiple exercise 5-52 weeks after infarction were more prevalent with recurrent myocardial infarction. On the other hand, exercise-induced ventricular arrhythmias on a single test at 3 weeks was less powerful predictor of subsequent cardiac events. This study showed that exercise-induced ST-segment depression 3 weeks after infarction predicted early fatal events, while ventricular
arrhythmias on serial testing predicted later nonfatal events. Similar prognostic information was obtained by Smith et al (1979) who exercised patients 3 weeks after infarction to 60% of their maximal heart rate.

In 1980, DeBusk and Haskell compared symptom-limited versus heart-rate-limited exercise testing in two groups 3 weeks following infarction. The prevalence of exercise-induced ST-segment depression and ventricular ectopic activity was similar in the two groups. Regardless of the test protocol used, early events were more common in patients with ST-segment depression than in patients without ischaemic responses, while exercise-induced ventricular arrhythmias were not predictive of early events. Symptom-limited exercise testing was repeated in all patients of the two groups 11 weeks after infarction and the prevalence of ST-segment depression and ventricular ectopic activity was similar to that at 3 weeks.

The effect of drug therapy was elucidated by Koppes et al (1980) when they studied 90 patients receiving no medication. Exercise testing was performed submaximally at 3 weeks and maximally at 8 weeks after infarction. Exercise variables (i.e heart rate, rate-pressure product and oxygen uptake) at submaximal equivalent exercise work did not change from 3 to 8 weeks. This study showed that ST-segment changes, angina or both, and inability to complete a maximal 8 weeks treadmill test could identify patients at risk for later complications.

The Ontario multicentre exercise-heart trial showed that exercise-induced ST-segment depression was associated with a higher frequency of fatal recurrences of infarction in high compared to low intensity
exercisers (Shephard R J, 1980). Patients were exercised submaximally using a bicycle ergometer up to 75% of their predicted maximum oxygen uptake. Furthermore, the presence of ST-segment depression, angina or an inadequate blood pressure response to treadmill exercise testing could identify patients with uncomplicated myocardial infarction who were at risk of subsequent cardiac events (Starling et al, 1980).

A stepwise multiple logistic regression analysis of clinical and treadmill test characteristics demonstrated that exercise-induced ST-segment depression, angina pectoris and maximal work load less than 4 multiples of resting energy expenditure (METS) were predictive of combined medical and surgical events (reinfarction, sudden death, cardiac arrest and coronary artery bypass surgery) in 2-year follow up period. These 'risk factors' were observed during a single exercise test 3 weeks after uncomplicated myocardial infarction (Davidson et al, 1980).

Sivarajan et al (1981) studied the effects of early, supervised exercise in preventing deconditioning due to prolonged bed rest after acute myocardial infarction. There were no differences between patients who had a low-level treadmill test on the day before hospital discharge in the clinical, haemodynamic or electrocardiographic responses compared with the control group. The study was unable to demonstrate any significant beneficial or deleterious effects of an early, in-hospital exercise programme.

Saunamaki et al (1981) studied the 5-year survival of 317 patients who underwent maximal exercise testing 3 weeks after an acute myocardial
infarction. They found that the mortality was increased significantly in those with a small increase in the pressure-rate product from rest to maximal exercise. Furthermore, recurrent ischaemia and sudden death were associated with premature ventricular ectopics during exercise testing at 2 weeks (Weld et al, 1981) and 3 weeks (Fein et al, 1981) after infarction as well as ST-segment depression and angina pectoris, which were reported to be predictive of multiple vessel disease (Starling et al, 1981b; Schwartz et al, 1981). In addition, DeFeyter et al (1982) looked at exercise testing variables, coronary anatomy and left ventriculography in 179 patients within 6-8 weeks of infarction. The prevalence of multivessel disease was 63% and 42% in inferior and anterior infarction respectively. During a mean follow-up of 28 months, 11 cardiac deaths and 12 reinfarctions occurred. Patients who had an exercise tolerance of 10 minutes or more (Bruce protocol) had a very low risk for cardiac death or reinfarction. Exercise data obtained from symptom-limited bicycle ergometry three weeks after infarction could not improve prediction of death but provided higher positive predictive value for new infarction (Madsen et al, 1983).

Submaximal treadmill variables were compared with clinical findings in 226 patients who sustained an acute myocardial infarction using linear discriminant analysis (Williams et al, 1984). The first four discriminant variables that contributed independent information for the prediction of cardiac mortality were: ST-segment depression at rest, creatine kinase level greater than 1,280 IU/litre, exercise duration less than 3 minutes and a history of previous myocardial infarction. Unlike other studies, ST-segment depression on the predischarge treadmill test did not predict any event, nor did it improve the
predictive accuracy of the clinical events.

Death during the first year after discharge from hospital following an acute myocardial infarction was found to be associated with exertional hypotension and a heart rate of greater than 130 beats per minute on predischarge treadmill testing (Jennings et al, 1984). Inability to complete the exercise protocol for any reason was also predictive of death. Ventricular arrhythmias and ST-segment depression were not significantly associated with an increased risk of death. Nevertheless, Akhras et al (1984) showed that maximal stress testing two weeks after infarction is an effective diagnostic test for the identification of patients with high risk multiple vessel coronary artery disease who might benefit from early bypass surgery. More recently, similar observations were reported by Sullivan et al (1985) who showed that an abnormal exercise blood pressure response and short exercise duration were predictors of multiple vessel disease but exercise-induced ST-segment changes and clinical variables were not. Krone et al (1985) confirmed these findings and suggested that low-level exercise testing before hospital discharge combined with clinical features could effectively identify patients at low risk for subsequent cardiac mortality (Waters et al, 1985; Madsen et al, 1985).

Maximal exercise testing 6 months after myocardial infarction was reported to provide information that is independent of and additive to clinical evaluation performed at the same time (Stone et al, 1986). Recurrent nonfatal myocardial infarction was predicted by patients' inability to perform the exercise test because of cardiac limitations, but not by any characteristics of exercise test performance. Coronary
artery bypass surgery was associated with the development of ST-segment depression of 1 mm or more during exercise testing.

Benjamin et al (1986) examined the usefulness of early exercise testing after non-Q-wave myocardial infarction in predicting prognosis. A negative response to exercise predicted the absence of three vessel disease or critical stenoses involving major coronary arteries (negative predictive value 92%), whereas a strongly positive response predicted their presence (positive predictive value 77%).

Maximal ST/HR slope was reported as an index of myocardial ischaemia in selected populations of patients with angina (Linden et al, 1982). It has been suggested that maximal ST/HR slope is also an index of exercise-induced myocardial ischaemia after recent infarction, however, it has been shown to be subject to the influence of coronary artery narrowing as well as scarring and cardiac enlargement (Bishop et al, 1987).

Early right atrial pacing was compared with early treadmill testing in a group of patients recovering from an acute myocardial infarction before hospital discharge (Tzivoni et al, 1984). In patients who, at discharge, achieved a low pressure-rate product on the treadmill, right atrial pacing provided important prognostic information. However, if a high pressure-rate product was achieved on the treadmill, then the results of the two tests were similar.
1.2.2. Equilibrium radionuclide ventriculography

The preliminary application of cardiovascular nuclear medicine methods in cardiac disorders was in patients with suspected or proven coronary artery disease. Radionuclide techniques have been employed extensively in the assessment of patients presenting with acute myocardial infarction. The evaluation of these patients can involve three distinct processes: diagnosis, prognosis, and evaluation of therapy.

Left ventricular ejection fraction was found to be depressed (less than 54%) in patients with anterior infarction compared with patients with inferior infarction (Shah et al, 1980). The mean ejection fraction was lower in the group who developed one or more complications (congestive failure, hypotension, shock, reinfarction, death) during the subsequent course, than those who had an uneventful recovery. Shah et al demonstrated that an ejection fraction of 30% or less was of prognostic value in predicting a high risk of hospital morbidity and mortality in patients with a first transmural infarction. The short-term prognostic value of ejection fraction was confirmed by other investigators; however, sequential changes in left and right ventricular ejection fraction did not correlate well with short-term prognosis (Nemerovski et al, 1982) as they were thought to reflect loading conditions rather than intrinsic changes in myocardial performance. Nevertheless, Wackers et al (1982) showed that a single assessment may not characterize cardiac performance in the early hours after infarction.

Previous studies focused on the assessment of left ventricular ejection fraction during the acute stage either from a single or sequential
measurements (Rigo et al, 1974; Schebert et al, 1976; Reduto et al, 1978 and Wackers et al, 1982). When patients with previous myocardial infarction underwent maximal semisupine bicycle exercise, there was little change in the ejection fraction and the increase in cardiac output was thought to be heart rate dependant (Tan et al, 1982). A fall in ejection fraction and stroke volume was seen, due to a disproportionate increase in end-diastolic volume when additional ischaemia developed.

Discriminant analysis of clinical and submaximal exercise radionuclide ventriculography performed before hospital discharge following an acute myocardial infarction showed that exercise-induced changes in left ventricular ejection fraction and end-systolic volume were most predictive of future cardiac events in the subsequent 6 months. The predictive accuracy of changes in ejection fraction and end-systolic volume were 93 and 91% respectively, and they were more sensitive than ST-segment depression or elevation (Corbett et al, 1983).

Left ventricular function measured by ejection fraction at rest and during exercise showed a significant association with time to death after acute myocardial infarction (Morris et al, 1985). On the other hand, the change in ejection fraction from rest to exercise predicted the time to coronary artery bypass grafting for medically refractory angina (Morris et al, 1985). They used Cox’s proportional hazards regression model to show that clinical and radionuclide angiography variables that were measures of left ventricular function, predicted subsequent mortality, whereas those that reflected residual potentially ischaemic myocardium were predictive of subsequent nonfatal ischaemic
events. The value and limitations of exercise radionuclide angiography for detecting myocardial ischaemia in healed myocardial infarction were assessed by Plotnick et al (1985). They found that group responses of ejection fraction or end-systolic volume appeared to correlate with the presence of myocardial ischaemia; however, some patients with exercise-induced transient thallium defects after infarction responded normally to exercise testing and some patients without any evidence of transient myocardial ischaemia responded abnormally to exercise radionuclide testing. The development of a new regional wall motion abnormality in the postinfarction patient was found to be a relatively specific but insensitive indicator of myocardial ischaemia. Buda et al (1986) confirmed the importance of radionuclide assessment of regional left ventricular function in acute myocardial infarction. They demonstrated that regional ejection fraction was a sensitive technique for identifying segmental dysfunction associated with myocardial infarction. In addition, significant changes in regional left ventricular function were found to occur despite stable serial global performance.

Left ventricular ejection fraction measured by radionuclide and contrast ventriculography was correlated with a QRS scoring system in patients with acute myocardial infarction (Jones et al, 1985). They showed that a QRS score of 4 or less achieved 100% specificity and 8 or less 100% sensitivity for predicting a left ventricular ejection fraction greater than 40%. The Selvester QRS scoring system (Selvester et al, 1968) was found to be of value in risk stratification and in identifying patients with or without markedly impaired ejection fraction.
Additional information can be obtained by applying Fourier analysis of the gated blood pool studies (Picozzi et al, 1984). The phase and amplitude images generated from Fourier analysis could yield further information about regional wall motion abnormality; therefore hypokinesia, akinesia and dyskinesia could easily be identified by the colour scale of the functional image. Early formation of a functional left ventricular aneurysm was reported to occur frequently after anterior myocardial infarction and to carry a high risk of death within one year that is independent of ejection fraction (Meizlish et al, 1984). In addition, the absence of a functional aneurysm identifies a large group with a low one-year mortality despite a markedly impaired ejection fraction.

Although left ventricular diastolic function has been assessed in patients with coronary artery disease and essential hypertension (Bonow et al, 1981; Mancini et al, 1983; Reduto et al, 1981; Inouye et al, 1984), very little has been reported about left ventricular diastolic filling in patients with acute myocardial infarction. In patients with chronic stable angina pectoris, abnormal left ventricular filling at rest was independent of the systolic function or previous infarction (Bonow et al, 1981). On the other hand, Mancini et al (1983) showed abnormalities in peak filling fraction in patients with coronary artery disease both at rest and during exercise, but large overlaps were seen between normal subjects and patients.

Right ventricular systolic and diastolic performance has been investigated in patients with different cardiac disorders particularly coronary artery disease (Maddahi et al, 1979; Legrand et al, 1983;
Morrison et al, 1984; Brown et al, 1984). However, only a few reports have focused on right ventricular function in patients with an acute myocardial infarction (Rigo et al, 1975a; Tobinick et al, 1978). Right ventricular dysfunction was detected by gated blood pool studies in patients with acute inferior myocardial infarction (Rigo et al, 1975a) and patients with acute anterior myocardial infarction (Tobinick et al, 1978). Reduto et al (1978) related left ventricular function to the development of pump dysfunction in the hospital, but no relationship was found between subsequent in-hospital course and right ventricular ejection fraction. Although right ventricular assessment clearly has been a valuable adjunct to the diagnosis of right ventricular infarction (Rigo et al, 1975a) and the establishment of individualized therapeutic regimens, there has not yet accumulated enough experience to outline a prognostic value from quantitation of right ventricular function.

The effect of exercise-induced myocardial ischaemia on cardiopulmonary blood volume was evaluated in patients with coronary artery disease using inhaled carbon monoxide labelled with cyclotron produced Carbon-11 and a multicrystal positron camera (Nichols et al, 1979b). For patients developing angina pectoris and ST-segment depression, blood volume increased over the upper and lower lung fields at peak exercise. Conversely, for patients without angina or ST-segment depression at peak exercise, the regional pulmonary blood volume was unchanged. Coronary arteriography revealed double or triple vessel coronary disease in all patients with increased regional pulmonary blood volume, and normal coronary arteries or single-vessel disease in patients with unchanged pulmonary blood volume. This increase in regional pulmonary blood volume was thought to be due to ischaemia-induced left ventricular
dysfunction. These results encouraged other investigators to calculate the ratio of pulmonary blood volume at rest to that during exercise using equilibrium blood pool ventriculography (Okada et al, 1979). Patients with coronary artery disease not confined to the right coronary artery showed an increase in pulmonary blood volume ratio. This was thought to be a useful noninvasive means of estimating exercise-induced changes in left ventricular filling pressure (Okada et al, 1982). In 74 patients, thallium-201 lung uptake was correlated with changes in pulmonary blood volume ratio (Wilson et al, 1983). The prevalence of an abnormal thallium-201 lung uptake was less than that of pulmonary blood volume ratio in patients with coronary artery disease, and both tests were normal in patients without coronary artery disease. The likelihood of multiple vessel disease was higher when both tests were abnormal.

Pulmonary blood volume ratio was abnormal as frequently as the ejection fraction in patients with single vessel disease (Liu et al, 1986). Unlike ejection fraction, pulmonary blood volume ratio was improved significantly after successful angioplasty, which might indicate a higher sensitivity to changes in left ventricular function after an intervention in patients with single vessel disease (Liu et al, 1986).

1.2.3 Thallium-201 myocardial perfusion scintigraphy

The initial accumulation of thallium-201 in the myocardium is dependant on both coronary blood flow and cellular extraction (Strauss et al, 1975; Di Cola et al, 1977). Thallium-201 myocardial perfusion scintigraphy provides a sensitive and reliable method of detecting acute myocardial infarction and ischaemia when imaging is performed during the
first 6 hours after chest pain. Almost all patients with acute infarction and approximately 50% of patients with unstable angina demonstrate thallium-201 perfusion defects, the size of which reflect the extent of the infarcted and/or jeopardized myocardium (Wackers FJT, 1980). Accurate location of the infarcted myocardium has clinical relevance since the location of infarction has prognostic significance. It is well known that patients with an anterior wall infarction have a poorer prognosis than patients with an inferior wall infarction (Kannel et al, 1979b). Moreover, involvement of the septum in anterior wall infarction always indicates massive infarction and is associated with a three-times higher mortality than infarction in other locations (Lie et al, 1974; Ritchie et al, 1978).

Since thallium scintigraphy visualizes the normal myocardium, thallium defects can be expressed as a percentage of the total left ventricular myocardium. Moreover, the total amount of lost myocardial mass can be determined since thallium scans demonstrate both acute and old infarction. As the immediate prognosis of a patient with acute myocardial infarction is directly related to the total amount of damaged myocardium, the potential prognostic value of thallium scans becomes evident.

Gibson et al (1980) studied the prognostic value of thallium-201 scanning performed at rest during the late hospital phase in 25 patients with proven inferior myocardial infarction. Patients were divided into those with inferior and anterior perfusion defects (Group 1, n=13) and those with inferior defects alone (Group 2, n=12). Coronary events were recorded over an average of 7.2 months follow-up for all patients (new
onset or progression of angina pectoris, sudden death, reinfarction and congestive heart failure). In group 1, 77% of patients had 17 coronary events and 33% of patients in group 2 had 6 coronary events. Therefore, resting thallium scintigraphy was able to identify those patients with inferior infarction at higher risk of subsequent coronary events. Other investigators (Fletcher et al, 1980) suggested sequential thallium-201 scintigraphy after acute myocardial infarction to study the temporal behaviour of thallium defects in relation to the size of infarction and the presence of extension.

The introduction of exercise thallium imaging has added to the diagnostic value of this technique in the evaluation of patients with an acute myocardial infarction before hospital discharge. Segments with fixed perfusion defects were thought to be due to 'scar' formation after infarction, while reversible defects were due to viable myocardium with inadequate blood supply during exercise. Bone et al, (1980) exercised 55 patients 2-3 weeks after infarction before hospital discharge. Thallium-201 scintigraphy was performed after submaximal bicycle exercise and 2-4 hours later. Thallium-201 images showed defects in 51 of the 55 patients studied immediately after exercise. The image defect score did not correlate with the maximum enzymatic change even when patients with previous infarction were excluded. Patients were followed-up for an average period of 20.6 months during which five patients died due to cardiac causes. These patients did not have a significantly higher defect score than the survivors. However, short-term survival was related to the left ventricular dilatation as assessed by thallium scintigraphy and chest roentgenogram. The timing of the delayed imaging after exercise thallium-201 scintigraphy varied in
different centres. Weiner et al (1981) suggested that imaging be performed 24 hours following stress testing to differentiate infarcted from viable myocardium. In 43 patients, the positive predictive value of thallium imaging in identifying patients with previous infarction was 75% and the negative predictive value was 92% as assessed by 24-hour delayed images.

Other investigators have demonstrated the ability of thallium-201 imaging to predict subsequent coronary events after myocardial infarction (Bukley et al, 1979; Pitt et al, 1980) and the presence of multiple vessel disease (Turner et al, 1980). However, more recently VanderWall et al (1985) reported that qualitative assessment of exercise thallium scintigraphy, alone or combined with electrocardiography, should not be used to predict the absence or presence of multivessel disease in patients after myocardial infarction. They based their observations on 176 patients who underwent exercise thallium-201 imaging 6-8 weeks after a first myocardial infarction. Seventy-seven patients had angiographically proven multiple vessel disease (prevalence 44%). The sensitivity of exercise electrocardiography and thallium scintigraphy in detecting multiple vessel disease was 64% and 31% respectively. When the results of both procedures were added, the sensitivity was 66% and specificity 62%, and the positive and negative predictive values were 57% and 70% respectively, which were considered too low for the adequate clinical diagnosis of multivessel disease after myocardial infarction.

On the other hand, patients with suspected coronary artery disease with no history of myocardial infarction or coronary artery bypass surgery
were studied by Thallium-201 imaging after maximal symptom-limited treadmill exercise using the Bruce protocol (Ladenhiem et al, 1986). A stepwise logistic regression model could identify only three independent predictors of subsequent coronary events during a one-year follow-up period: the number of myocardial regions with reversible hypoperfusion (an index of the extent of hypoperfusion), the maximal magnitude of hypoperfusion (an index of the severity of hypoperfusion), and the achieved heart rate (an index of exercise performance). There was an exponential correlation between event rate and both the extent and severity of hypoperfusion (r=0.97 and P<0.01 for each), whereas achieved heart rate was linearly correlated with event rate (r=0.79 and P<0.05).

Figueras et al (1986) performed thallium-201 myocardial imaging in 28 men during atrial pacing early after their first acute myocardial infarction. A positive pacing response (i.e. at least 1 mm of ST-segment shift) was seen in 82% of patients (Group 1), whereas pacing results were negative in 18% of patients (Group 2). A significant thallium-201 redistribution localized near or within the infarction site was present in 43% of patients in group 1 and 20% of group 2. A 90% or greater coronary stenosis of at least 1 artery was found in 83% of patients in group 1 and 20% of group 2. Multiple vessel disease (more than 70% diameter narrowing) was found in 61% of patients in group 1 and 20% of group 2.

During an average follow-up period of 15 months, effort angina developed in 39% of patients in group 1 and none in group 2. No deaths or reinfarction occurred in either group. Thus, atrial pacing-induced changes in the electrocardiogram and myocardial thallium-201
redistribution were predictive of the severity of coronary artery disease and subsequent cardiac events in patients with acute myocardial infarction. However, this study was performed on a small number of patients with strict inclusion criteria. Patients were relatively young (only 3 were older than 60 years) with no conduction disturbance, atrial fibrillation, previous infarction or significant heart failure. In addition, group 2 had only 5 patients, which precludes definite conclusions with respect to the diagnostic and prognostic implications of the technique.

Planar thallium-201 stress scintigraphy is firmly established as a noninvasive diagnostic method for patients suspected of having coronary artery disease and for the evaluation of patients with documented coronary artery disease and myocardial infarction. The use of qualitative thallium-201 analysis i.e visually interpreting transient defects in order to detect myocardial ischaemia (Pohost et al, 1977) does not reveal all myocardial regions supplied by a stenosed coronary artery and frequently results in underestimation of multivessel coronary artery involvement (Rehn et al, 1981; Rigo et al, 1980; Nygaard et al, 1984). A major disadvantage of this approach is that interpretation of thallium-201 images is frequently difficult and requires considerable expertise. The limitations of subjective visual analysis are reflected in considerable intraobserver and interobserver variability. Moreover, qualitative analysis does not allow for analysis of thallium-201 myocardial kinetics, and thus, important potentially available diagnostic information is not used. Thallium-201 kinetics are markedly different in ischaemic myocardium compared to normal myocardium or scar tissue. Thallium-201 activity gradually decreases (washout) with time
after termination of exercise. In contrast, exercise-induced ischaemic myocardium is characterized by accumulation, no change, or abnormally slow washout of thallium-201 (Wackers et al, 1985). These differences cannot be readily appreciated by visual inspection alone and therefore myocardium that appears normal by visual analysis may demonstrate abnormal kinetics.

Recently, an objective computerized method for quantitative analysis of thallium-201 kinetics and the measurement of washout rate, based on the spatially non-relative approach, has been developed (Watson et al, 1981; Garcia et al, 1981). Slow myocardial washout in the absence of a persistent defect has been shown to correlate highly with segmental myocardial hypoperfusion (Maddahi et al, 1981; Massie et al, 1983). Diffuse slow washout from all myocardial regions has been defined as an indicator of extensive coronary artery disease (Bateman et al, 1984). However, diffuse slow washout has occasionally been observed in normal patients and in the contralateral regions supplied by a normal coronary artery in patients with a single or double vessel disease. This false positive occurrence of slow washout decreases the specificity of washout rate analysis in the detection of myocardial ischaemia. However, reliable quantitation of planar thallium-201 images requires rigorous quality control and scrupulous attention to technical details. Nishimura et al (1987) tried to explain the causes of false positive diffuse slow washout as a result of an increase in splanchnic blood flow after a meal, subcutaneous infiltration of thallium-201 at the injection site, faulty data acquisition with lower counting statistics and finally processing errors such as malpositioning of the background subtraction or misalignment of the initial and/or delayed images. Kaul et al (1986)
determined the quantitative thallium imaging variables that optimize the
detection of coronary artery disease in 325 patients who underwent
stress thallium-201 imaging and cardiac catheterization. Initial
thallium-201 uptake was the most sensitive but least specific for the
detection of coronary artery disease, whereas redistribution was the
least sensitive and most specific. Using stepwise logistic regression
analysis, the best correlate of coronary artery disease was initial
thallium uptake. Addition of redistribution to the mathematical model
did not alter sensitivity, but increased specificity. Once initial
uptake and redistribution were considered, myocardial thallium-201
clearance (washout) provided no additional improvement to the
correlation. Therefore, there is a dramatic improvement in the
detection of patients with coronary artery disease by quantitative
thallium-201 analysis compared with visual analysis. The ability to
accurately predict the number of vessels diseased, is still suboptimal
but considerably better than by visual analysis. The prediction of
significant disease in a particular vessel is better for the left
anterior descending artery, but worse for the right and left circumflex
arteries (Wackers et al, 1985).

It is conceivable that quantitative thallium-201 single photon emission
tomography is the most useful technique for precisely predicting disease
of individual coronary arteries and the extent of myocardial ischaemia
and infarction. The limitations of the classical two-dimensional
imaging could be eliminated by using the reconstructed sections of
emission tomography (Holman et al, 1979; Maublant et al, 1979).

In a series of 15 patients with documented myocardial infarction and 5
more patients with uncertain diagnosis, Maublant et al (1981) studied the usefulness of transverse, sagittal and frontal tomographic images. The reconstructed sections from 32 views obtained with a rotating scintillation camera were compared with the conventional views. Quantitatively, the mean myocardium-to-background activity ratio improved significantly from 1.60 to 2.57 (P<0.001); qualitatively, the presence, site, and size of the defect were more easily determined on the sections and generally revealed a sharp contrast to the normal tissue. The tomographic images were normal in only one patient whose diagnosis was uncertain; therefore it appeared that three-dimensional emission tomography could improve both detection and quantification of myocardial infarction.

The diagnostic value of thallium-201 imaging for the detection of small infarcts was markedly improved when emission computed tomography was performed in 160 patients with documented first myocardial infarction and 39 patients without infarction (Tamaki, et al 1984). Tomography was performed after planar imaging at rest and the results were interpreted qualitatively. The sensitivity of tomography was significantly higher than planar imaging in detecting non-transmural infarction (87% vs 47%) respectively. The overall sensitivity was 96% for tomography and 78% for planar imaging. The specificity was similar (92%) with the two techniques.

Garty (1984) criticized planar thallium-201 imaging because the blurring of the static image by heart motion during contraction resulted in many false negative scans and considerable interobserver variations. Instead, to optimize the diagnostic accuracy of thallium-201 in
detecting coronary artery disease and myocardial infarction, it was suggested that thallium-201 imaging could be carried out using electrocardiographic gating similar to equilibrium blood pool imaging. This approach was thought to reduce blurring of the image and improve resolution and quality. Moreover, the addition of frames occurring at or near the end-diastolic phase, when cardiac motion is minimal, could minimize the effect of poor imaging statistics which may be apparent in single frame studies. Forty consecutive patients were studied by gated thallium-201 performed in three projections (anterior, left anterior oblique $45^\circ$ and $60^\circ$). Gated thallium-201 scans were of higher resolution and smaller areas of reduced perfusion could easily be identified. In addition, regional wall motion abnormalities could be recognised when the left anterior oblique view ($45^\circ$) was replayed in a continuous cine loop.

Increased lung thallium-201 uptake during exercise was reported to be related to the severity of coronary artery disease and the number of myocardial perfusion defects (Boucher et al, 1980). In the same group of patients, this had been associated with a lower resting ejection fraction and a greater prevalence of previous myocardial infarction. In experimental animals and in patients with coronary artery disease, increased lung thallium-201 concentration was due to a transient absolute uptake immediately after maximal exercise (Bingham et al, 1980) which was a consequence of left ventricular failure (Kusher et al, 1981; Lahiri et al, 1984).

Gibson et al (1982) investigated 61 patients before hospital discharge after acute myocardial infarction. Increased thallium-201 concentration
in the lungs after submaximal exercise testing was found to be related to a greater prevalence of prior infarction, less global cardiac reserve as assessed by the four level New York Heart Association classification, more advanced Killip class in the coronary care unit, a higher Norris coronary prognostic index, failure to achieve the target heart rate, a greater prevalence of exercise-induced ST-segment depression, a greater number of myocardial perfusion defects, a lower resting ejection fraction and a greater number of asynergic left ventricular segments. In the postinfarction patient, increased thallium-201 lung uptake appears to be a marker of severe and functionally more important coronary artery disease associated with left ventricular dysfunction (Gibson et al, 1982; Levy et al, 1983).

In patients with single-vessel coronary artery disease, increased thallium-201 lung uptake was related to the severity of stenosis of the coronary artery and the extent of ischaemia (Liu et al, 1985). After percutaneous transluminal coronary angioplasty, thallium-201 lung uptake reverted to normal in patients who showed increased uptake.

To optimize detection of elevated lung thallium-201 uptake, initial imaging should be performed in the anterior view early after cessation of exercise (Rothendler et al, 1985). The sensitivity of increased lung thallium-201 on post-exercise images falls off rapidly with time, due to a more rapid clearance of thallium from the lung when the initial concentration is increased. Brown et al (1986) studied the haemodynamic determinants of thallium-201 lung uptake during atrial pacing stress. Stepwise multiple regression analysis showed that changes in the cardiac index from the rest to peak pacing was negatively correlated, while
pulmonary capillary wedge pressure at peak pacing was positively correlated to lung thallium-201 uptake. In addition, perfusion defects in more than one discrete vascular region and the presence of delayed redistribution were more sensitive predictors of subsequent cardiac events than ST-segment depression, angina or extent of angiographic coronary artery disease.

1.2.4 Multivariate analysis of noninvasive investigations

The usefulness of noninvasive testing in predicting severity and prognosis of coronary artery disease has been thoroughly investigated. At present, exercise electrocardiography, radionuclide ventriculography and thallium-201 myocardial perfusion imaging have all been shown to be of diagnostic and prognostic value in patients with stable coronary artery disease and after acute myocardial infarction (Helfant et al, 1987). Coronary arteriography is currently the only method that provides unequivocal diagnostic and prognostic information particularly in the presence of conflicting noninvasive test results. Therefore, early identification of patients who are at higher risk of subsequent cardiac events leads to early intervention and has a substantial impact on the outcome.

The introduction of the coronary care unit treatment reduced mortality early after acute myocardial infarction from 26 to 7% (Killip et al, 1967). A coronary prognostic index was constructed from 757 patients investigated prospectively to study the hospital mortality rate following acute myocardial infarction (Norris et al, 1970). It was found that six factors could be best related to hospital survival, and
these were age, systolic blood pressure on admission to hospital, heart size and degree of congestion of the lung fields on a chest X-ray taken as soon as possible after admission, the position and degree of infarction assessed from a 12-lead electrocardiogram, and a history of previous ischaemia. Factors not related to survival were sex, the time between onset of infarction and admission to hospital, previous diabetes, hypertension and obesity.

Scheidt et al (1973) performed objective haemodynamic assessment in patients after admission to a coronary care unit. Patients without acute myocardial infarction had haemodynamic findings which were no different from those with definite uncomplicated myocardial infarction. In complicated cases (i.e. congestive cardiac failure or cardiogenic shock), the haemodynamic derangements were more severe. Heart rate, cardiac index, stroke volume index, peripheral vascular resistance and left ventricular filling pressure all proved unreliable as single variables in predicting ultimate survival or death. However, left ventricular work index less than 1.75 Kgm/min per m² was associated with a very high mortality with a predictive accuracy of 90%.

The occurrence of complicated ventricular arrhythmias significantly increases the risk of sudden death in the early phase after hospitalization in patients with acute myocardial infarction and low ejection fraction (Schulze et al, 1977). Others have found that ventricular arrhythmias did not provide additional prognostic information (Taylor et al, 1980). Using univariate analysis, Taylor et al have shown that a low ejection fraction, proximal left anterior descending coronary disease and significant disease in all three
coronary arteries were associated with a high risk of sudden cardiac death. The electrocardiographic site or type of infarction were not helpful in predicting mortality, reinfarction or angina pectoris. In addition, they carried out a multivariate analysis of 30 clinical and laboratory variables which identified previous myocardial infarction and an ejection fraction less than 40% as the best predictors of mortality. Recurrent myocardial infarction during 30 months of follow-up was best predicted by hypertension, three-vessel coronary disease, postinfarction angina pectoris and previous infarction (Taylor et al, 1980).

Comparative studies of thallium-201 myocardial perfusion scintigraphy and stress electrocardiography have shown thallium-201 scanning to be more sensitive in detecting coronary artery disease (Ritchie et al, 1978; Okada et al, 1980). Furthermore, thallium imaging was found to be superior to stress electrocardiography in the detection of residual jeopardized myocardium and the prediction of multivessel coronary artery disease after acute myocardial infarction (Dunn et al, 1980; Turner et al, 1980; Gibson et al, 1981).

The natural history of left ventricular function and survival during one year after acute myocardial infarction were studied in 45 patients (Borer et al, 1980). Ejection fraction correlated significantly with the complexity of ventricular arrhythmias during 24-hour electrocardiography, but neither exercise-induced ST-segment change nor plasma norepinephrine levels correlated with ejection fraction or with frequency or complexity of arrhythmias. Four of the 45 patients (9%) died within 1 year of infarction; each had an ejection fraction less than 35% at rest before hospital discharge, but neither the presence of
complex arrhythmias nor the determination of ejection fraction during
the exercise provided additional information in predicting these deaths.
Ejection fraction in a later study (6-14 months after infarction) was
not significantly different from that in the predischarge study. There
was a small but significant increase in ejection fraction in the later
study in the subgroup of patients who showed an exercise ejection
fraction greater than 40%, which indicates that left ventricular
function has the capacity to improve during the year after acute
myocardial infarction. Similarly, Dewhurst et al, (1983) studied
sequentially 100 consecutive patients after their first myocardial
infarction. Left ventricular ejection fraction was measured at rest one
day before hospital discharge and again one, four, and 12 months later
at rest and during submaximal exercise. A low left ventricular
ejection fraction observed in 25 patients was poorly predicted either
clinically, radiologically or electrocardiographically. A low ejection
fraction before hospital discharge was associated with left ventricular
failure, ventricular arrhythmias, and sudden death (10 patients). Of
the remaining patients exercised one month after infarction, 27 showed
a significant fall (>5%) in left ventricular ejection fraction and 23 of
these developed postinfarction angina, four suffered non-fatal
reinfarction and five patients died. Thus, exercise radionuclide
ventriculography was able to identify 88% of patients who died suddenly
in the first two years after infarction.

Stepwise discriminant analysis was performed to assess the degree to
which the clinical, exercise and radionuclide ventriculography variables
were able to predict the occurrence of subsequent cardiac events
(cardiac death, recurrent infarction, unstable angina, congestive
cardiac failure or limiting angina) in 61 postinfarction patients (Corbett et al, 1981). The sensitivity and specificity of exercise radionuclide ventriculography in predicting cardiac events were 95% and 96% for failure to increase ejection fraction by at least 5%, 95% and 96% for an increase in end-systolic volume of more than 5%, 97% and 88% for failure of end-systolic pressure/volume index to increase by more than 35% and 81% and 88%, respectively, for deterioration in regional wall motion. The sensitivity and specificity of exercise electrocardiography for the prediction of important cardiac events were 54% and 58% respectively. The best predictors of prognosis during a 6 months follow-up period were the change in ejection fraction, end-systolic volume and the pressure/volume index. When patients with subsequent cardiac events were grouped into those with 'major events' (death, recurrent infarction and unstable angina) and those with 'minor events' (limiting angina and persistent cardiac failure), only the peak submaximal exercise ejection fraction and history of previous myocardial infarction were significant in distinguishing the two groups. In patients without important cardiac events during follow-up, 70% and 88% respectively had no abnormality in the responses of ejection fraction, end-systolic volume, or the pressure/volume index to submaximal exercise. These results suggest that exercise radionuclide ventriculography before hospital discharge is a highly sensitive means of classifying patients as to the likelihood of developing cardiac events during 6 months after myocardial infarction. On the contrary, myocardial infarction size assessed by technetium-99m pyrophosphate imaging, and myocardial infarction size assessed by thallium-201 were the best indicators to separate those who were asymptomatic on follow-up from those who died after each acute myocardial infarction (Perez-
Gonzalez et al, 1982). However, ejection fraction could not differentiate among prognostic subgroups (Botvinick et al, 1983).

The prognostic value of exercise testing, coronary arteriography and left ventriculography were evaluated in 179 survivors 6-8 weeks after an acute myocardial infarction (De Feyter et al, 1892). The prevalence of multiple vessel coronary artery disease was higher in the symptomatic survivors (79%). The prevalence of multivessel disease in inferior and anterior infarction was 63% and 42% respectively. During a mean follow-up of 28 months, 11 cardiac deaths and 12 reinfarction occurred. The total mortality rate was 22% in patients with an ejection fraction <30% or three-vessel disease and only 1% in patients with an ejection fraction equal or greater than 30% and one or two vessel disease. The total reinfarction rate was 9% in patients with an exercise tolerance of less than 10 minutes or more. Therefore, a group of patients at high risk of mortality or reinfarction could be identified either angiographically or according to their exercise tolerance (De Feyter et al, 1982).

Different prognostic indices have been developed from clinical symptoms and signs, haemodynamic changes, cardiac enzyme levels, electrocardiographic abnormalities and Holter-recorded ventricular arrhythmias (Peel et al, 1962; Norris et al, 1970; Vedin et al, 1975; Bigger et al, 1978; Luria et al, 1979; Davis et al, 1979). In a study of 866 patients with acute myocardial infarction, the Multicentre Postinfarction Research Group (1983) defined four risk factors as independent predictors of mortality: an ejection fraction below 40%, ventricular ectopy of 10 or more per hour, advanced New York Heart
Association functional class before infarction, and rales heard in the upper two thirds of the lung fields while the patient was in the coronary care unit. During an average follow-up period of 22 months per patient, 101 patients died, and 76 of the deaths occurred in the first year after hospital discharge (a 9% mortality rate in the first year). Eighty-two per cent of the deaths were classified as due to coronary artery disease (cardiac death), and 37% of these cardiac deaths were of sudden onset i.e. death within one hour of symptoms, or death during sleeping. Ventricular ectopic activity was less strongly associated with mortality than the mechanical variables, and the variable for ischaemia (i.e the presence of predischarge angina pectoris) did not discriminate significantly between those who survived and those who died. The left ventricular radionuclide ejection fraction (graded into four categories) and ventricular arrhythmias (subdivided into 5 frequency groupings) were related to cardiac mortality. There was a progressive increase in one-year cardiac death as the ejection fraction fell below 40% and as the frequency of ventricular arrhythmias rose above one per hour. Ejection fraction had a considerably stronger effect on mortality than did ectopic depolarization. The analysis of survival in this study used the GLIM system (Generalized Linear Interactive Modelling) which is different from the Cox life-table regression technique (Cox DR, 1972) in that fixed time intervals were used in the survival distribution (Nelder et al, 1975).

The search for reliable prognostic information to determine the short and long term outcome after acute myocardial infarction continues. Various reports have confirmed the importance of haemodynamic variables (Wolffenbuttel et al, 1983) and early thallium-201 scintigraphy and
gated blood pool ventriculography (Becker et al, 1983; Fioretti et al, 1984; Kelly et al, 1985) in separating high and low-risk groups of postinfarction patients (Starling et al, 1986; Ong et al, 1986). However, Gibson et al (1983) showed that predischarge submaximal exercise thallium-201 myocardial perfusion imaging can distinguish high and low-risk groups and thallium-201 defects in more than one discrete vascular region, the presence of delayed redistribution, or increased lung thallium-201 uptake were more sensitive predictors of subsequent cardiac events than ST-segment depression, angina, or the extent of angiographic coronary artery disease. Low-risk patients were best identified by a single-region thallium-201 defect without redistribution and no increased thallium-201 lung uptake.

However, when patients were studied 3 weeks after a clinically uncomplicated myocardial infarction, peak treadmill workload and the change in left ventricular ejection fraction during exercise were the best predictors of 'hard' cardiac events (cardiac death, recurrent infarction or nonfatal ventricular fibrillation). In addition to these two factors, recurrent ischaemic chest pain in the coronary care unit was also significantly predictive for combined cardiac events (hard events, unstable angina pectoris, congestive cardiac failure or coronary bypass surgery) (Hung et al, 1984). The prognosis of postinfarction patients appears to depend largely on the degree of myocardial damage and the extent of the underlying coronary artery disease. Morris et al (1984) investigated the noninvasive prediction of angiographic extent of coronary artery disease 6 weeks after an acute myocardial infarction. They compared the clinical, bicycle electrocardiographic and radionuclide ventriculographic ejection fraction and regional wall
motion responses in 110 patients undergoing coronary arteriography after infarction. The conventional diagnostic criteria for abnormal clinical, electrocardiographic or scintigraphic results did not identify patients with additional coronary artery disease after infarction with high accuracy. A fall in ejection fraction and worsening of wall motion abnormality during exercise were similar to clinical parameters in specificity, but had a higher sensitivity and information content.

Nestico et al (1986) examined abnormal right ventricular thallium-201 uptake in 116 patients with documented acute myocardial infarction who underwent predischarge thallium-201 imaging at rest, radionuclide ventriculography and 24-hour electrocardiography. Compared with patients who had normal right ventricular thallium-201 uptake, patients who had an increased uptake showed a lower mean left ventricular ejection fraction, a higher prevalence of increased lung thallium-201 uptake, more extensive perfusion defects and more complex ventricular arrhythmias. At a mean follow-up of 6 months, 26% of patients with increased right ventricular thallium uptake and 11% of patients with normal uptake died from cardiac causes. Thus, increased right ventricular thallium uptake was more apparent in patients with impaired left ventricular function, more complex ventricular arrhythmias and a worse prognosis. However, multivariate analysis showed that left ventricular ejection fraction and complex ventricular arrhythmias were independent predictors while an abnormal right ventricular thallium uptake did not.

