THE IMPACT OF MYOCARDIAL INFARCTION ON VENTRICULAR FUNCTION

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SUMMARY

Eighty one patients were studied using radionuclide ventriculography to study the effects of myocardial infarction (36 anterior and 45 inferior) on ventricular function during the early and convalescent phases. Left and right ventricular function was assessed during hospitalisation on day 1, day 3 and at hospital discharge and repeated after a mean of 16 ± 3 months following the index infarction.

Chapter 1 is a review of the literature relating to the impact of acute myocardial infarction on ventricular function. This chapter is in 3 sections; the first two deal with the effects of myocardial infarction on global and regional left ventricular function, respectively, and the final section relates to the natural history of right ventricular function following myocardial infarction. Within each section the findings from animal experiments and early haemodynamic studies are reviewed first, followed by the findings of clinical studies which have mainly utilised non-invasive techniques to assess ventricular function.

Chapter 2, "Methods", contains the details of the patient population studied, study design, statistical methods and the radionuclide techniques employed. Details regarding the use of Xenon-133 in the evaluation

of right ventricular function and the analysis of regional ventricular function are dealt with in later chapters.

Chapter 3, "The impact of acute myocardial infarction on global left ventricular function", presents the findings from the analysis of global left ventricular function during the hospitalisation phase. Anterior myocardial infarction was associated with lower ejection fractions than inferior myocardial infarction. Little variation was found in the left ventricular ejection fraction when patients were grouped according to the site of infarction. Variability in the left ventricular ejection fraction was found to occur in certain individuals and some patient subgroups. This did not appear to be related to any of the measured patient demographics or prognosis. A good correlation was found between the left ventricular ejection fraction and the size of infarction as estimated by Tl-201 scintigraphy. The correlation between the left ventricular ejection fraction and the enzymatic estimate of infarct size was closer following anterior in comparison with inferior infarction. The Killip and Norris classifications were not closely related to the left ventricular ejection fraction. A low left ventricular ejection fraction was associated with increased mortality; in addition the relationship between the left ventricular ejection fraction and mortality appeared to be influenced by the

site of infarction.

Chapter 4, "The impact of acute myocardial infarction on right ventricular function", deals with the data pertaining to right ventricular function obtained from gated technetium-99m equilibrium ventriculography during the hospitalisation phase. Right ventricular dysfunction was identified in 64% and 39% of patients following inferior and anterior infarction, respectively. No significant change in the right ventricular ejection fraction occurred following either anterior or inferior infarction during this period. However, variability in the right ventricular ejection fraction was observed in certain individuals, but this did not correlate with any of the measured demographics or prognosis. There was a correlation between the enzymatically estimated infarct size and the right ventricular ejection fraction following both anterior and inferior myocardial infarction. The right ventricular ejection fraction was not related to the Killip Class, Norris Index or prognosis.

Chapter 5, "Assessment of right ventricular function following acute inferior myocardial infarction using 133-Xenon imaging", presents the findings from the use of gated 133-Xenon imaging to assess right ventricular function acutely following acute inferior myocardial infarction. The use of this techniques overcomes many of the limitations of other techniques in

the assessment of right ventricular function. Acute inferior myocardial infarction was found to result in a wide spectrum of right ventricular dysfunction. The right ventricular ejection fraction ranged from 7-54%, mean 30 ± 11%. The findings were compared to clinical assessment of right
ventricular function, and revealed that significant right ventricular dysfunction often goes undetected clinically.

Chapter 6, "The natural history of ventricular function in the sixteen months following acute myocardial infarction", examines the course of left and right ventricular function during the convalescent phase (mean follow-up period 16 ± 3 months). A slight improvement was observed in the left ventricular ejection fraction following inferior myocardial infarction. Improvement in the left ventricular ejection fraction was also noted in patients with severe left ventricular dysfunction, which was greatest following inferior infarction.

No significant change in the right ventricular ejection fraction occurred in the 16 months following inferior infarction, however there was a progressive fall following anterior myocardial infarction during this period. The natural history of right ventricular function also varied during this period according to the degree of right ventricular dysfunction observed during the in-hospital phase. Patients with severe right

ventricular dysfunction showed an improvement in the right ventricular ejection; whilst there was a highly significant fall in patients with normal right ventricular function following both anterior and inferior infarction.

During the in-hospital period there was a correlation between the right and left ventricular ejection fractions following anterior but not inferior myocardial infarction. After the 16 month follow-up period a significant correlation was found following both anterior and inferior myocardial infarction. The presence of both right and left ventricular dysfunction in a patient following myocardial infarction was found to be an adverse prognostic factor, with a cumulative mortality of 40% after 18 months. However, the presence of right ventricular dysfunction without significant impairment of left ventricular dysfunction was associated with a relatively benign prognosis.

Chapter 7, "Assessment of regional ventricular function following myocardial infarction" describes the method employed to evaluate regional ventricular function; in addition other techniques used in the assessment of regional ventricular function are discussed. The technique used involves a computer-assisted quantitative analysis of the regional ejection fraction image. The regional ejection fraction image is divided into 12 equal sectors, with the regional ejection

fraction being expressed as a percentage of the total left ventricular value. Normal values were obtained from normals and compared with patients with anterior and inferior infarction. Anterior infarction resulted in a reduction in the contributions from the anteroseptal and anteroapical regions; following inferior infarction there were reductions from the sectors located in the apical region of the left ventricle.

Chapter 8, "The relationship between the left ventricular ejection fraction and regional ventricular function", examines the relationship between alterations in the left ventricular function and regional ventricular function using the technique described in Chapter 7. No change was found in regional ventricular function following anterior myocardial infarction during the in-hospital phase. During the 16 month follow-up phase there was an increase in the contributions from the basal-septal and basal-lateral aspects of the left ventricle which was not associated with any change in the left ventricular ejection fraction. Following inferior myocardial infarction there was a progressive decrease in the contribution from the zone of infarction in the apical region of the left ventricle both during the in-hospital and the follow-up period. During the in-hospital period this was associated with a slight fall and following hospital discharge a slight increase in the left ejection fraction. Although variation in the left

ventricular ejection fraction occurred in individual patients and when grouped according to the degree of left ventricular dysfunction, these changes were not associated with detectable alterations in regional ventricular function. Therefore, it was found that changes in the left ventricular ejection fraction usually occurred without alteration in regional ventricular function, and conversely that variation in regional ventricular function can occur without change in the left ventricular ejection fraction.

Chapter 9, "The impact of myocardial infarction on ventricular function", reviews the subject of ventricular function following myocardial infarction with reference to the major findings presented in this thesis and possible areas for future study are discussed.

INTRODUCTION

The impact of myocardial infarction on ventricular performance has been extensively investigated over the last fifty years. From the early experimental studies of Tennant and Wiggers (1), who first described the dramatic consequences of coronary occlusion which resulted in paradoxical systolic expansion, there has been a myriad of experimental studies examining the impact of coronary occlusion on ventricular performance. These have been accompanied by numerous clinical studies which have evaluated ventricular function following myocardial infarction using various invasive and noninvasive techniques relating these findings to the clinical status of the patient and to their subsequent prognosis.

The initial effect of myocardial infarction on ventricular function is primarily a regional phenomenon resulting from the occlusion of one of the epicardial coronary arteries or one of their major branches. Experimental studies in animals have shown that the effects on regional ventricular function are profound and of almost immediate onset (1,2) and that these changes alter during the following hours and days (3,4). The degree and extent of the regional dysfunction largely determine the effect that myocardial infarction has on overall ventricular performance. The inability of global

parameters of ventricular function to adequately characterise left ventricular function is related to the presence of regional differences in ventricular function being present and also their dependence on the prevailing loading conditions (5,6). For these reasons global parameters have significant shortcomings, especially in the setting of acute myocardial infarction.

One of the objectives of this thesis was to describe the evolution of alteration in left ventricular function during the early and convalescent stages of myocardial infarction, evaluating the prevalence and clinical significance of changes in left ventricular function and examining the relationship to regional ventricular function.

The clinical importance of right ventricular dysfunction following acute inferior myocardial infarction has been demonstrated by Cohn et al (7). Subsequently it has been shown that a wide spectrum of right ventricular dysfunction can occur following inferior myocardial infarction (8). However, the natural history of right ventricular function, particularly in the longer term following both inferior and anterior myocardial infarction is unclear. Therefore, another major objective of this thesis was to ascertain the natural history of right ventricular function following myocardial infarction.

The last main objective of this thesis was to examine the interplay between the function of the right and left ventricles, determining the influence of left ventricular dysfunction on right ventricular function in the days and months following myocardial infarction.

CHAPTER 1

HISTORICAL REVIEW

1.1 INTRODUCTION

Since the dramatic changes in ventricular function that occur following coronary artery occlusion were demonstrated by Tennant and Wiggers (1), there has been a plethora of animal experimental work describing the effects of acute myocardial ischaemia and infarction on ventricular function. The advent of bedside haemodynamic monitoring allowed the haemodynamic effects of acute myocardial infarction in humans to be observed. The development of left ventricular imaging devices, particularly the noninvasive techniques of echocardiography and radionuclide ventriculography, has allowed the consequences of myocardial infarction on ventricular function to be examined in greater detail and made sequential studies of ventricular function more practical. This historical review discusses the previous work relating to ventricular function following myocardial infarction, from the early experimental work through to the present day.

1.2 GLOBAL CHANGE IN VENTRICULAR FUNCTION FOLLOWING MYOCARDIAL INFARCTION

The immediate result of myocardial infarction is a reduction in the forward output and the total force of the left ventricle as a consequence of the loss of contractile myocardium. The subsequent course of events following this insult is variable and not purely related to the size of infarction (5,9).

The haemodynamic consequences of acute myocardial infarction vary widely from little or no change to marked derangement in measured parameters of left ventricular performance such as the left ventricular filling pressure, cardiac index, left ventricular stroke work index and compliance (dP/dV) (10-13). It has been shown that the enzymatically determined size of an infarct correlates with the degree of impairment of these haemodynamic parameters (12).

Kupper et al studied 70 patients sequentially with acute myocardial infarction at five hours, four to six weeks, and at six to twelve months (11). In those patients with no change acutely in the pulmonary artery diastolic pressure, cardiac index or stroke work index showed no change in these parameters by the end of the 4-6 week period. In those with only mild to moderate elevation in the pulmonary artery end-diastolic pressure (13-20 mm.Hg.) acutely, there was a significant fall in

the pulmonary artery end-diastolic pressure and an increase in the stroke work index, but no change in the cardiac index by the end of the 4-6 week period. In the third group, whose pulmonary artery end-diastolic pressure was >20 mm.Hg. at time of initial study, there was also a decrease in the pulmonary end-diastolic pressure and an increase in the stroke work index over the same period. There was also an increase in the cardiac index, however this was attributable to changes in heart rate. During the late recovery phase i.e. from 4-6 weeks to 6-12 months, there was no significant change in the haemodynamic status in any of the three groups.

Findings were similar in a smaller group of patients studied over a 3-5 month period by Rahimtoola et al where 55% of the patients showed an improvement over the period of study, however 18% showed a deterioration in ventricular function (13). The patients in this latter group had significantly poorer haemodynamic indices at the time of initial study.

There is a strong relationship between the haemodynamic disturbance following myocardial infarction and subsequent prognosis. Shell et al measured the left ventricular filling pressure, using Swan-Ganz catheterisation, in 99 patients within 12 hours of acute myocardial infarction (10). They found the left ventricular filling pressure at time of initial presentation, the sequential trend of the left

ventricular filling pressure and the last recorded left ventricular filling pressure to be predictive of short term (72 hours) and medium term mortality (30 days). Considering the initial left ventricular filling pressure, patients with a left ventricular filling pressure <18 mm.Hg., were found to have a mortality of 4% and 10% at 72 hours and 30 days, respectively. Whilst in patients with a left ventricular filling pressure >18 mm.Hg. the mortality was 21% and 33% at 72 hours and 30 days respectively.

Mathey et al related infarct size and haemodynamics with mortality (12). The mortality ranged from 4% in patients with no, or only minor, haemodynamic embarrassment and an enzymatically determined mean infarct size of 17 grams to 20% in patients with a pulmonary end-diastolic pressure between 12-20 mm.Hg. with a slight decrease in the cardiac index and left ventricular stroke work index, and a mean infarct size of 42 grams. A mortality of 85% was found in patients with pulmonary artery end-diastolic pressure >20 mm.Hg. which was associated with more marked changes in the cardiac index and left ventricular stroke work index, and a mean infarct size of 92 grams.

A decrease in compliance following myocardial infarction has been noted (12,14) which is in keeping with the experimental studies (2,15,16). The decrease in the compliance is thought to be a major contributing

factor in the increase of the left ventricular filling pressure following myocardial infarction, although this may be explained in part by an increase in left ventricular end-diastolic volume (15,17). The increased stiffness in the region of the infarct is mechanically more advantageous and results in an increase in the stroke volume and cardiac output (12). It is postulated that another compensatory mechanism that occurs is increased function in the noninfarcted region (12), which would explain why the cardiac index does not fall in direct relation to the size of the infarcted myocardium. Again there is experimental evidence to support this finding (18).

The alterations in ventricular volume that occur following myocardial infarction are complex. Klien et al proposed a theoretical model in which, beyond a critical infarct size involving 20-25% of the ventricular surface area, forward output could not be maintained unless ventricular dilation occurred, as the myocardial shortening capacity would be exceeded (19).

The changes in left ventricular function following myocardial infarction in a canine model can be abstracted as follows. Small increases in the left ventricular volume occur early, within the first hour of infarction (20), which is followed by a leftward shift in the pressure/volume curve due to increased stiffness of the infarcted segment (15,18). The presence of relatively

normal ventricular volumes following coronary occlusion is probably related to the small size and range of infarct sizes which are associated with only minor abnormalities of ventricular function in the recovery phase (21,22). Therefore, the relevance of this particular model to the clinical situation in this regard has been called into question (23).

Different findings have been reported using a rat model which results in a wider variation in infarct sizes and in this respect is more akin to the situation in humans. Using this model, three weeks following myocardial infarction Fletcher et al found that the end-diastolic volume increased in proportion to the infarct size and that there was a rightward shift in the pressure volume curve, thus preserving the pumping ability of the ventricle (23). Rats with healed infarcts had pressure-volume curves of similar shape to non-infarcted rats, but operated at higher end-diastolic pressures and therefore on the steeper portion of the curve. Volume loading produced smaller increases in both the diastolic and stroke volume, reflecting a reduced preload reserve. The rats with large infarcts (>40% of left ventricular circumference) were operating at almost maximum preload to maintain an adequate resting cardiac output and therefore in this situation volume loading resulted in minimal increases in diastolic and stroke volumes.

A subsequent study by the same workers (24) examining the changes in ventricular performance at 3-4 months following infarction found a similar haemodynamic profile to that observed at three weeks. However, in addition, it was noted that the ventricular volumes were further increased at any given filling pressure e.g. by 30% at 20 mm.Hg. in rats with infarcts of >40% in size and also that ventricular stiffness tended to decline as infarct size increased.

The changes which occur in the clinical situation are more difficult to expound as it is not possible to measure the pressure-volume relationship as investigators are restricted to examining only a small proportion of the diastolic pressure-volume relationship when attempting to characterise the diastolic properties of the ventricle. In studies examining the effects of myocardial infarction on the pressure-volume relationship within three weeks, shifts of the curve in either direction have been noted (25). Baxley et al, in a study of 25 patients within 2 to 12 months of infarction, noted that almost half the patients had increased end-diastolic volumes, and in patients with clinical heart failure 90% had increased end-diastolic volumes (26). Increased end-diastolic volumes were noted to occur in anterior infarcts when the antero-apical akinetic or dyskinetic area was greater than 20% of the left ventricular circumference. However, it can be difficult to determine

whether the increase in the end-diastolic volume is a result of ventricular distension i.e. dilation representing an upward movement along the normal diastolic pressure volume curve or whether it represents the result of ventricular dilation i.e. a rightward shift of the pressure volume curve. The situation is probably even more complex with the predominant mechanism depending on the distending pressure (24).