The functional and prognostic significance of right ventricular dysfunction after acute inferior wall myocardial infarction were
investigated in 74 consecutive patients (Haines et al, 1985). Patients underwent predischarge gated blood pool ventriculography at rest, submaximal exercise thallium-201 scintigraphy and coronary angiography. Patients were grouped into those who had normal, mild to moderate or severe right ventricular dysfunction. Exercise tolerance, blood pressure-heart rate double product and peak work load were comparable among the three groups, both before hospital discharge and at 3 months follow-up. There were no differences among the groups in the prevalence of redistribution thallium-201 defects, ST-segment depression, cardiac mortality, reinfarction rate and the incidence of medically refractory angina pectoris, which might indicate that right ventricular dysfunction after acute inferior wall infarction did not limit exercise tolerance or identify patients at higher risk for subsequent cardiac events. Other investigators confirmed the value of radionuclide ventriculography in detecting right ventricular infarction in patients with inferior myocardial infarction (Rodrigues et al, 1986). This was superior to electrocardiographic methods and, in addition, it was possible to categorise patients into low and high risk groups for subsequent cardiac events.

More recently, exercise-induced ST-segment elevation 2 weeks after uncomplicated myocardial infarction was reported to be associated with greater impairment of global and regional left ventricular function due to more extensive damage, rather than extent of underlying coronary artery disease or residual ischaemia (Haines et al, 1987). During long-term follow-up (median 34 months), the total and individual nonfatal cardiac event rates were similar in patients with or without ST-segment elevation.
Weiss et al (1987) reported transient post-stress left ventricular ischaemic dilatation during thallium-201 imaging as a marker of severe and extensive coronary artery disease. An abnormal transient dilatation ratio had a sensitivity of 60% and a specificity of 95% for identifying patients with multiple vessel critical stenosis and was more specific than were other known markers of severe and extensive coronary artery disease, such as the presence of multiple perfusion defects or washout abnormalities, or both. Patients with multiple vessel critical stenoses frequently had an abnormal transient dilatation ratio in the absence of multiple reversible defects. On the other hand, exercise-induced changes in end-diastolic volume during supine exercise were related to the extent of myocardial scar (Mann et al, 1987) when assessed by thallium-201 scintigraphy. Different findings were reported by Jeremy et al (1987) who found that the degree of perfusion of the infarct-related artery at predischarge coronary angiography was an important predictor of changes in left ventricular volume in the month after infarction, independently of infarct size. Absent perfusion of the infarct artery was associated with the development of left ventricular dilatation and impaired left ventricular function.

Early identification of patients as belonging to a high risk subgroup leads to the potential for early intervention, and has a substantial impact on outcome whether we use exercise electrocardiography, radionuclide ventriculography, thallium-201 myocardial perfusion imaging or any combination of these.

In addition to the currently available techniques, new modalities are becoming available for the diagnosis and evaluation of heart disease particularly after acute myocardial infarction. Both positron emission
tomography and tomographic thallium imaging have been employed to evaluate patients with coronary artery disease (Selwyn et al, 1985; Fintel et al, 1985). Positron emission tomography has the advantage of very rapid acquisition and the ability to perform sequential studies after various interventions (Selwyn et al, 1985). Tomographic thallium-201 imaging is possibly the more accurate and quantitative technique to assess the size of perfusion defects as compared with routine thallium scans (Fintel et al, 1985).

The use of nuclear magnetic resonance imaging for cardiac diagnosis is recognised to hold vast potential (Kaufman et al, 1983, Pohost et al, 1985). Recently, cardiac gating techniques have been used to control magnetic resonance imaging pulse sequence timing, which allows the acquisition of both anatomic and functional data. The transverse views are excellent in demonstrating anatomical myocardial and chamber abnormalities. In addition it is possible to produce images of the coronary anatomy (including areas of obstruction), direct tissue characterization, blood flow measurements and assessment of myocardial metabolism.

1.3 PATHOPHYSIOLOGY

1.3.1 Atherosclerosis

Atherosclerosis is a special type of thickening and hardening of the medium-sized and large arteries that accounts for a large proportion of cases of ischaemic heart disease, cerebral ischaemia and peripheral vascular disease (Figure 1.3.1). It is a progressive process which is
MECHANICAL BASIS FOR IHD.

**Figure 1.3.1**

Schematic illustration of coronary blood flow: Normal (top), atherosclerotic lesions (middle) and coronary artery spasm (bottom).
unevenly distributed geographically.

1.3.1.1 Microscopic structure of arterial wall

In arteries of all sizes, the transected wall shows three major microscopic layers: the intima, the media and the adventitia. The major constituents of the normally thin intima are endothelium, basement membrane and occasional smooth muscle myointimal cells, a few collagen and/or elastic fibres and an infrequent blood-derived mononuclear cell. The arterial endothelium probably both admits and discharges macromolecules of the size of low-density lipoproteins (LDL) (Gimbrone, 1981). Although most plasma proteins can enter the arterial wall (Smith et al 1972), lipoproteins and fibrinogen are particularly likely to accumulate in the intima (Day et al, 1975).

The media of the mammalian artery is formed by multiple layers of smooth muscle cells, usually two cells wide and separated by a prominent elastic membrane. Each of these recurring structures, which contain an elastic membrane in the centre and a smooth muscle cell on each side, is called a 'lamella unit'. The arterial smooth muscle cell can synthesize collagen, elastin and glycosaminoglycans (Ross R et al, 1971). Blood-derived monocytes, macrophages and platelets can exert a strong influence on the atherosclerotic process during various stages of development and regression of the plaque. (Ross, 1976).

The adventitia of the artery is important to arterial function. Its mainly collagenous structure provides the major mechanical support when the media is weakened due to advanced atherosclerosis. It is also
important because it provides the media of larger arteries with much of its nutrition by means of vasa vasora, as well as with lymphatic drainage and innervation. The predominant cell of the adventitia is the fibroblast.

1.3.1.2 Features of human atherosclerosis

Human atherosclerosis produces its effects largely in the medium-sized muscular arteries such as the coronary, carotid, basilar and vertebral arteries. It also affects arteries supplying the lower extremities and the larger arteries such as the aorta and the iliac artery. It is different from arteriosclerosis which rarely produces clinical effects due to minor intimal and medial changes. The feature that sets atherosclerosis apart from other forms of arteriosclerosis is the lipid, which in the advanced plaque is often represented by a central necrotic core that is rich in cholesterol esters and is often accompanied by visible cholesterol crystals (Wissler, 1984). The atherosclerotic lesion is grossly soft and grumous with a necrotic core which is responsible for the name of the disease process, derived from the Greek stem 'athera', meaning gruel or porridge. The major components of atherosclerotic plaque are its cells, mostly smooth muscle cells, and its lipids, much of which is extracellular (Ross et al, 1976). In addition, there are fibrous proteins and complex carbohydrate products. The relative proportions of these components vary greatly from one plaque to another and during the sequence of development or regression of a given plaque. The clinical effects of advanced plaques of most medium-sized arteries, which include the main coronary vessels, are due to either their space-occupying characteristics, which lead to stenosis,
or their thrombogenic qualities, which often appear related to fracture or rupture of the fibrous cap and the resulting ulceration of the plaque surface. This frequently results in an obstructing thrombus, which in a major coronary artery can form over a well developed atheromatous plaque and lead to sudden coronary occlusion and acute myocardial infarction.

1.3.2 Risk factors for coronary artery disease

The majority of people below the age of 65 afflicted with atherosclerosis have one or more identifiable risk factors other than aging per se. The risk factor concept implies that a person with at least one risk is more likely to develop a clinical atherosclerotic event and to do so earlier than a person with no risk factors. The presence of multiple risk factors further accelerates atherosclerosis. They vary in terms of importance in the population but there is a general agreement that hypercholesterolaemia, hypertension and cigarette smoking may be the most potent factors involved in causation of atherosclerosis. Risk factors also vary in terms of their potential reversibility with current techniques of preventive management. Thus age, sex and genetic factors are currently considered to be irreversible risk factors, whereas elimination of cigarette smoking and treatment of hypertension reverses the high risk for atherosclerosis attributable to these factors.

These factors are not mutually exclusive since they clearly interact. For example, obesity appears to be causally associated with hypertriglyceridaemia. Genetic factors may play a role by exerting
direct effects on arterial wall cell structure and metabolism, or they may act indirectly via such factors as hypertension, hyperlipidaemia, diabetes and obesity. Aging appears to be one of the more complex factors associated with the development of atherosclerosis, since many of the risk factors in themselves are related to aging e.g. elevated blood pressure, hyperglycaemia and hyperlipidaemia. Thus in addition to the possible involvement of intrinsic aging in atherosclerosis (perhaps through effects on arterial wall metabolism), a variety of associated metabolic factors are also age dependant.

1.3.2.1 Hyperlipidaemia

One of the best documented risk factors for the development of atherosclerosis is the association between blood lipids and coronary artery disease. The evidence of the association between serum cholesterol level and atherosclerosis is extensive and unequivocal (Kannel et al, 1979). Although triglyceride levels have been associated with coronary artery disease in several cross-sectional studies, prospective studies remain inconclusive in their indictment of serum triglyceride as a coronary risk factor (Carlson L A, 1960 and Hulley S B et al, 1980). The accuracy of predicting the risk of coronary artery disease according to cholesterol concentration is, however, greater in the young (under 65 years) than in the elderly. Subjects with the highest cholesterol levels are at greater risk of developing coronary artery disease, but even those with the lowest levels are not completely immune to the disease (Stamler J, 1978). When considering coronary artery disease risk, there is little justification for using the Gaussian distribution to define 'normal' levels. The higher the
cholesterol level, the greater the need for concern, but no single level of plasma cholesterol separates those at risk from those who are not.

The major plasma lipids, including cholesterol and triglyceride, do not circulate freely in solution in the blood but rather are transported in the form of lipoprotein complexes (Frederickson et al, 1967). The major lipoprotein families are usually classified in terms of physicochemical properties such as density or electrophoretic mobility. Sufficient elevation in the concentration of any of the lipoproteins can result in hypercholesterolaemia. Similarly, hypertriglyceridaemia can result from increased concentrations of chylomicrons, very low-density lipoproteins (VLDL) or intermediate-density lipoproteins (IDL) alone or in various combinations.

Plasma concentrations of low-density lipoproteins (LDL) correlates closely with plasma concentrations of cholesterol, since 60 to 75 per cent of the total plasma cholesterol is normally transported in this lipoprotein. High-density lipoprotein (HDL), which normally accounts for 20 to 25 per cent of the total plasma cholesterol, is also a potent risk factor for coronary artery disease. Whereas LDL cholesterol is directly related to risk, however, HDL shows an inverse relationship (Gordon et al, 1977).

The Framingham Study has shown that in both men and women older than the age of 50 years, HDL cholesterol has the strongest relationship to coronary artery disease (Gordon et al, 1977). The study suggests that HDL should be integrated into the risk of profile for coronary artery
disease, together with LDL and VLDL.

1.3.2.2. Hypertension

Elevated blood pressure, either systolic or diastolic, is predictive of an increased risk of developing coronary artery disease (Kannel, 1975). Both systolic and diastolic blood pressure have a continuous, unimodal distribution in the population when measured under standard conditions. Although there is some skewing of the distribution towards high values, there is no evidence of bimodality. Thus, although the level of blood pressure appears to have a major genetic determination, it occurs as a continuously distributed trait with no clear cut-off points to differentiate qualitatively distinct entities. As with the concentration of plasma cholesterol, there are no cut-off points at which risk suddenly changes from low to high values. As an individual predictor, blood pressure has been found to be more reliable than the level of cholesterol or cigarette smoking. Although blood pressure normally tends to rise with age, elevated blood pressure is still a risk factor in the elderly. Furthermore, the relationship between blood pressure and the risk of developing coronary artery disease is as strong in women as it is in men (Kannel, 1975).

Systolic blood pressure has been found to be a better predictor of the risk of developing coronary artery disease than is diastolic blood pressure (The Framingham Study). Since both systolic and diastolic blood pressure are highly correlated in the general population, their relative merits as risk predictors may be academic. Yet it would be imprudent to dismiss isolated systolic hypertension as being a normal
concomitant of aging, unrelated to the risk of developing coronary artery disease.

1.3.2.3 Tobacco smoking

Tobacco smoking is a well established health hazard that is particularly harmful to the lungs. It is also a major risk factor for myocardial infarction and death due to coronary artery disease (Aronow, 1976 and Wilhelmsson et al, 1975). Total mortality, total cardiovascular mortality and incidence of coronary artery disease are increased by about 1.6 times in male cigarette smokers. Pipe and cigar smokers, however, have only slight increases in total cardiovascular deaths and morbidity (Feinleib et al, 1976). The risk of developing coronary artery disease is directly related to the number of cigarette smoked per day. Furthermore, those who discontinue smoking assume a lesser risk than those who continue to smoke (Gordon et al, 1974).

The relationship of cigarette smoking to development of coronary artery disease among women is somewhat more complex. Women show about the same gradient of risk correlated with the amount of smoking as do men in relation to myocardial infarction (Slone et al, 1978). A variety of mechanisms have been suggested for the adverse effects of cigarette smoking on the heart and blood vessels, and could be reversed upon discontinuation of the smoking habit. Among these mechanisms is the effects of nicotine and carbon monoxide upon the heart, the coronary arteries, and the blood. Specific changes include increased myocardial demand for oxygen, induced by nicotine; interference with oxygen supply by carboxyhaemoglobin; increased adhesiveness of platelets; and the
lowering of the threshold for ventricular fibrillation. Cigarette smoking has also been found to be associated with decreased levels of HDL cholesterol, compared with those in non-smokers and ex-smokers, (Garrison et al, 1978.).

### 1.3.2.4 Diabetes Mellitus

Diabetes mellitus has been recognised as a precursor of vascular diseases. Hyperglycaemia and an abnormal glucose tolerance test are associated with increased risk of developing coronary artery disease (Fuller et al, 1980). Although early-onset diabetes appears to be primarily associated with mortality from renal disease, adult-onset diabetes is associated with death from coronary artery disease. In adults, both insulin-dependant and non-insulin-dependant diabetes appear to be at an increased risk for development of coronary artery disease (Vigorita et al, 1980). The mechanism associating hyperglycaemia and increased risk of coronary artery disease is obscure, although several aspects have been investigated. Hyperlipidaemia, particularly hypertriglyceridaemia and hyperglycaemia tend to be associated with obesity and thereby indirectly with hypertension (Sosenko et al, 1980). Insulin or glucose or both have potential effects on the synthesis and catabolism of cellular and extra-cellular elements in the arterial wall which lead to the initiation or promotion of atherosclerosis. There is an association between hyperglycaemia and the increased adhesiveness of platelets and other abnormalities of coagulation. Therefore, several complex mechanisms may be involved, separately or in concert.
1.3.2.5 Other risk factors

Several additional risk factors can be considered such as age, sex, race and geographical factors. A family history of coronary artery disease, obesity, gouty arthritis, menopause, oral contraceptives, vasectomy, physical inactivity and type of personality are among other factors which are considered important in the development of coronary artery disease (Levy et al, 1984). Dietary, psychological and social risk factors are believed to be related to the occurrence of coronary artery disease. Undoubtedly, other risk factors exist. Studies comparing the currently known risk factors have failed to explain all the differences that have been found.

1.3.3 Acute myocardial infarction

Almost all cases of myocardial infarction result from atherosclerotic lesions in the coronary arteries. Regardless of the aetiology and pathogenesis of the atherosclerotic process, the end result is plaques that cause luminal narrowing in the coronary arterial tree and thus reduce the blood supply to the myocardium. Below a certain critical level of blood flow, myocardial cells develop ischaemic injury. When severe ischaemia is prolonged, irreversible damage i.e. myocardial infarction, occurs. Since the coronary intraluminal narrowing affects the major coronary arteries and their various branches to a different extent, myocardial infarction usually occurs focally in specific regions of the myocardium. The location and size of a particular infarction depend upon a number of different factors such as the location and severity of atherosclerotic narrowing in the coronary arterial tree and
the presence of coronary arterial spasm (Figure 1.3.1); secondly, the size of the vascular bed perfused by the narrowed vessel and the extent of collateral blood vessels; and finally the oxygen needs of the poorly perfused myocardium.

1.3.3.1 Gross pathological changes

Myocardial infarction is divided into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both without extending all the way through the ventricular wall to the epicardium.

Gross changes do not appear in the myocardium until 6 hours after the onset of myocardial infarction. Initially, the myocardium in the affected region appears pale, bluish and slightly swollen. Eighteen to 36 hours after the onset of the infarct process, the myocardium appears tan or reddish-purple, with a serofibrinous exudate evident on the epicardium with transmural infarcts. These changes persist for approximately 48 hours; the infarct then turns grey, and fine yellowish lines, secondary to neutrophilic infiltration, appear at its periphery. This zone gradually widens and during the next few days extends throughout the infarct. Eight to 10 days later, the thickness of the cardiac wall in the affected area is reduced as necrotic muscle is removed by mononuclear cells. The cut surface of an infarct of this age is yellow, surrounded by a reddish-purple band of granulation tissue that extends through the necrotic tissue by 3 to 4 weeks. Over the
following 2 to 3 months, the infarcted area gradually acquires a gelatinous, ground-glass, grey appearance, eventually converting into a shrunken, thin, firm scar, which whitens and firms progressively with time; this process begins at the periphery of the infarct and gradually moves centrally. The endocardium below the infarct increases in thickness and becomes grey and opaque. (Fishbein et al, 1978).

1.3.3.2 Histological changes

On light microscopy, severe ischaemia, which is potentially reversible, causes cloudy swelling, as well as hydropic, vascular and fatty degeneration. Within 8 hours of interruption of blood flow, contraction bands and small spaces between the myocardial cells are evident. After 8 hours, oedema of the interstitium, increased fatty deposits in the muscle fibres and neutrophilic infiltration can be seen with careful light microscopy. Muscle cell nuclei become pyknotic and then undergo karyolysis, and small blood vessels become necrotic.

By 24 hours there is clumping of the cytoplasm and loss of cross striations, with appearance of focal hyalinization and irregular cross bands in the involved myocardial fibres. The myocardial capillaries in the involved area dilate, and polymorphonuclear leucocytes accumulate. During the first 3 days, the interstitial tissue becomes oedematous and red blood cells may extravasate. Removal of necrotic fibres begins on about the fourth day after infarction. Later, lymphocytes, macrophages, and fibroblasts infiltrate between myocytes, which become fragmented. The number of polymorphonuclear leucocytes is reduced by the 10th day and the necrotic fibres become dissolved with granulation tissue.
appearing first at the periphery. Ingrowth of blood vessels and fibroblasts continues, along with the removal of necrotic muscle cells, until the fourth to sixth week following infarction, by which time much of the necrotic myocardium is removed. This process continues along with increasing collagenization of the infarcted area. By the sixth week, the infarcted area usually becomes converted into a firm connective tissue scar with interspersed intact muscle fibres (Fishbein et al, 1978).

1.3.3.3 Effects of coronary arterial obstruction

Myocardial infarction usually occurs in hearts with more than one severely narrowed coronary artery. One-third to two-thirds of patients with acute myocardial infarction have critical obstruction (greater than 75% intraluminal narrowing), whereas the remainder is equally divided between patients having one-vessel disease and those having two-vessel disease (Betrice et al, 1982 and Silver et al, 1980).

Most transmural infarcts occur distal to a totally occluded coronary artery. However, the converse is not the case, in that total occlusion of a coronary artery is not always associated with myocardial infarction. Collateral blood flow and other factors, such as the level of myocardial metabolism, the presence and location of stenoses in other coronary arteries, the rate of development of the obstruction, and the quantity of myocardium supplied the obstructed vessel, all influence the viability of myocardial cells distal to the occlusion. In many series of patients studied at necropsy or by coronary arteriography, a small number (less than 5%) of patients with myocardial infarction are found
to have normal coronary vessels (Rosenblatt et al, 1977). In these patients, an embolus that has lysed or a prolonged episode of severe coronary spasm may have been responsible for the reduction in coronary flow.

Obstruction of the left anterior descending coronary artery usually produces infarction or threatens the viability of the anterior and apical regions of the left ventricle; portions of the septum, anterolateral wall, papillary muscles, and inferoapical wall of the left ventricle may also be involved. Obstruction of the left circumflex artery can cause infarction of the lateral or infero-posterior wall of the left ventricle, whereas occlusion of the right coronary artery usually results in infarction of the infero-posterior wall of the left ventricle, the inferior portions of the septum, and the postero-medial papillary muscle. The size of the infarction and its location depend upon the distribution of the obstructed coronary vessels. Thus, occlusion of a dominant right coronary artery, which supplies the posterior descending artery and posterior left ventricular wall, produces infarction of the infero-posterior wall of the left ventricle whereas the same region of the myocardium may be involved with occlusion of the left circumflex coronary artery in the presence of a dominant left coronary artery.

Transmural infarctions are found at postmortem examination to be associated with fresh or organizing thrombosis in the coronary artery supplying the infarcted regions in slightly more than half of the cases (Silver et al, 1980). Transmural infarcts are more frequently localized to the zone of distribution of a single coronary artery. Nontransmural
infarctions, however, often occur in the setting of severely narrowed but still patent coronary arteries.

Patients with transmural infarction of left ventricular infero-posterior wall and the posterior portion of the septum are more likely to develop right ventricular infarction as well. Approximately one-third of patients with inferior infarction have some involvement of right ventricle (Wackers et al, 1978 and Isner et al, 1978). Isolated infarction of the right ventricle occurs in 3-5% of autopsy-proven cases of myocardial infarction.

1.3.3.4 Pathophysiology of acute myocardial infarction

The fundamental pathological alteration underlying left ventricular dysfunction in acute myocardial infarction is loss of functioning segments of myocardium. Depression of cardiac function is directly related to the extent of left ventricular damage. Cessation of blood flow to a region of myocardium produces abnormal contraction patterns such as hypokinesis, akinesis or dyskinesis according to the severity and extent of myocardial damage. If a sufficient amount of myocardium undergoes ischaemic injury, left ventricular pump function becomes depressed, and cardiac output, stroke volume, and blood pressure are reduced. Oedema and cellular infiltration and ultimately fibrosis increase the stiffness of the infarcted myocardium back to and beyond control values (Diamond et al, 1972). Increasing stiffness in the infarct zone of myocardium improves left ventricular function, since it prevents paradoxical systolic wall motion.
Areas with reduced or absent wall motion are usually seen in patients with acute transmural myocardial infarction. The earliest abnormality is a reduction in diastolic distensibility, which can be observed with infarcts that involve only 8% of the total left ventricular myocardium (Rackley et al, 1977). Unless extension of the infarct occurs, some improvement in abnormal wall motion takes place during the healing phase, as recovery of function occurs in initially reversibly injured myocardium. Regardless of the age of the infarct, patients who continue to demonstrate abnormal wall motion of 20-25% of left ventricular myocardium manifest haemodynamic signs of left ventricular failure (Klein et al, 1967), and this is proportional to the areas of abnormal wall motion. Left ventricular diastolic properties are altered in infarcted and ischaemic myocardium leading initially to an increase but later to a reduction in left ventricular compliance and ultimately raising its diastolic pressure at any given volume (Diamond et al, 1972). Patients who recover from acute myocardial infarction frequently continue to manifest decreased left ventricular compliance secondary to the fibrous scar that remains in the left ventricle.

Reduced ventricular diastolic compliance and systolic function lead to pulmonary venous hypertension. Both of these mechanisms are responsible for elevation of left ventricular diastolic pressure, which is often associated with pulmonary congestion and depressed cardiac output. Clinical manifestations of both mechanisms of left ventricular failure become more common as the extent of the injury to the left ventricle increases (Rackley et al, 1977).

In right ventricular infarction there is elevation of right-heart
filling pressures with normal or modestly elevated left ventricular filling pressure (Coma-Canella et al, 1979). Right ventricular systolic and pulse pressures are decreased, and cardiac output is depressed. The haemodynamic importance of right ventricular infarction in patients with inferior infarction is reflected in the observation of Marmor et al (1981), who noted that although infarct size (reflected in CK release curves) was similar in patients with anterior and inferior infarctions, the former had more severe depression of left ventricular ejection fraction and the latter had more severe depression of right ventricular ejection fraction.

1.4 OBJECTIVES

The identification of high risk and low risk subjects among those who have recovered from acute myocardial infarction remains a major aim in clinical practice. Several clinical criteria and diagnostic procedures have been used to identify patients at risk of subsequent complications. However, the sensitivity and specificity of these tests vary widely. Exercise electrocardiographic testing has been used as a screening test for the presence of physiologically important coronary artery disease and has been shown to be a relatively safe and effective means of predicting future cardiac events both remote from and early after myocardial infarction.

Rest and maximal exercise radionuclide ventriculography provides an additional means to evaluate patients with coronary artery disease. In addition to alterations in the electrocardiogram, changes in both left and right ventricular function may provide important functional
information in patients with recent myocardial infarction.

Exercise thallium-201 myocardial perfusion scintigraphy provides more information about the extent of myocardial damage, the extent of reversible ischaemic myocardium and the degree of left ventricular dysfunction in patients who suffered a recent myocardial infarction.

Therefore, exercise-induced electrocardiographic abnormalities, left and right ventricular dysfunction and the presence of reversible ischaemia may have important diagnostic and prognostic value. It would be essential to develop an algorithm to identify patients at highest risk, in whom more aggressive management would be indicated for the salvation of the myocardium following acute myocardial infarction. The purpose of this study is to define and characterise such an algorithm which should use the most sensitive and specific tests and eliminate those that are costly and redundant. This study aims to evaluate the predictive value of clinical characteristics, symptom-limited treadmill testing, rest and exercise radionuclide ventriculography and exercise thallium-201 myocardial perfusion scintigraphy performed 6-8 weeks after an episode of acute myocardial infarction. There is a significant degree of controversy regarding the method of choice for delineating the problem of 'high risk' of complication after myocardial infarction. The predictive value of these tests was assessed with regard to the coronary arteriography findings and the prognosis during 12-24 months after an episode of acute myocardial infarction.
CHAPTER 2

PATIENTS AND METHODS
2. PATIENTS AND METHODS

2.1 PATIENTS

2.1.1 Inclusion criteria

Patients of either sex under the age of 75 years were considered for inclusion into the study from routine admissions to the coronary care unit with a clinical diagnosis of acute myocardial infarction. At least two out of three criteria of acute myocardial infarction were required for inclusion in the study: 1) a history of typical chest pain lasting more than 30 minutes and not relieved by rest or sublingual glycercyl trinitrate; 2) typical electrocardiographic changes indicative of myocardial damage including ST-segment elevation, T-wave inversion and the appearance of new QS complexes or Q wave more than 0.04 sec in duration; 3) characteristic elevation and fall of total creatine kinase and its MB isoenzyme fraction levels.

2.1.2 Exclusion criteria

Patients were excluded from the study if they had unstable angina manifested by typical chest pain and electrocardiographic findings but normal enzyme levels. Similarly, patients with serious arrhythmias resistant to conventional therapy e.g. atrial fibrillation and patients with complete heart block or any other conduction defects requiring permanent pacemakers were not included in the study. Other criteria such as valvular heart disease, cardiomyopathy, metastases to the myocardium, primary myocardial growth (e.g. atrial myxoma), malignancies
with or without metastases, orthopaedic disorders interfering with exercise performance, peripheral vascular disease, chronic obstructive airway disease, cerebrovascular accidents and possible pregnancy were carefully excluded.

2.1.3 Classifications

Patients were classified prospectively into three groups according to the site of myocardial infarction from the electrocardiogram. 1) Anterior transmural (full thickness) infarction included patients with antero-septal, true anterior, and anterolateral myocardial infarction. 2) Inferior transmural (full thickness) infarction included posterior, true inferior and infero-posterior infarction. All patients with transmural infarction showed new QS complexes or a Q wave more than 0.04 sec in duration in more than one electrocardiographic lead. 3) Subendocardial (partial thickness) infarction included active evolution of ST-segment and T-wave changes without the appearance of new QS or Q waves in the electrocardiogram.

2.2 METHODS

2.2.1 Study design

On arrival in the coronary care unit, each patient had 12-lead electrocardiogram, and blood samples were drawn for blood chemistry analysis including total creatine kinase and its MB-fraction. Blood sampling and 12-lead ECG were repeated at least daily for a minimum of 3 days. Full clinical history and physical examination were performed
and a chest x-ray was carried out shortly after admission. The purpose and design of the study were explained and verbal consent obtained from all patients. Patients remained in the coronary care unit for 2-3 days and then were moved to a general ward for recovery and mobilization for a further 3-4 days before discharge from hospital. Male patients under the age of 60 years were included in a cardiac rehabilitation programme. Approximately 6 weeks after discharge, patients were recalled for a graded treadmill electrocardiographic testing. Patients were asked to continue their usual medications but not to take short-acting nitrates, a heavy meal or smoke before attending for the test. After completion of the treadmill testing, the patients went home and returned to hospital the following day for rest and exercise radionuclide ventriculography. Three days later, thallium-201 myocardial perfusion scintigraphy was performed after maximal symptom-limited bicycle exercise and three hours of rest. Selective coronary angiography was performed within the following two weeks after the radioisotopic studies without any change in the patients' condition or medications.

At the end of the investigational period, the results were discussed with the patients and their general condition was assessed. Follow-up appointments were arranged for 3, 6 and 12 months for further assessment and evaluation of prognosis. At each follow-up period, patients were classified according to the occurrence of subsequent events into those with no cardiac events, relatively 'minor' cardiac events e.g. limiting angina or congestive heart failure, and at least one 'major' cardiac event e.g. sudden death, new myocardial infarction, medically refractory angina, percutaneous transluminal angioplasty or coronary bypass surgery.
The effect of medications was not considered in this study and patients continued taking their drugs during different investigational procedures. The name of the drugs, dosage and frequency were recorded at each follow-up visit.

2.2.2 Exercise electrocardiography

2.2.2.1 Equipment

Maximal, symptom-limited exercise testing was performed using a treadmill (Marquette CASE system) which comprised a motor-driven nylon belt with an accurate speed control running on a platform, the front end of which could be elevated to provide a gradient and increase the workload (Figure 2.2.2.1). Dynamic treadmill exercise was chosen in preference to bicycle exercise, as walking was considered to be a more realistic form of exercise and electrocardiographic recordings were easier to obtain.

A three-channel electrocardiographic machine with a frequency response flat to 100 Hz was linked to a microcomputer. Input data was obtained from a simultaneous three-channel digitization of the patient's ECG signals from three bipolar leads. Suitable disposable electrodes were placed over the manubrium sterni, fifth rib at the left anterior axillary line (LV5), fifth rib at the right anterior axillary line (RV5) and sixth rib at the right midaxillary line (RV6). Care was taken to shave excess hair, clean the skin with isopropyl alcohol and lightly abrade the area with a battery-operated high-speed burr.
Figure 2.2.2.1

Treadmill exercise electrocardiography using computer assisted system for exercise (CASE).
The right-arm cable was connected to the electrode at RV6, the left-arm cable to the manubrium sterni, the left-foot cable to LV5 and the right-foot cable to RV5. The lead selector was placed at I, II and III positions and the top channel yielded a right-sided monitoring lead ideal for detecting arrhythmias. Channels II and III yielded leads CM5 (lateral wall) and CC5 (inferior wall) consecutively, which were used for heart rate and ST-segment analysis.

2.2.2.2 Exercise protocol

The Bruce protocol was considered unsuitable for patients 6 weeks following acute myocardial infarction. The first stage of the Bruce protocol with a speed of 1.7 mph and a gradient of 10% could be difficult for ill patients, and the third stage at 3.4 mph involves jogging rather than walking which could result in physical discomfort and unstable electrocardiographic tracings. Instead, a modified Balke's protocol was used in all patients and this protocol was automatically controlled by a computer using special software (Figure 2.2.2.1).

Essentially, the protocol comprised level walking at 2 mph during the first stage, with the speed being increased to 3 mph in the second stage and maintained at this level until the end of stage VI (Figure 2.2.2.2). The predicted oxygen consumption and metabolic equivalent of exercise (METS) were obtained from standard nomograms. (Table 2.2.2.1)

All exercise tests were defined as maximal symptom-limited. Patients were clearly instructed to stop when anginal pain of sufficient severity occurred which would have resulted in termination of their normal daily
Modified Balke's protocol of exercise testing.

<table>
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<th>Stage</th>
<th>Time (min)</th>
<th>Speed (mph)</th>
<th>Gradient (%)</th>
<th>METS (units/min)</th>
<th>Predicted $O_2$ consumption (ml/min)</th>
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<td>2</td>
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<td>4.5</td>
<td>20</td>
<td>13.0</td>
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</tbody>
</table>
Figure 2.2.2.2

Modified Balke's exercise protocol used in Treadmill testing of postmyocardial infarction patients.
activity. In addition, tests were stopped when pain in the legs, fatigue or shortness of breath occurred. For safety reasons, ataxia, ventricular tachycardia, ST-depression greater than 4 mm and a reduction of systolic blood pressure by more than 20 mmHg during exercise were also considered to be end-points.

2.2.2.3 Software

A commercially available microcomputer-assisted system for exercise was modified so that it could control the exercise protocol and analyse the electrocardiographic changes (CASE system). The computer detected each QRS complex and classified each beat according to the morphology and time of occurrence. During the pre-exercise phase, the dominant rhythm beat type was detected and the template of a normal beat was constructed; the QRS onset and offset points (E- and J-points) were also detected. Thereafter, the software determined whether all subsequent beats were normal or ectopic. Only normal beats were processed for ST-segment values and all abnormal beats were recorded at a paper speed of 25 mm/sec. The normal beats then underwent incremental averaging and the J-point depression or elevation and slope at 1/8 of the R-R interval after the J-point were measured. In most cases the slope was calculated at J+60 msec segment using a reference point which was the most horizontal part of the PR segment. The ECG was continuously recorded as a 25:1 time-compressed record by displaying the template of the normal cardiac cycle at a rate of 1 mm/sec. The location of the PR segment was selected as a reference point and the J-point was marked automatically by vertical markers on the top lead for each complex, permitting visual validation. At one-minute intervals
during exercise and post-exercise periods, a summary was printed at the
top of the record and included: minutes of exercise, heart rate, ectopic
rate and ST-segment depression and slope for leads CM5 and CC5. When
the test was completed, a final report was generated, which specified:
the exercise protocol, duration of exercise, maximum heart rate, ectopic
counts, location of ST measurement and worst cases of ST-depression and
slope and their time of occurrence. Also presented in graphic form
(Figure 2.2.2.3) were trend charts for ST-depression and slope in each
lead, heart rate, ectopic rate and blood pressure. Blood pressure was
measured manually by a mercury-in-glass sphygmomanometer and entered
into the computer with a toggle switch. Finally, average ECG complexes
and digital values for rest, immediate pre-exercise period, every three
minutes of exercise, immediate recovery period and each minute
thereafter were printed out. The maximal ST-segment changes were also
recorded. The final reports were stored in a digital recorder for
future reference and analysis.

2.2.2.4 Exercise testing

Following the recommendations of the American Heart Association (1975),
the following safety precautions were carefully standardised:

i. Temperature - controlled exercise laboratory at 24 ± 2°C

ii. All tests were performed with the patient fasting or at least
two hours after a light meal.

iii. Patients arrived in the laboratory at least 30 minutes before
Figure 2.2.2.3

Exercise trend charts: Summary report of exercise electrocardiography. ST-segment shift and slope are presented for bipolar leads with a vertical line denoting the end of exercise. Anterior lead (top), CM5 (middle) and CC5 (bottom).
the test and rested in a comfortable area.

iv. They were not allowed to smoke or consume glycercyl trinitrate tablets on the morning of the test.

v. Patients were allowed to use handrails for balance but not to grip them or support their weight on them.

vi. The speed and gradient of the treadmill were controlled by the computer. The only manual intervention required was identification of the start and end of each stage by the operator.

After arrival at the exercise laboratory and resting for at least 30 minutes to achieve a basal state, all patients had a 12-lead electrocardiogram and clinical examination. Patients did not stop their usual medications but none took short-acting nitrates, either in a tablet or a spray form before performing the test. The patients were asked to lie down and electrodes were placed after proper skin preparation. The cables were connected and the exercise system was switched on so that the three bipolar leads were fed into the computer. The resting ECG was analysed and a print out was obtained. Patients then stood on the treadmill and cuff blood pressure was measured using a mercury sphygmomanometer. The standing systolic blood pressure was fed into the computer and the procedure was explained. After warning, the treadmill was started and exercise continued until the patient's symptoms or one of the end-points warranted stopping the test.
Systolic blood pressure was fed into the computer at the end of each stage and at peak exercise. Post-exercise monitoring was carried out with the patients in the supine position for a minimum of five minutes. A final report was generated at the end of the recovery period and stored on a digital tape.

2.2.3 Equilibrium radionuclide ventriculography

2.2.3.1 Equipment

A single crystal, mobile and fully digital gamma camera (Elscint-Apex 215M) was employed in all the studies (Figure 2.2.3.1). The camera head contained a detector made of 1/2 inch NaI (Tl) crystal and shielded with 1 mm lead-equivalent. In addition, the head contained 37 high-performance photomultiplier (PM) tubes arranged in a hexagonal array. The camera performance and data acquisition were controlled by a minicomputer (Apex processor) with advanced software (Fl). Operations and programmes were selected from a menu list and routine acquisition procedures were programmed into function buttons on the keyboard.

The camera head was equipped with an all-purpose, parallel-hole, low-energy, high-resolution collimator. The system was programmed to perform self-testing once it was switched on, enabling adequate sensitivity and efficiency.

2.2.3.2 Cardiac stress ergometer

Cardiac stress testing system (EDC-8450) was employed in patients
studies. This consisted of imaging table, pedal unit and control unit (Figure 2.2.3.1). The work load could be controlled either manually or automatically using the microprocessor of the control unit. The system was programmed to start at a 25 Watt work load for 3 minutes and to increase the work load by a further 25 Watt every 3 minutes with continuous display of elapsed time, workload and heart rate. The system was connected to a three channel electrocardiographic monitor which displayed heart rhythm on the top channel and CM5 and CC5 on the other two channels. ECG tracings were obtained at rest, every 3 minutes during exercise, peak exercise and every 1 minute during recovery.

2.2.3.3 Blood pool labelling

In order to produce satisfactory labelling of the blood pool, in-vivo labelling of the patient's own red blood cells was accomplished by the method of Pavel et al (1977). This was achieved by first injecting intravenously approximately 10 mg of nonradioactive stannous pyrophosphate that contained a small quantity of tin as a reducing agent sufficient to reduce red blood cells. A commercial kit of stannous pyrophosphate (available for bone scanning) was reconstructed with 5.0 ml of 0.9% NaCl and injected directly into a peripheral vein. Patients received 200mg of sodium perchlorate to block the thyroid gland, gastric mucosa and subarachnoid space therefore reducing the possibility of labelling these organs with the tracer.

Technetium-99m (Tc-99m) 740 MBq (20m Ci) was injected intravenously approximately 30 minutes after the injection of stannous pyrophosphate. Tc-99m was injected as pertechnetate from the generator (Tc O₄) and 5
The gamma camera with the head positioned in the LAO projection allowing best separation of the left ventricle both at rest and during supine bicycle exercise.
minutes were allowed for complete equilibrium.

### 2.2.3.4 Data acquisition

Patients were asked to lie on a special imaging table incorporated with a dynamic exercise ergometer. Disposable electrodes were placed on the chest wall, after skin preparation, to allow for electrocardiographic monitoring and ECG gating during imaging. The electrodes were placed on the manubrium sterni, LV6, RV5 and RV6 as described above.

The camera head was placed close to the chest wall in the anterior projection and acquisition was commenced. The cardiac cycle was divided into 24 frames and gating was set at 5% ECG tolerance. The energy window was set at 20% focused at 140 keV photopeak of Tc-99m. At least 3 million counts were collected for these 24 frames.

Imaging was then carried out in the left anterior oblique (LAO) view. The cardiac cycle was divided into 32 frames using the same settings. The camera head was adjusted to produce the best septal separation with 5-10° caudal tilt. At least 5 million counts were acquired, and images were stored in a 64x64 matrix.

Patients were asked to put their feet onto the pedals of the ergometer and assess their ability to cycle. The position of the pedals could be adjusted according to the patient's requirements either forwards or backwards. The ECG was monitored using bipolar CM5 and CC5 and a pre-test recording was obtained. The workload was computer-controlled and exercise was commenced at 25 watts for 3 minutes and increased
automatically by 25 Watts every 3 minutes. Imaging was performed during the last 2 minutes of each 3-minute period. The angle of acquisition was not changed and the energy window was set at 25% focused at 140 keV photopeak. The cardiac cycle was divided into 16 frames using 15% ECG tolerance. Approximately 3 million counts were collected for each exercise period. The exercise testing was maximal symptom-limited and patients continued the exercise until they developed anginal pain of sufficient severity which would have resulted in termination of their normal daily activity. In addition, ergometry was stopped when pain in the legs, fatigue or shortness of breath occurred. Similar to treadmill testing, ventricular tachycardia, ST-depression greater than 4 mm and a reduction of systolic blood pressure by more than 20 mmHg during exercise were considered end-points. Blood pressure was measured by cuff sphygmomanometer at rest and at the end of each exercise period. ECG monitoring continued during the recovery period for 5 minutes and a final report was printed out. A skin marker, made of Cobalt-57 (Co-57), was placed on the chest wall superimposed on the centre of the left ventricular silhouette while the camera head was in the same position using the persistence oscilloscope. Patients were then imaged in the anterior view for one minute using a static acquisition programme in a 128x128 matrix (Figure 2.2.3.2). A peripheral blood sample was drawn in 1 ml syringe and imaged for 5 minutes using the same collimator/camera system and the same energy window setting. The syringe was placed 5 cm from the collimator over additional photomultiplier tubes.