Swan et al hypothesised that before any alteration in ventricular volume occurred, the stroke volume could increase by 20% resulting from an increase in the contractility of the remaining viable myocardium (27). This results in a return to the normal forward output in a small infarct (10% of the left ventricle) but not in a large infarct (>40% of the left ventricle). Stroke volume was maintained as a result of normal or increased fibre shortening and not by increased ventricular volume in both small (17%) and moderately (28%) sized infarcts in a study utilising a canine model (28). Parmley et al estimated the contractile element velocity as a measure of the ventricular contractility and found it to be within normal in 66% of the patients following myocardial infarction. This suggests that there had been an increase in the myocardial contractility possibly occurring as a result of sympathetic stimulation (29).

To summarise, the haemodynamic consequences of myocardial infarction on ventricular function appear to be variable depending on the size of the infarct, ranging from minor changes in parameters of global left ventricular performance through to marked reduction in cardiac and left ventricular stroke work indices and elevation of the left ventricular filling pressure. Should the increase in the contractility be inadequate at maintaining the stroke volume then an attempt to preserve the forward output is made by increasing the myocardial fibre length. The increase in the fibre length (end-diastolic volume) can be brought about by an increase in the end-diastolic pressure (ventricular distension) i.e. by moving up an unchanged pressure volume curve, or by a rightward shift in the curve (ventricular dilation). The former mechanism is more likely to occur during the acute phase of myocardial infarction while the latter compensatory mechanism is more likely to be important in the more chronic phase in the subsequent months following infarction. The magnitude of the haemodynamic derangement, and to a lesser extent the capacity for improvement, is related to prognosis in patients following myocardial infarction.

The advent of the non-invasive techniques of two dimensional echocardiography and radionuclide ventriculography allowed left ventricular function to be assessed serially with relative ease during the acute and

convalescent phases of myocardial infarction.

The accuracy and relative geometrical independence of radionuclide ventriculography has led to its widespread use in the characterisation of patients following myocardial infarction (30). The effects of myocardial infarction on left ventricular function, as assessed by this technique, result in varying reductions in the ejection fraction and stroke volume with variable increases in the end-diastolic and end-systolic volumes (31-37).

The ejection fraction (stroke volume/end-diastolic volume) is used as a measurement of the state of ventricular performance and is strongly related to the histological extent of fibrotic tissue within the left ventricle (38). There is a strong inverse correlation between the left ventricular ejection fraction and subsequent prognosis following myocardial infarction (39-43). The Multicenter Postinfarction Research Group in a prospective study of 886 survivors of myocardial infarction found that a left ventricular ejection fraction of <40%, calculated from radionuclide ventriculography prior to discharge, resulted in a progressive increase in mortality at one year (39).

The propensity for left ventricular function to improve following myocardial infarction has been shown in both experimental (3) and clinical haemodynamic studies (10-12). Improvement in left ventricular function has

also been observed using serial radionuclide ventriculography in some studies (33,34,43,44). The improvement has been found to be limited to certain subgroups in two of these studies.

Dewhurst et al found this to be dependent on the degree of regional ventricular dysfunction (43). No significant improvement in the mean left ventricular ejection fraction was found after 12 months in patients who had normal wall motion, segmental hypokinesis or dyskinesis at time of discharge as detected by radionuclide ventriculography, but there was a significant increase in the mean left ventricular ejection fraction in patients with segmental akinesis, rising from 37% to 45%. Borer et al found that the improvement in the left ventricular ejection fraction (after 6 to 14 months) was confined to those patients who attained a left ventricular ejection fraction of >40% on submaximal exercise prior to discharge (44).

Reduto et al reported on 31 patients who underwent sequential radionuclide ventriculography following myocardial infarction found no significant difference during the hospitalisation phase (35). However the patient population was select in that patients who had pulmonary oedema, shock or had a previous history of angina, myocardial infarction or cardiac failure were excluded from the study.

Substantial changes in the left ventricular performance, as reflected by the left ventricular ejection fraction, occur spontaneously during the early hours of infarction in a significant proportion (56%) of patients (45). One of the reasons for this variability may be due to changes in the loading conditions of the ventricle. Changes in the double product, reflecting afterload, were notable in some of the patients in the aforementioned study who demonstrated changes in the left ventricular ejection fraction. End-diastolic volume, which would have given an indication of preload, however was not measured in this study. Another possible aetiology for the changes in the left ventricular ejection fraction may have been alterations in regional ventricular performance.

It has been suggested that it is important to identify changes in left ventricular function occurring during the first days following myocardial infarction (39,46). The Multicenter Postinfarction Research Group (39) found that the presence of rales in the Coronary Care Unit and a pre-discharge left ventricular ejection fraction were prognostically independent of one another. 52/866 patients who had advanced rales (diffuse or greater than one third of the way up the posterior lung field) and a discharge left ventricular ejection fraction $\geqslant$40% had a 21% two year mortality rate, whilst 208/866 patients with few rales and a discharge left ventricular

ejection fraction ≥40% had a mortality of only 15%. It was postulated that the reason for this difference in mortality was that the rales present on admission reflected a dynamic acute phase dysfunction, possibly secondary to myocardial ischaemia, which on reversal results in a restoration of ventricular function towards normal. In these patients this may result in a complicated post-infarction course resulting from an increased incidence of future cardiac events.

This hypothesis is consistent with the work of Warnowicz et al who examined patients with documented radiological evidence of pulmonary oedema during the hospital phase of myocardial infarction but who subsequently had a normal ejection fraction at the time of discharge from hospital (46). Sixteen patients had pulmonary oedema with a left ventricular ejection fraction >45% and 23 with pulmonary oedema had a left ventricular ejection fraction of <45%. Despite the significant differences in left ventricular ejection fraction the mortality at nine months was not significantly different. In the group with a left ventricular ejection fraction of >45%, half were re-admitted for recurrent pulmonary oedema or recurrent infarction. Four patients had coronary arteriography performed for unstable angina, all of whom had triple vessel disease, including two with left main stem disease. It would appear, therefore, that acute phase

left ventricular dysfunction may be related both to infarction and also to myocardial ischaemia, possibly as a result of coronary disease in the non-infarct vessels. Therefore, any subsequent improvement in ventricular performance may be due not only to improvement in the mechanical properties of the infarct and compensatory hyperfunction in the non-infarcted myocardium but also the resolution of ischaemia in the non-infarcted areas.

Anterior myocardial infarction tends to result in lower left ventricular ejection fractions than inferior myocardial infarction (32,35,37,41,43,47).

The reported relationship that exists between the left ventricular ejection fraction and enzymatic estimates of infarct size tends to be variable (36, 40-43), the reasons for this are probably multiple and are discussed in subsequent chapters.

The relationship between the left ventricular ejection fraction and clinical or radiological evidence of left ventricular dysfunction is not particularly good (32,34,39,47) with frequent failures in its identification in individual cases. Sanford et al used a stepwise linear regression analysis of history, physical examination, electrocardiographic and chest x-ray findings to predict the left ventricular ejection fraction and found that these findings could only account for 42% of the variability (32).

Many prognostic indices using a combination of clinical and radiological parameters have been developed in an attempt to stratify patients following myocardial infarction according to risk of subsequent cardiac events (48-51). These prognostic indices have been found to have a poor correlation with left ventricular ejection fraction and to be of only limited value in predicting subsequent events on an individual patient basis and therefore of little clinical use (32,43,47,52).

1.3 REGIONAL CHANGE IN VENTRICULAR FUNCTION FOLLOWING MYOCARDIAL INFARCTION

Despite the importance of parameters of global ventricular function they do have significant shortcomings as mentioned previously, namely their dependence on prevailing loading conditions of the heart and their inability to adequately characterise the entire left ventricle particularly in myocardial infarction where the primary disturbance of function is regional in origin. The importance of these regional changes are becoming increasingly realised both in terms of prognosis and of their effect on overall ventricular function (9,36,53,54).

It was from experimental work that the description of the functional changes which occur in the myocardium following coronary occlusion and the temporal sequence of

events were first noted. The early workers in this field described the paradoxical systolic expansion that occurs rapidly following coronary occlusion in the subtended myocardium (1). Subsequent work has shown that there is an increase in the segment length and decrease in the developed tension in both the central ischaemic and border zones (2).

The time sequence of these functional abnormalities has also been described. Banka and Helfant using coronary occlusion in a canine model, determined the changes that occur in the first four hours following coronary occlusion (2). They describe how the systolic expansion becomes apparent almost immediately, within 3-12 seconds, reaching a maximum after 15 minutes and decreasing thereafter as a result of the decreasing compliance.

Echocardiographic techniques have also been used in a canine model to follow the natural history of regional dysfunction following myocardial infarction both in the acute and convalescent phases. Gillam et al reported that once the abnormal wall motion was established in the 10 minutes following coronary occlusion the circumferential extent and magnitude of abnormal wall motion did not alter significantly over the subsequent 6 hours (4). Another echocardiographic based experimental study followed the course of regional function over a 6 week period (3). It was found that the maximal circumferential

extent of abnormal wall motion was observed after 48 hours and improved significantly over the 6 week period.

Evidence of regional changes in ventricular function in the border zones and also the zones remote from the area of the infarction have been reported. Studies using two-dimensional echocardiography have repeatedly demonstrated reduced function in regions bordering the histochemically defined zone of infarction (4,55-58) resulting in an overestimation in infarct size. Abnormalities in the border region have also been demonstrated using other experimental techniques (16,18), but others have demonstrated none (2). The aetiology of this disturbance of function is thought to be either ischaemic or mechanical (the so called "tethering effect") in origin. The latter explanation is supported by work, using radioactive microspheres, that found no significant reduction in normalised blood flow in the border zone (57). The "parallel fibre" hypothesis has been suggested as a mechanism for the tethering effect, which in essence implies that a muscle fibre only acts as its neighbour allows it to act. Therefore, an abnormal and a normal area of functioning muscle lying in "parallel" might be expected to function in parallel resistance, particularly if the contraction is not synchronous, thereby transmitting some of the abnormal muscle fibre characteristics to the adjacent normal

myocardium (16).

There is also controversy over the functional status of areas of myocardium remote from the area of infarction, with some work showing evidence of normal function (2,59), abnormal function (16,18) and also hyperfunction (60) in the non-occluded regions. It has been argued that the reasons for these apparently contradictory findings may be largely explained by differences in animal models and the functional variables measured (2).

The use of echocardiography in the investigation of regional function in myocardial infarction has also allowed another parameter to be measured, namely that of wall thickening. Normal myocardium demonstrates not only inward movement of the endocardium but also systolic thickening of the myocardium. The relationship of this to myocardial infarction was defined by Leiberman et al (57). However they did not find a close relationship between the transmural extent of infarction and the severity of impairment of systolic thickening. When the transmural extent was <20% reduced systolic thickening was observed; when the transmural extent was >20% systolic thinning was observed, but the degree of thinning was not related to the degree of transmural involvement.

The use of these experimental studies has been invaluable in increasing our knowledge of the basic

functional changes and the temporal sequence of these changes. However, one has to exercise caution in extrapolating these findings into a clinical setting. This is particularly true when one considers that most of these studies are performed using canine models, where there is essentially a single vessel coronary occlusion with a rich and uncompromised collateral bed. This is in contrast to the clinical setting of myocardial infarction, where the population is heterogeneous comprising of patients with single, double or triple vessel disease; with varying degrees of collateral development; with subtotal or total occlusion of the infarct related vessel with and without spontaneous reperfusion of the vessel.

Ohsuzu et al, using semi-quantitative analysis of radionuclide ventriculography, showed that the left ventricular ejection fraction correlated with the degree of regional dysfunction (36). In addition, with milder degrees of regional dysfunction there were no changes in the end-diastolic volume but there were increases in both the end-systolic volume and stroke volume. However with increasing degrees of regional dysfunction there was an increase in all the volumes. Similar findings have been obtained using biplane contrast ventriculography (61).

The effects of myocardial infarction on regional ventricular function using functional images, such as the stroke volume image and regional ejection fraction image,

have also been studied (53,54,62). The advantages of using functional images over the semi-quantitative analysis of a cine loop display are that it provides a more objective, reproducible and accurate means of analysing of radionuclide ventriculography (63,64).

Wynne et al, showed that inferior myocardial infarction was associated with less severe abnormalities of regional ejection fraction as well as higher global left ventricular ejection fraction than anterior infarction (53). In 30% of the patients studied there was also evidence of depressed regional function in non-infarct areas, especially in the patients who had sustained anterior infarction. The prognosis and clinical functional class was related to performance in both the infarct and the noninfarct areas. Buda et al showed that significant changes in regional ventricular function, as evaluated by the regional ejection fraction, occurred in the ten days following myocardial infarction which were not reflected by the left ventricular ejection fraction (54).

Despite the disadvantages of applying geometric methods to the analysis of regional ventricular function from radionuclide ventriculography, Ramanathan et al (65,66) have examined the changes in regional function which occur with time following myocardial infarction using hemiaxes. They showed that there was an improvement in regional ventricular function both in the

region of the infarct as well as the non-infarcted areas following sublingual nitroglycerin administration within 24 hours of infarction. This improvement was still apparent after 5-7 days (although less marked), however after 4-6 weeks there was no improvement in function in the region of the infarct.

The importance of regional ventricular function in relation to subsequent morbidity and mortality has been studied by Dewhurst et al (43,47). They found that patients with segmental akinesis tended to show an increase in the left ventricular ejection fraction in the 3-4 months following infarction. However, patients who exhibited areas of dyskinesis did not show this trend. In addition, this latter group of patients had a higher incidence of life threatening arrhythmias and subsequent development of episodes of left ventricular failure requiring treatment. These areas of dyskinesis were found more commonly in the patients who had sustained an anterior myocardial infarction.

The early regional topographical changes that occur following myocardial infarction and their implications are well known (67-70). The recognition of acute regional dilation and thinning of an infarct in the first few days following the onset of infarction was shown first in a clinico-pathological study by Hutchins and Bulkley (67) and subsequently its occurrence was demonstrated using two-dimensional echocardiography (68).

The expansion of the infarct was more common in anteriorly situated infarcts and resulted in an increased overall left ventricular dimensions and a significantly poorer prognosis than in those patients where evidence of expansion was not detected (68).

Meizlish et al commented on regional topographical changes following anterior myocardial infarction using radionuclide ventriculography (71). Patients were identified who developed functional aneurysms early following anterior myocardial infarction. A functional aneurysm was defined as an area displaying the following criteria: the presence of a well-localised area of akinesis or dyskinesis; a discrete deformity in the left ventricular contour present both in systole and diastole; and normally contractile myocardium adjacent to the area of regional dysfunction. The one year mortality in these patients was 61% as compared to a group without evidence of early functional aneurysm formation, who had a one year mortality of 9%. This difference in mortality occurred despite no significant differences in the left ventricular ejection fraction between the two groups. In the deaths that occurred the group with functional aneurysms 55% were sudden.

1.4 RIGHT VENTRICULAR FUNCTION FOLLOWING ACUTE MYOCARDIAL INFARCTION

Assessment of right ventricular function following acute myocardial infarction has attracted less attention than that shown towards the left ventricle for several reasons. Firstly, until the last decade the right ventricle was largely ignored as it was generally thought that it was of little functional importance and regarded merely as a conduit for the blood returning from the systemic circulation passing through to the pulmonary circulation. Therefore, it was considered that the right ventricle could have little role in pathophysiological processes affecting the cardiovascular system and that the left ventricle, which generated the output for the systemic circulation, was of prime importance. Secondly, until the development of two dimensional echocardiography and radionuclide ventriculography, there had been no satisfactory method of assessing right ventricular function. Contrast ventriculography, the gold standard by which left ventricular function is assessed, could not be so readily applied to the right ventricle because of its complex geometrical shape (72).