At the end of the study, patients were instructed to take their usual medications and the study was stored on a floppy disk for further analysis.
Figure 2.2.3.2

The calculation of left ventricular depth using a radioactive point source. Note the orientation of the detector in LAO view (A) and the anterior view (B).

The equation is:

\[ d = \frac{\hat{d}}{\sin 40^\circ} \]
2.2.3.5 Analysis of equilibrium radionuclide ventriculography

Equilibrium radionuclide studies were analysed using a dedicated nuclear medicine computer (Elscint). The analysis included regional wall motion, left and right ventricular function, absolute left ventricular volume, velocity of circumferential fibre shortening and equilibrium pulmonary blood volume ratio. Image preparation required a single nine-point weighted smoothing operation, time smoothing and time correction (Hains et al, 1986). Time correction was necessary to correct for fluctuation in heart rate during data acquisition both at rest and during exercise. This was achieved by selecting a small region-of-interest in a non-contracting part of the blood pool image such as the lung either side of the cardiac silhouette. Then, the counts in all the frames were corrected for that region-of-interest which was usually at the end-diastolic frame. This was performed by a commercially available algorithm which could correct for the sudden drop in counts at the end of the cardiac cycle due to changes in heart rate. Following image preparation, which was performed for the anterior, left anterior oblique and the last phase of exercise study, the analysis of cardiac performance was carried out.

2.2.3.5.1 Regional wall motion analysis

If we assume a homogenous distribution of radioactivity throughout the blood pool, then changes in the spatial distribution of radioactivity within the cardiac blood pool is analogous to visualizing the deformations of blood within the left ventricle. Thus changes in the regional radioactivity are proportional to the changes in regional wall
motion in spite of the inherent poor resolution of blood pool images. The ventricular wall was divided into anterior, septal, apical and inferoposterior segments which represented the appropriate wall. Each segment was given a score according to a pre-defined scoring system as follows:

0 - Normal segment
1 - Hypokinetic segment
2 - Akinetic segment
3 - Dyskinetic segment
4 - Two adjacent dyskinetic segments

Images were played in a continuous cine mode which represented an endless loop of a full cardiac cycle. Scores were given to the anterior, left anterior oblique view at rest and last phase of exercise to produce the total score (Figures 2.2.3.3 and 2.2.3.4).

2.2.3.5.2 Left ventricular systolic function

Data obtained from the left anterior oblique projection was used for the analysis of left ventricular function both at rest and during exercise. A modified commercially available programme was applied to the smoothed raw data (Hains et al, 1987). Frames were displayed in a continuous cine mode and a master region-of-interest was carefully drawn around the boundaries of the left ventricle. Then a semi-automatic algorithm using the second derivative and local threshold techniques was applied to produce regions-of-interest around the left ventricular boundaries in 32 frames in the resting study and 16 frames of the exercise study (Haines
Figure 2.2.3.3

Typical end-diastolic frames of Equilibrium Radionuclide Ventriculography: Anterior view (top) and LAO view (bottom).
Figure 2.2.3.4

Isocontour image in LAO view of Equilibrium Radionuclide Ventriculography. Both ventricles, the septum and valve planes are easily identified.
et al, 1987). This algorithm allowed individual alteration of these regions if there was any inclusion of structures outside left ventricular blood pool. A histogram was then plotted from the changing counts in these regions against time (R-R interval). The lowest point of this histogram was defined as the end-systolic point which represented counts in the end-systolic frame. Background region-of-interest was automatically defined on the end-systolic frame as a small crescent shape inferior and lateral to the left ventricular silhouette. This region was 2 pixels wide and 2 pixels away from the blood pool covering an arc of approximately 90°. The programme was designed to allow alterations in this region to be made should it include parts of the blood pool or other vascular structures. Another histogram was then plotted from the changing counts in this region throughout the frames. Then by subtracting the second histogram from the first, a background corrected time-activity curve was produced. This curve represented changes in left ventricular volume in one cardiac cycle. The maximum point of this curve was defined as the end-diastolic point and the minimum point was defined as the end-systolic point. The difference in counts between these two points was the stroke counts and the ejection fraction was then calculated from the stroke counts divided by background-corrected end-diastolic counts. Ejection fraction was generated as a ratio and converted into percentage from both the resting and exercise studies.

2.2.3.5.3 Right ventricular systolic function

It was not possible to draw a region-of-interest around the right ventricular blood pool similar to that of the left ventricle.
Therefore, it was important to develop an objective method to delineate right ventricular blood pool and separate it from right atrial and pulmonary artery activity (Rodrigues et al, 1987). This was achieved by producing functional images generated by applying the first harmonic of Fourier analysis to the smoothed raw data. Fourier analysis produced two functional images, namely, the amplitude and phase images (Figure 2.2.3.5). The amplitude image represented the magnitude of contraction produced from the spatial distribution of the tracer during the cardiac cycle. This allowed good separation between the right and left ventricles and between the ventricles and the atria. The phase image showed the distribution of the timing of contraction occurring early in the cardiac cycle (the ventricles) and were assigned lower values of phase, and those where contraction was a late event (the atria) had high phase values. With the help of a colour monitor, the scale could be divided into a full circle ranging from 0° to 360° which helped in the construction of a phase image. Low values were colour-coded as red or purple. Non-contracting structures such as the pulmonary artery were not colour-coded and therefore, it was possible to identify the boundaries of all the cardiac chambers (Caruana et al, 1987). The algorithm which I developed included superimposition of the phase image onto the end-diastolic frame and then drawing the master region-of-interest on the combined image avoiding right atrial and pulmonary artery activity. The master region-of-interest was then copied onto the raw data which was displayed in a cine-mode. The programme was designed to allow final adjustment before the application of multiple region-of-interest generation using an algorithm similar to that applied to left ventricular function. Rest and exercise right ventricular ejection fractions were produced, using the same formula, from time-activity
Figure 2.2.3.5

Functional images produced from equilibrium radionuclide ventriculography: Fourier analysis applied to the smoothed data to generate an amplitude image (upper left), phase image (upper right) and phase distribution histogram (lower half). Note the importance of the colour scale.
2.2.3.5.4 Ventricular diastolic function

Commercially available programmes are mainly concerned with the production of ejection fraction as a single indicator of left ventricular function. Left ventricular filling indices were thought to be an important indicator of left ventricular dysfunction in addition to ejection fraction (Lahiri et al, 1987d). A special programme was designed to analyse the systolic and diastolic parameters from high resolution time-activity curve generated from 32 frame during resting study (Lahiri et al, 1987b). Exercise studies were performed using 16 frames only to improve counting statistics and therefore were not included in the analysis of diastolic function. The time-activity curves for both the left and right ventricles represented changes of ventricular volume during the cardiac cycle and therefore it included both the emptying and the filling phases (Figure 2.2.3.6). The first-derivative of this curve represented the rate of change of volume during the cardiac cycle i.e. \( \frac{dV}{dt} \). Therefore, the first negative deflection was defined as the point of peak emptying, and the late positive deflection was defined as the point of peak filling. If the first-derivative curve was superimposed onto the original time-activity curve, then the two points could easily be identified. The slope of the curve over the emptying phase was defined as 'ejection rate'. Similarly, the slope of the curve (100 msec segment) around the peak filling point was defined as 'peak filling rate' (Lahiri et al, 1986 and 1987b; Caruana et al, 1986 and 1987). The time from the end-systolic point to the point of peak filling was defined as the 'time to peak
High Resolution LV Time Activity Curve

Diastolic Indices

Figure 2.2.3.6

High resolution left ventricular time-activity curve generated from 32 frames/cardiac cycle.
filling'. The 'systolic time' was defined as the difference in time between end-diastole and end-systole, while 'ejection time' was defined as the difference in time between the sudden reduction in counts, shortly after end-diastole, and the end-systolic point. The time difference between the 'systolic time' and 'ejection time' produced the 'isovolumetric phase'. The diastolic phase was divided into three segments and the difference in counts between end-systole and the end of the first third of the diastolic phase was divided by the total stroke counts to produce the 'filling fraction' which was normalized to the R-R interval. Ejection fraction was recalculated from the total stroke counts divided by the end-diastolic counts. The systolic and diastolic indices were computed for both the left and right ventricles at rest. These calculations were integrated in a programme which could run automatically once the time-activity curve was produced. The algorithm required minimal operator intervention and therefore, secured good repeatability and reproducibility.

2.2.3.5.5 Absolute left ventricular volume

After equilibrium of an intravenous injection of technetium-99m, there is a homogenous distribution of the tracer throughout the blood pool. The spatial distribution of this tracer is identical to that of blood and the radioactivity per unit volume of tissue is then proportional to the volume of blood contained within that tissue. External monitoring of the changing spatial distribution of radioactivity within the cardiac blood pool is analogous to visualizing the deformations of blood within the cardiac chamber. If the gamma camera records a bidimensional image of tridimensional radioactivity within the cardiac pool, then the
density of each picture element (pixel) in the resulting image matrix represents the activity of blood contained within the volume defined by the projections of the pixel area. If the detectable radioactivity originating from the left ventricle could be isolated from radioactivity originating from other major vascular structures by suitable selection of projection angle then the total activity of these pixels constituting the left ventricular silhouette should be proportional to left ventricular blood volume. Absolute left ventricular volume could then be obtained by normalization of left ventricular activity for the activity of a peripheral venous blood sample. Left ventricular activity should be corrected for background and for photon attenuation by tissues (Links et al, 1982). If a known volume of blood is drawn from a peripheral vein and counted in a small syringe or a test tube so that there is no self-attenuation, the activity in this sample could be used to correct for detector system sensitivity (Al-Khawaja et al, 1984). If both the left ventricle and blood sample are counted by the same collimator/camera system, then the sensitivity term is the same.

In this study, absolute left ventricular volume at end-diastole (LVEDV) was calculated from the equation:

\[
\text{LVEDV} = \frac{\text{Background and attenuation corrected ventricular activity}}{\text{Activity concentration of peripheral blood}}
\]

Therefore, LVEDV was calculated from background-corrected count rate at end-diastole, count rate per 1 ml of peripheral blood corrected for decay, and the depth of the left ventricle in the body to correct for tissue attenuation (Figure 2.2.3.7) assuming that the effective linear attenuation coefficient of intervening tissues was equal to that of water (\(\mu = 0.15 \text{ cm}^{-1}\)). If \(d\) was the depth of the left ventricle from the
Absolute L.V. Volume.

\[
L.V.V. = \frac{\text{COUNT RATE OF L.V.} \cdot e^{-\mu d}}{\text{COUNT RATE / ml. OF BLOOD SAMPLE}}
\]

COUNT RATE OF L.V. = \frac{\text{TOTAL COUNTS OF L.V.}}{\text{TIME PER FRAME} \times \text{No. OF CYCLES}}.

\( \mu \) = LINEAR ATTENUATION COEFFICIENT OF WATER.

\( d \) = DEPTH OF L.V. FROM CHEST WALL.

\( e \) = EXPONENTIAL FUNCTION.

Figure 2.2.3.7

Formulae used in the calculation of absolute left ventricular volume from equilibrium radionuclide ventriculography.
skin in the left anterior oblique view so LVEDV could be calculated from the equation:

\[ LVEDV = \frac{\text{Count rate at end-diastole}}{\text{count rate/l ml of blood sample}} \]

Left ventricular depth (d) was calculated from the distance between the centre of activity of the skin marker and the centre of left ventricular activity in the anterior view divided by the sine of angle of acquisition. The count rate of left ventricular (LV) activity at end-diastole (ED) was obtained from the equation:

\[ \text{LV count rate at ED} = \frac{\text{Total counts of LV at ED frame}}{\text{time per frame x number of cardiac cycles}} \]

As the half life \( T_{1/2} \) of technetium-99m is relatively short (approximately 6 hours), the correction for decay of radioactivity was a fundamental step for the accuracy of the results. Correction for decay was calculated from the standard empirical formula:

\[ R_t = R_0 e^{-\left(\frac{0.693t}{T_{1/2}}\right)} \]

where (t) was the time period from the midpoint of blood sample counting period to the midpoint of the gated acquisition period, \( T_{1/2} \) was the half life of technetium-99m, \( R_t \) was the counts at time \( t \), and \( R_0 \) was the counts at time 0.

These cumbersome equations were integrated into an automatic programme which could read data directly from the gated study and produce absolute end-diastolic and end-systolic left ventricular volumes. Absolute left ventricular volume was measured in all patients and in 14 normal healthy
In addition, peak systolic blood pressure was divided by the end-systolic volume to produce pressure/volume index (P/V index). This index was calculated for both rest and exercise studies.

2.2.3.5.6 Velocity of circumferential fibre shortening

As described in the measurement of absolute left ventricular volume 2.2.3.5.5, the gamma camera records a bidimensional image of tridimensional radioactivity within the cardiac blood pool. Then the density of each picture element (pixel) in the resulting image matrix represents the activity of blood contained within the volume defined by the projections of the pixel area throughout the blood pool. Therefore, the count density represents the third dimension of the scintigraphic image which can be used to produce an index of left ventricular volume. Although, it was felt that it was essential to obtain ventricular volumes in absolute terms, these volumes were not used for the calculation of the velocity of circumferential fibre shortening (Vcf). Instead, a volume index was calculated from the total counts divided by the count density (Nickle et al, 1982) i.e. maximum counts per pixel to produce a normalised total counts (NTC). Then Vcf was computed automatically from NTC at end-diastole minus NTC at end-systole divided by NTC at end-diastole multiplied by the ejection time (Bhargava et al, 1982).

Theoretically, the calculation of Vcf was similar to that of ejection fraction but included the ejection time. The ejection time was
corrected for the isovolumetric phase which was 50 msec in our laboratory (Al-Khawaja et al, 1986a and b). As the ejection time and isovolumetric phase were shorter at faster heart rates during exercise, this correction was not necessary in the calculation of Vcf at maximal exercise. Velocity of circumferential fibre shortening was measured in all patients and in 10 healthy normal volunteers.

2.2.3.5.7 Equilibrium pulmonary blood volume ratio

The measurement of pulmonary blood volume ratio (PBVR) from equilibrium radionuclide angiography was first reported by Okada et al, (1979). It was thought that PBVR was a good indicator of left ventricular dysfunction, increased left ventricular end-diastolic pressure and the severity of coronary artery disease. An attempt was made to calculate PBVR by selecting a region-of-interest over the lung avoiding major vascular structures. Pulmonary blood volume ratio was calculated from the average counts of lung region-of-interest at maximal exercise divided by the average counts of a similar region of lung at rest. Rest and exercise studies were corrected for differences in acquisition time by dividing the average counts by the time per frame multiplied by the number of cardiac cycles (Al-Khawaja et al, 1987a). In different cases, the counts of lung region-of-interest were expressed as a function of time to exclude count fluctuation due to the inclusion of part of the blood pool or any vascular structure (Al-Khawaja et al, 1988c). In those cases, the region-of-interest was repositioned in a way that avoided count fluctuation (Figure 2.2.3.8).

Pulmonary blood volume ratio was measured in all patients and in 62
Figure 2.2.3.8

Equilibrium Pulmonary Blood Volume Ratio: Note the fluctuation of counts (left), due to the inclusion of vascular structures, which disappeared after repositioning the region of interest (right).
normal healthy volunteers to establish a normal range.

2.2.4 Thallium-201 myocardial perfusion scintigraphy

2.2.4.1 Bicycle exercise testing

After arrival in the scanning room, patients had an intravenous cannula inserted in the forearm just before the exercise test. The same ergometer used for equilibrium radionuclide ventriculography (EDC-8450) was employed for thallium-210 exercise testing. Graded, upright exercise was performed and the electrocardiogram was monitored continuously using bipolar CM5 and CC5 leads. The blood pressure was measured at rest and every three minutes during exercise using a standard cuff and mercury-in-glass sphygmomanometer. Work-load was started at 25 Watts and automatically increased by 25 Watts every 3 minutes until chest pain, dyspnoea, leg fatigue or ST-segment depression equal or greater than 4 mm developed. ST-segment change was measured at J+60 msec. At peak exercise, 74 MBq (2mCi) of thallous chloride was injected through the indwelling cannula and patients were encouraged to continue the exercise for at least an additional 30 seconds.

2.2.4.2 Thallium-201 imaging

The same single crystal, mobile gamma camera used for equilibrium radionuclide ventriculography, was employed for thallium-201 imaging. The camera's detector was set at 68 KeV focused at the photopeak of thallium-201 with an energy window of 15%. The camera was equipped with a low-energy, high-resolution, parallel-hole collimator. Imaging was
commenced within 5 minutes after injection of the tracer with the patient in the supine position in the anterior projection, and followed by 45° left anterior oblique projection. While patients were in the lateral decubitus position, a further view was performed in the left lateral projection, (Al-Khawaja et al, 1987c) Imaging was repeated in the same order 3-4 hours after thallium-201 administration. Acquisition of data was stopped after collection of 300,000 counts in each view and data was stored in a 128x128 matrix on a dedicated computer (O'Hara et al, 1985).

2.2.4.3 Quantitative heart/lung ratio

Quantitative analysis of lung thallium-201 concentration was performed semi-automatically as described by Lahiri et al, (1984). The colour scale of the monitor was used to produce computer-generated regions-of-interest at maximal count density over the myocardium and lungs. The average counts per pixel in the myocardial region-of-interest was divided by the average counts per pixel in the lung region-of-interest to produce a heart-to-lung ratio. The programme allowed operator intervention to alter the size or site of regions-of-interest according to the maximal count density (Al-Khawaja et al, 1987b). Heart-to-lung ratio analysis was carried out on both exercise and delayed thallium-201 images (Figure 2.2.4.1). In addition, the average counts of lung region-of-interest after stress was divided by the average counts in the delayed image to produce thallium washout index over a fixed period of time (Al-Khawaja et al, 1988b).
Figure 2.2.4.1

Quantitative Thallium-201 Heart/lung ratio: Increased concentration of tracer in the lungs immediately after exercise with slow washout in the delayed image.
2.2.4.4 Qualitative thallium analysis

Thallium images after stress and delayed images were examined for image quality, gross perfusion defects, gross redistribution, high right ventricular uptake and uniformity of left ventricular distribution (Figure 2.2.4.2).

The left ventricular myocardium was divided into five segments; anterolateral wall, inferior wall, apex, septum and posterolateral wall. Visual scoring was carried out by allocating '1' for a visualized segment and '0' for an absent or equivocal segment. Therefore, if all segments were seen then a score of '5' would be given and if only two segments were seen then a score of '2' would be given, etc. The presence of gross redistribution or reversible ischaemia was indicated if the score changed from a lower to a higher value in the delayed images. If the score remained unchanged and it was less than '5', then the presence of 'scar' or fixed perfusion defects due to infarction was indicated.

In addition, the left ventricular myocardium was outlined manually in the anterior view from both the stress and delayed images. The area of the myocardial silhouette after stress was divided by that in the delayed image to produce an exercise/rest thallium index. This attempt aimed at producing an index of left ventricular dilatation induced by maximal exercise (Weiss et al, 1987; Al-Khawaja et al, 1988c).
Figure 2.2.4.2

Qualitative Thallium-201 Analysis:
Anterior view: Perfusion defects in the apex and inferior wall with redistribution of tracer
LAO view: Perfusion defects in the inferior wall with redistribution
Left Lateral view: Perfusion defects in the inferolateral wall with redistribution.
2.2.4.5 Quantitative thallium analysis

The first step in the computer processing was to separate myocardial activity from the non-cardiac tissue i.e. background activity. Tissue 'crosstalk' is not uniformly distributed across the myocardium and cannot be removed by subtracting a constant background value from the myocardial images. Interpolative background subtraction techniques provide an adequate method for removing the non-cardiac tissue 'crosstalk'.

After nine-point-smoothing, each image was compensated for extra-cardiac activity by performing a bilinear interpolative background subtraction as developed by Goris et al, (1976) and modified by Watson et al, (1981). For this purpose, a circular region-of-interest was placed around the heart approximately 4 pixels from the visual edge of the myocardium. Within this boundary region, a cardiac background image was generated and subtracted from the smoothed images. The background subtraction procedure was applied to the immediate post-exercise (stress) images as well as the delayed (redistribution) images. Thus all images were corrected for their individual background contributions. The centre of the circular region-of-interest was positioned at the centre of the left ventricular cavity to correct for changes in patient position between the stress and delayed images. The computer next generated angular profiles of the myocardial distribution of activity in a manner similar to that proposed by Vogel et al (1978) and Burow et al (1979). Angular profiles were generated by sampling the myocardial activity along 60 radii spaced at 6 degree intervals in a clockwise fashion from the region-of-interest compass direction. The average
value of myocardial activity along each radius was obtained. The angular profiles were thus able to quantitate segmental myocardial activity as an angular function from the visually located centre of the left ventricle. Each profile was then plotted as a 60 point corresponding to the position of the compass and the middle points to the cardiac apex. The position of the cardiac apex was adjusted accordingly by visual judgement and individual profiles were generated for each of the three views both for the stress and delayed images. The resulting histograms represented the relative distribution of thallium-201 activity in different segments of the myocardium and the absolute thallium activity in corresponding segments in the immediate post-exercise and redistribution images (Al-Khawaja et al, 1987c).

In order to compare the patient's profiles with normal limits, the redistribution histograms were normalized to the same standard time delay after injection. The actual time at which the delayed images were obtained was used to interpolate the redistribution profiles to the standard delay interval which was 240 minutes. That was done for each patient by assuming a monoexponential washout of thallium-201 from the myocardium (Okada et al, 1982) between the stress and delayed imaging.

In addition to angular stress and redistribution thallium-201 profiles, an angular washout profile was calculated as the percent washout from the stress to the standard delayed profiles (Figure 2.2.4.3).

Abnormal thallium-201 distribution and washout were identified by comparing each patient's profiles with corresponding lower limits of normal which were determined by accumulating data from individuals with
Quantitative Thallium-201 Analysis: Typical report demonstrating circumferential and angular profiles of the three views (Anterior, LAO and Left lateral) compared with the lower limits of normals.
low likelihood of coronary artery disease. The mean and standard
deviation of thallium distribution and washout in each segment for all
three views was obtained from the pooled data of normal subjects. The
threshold value of 2.5 standard deviations below the normal mean was
pooled data was provided by the manufacturer of the computer software
(Elscint) and included 18 subjects with low probability of coronary
artery disease (11 male, 7 females; mean age 52±13(SD) years). All the
individuals had no known risk factors and a normal rest and exercise 12-
lead electrocardiogram. A stress defect on the post-exercise profile
was defined as at least three adjacent points (an 18° arc from three
consecutive radii i.e triplet) below the lower limit of normal for the
stress distribution profile. A slow washout defect on the washout
profile was defined as at least three adjacent points (18° arc) below
the lower limit of normal for the washout profile. The extent of an
abnormality was defined as the width in degrees between the starting
and ending points of the abnormal segment. The severity of a defect was
a measure of the intensity of the defect i.e how much it deviated from
the lower limit of normal. To be considered abnormal a patient should
have at least two abnormal 18° segments in the combined stress and
washout profiles in three views.

In addition, the stress histograms were superimposed onto the washout
histograms for each view to assess the degree of redistribution in all
segments. The circular region-of-interest around the left ventricle was
automatically segmented into three sections for each image excluding the
valve plane. The percentage change in counts in each subsegment was
calculated from stress and redistribution images and the results were
presented in a 'minus' or 'plus' format. Normal washout of each segment
was considered to be present if the change was greater than -20%. Significant redistribution was considered to be present if the change was greater than +20%. When the percentage change in counts was within ± 20%, the segment was considered equivocal and other parameters were needed to identify the state of distribution and washout. The histogram of each view was labelled with the corresponding myocardial segment and coronary artery to allow easy interpretation.

2.2.5 Cardiac catheterization

Cardiac catheterization was performed within two weeks of the radioisotopic studies. Patients were admitted to hospital the day before the procedure and had a full blood count, blood chemistry, ABO grouping and chest X-Ray. Patients gave informed consent to undergo cardiac catheterization and coronary angiography. The groin was prepared by removing the pubic hair and patients had night sedation. Diazepam 10 mg by mouth was given the following morning before sending the patient to the catheterization laboratory.

2.2.5.1 Left heart catheterization

Patients were positioned on the fluoroscopic table and under complete aseptic conditions, the right groin was exposed and the inguinal ligament identified. An intradermal wheal of 1% lignocaine was raised slowly over the pulsation of the right femoral artery using a 25-gauge needle. Transverse skin puncture was made over the femoral artery using the tip of a number 11 scalpel blade and further infiltration of deeper tissues with 1% lignocaine was carried out.
The femoral artery was cannulated by inserting a Seldinger needle and a 145 cm J-guide wire was then advanced carefully through the needle to the level of the diaphragm. The needle was then removed and an 8 Fr sheath was introduced over the guide wire, following which the wire was removed and the sheath was aspirated, flushed and connected by its sidearm to a manifold for monitoring arterial pressure. A pigtail left heart catheter was then flushed and loaded with a 145 cm J-guide wire and introduced into the backbleed valve of the sheath. The soft end of the guide wire was then advanced carefully through the catheter to the level of the diaphragm before the catheter itself was advanced. The guide wire was then removed and the catheter was connected to the arterial manifold and double flushed with heparinized saline solution. Full intravenous heparinization with 5000 units was established immediately after the left heart catheter was inserted. Pressures from the ascending aorta and left ventricle were recorded. Left ventriculography was performed by injection of Renografin from a power injector. Continuous fluoroscopic monitoring and recording of results on cine film were carried out in the 30° right anterior oblique projection.

2.2.5.2 Coronary arteriography

At the end of ventriculography, the pigtail catheter was withdrawn, and the sheath was immediately double flushed. A size 8 Fr Judkins' coronary catheter with end-hole design was used for cannulation of the left and right coronary arteries. The catheter was advanced to a point just above the diaphragm with a guide wire in place. The guide wire was
then removed, and the catheter was attached to a specially designed manifold system which permitted the maintenance of a 'closed system' during pressure monitoring, catheter flushing, and contrast agent administration. Left coronary cannulation was performed using a left Judkins' catheter with a 4 cm curve (JL 4). The right Judkins' catheter (JR 4) with a 4 cm curve was used for right coronary cannulation. Contrast media was injected into each coronary artery under continuous pressure monitoring and fluoroscopic imaging was carried out in the anteroposterior, right anterior oblique and left anterior oblique projections.

At the termination of the cardiac catheterization, heparin was reversed by the administration of protamine (10 mg for every 1000 U of heparin) and possible adverse reactions were observed. The catheter and sheath were removed, and firm manual pressure was applied at skin puncture over the femoral artery for at least 15 minutes. The puncture site and surrounding area were then inspected for haematoma formation and active oozing, and the quality of the distal pulses was assessed before the application of a bandage. Patients were transferred to the ward and kept on bed rest with the leg straight overnight. Before full ambulation, the puncture site was again inspected for recurrent bleeding, haematoma formation, development of bruit or loss of digital pulses.

2.2.5.3 Scoring of coronary artery lesions

Left ventricular angiograms and coronary arteriograms were reported 'blind' by two independent and experienced observers. The assessment of
myocardial contractility and wall motion was carried out visually. A special scoring system was developed for the purpose of this study. The score was considered '0' if no abnormality was seen throughout the course of an artery. A score of '1' was considered if the lesion caused less than 70% obstruction in any of the major coronary arteries or less than 50% obstruction of the left main stem. A score of '2' was considered if the obstruction produced 70% or more intraluminal narrowing of a distal segment of any of the major coronary arteries. Lesions producing 70% or more intraluminal narrowing of a proximal segment of a major coronary artery or 50% or more of the left main stem were allocated a score of '3'. When the coronary artery was completely blocked (100% obstruction), then a score of '4' was allocated. The scores were given to each major coronary artery i.e. left anterior descending, left circumflex and right coronary arteries, in addition to the left main stem. The presence of collateral circulation and retrograde filling was also noted. When there was a significant difference between the reports of the two observers, a consensus was reached by collaboration.

Patients were then grouped into those with one vessel disease (1VD), two vessel disease (2VD) and three vessel disease (3VD) according to the number of diseased vessels.

2.2.6 Statistical analysis

2.2.6.1 Data presentation and normal range

Continuous data were recorded as a mean ±SD (standard deviation) or
mean±SEM (standard error of the mean). To determine differences between means of independent observations in patient subgroups, one-way analysis of variance and/or unpaired Student's test were performed. In addition, two-tailed paired Student's test was used when relevant. For non-continuous variables and categorical factors, chi-square analysis was performed. Linear regression analysis using least-squared models was used to assess the association of different variables. Normal ranges obtained from healthy volunteers were recorded as the mean ±2SD, (Threshold = 2SD). Differences between the means of variables in healthy subjects and patients were assessed by unpaired Student's t-test.

Sensitivity was defined as the ability of the test to identify those who have the disease. Specificity was defined as the ability to identify those who do not have the disease. The positive predictive value was defined as the degree to which a positive test confirms the diagnosis. The negative predictive value was defined as the degree to which a negative test excludes the diagnosis. The accuracy of the test was all the correct outcomes divided by the total number of tests done.

2.2.6.2 Multivariate analysis

Multivariate (multiple linear regression) analysis was performed using the generalised linear interactive system (GLIM, Royal Statistical Society, 1986). GLIM is a program specially designed to facilitate the fitting of generalised linear models (GLMs). It contains a kernel concerned with specifying and fitting GLMs, together with facilities for reading in data, transforming them, and displaying the results. It uses a simple and powerful interpretive language which allows blocks of
instructions to be named as GLIM 'macros'. The addition of branching and looping instructions acting on macros produces a programming language of considerable generality suited for describing and manipulating more complex analytical techniques. GLIM can be used to explain the variations in a response (or y-) variable in terms of variations in certain explanatory variables. In addition to this response-explanatory distinction, there is the classification of a variable into different data types. These include continuous, count, proportion and categorical types. GLIM expects to find the data for analysis in the form of a data matrix. This is a two-dimensional structure indexed by units and variables. Units is the neutral name adopted to cover the patient population which represents the rows of data matrix. The columns are the variables which are obtained from the investigational procedures carried out in this study. GLIM itself does not distinguish between continuous, count or proportional type of data and regards them all as vectors. However, categorical factors must be declared explicitly, and their level may only be coded as 1, 2, 3 etc.

A data matrix is defined when the number of rows (Units), and the names and types of (variates or factors) the variables in each column are known. GLIM is primarily a tool for fitting a certain class of generalised linear models to data. The modelling process may be thought of as one in which the data e.g. $Y_1, Y_2, \ldots Y_n$ are matched by a set of theoretical values e.g. $U_1, U_2, \ldots U_n$. For a good model the $U$s must have the following properties:

i. They are all derived from a small number of basic quantities called parameters, and
ii. The resulting set of U's is close to the original data, the Y's. Thus the U's are highly patterned and therefore easier to understand and think about than the Y's, which will be 'rough' by comparison.

The model fitting process involves two basic decisions:

i. The choice of the relation between the U's and the underlying parameters of the model, and

ii. The choice of a measure of discrepancy which defines how close a given set of U's is to the data.

The first relates to the systematic component of the model, and the second is governed by assumptions we make about the random component. The latter is a statistical description of that part of the variation which the systematic component does not account for.

In the generalized linear models, the systematic component is assumed to take the following two-stage form for each unit:

i. The linear predictor

ii. The link function

The random component in the generalised linear models allows each Y to have a distribution with mean U from an exponential family. This includes the Normal distribution (suitable for many continuous Y-variables), the binomial distribution (suitable for models for proportions), plus the gamma, negative binomial, and the inverse
Gaussian distributions.

To specify a generalised linear model, we have to define:

i. The terms to be included in the linear predictor.

ii. The link function connecting the linear predictor to the theoretical values.

iii. The distribution for the random component.

GLIM can then fit the model, by choosing as estimates of the parameters those values which minimize the discrepancy, called in GLIM the 'deviance'. The actual form of the deviance depends upon the distribution assumed.

The deviance is simply the residual sum of squares about the regression line, which has been chosen to minimize this residual sum, and is a measure of how closely the linear regression model fits the data. The number of degrees of freedom indicates how much information is available for estimating the 'background noise' with the residual variance (which is the deviance divided by the number of degrees of freedom). Degrees of freedom is the number of observations (units) used in the model fitting less the number of parameters in the fitted model.

Multivariate analysis was applied to the following variables using GLIM:

1. Exercise time (min) obtained from treadmill testing
2. Peak exercise heart rate (bpm)
3. Peak exercise systolic blood pressure (mmHg)
4. ST-segment depression during exercise: present or absent
5. ST-segment elevation during exercise: present or absent
6. Resting left ventricular ejection fraction (%)
7. Percentage change of left ventricular ejection fraction (LVEF) on maximal exercise: (exercise LVEF - rest LVEF)/rest LVEF
8. Resting left ventricular peak filling rate (EDV/sec)
9. Resting left ventricular normalized filling fraction
10. Resting left ventricular end-diastolic volume (ml)
11. Percentage change of end-diastolic volume (EDV) on maximal exercise: (exercise EDV - rest EDV)/rest EDV
12. Resting right ventricular ejection fraction (%)
13. Percentage change of right ventricular ejection fraction (RVEF) on maximal exercise: (exercise RVEF - rest RVEF)/rest RVEF
14. Total regional wall motion score
15. Exercise thallium-201 scores
16. Delayed thallium-201 scores
17. Thallium-201 redistribution
18. Exercise heart/lung ratio
19. Coronary artery disease scores: single or multiple vessel disease
20. Prognosis: no cardiac events, minor events or major events

2.3 EXPERIMENTAL WORK

The experimental work discussed here is mainly concerned with the instrumentation and application of radioisotopic studies in post-myocardial infarction patients. The digital gamma camera which was employed in all patient’s studies had the facility to perform self-checking on all the electronics involved in data acquisition and
storage. The photomultiplier tubes were regularly checked for high voltage-gain characteristics and their individual variability in precisely amplifying input signals of a given size by the same relatively constant factor. Energy resolution was checked daily since it affects overall instrument spatial resolution. The analyzer window was usually set symmetrically on the photoelectric peak as this would improve flood field uniformity of the detector. Spatial resolution was checked by full width at half maximum of the line spread function and modulation transfer function. System uniformity was assessed by flood field imaging without collimator. Non-linearity was corrected using a bar phantom. Adequate quality control was achieved by regular calibration of single-channel pulse-height analyser, uniformity, linearity and sensitivity of the system.

2.3.1 Image calibration

Data acquisition was performed without magnification or minification (zoom=1). However, the image structure was made up by picture elements (pixels) which could be determined by selecting the appropriate frame size. In order to calibrate the screen in terms of absolute dimension, two point sources made of Cobalt-57 (Co-57) were placed 10 cm apart on top of the camera’s head. Acquisition was carried out using the most frequent frame size applied in patient’s studies: 64 x 64 matrix, 128 x 128 matrix and 256 x 256 matrix. After nine-point smoothing, a cross sectional image profile histogram displaying count distribution in each of the three frames was produced. The distance (in pixels) between the two count peaks in the image profile represented the equivalent of 10 cm distance between the two point sources, which was 30 pixels for 64 x 64,
60 pixels for 128 x 128 and 120 pixels for 256 x 256 frame sizes. Therefore, the actual pixel dimension was 0.333, 0.167 and 0.083 cm respectively.

2.3.2 Measurement of linear attenuation coefficient

The effective linear attenuation coefficient of gamma photons was considered similar to that of water ($\mu=0.15/cm$). This was justified on the basis of water's similarity to blood and soft tissue (Links et al, 1982). Although lung tissue, which is less dense than water, is in the path of photons from the left ventricle; bone, which is denser than water, is also in the path, tending to make the effective linear attenuation coefficient close to that of water. However, the theoretical value of the linear attenuation coefficient ($\mu=0.15/cm$) is applied to the attenuation of a narrow beam of photons passing through an infinitely thin section of water, which is different in the case of patient studies, where there is a bulk source of photons located some distance from the camera detector. In this condition some photons would be expected to undergo multiple scatters and be directed back towards the detector altering the effective linear attenuation coefficient. To test this hypothesis, linear attenuation coefficient was measured using a bulk source of 140-KeV photons of technetium-99m. A heart phantom made of a flask contained 100 ml of technetium-99m solution (5 uCi/ml) was placed 15 cm in front of a parallel-hole, low energy collimator, and counted for one minute. Successively, perspex sheets, of one centimeter thickness, were placed between the flask and the collimator, and counting was performed for 1 minute in each data acquisition. A stopwatch was used to record the precise time of each image. Correction
of counts in each image for decay of radioactivity was thought to be essential as the half life ($T_{1/2}$) of technetium-99m is relatively short (360 minutes). Manually drawn regions of interest of fixed size were used to obtain the total counts in each image and the counts were then corrected for decay. Results were plotted against perspex thickness on a linear and semi-log graph papers. The effective linear attenuation coefficient was calculated from the slope of the curve.

2.3.3 Phantom studies

The object of phantom studies was to provide validation of the theoretical principles when applied to simpler models and to demonstrate that the count rate of a specific volume was directly proportional to changes in this volume for a specific activity and concentration of the radioactive tracer.

A container with 600 ml of water was used to prepare a solution resembling the 'blood pool'. Technetium-99m was added to the water in the container in the form of Tc-pertechnetate 3mCi (111 MBq) producing a concentration of 5uCi/ml. Several samples were taken from the container and placed in different tubes of known volumes 1, 20, 60, 80, 100, 120 and 200 ml. These were imaged by the same camera/computer system used in the patient studies (Elscint). Acquisition of data was terminated after 2 minutes for each image and data was stored in a 64x64 matrix. A thin 1 ml diabetic syringe was used to image the 1 ml sample to mimic the 'peripheral blood sample' acquisition and the count/ml/sec was obtained. Regions of interest were drawn manually for each image and the count rate of each 'volume' was obtained. Relative volumes were
generated by dividing the count rate of each image by the count rate of 1 ml of the solution.

2.3.4 Measurement of left ventricular volume

The technique used for the measurement of absolute left ventricular volume was described in detail in section 2.3.3. In order to demonstrate the linearity of these measurements with values obtained from contrast ventriculography, 15 additional patients were studied with equilibrium radionuclide angiography within 2 weeks of cardiac catheterization. Contrast ventriculography was performed using techniques described in section 2.3.5, and images were recorded in a cine format in 30° right anterior oblique projection. A special scale of 10 cm length made of 0.5 mm lead was placed on the precordium prior to the injection of contrast media and imaging was performed for 5-10 frames. This was used for calibration purposes to correct for magnification of non-parallel X-ray beams. The film was replayed on a screen and end-diastolic and end-systolic frames were identified after the first injection of contrast media. The outline of end-diastole and end-systole were drawn manually on graph paper and the magnification factor was recorded. Care was taken to avoid extra-systolic cycles and those occurring immediately after an extra-systolic contraction. Planimetry was performed by computer to determine the end-diastolic and end-systolic area after correction for magnification (Kennedy et al, 1970). The long axis was measured manually as the distance between the root of aortic valve and the cardiac apex. Left ventricular volume (LVV) was then calculated from the ellipsoidal formula:
where L is the longest measured length (long axis), D is the short axis as derived from the long axis and planimetered area of the ventricle (A) and CF is the linear correction factor. Left ventricular short axis was calculated from the formula: \( D = \frac{4A}{\pi L} \). These measurements were performed from single plane contrast ventriculography (Dodge et al, 1960 and Sandler et al, 1968).

Linear regression analysis was performed between left ventricular volumes measured by the two techniques. In addition, the difference between the means was assessed by one-way analysis of variance and Student's t-test. The difference between individual measurements in each patient was plotted against the average of the two measurements (Altman et al, 1983; Bland et al, 1986).

2.3.5 Normal values of left ventricular function

In order to establish a normal range, mean value and standard deviation of continuous variables of ventricular function, a group of normal subjects, of either sex, volunteered to undergo equilibrium radionuclide ventriculography at rest and during maximal bicycle exercise. All the normal subjects had no history of cardiovascular symptoms, normal 12-lead electrocardiogram at rest and maximal exercise with low pre-test likelihood of coronary artery disease. Some of these 'normal subjects' were studied specifically for the purpose of this study, while others were part of the Department's bank of normal studies. The normal range for the systolic and diastolic function measurements for both the left
and right ventricle was obtained from 50 normal subjects at rest and
during exercise. Equilibrium pulmonary blood volume ratio was
successfully calculated in 62 normal studies. Absolute left ventricular
volumes, end-systolic pressure/volume ratio and velocity of
circumferential fibre shortening were obtained from 14 normal subjects
as part of this study.

Normal values of thallium-201 uptake, washout and redistribution were
obtained from a database of 18 normal subjects provided by the
manufacturer of the software (Elscint). In addition, lung thallium-201
uptake was quantitated in 14 normal subjects whose studies were part of
the department's bank of normal studies. The upper and lower limits of
normal values were taken as the mean ± 2.5 SD as recommended by the
manufacturer.

2.3.6 Reproducibility studies

The analysis of ventricular variables were repeated by another
experienced operator in a group of normal subjects and patients (n=30)
in order to confirm the reproducibility of these variables. Neither of
the two operators was aware of the results obtained by the other.

The scoring of coronary artery lesions was performed (blind) by two
experienced independent observers without the knowledge of any clinical
or non-invasive parameters. Where the two scores were differed the
observers reviewed the coronary arteriogram together and reached a
consensus opinion.
For continuous variables, multiple measurements were assessed for differences by one-way analysis of variance and Student’s t-test. In addition, the mean difference, and standard error of the mean difference were obtained.
CHAPTER 3

RESULTS
3. RESULTS

3.1 DEMOGRAPHIC AND CLINICAL DATA

The study population consisted of 105 consecutive patients admitted to the coronary care unit at Northwick Park Hospital over a one year period starting in March 1985. All the patients fulfilled the entry criteria with a definite diagnosis of acute myocardial infarction. There were 93 men and 12 women with an age range of 38-75 years (mean 56±8.2 years). Among these, 10 patients were younger than 45 years, 74 patients were between 45 and 65 years and 21 patients were older than 65 years (Figure 3.1.1). There were 72 Caucasian, 29 Asian and 4 Negro patients (Figure 3.1.2).