When considering the right ventricle in the setting of myocardial infarction there are two aspects to be considered: firstly, right ventricular infarction and the right ventricular dysfunction resulting from this.

Secondly, the effect of left ventricular dysfunction following myocardial infarction on right ventricular function.

Before discussing these points, it is convenient to briefly describe the normal physiology and the pathophysiology of the right ventricle. "Ventricular interdependence" is a term used to describe the relationship which exists between the right and left ventricles whereby changes in the functional status in one can result in an alteration in performance of the other ventricle. The existence of such a relationship was first described by Bernheim (73) when the performance of the right ventricle was impaired as a result of right ventricular compression secondary to left ventricular dilation and hypertrophy. Ventricular interdependence exists because of the arrangement of the myocardial fibres; some are arranged to encircle only one particular ventricle whilst other fibres encircle both ventricles. Another important contributing factor is the pericardium which accentuates the phenomenon of interdependency (74).

Therefore, dilation or distension of one ventricle results in an alteration in the compliance and geometry of the other ventricle. An example of the importance of this interplay is illustrated in the normal physiological adaptive mechanisms resulting from the change from the supine to the erect position. On assuming the erect position there is a decrease in the venous return, which

leads to a reduction in the right ventricular end-diastolic volume. However, as a result of the inter-dependence between the two ventricles there is an increase in the left ventricular compliance which facilitates left ventricular filling and maintenance of the left ventricular stroke volume (72).

The interaction between the two ventricles is also pertinent to the understanding of the pathophysiological mechanisms involved in right ventricular infarction. Animal experiments which inflicted severe damage, by the use of cautery, to the right ventricular free wall did not significantly impair right ventricular pump function either acutely or chronically (75). The right ventricle is extremely stiff following cautery resulting in very efficient coupling of the ventricles, where contraction of the left ventricle results in the free wall of the right ventricle being pulled towards the interventricular septum, thereby maintaining the right ventricular output. This is different from the clinical situation of right ventricular dysfunction occurring following acute inferior myocardial infarction when the right ventricular free wall is much less rigid with loss of the mechanical coupling (75). Additionally, right ventricular infarction rarely occurs in isolation (76) and is usually associated with varying degrees of infarction of the inferior aspects of the left ventricle (77,78) and in particular the interventricular septum and crista

supraventricularis which has a detrimental effect on right venticular performance (79).

In 1974 Cohn et al (7) described the clinical syndrome of "right ventricular infarction" which results in hypotension, oliguria, clear lung fields and elevation of the jugular venous pulse. Early postmortem studies suggested a relatively low incidence of right ventricular infarction (76,77). However, with the development of noninvasive imaging techniques it has become apparent the incidence is much higher. Using these techniques the incidence of right ventricular dysfunction following inferior wall myocardial infarction has been reported by Rigo et al (80), Baigrie et al (8) and McGhie et al (81) as 64%, 78% and 69% respectively.

Sharpe et al using M-mode echocardiography found a significant increase in the right ventricular end-diastolic dimensions and the ratio of right to left ventricular dimensions in patients with right involvement when compared with patients without right ventricular involvement following inferior myocardial infarction (82). Using two dimensional echocardiography evidence of both regional and global right ventricular dysfunction following inferior myocardial infarction have been described (8,83). To date, however, there has been no prospective study evaluating the use of echocardiography in a large number of consecutive patients which is probably a reflection of the inherent difficulties of

this technique in overcoming the geometrical complexity of the right ventricle and obtaining satisfactory definition of the right ventricular endocardium in a significant proportion of patients.

The haemodynamic consequences of right ventricular involvement following left ventricular inferior wall myocardial infarction have been widely reported and various criteria have been suggested for its diagnosis (7,84,85). These criteria include a ratio of the right/left ventricular filling pressure equal to or greater than 1.0 (7), 0.80 (84) or 0.65 (8,82); an abnormal "non-compliant" pattern in the right ventricular pressure waveform (84) or a right ventricular stroke work index <0.5 m/m2 (82). Although haemodynamic criteria are quite specific in the detection of right ventricular dysfunction, they are not particularly sensitive at detecting less severe degrees of right ventricular dysfunction (8). These criteria may be absent in the presence of hypovolaemia or marked right ventricular dilation only becoming apparent following volume loading (8,72,80).

The application of radionuclide techniques in the setting of right ventricular involvement is two-fold. Firstly, technetium-99m pyrophosphate and thallium imaging (82,86) can be used to detect the presence of right ventricular infarction. Secondly, radionuclide ventriculography can be used to assess right ventricular

function (8,80,81,87). Using these latter techniques the spectrum of right ventricular dysfunction following inferior myocardial infarction has been observed to range from the presence of isolated regional wall motion abnormalities without any associated abnormality in global right ventricular function to varying degrees of depression of global right ventricular performance resulting in depression of the right ventricular ejection fraction (8).

The natural history of right ventricular dysfunction following inferior myocardial infarction is still somewhat obscure. A propensity for right ventricular function to improve has been reported by some workers (88-91). Haines et al reported on a group of 74 patients with acute inferior myocardial infarction with varying degrees of right ventricular dysfunction (92). They found that the presence of right ventricular dysfunction did not limit exercise tolerance or identify a sub-group of patients at a higher risk of recurrent events.

However, Rodrigues et al found that in 51 patients with acute inferior myocardial infarction, 25 had severe right ventricular dysfunction which was associated with a somewhat poorer prognosis (93). Of these 25 patients, six died and the remainder failed to show improvement in the right ventricular ejection fraction with six developing clinical evidence of right ventricular

failure. A higher mortality rate, as well as a higher incidence of shock and arrhythmia has been documented when the diagnosis of right ventricular infarction has been made on haemodynamic grounds (94,95).

Therefore, the natural history of right ventricular dysfunction complicating inferior myocardial infarction, particularly in the out-of-hospital phase, remains to a certain extent an enigma. It is likely to be dependent on a variety of factors, in particular the degree of right ventricular dysfunction and also the functional status of the left ventricle.

The impact of anterior myocardial infarction on right ventricular function is also not well understood. Some investigators have not found right ventricular dysfunction following anterior myocardial infarction (35,87) whilst others have found abnormalities in right ventricular function (88,96-98). Two mechanisms by which anterior myocardial infarction can result in right ventricular function have been postulated. Firstly, by means of ventricular interdependence, with anterior myocardial infarction resulting in significant left ventricular dysfunction with an increase in the left ventricular volumes and/or pressure, leading to corresponding changes in right ventricular performance. These changes either being transmitted via the interventricular septum or resulting from increased pulmonary arterial pressure and right ventricular afterload.

Secondly, an alternative (or additional) mechanisms in the setting of a large anterior myocardial infarction involving a significant proportion of the inter-ventricular septum. As the interventricular septum is a functionally important structure of the right ventricle it can result in right ventricular dysfunction, as discussed earlier.

Marmor et al (96), Caplan et al (97) and Shah et al (98) have all reported a significant correlation between the right and left ejection fractions following anterior infarction but not following inferior infarction during the in-hospital phase. Caplan et al (97) have suggested that right ventricular dysfunction following anterior myocardial infarction was the result of involvement of the interventricular septum citing the presence of regional wall motion abnormalities identified in this region as evidence to support this hypothesis. Others have suggested that the aetiology of the right ventricular dysfunction is related to the former mechanism of ventricular interdependence as only diffuse abnormalities in right ventricular performance were noted (96,98).

Therefore, in light of this most recent work it would appear that right ventricular dysfunction does occur following anterior myocardial infarction. However the mechanism by which this occurs is unclear. In addition, the natural history of right ventricular

dysfunction following myocardial infarction in the longer term is uncertain.