Thirty two patients had no history of cigarette smoking, 17 were ex-smokers, 36 smoked less than 20 cigarettes per day and 20 smoked more than 20 cigarettes per day (Figure 3.1.3). A history of diagnosed essential hypertension was present in 32 patients, and diabetes mellitus in 14 patients. Twelve patients had both essential hypertension and diabetes mellitus before the acute episode of myocardial infarction.

Sixty seven patients had no previous history of ischaemic heart disease and 19 patients had angina pectoris of more than 3 months duration prior to the myocardial infarction. In addition, 11 patients had a history of a single myocardial infarction, and 7 patients had multiple myocardial infarctions in the past. Only one patient had a history of coronary artery bypass graft operation (Figure 3.1.4). There was a family history of ischaemic heart disease (angina pectoris, myocardial
Age distribution in M.I. patients (years)

(\(n = 105\))

- 29.5% (45 - 54)
- 9.5% (< 45)
- (55 - 65) 41.0%
- 20.0% (> 65)

Figure 3.1.1

Age distribution (%) in patients with myocardial infarction
Myocardial infarction study
(n = 105)

Caucasians 68.6%
3.8% Negroes
27.6% Asians

Figure 3.1.2
Racial distribution (%) in study population.
Smoking habit in M.I. patients
(n = 105)

Ex - Smokers 16.2%

< 20 Cig / day 34.3%

30.5% Non - Smokers

19.0% ≥ 20 Cig / day

Figure 3.1.3

Cigarette smoking pattern in study population.
History of CAD before M.I.
(n = 105)

None 67.00

1.00 Bypass surgery

7.00 Multiple infarcts

11.00 Single infarction

Stable angina 19.00

Figure 3.1.4

History of coronary artery disease (CAD) prior to the acute episode of myocardial infarction (M.I.).
infarction, congestive heart failure, cardiac death) in 42 patients (40%).

According to the electrocardiographic criteria, 48 patients were deemed to have acute transmural anterior infarction, 45 patients transmural inferior infarction, and 12 patients subendocardial (non Q-wave) infarction (Figure 3.1.5). Non-fatal cardiac arrest (ventricular asystole, fibrillation or tachycardia) occurred in 12 patients and 2 others required temporary pacing for profound bradycardia and conduction disturbance.

Seventy one patients (67.6%) were in Killip class I (Killip et al, 1976) on admission to the coronary care unit and Killip class II in 34 patients (32.4%) (Figure 3.1.6). The Norris coronary prognostic index (CPI) was calculated in all patients on arrival to the coronary care unit. Thirteen had a CPI less than 4, 62 had a CPI between 4 and 8, and 30 had a CPI more than 8 (Norris et al, 1970).

On discharge from the hospital, 39 patients were receiving no cardiac medication except short acting nitrates as required. Eight patients were receiving long acting nitrates (oral or buccal), 13 were on calcium antagonists, 13 were on beta-adrenergic blockers and 32 were on combination therapy. There was no change in this therapy during the following 6-8 weeks and the patients continued receiving the same medication during the non-invasive and the invasive investigations. Patients were followed-up for an average period of 18.8±3.4 months (range 12-24 months).
Myocardial infarction site

\( n = 105 \)

45.7% Anterior M.I.

11.4% Subendocardial M.I.

Inferior M.I. 42.9%

**Figure 3.1.5**

Myocardial infarction (M.I.) site in study population.
Killip classification
C.C.U. ( n = 105 )

Class I 67.6%

32.4% Class II

Figure 3.1.6

Killip classification during the acute phase in the coronary care unit.
3.2 GRADED EXERCISE ELECTROCARDIOGRAPHY

The mean total exercise time was 8.5±4.1 minutes (range 0.6-20 minutes). Exercise was terminated because of angina pectoris in 25 patients, dyspnoea in 24 patients, self-limiting ventricular tachycardia in 3 patients and exercise-induced systolic hypotension (fall of more than 20 mmHg) in 7 patients. The remaining patients were either asymptomatic or stopped with leg fatigue.

Male patients showed a significantly greater exercise tolerance (8.82±3.99 minutes) compared with females (5.53±3.71 minutes; P<0.01) (Figure 3.2.1). There was no difference in exercise time between patients with anterior infarction (8.22±3.95 minutes) and patients with inferior infarction (8.74±4.1 minutes; P=NS). Similarly, there was no difference in exercise time between patients with transmural and subendocardial infarction. The exercise time was significantly shorter in hypertensive patients (6.54±3.19 minutes) compared with normotensive patients (9.35±4.2; P<0.001) (Figure 3.2.2). ST-segment horizontal or downsloping depression (more than 1 mm) was seen in 53 patients, ST-segment elevation was seen in 13 patients and non-significant changes in 39 patients. Five out of 53 patients with ST-segment depression showed simultaneous ST-elevation in other leads. There were no significant differences in exercise time between patients with non-significant ST-segment changes (9.35±4.63 minutes) compared with patients with significant ST-segment depression (8.5±3.44 minutes; P=NS) and ST-elevation (6.8±3.75 minutes; P=NS) (Figure 3.2.3). Similarly, there was no significant difference in exercise time between patients with ST-segment depression and elevation (Figure 3.2.4).
Figure 3.2.1

Treadmill exercise time in men and women patients postmyocardial infarction.
Figure 3.2.2

Treadmill exercise time in hypertensive patients compared to normotensive patients.
Figure 3.2.3

Treadmill exercise time in patients following myocardial infarction: The effect of ST-segment shift on exercise duration.
Figure 3.2.4

The effect of ST-segment shift on treadmill exercise duration.
Exercise-induced systolic hypotension greater than 20 mmHg was seen in 7 patients. A normal blood pressure response was seen in the remaining 98 patients. The total exercise time was significantly shorter in the patients who developed hypotension (5.27±4.8 minutes) compared with the patients who had a normal response (8.79±3.98 minutes; P<0.05) (Figure 3.2.5).

The total exercise time in the patients who had fixed perfusion defects on thallium-201 myocardial scintigraphy (n=26) was 9.04±4.61 minutes; this was not significantly different from that in patients with evidence of reversible ischaemic defects (n=75; 8.2±3.98 minutes; P=NS) (Figure 3.2.6). The resting heart rate - blood pressure product (double product = heart rate x systolic pressure/1000) was higher in the patients with fixed perfusion defects (11.46±3.47) compared with patients with reversible defects (9.98±2.63; P<0.05) (Figure 3.2.7). At peak exercise, the double product was significantly different in the patients who had fixed perfusion defects (25.2±7.65) compared with those with reversible defects (20.38±5.14; P<0.001) (Figure 3.2.8). Similarly, the gain in the double product was significantly higher in patients with fixed defects 13.71±5.78) compared with those with reversible defects (10.37±4.66; P<0.005) (Figure 3.2.9).

The exercise tolerance of the patients who had single vessel disease was 9.24±4.14 minutes, which was not significantly different from that of patients with multiple vessel disease (7.78±3.9 minutes; P=NS) (Figure 3.2.10). The resting, exercise and the gain in the double product were not different in the two groups (Figures 3.2.11, 3.2.12, 3.2.13). Linear regression analysis revealed a poor correlation between the total
Figure 3.2.5

Treadmill exercise duration in patients with exercise-induced hypotension compared to patients with normal blood pressure response.
Fixed perfusion defects (n=26)

Reversible ischaemic defects (n=75)

Figure 3.2.6

The effect of reversible ischaemic myocardium on exercise duration.
Fixed perfusion defects (n=26)

Reversible ischaemic defects (n=75)

Figure 3.2.7

The effect of reversible ischaemic myocardium on resting heart rate-pressure double product.
Figure 3.2.8

The effect of reversible ischaemic myocardium on exercise double product.
Figure 3.2.9

The effect of reversible ischaemic myocardium on the gain in double product during exercise.
Figure 3.2.10

The effect of multiple vessel disease on treadmill exercise duration compared to single vessel disease.
Figure 3.2.11

The effect of multiple and single vessel coronary artery disease on resting double product.
Figure 3.2.12

The effect of multiple and single vessel coronary artery disease on exercise double product.
Multiple vessel disease (n=46)

Single vessel disease (n=49)

Figure 3.2.13

The effect of multiple and single vessel coronary artery disease on the gain of double product during exercise.
exercise time and the resting double product (r=0.17). On the other hand, there was a significant positive correlation between the total exercise time and the gain in double product (r=0.59, P<0.001).

Patients were grouped into Group I (n=31) who were asymptomatic with no ST-segment depression, Group II (n=28) who stopped with angina and/or dyspnoea with a significant ST-depression, Group III (n=25) who were asymptomatic but had a significant (>1 mm) ST-depression and group IV (n=21) who were symptomatic with no ST-segment depression. The total exercise time in group III was 9.1±3.6 minutes which was not significantly different from group I (10±4.4) or group II (7.9±3.3) but was significantly different from group IV (6±4.1; P<0.01), (Figure 3.2.14).

Out of 53 patients with ST-segment depression, there were 31 patients with multiple vessel disease (sensitivity 59%). On the other hand, single vessel disease was seen in 30 patients out of 39 who showed no ST-segment change (specificity 77%).

3.3 GATED BLOOD POOL VENTRICULOGRAPHY

3.3.1 Image Calibration

From the cross sectional image profiles of two point sources, each 1 cm was equivalent to 3 pixels in 64 x 64 frame size, 6 pixels in 128 x 128 frame size and 12 pixels in 256 x 256 frame size. Thus, the absolute pixel dimension was 0.333, 0.167 and 0.083 cm respectively.
Total exercise capacity in patients' subgroups

Figure 3.2.14

<table>
<thead>
<tr>
<th>Patients' groups</th>
<th>Group I (n=31)</th>
<th>Group II (n=28)</th>
<th>Group III (n=25)</th>
<th>Group IV (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td>No ST-depression</td>
<td>ST-depression</td>
<td>No ST-depression</td>
<td>No ST-depression</td>
</tr>
</tbody>
</table>

P = N.S.  
P<0.01
TABLE 3.3.2

Relationship between perspex thickness and counts.

<table>
<thead>
<tr>
<th>Thickness (cm)</th>
<th>Total counts</th>
<th>Nt/No</th>
<th>Ln counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>118018</td>
<td>1.00</td>
<td>11.68</td>
</tr>
<tr>
<td>1</td>
<td>104065</td>
<td>0.882</td>
<td>11.55</td>
</tr>
<tr>
<td>2</td>
<td>90573</td>
<td>0.767</td>
<td>11.41</td>
</tr>
<tr>
<td>3</td>
<td>80228</td>
<td>0.680</td>
<td>11.29</td>
</tr>
<tr>
<td>4</td>
<td>66773</td>
<td>0.570</td>
<td>11.11</td>
</tr>
<tr>
<td>5</td>
<td>51856</td>
<td>0.493</td>
<td>10.97</td>
</tr>
<tr>
<td>6</td>
<td>48689</td>
<td>0.412</td>
<td>10.79</td>
</tr>
<tr>
<td>7</td>
<td>42436</td>
<td>0.360</td>
<td>10.66</td>
</tr>
<tr>
<td>8</td>
<td>35976</td>
<td>0.304</td>
<td>10.49</td>
</tr>
<tr>
<td>9</td>
<td>31307</td>
<td>0.270</td>
<td>10.35</td>
</tr>
<tr>
<td>10</td>
<td>26560</td>
<td>0.230</td>
<td>10.19</td>
</tr>
<tr>
<td>11</td>
<td>22707</td>
<td>0.192</td>
<td>10.03</td>
</tr>
</tbody>
</table>

Nt: Counts at time t
No: Counts at time 0
Ln: Natural logarithm
3.3.2 Linear attenuation coefficient

The total counts corrected for decay, the ratio of the counts at thickness $t$ relative to the counts at thickness 0 ($N_t/No$) and the natural logarithm ($Ln$) of counts are displayed in Table 3.3.2. There was an exponential reduction of the total counts with successive increments of perspex sheets (Figure 3.3.2.1). Similarly there was an exponential reduction of $N_t/No$ (Figure 3.3.2.2.). Linear regression analysis between the natural logarithm ($Ln$) of counts and the thickness of perspex sheets revealed a significant negative correlation (Figure 3.3.2.3). The slope of this curve was -0.1515 which represented the linear attenuation coefficient ($\mu$). This demonstrated that the theoretical value of $\mu$ (0.15) and the estimated value obtained from a bulk source of photons passing through a relatively thick layer of perspex were almost identical.

3.3.3 Phantom studies

There was a positive linear relationship between the total counts in each of the tubes and the actual volume ($r=0.99$; Figure 3.3.3.1). The total counts were normalised for the count density (maximum counts/pixel) to take into account the effect of the depth of any given volume (Table 3.3.3). Similar positive linear relationships were seen between the actual volume and the count density ($r=0.98$; Figure 3.3.3.2) and the normalised total counts ($r=0.91$; Figure 3.3.3.3). The mean difference between the actual and estimated volume was 11.6 ml. There was a tendency to over-estimate volumes when measured from the total counts using a simple dilution formula.
Figure 3.3.2.1

Calculation of the linear attenuation coefficient: The change in total counts with increasing thickness of perspex sheets.
Figure 3.3.2.2

Calculation of the linear attenuation coefficient:
Nt- Counts at thickness t; No- Counts at thickness 0.
The change in Nt/No with increasing thickness of perspex sheets.
Figure 3.3.2.3

Calculation of the linear attenuation coefficient:
Change of the natural logarithm of counts (Ln Cts) with increasing thickness of perspex sheets.
### TABLE 3.3.3

Relationship between actual volumes and counts.

<table>
<thead>
<tr>
<th>Actual volume</th>
<th>Total counts</th>
<th>Count density</th>
<th>Normalised counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1661</td>
<td>4</td>
<td>415</td>
</tr>
<tr>
<td>20</td>
<td>45024</td>
<td>29</td>
<td>1552</td>
</tr>
<tr>
<td>60</td>
<td>120335</td>
<td>59</td>
<td>2039</td>
</tr>
<tr>
<td>80</td>
<td>163674</td>
<td>72</td>
<td>2273</td>
</tr>
<tr>
<td>120</td>
<td>234663</td>
<td>94</td>
<td>2496</td>
</tr>
</tbody>
</table>
Phantom studies:
Relationship between the total counts and actual volumes.
Phantom studies:
Relationship between maximal counts/pixel (Max cts/pix) and actual volumes.
Phantom studies

Figure 3.3.3.3

Phantom studies:
Relationship between the normalized counts (cts) and actual volumes.
3.3.4 Validation of volume measurement

Linear regression analysis between end-diastolic volume measured by contrast angiography and radionuclide ventriculography showed a positive linear relationship ($r=0.97; \ P<0.0001$) (Figure 3.3.4.1). The mean difference was 2.20 ml and the standard error of the mean difference (SEMD) was 6.2 ml (Figure 3.3.4.2). Student's paired t-test showed no significant difference between the two groups. However, because of the difficulties in delineating left ventricular end-systolic contour and perhaps left atrial contribution to the total counts, there was a less significant positive correlation between end-systolic volume measured by the two techniques ($r=0.66; \ P<0.01$) (Figure 3.3.4.3). The mean difference was 29.8 ml and SEMD was 12.44 ml (Figure 3.3.4.4). Student's paired t-test showed a significant difference between the two groups of observations ($P<0.05$). Furthermore, a positive linear correlation was found between ejection fraction measurements by the two techniques ($r=0.74; \ P<0.002$) (Figure 3.3.4.5). The mean difference was 11% and SEMD was 2.65% (Figure 3.3.4.6). Student's paired t-test showed a significant difference between the two observations ($P<0.001$).

3.3.5 Reproducibility

When the analysis was repeated by the same observer there were no significant differences between the measurement of left and right ventricular indices. In a group of 30 patients, the analysis was repeated by another experienced observer. The mean difference in left ventricular ejection fraction at rest was 1.8% and the SEMD 0.935 (P=NS). There were no differences between the two measurements of
Validation of end-diastolic volume

Figure 3.3.4.1

Validation of end-diastolic volume:
Correlation between left ventricular end-diastolic volume measured by both radionuclide and contrast ventriculography.
Validation of end-diastolic volume

Figure 3.3.4.2

Validation of end-diastolic volume:
The difference of left ventricular end-diastolic volume measured by both radionuclide and contrast ventriculography plotted against the average of the two measurements.
Validation of end-systolic volume

Figure 3.3.4.3

Validation of end-systolic volume:
Correlation between left ventricular end-systolic volume measured by both radionuclide and contrast ventriculography.
Validation of end-systolic volume:
The difference of left ventricular end-systolic volume measured by both radionuclide and contrast ventriculography plotted against the average of the two measurements.
Validation of ejection fraction

Figure 3.3.4.5

Validation of ejection fraction:
Correlation between left ventricular ejection fraction measured by both radionuclide and contrast ventriculography.
Validation of ejection fraction:

The difference of left ventricular ejection fraction measured by both radionuclide and contrast ventriculography plotted against the average of the two measurements.
ejection rate, ejection time, peak filling rate, time to peak filling, normalised filling fraction and exercise ejection fraction (Table 3.3.5.1). However, there was a significant difference between the two observers in the measurement of resting right ventricular ejection fraction (P<0.0001). The mean difference was 7.87% and the SEMD 1.59%. Similar significant difference were seen in right ventricular ejection rate (P<0.02) and time to peak filling (P<0.0005). There were no differences in the measurement of other indices (Table 3.3.5.2). The mean difference in the measurement of absolute resting left ventricular end-diastolic volume was 9.97 ml and the SEMD 9.07 (P=NS). Similarly, there were no differences between the two measurements of end-systolic volume, P/V ratio, pulmonary blood volume ratio and left ventricular depth (Table 3.3.5.3). However, there was a significant difference in the velocity of circumferential fibre shortening (Vcf) (P<0.05) with a mean difference of 0.059 and SEMD 0.027.

3.3.6 Normal values

The normal range of both left and right ventricular indices was calculated from the mean±2SD. The mean (±SD) left ventricular ejection fraction at rest was 61(6.5)% which increased to 65(8.9)% at maximal exercise. Other left ventricular parameters are shown in Table 3.3.6.1. The mean resting end-diastolic volume was 186(72)ml and rose to 231(91)ml at maximal exercise. End-systolic volume at rest was 69(28)ml and rose to 74(31) at maximal exercise.

The mean right ventricular ejection fraction at rest was 44.2(8.12)%
TABLE 3.3.5.1

Reproducibility of left ventricular indices.

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>SEMD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.80</td>
<td>0.935</td>
<td>0.064 (NS)</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.83</td>
<td>1.14</td>
<td>0.472 (NS)</td>
</tr>
<tr>
<td>Ejection rate</td>
<td>0.001</td>
<td>0.04</td>
<td>0.987 (NS)</td>
</tr>
<tr>
<td>Ejection time</td>
<td>0.01</td>
<td>0.007</td>
<td>0.226 (NS)</td>
</tr>
<tr>
<td>Peak filling rate</td>
<td>0.1</td>
<td>0.113</td>
<td>0.372 (NS)</td>
</tr>
<tr>
<td>Time to peak filling</td>
<td>0.02</td>
<td>0.01</td>
<td>0.090 (NS)</td>
</tr>
<tr>
<td>Filling fraction</td>
<td>0.04</td>
<td>0.03</td>
<td>0.254 (NS)</td>
</tr>
</tbody>
</table>

SEMD: Standard error of mean difference
P: Probability - Student's paired t test
NS: Not significant
<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>SEMD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>7.87</td>
<td>1.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.4</td>
<td>2.73</td>
<td>0.223 (NS)</td>
</tr>
<tr>
<td><strong>Ejection rate</strong></td>
<td>0.173</td>
<td>0.063</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>Ejection time</strong></td>
<td>0.02</td>
<td>0.01</td>
<td>0.11 (NS)</td>
</tr>
<tr>
<td><strong>Peak filling rate</strong></td>
<td>0.31</td>
<td>0.16</td>
<td>0.06 (NS)</td>
</tr>
<tr>
<td><strong>Time to peak filling</strong></td>
<td>0.118</td>
<td>0.03</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td><strong>Filling fraction</strong></td>
<td>0.046</td>
<td>0.052</td>
<td>0.385 (NS)</td>
</tr>
</tbody>
</table>

SEMD: Standard error of mean difference
P: Probability - Student's paired t test
NS: Not significant
TABLE 3.3.5.3

Reproducibility of left ventricular indices.

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>SEMD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVD Rest</td>
<td>9.97</td>
<td>9.07</td>
<td>0.281 (NS)</td>
</tr>
<tr>
<td>Exercise</td>
<td>19.97</td>
<td>17.27</td>
<td>0.257 (NS)</td>
</tr>
<tr>
<td>ESV Rest</td>
<td>7.13</td>
<td>4.28</td>
<td>0.106 (NS)</td>
</tr>
<tr>
<td>Exercise</td>
<td>12.37</td>
<td>7.22</td>
<td>0.098 (NS)</td>
</tr>
<tr>
<td>P/V Rest</td>
<td>0.228</td>
<td>0.124</td>
<td>0.076 (NS)</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.243</td>
<td>0.238</td>
<td>0.316 (NS)</td>
</tr>
<tr>
<td>PBVR</td>
<td>0.069</td>
<td>0.062</td>
<td>0.277 (NS)</td>
</tr>
<tr>
<td>Vcf</td>
<td>0.059</td>
<td>0.027</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV depth</td>
<td>0.96</td>
<td>0.76</td>
<td>0.215 (NS)</td>
</tr>
</tbody>
</table>

EDV: End-diastolic volume
ESV: End-systolic volume
P/V: Pressure/volume ratio
PBVR: Pulmonary blood volume ratio
Vcf: Velocity of circumferential fibre shortening
LV: Left ventricle
NS: Not significant
TABLE 3.3.6.1

Normal left ventricular parameters.

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>61 (6.5)</td>
<td>65 (8.9)</td>
</tr>
<tr>
<td>Ejection rate (EDV/sec)</td>
<td>1.98 (0.35)</td>
<td>3.2 (0.8)</td>
</tr>
<tr>
<td>Ejection time (sec)</td>
<td>0.32 (0.04)</td>
<td>0.2 (0.03)</td>
</tr>
<tr>
<td>Peak filling rate (EDV/sec)</td>
<td>2.94 (0.17)</td>
<td>5.98 (1.28)</td>
</tr>
<tr>
<td>Time to peak filling (sec)</td>
<td>0.17 (0.04)</td>
<td>0.12 (0.03)</td>
</tr>
<tr>
<td>Filling fraction (normalised)</td>
<td>0.50 (0.19)</td>
<td>0.40 (0.17)</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>186 (72)</td>
<td>231 (91)</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>69 (28)</td>
<td>74 (31)</td>
</tr>
</tbody>
</table>

normal mean (±SD)
which increased to 47.5(8)% at maximal exercise. Other right ventricular parameters are shown in Table 3.3.6.2. The normal equilibrium pulmonary blood volume ratio was 1.24(0.25).

### 3.3.7 Left ventricular function Post-infarction

The left ventricular ejection fraction at rest was 47.7±13.8%, which was significantly lower than the normal subjects (P<0.001). During maximal exercise, the ejection fraction was lower than the normal (43±15.5%; P<0.001). In the normal subjects, ejection fraction increased by 4% during exercise; however, there was a reduction of ejection fraction of 4.7% in the patients. Similar significant differences were seen in ejection rate (1.42±4.2 EDV/sec; P<0.001), ejection time (0.34±0.05 sec; P<0.005), peak filling rate (1.82±0.62 EDV/sec; P<0.001) and normalised filling fraction (0.43±0.2; P<0.05). There was no significant difference in the time to peak filling (0.16±0.05 sec; P=NS) compared with the normal subjects (Table 3.3.7.1).

In patients with transmural anterior myocardial infarction, the left ventricular ejection fraction at rest was 42±14.7% which was significantly higher than that during maximal exercise (37±15.7%; P<0.002). Similarly, there was a significant reduction in ejection fraction in patients with inferior infarction from 52±10.3% at rest to 46.5±13.2% (P<0.001) during maximal exercise. On the other hand, there was no change in ejection fraction in patients with subendocardial infarction from rest to exercise (53.2±13.8% and 53.2±13.7% respectively; P=NS). There was a significant difference between the ejection fraction at rest in patients with anterior infarction
### TABLE 3.3.6.2

Normal right ventricular parameters.

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>44.2 (8.12)</td>
<td>47.5 (8)</td>
</tr>
<tr>
<td><strong>Ejection rate (EDV/sec)</strong></td>
<td>1.42 (0.37)</td>
<td>2.6 (0.75)</td>
</tr>
<tr>
<td><strong>Ejection time (sec)</strong></td>
<td>0.31 (0.04)</td>
<td>0.20 (0.05)</td>
</tr>
<tr>
<td><strong>Peak filling rate (EDV/sec)</strong></td>
<td>1.98 (0.28)</td>
<td>4.39 (1.11)</td>
</tr>
<tr>
<td><strong>Time to peak filling (sec)</strong></td>
<td>0.18 (0.06)</td>
<td>0.11 (0.03)</td>
</tr>
<tr>
<td><strong>Filling fraction (normalised)</strong></td>
<td>0.47 (0.2)</td>
<td>0.47 (0.21)</td>
</tr>
</tbody>
</table>

*normal mean (±SD)*
TABLE 3.3.7.1

Left ventricular function (n=105 patients).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>47.7</td>
<td>13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise</td>
<td>43</td>
<td>15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ejection rate</strong></td>
<td>1.42</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ejection time</strong></td>
<td>0.34</td>
<td>0.05</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>Peak filling rate</strong></td>
<td>1.82</td>
<td>0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Time to peak filling</strong></td>
<td>0.16</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Filling fraction</strong></td>
<td>0.43</td>
<td>0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>End-diastolic volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>228</td>
<td>139</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise</td>
<td>309</td>
<td>182</td>
<td>NS</td>
</tr>
<tr>
<td><strong>End-systolic volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>124</td>
<td>104</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise</td>
<td>176</td>
<td>126</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

SD: Standard deviation
P: Probability based on Student's unpaired t test compared with normal subjects
NS: Not significant
(42±14.7%) compared with patients with inferior infarction (52±10.3%; P<0.001) and patients with subendocardial infarction (53.2±13.8%; P<0.05). However, there was no significant difference between patients with inferior infarction and subendocardial infarction.

The resting ejection fraction was 51.5±11.7% in patients who had single vessel coronary artery disease (n=49), falling to 49±11.4% (P=NS) at maximal exercise. In the patients who had multiple vessel disease (two lesions or more), the resting ejection fraction was 45.4±14.7%, falling to 38±17% (P<0.001) at maximal exercise. The patients with single vessel disease had a significantly higher resting ejection fraction (51.5±11.7%) compared to the patients with multiple vessel disease (45.4±14.7%; P<0.05). At maximal exercise, the ejection fractions were 49±11.4% vs 38±17% respectively (P<0.001).

In the patients who showed only fixed myocardial perfusion defects on thallium-201 imaging, the mean left ventricular ejection fraction was 49±14%, decreasing to 45±14.5% (P<0.05) at maximal exercise. On the other hand, the patients who developed reversible myocardial perfusion defects had a resting ejection fraction of 47±13.7% which was significantly higher than that during maximal exercise (41±15.4%; P<0.001). There was no significant difference in resting ejection fraction between the two groups.

The total score of regional wall motion was calculated from the scores of the anterior view and the left anterior oblique view at rest and during maximal exercise (see section 2.2.3.5.1). The patients with transmural anterior myocardial infarction had significantly higher
scores (9.9±4.8%) compared with the patients with inferior infarction (5.7±4.2%; P<0.001) and those who had subendocardial infarction (4.7±4.4%; P<0.002). There was no significant difference between patients with inferior and subendocardial infarction. Similarly, regional wall motion scores were higher in those with multiple vessel disease (8.7±5.1%) compared with single vessel disease (5.6±3.9%; P<0.002). There was no significant difference in regional wall motion scores in the group with fixed perfusion defects (7.2±5%) compared with the group who showed reversible myocardial perfusion defects (7.9±4.9).

3.3.8 Right ventricular function

Right ventricular ejection fraction at rest was 44.3±10%, which was not different from the normal subjects (44.2±8.12%). However, during maximal exercise, the ejection fraction was 41±15.6%, which was significantly lower than the normal subjects 47.5±8% (P<0.01). In the normal subjects, right ventricular ejection fraction was increased by 3.3% during exercise. However, it was reduced by 3.3% in the patients with myocardial infarction. The right ventricular ejection rate (1.33±0.4) was not different from the normal subjects (1.42±0.37; P=NS), but the ejection time was significantly higher (0.35±0.06) compared with the normals (0.31±0.04; P<0.001). Similar to the left ventricle, the right ventricular peak filling rate was 1.76±64 EDV/sec, which was significantly lower than the normal subjects (1.98±0.28 EDV/sec; P<0.05). There were no significant differences in time to peak filling 0.172±0.08 sec and normalised filling fraction (0.412±0.19 sec) (Table 3.3.8.1)
### TABLE 3.3.8.1

Right ventricular function (n=105 patients).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>44.3</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise</td>
<td>41</td>
<td>15.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Ejection rate</strong></td>
<td>1.33</td>
<td>0.40</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Ejection time</strong></td>
<td>0.35</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Peak filling rate</strong></td>
<td>1.76</td>
<td>0.64</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Time to peak filling</strong></td>
<td>0.17</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Filling fraction</strong></td>
<td>0.41</td>
<td>0.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

SD: Standard deviation  
P: Probability based on Student’s unpaired t test compared with normal subjects  
NS: Not significant
Right ventricular ejection fraction at rest in the patients with transmural anterior myocardial infarction was 43±10%, which was not different from those with inferior infarction (45±9.6%), and those with subendocardial infarction (48±11.8%). There was no difference in resting ejection fraction in patients with inferior and subendocardial infarction. In addition, there was no demonstrable effect of the distribution of coronary artery lesions on the right ventricular ejection fraction.

3.3.9 Velocity of circumferential fibre shortening

When the velocity of circumferential fibre shortening (Vcf) was calculated from the normalised total counts (section 2.2.3.5.6), there was a poor correlation with Vcf calculated from contrast angiography using the short axis method (r=0.47) and the cube root of the volume (r=0.45). On the other hand, a similar poor correlation was seen when Vcf was calculated from the total counts (without normalization to the maximum counts per pixel) of the equilibrium radionuclide ventriculography. The correlation coefficient was r=0.6 (P=NS) with the short axis method and r=0.65 (P=NS) with the cube root of the volume. The normal values in 14 healthy subjects ranged between 0.3 to 1.3 circumference/sec (mean 0.64±0.23 SD). There was a poor correlation between resting Vcf and resting ejection fraction in the normal subjects (r=0.19). A similar poor correlation was seen with ejection rate (r=0.45; P=NS). Mean Vcf in the patients was 0.38±0.21, which was significantly lower than the normal subjects, (0.64±0.23; P<0.001). There was a significant positive correlation between Vcf and ejection fraction (r=0.66; P<0.001) and ejection rate (r=0.72; P<0.001).
However, a poor correlation was seen with ejection time (r=0.36). The mean radioisotopic Vcf in the patients with anterior transmural infarction was 0.36±0.18, which was not different from the patients with inferior infarction, 0.37±0.15. In patients with subendocardial infarction, Vcf was 0.49±0.23, which was significantly higher than in the patients with transmural infarction (0.37±0.17; P<0.05). In those who showed fixed myocardial perfusion defects on thallium-201 scintigraphy, the mean Vcf was 0.36±0.17, which was not different from those who had evidence of reversible ischaemic defects, (0.39±0.18).

The mean Vcf in the patients who had a normal ejection fraction (>48%) was 0.48±0.15, which was significantly higher than in the patients who had an abnormally low ejection fraction, (0.26±0.12; P<0.001). Similarly, Vcf was higher in the patients with documented essential hypertension (diastolic blood pressure more than 95 mmHg), (0.44±0.18) when compared with normotensive patients (0.36±0.17; P<0.05).

In the patients who showed single vessel coronary artery disease on coronary arteriography, the mean Vcf was 0.41±0.14, which was not significantly different from the patients who showed multiple vessel disease (0.38±0.13).

When the measurements of radioisotopic Vcf were repeated by another experienced observer in 30 subjects, the mean difference was 0.03, (P<0.05). A similar significant difference was seen when the measurements were repeated by the same observer (P<0.01).
3.3.10 Pulmonary blood volume ratio

Pulmonary blood volume ratio (PBVR) in 62 normal subjects studied in our laboratory ranged between 0.74 and 1.74. The mean PBVR in the patients was 1.36±0.39, which was significantly higher than the mean in normal subjects (1.24±0.25; P<0.05).

There was a poor correlation between PBVR and resting ejection fraction (r=0.1; Figure 3.3.10.1). Similarly, a poor correlation was seen between PBVR and exercise ejection fraction (r=0.14; Figure 3.3.10.2). Patients with a normal ejection fraction at rest (>48%) had a significantly higher PBVR, (1.36±0.3) compared with the normal subjects (P<0.05). Conversely, patients with an abnormal ejection fraction showed a PBVR of 1.35±0.4, which was not significantly different from that seen in normal subjects. There was no significant difference between PBVR in patients with normal or abnormal ejection fraction (Figure 3.3.10.3).

Linear regression analysis showed a poor positive correlation between time to peak filling rate and PBVR (r=0.36; P<0.002). A similar poor negative correlation was seen between left ventricular normalised filling fraction and PBVR (r=0.3; P<0.005). There was no correlation between PBVR and ejection rate or peak filling rate.

Patients with transmural inferior myocardial infarction had higher values for PBVR (1.38±0.32) compared with normal subjects (P<0.02). There was no difference between PBVR in patients with transmural anterior infarction (1.28±0.34) and the normal subjects (Figure
Correlation between equilibrium pulmonary blood volume ratio and resting left ventricular ejection fraction.

Figure 3.3.10.1
Pulmonary blood volume ratio

$N = 105$

$y = 0.004x + 1.2$

$r = +0.14 \ p = NS$

Figure 3.3.10.2

Correlation between equilibrium pulmonary blood volume ratio and exercise left ventricular ejection fraction.
Pulmonary blood volume ratio

(mean ± SEM)

P = NS

P < 0.05

P = NS

Pulmonary blood volume ratio

n= 62

n= 59

n= 46

Normal subjects

Patients with normal rest

EF > 48

Patients with abnormal EF

Figure 3.3.10.3

Equilibrium pulmonary blood volume ratio in patients with normal and abnormal left ventricular ejection fraction (EF).
3.3.10.4). Similarly, the ratio was not different in patients with anterior and inferior infarction, nor in patients with subendocardial and transmural infarction. Patients with subendocardial infarction had a significantly higher PBVR, (1.52±0.69) than normal subjects (P<0.02).

There was no significant difference in PBVR between patients who showed fixed myocardial perfusion defects on thallium-201 imaging, (1.31±0.34) and those with reversible ischaemic defects, (1.37±0.41). However, the patients with reversible defects had a significantly higher PBVR compared with the normal subjects (P<0.05). There was a poor correlation between PBVR and exercise thallium heart/lung ratio.

There was a significant difference in PBVR between patients with single vessel disease (1.39±0.36) and normal subjects (1.24±0.25; P<0.05), although no differences were found between the normals and patients with 2 vessel or 3 vessel disease (Figure 3.3.10.5). Within-group comparison in the patients showed no differences between patients with single vessel disease, 2 vessel disease or 3 vessel disease. There was a wide overlap in PBVR between patient's subgroups. Seventeen patients had isolated right coronary artery disease and the PBVR in this group was 1.39±0.37 which was not statistically different from normal subjects. There was no correlation between PBVR and left ventricular end-diastolic pressure recorded at cardiac catheterization.

3.3.11 Absolute left ventricular volume

Mean left ventricular end-diastolic volume (EDV) in the patients was 228±139 ml, which was not significantly different from normal subjects
Effect of myocardial infarction (MI) site on equilibrium pulmonary blood volume ratio.
Figure 3.3.10.5

Effect of the number of diseased coronary vessels on equilibrium pulmonary blood volume ratio.
(186±72 ml). At maximal exercise, EDV was 309±182 ml which was significantly higher than the resting value (P<0.001). However, there was no difference in exercise EDV in patients when compared with normal subjects (231±91 ml).

Mean left ventricular end-systolic volume (ESV) in patients was 124±105 ml, which was higher than in normal subjects, (69±28 ml) but the difference was not statistically significant. At maximal exercise, ESV was 176±126 ml, which was significantly higher than the resting value (P<0.002), and statistically different from the normal subjects (74±31 ml; P<0.005).

There was a poor negative correlation between resting EDV and resting ejection fraction (r=0.33, P<0.001) (Figure 3.3.11.1). On the other hand, there was a poor positive correlation with the resting left ventricular filling fraction (r=0.37; P<0.001) (Figure 3.3.11.2). There was a positive linear relationship between resting and exercise end-diastolic volume (r=0.88; P<0.001) (Figure 3.3.11.3). Similarly, there was a positive linear relationship between resting end-systolic and end-diastolic volume (r=0.93; P<0.001) (Figure 3.3.11.4).

Resting end-diastolic volume increased by more than 10% in 88 patients during exercise, decreased by more than 10% in 3 patients, and remained within ±10% in 14 patients. The behaviour of end-systolic volume was similar to that of end-diastolic volume. It increased by more than 10% in 89 patients, decreased by more than 10% in 5 patients, and remained within ±10% in 11 patients.
Figure 3.3.11.1

Correlation between resting left ventricular ejection fraction and resting end-diastolic volume.
Correlation between resting left ventricular first filling fraction and resting end-diastolic volume.
Figure 3.3.11.3

Correlation between resting and exercise left ventricular end-diastolic volume.
Relationship between end-diastolic and end-systolic volumes

N=105
y=0.7017x-36.0909
r=+0.932, p<0.0001

Figure 3.3.11.4

Correlation between resting left ventricular end-systolic and end-diastolic volumes.
Within patient comparison showed that men had a significantly higher EDV (238±144 ml) than women (150±50 ml; P<0.05) (Figure 3.3.11.5). Similarly, ESV was higher in men (131±109 ml) than women (69±32 ml) but the difference was not significant (Figure 3.3.11.6).

Resting EDV in hypertensive patients was 217±114 ml, which was not different from the normotensive patients (232±148 ml). Moreover, resting ESV in hypertensive patients (106±72 ml) was not different from normotensive patients (128±115 ml).

In the patients who had transmural anterior infarction, resting EDV was 247±167 ml, which was not different from patients with inferior infarction (216±112 ml) (Figure 3.3.11.7). Resting end-systolic volume was 151±136 ml in patients with anterior infarction, which was significantly greater than patients with inferior infarction (106±70; P<0.05) (Figure 3.3.11.8). Furthermore, patients with anterior infarction had a significantly higher ESV than normal subjects (P<0.05). There were no significant differences in EDV or ESV between patients with transmural and subendocardial infarction.

Patients with fixed myocardial perfusion defects on thallium-201 imaging had lower EDV and ESV (211±97 ml and 107±62 ml respectively) than patients with reversible ischaemic defects (232±151 ml and 131±118 ml respectively) but the differences were not statistically significant (Figures 3.3.11.9 and 3.3.11.10).

Resting EDV in patients with single vessel disease was 212±120 ml, which was not significantly different from patients with multiple vessel
End-diastolic volume (ml) mean ± SD

Figure 3.3.11.5

Effect of gender on resting left ventricular end-diastolic volume after myocardial infarction.
Figure 3.3.11.6

Effect of gender on resting left ventricular end-systolic volume after myocardial infarction.
Figure 3.3.11.7

Effect of the site of myocardial infarction on resting left ventricular end-diastolic volume.
Effect of the site of myocardial infarction on resting left ventricular end-systolic volume.
Normal subjects (n=14)  
Fixed perfusion defects (n=26)  
Reversible ischaemic defects (n=75)

**Figure 3.3.11.9**

Effect of reversible ischaemic myocardium on resting left ventricular end-diastolic volume.
Normal subjects (n=14)
Fixed perfusion defects (n=26)
Reversible ischaemic defects (n=75)

Effect of reversible ischaemic myocardium on resting left ventricular end-systolic volume.
disease (241±156 ml). Similarly, resting ESV was not different in the two groups (104±70 ml and 138±125 ml respectively; P=NS).

3.3.12 Pressure/volume index

The normal values of left ventricular end-systolic pressure/volume index ranged from 1.1 to 7.7 mmHg/ml at rest (mean 2.32±1.48 SD) and 1.5 to 17.0 mmHg/ml at maximal exercise (mean 3.79±4.1 SD) (P=NS). It was observed that in one 'normal' subject the values of rest and exercise pressure/volume index were skewed to the right. Excluding the results of this subject, the range was 1.1 to 3.8 at rest (mean 2±0.93) and 1.5 to 6.7 at maximal exercise (mean 2.73±1.5) (P<0.02).

Resting pressure/volume index in patients was 1.71±1.15, which was not significantly different from normal subjects (even after excluding the skewed value). However, exercise pressure/volume index was 1.5±1.1, which was significantly lower than in normal subjects (P<0.001).

Unlike normal subjects who showed an increase in the pressure/volume index during exercise, in patients this index decreased during exercise although the difference was not significant. Surprisingly, linear regression analysis showed a significant positive correlation (r=0.8; P<0.001) between rest and exercise pressure/volume index (Figure 3.3.12.1).

The resting pressure/volume index in men was 1.57±0.98, which was significantly lower than in women (2.76±1.81; P<0.001) (Figure 3.3.12.2). Hypertensive patients had a significantly higher resting
End-systolic pressure/volume index

Figure 3.3.12.1

Correlation between resting and exercise left ventricular end-systolic pressure/volume index.
Effect of gender on resting left ventricular end-systolic pressure/volume index.
pressure/volume index (2.1±1.5) compared with normotensive patients (1.55±0.93; P<0.05) (Figure 3.3.12.3). There was no difference in pressure/volume index in patients with fixed myocardial perfusion defects and those who showed reversible ischaemic defects on thallium-201 imaging (1.78±1.03 vs 1.67±1.19 respectively; P=NS).

Patients who had suffered an anterior transmural infarction had a pressure/volume index of 1.43±0.99, which was significantly lower than patients with inferior infarction (1.97±1.34; P<0.05) (Figure 3.3.12.4). There was no difference between pressure/volume index in patients with transmural infarction compared with patients with subendocardial infarction (1.86±0.7).

In addition, patients with single vessel disease had a pressure/volume index of 1.99±1.33, which was significantly higher than in patients with multiple vessel disease (1.48±0.9; P<0.05). There was a significant difference between the latter group and normal subjects (P<0.02) (Figure 3.3.12.5).

In general, end-systolic pressure/volume index increased by exercise in 26 patients, decreased in 59 patients and remained within ±10% in 20 patients.

3.4 THALLIUM-201 MYOCARDIAL SCINTIGRAPHY

3.4.1 Qualitative thallium-201 analysis

Exercise thallium-201 images were scored according to the presence or
Figure 3.3.12.3

Resting left ventricular end-systolic pressure/volume index in hypertensive patients compared to normal subjects and normotensive patients.
**Figure 3.3.12.4**

Effect of the site of myocardial infarction on left ventricular end-systolic pressure/volume index.
Figure 3.3.12.5

Resting left ventricular end-systolic pressure/volume index in patients with multiple vessel disease compared to normal subjects and patients with single vessel disease.
absence of myocardial segments. The score for a normal scan with no perfusion defects was '5'. The delayed images were scored similarly and compared with the stress results (section 2.2.4.4).

If we assume that the scores reflected the severity of the disease and therefore were normally distributed, we could examine the difference in the average score in patient subgroups. The mean (±SD) score in all patients after exercise was 2.74±0.99, which was significantly lower than that seen in the delayed images (3.35±0.97; P>0.001). On exercise, the mean score of patients with anterior transmural infarction was 2.41±0.93, which was significantly lower than inferior infarction (2.91±0.94; P<0.02) and subendocardial infarction (3.45±0.94; P<0.002). There was no significant difference between inferior and subendocardial infarction. In the delayed images, there was no difference in scores between anterior transmural infarction (3.26±0.98) and inferior infarction (3.25±0.94) but patients with subendocardial infarction had significantly higher scores (4.1±0.83) than anterior (P<0.02) and inferior infarction (P<0.01). Comparison of the stress and delayed images in patient subgroups using the chi-square test showed Χ²=0.028 (DF=2; P=NS).

In patients with single vessel coronary disease, the mean stress score was 3.13±0.84 which was significantly higher than patients with two vessel disease (2.45±0.85; P<0.001) and three vessel disease (2.36±1.28; P<0.01). There was no significant difference between patients with two or three vessel disease. However, in the delayed images there were no differences in score between patients with single vessel disease (3.42±0.92), two vessel disease (3.39±0.92) and three vessel disease
Chi-square test showed no significant difference between stress and delayed scored in patient subgroups ($X^2=0.04$, DF=2, P=NS).

Fixed myocardial perfusion defects due to 'scar' were seen in 45 patients with no evidence of reperfusion. In 48 patients there was evidence of reversible perfusion defects in addition to the presence of 'scar'. Four patients had higher scores after exercise than the delayed images and another 4 patients had grossly 'normal' myocardium with no evidence of perfusion defects neither after stress nor in the delayed images.

The sensitivity of qualitative thallium-201 analysis for prediction of multiple vessel disease was 67%, specificity 50%, positive predictive value 56%, negative predictive value 62% and diagnostic accuracy 58%.

### 3.4.2 Quantitative thallium-201 analysis

The number of abnormal triplets obtained from quantitative thallium-201 analysis was used to assess the extent of disease. Abnormal stress and/or washout curves were seen in 74 patients among whom 19 showed fixed perfusion defects, and 3 patients with normal scans on qualitative analysis. A further 26 patients with fixed perfusion defects did not show any evidence of reversible ischaemic myocardium. Only one patient with 'normal' segments qualitatively showed normal stress and washout curves on the quantitative analysis.

The sensitivity of quantitative thallium-201 analysis for prediction of multiple vessel disease was 78%, specificity 50%, positive predictive
value 59%, negative value 71% and diagnostic accuracy 63%. However, when the images were assessed both qualitatively and quantitatively the sensitivity was improved to 85%, specificity 53%, positive predictive value 64%, negative predictive value 78% and diagnostic accuracy 69%.

3.4.3 Left ventricular dilatation during thallium imaging

The mean (±SD) left ventricular exercise/rest index in patients with anterior infarction was 1.07±0.12, which was not different from patients with inferior infarction (1.03±0.11) or subendocardial infarction (1.0±0.08) (Figure 3.4.3.1). Similarly, there was no difference between patients with inferior and subendocardial infarction, and no difference between patients with fixed perfusion defects (1.06±0.1) and those who showed reversible ischaemic myocardium (1.04±0.12) (Figure 3.4.3.2).

Left ventricular exercise/rest index was 1.03±0.11 in patients with single vessel coronary artery disease, which was not different from that in patients with two vessel disease (1.04±0.11), but was significantly lower in patients with three vessel disease (1.13±0.15; P<0.01) There was also a significant difference between two and three vessel disease (P<0.05) (Figure 3.4.3.3). Patients with multiple (two to more) vessel disease had an exercise/rest index of 1.07±0.13, which was not different from those with single vessel disease.

3.4.4 Right ventricular thallium-201 uptake

Increased thallium-201 uptake by the right ventricle was seen in 33 patients (32.7%). Of these 33 patients, 23 had anterior infarction
Figure 3.4.3.1

Effect of myocardial infarction site on transient left ventricular (LV) dilatation during exercise thallium-201 imaging.
Fixed perfusion defects
Reversible perfusion defects

Figure 3.4.3.2

Transient left ventricular (LV) dilatation during exercise thallium-201 imaging in patients with reversible ischaemia compared to patients with fixed perfusion defects only.
Figure 3.4.3.3

Effects of severity of coronary artery disease on transient left ventricular dilatation during exercise thallium-201 imaging.
(70%), 7 had inferior infarction (21%) and 3 had subendocardial infarction (9%).

The mean scores during exercise imaging in patients with increased right ventricular uptake was 2.39±1.03, which was significantly lower than those who showed normal uptake (2.91±0.94; P<0.02). However, there was no difference in scores in the delayed images (3.36±1.11 and 3.34±0.91). Chi-square testing showed no significant difference between exercise and resting images in the two groups (X²=0.03, DF=1; P=NS).

In the patients with increased right ventricular thallium-201 uptake, 10 had single vessel disease (33%), 13 had two vessel disease (43%) and 7 had three vessel disease (23%). Three patients were not catheterized. On the other hand, single vessel disease seen in 38 patients (60%), two vessel disease in 18 patients (29%) and three vessel disease in 7 patients (11%) with normal right ventricular uptake. Chi-square testing showed significant differences in coronary artery disease distribution in patients with increased and normal right ventricular thallium-201 uptake (X²=6.21, DF=2; P<0.05).

3.4.5 Exercise thallium-201 heart/lung ratio

Mean exercise heart/lung ratio values in 14 normal healthy volunteers was 2.74±0.12 (SEM). The mean exercise heart/lung ratio in the patients was 1.86±0.05, which was significantly lower (P<0.001) (Table 3.4.5.1).

Mean exercise duration for the patients before thallium-201 imaging was 10.6±0.4 minutes. Linear regression analysis revealed a poor
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
<th>P value</th>
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<tbody>
<tr>
<td>Normal volunteers</td>
<td>14</td>
<td>2.74</td>
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<tr>
<td>Study patients</td>
<td>101</td>
<td>1.86</td>
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</tr>
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<td>Normal EF</td>
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<td>0.07</td>
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<tr>
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<tr>
<td>Single vessel disease</td>
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<td>2.29</td>
<td>0.32</td>
<td>NS</td>
</tr>
<tr>
<td>Two vessel disease</td>
<td>31</td>
<td>1.76</td>
<td>0.09</td>
<td>&lt;0.001</td>
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<tr>
<td>Three vessel disease</td>
<td>15</td>
<td>1.81</td>
<td>0.17</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

n: Number of patients
SEM: Standard error of mean
P: Unpaired t test probability value
EF: Ejection fraction
correlation between exercise heart/lung ratio and exercise time (r=0.3). The patients achieved a mean peak exercise heart rate of 126±2 beats per minute. There was no significant correlation between exercise heart/lung ratio and heart rate on exercise (r=0.3).

In patients with anterior transmural infarction, the mean exercise heart/lung ratio was 1.7±0.07, which was significantly lower than patients with inferior transmural infarction (2.03±0.08; P<0.005). The mean exercise heart/lung ratio in patients with subendocardial infarction was 1.84±0.1, which was not different from that seen in patients with transmural infarction (1.87±0.05) (Figure 3.4.5.1).

In the patients with only fixed perfusion defects; the mean heart/lung ratio was 2.08±0.1, which was significantly higher than in the patients with reversible ischaemic segments (1.79±0.05; P<0.02) (Figure 3.4.5.2).

There was no significant difference between mean heart/lung ratio in the patients who had essential hypertension prior to the acute infarction (n=32; 1.83±0.08), and normotensive patients (n=69; 1.88±0.06; P=NS).

There was a significant positive correlation (r=0.48; P<0.01) between resting left ventricular ejection fraction and heart/lung ratio (Figure 3.4.5.3). In patients with normal resting ejection fraction (>48%), the mean heart/lung ratio was 2.06±0.07, which was significantly lower than in the normal subjects (P<0.001). Similarly, mean heart/lung ratio in the patients with abnormally low ejection fraction was 1.62±0.05, which was significantly lower than the normal controls (P<0.001) (Figure 3.4.5.4) and the patients with a normal ejection fraction (P<0.001).
Exercise heart/lung ratio (mean ± sem)

\[ P = \text{NS} \]

\[ P < 0.005 \]

Myocardial infarction (MI) site

- Anterior MI
- Inferior MI
- Subendocardial MI

Figure 3.4.5.1

Effect of myocardial infarction site on quantitative exercise thallium-201 heart/lung ratio.
Exercise heart/lung ratio
(mean ± sem)

P<0.001

Effects of myocardial perfusion

□ Normals
■ Fixed defects
■■ Reversible ischaemia

Figure 3.4.5.2

Effects of myocardial perfusion on quantitative exercise thallium-201 heart/lung ratio.
Figure 3.4.5.3

Correlation between resting left ventricular ejection fraction and quantitative exercise thallium-201 heart/lung ratio.
Exercise heart/lung ratio

![Bar chart showing exercise heart/lung ratio for different groups.](image)

- **Normals**
- **All patients (101)**
- **Patients with normal EF (56)**
- **Patients with abnormal EF (49)**

EF: ejection fraction
* $P < 0.001$

**Figure 3.4.5.4**

Effects of normal and abnormal resting left ventricular ejection fraction on quantitative exercise thallium-201 heart/lung ratio.
There was a poor correlation between heart/lung ratio and resting left ventricular peak filling rate \((r=0.25)\) and pulmonary blood volume ratio \((r=0.03)\) (Figure 3.4.5.5).

There was a significant negative correlation between heart/lung ratio and left ventricular end-diastolic pressure measured at cardiac catheterization \((r=0.43; P<0.001)\) (Figure 3.4.5.6). The patients with single vessel disease had a similar mean exercise heart/lung ratio to normal controls \((2.29\pm0.32\text{ and } 2.74\pm0.12\text{ respectively; } P=\text{NS})\). However, in the group with two vessel disease the ratio was \(1.76\pm0.09\) \((P<0.001)\) and in the group with three vessel disease it was \(1.81\pm0.18\) \((P<0.001)\), which was significantly lower (Figure 3.4.5.7). The group with three vessel disease had a lower heart/lung ratio than those with single vessel disease but this difference was not significant (Figure 3.4.5.8).

In patients with definite collateral vessels and retrograde filling of blocked arteries, the mean exercise heart/lung ratio was \(1.84\pm0.07\), which was not different from those without collateral circulation \((1.96\pm0.08; P=\text{NS})\) (Figure 3.4.5.9).

Thallium-201 heart/lung ratio was measured immediately after stress and after redistribution 3-4 hours later. The mean redistribution heart/lung ratio was \(2.32\pm0.04\) which was significantly higher than the exercise value \((1.86\pm0.05; P<0.001)\). In the 34 patients with a normal exercise heart/lung ratio, the mean redistribution value was \(2.62\pm0.06\), which was higher than that recorded after stress \((2.42\pm0.07; P<0.02)\). In those with an abnormal exercise heart/lung ratio, the mean redistribution value was \(2.17\pm0.05\), which was again significantly higher than that recorded after stress \((1.58\pm0.03; P<0.001)\). There was a
Figure 3.4.5.5

Correlation between quantitative exercise thallium-201 heart/lung ratio and equilibrium pulmonary blood volume ratio.
Exercise thallium heart/lung ratio

\[ N = 93 \]
\[ y = -0.02x + 2.19 \]
\[ r = -0.427 \quad p < 0.0001 \]

Figure 3.4.5.6

Correlation between quantitative exercise thallium-201 heart/lung ratio and left ventricular end-diastolic pressure measured during cardiac catheterization.
Exercise heart/lung ratio
(mean ± sem)

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<thead>
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<th>Heart/lung ratio</th>
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<tr>
<td>0.5</td>
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<td>1.5</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

P = NS
P < 0.001
P < 0.001

Normals 1VD 2VD 3VD

Number of vessel disease (VD)

Figure 3.4.5.7

Quantitative exercise thallium-201 heart/lung ratio distribution in patients' subgroups according to the severity of coronary artery disease.
Figure 3.4.5.8

Effect of severity of coronary artery disease on quantitative exercise thallium-201 heart/lung ratio.
Figure 3.4.5.9

Effects of collateral coronary circulation on quantitative exercise heart/lung ratio.
Exercise thallium heart/lung ratio

\[ N = 101 \]
\[ y = -1.1x + 3.3 \]
\[ r = -0.58 \quad p < 0.0001 \]

Figure 3.4.5.10

Relationship between quantitative exercise thallium-201 heart/lung ratio and lung thallium-201 washout.
TABLE 3.4.5.2

Prediction of multiple vessel disease.

<table>
<thead>
<tr>
<th></th>
<th>EF</th>
<th>QLT</th>
<th>QNT</th>
<th>HLR</th>
<th>QNT+QLT</th>
<th>QNT+HLR</th>
<th>QNT+QLT+HLR</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>46</td>
<td>67</td>
<td>78</td>
<td>73</td>
<td>85</td>
<td>80</td>
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<td>Specificity (%)</td>
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<td>50</td>
<td>40</td>
<td>53</td>
<td>17</td>
<td>37</td>
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<tr>
<td>Predictive value (%)</td>
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<td>71</td>
<td>61</td>
<td>78</td>
<td>47</td>
<td>67</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>55</td>
<td>58</td>
<td>63</td>
<td>56</td>
<td>69</td>
<td>47</td>
<td>62</td>
</tr>
</tbody>
</table>

EF: Ejection fraction at rest
QLT: Qualitative thallium analysis
QNT: Quantitative thallium analysis
HLR: Exercise heart/lung ratio
significant negative correlation between heart/lung ratio and thallium-201 lung washout index ($r=0.58; P<0.001$) (Figure 3.4.5.10).

The sensitivity of exercise heart/lung ratio for prediction of left ventricular dysfunction was 80%, specificity 45%, positive predictive value 54%, negative predictive value 74% and diagnostic accuracy 60%. The sensitivity of thallium-201 exercise heart/lung ratio for identifying patients with multiple (two or more) vessel disease was 73%, with a specificity of 40%, a positive predictive value of 53%, a negative predictive value of 61% and a diagnostic accuracy of 56%. When increased thallium-201 concentration in the lung was added to qualitative myocardial thallium-201 analysis, the sensitivity improved to 80%, but specificity was reduced to 17%, positive and negative predictive values and diagnostic accuracy to 47%. On the other hand, when the images were interpreted using all the variables i.e qualitative, quantitative and lung thallium-201 uptake analyses, the sensitivity of the test for prediction of multiple vessel disease was 84%, with a specificity of 37%, a positive predictive value of 61%, a negative predictive value of 67% and a diagnostic accuracy of 62% (Table 3.4.5.2).

3.4.6 Example of thallium-201 application

Myocardial and lung thallium-201 analysis was reported retrospectively in 41 patients suffering from transmural inferior myocardial infarction (Figure 3.4.6.1). There were 35 men and 6 women with a mean age of 56.5±7.6 years. The mean exercise thallium-201 heart/lung ratio was 2.03±0.08 (SEM), which was significantly different from the normal
Quantitative Thallium-201 Analysis (LAO view):
Large inferior perfusion defects with no evidence of redistribution.
controls (2.74+0.12; P<0.001). Qualitative thallium-201 analysis in this group revealed fixed myocardial perfusion defects in 27 patients; 12 had gross reversible perfusion defects, and 2 had 'normal' scans. However, quantitative analysis revealed 11 patients with fixed defects due to scar, 29 patients with additional significant redistribution and only one with a normal distribution and washout pattern. The sensitivity of a quantitative thallium-201 analysis for predicting multiple vessel disease in this group was 30% and 80% respectively and the specificity was 71% and 67% respectively. The diagnostic accuracy of the two techniques was 51% and 73% respectively. Quantitative analysis was able to detect significant reversible ischaemia in an additional 17 patients (41%). Exercise heart/lung ratio detected multiple vessel disease with a sensitivity of 63% and specificity of 64% (Table 3.4.6.1).

3.5 SELECTIVE CORONARY ARTERIOGRAPHY

Selective coronary arteriography was performed in 95 patients. Two patients died before cardiac catheterization due to cardiogenic shock resulting from massive reinfarction and 8 patients refused to give informed consent to undergo an invasive procedure.

The total number of vessels scored by two observers was 380, of which 177 showed no abnormality (Score '0'); 54 showed lesions producing 70% or more distal intraluminal narrowing (score '2'), 63 showed 70% or more proximal intraluminal narrowing (Score '3'), and 75 showed complete obstruction (100% stenosis) of the vessel (score '4'). In the left main stem, lesions producing 50% or more were considered significant, and
TABLE 3.4.6.1

Prediction of multiple vessel disease after transmural inferior infarction.

<table>
<thead>
<tr>
<th></th>
<th>QLT</th>
<th>QNT</th>
<th>HLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>30</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>71</td>
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</tr>
<tr>
<td>Accuracy (%)</td>
<td>51</td>
<td>73</td>
<td>63</td>
</tr>
</tbody>
</table>

QLT: Qualitative thallium analysis
QNT: Quantitative thallium analysis
HLR: Exercise heart/lung ratio
this was seen in only 3 cases. Significant lesions involving the left anterior descending artery were seen in 55, the left circumflex artery in 37, and the right coronary artery in 53. Collateral vessels and retrograde filling of blocked arteries were seen in 45 cases.

In 7 patients, there were lesions producing less than 70% intraluminal narrowing of the coronary arteries, and in 42 there were lesions producing significant narrowing in one vessel only. These patients were considered to have single vessel disease. Furthermore, significant lesions in two vessels were seen in 31 cases and in three vessels in 15 cases (including 3 patients with left main stem lesions). These patients were considered to have multiple vessel disease. The effect of single and multiple vessel disease was discussed previously.

The mean left ventricular end-diastolic pressure (LVEDP) during cardiac catheterization was 15.2±9.7 (SD) mmHg. There was a poor negative correlation between left ventricular end-diastolic pressure and resting radioisotopic ejection fraction (r=-0.3; P<0.005) (Figure 3.5.1). Patients with single vessel disease had a mean left ventricular end-diastolic pressure of 13±7 mmHg, which was significantly lower than in patients with multiple vessel disease (17.6±11.6 mmHg; P<0.05). Moreover, patients with two vessel disease had LVEDP (16.6±10.1), similar to that in patients with three vessel disease (19.6±14.4; P=NS). Although the LVEDP in patients with single vessel disease was not different from that in two vessel disease, it was significantly lower than that in three vessel disease (P<0.02).
Figure 3.5.1

Correlation between resting radionuclide ejection fraction and left ventricular (LV) end-diastolic pressure during cardiac catheterization.

\[ y = -0.42x + 54.89 \]

\[ r = -0.3 \quad p < 0.005 \]
3.6 PROGNOSIS AFTER MYOCARDIAL INFARCTION

3.6.1 Outcome after the acute episode

Patients were followed-up for an average period of 18.8±3.4 months (range 12-24 months). No cardiac events were seen in 64 patients although a permanent pacemaker was implanted in one patient 20 months after the acute infarction due to sick sinus syndrome. Chronic stable effort angina at a rate of 3-6 attacks per week was seen in 15 patients. In 7 patients, congestive cardiac failure (NYHA class II-III) required additional diuretics/vasodilators. Reinfarction developed in 5 patients who also survived the second episode. Four additional patients died in hospital within 24 hours of the second myocardial infarction. One patient died due to an attack of unstable angina which developed following cardiac catheterization. Another patient died within 7 days of percutaneous transluminal coronary angioplasty due to poor left ventricular function. A further patient did not survive an attempt at heart transplantation due to multiple infarction and poor left ventricular function. Successful percutaneous transluminal coronary angioplasty was carried out in one patient and coronary artery bypass grafting was performed in 6 more patients. The total mortality was 6.7% during the follow-up period.

For the purpose of this study, the outcome of all patients was categorised into those with no cardiac events (n=64), minor cardiac events (n=22) and major cardiac events (n=19) (Figure 3.6.1.1.).
Prognosis after myocardial infarction

Total outcome (n = 105)

- No Cardiac Events 61.0%
- Minor Events 21.0%
- 18.0% Major Events

Figure 3.6.1.1

Percentage of cardiac events during follow-up after uncomplicated myocardial infarction.
3.6.2 Graded exercise electrocardiography

Patients were subgrouped according to the presence or absence of symptoms and ST-segment depression at maximal exercise. In group I, there were 31 asymptomatic patients with no ST-depression. Group II consisted of 28 patients who were symptomatic (angina and/or dyspnoea) with significant ST-depression (1>mm). In group III, 25 patients were asymptomatic but developed significant ST-depression. Finally, group IV consisted of 21 patients who were symptomatic but developed no ST-depression.

In group I, 20 patients (64%) had no cardiac events, 8 patients (26%) developed minor cardiac events and 3 patients (10%) developed major cardiac events. In group II, 13 patients (46%) had no events, 8 patients (29%) developed minor events and 7 patients (25%) developed major events. On the other hand, 20 patients (80%) of group III had no events, 1 patient (4%) developed a minor cardiac event and 4 patients (16%) developed major events. No cardiac events were seen in 11 patients (52%) of group IV, 5 patients (24%) developed minor events and 5 more patients (24%) developed major events (Figure 3.6.2.1).

Within-group comparison using the chi-square test showed no differences between group I and the other groups. However, when patients in group II were compared with group III, there was a significant difference ($X^2$ = 7.6, DF=2; P<0.05). When patients were categorised into those with no cardiac events and those who developed any cardiac event, there was again a significant difference between groups III and IV ($X^2$ =3.96, DF=1; P<0.05). There were no differences between other groups. Moreover,
Figure 3.6.2.1

Prevalence of cardiac events during the follow-up period:
Group I (n=31) : Asymptomatic patients with no ST-depression
Group II (n=28) : Symptomatic patients with ST-depression
Group III (n=25) : Asymptomatic patients with ST-depression
Group IV (n=21) : Symptomatic patients with no ST-depression
when patients were grouped into those with (n=53) and those without ST-depression (n=52) regardless of symptoms, there were no significant differences between the groups. On the other hand, when patients were grouped into those who were asymptomatic (n=56) and those who were symptomatic (n=49) at maximal exercise, there was no difference between the two groups if the outcome was categorised into those with no cardiac events, minor events and major events. However, when patients were grouped into those with no cardiac events and any cardiac event, there was a significant difference between the two groups (X²=5.5, DF=1; P<0.05).

ST-segment elevation (>1mm) was seen in 18 patients (17%) among whom 5 patients (28%) developed significant ST-depression in other leads and 6 patients (33%) suffered from dyspnoea at maximal exercise. Due to the small numbers in each of these subgroups, all patients with ST-elevation were compared with other groups. No cardiac events were seen in 8 patients (44.4%), minor cardiac events developed in 6 patients (33.3%) and major cardiac events were seen in 4 patients (22.2%). There were no significant differences in prognosis between patients with ST-elevation and those in other groups.

3.6.3 Gated blood pool ventriculography

The mean resting left ventricular ejection fraction in the patients who experienced no cardiac events was 52±11%, which was significantly higher than that at maximal exercise (47.9±13%; P<0.005). In the patients who developed minor events, the mean resting ejection fraction (44.8±15%) was significantly different from that at maximal exercise (39.9±14.8%);
Similarly, the mean resting ejection fraction in those who developed major events was 36.5±13.5%, which was significantly higher than at maximal exercise (29.5±15.8%; P<0.001). Moreover, when the patients who developed any cardiac event were considered as one group, the mean resting ejection fraction was 41±14.8%, which was significantly different from that at maximal exercise (35±16%; P<0.001).

There were significant differences between resting ejection fraction in patients who experienced no cardiac events and those who developed minor events (P<0.02), major events (P<0.001) and any cardiac event (P<0.001). Similar significant differences were seen in ejection fraction at maximal exercise. Although there was no difference in resting ejection fraction in patients who developed minor cardiac events compared with those who developed major events, there was a significant difference in exercise ejection fraction between the two groups (P<0.02).

The mean total regional wall motion score in patients who experienced no cardiac events was 5.8±4.3, which was significantly lower than that in patients who developed minor events (8.6±5; P<0.02), major events (12±4.3; P<0.001) and any cardiac events (10.2±4.9; P<0.001). There was a significant difference in wall motion scores in patients with minor events, compared with those who developed major events (P<0.05). The distribution of regional wall motion score in patient subgroups is shown in Figure 3.6.3.1 and Figure 3.6.3.2.

Resting left ventricular peak filling rate in patients who experienced no cardiac events was 1.81±0.55 EDV/sec, which was not different from that observed in patients who developed minor events (1.97±0.79; P=NS),
Figure 3.6.3.1

Distribution of regional wall motion scores in patients with and without cardiac events during follow-up.
Figure 3.6.3.2

Distribution of regional wall motion scores in patients with no events, minor events, and major events during follow-up.
major events (1.65±0.46; P=NS) and any cardiac event (1.82±0.67; P=NS). Patients with minor events had a higher peak filling rate than patients with major events, but the difference was not significant.

Resting right ventricular ejection fraction in patients without cardiac events was 45.5±9.9%, which was not different from patients with any cardiac events, (42.8±10.3%). However, patients who experienced major cardiac events had a significantly lower right ventricular ejection fraction (38.8±7.9%) than patients without cardiac events (45.5±9.9%; P<0.01) and patients with minor cardiac events (46.9±10.8%; P<0.02).

Resting left ventricular end-diastolic volume (EDV) in the group who developed no cardiac events was 209±111 ml, which was not different from those with minor events, (216±113 ml; P=NS) but significantly lower than that seen in patients who experienced major events (307±213 ml; P<0.01). It was not different from those who experienced any cardiac event (258±171 ml; P=NS). There was no difference between EDV in patients who experienced minor or major cardiac events. On exercise, there were no differences between those who developed no cardiac events (293±166 ml), minor events (314±158 ml), major events (379±234 ml) and any cardiac event (344±197 ml).

On the other hand, resting left ventricular end-systolic volume (ESV) in patients who developed no cardiac events was 102±71 ml, which was not significantly different from those who experienced minor events, (117±65 ml), but significantly lower than in patients who experienced major events, (206±178; P<0.001) and patients who experienced any cardiac event, (158±136 ml; P<0.01). There was a significant difference between
ESV in patients who experienced minor and major events (P<0.05). On
exercise, ESV in patients who developed no cardiac events was 151±108
ml, which was not significantly different from those who experienced
minor events, (182±91 ml), but significantly lower than those who
experienced major events (263±170 ml; P<0.001) and any cardiac event
(221±138 ml; P<0.005). There was no difference in exercise ESV between
patients with minor and major cardiac events.

Similarly, the resting end-systolic pressure/volume (P/V) ratio in
patients who developed no cardiac events was 1.93±1.21, which was not
different from those who developed minor events (1.66±1.11) but
significantly higher than in patients who developed major events
(1.01±0.64; P<0.002) and patients who developed any cardiac events
(1.36±0.97; P<0.02). There was a significant difference in resting P/V
ratio between patients with minor and major cardiac events (P<0.05). On
exercise, the mean P/V ratio in patients with no cardiac events was
1.74±1.1, which was not significantly different from patients with minor
events (1.35±1.04) but significantly higher than in patients with major
events (0.94±0.74; P<0.005) and any cardiac event (1.16±0.93; P<0.01).
There was no significant difference in exercise P/V ratio between
patients who experienced minor or major cardiac events.

The velocity of circumferential fibre shortening in patients who
developed no cardiac event was 0.41±0.16 circumference/sec, which was
not different from patients with minor events, (0.39±0.23) but
significantly higher than in patients with major cardiac events,
(0.30±0.15; P<0.01). There were no significant differences between
patients with minor and major events, nor patients with no events and
any cardiac event (0.35±0.2).

The mean pulmonary blood volume ratio in patients with no cardiac events was 1.41±0.42, which was not different from that seen in patients with minor events, (1.42±0.55) major events (1.22±0.31) or any cardiac event (1.33±0.46). Although patients who experienced major events had lower values of pulmonary blood volume ratio than patients with no events and minor events, the differences were not statistically significant.

3.6.4 Thallium-201 myocardial scintigraphy

The mean exercise thallium-201 scores in patients who developed no cardiac events was 3±1, which was not different from that in patients who experienced minor events, (2.7±0.83) but significantly higher than in patients with major events (1.9±0.78; P<0.001) and patients with any cardiac event (2.4±0.9; P<0.005). There was a significant difference between patients with minor and major events (P<0.005). In the delayed images, the mean thallium-201 scores in patients with no cardiac events was 3.5±0.9, which was not different from those with minor events (3.32±1.04) and any cardiac event (3.13±1.06) but significantly higher than in patients with major events (2.88±1.05; P<0.02). There was no difference in scores of the delayed images between patients with minor and major cardiac events. Chi-square analysis showed no difference between scores on exercise and delayed images in patient subgroups.

In 26 patients with no evidence of redistribution of thallium-201 there were 19 (73%) who developed no cardiac events, 6 (23%) who experienced minor events and one (4%) who developed a major event. Of 74 patients
who showed evidence of significant redistribution and/or abnormal washout on quantitative thallium-201 analysis, 42 (56%) developed no cardiac events, 16 (22%) experienced minor cardiac events and 16 (22%) developed major cardiac events. Although 27% of patients with no redistribution in contrast to 43% of patients with significant redistribution developed cardiac events, the difference was not significant ($X^2 = 4.43, \text{DF}=2; \ P=\text{NS}$).

In 33 patients with right ventricular thallium-201 uptake, there were 19 (58%) who developed no cardiac events, 6 (18%) who experienced minor events and 8 (24%) who experienced major events. Furthermore, in 68 patients with normal right ventricular uptake, there were 43 (63%) who developed no events, 16 (24%) who experienced minor events and 9 (13%) who experienced major events. Although 42% of patients with high uptake in contrast to 37% of patients with normal uptake developed cardiac events, the difference was not significant ($X^2 = 2.0, \text{DF}=2; \ P=\text{NS}$).

Left ventricular dilatation on exercise thallium-201 scintigraphy did not correlate with prognosis. Exercise/stress index was $1.03\pm0.11$ in patients who developed no cardiac events, which was not significantly different from that in patients with minor events ($1.06\pm0.11$) major events ($1.09\pm0.13$) and any cardiac event ($1.07\pm0.12$). There was no difference between patients with minor and major cardiac events (Figure 3.6.4.1).

Quantitative exercise heart/lung ratio in patients with no cardiac events was $2.01\pm0.51$, which was significantly higher than in patients with minor cardiac events ($1.7\pm0.38; \ P<0.02$), major events, ($1.55\pm0.43$;
Figure 3.6.4.1

Distribution of left ventricular exercise/rest thallium-201 index in patients' subgroups: (0) no cardiac events, (1) minor cardiac events, and (2) major cardiac events.
P<0.001) and any cardiac event (1.64±0.40; P<0.001). There was no
difference between patients with minor or major cardiac events (Figures
3.6.4.2 and 3.6.4.3).

If 1.9 was considered as the lower limit of normal (threshold), the
sensitivity of exercise heart/lung ratio for predicting cardiac events
was 69%, specificity 55% and predictive accuracy 60% ($X^2=4.78$, DF=2;
P=NS). It was not able to discriminate between minor and major events
($X^2=2.197$, DF=1; P=NS). However, when 1.7 was taken as the threshold,
the sensitivity was 54%, specificity 77% and predictive accuracy 68%,
($X^2=12.14$, DF=2; P<0.01). There was a significant difference between
patients with minor and major cardiac events ($X^2=6.21$, DF=1; P<0.02).
Moreover, when 1.5 was considered as the threshold, the sensitivity was
36%, specificity 90% and predictive accuracy 69%, ($X^2=32.97$, DF=2;
P<0.001). Unfortunately, it was not able to discriminate between
patients with minor and major cardiac events ($X^2=1.88$, DF=1; P=NS) (Table
3.6.4.1).

3.6.5 Cardiac catheterization and coronary arteriography

Of the patients who developed no cardiac events, there were 35 (60%)
with single vessel disease, 15 (26%) with two vessel disease and 8 (14%)
with three vessel disease. In those who experienced minor cardiac
events, 13 (65%) had single vessel disease, 7 (35%) had two vessel
disease, and none with three vessel disease. Furthermore, in those who
experienced major events, 2 (12%) had single vessel disease, 8 (47%)
with two vessel disease and 7 patients (41%) had three vessel disease.
Chi-square analysis showed significant differences between patient
Figure 3.6.4.2

Distribution of quantitative exercise thallium-201 heart/lung ratio in patients' subgroups during follow-up.
Figure 3.6.4.3

Distribution of quantitative exercise thallium-201 heart/lung ratio in patients with and without cardiac events during follow-up.
TABLE 3.6.4.1

The value of exercise heart/lung ratio for predicting prognosis.

<table>
<thead>
<tr>
<th>Threshold level</th>
<th>1.9</th>
<th>1.7</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>69</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>55</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>Predictive value (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>49</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Negative</td>
<td>74</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>60</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Significance 'P'</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

'P' value is based on Chi-square test
NS: Not significant
subgroups ($X^2=18.84$, DF=4, $P<0.001$). However, when the patients with any cardiac event were considered as one group, there were 15 (40.5%) with single vessel disease, (40.5%) with two vessel disease and 7 (19%) with three vessel disease. Chi-square testing showed no significant difference between patients with no cardiac events and any cardiac event ($X^2=3.6$, DF=2; $P=NS$). On the other hand, there was a significant difference between patients with minor and major cardiac events ($X^2=14.98$, DF=2; $P<0.001$). Left ventricular end-diastolic pressure in patients with no cardiac events was $13.8\pm9$ mmHg, which was not different from patients with minor events ($15\pm8.6$ mmHg) and any cardiac event ($17.5\pm10.4$ mmHg), but significantly lower than in patients with major events, ($21\pm11.9$ mmHg; $P<0.02$). There was no difference between patients with minor and major events. Chi-square testing showed significant differences between patient subgroups, ($X^2=15.6$, DF=2; $P<0.001$).

3.7 MULTIVARIATE ANALYSIS

3.7.1 Diagnosis

Multivariate analysis was used to predict the presence or absence of multiple vessel coronary artery disease. The scores of coronary arteriography were used to group patients into those who had single vessel disease and multiple vessel disease. Coronary anatomy was the 'gold standard' against which the non-invasive indices were evaluated.

All the patients in this study (n=105) underwent graded exercise electrocardiography and gated blood pool ventriculography. However,
only 101 patients underwent thallium-201 myocardial scintigraphy and 95 patients underwent selective coronary arteriography. Completed data suitable for the multivariate analysis was obtained from 93 patients.

The deviance, degrees of freedom (DF), residual variance, 'F' values and 'P' level of different combinations of variables are shown in Table 3.7.1.1. From this analysis, the single best predictor of multiple vessel disease was exercise thallium-201 scores (Deviance=20.188, DF=91; P=0.00037). However, the fitted value of 0.60 (Figure 3.7.1.1.) showed poor sensitivity for predicting multiple vessel disease (53%), specificity (67%), positive predictive value (62%), negative predictive value (59%) and predictive accuracy (60%). Moreover, the best two predictors of multiple vessel disease were ST-segment depression on exercise and the total regional wall motion scores (Deviance=18.181, DF=90; P=0.0022), followed by ST-depression on exercise and the total score of exercise thallium-201 scintigraphy (Deviance = 18.527, DF=90; P=0.0056) as illustrated in Table 3.7.1.1. Unfortunately, there was no significant change in sensitivity, specificity, predictive value or predictive accuracy. On the other hand, the best three predictors of multiple vessel disease were ST-segment depression on exercise, total regional wall motion scores and the presence of redistribution on thallium-201 scintigraphy (Deviance=16.392, DF=89; P=0.0025). An algorithm was derived, therefore, to demonstrate the relationship between these three variables for the diagnosis of multiple vessel disease. The distribution of single and multiple vessel disease against the fitted value of this analysis is shown in Figure 3.7.1.2:

Fitted value (FV) = 0.3052 A + 0.03506 B + 0.3082 C - 0.1449 where (A)
TABLE 3.7.1.1

Results of the multivariate analysis for the diagnosis of multiple vessel disease.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Deviance</th>
<th>DF</th>
<th>RV</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLX</td>
<td>20.188</td>
<td>91</td>
<td>0.222</td>
<td>13.7</td>
<td>0.00037</td>
</tr>
<tr>
<td>STD+RWM</td>
<td>18.181</td>
<td>90</td>
<td>0.202</td>
<td>9.94</td>
<td>0.0022</td>
</tr>
<tr>
<td>STD+TLX</td>
<td>18.527</td>
<td>90</td>
<td>0.206</td>
<td>8.07</td>
<td>0.0056</td>
</tr>
<tr>
<td>STD+RWM+RED</td>
<td>16.392</td>
<td>89</td>
<td>0.184</td>
<td>9.71</td>
<td>0.0025</td>
</tr>
<tr>
<td>STD+TLX+LFFN</td>
<td>16.901</td>
<td>89</td>
<td>0.189</td>
<td>8.56</td>
<td>0.0044</td>
</tr>
<tr>
<td>STD+RWM+LFFN</td>
<td>17.024</td>
<td>89</td>
<td>0.191</td>
<td>6.05</td>
<td>0.016</td>
</tr>
<tr>
<td>STD+RWM+TLX</td>
<td>17.392</td>
<td>89</td>
<td>0.195</td>
<td>4.04</td>
<td>0.048</td>
</tr>
<tr>
<td>STD+RWM+RED+LFFN</td>
<td>15.561</td>
<td>88</td>
<td>0.177</td>
<td>4.70</td>
<td>0.033</td>
</tr>
<tr>
<td>STD+RWM+RED+LEFD</td>
<td>14.753</td>
<td>87</td>
<td>0.169</td>
<td>4.76</td>
<td>0.032</td>
</tr>
</tbody>
</table>

DF: Degrees of freedom  
RV: Residual variance  
F: F value  
P: Probability level  
TLX: Exercise thallium-201 scores  
RWM: Regional wall motion scores  
STD: ST-segment depression  
RED: Thallium-201 redistribution  
LFFN: Left ventricular filling fraction  
LEFD: Percentage change in left ventricular ejection fraction
Figure 3.7.1.1

GLIM: Distribution of the fitted value of exercise thallium-201 scores in patients with single and multiple coronary artery disease.
Figure 3.7.1.2

GLIM: The fitted value of ST-segment depression (STD), regional wall motion score (RWM), and the presence of thallium-201 redistribution (Red) in patients with single and multiple coronary artery disease.
was ST-depression on exercise, (B) was regional wall motion score and (C) was the presence of redistribution on thallium-201 scintigraphy. For (A) and (C), the values were either (0) or (1) denoting absent or present, while for (B) the value was a real number. By selecting a threshold for the fitted value greater than 0.75, the sensitivity of this algorithm for predicting multiple vessel disease was 29%, with a specificity of 96%, a positive predictive value of 87%, a negative predictive value of 59%, and a predictive accuracy of 63%. However, when the threshold of the fitted value was lowered to 0.70, the sensitivity was improved to 42% with little effect on specificity (94%), positive predictive value (86%), negative predictive value (59%) and predictive accuracy (69%). Chi-square testing revealed no significant difference in the numbers of true positive, false positive, true negative and false negative whether a threshold of 0.70 or 0.75 was used ($\chi^2 = 1.96$, DF=3; P=NS). Furthermore, when the threshold was reduced to 0.55, the sensitivity was markedly improved to 77%, the specificity was reduced to 82%, the positive predictive value was 79%, the negative predictive value was 80%, and the predictive accuracy was 80%. There were significant differences between a threshold of 0.55 and 0.70 ($\chi^2 = 14.65$, DF=3; P<0.01), and 0.75 ($\chi^2 = 25.78$, DF=3; P<0.001) (Table 3.7.1.2).