CHAPTER 2

METHODS

2.1 INTRODUCTION

This chapter describes the patient population, the methodology and the validation of the techniques used in this thesis. However, the use of 133-Xenon in the assessment of right ventricular function and the evaluation of regional ventricular function will be described in Chapters 5 and 7 respectively which include details of methodology and validation.

2.2 PATIENT POPULATION

The patient population studied consisted of 121 consecutive patients admitted to the Coronary Care Unit in the Royal Infirmary, Glasgow, between October 1984 and July 1985. Informed consent was obtained from all patients. Approval for the study was obtained from the local ethical review committee and appropriate A.R.S.A.C. certification was held.

The inclusion criteria for entry into this study were all patients admitted into the Coronary Care Unit with a history of chest pain consistent with myocardial ischaemia or infarction within the preceding 24 hours who

were aged less than 75 years old.

Eighty one patients were subsequently shown to have sustained an acute myocardial infarction using the following criteria. All patients gave a history of prolonged cardiac pain occurring at rest which lasted for at least 30 minutes and subsequently developed a rise in serum levels of creatine kinase, aspartate and alanine transferase in a pattern consistent with acute myocardial infarction. All patients developed sequential electrocardiographic changes. The site was considered to be anterior if the electrocardiographic changes involved leads V1 to V6 and leads 1 and aVL and inferior if the changes involved leads 2, 3 and aVF. Electrocardiographic changes of true posterior infarction were included within the inferior group. Using these criteria 45 of the patients sustained an inferior and 36 an anterior myocardial infarction. Patients were not subdivided into those with Q wave and non-Q wave myocardial infarction.

There were five patients in addition to the above mentioned 81 patients who had sustained a myocardial infarction, however they died prior to assessment of ventricular function and were therefore not included in the patient population for analysis.

An estimation of infarct size was made using the peak creatine kinase level using routine laboratory facilities. Patients had blood samples taken for the estimation of creatine kinase level every four hours for

the first 32 hours following the onset of symptoms.

59/81 (73%) of the patients were male. The mean age of the patients was 56 years and ranged from 24 to 74 years. 48% (39/81) gave a history of exertional chest pain for more than two months prior to their admission and 18.5% (15/81) had a history and electrocardiographic evidence of previous myocardial infarction. Six patients gave a history of treated systemic hypertension and four patients a history of diabetes mellitus.

On admission the patients were specifically examined for evidence of left or right ventricular failure by the admitting member of the Coronary Care staff. They were also classified retrospectively from the clinical records during their admission as to their Killip Class as described by Killip and Kimball (51). 57/81 (71.3%) of the patients fell into Class 1 (no clinical signs of cardiac decompensation), 17/81 (21%) in Class 2 (signs of heart failure including rales, third heart sound, pulmonary venous hypertension), 4/81 (4.9%) in Class 3 (frank pulmonary oedema) and 3/81 (3.7%) in Class 4 (cardiogenic shock). Patients were additionally classified according to Norris et al (49). The mean Norris Index was 6.2 ± 2.5 (range 2.7 - 14.7).

Fifty four patients were reviewed at a special recall follow-up visit; the mean time interval between this visit and the index infarction was 16 ± 3 months. At that time patients underwent full physical examination,

radionuclide ventriculography and exercise testing where appropriate. Patients were followed for 12-24 (mean 18) months following the index myocardial infarction. Follow-up information was obtained in all patients, either from attendance at the follow-up visit, from medical records or from the patient's General Practitioner.

The circumstances of each death was obtained from the staff in attendance and from patients' hospital case-notes if deaths occurred during a hospital admission. If deaths occurred in the community the patient's General Practitioner was contacted. In all cases he was able to give details of the circumstances of the concerned patient's death. All deaths fell into either Hinkle class I (abrupt loss of consciousness without prior collapse of circulation) or Hinkle class II (gradual circulatory failure and collapse of circulation) and were therefore considered to be cardiac in origin (99).

The in-hospital mortality was 10% (8/81), the out-of-hospital mortality was 14% (10/73) and the total cumulative mortality was 22% (18/81). Mortality following anterior myocardial infarction was higher. The in-hospital mortality was 14% (5/36) and cumulative mortality after 18 months 31% (11/36); in comparison the in-hospital and cumulative mortality following inferior myocardial infarction was 4% (2/45) and 16% (7/45). These differences failed to reach statistical

significance with Chi-squares of 2.6 and 2.3 respectively. Table 1 lists events following the index infarction.

At time of discharge 16% of patients were receiving beta adrenoreceptor antagonists, 14% were receiving calcium-channel blocking agents, 12% long-acting nitrates, 33% diuretics, 10% digoxin and 2% angiotensin converting enzyme inhibitors. At the time of the follow-up visit this had changed to 21% receiving beta-adreno-receptor antagonists, 25% receiving calcium antagonists, 22% receiving long-acting nitrates, 31% receiving diuretics, 7% receiving digoxin and 1% receiving angio-tensin-converting enzyme inhibitors.

2.3 GATED EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Patients' ventricular function was assessed using gated technetium equilibrium ventriculography. This was performed, where possible, on three occasions during the patient's hospital admission. At 24 hours (mean time after onset of symptoms 29 ± 13 hours), three days (mean 3 ± 0.7 days), at time of hospital discharge (mean 15 ± 12 days) and again at the time of their follow-up visit (mean 16 ± 3 months) following myocardial infarction.

The patient's red cells were labelled in-vivo with 800 MBq of technetium pertechnetate. Data was acquired using a mobile gamma camera fitted with a high

Event	Number of patients
Post infarction angina	14
Coronary arteriography	28
Coronary artery surgery	6
Reinfarction	1
Hospital admissions with heart failure	9
Scar-related ventricular tachycardia	1
Brachial embolism	1
Cerebrovascular accident	1
Other: renal carcinoma	1

TABLE 1

Events after hospital discharge in the 18 months following the index infarction

sensitivity parallel collimator interfaced with a mobile computer system (MAPS, Link, UK). A 35-45^{o} left anterior oblique projection, affording optimal separation of the right and left ventricles with a 5^{o} caudal tilt, was used. Data was acquired gated to the electrocardiogram and was stored in a list-mode file allowing subsequent retrospective construction of a 16 frame cardiac cycle for subsequent analysis. Cycles with a R-R interval of greater than 20% outwith the average R-R interval were not included for analysis.

Normal values were obtained from 10 patients undergoing coronary arteriography for the diagnosis of chest pain. In all cases the patients had normal exercise tests and thallium imaging. There was no evidence of cardiomyopathy or valvular heart disease. Five of the patients were male, their ages ranged from 34 to 62 years with a mean of 47 years. Coronary arteriography and left ventriculography was performed by the Judkins technique. None of the patients had evidence of coronary artery disease or evidence of ventricular dysfunction.

The left ventricular ejection fraction was calculated in the following manner. A single left ventricular region of interest was drawn manually around the left ventricle in end-diastole, permitting the computer to analyse the acquired data and produce a time-activity curve of high temporal resolution. The end-

systolic frame was identified as being the point at which the activity within the left ventricle reached a minimum. A stroke volume image was produced by subtracting the end-systolic image from the end-diastolic image to assist in the correct assignation of the left ventricular region of interest. Correction for background activity was made by defining a crescent shaped region of interest outlining the lateral border of the left ventricular region of interest from the apex to the base approximately three pixels wide. This allowed the calculation of the left ventricular ejection fraction using the formula in Figure 1. It has been previously found that this technique correlates well with right anterior oblique contrast ventriculography ($R = 0.89$, $n = 100$), although with lower values for the left ventricular ejection fraction than are obtained using contrast ventriculography (100).

The normal values for the left ventricular ejection fraction obtained using this technique are as follows. The mean value of 50 ± 4.6% (mean ± standard deviation) with a range of 42 - 55%, with a left ventricular ejection fraction of >40% being considered as normal.

The reproducibility with repeat acquisition was performed in 5 patients by repeating the studies after 30 minutes. The difference in the ejection fraction ranged from 1.0 ± 3.0%, with a mean difference of 2%. The inter- and intra-observer variation in 40 studies was 2.4% and 1.2% respectively.