3.7.2 Prognosis

In order to identify the best variable (or combination of variables) for prediction of subsequent cardiac events, multivariate analysis was applied to the data using GLIM program. Patients were grouped into those who developed no cardiac events during follow-up, and those who
TABLE 3.7.1.2

Effects of the threshold of the fitted value on the diagnosis of multiple vessel disease.

<table>
<thead>
<tr>
<th>Threshold level</th>
<th>0.75</th>
<th>0.70</th>
<th>0.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>13</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>False positive</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>True negative</td>
<td>46</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>False negative</td>
<td>32</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>
experienced any cardiac event. Thereafter, further analysis was carried out between patient subgroups.

Multivariate analysis revealed that the best predictor of cardiac events was the total score of regional wall motion (RWM) analysis (Deviance=17.772, DF=91; P=1.6 x 10^{-5}) Table 3.7.2.1:

Fitted value = 0.0446 RWM + 0.0547

By choosing a threshold of the fitted value greater than 0.42 (Figure 3.7.2.1), the sensitivity of regional wall motion scores for prediction of cardiac events was 62%, with a specificity of 77%, a positive predictive value of 63%, a negative predictive value of 76%, and a predictive accuracy of 71%.

The second important predictor of cardiac events was left ventricular peak filling rate (PFR) which together with regional wall motion (RWM) scores showed (Deviance=16.771, DF=90; P=0.023):

Fitted value = 0.0516 RWM + 0.1919 PFR - 0.3429

A threshold value greater than 0.42 revealed a sensitivity for prediction of cardiac events of 72%, a specificity of 76%, a positive predictive value of 65%, a negative predictive value of 81% and a predictive accuracy of 74% (Figure 3.7.2.2).

The third predictor of cardiac events was exercise thallium-201 heart/lung ratio (HLR) which together with regional wall motion (RWM)
**TABLE 3.7.2.1**

Multivariate analysis for prediction of any cardiac events.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Deviance</th>
<th>DF</th>
<th>RV</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWM</td>
<td>17.772</td>
<td>91</td>
<td>0.1953</td>
<td>20.77</td>
<td>1.6x10⁻⁵</td>
</tr>
<tr>
<td>RWM+PFR</td>
<td>16.771</td>
<td>90</td>
<td>0.1863</td>
<td>5.37</td>
<td>0.023</td>
</tr>
<tr>
<td>RWM+PFR+HLR</td>
<td>15.921</td>
<td>89</td>
<td>0.1789</td>
<td>4.75</td>
<td>0.032</td>
</tr>
</tbody>
</table>

DF: Degrees of freedom  
RV: Residual variance  
F: F value  
P: Probability level  
RWM: Regional wall motion scores  
PFR: Left ventricular peak filling rate  
HLR: Exercise thallium-201 heart/lung ratio
Figure 3.7.2.1

GLIM: The fitted value of regional wall motion scores in patients with and without cardiac events during follow-up.
GLIM: The fitted value of regional wall motion scores (RWM) and left ventricular peak filling rate (PFR) in patients with and without cardiac events during follow-up.
and peak filling rate (PFR) showed (Deviance=15.921, DF=89; P=0.032):

\[
\text{Fitted value} = 0.0399 \text{ RWM} + 0.223 \text{ PFR} - 0.2288 \text{ HLR} - 0.1135
\]

By using the same threshold (0.42), the sensitivity of this algorithm for prediction of cardiac events was 74%, with a specificity of 77%, a positive predictive value of 67%, negative predictive value of 83%, and a predictive accuracy of 76% (Figure 3.7.2.3). There were no significant differences between the number of true positive, false positive, true negative and false negative (Table 3.7.2.2) whether regional wall motion score was used alone or in combination with peak filling rate and exercise heart/lung ratio ($X^2 = 1.74$, DF=6; P=NS).

The analysis was repeated with patients grouped into those who developed no cardiac events, minor cardiac events and major cardiac events. The most predictive variable of cardiac events was the total score of regional wall motion (RWM) analysis (Table 3.7.2.3):

\[
\text{Fitted value} = 0.0777 \text{ RWM} - 0.0438
\]

When the threshold (0.42) was used, the sensitivity of regional wall motion to predict no cardiac events was 66%, minor cardiac events 55% and major cardiac events 94% (Figure 3.7.2.4). In addition, when peak filling rate (Figure 3.7.2.5) and exercise thallium-201 heart/lung ratio (Figure 3.7.2.6) were added as best predictors, there were no significant differences in sensitivity compared with regional wall motion alone ($X^2=0.51$, DF=4; P=NS) (Table 3.7.2.4).
Figure 3.7.2.3

GLIM: The fitted value of regional wall motion scores (RWM), left ventricular peak filling rate (PFR) and quantitative exercise thallium-201 heart/lung ratio (HLR) in patients with and without cardiac events.
TABLE 3.7.2.2

Predictors of any cardiac event (threshold 0.42).

<table>
<thead>
<tr>
<th></th>
<th>RMW</th>
<th>RMW+PFR</th>
<th>RMW+PFR+HLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>24</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>False positive</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>True negative</td>
<td>48</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>False negative</td>
<td>15</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

RMW: Regional wall motion scores
PFR: Left ventricular peak filling rate
HLR: Exercise thallium-201 heart/lung ratio
### TABLE 3.7.2.3

Prediction of no cardiac events, minor events and major events.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Deviance</th>
<th>DF</th>
<th>RV</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMW</td>
<td>36.926</td>
<td>91</td>
<td>0.4058</td>
<td>30.31</td>
<td>2.5X10^-7</td>
</tr>
<tr>
<td>RMW+PFR</td>
<td>34.958</td>
<td>90</td>
<td>0.3884</td>
<td>5.07</td>
<td>0.027</td>
</tr>
<tr>
<td>RMW+PFR+HLR</td>
<td>33.138</td>
<td>89</td>
<td>0.3723</td>
<td>4.89</td>
<td>0.030</td>
</tr>
</tbody>
</table>

DF: Degrees of freedom  
RV: Residual variance  
F: F value  
P: Probability level  
RMW: Regional wall motion scores  
PFR: Left ventricular peak filling rate  
HLR: Exercise thallium-201 heart/lung ratio
Figure 3.7.2.4

GLIM : The fitted value of regional wall motion scores in patients' subgroups during follow-up.
Figure 3.7.2.5

GLIM: The fitted value of regional wall motion scores (RWM) and left ventricular peak filling rate (PFR) in patients' subgroups during follow-up.
Figure 3.7.2.6

GLIM: The fitted value of regional wall motion scores (RWM), left ventricular peak filling rate (PFR), and quantitative exercise thallium-201 heart/lung ratio (HLR) in patients' subgroups during follow-up.
### TABLE 3.7.2.4

Sensitivity (%) for prediction of cardiac events.

<table>
<thead>
<tr>
<th></th>
<th>RMW</th>
<th>RWM+PFR</th>
<th>RMW+PFR+HLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cardiac events</td>
<td>61%</td>
<td>63%</td>
<td>66%</td>
</tr>
<tr>
<td>Minor cardiac events</td>
<td>55%</td>
<td>73%</td>
<td>68%</td>
</tr>
<tr>
<td>Major cardiac events</td>
<td>94%</td>
<td>88%</td>
<td>94%</td>
</tr>
</tbody>
</table>

RWM: Regional wall motion scores  
PFR: Left ventricular peak filling rate  
HLR: Exercise thallium-201 heart/lung ratio
An attempt was made to identify the patients who experienced major cardiac events from those who developed no events or minor cardiac events. The sensitivity of regional wall motion scores alone was 94%, with a specificity of 57%, a positive predictive value of 31%, a negative predictive value of 98%, and a predictive accuracy of 63%. For regional wall motion and peak filling rate, these values were 94%, 52%, 29%, 98% and 59% respectively. When exercise heart/lung ratio was added they became 94%, 56%, 30%, 98% and 62% respectively. The same threshold value (0.42) was used in all calculations. Chi-square testing revealed no significant differences in the number of true positive, false positive, true negative or false negative in the three models ($X^2=0.417$, DF=6; P-NS). Similarly, when an attempt was made to identify major events from minor events using regional wall motions score alone, these were 94%, 45%, 57%, 91% and 67% respectively. When peak filling rate was added to regional wall motion scores, these were 94%, 27%, 50%, 86% and 56% respectively. Furthermore, when exercise heart/lung ratio was added, these were 94%, 32%, 52%, 88% and 59% respectively. There were no significant differences between the three models ($X^2=1.735$, DF=6; P-NS).

It appears, therefore, that the total score of regional wall motion analysis alone is the most predictive index of subsequent major cardiac events over a mean follow-up period of 18.8±3.4 months after acute myocardial infarction. The addition of either peak filling rate or exercise thallium-201 heart/lung ratio or both did not alter the sensitivity, specificity, positive and negative predictive values and the predictive accuracy significantly.
CHAPTER 4

DISCUSSION
4 DISCUSSION

Although the mortality from coronary artery disease is declining, physicians still face the task of identifying potential victims, especially when coronary artery disease has been manifested by a first myocardial infarction. There are two basic groups of these patients: 1) survivors of complicated myocardial infarction who have residual left ventricular dysfunction, or complex ventricular dysrhythmia, or both; and 2) 'asymptomatic' survivors of uncomplicated infarction. One would anticipate that these two groups of patients have a distinctly different prognosis (Luria et al, 1979). However, some in the latter group may still experience unstable angina, recurrent myocardial infarction, or even sudden death in the months or years that follow infarction. It is for these patients that a full assessment was carried out in this study to identify those who are at a higher risk of subsequent cardiac events (Fuller et al, 1981).

In recent years, clinical assessment has been supplemented by the use of haemodynamic subsets (Weber et al, 1979). In addition, Bigger (1979) focused attention on the importance of examining 'functional components', namely, ischaemic potential, haemodynamic status and dysrhythmia potential. The tools for such assessment included systolic time intervals, ambulatory electrocardiographic monitoring, myocardial perfusion scintigraphy, gated blood pool ventriculography, programmed electrical stimulation, biochemical studies of cardiac enzymes, as well as exercise testing. Much of this effort was designed to identify those patients who seemed to need coronary angiography.
In this study, patients underwent graded exercise electrocardiography, gated blood pool ventriculography, thallium-201 myocardial perfusion scintigraphy and selective coronary arteriography, 6-8 weeks after acute myocardial infarction. The non-invasive tests were used to identify patients with more severe coronary artery disease and at a higher risk of subsequent cardiac events over a two-year follow-up period.

4.1 GRADED EXERCISE ELECTROCARDIOGRAPHY

Over the past two decades, considerable experience with exercise testing after acute myocardial infarction has been reported worldwide. This experience has demonstrated the safety of exercise testing, despite the presumed 6 weeks required for complete healing of the pathological process. Very few fatalities have been reported in the literature, one from ventricular fibrillation (Pederson et al, 1980) and another from myocardial rupture (Lindsay J. 1979). However, the true incidence of such complications is probably not known.

One of the potential negative aspects of early exercise testing (i.e. before discharge from hospital or after 3 weeks of the episode) would be the discovery of seemingly important findings that then disappear on subsequent testing. Starling et al (1981a), however, showed that an early ischaemic electrocardiographic response persisted as a positive test at a later date, thus supporting the legitimacy of the early test. On the other hand, a report from DeBusk et al (1980) implied that early tests yield ischaemic responses which are not seen on later tests, but still had important predictive power for subsequent events. These controversial reports and the fact that the pathological process
requires around 6 weeks for complete healing influenced the design of this study in such a way that all exercise tests, both treadmill and bicycle ergometry, were performed 6-8 weeks after the infarction.

In addition to differences in inclusion criteria and the timing of exercise in relation to the infarction, studies have varied widely in terms of the specific exercise protocols utilized and the termination points of the studies. In some reports, tests have been symptom-limited, and in some, heart rate-limited, often with submaximal heart rate end points. In this study, patients underwent maximal symptom-limited exercise tests using a modified Balke protocol (Table 2.2.1).

The results of this study confirm previous reports in spite of variations in the timing of exercise, patient selection and exercise protocol. Starling et al (1981) found that the sensitivity of ST-segment depression during modified treadmill exercise testing before discharge from hospital for predicting multiple vessel disease was 54% with a specificity of 75%. In this study, the sensitivity of exercise-induced ST-depression was 59% with a specificity of 77%. On the other hand, Sullivan et al (1985) did not find ST-depression on exercise to be predictive of multiple vessel disease. More recently, Bishop et al (1987) reported that ST/HR slope failed to predict the severity of coronary artery narrowing in 67% of patients studied 4-6 weeks after myocardial infarction. Other studies (Schwartz et al 1981, Mannering et al, 1987) demonstrated that exercise-induced ST-depression within 3 weeks of infarction was a useful indicator of multiple vessel disease (sensitivity 90%). The degree of reproducibility of exercise testing variables after myocardial infarction remains uncertain even when
similar exercise timing, protocols and end-points were used. Handler and Sowton (1984) reported diurnal variations in the results of predischarge submaximal exercise testing after infarction. They found that exercise-induced ST-segment depression was reproducible in 57% of patients. Moreover, ST-elevation was reproducible in 71% of patients and angina was reproducible in 40% of patients.

In this study, men showed significantly better exercise tolerance compared with women; however, there was no relationship between the site or extent of infarction and exercise tolerance. Similarly, there were no effects of exercise-induced ST-segment displacement, the presence of reversible ischaemia and the severity of underlying coronary artery disease on exercise tolerance. The resting and maximal exercise double product were significantly higher in patients with fixed myocardial perfusion defects compared with those who showed reversible ischaemia on thallium-201 scintigraphy.

Exercise-induced hypotension has been reported to be a reliable sign of severe coronary artery disease. Thomson and Keleman (1975) described 15 patients with hypotension accompanying the onset of angina and postulated that critical coronary artery narrowing caused the systolic pressure to fall, because during exercise a large portion of the left ventricular mass became ischaemic, thus producing left ventricular dysfunction. A sustained exercise-induced decrease in peak systolic blood pressure of 10 mmHg or more was found to be highly specific for multiple vessel disease (Morris et al, 1978 and Gibbons et al, 1987). Moreover, Sullivan et al (1985) found that the only statistically significant predictors of multiple vessel disease were an abnormal blood
pressure response to submaximal exercise or limited effort capacity. In this study, hypotension was seen in 7 (6.7%) of patients among whom 3 had multiple vessel disease, 2 had single vessel disease and 2 refused to give informed consent to undergo cardiac catheterization. The total exercise time was significantly shorter in this group, compared with the patients who had a normal blood pressure response. Similar findings were reported by Levites et al (1978) who in addition found a higher percentage of females in the group who developed hypotension. In this study, there was only one female patient among this group.

The value of exercise testing after infarction in the determination of short- and long-term prognosis has been widely studied. The development of symptoms during early post-infarction exercise testing has been of value in predicting subsequent chronic angina and, to a lesser extent, mortality. In addition, the results of exercise testing can predict those patients who subsequently will undergo coronary artery bypass grafting. Theroux et al (1979) studied 210 selected patients soon after acute infarction and found that 65% of patients who reported chest pain during exercise testing subsequently developed angina over a 12-month period; however, only 36% of patients who did not report chest pain during the study subsequently developed angina. Exercise-induced angina pectoris in the absence of ST-segment depression was found to correlate with subsequent coronary bypass surgery, but not with the occurrence of subsequent 'medical' events (sudden death, ventricular fibrillation and reinfarction; Davidson and DeBusk, 1980). Granath et al (1977) compared the prognostic value of exercise testing three and nine weeks after infarction. While there was no statistically significant difference in prognosis between symptomatic and asymptomatic patients on exercise 3
weeks after infarction, exercise-induced angina nine weeks post infarction conferred a modestly increased mortality risk (34% with angina vs 19% without angina; P<0.05). Furthermore, in another report utilizing maximal exercise testing 8 weeks after infarction (Koppes et al, 1980), it was found that 27% of patients with exercise-induced angina and ST-depression, 25% of patients with angina alone and 29% of patients with ST-depression alone had complications during the subsequent 2 years, (death, reinfarction, bypass grafting and congestive cardiac failure). However, the incidence of such events was only 12% in those patients without symptoms or electrocardiographic abnormalities during exercise. In this study, the presence of symptoms at maximal exercise did not differentiate between minor and major cardiac events; however, it was able to predict cardiac events during the follow-up period. Similarly, the occurrence of ST-segment depression, regardless of symptoms, was unable to predict cardiac events. Moreover, 36% of asymptomatic patients with no ST-depression, 54% of symptomatic patients with significant ST-depression, 20% of asymptomatic patients with significant ST-depression and 48% of symptomatic patients with no ST-depression experienced cardiac events. These findings confirm previous reports (Sami et al, 1979; Theroux et al, 1979 and Smith et al 1979) demonstrating the value of exercise-induced ST-depression in predicting cardiac events. In addition, DeBusk et al (1980b) found ST-depression of 0.2 mV or more to be the single most valuable prognostic indicator of clinical, electrocardiographical and exercise-related variables. Once more, it must be noted that the exercise timing and protocols of these reports were different from that conducted in this study.

Saunamaki and Anderson (1981 and 1982) found that mortality increased
significantly among patients with major ventricular arrhythmias and among those with a small increase in the pressure-rate product from rest to maximal exercise 3 weeks after infarction. In this study, only three patients developed significant ventricular arrhythmia during exercise testing, none of whom experienced a major cardiac event. However, the change in the pressure-rate product was significantly higher in those who did not experience cardiac events than those who did.

The use of exercise testing to study prognosis in the postinfarction population was further examined by Starling et al (1981a). They evaluated the value of predischarge and 6-week postinfarction treadmill exercise tests and found that exercise-induced ST-segment depression was highly reproducible, while angina, inadequate blood pressure response and ventricular arrhythmias were of limited reproducibility between the early and 6-week tests. Twenty one percent of their study population were able to complete only the pre-discharge exercise test, among whom 43% experienced an early cardiac event precluding repeat testing. ST-segment elevation occurred in the area of infarction in 31% during the predischarge test and in 14% during the 6-week test. In this study 17% of patients developed ST-elevation but without any evidence that it influenced prognosis. The exact mechanism of ST-elevation on exercise is not fully understood, but most studies have suggested that this phenomenon is related to abnormal left ventricular wall movement associated with a ventricular scar rather than to myocardial ischaemia (Chahine et al, 1976; Castellanet et al, 1978). It was reported as a predictor of single vessel disease rather than multiple vessel disease (Weiner et al, 1978), and the only exercise variable which predicted cardiac death (Sullivan et al, 1984). On the other hand, Fox et al
(1983) suggested that ST-elevation should be considered as important as ST-depression in terms of left ventricular function, coronary anatomy and myocardial ischaemia.

In a series of 456 patients tested shortly before hospital discharge, (Madsen and Gilpin; 1983) compared with a group of 430 patients who did not undergo exercise testing, correct prediction of death after infarction could not be improved by adding exercise data to the clinical variables. However, exercise test data alone or added to clinical variables could improve the prediction of new infarction. Moreover, Williams et al (1984) compared clinical and treadmill variables for the prediction of outcome after myocardial infarction. They found that a history of previous myocardial infarction and ST-segment depression on the resting electrocardiogram indicated a poor prognosis after acute infarction. Poor endurance was the only exercise variable that suggested a future cardiac event. Surprisingly, in this study ST-segment depression on exercise did not predict any event, nor did it improve the predictive accuracy of the clinical variables. In this study, there was no difference in prognosis between patients with or without ST-depression, confirming previous reports. However, when patients with ST-depression were subdivided according to their symptoms, there was a significant difference between those who developed angina and/or dyspnoea on exercise compared with those who were asymptomatic (Al-Khawaja et al, 1988a). Similarly, Jennings et al (1984), found ST-segment changes on exercise testing to be less predictive of later complications than haemodynamic signs (e.g. exertional hypotension or undue acceleration of heart rate). The importance of exercise-induced hypotension in stratification of patients into high- and low-risk groups
was further emphasised by Krone et al (1985), Stone et al (1986) and Waters et al (1985). In those who were evaluated in this study, 7 (6.6%) patients developed systolic hypotension among whom 2 (28.6%) experienced no cardiac events, 4 (57%) developed minor cardiac events and only 1 (14.3%) developed major events. These findings support previous reports in spite of differences in exercise timing and protocols.

The results presented here indicate that exercise testing can be a very useful prognostic tool, particularly when added to basic clinical data. The controversy about its diagnostic and prognostic value and the need for further stratification of postinfarction patients at higher risk, have lead to the use of other non-invasive tools in the postinfarction assessment. These include radionuclide determination of left and right ventricular performance and exercise thallium-201 myocardial perfusion scintigraphy.

4.2 GATED BLOOD POOL VENTRICULOGRAPHY

Exercise testing has been shown to offer potentially important benefits after acute myocardial infarction. However, controversy remains regarding the precise value of such testing in the individual patient. The lack of uniformity of patient selection criteria (study populations) has caused difficulties in interpreting currently available data. Differences in study populations are evidenced by wide variations in mortality rate during the year following infarction. Annual mortality has ranged from as low as 2% (Sami et al, 1979) to near 10% (Theroux et al, 1979) in the studies involving exercise assessment. There is some
evidence that differences in results obtained in previous studies may have reflected differences in left ventricular function among study patients. Risk stratification studies by Bigger et al (1978) and Moss et al (1976) first demonstrated the importance of left ventricular function (assessed clinically) as an indicator of post-infarction mortality. Abnormalities of left ventricular function can provide an index of the extent of ischaemic damage associated with infarction. The extent of myocardial damage has been long known experimentally and from clinical autopsy studies to be a major determinant of survival after infarction. Therefore, the apparent relationship between left ventricular function and prognosis after infarction is not unexpected. Noninvasive radionuclide angiography has been employed in determination of left and right ventricular function in the post-infarction setting. The prognostic value of left ventricular function at rest by radionuclide angiography has been demonstrated in the early peri-infarction period by several investigators (Kostuk et al, 1973; Schelbert et al, 1976; Battler et al, 1980; Wackers et al, 1982). However, the results of Shulze et al (1977) and Borer et al (1980) suggested that assessment of left ventricular function two weeks after infarction was of greater predictive value than determinations obtained earlier.

4.2.1 Left ventricular function

Left ventricular function assessed by radionuclide angiography during exercise has been shown to be more sensitive than exercise electrocardiography in detecting ischaemia in patients with chronic stable angina (Borer et al, 1979; Heber et al, 1988) and after acute
In this study left ventricular ejection fraction in patients was significantly lower than the normal controls. In addition, ejection fraction fell by 4.7% at maximal exercise which was thought to be an indicator of further myocardial ischaemia (Tan et al, 1982). There are controversial reports of the response of ejection fraction to exercise in coronary artery disease. Borer et al (1977) and Schoolmeester et al (1981) reported a decrease in ejection fraction during exercise, Port et al (1981) reported an increase in ejection fraction and Caldwell et al (1980) found ejection fraction to be unchanged with exercise. More recently, radionuclide angiography was reported to be of limited value in the non-invasive diagnosis of coronary artery disease (Wieshammer et al, 1985; Heber et al, 1988). However, the patient population in this study consisted of a selected group in whom coronary artery disease was manifested by an episode of myocardial infarction. The site of myocardial damage due to the infarction process appeared to affect left ventricular performance. Both systolic and diastolic parameters were abnormal compared with the normal controls. In addition, patients with transmural anterior infarction showed significantly depressed left ventricular function compared with those with transmural inferior infarction (Shah et al, 1980) and subendocardial infarction, both at rest and during maximal exercise. Moreover, there were no differences between the latter two groups.

Surprisingly, patients who showed significant reversible ischaemia on thallium-201 imaging had similar resting left ventricular function to those who showed fixed perfusion defects due to 'scar'. Nevertheless,
both groups reduced the ejection fraction significantly during maximal exercise. These results contradict previously reported data; Plotnick et al, (1985) showed that patients without reversible ischaemia responded to exercise by increasing the ejection fraction, similar to normal subjects. This discrepancy could be explained by differences in patients selection, timing of studies after infarction and the exercise protocol. In this study, patients were studied 6-8 weeks after infarction and supine exercise was carried out while patients continued to take their usual medications. On the other hand, Plotnick et al (1985) studied their patients 2-12 months after infarction and patients stopped receiving their medications to undergo upright bicycle exercise.

Resting and exercise left ventricular ejection fraction has been shown to correlate with the coronary anatomy in patients with coronary artery disease, (Jones et al, 1985; Clements et al, 1987). The results of this study confirmed previous reports of depressed left ventricular ejection fraction in patients with multiple vessel disease. In addition, both groups with single and multiple vessel disease showed a significant fall in ejection fraction during maximal exercise. The sensitivity of resting ejection fraction in predicting multiple vessel disease was 46%, with a specificity of 63% and a predictive accuracy of 55%. On exercise, the sensitivity was improved to 89%, with a specificity of 24% and predictive accuracy of 56%, assuming that the normal response is an increase of 5% in ejection fraction relative to the resting value (Borer et al, 1977 and 1979).

Abnormalities in diastolic properties of the left ventricle in patients with coronary artery disease have been reported in numerous studies
(Bonow et al, 1981; Mancini et al, 1983; Inonye et al, 1984; Lahiri et al, 1987). In this study, patients showed significantly abnormal diastolic indices (peak filling rate and first third filling fraction) compared with the normal controls. However, unlike Mancini et al (1983) this study showed a non-significant difference in time to peak filling in post-infarction patients compared with the normal subjects. This could be explained by the relatively large number of subjects included in this study who had a myocardial infarction 6-8 weeks before the assessment. In spite of using the same technical approach, Mancini et al (1983) studied a total of 34 patients with coronary artery disease among whom 14 only had a previous myocardial infarction.

The total score of regional wall motion analysis showed significantly higher scores in patients with anterior infarction compared with those with inferior or subendocardial infarction. This is probably related to the extent of myocardial damage after infarction as shown in previous reports (Neumann et al, 1984; Wieshammer et al, 1985; Buda et al, 1986). In addition, regional wall motion score was significantly higher in patients with multiple vessel disease compared with those who had single vessel disease. In this study, wall motion abnormalities were assessed by a qualitative approach as it was reported that quantitative analysis was unable to provide any significant additional diagnostic accuracy compared with the visual interpretation by experienced observers (Wieshammer et al, 1985).

Left ventricular ejection fraction determined by radionuclide ventriculography in the early stages of myocardial infarction was found to be predictive of short term prognosis (Shah et al, 1980; Nemerovski
et al, 1982). On the other hand, sequential measurements of ejection fraction after infarction showed that changes tended to occur early in the hospital course, with little subsequent change (Nemerovski et al, 1982). Significant changes in ejection fraction typically occurred without concurrent change in regional wall motion, suggesting alteration in ventricular loading rather than change in intrinsic myocardial contractility. Therefore, these workers found that the initial depression (not the sequential change) in ejection fraction was correlated with in-hospital mortality and morbidity.

Corbett et al (1983) performed submaximal exercise radionuclide ventriculography before hospital discharge and found that exercise changes in left ventricular ejection fraction and end-systolic volume were more reliable than clinical, exercise and other scintigraphic variables for predicting future cardiac events.

In this study, patients with no cardiac events had a significantly different ejection fraction than those with minor or major events both at rest and during maximal exercise. Resting ejection fraction was unable to differentiate between patients with minor and major cardiac events; however, there was a significant difference in exercise ejection fraction between the two groups (Morris et al, 1985). In addition, the total scores of regional wall motion analysis appeared to be predictive of subsequent cardiac events. There was a consistent increase in wall motion score with increasing severity of cardiac events. Morris et al (1985) reported the change in ejection fraction from rest to exercise and exercise-induced wall motion abnormalities to be most specifically related to exercise-induced ischaemia and not
predictors of subsequent mortality. However, they found that exercise-induced wall motion abnormality was the only variable that was related to recurrent infarction.

### 4.2.2 Absolute left ventricular volumes

The measurement of absolute left ventricular volume has been described and validated previously (Links et al, 1982; Al-Khawaja et al, 1984 and 1988F). Although resting end-diastolic volume in patients was not statistically different from the normal subjects, resting end-systolic volume was higher than in the normal controls. These findings in part confirm previous reports (Kostuk et al, 1973; Hammermeister et al, 1979; Lamas et al, 1986). The similarity of end-diastolic volume, both at rest and during exercise, to that seen in normal subjects is contrary to previously published data. However, left ventricular volumes were found to be only modestly elevated during the initial 48 hours of myocardial infarction (Rigo et al, 1974b; Ohsuzu et al, 1983), even in patients with most severe wall motion abnormalities and the lowest ejection fraction.

Echocardiographic studies have described thinning and dilatation of the infarcted myocardium occurring from the time of presentation up to 14 days after the acute infarct (Hutchins et al, 1978; Eaton et al, 1979; Erlebacher et al, 1984). Moreover, this process of ventricular enlargement may continue well after the histological healing of the infarct region (Pfeffer et al, 1982; Jeremy et al, 1987). Progressive left ventricular dilatation may occur in the late post infarct period and involves a process distinct from infarct expansion, since it
continues after scar tissue formation and may involve the noninfarcted myocardium (Erlebacher et al, 1982). Lamas and Pfeffer (1986) studied retrospectively a uniform group of patients with a history of myocardial infarction and obstructive coronary artery disease (more than 50% narrowing) confined to the left anterior descending artery. They found that left ventricular remodelling in the chronic phase of infarction, resulted in alterations in left ventricular volumes that were proportional to the degree of wall motion abnormality. In this study, a non-uniform group of patients with a variety of coronary anatomy were studied 6-8 weeks after infarction. Both resting end-diastolic and end-systolic volumes were found to be higher than the normal controls, but the difference was not statistically significant. In addition, these volumes were significantly higher in men than in women and in patients with reversible ischaemic myocardium than in those with fixed perfusion defects only.

During exercise, both end-diastolic and end-systolic volumes increased significantly, confirming previous reports (Tan et al, 1982). The disproportionate increase in volumes could explain the changes in ejection fraction in response to exercise (Corbett et al, 1983; Plotnick et al, 1985; Mann et al, 1987).

The resting end-diastolic volume was significantly different in patients with no cardiac events compared with those who experienced major cardiac events. This parameter was unable to differentiate between minor and major events. Similar findings were seen in end-systolic volume, but it did differentiate between minor and major events. On exercise, both end-diastolic and end-systolic volumes were similar in patients with no
events and minor cardiac events. However, exercise end-systolic volume was useful in identifying the patients who subsequently developed major cardiac events, confirming previous reports (Corbett et al, 1983; White et al, 1987). In a series of 605 male patients, 1-2 months after infarction White et al (1987) used a multivariate analysis and showed that end-systolic volume had a greater predictive value for survival than end-diastolic volume or ejection fraction.

4.2.3 End-systolic pressure/volume index (ratio)

Left ventricular function has been defined by the relationship between the instantaneous left ventricular pressure and left ventricular volume at the end of systole in both canine (Sagawa et al, 1977) and human studies (Grossman et al, 1977; Nivatpumin et al, 1979; Dehmer et al, 1981; Mehmel et al, 1981). This relationship has the advantage of being relatively independent of preload over a wide range of left ventricular pressures and volumes (Ginzton et al, 1984). The ability to determine noninvasively, left ventricular pressure/volume ratio is dependent on three factors: an accurate estimate of peak systolic pressure, an accurate measurement of left ventricular end-systolic volume, and obtaining these values as simultaneously as possible. Reicheck et al (1982) demonstrated a close correlation between sphygmomanometric peak systolic pressure and both left ventricular peak systolic and end-systolic pressures. The noninvasive measurement of end-systolic volume and left ventricular pressure/volume ratio have been validated in this study with good reproducibility (Table 3.3.5.3).

In this study, normal subjects increased the pressure/volume ratio on
exercise confirming previous reports (Ginzton et al, 1984; Iskandrian et al, 1983). In patients, both rest and exercise pressure/volume ratio were different from the normal controls. However, there was a non-significant reduction in the pressure/volume ratio with exercise. In addition, there was no difference between patients with a fixed perfusion defect and those with a reversible ischaemic myocardium implying a limited value of pressure/volume ratio in identifying patients with further ischaemia. Moreover, the site of infarction appeared to affect the left ventricular pressure/volume ratio, because patients with anterior infarction showed significantly lower values than patients with inferior infarction. Nevertheless, there was no difference between transmural and subendocardial infarction which might indicate important haemodynamic changes even in the absence of full thickness myocardial necrosis. Peak systolic pressure/volume ratio had an additional diagnostic value in patients with multiple vessel disease, who showed a significantly lower ratio than patients with single vessel disease. More recently, Gibbons et al (1987) reported their observations in 243 patients with coronary artery disease. They found that the left ventricular pressure/volume ratio did not offer any advantage over ejection fraction for the detection of exercise-induced ischaemia.

Left ventricular peak systolic pressure/volume ratio has a potential prognostic value as it was significantly different, both at rest and during exercise, in patients with subsequent cardiac events than in those without events. In addition, it was able to discriminate between patients with minor and major events. Unfortunately, there was no difference between patients without cardiac events and those who
experienced minor events. These findings are consistent with data reported by Corbett et al (1983) who found that the pressure/volume ratio was the third highest rated variable in the first step of the discriminant analysis (after ejection fraction and end-systolic volume index). The controversy over the diagnostic and prognostic value of the left ventricular pressure/volume ratio, especially during exercise, is probably related to the exponential relationship between the end-systolic pressure/volume ratio and ejection fraction at peak exercise (Ginzton et al, 1984). This ratio has been shown to be a more sensitive indicator of left ventricular function than ejection fraction in the normal and mildly depressed ventricle. Conversely, it appears to be less sensitive than ejection fraction in assessing left ventricular function in a severely depressed ventricle (Ginzton et al, 1984).

4.2.4 Velocity of circumferential fibre shortening

The noninvasive measurement of the velocity of circumferential fibre shortening (Vcf) using radionuclide ventriculography was found to be well correlated with measurements obtained from contrast angiography (Steele et al, 1976; Bhargava et al, 1982). Vcf has been shown to be an important and useful index of left ventricular systolic performance (Karliner et al, 1971). It is preload and afterload independent (Al-Khawaja et al, 1986) and may be more sensitive than ejection fraction for discerning left ventricular dysfunction in patients with coronary artery disease.

Using similar techniques, there was a poor correlation between Vcf measured by radionuclide ventriculography and contrast angiography. In
addition, there were significant intraobserver (P<0.01) and interobserver (P<0.05) differences when the measurements were repeated in a group of patients. Although Vcf was significantly different in patients than in the normal subjects, it was unable to discriminate between patient subgroups. There was no effect of the site of infarction, the presence of reversible ischaemic myocardium and the number of diseased coronary vessels on Vcf. Similarly, there was no difference in Vcf between patients who developed minor or major cardiac events, although it was significantly different between those who developed major events than those without. This finding imply a limited value in identifying patients who are at a higher risk of major events.

4.2.5 Pulmonary blood volume ratio

Exercise-induced left ventricular dysfunction may result in elevated left ventricular filling pressure, which is thought to be responsible for an increase in pulmonary blood volume (Nichols et al, 1979; Okada et al, 1982). Equilibrium radionuclide ventriculography was reported to be a useful method for determining exercise-induced changes in pulmonary blood volume ratio (Okada et al, 1979 and 1980; Wilson et al, 1983). In this study, pulmonary blood volume ratio was measured in 62 normal subjects using similar techniques. There was a wide variation in the measurements with a mean value of 1.24±0.25. Although some studies have suggested that pulmonary blood volume ratio in normal subjects falls with exercise (Nichols et al, 1979; Levinson et al, 1966), Braunwald et al (1963) found no consistent change in left ventricular filling pressure in patients with "nearly normal" hearts. In addition Ross et al (1966) reported a fall in left ventricular end-diastolic pressure
with exercise in 5 out of 7 normal subjects. Furthermore, in normal
dogs, Vatner et al (1972) reported an increase in left ventricular end-
diastolic pressure on exercise.

Using noninvasive radionuclide ventriculography, pulmonary blood volume
ratio was reported to be 0.94 (Okada et al, 1979) and 0.924 (Okada et
al, 1982) in normal subjects, suggesting a fall in pulmonary blood
volume on exercise. However, their normal values were based on data
obtained from a small number of subjects (10 and 9 respectively). In
view of the variable findings from invasive studies, larger number of
normal subjects were required to establish a 'normal' range. This study
examined at rest and during maximal exercise 62 normal subjects and
showed an increase in pulmonary blood volume on exercise yielding a
ratio of 1.24±0.25.

Experimental evidence suggests that exercise-induced myocardial
ischaemia is associated with haemodynamic alterations resulting in
increased left ventricular end-diastolic pressure, decreased ejection
fraction (Borer et al, 1977), increased left ventricular wall tension
and left ventricular volume (Nichols et al, 1979). The resultant
increase in left atrial pressure is thought to be responsible for
transient pulmonary oedema which occurs during exercise-induced
ischaemia (Lahiri et al, 1984). Left ventricular filling pressure has
been shown to increase dramatically during supine bicycle exercise
(Carroll et al, 1983) and pulmonary blood volume ratio has therefore
been thought to be a good indicator of abnormal increase in left
ventricular filling pressure during exercise (Okada et al, 1982).
In this study, pulmonary blood volume ratio was not found to be of value since the large normal group also exhibited an increase in this ratio on exercise. Although the patients had a significantly higher pulmonary blood volume ratio than normal, there was a great overlap between the two groups with only 12.4% of patients having ratios above the upper limit of normal. In addition, pulmonary blood volume ratio was unable to discriminate between patients with normal or abnormal left ventricular function as assessed by ejection fraction (Al-Khawaja et al, 1988c). Surprisingly, pulmonary blood volume ratio was higher in patients with normal ejection fraction, those with inferior myocardial infarction, subendocardial infarction and patients with single vessel disease. The reason for this finding remains obscure. Therefore, this study failed to support previous reports (Okada et al, 1979; 1980; 1982) of the value of pulmonary blood volume ratio estimated by equilibrium radionuclide ventriculography. This study underlines the importance of studying large enough numbers of subjects to establish a normal range for any given laboratory before applying reported techniques to clinical use. Therefore, non-invasive assessment of pulmonary blood volume ratio remains of doubtful diagnostic and prognostic value.

4.2.6 Right ventricular function

Although the pathophysiology of myocardial infarction has been known for at least a century (Lie, 1978), dominant right ventricular involvement was only described within the past twenty years (Wade, 1959; Cohn et al, 1974). Isner et al (1978) found that the right ventricle was affected only when there was transmural inferior left ventricular infarction. Other investigators found that the right ventricle was
affected in 34% of such patients (Ratliff and Hacket, 1980). The right ventricular free wall, in man, is exclusively supplied by the right coronary artery (Farrer-Brown G, 1968); however, free wall contraction contributes only a small part of the total systolic volume change of the right ventricle. Contraction of the interventricular septum and the crista supraventricularis may be far more important than that of the free wall (James, 1985). Since the interventricular septum receives blood from the left anterior descending coronary artery, right ventricular dysfunction might occur not only in patients with inferior infarction but also in those with anterior infarction.

Rigo et al (1975) showed that the ratio of right ventricular to left ventricular area after inferior infarction was higher than after anterior infarction, suggesting disproportionate dilatation of the right ventricle. Other investigators found that the right ventricular ejection fraction was depressed in patients after inferior infarction but normal in patients after anterior infarction (Reduto et al, 1978; Tobinick et al, 1978). Steele et al (1977) reported that all patients on the first day after inferior infarction had impaired right ventricular function that appeared to recover rapidly, whereas after anterior infarction only one third of patients developed transient abnormalities. Other investigators found impaired right ventricular function in patients after both inferior and anterior infarction which persisted in the group with inferior infarction but not in those with anterior infarction (Marmor et al, 1981). Moreover, while right ventricular free wall infarction is related to inferior infarction (Rodrigues et al, 1986) and right coronary artery disease (Ratliff and Hacket, 1980), right ventricular dysfunction may occur independently of
these features when it is associated with anterior infarction (Marmor et al, 1981; Steele et al, 1977).

In this study, resting right ventricular ejection fraction in patients was not different from normal when measured 6-8 weeks after infarction confirming previous reports (Steele et al, 1977) of reversal of the transient impairment in right ventricular function. However, while normal subjects increased right ventricular ejection fraction on exercise, patients dropped their ejection fraction significantly in response to maximal exercise, (Underwood et al, 1987). Furthermore, both right ventricular ejection time and peak filling rate were significantly different in patients than the normal controls.

Caplin et al (1987) found that right ventricular ejection fraction did not differ in patients with anterior infarction compared to those with inferior infarction. Similar findings were seen in this study and in addition patients with transmural infarction showed similar right ventricular ejection fraction to those with subendocardial infarction. Surprisingly, in 17 patients with isolated significant lesions in the right coronary artery, the right ventricular ejection fraction was not different from those who had either a single lesion in other coronary vessels or even those with multiple coronary artery lesions. These findings are contrary to previous reports of the importance of right coronary artery disease in determining right ventricular function after myocardial infarction (Ratliff and Hacket, 1980; Shah et al, 1985).

None of the previous studies looked at the effect of right ventricular function on prognosis after myocardial infarction. In this study,
resting right ventricular ejection fraction appeared to identify patients who subsequently developed major cardiac events. There was no difference in ejection fraction in patients who developed no events compared to those who experienced minor events. Moreover, a significant difference was seen between minor and major events. These findings may indicate that right ventricular function has a limited diagnostic value with additional prognostic implications after acute myocardial infarction.

4.3 THALLIUM-201 MYOCARDIAL SCINTIGRAPHY

Exercise thallium-201 scintigraphy has principally concentrated on the detection and to some extent the quantification of coronary artery disease. Nevertheless, even more than a decade after its introduction, its clinical value is not undisputed (Ritchie et al, 1977; Bailey et al, 1977; Van der Wall et al, 1985). In some centres almost all exercise tests are performed in conjunction with thallium-201 imaging, whereas in others, thallium-201 imaging is viewed with suspicion and not performed at all. This varying degree of acceptance can be traced back to the early years of thallium-201 imaging when studies were interpreted by visual inspection. Thallium-201 images are difficult to interpret and intraobserver variability is high (Trobaugh et al, 1977; Atwood et al, 1981). Although no physician would have problems in recognizing and interpreting the significance of definite transient defects, it is more difficult to determine whether, in addition to a fixed defect, transient changes are also present.

Extensive experimental and clinical knowledge on myocardial kinetics of
thallium-201 has been accumulated. At maximal exercise, thallium-201 accumulates rapidly in the normal myocardium and subsequently gradually washes out. In ischaemic myocardium however, accumulation of thallium-201 is delayed and clearance occurs at a slower rate than from normal tissue. Thallium-201 images show the relative distribution of the tracer in the myocardium and, consequently, 'normal' appearing myocardium may in fact be supplied by diseased coronary arteries. Therefore, quantitative data on thallium-201 kinetics are imperative even when images appear 'normal'. The clinical usefulness of quantitation of exercise thallium-201 images was first demonstrated by Berger et al (1981) and Maddahi et al (1981). They demonstrated greatly improved detection of coronary artery disease by quantitative methods. More recently, Wackers et al (1985) critically evaluated the quantitative approach to planar thallium-201 images, and showed increased sensitivity for the detection of coronary artery disease with maintenance of specificity. They emphasized the importance of rigorous quality control and strict adherence to standardized imaging protocols to obtain reliable and reproducible results. For this study, a comprehensive program for quantitative thallium-201 analysis was developed with easy-to-follow on-screen instructions that enables physicians with limited computing and nuclear medicine experience to acquire, process and interpret exercise thallium-201 images (Al-Khawaja et al, 1987c).

4.3.1 Quantitative thallium-201 analysis

Exercise thallium-201 myocardial perfusion scintigraphy has been shown to be a relatively reliable predictor of the extent of coronary artery
disease (Ritchie et al, 1978; Dunn et al, 1980; Patterson RE et al, 1983) after myocardial infarction. Turner et al (1980) found that exercise-induced perfusion defects after acute myocardial infarction permitted identification of 63% of patients with 70% or more stenoses of multiple coronary arteries, while exercise-induced angina or ST-segment depression of 0.1 mV or more yielded a sensitivity of 56%. However, the development of angina or ST-segment depression or perfusion defects or of the combination of such abnormalities, improved the sensitivity to 81%. Similarly, Gibson et al (1981), using limited exercise electrocardiography and thallium-201 imaging, reported that exercise induced ST-segment depression of 0.1 mV or more yielded a predictive accuracy of 45% for the identification of patients with multiple vessel coronary disease, whereas the development of exercise-induced perfusion defects was associated with a predictive accuracy of 88%. Although low workload, exercise induced ST-segment depression, angina and multiple perfusion defects each contributed to the separation of patients with multiple vessel disease from those with single vessel disease, stepwise regression analysis indicated that thallium-201 perfusion scintigraphy was the best single discriminator. In 10 patients who could not undergo exercise testing, thallium-201 imaging at rest, with subsequent redistribution analysis, was also predictive of multiple vessel disease.

More recent studies (Abraham et al, 1986; Legrand et al, 1986) showed thallium-201 imaging to be superior to exercise electrocardiography in the prediction of multiple vessel disease after myocardial infarction. Moreover, if both tests were positive this predicted a risk ratio of over three for subsequent cardiac events. In addition, Legrand et al (1986) pointed out that studies performed somewhat later than the
routine predischarge tests may prove more helpful.

The results of this study have confirmed previous reports in a group of patients studied 6-8 weeks after myocardial infarction (Al-Khawaja et al, 1987c). Visual interpretation of exercise thallium images showed higher segmental scores in patients with single vessel disease compared with those who had two or more significant lesions in the coronary tree. However, there were no differences between patients subgroups in the delayed images. The sensitivity of this qualitative analysis in prediction of multiple vessel disease was 67%, with a specificity of 50% and a diagnostic accuracy of 58%. These results confirm previous report by Van der Wall et al (1985) of the limited value of qualitative thallium-201 analysis for the detection of multiple vessel disease after infarction.

On the other hand, quantitative thallium-201 analysis revealed additional significant reversible ischaemia in 19 out of 45 patients (42%) who showed only fixed defects on visual analysis. Furthermore, 3 out of 4 patients (75%) with a 'normal' appearing myocardium had significant redistribution and/or abnormal washout on quantitative analysis. The sensitivity of quantitative thallium-201 analysis for prediction of multiple vessel disease was 78%, with a specificity of 50% and a diagnostic accuracy of 63%. However, when both qualitative and quantitative analyses were combined the sensitivity was improved to 85%, with a specificity of 53% and a diagnostic accuracy of 69%. It appears, therefore, that thallium-201 imaging is a useful tool in the identification of patients with more severe coronary artery disease after myocardial infarction. This study supports previous reports of
the importance of quantitative thallium-201 analysis (Gibson et al, 1981; Wackers et al, 1985) in yielding more reliable and accurate results.

Left ventricular dilatation on exercise has been observed in patients with severe and extensive coronary artery disease (Weiss et al, 1987). In this study, only patients with three vessel disease showed significant transient ischaemic dilatation on exercise which disappeared in the delayed images (Al-Khawaja et al, 1988e). This observation was not seen in patients with single or two vessel disease, lending support to the belief that patients with extensive coronary artery disease develop exercise-induced left ventricular dysfunction which disappears after rest. However, care should be taken not to generalise this finding because of the overlap between patient subgroups (Grover-McKay and Froelicher, 1987), although it appears useful in the stratification of patients after infarction.

4.3.2. Prognostic value of thallium-201

The prognostic value of thallium-201 myocardial perfusion scintigraphy has been demonstrated when such studies have been performed at rest in the early post infarction period, before hospital discharge, and weeks to months after infarction. Gibson et al (1980) studied 25 consecutive patients 7-35 days following inferior infarction by thallium-201 scintigraphy. Twelve of the 25 patients manifested perfusion defects only in the inferior wall; four of the 12 (33%) patients had subsequent cardiac events during a mean follow-up of 7.2 months. In contrast, 10 of 13 (77%) patients with both inferior and anterior perfusion defects
had cardiac events during the follow-up period (P<0.02). Similarly, Silverman et al (1980) demonstrated the value of the extent of perfusion defects in determining prognosis when thallium-201 imaging was performed within 15 hours of onset of symptoms. Patients with 'large' perfusion defects manifested a six-months mortality of 62%, and a mortality at last follow-up of 92%. In contrast, patients with smaller defects had a six-months mortality of 7%, and last follow-up mortality of 7%. Similar results were reported by Becker et al (1983) who showed that prognosis was dependent upon the size of perfusion defects.

When combined with exercise testing, thallium-201 imaging has been shown to be a relatively reliable predictor of subsequent cardiac events (Gibson et al, 1983; Patterson et al, 1983; Smeets et al, 1981; Hung et al, 1984) after myocardial infarction. Perfusion defects in multiple vascular regions indicate worse prognosis after infarction than defects limited to one vascular region (Patterson et al, 1983). In addition, Gibson et al (1983) found that approximately 50% of patients with uncomplicated infarction who demonstrated multiple thallium-201 defects in more than one vascular region, delayed redistribution within or remote from the infarct zone, or abnormal thallium-201 lung uptake, experienced hard cardiac events (cardiac death, nonfatal recurrent infarction or hospitalization with class III or IV angina) at a mean follow-up of 15 months. More recently, the same group (Gibson et al, 1986) reported an increased prevalence of asymptomatic, remote ischaemia detected by predischarge exercise thallium-201 testing in patients who survived a non-Q wave myocardial infarction.

In this study, exercise thallium-201 imaging was shown to have
significant prognostic implications after myocardial infarction. The total scores of early post exercise images were significantly different in patients with no cardiac events compared with those who experienced cardiac events. In addition, there was a significant difference between those who developed minor events compared with patients with major events. These findings confirm previous reports (Staniloff et al, 1986) of the importance of the intensity of thallium-201 abnormalities in predicting prognosis. However, in the delayed images, the total scores were able to identify patients with major events, and there was no difference between patients with no events and those with minor events. Furthermore, the presence of significant redistribution and/or abnormal washout on quantitative analysis added to the prognostic value of thallium-201 imaging. Forty three percent of patients with redistribution of the tracer developed cardiac events compared with 27% of those with no redistribution. Therefore, it appears that thallium-201 myocardial imaging is useful in stratifying patients with myocardial infarction whether used alone or in combination with other clinical, electrocardiographic or scintigraphic variables.

4.3.3. Right ventricular thallium-201 uptake

The right ventricular myocardium is not usually visualized in thallium-201 images at rest because of low tracer concentration and high background activity (Nestico et al, 1986). Increased right ventricular thallium-201 uptake is seen in congenital and acquired cardiac diseases associated with right ventricular hypertrophy (Cohen et al, 1976; Ohzuzu et al, 1980; Newth et al, 1981). In experimental studies, right ventricular visualization by thallium-201 imaging in dogs is determined
by right ventricular myocardial blood flow per unit of muscle mass and by right ventricular myocardial mass (Wackers et al, 1981). In a recent report, Nestico et al (1986) studied the implications of increased right ventricular thallium-201 uptake in a group of patients who underwent predischarge thallium-201 imaging at rest. Using multiple logistic regression analysis, abnormal right ventricular thallium-201 uptake was a predictor of death by univariate analysis but did not provide any independent prognostic information by multivariate analysis.

In this study, nearly one third of the study population showed increased thallium-201 uptake by the right ventricle among whom 70% had anterior infarction, 21% had inferior infarction and 9% had subendocardial infarction. On exercise, patients with abnormal right ventricular thallium-201 uptake had more myocardial perfusion defects than the patients with no uptake. In addition, the former group had multiple vessel disease in 66% of patients compared to 40% in the latter group (P<0.05). Although Nestico et al (1986) showed a significant difference in prognosis of the two groups, in this study there was no significant difference in prognosis. Increase right ventricular thallium-201 uptake may be explained by marked left ventricular dysfunction resulting in abnormal left ventricular filling pressure and pulmonary hypertension. However, two major differences are to be noticed as Nestico et al performed the studies at rest before hospital discharge whereas in this study patients underwent maximal exercise 6-8 weeks after infarction. This may have played an important role in the differences between the two studies. In addition, these investigators followed-up their patients for an average period of 6 months while in this study, patients were followed-up for an average of 18 months.
4.3.4. Exercise thallium-201 heart/lung ratio

Lung uptake of thallium-201 has recently received attention, although it contributes considerably to the background activity of the cardiac scan (Narahara et al, 1977). Increased lung uptake of thallium-201 following exercise has been shown to correlate with mean pulmonary capillary wedge pressure (Boucher et al, 1980), left ventricular dysfunction (Kushner et al, 1981; Lahiri et al, 1984), and severity of coronary artery disease after acute myocardial infarction (Gibson et al, 1982; Bingham et al, 1980; Wilson et al, 1983).

When thallium-201 is injected at peak exercise in patients with poor left ventricular function and severe coronary artery disease, there is a high pulmonary uptake of radioactivity. It has been suggested that this phenomenon is caused by prolonged contact with the capillary bed producing higher uptake by the pulmonary capillaries (Bingham et al, 1980) or transient pulmonary oedema occurring as a result of the raised end-diastolic pressure, the thallium-201 mixing with extravascular water and being retained in the lung (Lahiri et al, 1984).

Bingham et al (1980) reported that the lung extraction fraction for thallium-201 in experimental animals correlates well with delayed pulmonary transit time. Similar findings were reported by Brown et al (1986) in man. From these data, it has been postulated that transudation of water from the intravascular space to the interstitial lung tissue carries thallium-201 with it providing a compartment in lungs for the tracer to accumulate. The rapid clearance might be explained by reabsorption of excess lung water into the intravascular
space following the resolution of the exercise-induced ischaemia and transient left ventricular dysfunction (Rothendler et al, 1985).

Previous studies have shown that lung water may be increased in patients with heart disease without radiological evidence of pulmonary oedema (Fazio et al, 1976). Patients presenting with pulmonary oedema following acute myocardial infarction demonstrated increased pulmonary tracer activity when injected at rest (Lahiri et al, 1982). Thus transient exercise-induced 'pulmonary oedema' may be responsible for the increased tracer retention in the lung, rather than vascular wall uptake as suggested by some investigators (Lahiri et al, 1982; Bingham et al, 1980; Lahiri et al, 1984). It has been shown from predischarge thallium-201 imaging that increased lung thallium-201 uptake was an independent predictor of high risk in patients following myocardial infarction (Gibson et al, 1983). Furthermore, these investigators found that quantitative thallium-201 analysis and lung thallium-201 uptake were more sensitive than angina, ST-segment depression or coronary anatomy for predicting subsequent cardiac events.

In this study, quantitative lung thallium-201 uptake, relative to myocardial uptake, was measured prospectively 6-8 weeks after myocardial infarction. Since thallium-201 uptake is not uniform throughout the lung and since regions of maximal uptake vary during redistribution, selection of a fixed region of interest over the heart and lungs after exercise does not necessarily give the highest count density during redistribution (Boucher et al, 1980; Kushner et al, 1981; Levy et al, 1983; Bingham et al, 1980). The results of this study confirmed previous reports in patients with established chronic obstructive
coronary artery disease and myocardial infarction (Lahiri et al, 1984; Gibson et al, 1982). Increased lung thallium-201 uptake was found to correlate with the severity of coronary artery disease, the degree of resting left ventricular dysfunction and the presence of residual jeopardized ischaemic myocardium assessed by thallium-201 redistribution (Al-Khawaja et al, 1987d).

There was no correlation between exercise heart/lung ratio and either peak filling rate, pulmonary blood volume ratio, or the presence of a collateral circulation. Patients with anterior transmural infarction showed a higher lung uptake than those with inferior infarction, but those with subendocardial infarction had a similar exercise heart/lung ratio to those with transmural infarction. Liu et al (1985) demonstrated a good correlation between peak exercise heart rate and increased lung thallium-201 uptake in patients with left anterior descending coronary artery disease. Similar findings were reported by Brown et al (1986) who showed that peak exercise heart rate affected normal lung thallium-201 uptake. In this study, there was no correlation between increased lung thallium-201 uptake with either peak exercise heart rate or total exercise capacity. However, there is undisputed evidence that increased lung thallium-201 concentration is related to the degree of left ventricular dysfunction and severity of coronary artery disease (Bureau et al, 1987).

In a recent report, Gill et al (1987) found that increased thallium uptake by the lungs was the most powerful independent predictor of future cardiac events among a group of clinical, exercise testing and thallium-201 imaging variables. Over five years, cardiac events
occurred in 67% of patients with increased lung thallium-201 uptake, as compared with 25% of patients with an abnormal thallium-201 scan and normal lung activity and 5% of patients with an entirely normal thallium-201 scan.

In this study, exercise heart/lung ratio, an indicator of increased lung thallium-201 uptake, was significantly different between patients with no cardiac events and those who experienced cardiac events (P<0.001). Patients with no cardiac events had a significantly higher exercise heart/lung ratio than those with minor events (P<0.02) and major cardiac events (P<0.001). The specificity of exercise heart/lung ratio for predicting subsequent cardiac events was 55% using the lower limit of normal as a threshold. However, lowering the threshold by 21% improved the specificity to 90% with little effect on the sensitivity and predictive accuracy.

Therefore, on the basis of this study and previous reports, increased lung thallium-201 concentration on exercise correlates with an increased severity of underlying coronary artery disease, left ventricular dysfunction and a worse outcome after acute myocardial infarction (Al-Khawaja et al, 1988b). Increased lung thallium-201 uptake appeared to provide an assessment of the degree of functional left ventricular impairment during exercise, which was thought to be more important in terms of prognosis than the presence of coronary artery disease (Gill et al, 1987). These workers found that even when clinical, and exercise testing electrocardiographic variables were included, increased lung thallium-201 uptake was the only thallium-201 imaging variable of prognostic value.
4.4 MULTIVARIATE ANALYSIS

The stratification of high- and low-risk subjects after acute myocardial infarction can be based on variables related to left ventricular dysfunction, the extent of coronary artery disease, residual myocardial ischaemia or ventricular arrhythmias. Clinical signs (Killip et al, 1967; Norris et al, 1974), haemodynamic monitoring (Wolffenbuttel et al, 1983; Verdouw et al, 1975), radionuclide studies (Perez-Gonzales et al, 1982; Gibson et al, 1983; Reduto et al, 1978), echocardiography (Gibson et al, 1982 (b)), exercise stress testing (Miller et al, 1982; Corbett et al, 1981; Dewhurst et al, 1983), ambulatory monitoring (Bigger et al, 1981), provocative electrophysiological testing (Richards et al, 1983) and cardiac catheterization (Sanz et al, 1982; Epstein et al, 1982) have all been used to identify patients at highest risk, in whom more aggressive management would be indicated. Therefore, the question asked of the test in a patient being diagnosed: (Is disease present?) differs from that in a postinfarction patient: (Is additional disease present?). For the postinfarction patient, in whom disease is almost always present, the goal of testing is to predict prognosis (Morris et al, 1984).

In this study, patients underwent graded exercise electrocardiography, rest and exercise radionuclide ventriculography, exercise thallium-201 scintigraphy and selective coronary arteriography, 6-8 weeks after acute myocardial infarction. Multiple regression analysis of twenty variables was carried out using GLIM (Royal Statistical Society, 1986). However, the accuracy of any test can be affected by using biased normal controls and an inadequate 'gold standard' (Rozanski and Berman, 1987). There
has been considerable debate as to what constitutes the appropriate normal population of tests for coronary artery disease. The appropriate normal controls for determining test specificity in catheterized patients are those without angiographically significant coronary artery disease (Rozanski et al, 1984) i.e. patients with normal coronary arteriograms or insignificant stenoses. However, these patients may have other disease processes which affect coronary blood flow or myocardial function (Kaul et al, 1986). In this study, normal healthy volunteers with low probability of coronary artery disease (<1%) were used as a control particularly for the less popular variables examined.

The other source of bias is the adequacy of the 'gold standard'. When radionuclide tests were first introduced as diagnostic tests for coronary artery disease, their efficacy was evaluated by their ability to predict the results of coronary arteriography. Since coronary arteriography is an imperfect describer of coronary anatomy and blood flow (White et al, 1984), discrepancy between radionuclide results and coronary angiography findings do not necessarily mean that the former is wrong. The frequency of positive thallium-201 studies in patients with normal coronary arteriograms is higher in those patients with 25% to 50% narrowing of the coronary arteries than in those with more minimal (<25%) stenoses (Kaul et al, 1986; Brown et al, 1985). Nevertheless, such patients are frequently categorised as having false-positive tests for coronary artery disease, reflecting the inadequacy of the 'gold standard'. However, radionuclide tests are increasingly used for assessing prognosis in patients with suspected or known coronary artery disease as well as after myocardial infarction (Rozanski and Berman, 1987).
Risk factors for coronary artery disease, including cigarette smoking, diabetes mellitus, obesity and hyperlipidaemia have been shown to have no significant effect on mortality after acute myocardial infarction (Humphries et al, 1974; Taylor et al, 1980). Therefore, these factors were not included in the multivariate analysis in this study as they lack any additional prognostic value once coronary artery disease has manifested itself clinically (Al-Khawaja et al, 1988d).

Among 30 clinical and laboratory variables, Taylor et al (1980) showed that previous myocardial infarction and left ventricular ejection fraction less than 40% were the best independent predictors of mortality. Age, history of essential hypertension, infarct location and type, Killip class, severity of coronary artery disease, postinfarction angina and recurrent infarction did not provide significant additional contributions to prediction of mortality. However, for the prediction of recurrent acute myocardial infarction during the 30-month follow-up period, multivariate analysis showed that a history of hypertension, three vessel coronary artery disease, postinfarction angina pectoris and previous myocardial infarction were independent predictors of reinfarction.

Hammermeister et al (1979) proposed that left ventricular ejection fraction determined by contrast cineangiography was the single variable most predictive of survival. Similar findings were reported by Dewhurst et al (1983) in a series of 100 consecutive patients who underwent radionuclide ventriculography after their first myocardial infarction. Moreover, they showed that an early exercise test was a safe procedure and a fall in ejection fraction of more than 5% in the resting value was
predictive of postinfarction angina pectoris and could identify a further group who were at risk of sudden death. In addition, exercise-induced changes in ejection fraction were related closely to the number and severity of coronary vessel disease determined by coronary angiography (Elkayam et al, 1981; Morris et al, 1984).

Corbett et al (1981) studied 61 patients with recent myocardial infarction before hospital discharge. Patients were followed-up for a mean period of 9.6 months. The change in left ventricular ejection fraction, end-systolic volume and pressure/volume index with exercise were the most significant variables in predicting prognosis during the follow up period. However, patients with major cardiac events (death, recurrent infarction, unstable angina) were identified by peak submaximal exercise ejection fraction and a history of previous infarction. The discriminant analysis used by these investigators was less successful in separating patients into major, minor and no-event groups than in simply distinguishing cardiac-event from no-event groups. Other variables such as resting ejection fraction, history of infarction, wall motion score, change in end-diastolic volume, Killip class and location of infarction did not provide any additional prognostic information. The ability of the discriminant function to categorize patients appeared best at the 6-month follow-up; after 6 months progression of disease may become important, which reduces the specificity of most variables to predict outcome (Corbett et al, 1981). Similar findings were reported by De Feyter et al (1982) who found that abnormalities of wall motion after infarction were not as useful as global abnormalities (left ventricular ejection fraction and end-diastolic pressure) in predicting prognosis. In addition, they
reported that an exercise tolerance of 10 minutes or more (Bruce protocol) resulted in the identification of a very low risk group for mortality and morbidity, while an ejection fraction of less than 30%, or the presence of three-vessel disease identified a high-risk group for subsequent mortality.

The Multicentre Postinfarction Research Group (1983) are the only investigators in the literature who applied a statistical model similar to that used in this study (Nelder and Baker, 1975) in postinfarction patients. The analysis of survival differed from the Cox life-table regression technique (Cox DR, 1972) in that fixed time intervals were used in the survival distribution. These models were developed and reported by Laird and Oliver (1981), Whitehead (1980) and Aitkin and Clayton (1980). Four risk factors among eight prespecified variables were independent predictors of mortality: an ejection fraction below 40%, ventricular ectopy of 10 or more depolarizations per hour, advanced New York Heart Association functional class before infarction and râles heard in the upper two thirds of the lung field while the patient was in the coronary care unit. The history of previous infarction, postinfarction angina pectoris, the heart rate on the qualifying electrocardiogram and the presence of anterior infarction did not provide any additional prognostic information. On the contrary, Botvinick et al (1983) found that resting left ventricular ejection fraction could not differentiate among prognostic subgroups. Instead, early scintigraphic measurement of infarct size and perfusion abnormalities correlated well with the outcome after complicated myocardial infarction without heart failure.
Similar findings were reported by Becker et al (1983) who used stepwise multiple logistic analysis of clinical and scintigraphic variables observed within 15 hours of onset of symptoms suggestive of acute myocardial infarction. They found that thallium score was the best predictor of mortality and the appearance of Q waves and ejection fraction were additive. Gibson et al (1983) performed submaximal exercise thallium-201 scintigraphy in 140 patients before hospital discharge following uncomplicated myocardial infarction, and compared the results with submaximal exercise treadmill testing and coronary angiography. They found that submaximal exercise thallium-201 scintigraphy could distinguish high- and low-risk groups and that thallium-201 defects in more than one discrete vascular region, presence of delayed redistribution or increased lung thallium-201 uptake were more sensitive predictors of subsequent cardiac events than ST-segment depression, angina or extent of angiographic coronary artery disease. In addition, low-risk patients were best identified by a single-region thallium-201 defect without redistribution and no increased lung uptake.

Morris et al (1984) found that abnormal clinical response, including chest pain, ST-segment depression and hypotension during bicycle exercise yielded high specificity but low sensitivity for the detection of multiple vessel disease in patients with previous myocardial infarction. In contrast, the conventional diagnostic criteria for blood pool ventriculography (Borer et al, 1977) were relatively sensitive but nonspecific for identifying additional disease in these patients. They proposed that worsening of wall motion in the distribution of the remote circulation and a fall in ejection fraction during exercise appeared to be more specific predictors of multiple vessel disease. Similar results
were reported by Wesserman et al (1982). In addition, Hung et al (1984) reported that peak treadmill workload and change in left ventricular ejection fraction during exercise were significant predictors of hard medical events (cardiac death, nonfatal ventricular fibrillation or recurrent infarction). They found that in patients who underwent evaluation 3 weeks after a clinically uncomplicated myocardial infarction, exercise radionuclide ventriculography contributed independent prognostic information to that provided by symptom-limited treadmill testing and was superior to exercise thallium-201 imaging for this purpose.

The prognostic value of predischarge ejection fraction has been demonstrated in several studies (Sanz et al, 1982; Mukharji et al, 1984; Multicentre Postinfarction Research Group, 1983). Moreover, the early assessment of ejection fraction in predicting early postinfarction mortality was examined by Shah et al (1980), Abrams et al (1983) and more recently Ong et al (1986) who used a stepwise logistic analysis to demonstrate that ejection fraction was the single best variable with the greatest prognostic value for predicting in-hospital death or survival, followed by Killip class (Killip et al, 1967). The addition of further covariants (including thallium-201 defects) did not significantly improve the predictive value.

A similar statistical model was used to study the prognosis over one-year follow-up in patients with uncomplicated infarction (Starling et al, 1986). The total cardiac events were predicted by exercise-induced ST-depression or angina, previous infarction, ventricular ectopic activity during exercise and digoxin therapy. However, cardiac death
was predicted by an ejection fraction of 40% or less supporting previous reports of the prognostic value of ejection fraction in early and late mortality after myocardial infarction (Shah et al, 1980; Abrams et al, 1983; Sanz et al, 1982; De Feyter et al, 1982).

Nestico et al (1986) found left ventricular ejection fraction and complex ventricular arrhythmias to be independent predictors of prognosis after myocardial infarction. Nevertheless, using a univariate analysis, they showed that the extent of thallium-201 perfusion abnormalities and abnormal right ventricular thallium-201 uptake to be additional predictors of death. In a more recent study, Haines et al (1987) used a discriminant function analysis of clinical, electrocardiographical, radioisotopic and angiographic variables to investigate 241 consecutive patients 2 weeks after uncomplicated myocardial infarction. They found that the number of akinetic or dyskinetic segments per patient, an infarct-related left anterior descending artery and the presence of new Q-waves were the only independent predictors of exercise ST-elevation. However, the strongest predictor was the severity of resting segmental wall motion abnormalities. During follow-up (median 34 months), the nonfatal cardiac event rates were similar in those with or without ST-segment elevation on exercise. On the other hand, when cardiac mortality was examined in a life-table analysis, a trend toward increased mortality was seen in patients with ST-elevation.

Abraham et al (1987) examined the prognostic value of left ventricular ejection fraction measured during maximal exercise testing one month after acute myocardial infarction. They found that the ejection
fraction change from rest to exercise was not related to coronary anatomy or prognosis over a mean follow-up period of 12 months. In addition, after inferior infarction the ejection fraction was lower in those with multivessel than in those with single vessel coronary artery disease at rest and during exercise; however, after anterior infarction, neither the rest, exercise or the change in ejection fraction during exercise was related to the extent of coronary artery disease.

In this study, the best predictor of multiple vessel disease was the total score of exercise thallium-201 images, supporting previously published reports (Becker et al, 1983; Gibson et al, 1983; Brown et al, 1985; Kaul et al, 1986). However, in the model used in this study, multiple regression analysis yielded a relatively inadequate sensitivity, specificity and predictive value. Moreover, when two predictors were examined, the total score of exercise thallium-201 was eliminated and instead ST-segment depression on exercise with the total scores of regional wall motion, followed by ST-depression with the total score of exercise thallium-201 images appeared to be the best predictors. Unfortunately, there was no significant improvement in the sensitivity, specificity or predictive value. The best three predictors of severe coronary artery disease were ST-segment depression on exercise, the total scores of regional wall motion and the presence of redistribution on thallium-201 scintigraphy (Al-Khawaja et al, 1988d). The combination of these variables was not sensitive (29%) but highly specific (96%) for multiple vessel disease. Even by lowering the threshold of the fitted value in the regression analysis, there was little effect on the specificity but a significant improvement in the
sensitivity and the predictive accuracy. This algorithm was not concluded in any of the previously published reports; however, using either univariate or multivariate analysis, several investigators have found that ST-segment depression (Starling et al, 1981; Schwartz et al, 1981; Mannering et al, 1987), regional wall motion scores (Neumann et al, 1984; Wieshammer et al, 1985; Buda et al, 1986), and redistribution on thallium scintigraphy (Turner et al, 1980; Gibson et al, 1981; Wackers et al, 1985; Gibson et al, 1983) as independent predictors of multiple vessel disease. None of the other electrocardiographic variables, ventricular function parameters, or thallium-201 indices showed additional diagnostic information.

The best single predictor of cardiac events was the total score of regional wall motion (Al-Khawaja et al, 1988d). Nevertheless, the sensitivity, specificity, predictive value and predictive accuracy were not satisfactory when patients were grouped into those with no cardiac events and those who experienced events. When the second (left ventricular peak filling rate) and the third (exercise thallium-201 heart/lung ratio) best predictors of cardiac events were included there was no significant improvement in the number of true positive, false positive, true negative and false negative cases. This may indicate that the inclusion of less significant cardiac events, eg angina pectoris or transient congestive cardiac failure, affected the ability of the test to accurately predict more important cardiac events. When patients were grouped into those with no cardiac events, minor cardiac events and major cardiac events, multiple regression analysis using the GLIM program revealed a sensitivity of 94% for major events, 55% for minor events and 66% for no events. Moreover, there was no significant
improvement in these values by adding left ventricular peak filling rate and/or exercise thallium-201 heart/lung ratio. Therefore, it appears that regional wall motion alone stands as a powerful prognostic index for prediction of major cardiac events. Its ability to predict 'minor' cardiac events is less satisfactory whether it is used alone or in combination with other predictors. When patients with no events and those with minor cardiac events were grouped in the same category, the sensitivity of regional wall motion for predicting major cardiac events was unchanged at 94%, with a specificity of 57%, a positive predictive value of 31%, a negative predictive value of 98%, and a predictive accuracy of 63%. Similarly, there was no significant change in these values by adding peak filling rate or exercise heart/lung ratio or both, lending support to the belief that the total score of regional wall motion alone is the most predictive index of subsequent major cardiac events over a mean follow-up period of 18.8 ± 3.4 months after acute uncomplicated myocardial infarction.

The results of this study were in part determined by eligibility for exercise testing 6-8 weeks after myocardial infarction and should not necessarily be extrapolated to the total acute infarction population. By design, patients in this study had an uncomplicated infarction, defined as the absence during convalescence of clinically severe left ventricular failure, shock, unstable angina, significant conduction defects, life-threatening arrhythmias or other serious noncardiac illnesses (Swan et al, 1976). As such, these results apply to postinfarction patients who as a group have adequate left ventricular function and who might be considered as candidates for early coronary arteriography.
The purpose of this study was to test the hypothesis that patients with a recent uncomplicated acute myocardial infarction who are at risk of subsequent cardiac events can be identified noninvasively 6-8 weeks after the acute episode using maximal exercise electrocardiographic and radioisotopic techniques. As such, this study is more clinical than epidemiological in nature, since the focus was more on the use of noninvasive methods for predicting the severity of coronary artery disease and subsequent clinical outcome than in quantifying the prevalence of coronary artery disease and its secondary complications in the postinfarction patients.

Unlike some previous reports (Davidson et al, 1980; Koppes et al, 1980) patients did not stop their cardiac medications before exercise testing and radionuclide studies. Medication, especially B-blocking agents, could account for the relatively poor sensitivity of exercise-induced ST-segment depression to predict future cardiac events. Since most patients will continue long-term therapy, it may be more realistic to conduct testing during drug treatment. This is particularly true for B-blockers in the light of the large multicentre trials demonstrating reduced mortality and reinfarction rate in patients receiving these drugs (Norwegian Multicentre Study group, 1981; B-blocker Heart Attack Trial Research Group, 1982).

In this study, patients underwent maximal, symptom-limited rather than heart rate limited exercise testing on both treadmill and bicycle ergometry. The potential advantage of rigorous maximal testing lies in the ability to detect residual ischaemia, serious ventricular arrhythmias and other abnormalities of prognostic significance.
Starling et al (1981) reported (in a small series of patients) that symptom-limited exercise was superior to heart-rate limited exercise for revealing ischaemic abnormalities before hospital discharge. On the other hand, Gibson et al (1983) and Debusk and Haskell (1980) in a much larger group of patients found the two tests to be equally effective in eliciting ischaemic ST-segment depression or ventricular ectopic activity after uncomplicated myocardial infarction. More importantly, they found that exercise-induced ischaemia (which is predictive of early recurrent cardiac events) could be detected with the heart rate-limited test because such ischaemia usually occurs at heart rates below 130 beats/minute. Therefore it is conceivable that electrocardiographic signs of ischaemia occurring only at high heart rates, or in postinfarction patients taking B-blockers, do not have as much prognostic value as those appearing at lower exercise heart rates (Ellestad and Wan, 1975; Goldschlager et al, 1976; Weiner et al, 1982).

The differences between the results of this study and previous reports may be related to differences in patient selection and the timing of radionuclide studies relative to the onset of infarction. This may have an important bearing on the predictive value of these tests or on the precise cut off points used to classify patients into high and low-risk groups. For example, thallium-201 defect size tends to decrease over time (Wackers et al, 1976) due to a reduction in ischaemia improved collateral flow, reopening of the occluded artery or stabilization of haemodynamic status. The rate at which defects can improve after infarction is unknown. Similarly, left ventricular ejection fraction changes in most patients over the first few days, usually improving, but frequently getting worse (Schelbert et al, 1976). These changes
probably depend on the severity of ischaemia, intensity of catecholamine drive, loading conditions of the left ventricle, and the changes in left ventricular geometry. Moreover, the thallium-201 defect size provides an estimate of the total sum of irreversible ischaemic damage, both old and new, plus potentially reversible ischaemic myocardium at risk for future infarction.

In this study, ambulatory electrocardiographic recordings to quantitate ventricular ectopic activity were not carried out. Previous reports (Schulze et al, 1975; Taylor et al, 1980; Henry et al, 1984) using multivariate analysis of clinical exercise testing and ambulatory electrocardiographic data did not show ventricular ectopic activity on 24 hour ambulatory monitoring to be of additional prognostic values beyond the clinical and exercise test data.

Caldwell et al (1980) compared supine and upright exercise modes and found that in patients with coronary artery disease, the pressure-rate product was the same for both treadmill and supine bicycle exercise, and they concluded that the patients' limiting symptoms occurred at the same level of myocardial oxygen consumption. In addition, the ST-segment response was similar for the two positions of testing. In spite of the different haemodynamic responses, it appears that changes in heart rate do not alter the ability to detect ST-segment shift, (Dewhurst et al, 1983). While ejection fraction response should reflect the sum of injured and ischaemic myocardium, it may be influenced to a great extent by other variables, such as left ventricular preload and afterload, ventricular geometry and sympathetic drive (Becker et al, 1983). Accordingly, an algorithm could be constructed for evaluating patients
after acute myocardial infarction. Rest and exercise blood pool ventriculography should be performed 6-8 weeks after infarction in all patients without contraindications. The presence of ST-segment depression and the total score of rest and exercise regional wall motion are enough to indicate the severity of underlying coronary artery disease and predict the clinical outcome. While the total score of regional wall motion was the best single predictor of major cardiac events, if additional information is required to identify those with more severe coronary artery disease, then the presence of redistribution on exercise thallium-201 imaging should be sought. It might be proposed on the basis of this study that high risk postinfarction patients identified noninvasively should be considered for early cardiac catheterization and coronary arteriography. This recommendation seems particularly relevant for those patients with relatively well-preserved left ventricular function (Epstein et al, 1982). This may imply that the knowledge of coronary anatomy above and beyond knowledge of a high-risk exercise radionuclide response will improve the clinical management of such patients. This seems to be reasonable in those with postinfarction angina, since several reports indicate that coronary artery bypass surgery improves survival in symptomatic patients with chronic stable angina and multiple vessel disease (Mathur et al, 1980; European Coronary Surgery Study Group, 1982).

In asymptomatic patients recovering from an uncomplicated myocardial infarction, the goal of therapy obviously cannot be relief of symptoms, (Rahimtoola et al, 1980). Instead the goal should include prolongation of life, prevention of further infarction, and preservation of an active, asymptomatic state. Therefore, coronary arteriography in
asymptomatic postinfarction patients should be selective and only applied to subgroups at high risk for major cardiac events as identified by noninvasive methods.
CONCLUSION
CONCLUSION

For the post-infarction patient, in whom coronary artery disease is almost always present, the goal of any investigation is to identify the severity of the disease and predict the prognosis. In this study, an algorithm was constructed for evaluating patients after acute uncomplicated myocardial infarction. The most predictive factors of the severity of coronary artery disease are ST-segment depression on exercise, total score of rest and exercise regional wall motion and the presence of significant redistribution on thallium-201 imaging. This algorithm was highly specific (94%) but not sensitive (42%) for predicting multiple vessel disease. However, the total score of regional wall motion abnormalities was highly sensitive (94%) but not specific (57%) for predicting major cardiac events. Therefore, rest and exercise blood pool ventriculography should be performed 6-8 weeks after myocardial infarction in all patients without contraindications. The presence of ST-segment depression and the total score of rest and exercise regional wall motion may be enough to indicate the severity of underlying coronary artery disease and predict the clinical outcome. However, if additional information is required to identify those who have more severe coronary artery disease, then the presence of redistribution on exercise thallium-201 imaging should be sought. Early cardiac catheterization and coronary arteriography should be considered for the high risk post-infarction patients who were identified noninvasively.
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Clinical Significance of Exercise-Induced Pulmonary Uptake of Thallium 201 in Uncomplicated Myocardial Infarction

Imad M. Al-Khawaja, Avijit Lahiri, Erwin A. Rodrigues, Mary E. Heber, and Edward B. Raftery

To evaluate the functional significance of exercise-induced lung uptake of thallium 201, 101 consecutive patients were studied 6 weeks after an acute uncomplicated myocardial infarction. Quantitative heart/lung ratio (HLR) of $^{201}$TI, as a measure of lung uptake of tracer, was computed by dividing maximal count density over the myocardium by the count density over a similar region of lung. Thus, a low HLR indicated increased lung uptake of the tracer. Radionuclide ventriculography was also performed at rest and exercise, and left ventricular ejection fraction (EP) calculated. The mean HLR ($\pm$SEM) in the patients ($n=101$) was $1.86 \pm 0.05$, which was significantly different from the value in 14 normal volunteers ($2.74 \pm 0.12; P < .001$). Patients with an abnormal resting EF ($<48\%$) had a lower HLR ($1.62 \pm 0.05$), i.e., increased tracer in the lungs, compared with those who had a normal EF ($2.06 \pm 0.07$; $P < .001$).

Increased lung uptake of $^{201}$TI appears to be an indicator of poor left ventricular function and severe coronary artery disease when studied 2 weeks after an uncomplicated myocardial infarction. Whatever the mechanism, this phenomenon of increased lung uptake of $^{201}$TI appears to be a useful indicator of poor left ventricular function due to underlying coronary artery disease, and as such may be a useful prognostic indicator in patients after recent myocardial infarction.

We have carried out a prospective study in order to evaluate the clinical significance of exercise-induced lung $^{201}$TI uptake in patients 6 weeks after an uncomplicated myocardial infarction.

MATERIALS AND METHODS

Patient Population

The study population consisted of 101 consecutive patients admitted to the Northwick Park Hospital Coronary Care Unit between February 1985 and February 1986, with acute myocardial infarction diagnosed on two of three criteria: (1) typical central chest pain; (2) electrocardiographic changes; or to transient pulmonary edema as a result of the raised end-diastolic pressure, the $^{201}$TI mixing with extravascular water and being retained in the lung.

Experimental evidence suggests that exercise-induced myocardial ischemia is associated with an increase in left ventricular end-diastolic pressure, a fall in ejection fraction, an increase in left ventricular wall tension, and increased left ventricular volumes. When $^{201}$TI is injected at peak exercise in patients with poor left ventricular function and severe coronary artery disease, there is a high pulmonary uptake of radioactivity. It has been suggested that this is due to prolonged contact with the capillary bed producing higher uptake by the pulmonary capillaries.
(3) rise in serum creatine kinase and its MB isoenzyme fraction above the normal limits for the laboratory. Infarction was considered transmural if new Q-waves > 0.04 seconds in duration appeared on the 12-lead ECG. Anterior infarction was diagnosed if these Q-waves were present in the anterior, anteroseptal, or anterolateral leads, while inferior infarction was deemed present if these changes were seen in the inferior or posterior leads. Nontransmural infarction was diagnosed when only T-wave changes were observed.

Medical therapy was not discontinued for the purpose of this study, but patients were excluded if they had serious cardiac arrhythmias, or any other condition which might hinder exercise testing.

In addition, 14 normal healthy volunteers (mean age, 38 ± 5 years) underwent exercise 201TI scintigraphy as a control group. All the normal subjects were asymptomatic, normotensive, and had normal rest and exercise ECGs.

Study Design

All patients were investigated 6 to 8 weeks after the acute myocardial infarction. They underwent rest and exercise-gated blood pool radionuclide ventriculography, and exercise 201TI scintigraphy. Coronary arteriography was performed within 2 weeks of the radionuclide tests.