The right ventricular ejection fraction was calculated using equilibrium technetium ventriculography in a similar fashion to that used in the determination of the left ventricular ejection fraction. Calculation of the right ventricular ejection fraction using gated equilibrium radionuclide has been previously shown to be a reliable and reproducible method of assessing right ventricular function (101).

A single right ventricular region of interest was drawn using the end-diastolic image. Stroke volume and paradox images were used to enable the accurate definition of the right ventricle from surrounding structures, in particular the tricuspid and pulmonary valve planes. The stroke volume image was obtained in the manner described for generation of the left ventricular region of interest and the paradox image was produced by subtracting the end-diastolic image from the end-systolic image and thereby identifying the right atrium. The right ventricular region of interest was confirmed by superimposing the cine display and modifying as necessary. The background region of interest was drawn along the lateral aspect of the right ventricular region of interest extending from the apex round to the right atrium. Time-activity curves were subsequently generated for these regions of interest, allowing the right ventricular ejection fraction to be calculated using the same formula, Figure 1.

$$EF = \frac{EDc - ESc}{EDc - B}$$

FIGURE 1

Formula used for calculation
of ejection fraction

EF = ejection fraction.
EDc = end-diastolic counts.
EDs = end-systolic counts.
B = background activity derived from the mean counts throughout the time-activity curve for the background region of interest.

The normal values for the right ventricular ejection fraction obtained were as follows. The mean value for the right ventricular ejection fraction is 47.3 ± 6.4%, with a range of 42-60%. A right ventricular ejection fraction of 35% or greater was considered normal. The reproducibility for the calculation of the right ventricular ejection fraction was performed as for the left ventricular ejection fraction. The intra-observer variation was 1.5%, and the inter-observer variability 3.5%. The reproducibility of the technique using data from repeat acquisition ranged from 0-5%, with a mean difference of 2.3%.

A single, end-diastolic, region of interest was used to calculate the ejection fraction. This was the technique used routinely in the department at the time that this work was being carried out. The use of a fixed region of interest tends to systematically underestimate the ejection fraction because of inclusion of atrial activity in end-systole; however, it has the advantage of improved inter- and intra-observer reproducibility which is particularly relevant to this thesis where serial analysis was performed (102), see Appendix 1.

2.4 MYOCARDIAL SCINTIGRAPHY

201-Thallium imaging was performed in all the patients on admission to the Coronary Care Unit.

Patients were injected intravenously with 80 MBq of 201-thallous chloride. Patients were imaged using a mobile gamma camera fitted with a high sensitivity parallel collimator and interfaced with a mobile computer system (MAPS, Link, UK) in three projections: anterior, 45^{o} and 75^{o} left anterior oblique projections. If the patient's condition dictated a minimum imaging period then only the 45^{o} left anterior oblique projection was performed. Data was acquired in listmode, gated to the electrocardiogram for 300 seconds for each projection. The acquired data was subsequently processed into an eight frame representative cardiac image, with any R-R cycles falling outwith 20% of the average being excluded from analysis (103).

The images were analysed visually using a semi-quantitative method to estimate the size of infarction. Each projection was analysed individually with the left ventricle being divided into five equal segments. The area of abnormal perfusion was outlined in each projection which was then expressed as a mean percentage of the total left ventricular area of all three projections. The right ventricle was not analysed from the thallium images because of its poor visualisation in a significant proportion of patients. If there appeared to be two distinct areas showing perfusion abnormalities then the defect that was thought to reflect the electro-cardiographic site of infarction was used.

2.5 STATISTICAL METHODS

All values are expressed as a mean ± the standard deviation. Non-parametric statistical tests were employed because of the lack of normal distribution of most of the parameters assessed and the small number of patients in some of the groups. Two by two contingency tables using Yates correction were employed for comparison of frequencies between groups and Wilcoxin's Signed-rank Test and Mann-Whitney Rank-sum Test were employed for statistical comparison of paired and unpaired data respectively. The correlation between variables was performed using Spearman Rank Correlation Estimates (Rs). A probability (p) value less than 0.05 was considered significant. Standard analysis was performed using BMDP Statistical Software (1983), University of California, Los Angeles.

CHAPTER 3

THE IMPACT OF ACUTE MYOCARDIAL INFARCTION ON GLOBAL LEFT VENTRICULAR FUNCTION

3.1 INTRODUCTION

The effect of myocardial infarction on left ventricular performance is a direct consequence of the loss of contractile myocardium, resulting in a reduction in the total force generated by the left ventricle. However, the subsequent course of events is not purely related to the size of infarction (9).

The use of the left ventricular ejection fraction as a parameter in the assessment of left ventricular performance is widely accepted. Its power as a prognostic parameter following myocardial infarction is well documented, and has been shown to be the most important independent predictor of subsequent mortality in the first year following myocardial infarction (39-43).

The use of radionuclide ventriculography allows quantitative assessment of left ventricular function during the early stages of myocardial infarction (32,37). The technique can be easily and safely performed in critically ill patients within the confines of a coronary care unit. The technique is non-invasive and the modest

radiation exposure involved allows sequential studies to be performed.

The aims of this chapter are to firstly describe the natural history of the changes in left ventricular performance that occur during the hospitalisation phase. The second aim is to determine what variations occur in left ventricular ejection fraction and to ascertain their significance. The third aim is to determine what relationship left ventricular dysfunction bears to the size of the myocardial infarct as determined in terms of size of the Thallium-201 perfusion defect and the enzymatically determined size of infarct. The final aim is to determine the relevance of left ventricular dysfunction to the clinical status following myocardial infarction and to subsequent cardiac morbidity and mortality.

3.2 CHANGE IN THE LEFT VENTRICULAR EJECTION FRACTION DURING THE HOSPITALISATION PHASE

The left ventricular ejection fraction was assessed, where possible, on 3 occasions during the hospitalisation phase following acute myocardial infarction. It was measured on the day following admission (mean of 29 hours following onset of symptoms) in 56 of 81 patients, on the third hospital day (mean 3 days) in 67 of 81 patients, and at time of hospital

discharge (mean 15 days) in 64 of 74 patients. The left ventricular ejection fractions were 28.2 ± 9.5%, 26.0 ± 9.8% and 29.0 ± 10.1% on day 1, day 3 and at hospital discharge respectively. A total of 38 patients had the left ventricular ejection fraction measured at all three time points during the in-hospital phase; the left ventricular ejection fraction was 29.9 ± 9.6%, 27.2 ± 9.6% and 29.6 ± 10.3% on day 1, day 3 and at hospital discharge respectively. This is not significantly different from the values quoted above, which includes patients whose left ventricular ejection fraction was not evaluated on three occasions.

The left ventricular ejection fraction was significantly lower in patients following anterior, as compared with inferior, myocardial infarction during hospitalisation. On day 1, the left ventricular ejection fraction was 23.4 ± 9.8% (n = 20) and 31.0 ± 8.4% (n = 36), $p<0.01$; on day 3, 21.1 ± 8.0% (n = 31) and 29.9 ± 9.5% (n = 36), $p<0.001$; and at hospital discharge 23.5 ± 8.7% (n = 28) and 32.4 ± 9.4% (n = 36), $p<0.001$ for anterior and inferior myocardial infarction respectively, Table 2.

Following anterior myocardial infarction there was no significant change in the left ventricular ejection fraction during hospitalisation. In patients who had sustained an inferior myocardial infarction there was a small but statistically significant disease in the left

	Anterior MI	Inferior MI	p value
LVEF1	23.4 ± 9.8	31.0 ± 8.4	$p<0.01$
LVEF2	21.1 ± 8.0	29.9 ± 9.5	$p<0.001$
LVEF3	23.5 ± 8.7	32.4 ± 9.4	$p<0.001$

TABLE 2

Difference in the left ventricular ejection fraction (mean ± standard deviation) between patients with anterior and inferior myocardial infarction (MI)

LVEF1 = left ventricular ejection fraction on day 1
LVEF2 = left ventricular ejection fraction on day 3
LVEF3 = left ventricular ejection fraction at hospital discharge
p value = significance level (p).

ventricular ejection fraction between day 1 and day 3, 31.0 ± 8.4% and 29.9 ± 9.5% (n = 36), $p<0.05$.