Thallium 201 Scintigraphy

A baseline 12-lead ECG was recorded, and an intravenous cannula inserted into an antecubital vein prior to the exercise test. Maximal-graded upright exercise testing was performed in the fasting state using a specially equipped nuclear cardiology ergometer (Cardiac Stress System; Engineering Dynamics Corp, Boston). The ECG and blood pressure response were monitored during exercise using leads CM5 and CC5, and a standard cuff sphygmomanometer. Workload was computer-controlled, commencing at 25 W and increasing by 25 W every three minutes until chest pain, dyspnea, leg fatigue or ST-segment depression > 4 mm developed. At peak exercise, 74 MBq thallous chloride (201TI) (Amersham International, Amersham, UK) was injected through the indwelling venous cannula, and patients were encouraged to continue to exercise for at least 30 seconds more.

A mobile digital gamma camera (Elscint, 215M; Haifa, Israel) equipped with an all-purpose collimator was employed. Imaging was commenced within five minutes of injection, with the patient in the supine position. Scans were acquired in the anterior, 45° left-anterior oblique, and left lateral projections. The redistribution images were acquired in the same projection three to four hours after 201TI administration. At least 300,000 counts were collected in each view, and data was stored for further analysis on a dedicated computer in a 128 × 128 matrix.

Lung Thallium 201 Analysis

Quantitative analysis of lung 201TI uptake was performed according to the method previously described by Lahiri et al.9 Briefly, the color scale on the monitor was used to produce computer-generated regions of interest, showing the maximal count density over the myocardium and lungs. The mean count per pixel in the myocardial region of interest was divided by the mean count per pixel in the lung region of interest, to obtain a heart-to-lung ratio (HLR). The program allowed operator intervention to alter the size or site of regions of interest according to the maximal count density. Analysis was carried out on both exercise and redistribution 201TI images. Lung thallium washout was calculated by dividing the average lung counts after stress by the average lung counts in the redistribution images.

Myocardial Thallium 201 Analysis

Myocardial distribution of 201TI was analyzed semiquantitatively in each of the myocardial segments—anterolateral, apical, and inferior segments in the anterior projection; septal, apical-inferior and posterior segments in the 45° left-anterior oblique projection; and inferolateral, anterolateral, and apical segments in the left lateral projection. The nonprocessed digital images were used to identify segments with fixed perfusion defects and reversible perfusion defects. Quantitative myocardial 201TI analysis was carried out using previously reported techniques.19,20 Briefly, after interpolative background subtraction, angular profiles were generated for each view and compared with those obtained from normal subjects. Quantitation was performed after correction for decay of radioactivity, and the number of abnormal segments was obtained from stress and washout images. Subsequently, the percentage change in activity within each segment was determined to quantitate the degree of redistribution.

Equilibrium-Gated Blood Pool Ventriculography

Equilibrium radionuclide ventriculography was performed at rest and at peak exercise within 1 week of 201TI myocardial perfusion imaging. After in vivo labeling of red blood cells with 740 MBq technetium 99m, patients were imaged supine in the left anterior oblique projection using the same gamma camera (Elscint, 215M). The angle of acquisition was adjusted to produce the best-septal separation, and the head of camera was tilted to five to ten degrees caudally in order to best isolate the left ventricle. A high-resolution, low-energy, parallel-hole collimator was used and the camera set at the 140-keV photo peak of 99mTc with a 20% energy window. This method has been previously described.21,22 An additional anterior projection acquisition was carried out to assess regional wall motion. The data was stored on a dedicated computer in a 64 × 64 matrix. The same ergometer exercise test as used for 201TI scintigraphy was performed, but in the supine position, and data acquisition was repeated during the last stage of exercise.

Equilibrium Radionuclide Ventriculography Analysis

Equilibrium radionuclide scans were reported without knowledge of the 201TI myocardial perfusion results. The left anterior oblique view was used to calculate the left ventricular ejection fraction. Initial processing was performed by nine-point smoothing, time smoothing, and time correction. A semi-automatic edge-detecting algorithm, utilizing second derivative and local threshold techniques, was used to generate regions of interest for each frame. Background activity
was determined automatically by the computer from the end-systolic frame, using a region of interest two pixels wide and two pixels away from the left ventricle. Then, a high resolution, background subtracted, time-activity curve was generated from the counts in each region of interest. Ejection fraction was calculated by standard formula, dividing stroke counts by background corrected end-diastolic counts. Peak filling rate was derived automatically using a previously reported technique. Regional wall motion analysis was assessed subjectively from both the anterior and left-anterior oblique views at rest and peak exercise. Pulmonary blood volume ratio was calculated by dividing the average counts in the lung region of interest at peak exercise by the average counts in the same region of interest at rest after correction for acquisition time. The selected lung region of interest was adjacent to the cardiac silhouette to avoid major vascular structures. The lower range of normal ejection fraction was taken as 48%, as described by Hains et al.

Coronary Arteriography

Selective coronary arteriography was performed in 95 patients using the Judkin's technique within 2 weeks of the radionuclide studies. An artery was considered significantly narrowed when there was a reduction of 70% or more in luminal diameter. The angiograms were reported by two experienced observers, and a consensus was reached when a significant difference was found between the two reports. Patients were grouped into those with single vessel disease, two vessel disease, and three vessel disease.

Statistical Analysis

Data was expressed as mean ± SEM. Comparisons between data obtained from patients and normal values established in our laboratory were performed using unpaired Student’s t tests. A similar test was used to compare the difference between the means of patient subgroups. Linear regression analysis was performed to assess the significance of correlation between variables. The normal range was established from the mean ± 2SD.

RESULTS

Eighty-nine men and 12 women, aged 38 to 74 years (mean, 56 ± 8 years), were studied. Of these, 46 had anterior infarction, 44 inferior infarction, and 11 non-Q-wave infarction. Selective coronary arteriography was performed in 95 patients, 42 of whom had single vessel disease, 31 had two vessel disease, and 15 had three vessel disease. Seven patients had lesions with less than 70% intraluminal narrowing of one coronary artery, and these patients were considered to have single vessel disease.

At the time of the nuclear studies, 13 patients were receiving β-blockers, 7 long-acting nitrates, 13 a calcium antagonist, and 30 had various combinations. Thirty-two patients had evidence of past or present hypertension.

Quantitative Lung Thallium 201 Uptake

The mean exercise HLR value in 14 normal healthy volunteers was 2.74 ± 0.12 (SEM). The mean exercise HLR in patients was 1.86 ± 0.05, which was significantly lower ($P < .001$; Table 1).

Exercise Testing

Mean exercise time for patients was 10.6 ± 0.4 minutes. Linear regression analysis revealed a poor correlation between exercise HLR and exercise time ($r = .3$). The patients achieved a mean peak exercise heart rate of 126 ± 2 beats per minute. There was no correlation between exercise HLR and heart rate on exercise ($r = .3$).

Site of Infarction

The mean exercise HLR in patients with anterior transmural infarction was 1.7 ± 0.07, which was significantly lower than that in patients with inferior transmural infarction 2.03 ± 0.08 ($P < .005$). The mean exercise HLR in patients with subendocardial infarction was 1.84 ± 0.1, which was similar to that seen in patients with transmural infarction (1.87 ± 0.05; $P = NS$; Fig 1).

Thallium 201 Myocardial Perfusion Imaging

Thallium 201 images were analyzed qualitatively and quantitatively. Fixed perfusion defects were present in 26 patients, and 75 patients had additional reversible defects either adjacent to, or remote from, the infarct site. In the 26 with only fixed perfusion defects, the mean HLR was 2.08 ± 0.1, which was significantly higher than in the 75 with reversible ischemic segments (1.79 ± 0.05; $P < .02$; Fig 2).

Table 1. Exercise Thallium Heart/Lung Ratio in Normals and Patients

<table>
<thead>
<tr>
<th>n Value</th>
<th>Mean ± (SEM) HLR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal volunteers</td>
<td>14</td>
<td>2.74 (0.12)</td>
</tr>
<tr>
<td>Study patients</td>
<td>101</td>
<td>1.86 (0.06)</td>
</tr>
<tr>
<td>Normal EF</td>
<td>56</td>
<td>2.06 (0.07)</td>
</tr>
<tr>
<td>Abnormal EF</td>
<td>45</td>
<td>1.62 (0.05)</td>
</tr>
<tr>
<td>0-1 VD</td>
<td>49</td>
<td>2.29 (0.32)</td>
</tr>
<tr>
<td>2 VD</td>
<td>31</td>
<td>1.76 (0.09)</td>
</tr>
<tr>
<td>3 VD</td>
<td>15</td>
<td>1.81 (0.17)</td>
</tr>
</tbody>
</table>

Abbreviations: HLR, exercise heart/lung ratio; SEM, standard error of the mean; $P$, unpaired t test probability value; EF, ejection fraction; VD, number of diseased vessels.
Systemic Hypertension

Thirty-two patients (30%) had essential hypertension prior to the acute myocardial infarction. There was no significant difference between mean exercise HLR in hypertensive ($n = 32; 1.83 \pm 0.08$) and normotensive ($n = 69; 1.88 \pm 0.06$; $P = NS$) patients.

Left Ventricular Dysfunction

There was a significant positive correlation ($r = 0.48; P < .001$) between resting left ventricular ejection fraction and exercise HLR (Fig 3). The mean exercise HLR in the 56 patients with normal resting ejection fraction (>48%) was significantly lower than that in normal subjects ($P < .001$; Table 1). Similarly, mean HLR in the 45 patients with abnormally low ejection fraction was $1.62 \pm 0.05 (P < .001)$, which was significantly lower than in the normal controls (Fig 4). Mean HLR in patients with an abnormal ejection fraction was significantly lower than in patients with a normal ejection fraction ($P < .001$).

There was a poor correlation between HLR and peak filling rate ($r = .25$). The correlation between HLR and pulmonary blood volume ratio was also poor ($r = .02$; Fig 5).

Severity of Coronary Artery Disease

The patients with single vessel disease had similar mean exercise HLRs to those in the normal controls ($2.29 \pm 0.32; 2.74 \pm 0.12$, respectively; $P = NS$). However, in the group with two vessel disease, the ratio was $1.76 \pm 0.09 (P < .001)$, and in the group with three vessel disease it was $1.81 \pm 0.18 (P < .001)$, which were both significantly lower than normal controls (Fig 6). The group with three vessel disease had lower exercise HLR values than those with single vessel disease, but the difference was not significant. The mean exercise HLR in patients with definite collateral vessels and retrograde filling of occluded arteries was $1.84 \pm 0.07$, which was not different from those without a collateral circulation ($1.96 \pm 0.08; P = NS$; Fig 7).

Effect of Thallium 201 Washout Index

Thallium 201 HLR was measured immediately after stress, and after redistribution three to four hours later. The mean redistribution HLR was $2.32 \pm 0.04$, which was significantly higher than the exercise value ($1.86 \pm 0.05; P < .001$).

In the 34 patients with a normal exercise HLR, the mean redistribution value was $2.62 \pm 0.06$, which was higher than that recorded after stress ($2.42 \pm 0.07; P < .02$). In those with an
abnormal exercise HLR, the mean redistribution value was 2.17 ± 0.05, which was again significantly higher than that recorded after stress (1.58 ± 0.03; \( P < .001 \)). There was a significant negative correlation between HLR and thallium lung washout index \((r = -0.58; \, P < .001; \) Fig 8).

### Sensitivity and Specificity of Heart/Lung Ratio

The sensitivity of thallium 201 stress HLR for identifying patients with multiple (two or more) vessel coronary artery disease following myocardial infarction was 73%, with a specificity of 44%, a positive predictive value of 55%, a negative predictive value of 64%, and a diagnostic accuracy of 58%.

In this study, the sensitivity of quantitative myocardial 201TI analysis for identifying patients with multiple vessel disease was 76% with a specificity of 60%. However, when stress HLR was added to the quantitative analysis, the sensitivity of the test was improved to 82% and specificity was reduced to 33%.

## DISCUSSION

Exercise-induced myocardial ischemia is associated with increased left ventricular end-diastolic pressure,\( ^{13} \) increased left ventricular end-systolic and end-diastolic volumes,\( ^{17,18} \) an abnormal response of the left ventricular ejection fraction, and the appearance of regional wall motion abnormalities.\( ^{16} \) The elevated left ventricular filling pressure increases the pulmonary transit time of a tracer injected during peak exercise.\( ^{13} \) Thus, when 201TI is injected intravenously during peak exercise in patients with significant myocardial ischemia, there is prolonged retention of the tracer within the pulmonary vasculature. Initial exercise-induced lung uptake of thallium has been reported by investigators who have measured this phenomenon,\( ^{8,12} \) and the initial tracer uptake has been correlated with low resting ejection fraction,\( ^{8,10,12} \) fall in ejection fraction with exercise,\( ^{14} \) number of dis-

![Fig 4. Exercise HLR in normals and patients following myocardial infarction.](image1)

![Fig 5. Correlation between exercise HLR and pulmonary blood volume ratio.](image2)

![Fig 6. Effects of severity of coronary artery disease on exercise HLR. 1VD, single vessel disease; 2VD, two vessel disease; 3VD, three vessel disease.](image3)
Exercise heart/lung ratio (mean ± SEM)

P < 0.001

P < 0.001

P = NS

Fig 7. Effect of collateral circulation on exercise HLR.

eased vessels,8-10 and an elevated mean pulmonary capillary wedge pressure.9 Bingham et al13 reported that the lung extraction fraction for thallium in experimental animals correlates well with delayed pulmonary transit time. Similar findings were reported by Brown et al15 in man. From these data, it has been postulated that transudation of water from the intravascular space to the interstitial lung tissue carries 201T1 with it, providing a compartment in the lungs for 201T1 to accumulate.13 The rapid clearance might be explained by reabsorption of excess lung water back into the intravascular space following the resolution of exercise-induced ischemia and transient left ventricular dysfunction.23

Previous studies show that lung water may be increased in patients with heart disease without radiologic evidence of pulmonary edema.24 Patients presenting with pulmonary edema following acute myocardial infarction demonstrated increased tracer activity when injected at rest.25 Thus, transient exercise-induced "pulmonary edema" may be responsible for the increased tracer retention in the lung, rather than vascular wall uptake, as suggested by some investigators.8,13,23

Gibson et al,26 using predischarge 201T1 imaging, have shown that elevated lung thallium uptake was an independent predictor of high risk in patients following myocardial infarction. Furthermore, they found that quantitative 201T1 imaging and lung uptake were more sensitive than angina, ST-segment depression, or coronary arteriography for predicting subsequent cardiac events in 140 postinfarction patients.

In this study, we prospectively evaluated the clinical significance of increased lung 201T1 uptake in patients 6 weeks after acute myocardial infarction. We measured lung thallium uptake quantitatively, relative to myocardial uptake. Since thallium uptake is not uniform throughout the lung, and since regions of maximal uptake vary during redistribution, selection of a fixed region of interest over the heart and lungs after exercise does not necessarily give the highest count density during redistribution.9,10,13 Our findings confirmed previous reports in patients with established chronic obstructive coronary artery disease and myocardial infarction.8,12 In our study, increased lung 201T1 uptake correlated with the severity of coronary artery disease, the degree of resting left ventricular dysfunction (ejection fraction), and the presence of residual jeopardized ischemic myocardium assessed by 201T1 redistribution, 6 weeks after infarction. There was no correlation between exercise HLR and either peak filling rate, pulmonary blood volume ratio, or the presence of collateral circulation. Patients with anterior transmural infarction showed higher lung uptake than those with inferior infarction, but those with subendocardial infarction had exercise HLRs similar to those with transmural infarction. Liu et al27 demonstrated a good correlation between peak exercise heart rate and increased lung thallium uptake in patients with left anterior descending coronary artery disease. Similar findings were reported by Brown et al,15 who showed that peak exercise heart rate affected normal lung thallium uptake. In this study, we could not demonstrate any correlation between increased lung 201T1 with either peak exercise heart rate or total exercise capacity.

We conclude that increased lung 201T1 uptake
during maximal symptom-limited exercise testing, 6 weeks after myocardial infarction, appears to be an additional indicator of the severity of coronary artery disease and underlying left ventricular dysfunction. Since increased 201Tl uptake by the lungs is easily identified qualitatively and quantitatively, its presence should be taken into account in the interpretation of routine exercise 201Tl imaging.

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REFERENCES

Measurement of absolute left ventricular volume by radionuclide angiography: a technical review

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Summary

Absolute left ventricular volumes have important clinical implications in the evaluation of cardiac performance. Several invasive and noninvasive techniques have been reported, none of which can be considered ideal for this purpose. Contrast angiography, echocardiography and radionuclide ventriculography are open to criticism. Different radioisotopic approaches are described with emphasis on the importance of accurate separation of left ventricular activity, the selection of background activity, and the correction for photon attenuation by body tissues. Improper use of statistics and validation techniques have obscured the value of these techniques. In the absence of a 'gold standard' there should be a 'radioisotopic' left ventricular volume with established independent characteristics, repeatability and reproducibility by which new approaches can be judged.

Introduction

The quantitative measurement of left ventricular volume has an important role in the evaluation of cardiac performance. An ideal method for the determination of left ventricular volume should be safe, rapid, noninvasive and easily reproducible both at rest and during exercise. Several techniques are widely used: single and biplane contrast angiography, M-mode and two-dimensional echocardiography, surgically implanted epicardial metallic markers in post-operative patients, and radionuclide angiography using first-pass studies or gated blood-pool ventriculography. Recent studies have shown that magnetic resonance can also be used with relative accuracy.

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Contrast left ventricular angiography is widely used to measure left ventricular volume. The haemodynamic changes produced by the procedure and the contrast media, are known to affect the accuracy of the results. Exercise studies are difficult to perform with this method and multiple measurements are not practicable.

Echocardiography is clinically useful, but asymmetrical abnormalities in wall motion, especially in patients with ischaemic heart disease, limit the use of the single dimension M-mode technique. This problem is partially eliminated by two-dimensional echocardiography but this also relies on geometrical assumptions that are not reasonable in the diseased heart. In addition, it is rarely standardized to measure absolute volume but rather relative volume.

Epicardial metallic markers implanted at the time of cardiac surgery are useful for the quantification of left ventricular volume in post-operative patients, but this method obviously cannot be used in patients who have not had cardiac surgery.

Radionuclide angiography is the most promising of the generally available techniques. Several reports have suggested that absolute left ventricular volumes can be obtained without relying on geometric assumptions. Such measurements would have both diagnostic and prognostic value for patients with valvular heart disease, would be invaluable for assessing the effect of therapeutic interventions on left ventricular contractility, and could be used for serial measurements of left ventricular function both at rest and during exercise in patients with coronary artery disease.

Methodological review

Many workers have tried to describe an ideal method for the absolute quantitation of left ventricular volumes since the early days of nuclear cardiology. Prinzmetal et al. used a shielded Geiger-Mueller tube placed over the precordium [1]. They recorded the radioactivity of a bolus of $^{24}$Na rapidly injected into one of the antecubital veins. This study was a landmark in the use of radioactive substances for studies of the circulation because it clearly demonstrated the possibilities of the technique.

Ishii et al. described a method for measurement of heart chamber volumes by analysis of dilution curves simultaneously recorded by a scintillation camera [2]. Other investigators suggested the use of planimetry [3, 4] assuming that the left ventricle is either an ellipsoid or a perolate spheroid and applying the formula used in contrast angiography which was described by Sandler and Dodge [5, 6]. Although this method avoids the invasive aspect of cardiac catheterization and the haemodynamic problems of contrast media, it is completely dependent on geometric assumptions. It relies on a length measurement and assumes the total blood volume in any particular patient to be normal [7]. Volumes calculated from length measurements made on scintigrams must be considered suspect due to the inherently low resolution of the gamma camera and the fact that volumes are proportional to the cube of length, so that even small errors in length can produce large errors in the calculated volume.
Slutsky et al. described a method to determine left ventricular end-diastolic and end-systolic volumes from counts derived from the time-activity curve recorded by a gamma camera interfaced to a dedicated computer [7]. These counts were divided by the total number of processed heart beats and then corrected for the administered dose and the time of each frame. Volumes were expressed as non-dimensional units and an equation was derived to calculate end-diastolic and end-systolic volume units. They assumed a uniform attenuation of gamma rays by tissues and used a regression equation to convert the units to actual volumes. Unfortunately, the need for a regression equation makes this method, though simple, unreliable and dependent on the same geometric assumptions as contrast ventriculography.

Dehmer et al. estimated the scintigraphic left ventricular volume after equilibration by obtaining the left ventricular activity corrected for the background and normalized for the radioactivity per millilitre of a peripheral venous blood sample, total study acquisition time, number of frames acquired per cardiac cycle and the percentage of the cycle acquired [8]. Their results were in volume units and also required a regression equation for conversion to actual volume. Once more, the need for a regression equation to produce an 'absolute volume' makes the techniques unreliable and dependent on the same geometric assumptions as contrast ventriculography.

Bourguignon et al. assumed that the attenuation of the left ventricular blood-pool activity was the same as that of the blood pool in the aorta [9]. Thus, by measuring the counts and volumes of two subregions of known shape, one in the middle and the other at the edge of the aortic arch, and calculating their difference in counts, a background-independent volume/count ratio could be obtained. When this ratio was multiplied by the count rate over the left ventricle at the end-diastolic frame it yielded an absolute measurement of left ventricular volume without the necessity to obtain a peripheral blood sample. To obtain this volume/count ratio, it was necessary to assume that the aortic arch was parallel to the collimator face when the patient was in the left anterior oblique position, that a segment at the top of the aortic arch (approximately 1 centimetre wide) was a cylinder, and that the edge of the aorta could be delineated automatically with the use of the second derivative of a cross-sectional count-rate profile. Furthermore, the aortic arch and the left ventricular counts were assumed to undergo the same attenuation because they are the same distance from the chest wall in the left anterior oblique position. This method has two advantages: it corrects for attenuation in a simple and noninvasive fashion which does not require drawing a blood sample, and it is background independent. Unfortunately, the accuracy of the method depends upon exact measurement of the aortic arch diameter, and it is frequently difficult to separate the aortic arch edges from those of the pulmonary artery. Therefore, this method may not be applicable to all patients without producing inaccurate results.

Links et al. tried to solve the problem of variation in tissue attenuation by determining the depth of the left ventricle geometrically from two scintigraphic views [10]. They assumed that the linear attenuation coefficient of soft tissues for the 140 keV of
"\textsuperscript{99}Tc\textsuperscript{m}" is the same as that of water. They then used almost the same equation as Dehmer et al. \cite{8} to obtain the absolute left ventricular volumes from the gated blood-pool studies. The volume was calculated from the background-corrected count rate of the left ventricular region of interest in the end-diastolic frame of the gated blood-pool study, corrected for the count rate per 1 ml of peripheral blood sample, for decay, and the depth of the left ventricle in the body was calculated using the effective linear attenuation coefficient of water ($\mu = 0.15 \text{ cm}^{-1}$) to correct for tissue attenuation. Although the lung, which is less dense than water, is in the path of photons from the left ventricle, bone (which is more dense than water) is also in the pathway, making the effective linear attenuation coefficient close to that of water. However, $\mu = 0.15 \text{ cm}^{-1}$ is theoretically applied to the attenuation of a narrow beam of gamma photons passing through an infinitely thin section of water, but that is not the case for the human body, where there is a bulk source located some distance from the camera. In this case, some photons would be expected to undergo multiple scattering and be directed back towards the detector, lowering the effective attenuation coefficient. Links et al. considered the left ventricle to be a point source and they used a point source of "\textsuperscript{99}Tc\textsuperscript{m}" placed on the chest wall superimposed on the left ventricular image. The acquisition was performed in the anterior view to measure the distance between the two centres of density of counts of the point source and left ventricle. They corrected the measurement for the actual angle of acquisition in the left anterior oblique position. Therefore, end-diastolic and end-systolic volumes could be derived in absolute terms. Thomsen et al. described a similar technique but they corrected for photon attenuation by using the depth to the centre of the left ventricle as determined by echocardiography \cite{11}.

Parrish et al. \cite{4} measured ventricular volumes in children by correction for attenuation and normalizing the result to the count rate of a peripheral blood sample. Photon attenuation was corrected by using a regression equation between the patient's body surface area and chest wall thickness measured from the radionuclide image. These techniques which correct for photon attenuation by body tissue appear to be more accurate as attenuation varies in different patients. Therefore, whether left ventricular depth is measured by a radioactive point source, echocardiography or from patient's body surface area, the measurement of absolute volume can be close to the actual volume.

Massie et al. compared geometric and nongeometric techniques using data from first-pass and equilibrium blood-pool scintigraphy \cite{12}. Two geometric approaches were used: directly measured long and short axes and the area-length method. Each approach was applied to the single-plane right anterior oblique view obtained by the first-pass technique and to biplane data, using the right anterior oblique first-pass and left anterior oblique blood-pool data together. For the nongeometric determination, background-corrected left ventricular counts were related to blood counts. This ratio was converted to volume by means of a linear regression analysis against angiographic volumes.
Anderson et al. demonstrated the ability of first-pass radionuclide angiography to detect accurately the left ventricular endocardial surface in the intact, conscious, chronically instrumented dog [13]. They showed a good correlation between end-diastolic volumes measured by ultrasound and radionuclide angiography relying on geometrical assumptions.

Nickel et al., using an experimental model, showed that the normalized total count rate (NTC; the total count rate divided by the maximum count density) was a linear function of volume if the object remained at a constant distance from the collimator [14]. They calculated the distance from the left ventricle to the collimator using the patient's height and weight and end-diastolic NTC, and produced results which compared well with contrast angiography.

Maurer et al. attempted to measure absolute left ventricular volume using an in vivo point source to correct for tissue attenuation [15]. They administered an oral capsule containing $^{99m}$Tc-labelled sulphur colloid counted before and after administration. The ventricular volumes were measured from the end-diastolic and end-systolic counts corrected for background, acquisition time, tissue attenuation (estimated from the point source) and the count rate of a peripheral blood sample. The direct measurement of the transmission factor for each individual patient helped in eliminating the assumption of a uniform linear attenuation coefficient (Links et al. [10]), and the need for regression curves (Dehmer et al. [8]; Slutsky et al. [7]). However, this method is not free of technical difficulties such as the need to swallow a radioactive capsule connected to a thread, the blind positioning of the angle of acquisition prior to blood-pool labelling and the effect of age-related changes in oesophageal motility. When the left atrium is enlarged, it may be difficult to separate left ventricular activity from left atrial activity in the standard left anterior oblique view. Moreover, a large left atrium can displace the oesophagus posteriorly leading to an underestimation of the transmission factor.

Seiderer et al. attempted to quantify left ventricular end-diastolic volume by emphasizing the importance of background superimposition, left ventricular self absorption and thoracic wall attenuation of photons [16]. They used parabolic background correction because the uniform background was thought to underestimate volumes. However, their method was dependent upon the assumption that left ventricular depth was 1.5 times that of the maximum ventricular width and that the thoracic wall and left ventricular wall were of the same thickness for each patient. These assumptions were made to correct for photon absorption by tissues and were dependent upon previously determined tomographic measurements.

Harpner et al. used a mathematical model for the analysis of the dynamics of a bolus of labelled red blood cells observed during the first pass through the ventricle prior to equilibrium [17]. They measured left ventricular volumes by correcting the counts at end-diastole and end-systole for attenuation and the injected activity. Ventricular volumes were expressed as a percentage of total blood volume which can be normalized for the specific activity of a peripheral blood sample to produce absolute volumes.
This method differs from the others by the nongeometric determination of the attenuation factors which eliminated large errors in the calculated volume produced by small errors in length measurements. Unfortunately, the technique requires careful counting of the injected radioactivity prior to imaging and uses in vitro labelling of red blood cells, a technique which is not widely used. In addition, it requires both first transit and gated blood-pool studies to be performed in order to obtain volumes.

Nicholoff et al. studied the physical basis of left ventricular attenuation correction by evaluating X-ray photon attenuation from computerized tomography (CT) scans of the thorax [18]. They converted CT numbers into a linear attenuation coefficient of 140 KeV (0.13 cm\(^{-1}\)). These workers based their methods on three facts: CT numbers correlate with the electron density of tissues; they depend upon the energy of the photon being studied; and, they relate directly to the linear attenuation coefficients of the tissue. Unfortunately, the linear attenuation coefficients determined by this method were for low energy X-ray photons from CT scanners which have an effective energy between 60 and 80 KeV. Therefore, they had to transform these coefficients to technetium-99m energy (140 keV) using a plastic phantom and specially designed software.

Rabinovitch et al. [19] described a count-based method similar to Links et al [10], although they corrected for tissue attenuation using a factor derived from a skin marker imaged in the left posterior oblique projection to measure left ventricular depth. Similarly, they normalized the results for the count rate of a peripheral blood sample to obtain volumes in absolute terms. However, they used a series of values for the linear attenuation coefficient ranging from 0.08 to 0.15 cm\(^{-1}\) and found a best estimate with a value of 0.10 cm\(^{-1}\) for end-diastolic volume and 0.12 cm\(^{-1}\) for end-systolic volume.

Petru et al. tried to solve the problem of attenuation correction by applying a similar geometric method using a radioactive skin marker imaged in the anterior view [20]. They used a higher linear attenuation coefficient of 0.16 cm\(^{-1}\) for 140 keV photons which was considered to be uniform throughout the cardiac cycle for all the tissues between the ventricle and the detector. This method was essentially similar to that described by Links et al. [10] with the same assumptions.

Starling et al. described a similar technique with emphasis on the importance of attenuation correction to produce absolute left ventricular volume [21]. Nichols et al. avoided geometric assumptions by using a new count-based method free of radiation attenuation corrections [22]. Their method required the acquisition of the first-pass of a bolus imaged in the right anterior oblique projection. Gated blood-pool images were collected in the left anterior oblique position under standard conditions. The left ventricle was located and outlined from the first-pass study and displayed simultaneously with the processed gated blood-pool image. Then a special program automatically calculated the volumes from the background-corrected count rates and the widest dimension of the right anterior oblique outline. This new technique had several inherent sources of error, the most important of which was the determination of
Left ventricular volume: review

ventricular depth as it is difficult to outline the left ventricle in the right anterior oblique projection. This involves judgement to separate the right ventricular boundaries and background activity which could produce large errors and poor reproducibility. In addition it was assumed that the maximum ventricular count rate and total diastolic count rate undergo the same average attenuation on emission from the left ventricle. Moreover, there is the possibility of changes in the magnification factor between the two projections. However, this method is free of attenuation correction.

Recently, Underwood et al. described a new approach to measure ventricular volumes by gated single-photon emission-computed tomography of the intracardiac blood pool [23, 24]. The heart was imaged three dimensionally by reconstructing the tomographic sections orthogonal to the long axis of the left ventricle. By summing the areas of the left ventricular sections, both end-diastolic and end-systolic volumes could be derived in absolute terms. This method has obviously many advantages over planar images as it makes no assumptions about the shape of the ventricle. However, it requires tomographic facilities with special software.

Discussion

The major differences between radionuclide techniques for ventricular volumes lie in the handling of scintigraphic images and the mathematical postulations regarding the total activity, background counts and tissue attenuation. Although scintigraphy produces three-dimensional data from two-dimensional images, there are many inherent sources of error unless great care is taken. One of these sources is the accurate separation of left ventricular activity both at end-diastole and end-systole. This can be minimized by semiautomatic edge defining algorithms utilizing the second derivative and local threshold techniques. A second source is the accurate selection of background activity so that noncardiac counts can be eliminated from the total counts. A third is correction for photon attenuation by body tissues. Most of the published work has concentrated on this aspect and attempted to correct for attenuation with minimal assumptions. These attempts have always introduced theoretical assumptions and there is a persistent error related to the geometry of the left ventricle and its anatomical orientation within the chest.

Another important problem is the methodology for validation of each of these techniques. Altman et al. reviewed methods of analysis used in the comparison of two methods of measurement, and criticized the use of correlation, regression and the difference between means, the most commonly used methods of analysis in validation studies [25]. None of these methods reveals whether the techniques can be considered equivalent. The most popular approach is to calculate the correlation coefficient between the two methods of measurement, but this is not a measure of agreement; it is a measure of association and, therefore, it is wrong to conclude from a close correlation that the methods may be used interchangeably. Linear regression is another technique which is used to predict the measurement obtained by one
method from the measurement obtained by the other, and allow calculation of a standard error for this prediction. This is a calibration approach and does not directly answer the question of comparability. Comparison of means is also commonly used, but the difference between means reveals very little about the accuracy of the methods even if it is not significant.

The problem of measuring left ventricular volume in absolute terms is that it lacks a 'gold standard'. The most conventional and universally acceptable standard is contrast angiography which produces ventricular volume by applying the Area-Length Method [5, 6]. This assumes that the ventricle is an ellipsoid or a prolate spheroid and the volume is calculated from the area and the long axis. Therefore, even small errors in length can produce large errors in the estimated volumes. This is in addition to the haemodynamic effect of contrast media on the ventricular dimensions.

It is important to establish a technique for the measurement of absolute left ventricular volume which is safe, easy to perform and reliably repeatable. The assessment of repeatability is an important aspect of studying alternative methods of measurement. The British Standards Institution defines a coefficient of repeatability as "the value below which the difference between two single test results may be expected to lie with a specified probability; in the absence of other indications, the probability is 95 per cent" [26]. Repeatability is not the same as reproducibility because many factors such as observer, time of day, position of subject, instrument, laboratory and so on may affect a measurement [25]. The British Standards Institution defines reproducibility as "the value below which two single test results obtained under different conditions may be expected to lie with a specified probability". In comparison studies, a simple method of analysis is to plot the raw data of the two methods and construct the line of identity which is much more informative than the regression line. Then, the difference between the methods should be plotted against their average. From such a plot it is easy to assess the magnitude of disagreement, identify the outliers and see whether there is any increase in the difference for high values. The 'relative bias' can be calculated from the mean of individual differences of the two methods and the 'estimate of error' is their standard deviation.

Conclusion

In the absence of a 'gold standard', the measurement of absolute left ventricular volume remains difficult. The question to be answered is whether the radionuclide approach is comparable with contrast angiography to the extent that it might replace the latter with sufficient accuracy. It appears that establishing a noninvasive technique which is interchangeable with contrast angiography is virtually impossible. The proposed solution of the problem is, therefore, to describe a method for measuring 'absolute' left ventricular volume by radionuclide studies in a large population of 'normal' subjects and to establish its characteristics, repeatability and reproducibility. This measurement can then be applied to different groups of patients to identify its clinical implications and usefulness.
References


FULLY AUTOMATED ALGORITHM FOR QUANTITATIVE MYOCARDIAL AND PULMONARY THALLIUM-201 SCINTIGRAPHY

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Summary

We have developed an automated algorithm for quantitative thallium-201 (Tl-201) scintigraphy which allows physicians and technologists to acquire, process and report Tl-201 images. A dedicated computer (Apex), attached to a digital gamma camera (Elscint), and advanced software (Fl), was employed. The algorithm was written in a mnemonic language (Clinical Interactive Programming - CLIP) and had four major sections. The first was concerned with data acquisition using preset parameters. The second was for analysis of quantitative heart/lung ratio. The third dealt with quantitative myocardial uptake and the fourth displayed curves which compared the results with a normograph derived from normal subjects. The curves were labelled to the corresponding myocardial segments according to coronary artery distribution along the X-axis. The operator was able to start at any point or recall previously analysed data. Thus, it is possible to standardize Tl-201 interpretation within and between different units using a fully automated programme.

Introduction

Since its early clinical application, thallium-201 myocardial imaging has achieved universal acceptance as a non-invasive test for detecting obstructive coronary artery disease (1,2). Exercise-induced redistribution visualised after a single injection of the tracer (3). The interpretation of Tl-201 images was carried out qualitatively by visual assessment of the degree of perfusion defect in different segments. More recently, quantitative analysis has been shown to improve the sensitivity of the technique (4). Unfortunately, the technical difficulties in processing and interpreting Tl-201 images (5) have limited the application of quantitative analysis and restricted its use to research centres employing highly trained and experienced physicists.

The purpose of this project was to develop a fully automated algorithm for quantitative Tl-201 analysis and to enable relatively inexperienced medical and technical staff to acquire, process and report Tl-201 images. In addition, we have applied this method to investigate the predictive value of quantitative Tl-201 analysis in detecting multiple vessel disease in patients with inferior myocardial infarction (MI).

Patients and Methods

Forty one patients were studied 6 weeks after documented transmural inferior MI. There were 35 men and 6 women with a mean age of 56.5 years. All the patients underwent selective coronary angiography within 2 weeks of Tl-201 imaging.

A single crystal, mobile digital gamma camera (Elscint), equipped with an all-purpose, parallel-hole, low-energy collimator, was employed. The camera was interfaced to a minicomputer with advanced software (Apex-215 M). The detector was set at 58 KeV around the photopeak of Tl-201 with an energy window of 15%.

Exercise testing

Maximal, symptom-limited, upright exercise was performed using a bicycle ergometer (EDC-8450) and the ZCG was monitored continuously using a bipolar CM5 and CC5 leads. The blood pressure was measured at rest and every minute during exercise using a standard cuff sphygmonanometer. Workload was increased automatically from 25 Watt every 3 minutes by 25 Watt increments until chest pain, dyspnoea, leg fatigue or ST-segment depression equal or greater than 4 mm developed. At peak exercise, 74 MBq (2m Ci) of Tl-201 was injected through an indwelling cannula and the patients were encouraged to continue the exercise for a further 30 seconds.

Data Analysis

Quantitative heart/lung ratio

Quantitative analysis of lung Tl-201 concentration was performed semi-automatically by using the colour scale of the monitor to compute regions-of-interest (ROI) in area regions of maximal count density over the myocardium and lungs (7). The average counts per pixel in the lung ROI to produce a heart-to-lung (H/L) ratio. The programme allowed the operator to alter the site of ROI according to the maximal count density and the H/L ratio was measured from exercise and delayed images.

Quantitative myocardial Tl-201 analysis

Tissue cross-talk is not distributed uniformly across the myocardium and cannot be removed by subtracting a constant background value from the myocardial images. After a nine-point smoothing each image was compensated for extra-cardiac activity by performing a bilinear interpolative background subtraction (8,9).
A circular ROI was placed around the heart, 4 pixels from the visual edge of the myocardium, and a background image was subtracted from the smoothed original stress and delayed images. The centre of the circular ROI was positioned at the centre of the left ventricular (LV) cavity to correct for changes in position. Angular profiles were generated by sampling the myocardial activity along 60 radii spaced at 6 degree intervals in a clockwise fashion from the ROI compass direction (10,11). The average value of myocardial activity along each radius was obtained. The angular profiles were used to quantitate the segmental activity as an angular function from the visually located centre of the LV. Each profile was then plotted as a 60-point histogram where the first point corresponded to the position of the compass and the middle points to the cardiac apex by visual judgement. Individual profiles were generated for each of the three views for both the stress and delayed images. The resulting histograms represented the relative distribution of Tl-201 activity in different segments of the myocardium and the absolute Tl-201 activity in corresponding segments in the immediate post-exercise and delayed images. In order to compare the patient profiles with normal data, the redistribution histograms were normalised to the same standard time delay after injection. The actual time at which the delayed images were obtained was used to interpolate the redistribution profiles to the standard delay interval (240 minutes). This manipulation was carried out for each patient by assuming a monoexponential washout of thallium-201 from the myocardium between the stress and delayed images. An angular washout profile was calculated as the percent washout from the stress to the standard delayed profiles. Abnormal Tl-201 distribution and washout were identified by comparing each patient profile with the corresponding lower limits which were determined by data from 18 normal subjects. The threshold value of 2.5 standard deviation below the normal mean was determined(4,13). A stress defect on the post-exercise profile was defined as at least three adjacent points (an 18 degree arc from three consecutive radii i.e. a triplet) below the lower limit of normal for the stress distribution profile. A slow defect on the washout profile was defined as at least three adjacent points (18 degree arc) below the lower limit of normal for the washout profile. To be considered abnormal, a patient required to have at least two abnormal (18 degree) segments in the combined stress and washout profiles in the three views. The stress histograms were superimposed onto the washout histograms for each view to assess the degree of redistribution in all segments. The circular ROI around the LV was automatically segmented into three sections for each image excluding the valve plane. The percentage change in counts in each subsegment was calculated from stress and redistribution images. Normal washout of each segment was present if the change was greater than -20% and redistribution was considered if the change was greater than +20%.

When the percentage change in counts was within ±20%, the segment was considered equivocal and other parameters were needed to identify the state of corresponding myocardial segment and coronary artery to allow easy interpretation.

Automated algorithm

All the above steps were integrated into a fully automated algorithm which was allocated to four function keys. The programme was written using a mnemonic language (Clinical Interactive programming - CLIP). The first function key was for data acquisition using preset acquisition parameters (energy setting, view and position) and the operator was able to change these parameters. The second function key was for quantitative heart/lung ratio, the third key for quantitative myocardial Tl-201 distribution and washout and the fourth key was for display and storage of a comprehensive report.

Results

Single vessel disease was found in 21 patients and the remaining 20 patients had multiple vessel disease. The mean H/L ratio was 2.01±0.25 (SEM) significantly lower than the normal values 2.74±0.12 (P<0.001). The sensitivity, specificity and predictive accuracy of quantitative Tl-201 analysis were 53, 57 and 73% respectively compared with visual interpretation 77, 71 and 81% respectively. Quantitative analysis was able to detect significant reversible ischaemia in 17 more patients (41%).

Discussion

Exercise Tl-201 imaging is widely used for the diagnosis and evaluation of obstructive coronary artery disease(3). We have confirmed previous reports(4) regarding the importance of absolute tracer uptake and washout after MI. Increased lung Tl-201 concentration appears to be an additional important diagnostic index(7). The application of automatic programmes for quantitative Tl-201 analysis may help in standardizing the technique and make it easily applicable.

References