Patients were grouped according to the degree of left ventricular dysfunction into those with severe ventricular dysfunction (left ventricular ejection fraction <25%), moderate dysfunction (left ventricular ejection fraction 25-34%), and minor dysfunction (left ventricular ejection fraction >35%). Significant intergroup differences were identified. Patients with moderate left ventricular dysfunction also showed significant alterations in the left ventricular ejection fraction during the first 3 days following infarction. Following anterior myocardial infarction the left ventricular ejection fraction fell between day 1 and day 3, from 28.5 ± 2.3 to 23.8 ± 6.5, $p<0.05$, whilst the left ventricular ejection fraction increased following inferior myocardial infarction from 30.6 ± 2.1 to 34.1 ± 4.8, $p<0.05$; Table 3. In the 7 patients with severe ventricular dysfunction following inferior myocardial infarction, the left ventricular ejection fraction increased from 16.6 ± 4.6% to 23.4 ± 7.0%, $p<0.05$ between day 1 and day 3 during hospitalisation, Table 3.

A wide variation in the left ventricular ejection fraction was observed in individual patients. The range of change in the left ventricular ejection fraction was from +19% to -16%, mean change +5% ± 4.2%. The distribution of these changes are shown in Figures 2 and

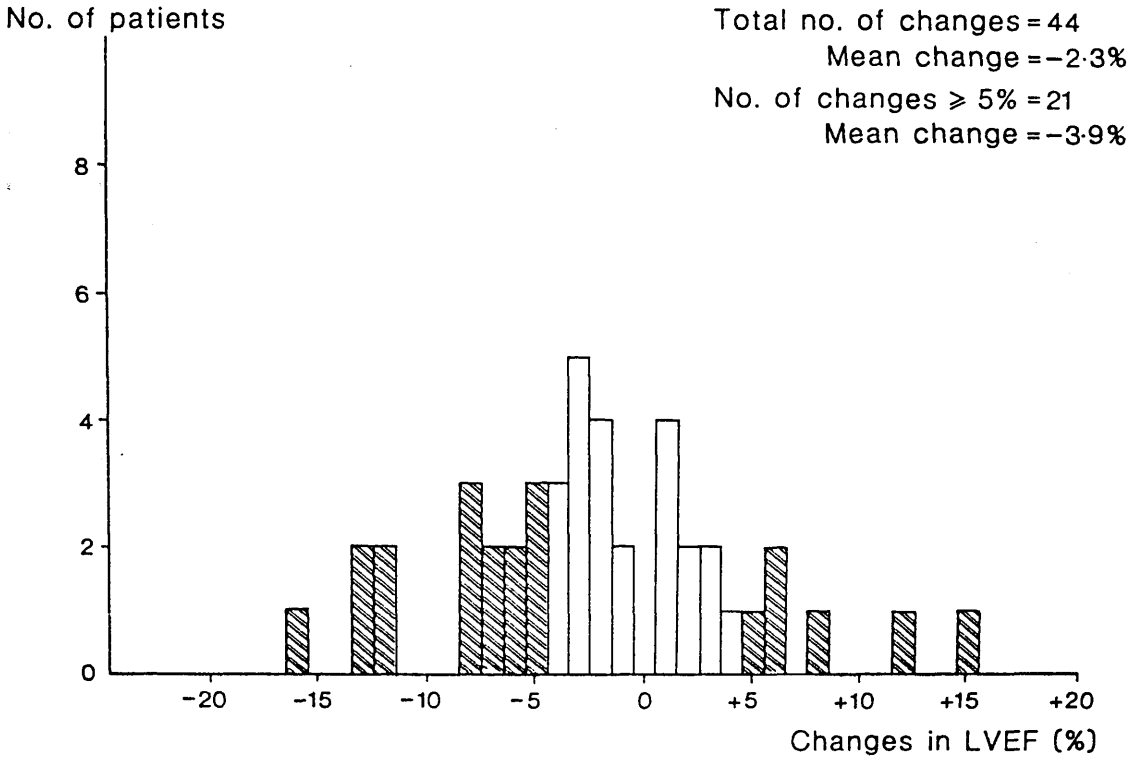

FIGURE 2. Change in left ventricular ejection fraction (LVEF) between day 1 and day 3. Hatched bars represent changes of $\geqslant$ 5% ejection fraction units, non-hatched bars represent changes of $<$ 5%.

A. LVEF <25%

ALL INFARCTS	LVEF1-LVEF2	LVEF2-LVEF3
LVEF (%)	19.3 - 20.8	18.3 - 20.9
SD (%)	5.4 - 7.3	5.2 - 7.4
Number	14	24
Significance	N.S.	N.S.
ANTERIOR MI		
LVEF (%)	17.3 - 18.2	19.1 - 19.8
SD (%)	7.0 - 9.3	5.4 - 7.5
Number	6	17
Significance	N.S.	N.S.
INFERIOR MI		
LVEF (%)	20.8 - 22.8	16.6 - 23.4
SD (%)	3.2 - 5.1	4.6 - 7.0
Number	8	7
Significance	N.S.	p <0.05

B. LVEF 25-34%

ALL INFARCTS	LVEF1-LVEF2	LVEF2-LVEF3
LVEF (%)	29.8 - 30.1	29.4 - 32.1
SD (%)	2.4 - 7.4	2.6 - 6.3
Number	21	18
Significance	N.S.	N.S.
ANTERIOR MI		
LVEF (%)	28.5 - 23.8	30.2 - 32.8
SD (%)	2.3 - 6.5	2.9 - 5.4
Number	8	6
Significance	p <0.05	N.S.
INFERIOR MI		
LVEF (%)	30.6 - 34.1	29.1 - 31.8
SD (%)	2.1 - 4.8	2.5 - 6.9
Number	13	12
Significance	p <0.05	N.S.

C. LVEF >35%

ALL INFARCTS	LVEF1-LVEF2	LVEF2-LVEF3
LVEF (%)	41.7 - 40.1	43.0 - 44.7
SD (%)	4.3 7.8	7.3 6.8
Number	10	11
Significance	N.S.	N.S.
ANTERIOR MI		
LVEF (%)	37.5 - 39.0	38.0 - 36.0
SD (%)	2.1 2.0	
Number	2	1
Significance	*	*
INFERIOR MI		
LVEF (%)	42.8 - 40.4	39.5 - 38.6
SD (%)	4.1 8.8	7.0 10.1
Number	8	10
Significance	N.S.	N.S.

TABLE 3

Change in left ventricular ejection fraction (mean ± standard deviation) in relation to the degree of left ventricular dysfunction

MI	=	myocardial infarction.
LVEF (%)	=	left ventricular ejection fraction.
LVEF1	=	left ventricular ejection fraction on day 1.
LVEF2	=	left ventricular ejection fraction on day 3.
LVEF3	=	left ventricular ejection fraction at hospital discharge.
SD (%)	=	standard deviation.
Number	=	number of paired cases available for comparison.
Significance	=	level of significance (p).
N.S.	=	not significant.
*	=	number of cases do not permit statistical analysis.

3. A change of 5% (5 ejection fraction units) was considered to be a significant difference as the reproducibility of the technique was 2-3%. There were 21 of 44 changes that were $\geqslant$5% between day 1 and day 3, with a mean difference of -3.9%; between day 3 and hospital discharge there were 26 of 51 changes in the left ventricular ejection fraction $\geqslant$5%, with a mean difference of +3.6%. These changes are represented by hatched bars in Figures 2 and 3.

No relationship was found between the magnitude of change in the left ventricular ejection fraction during hospitalisation and the site or size of the index infarction, the presence of previous myocardial infarction, the degree of left ventricular dysfunction or to subsequent events (development of angina, coronary artery surgery, or death).

Patients were also subdivided into 4 groups according to the character of the variation in the left ventricular ejection fraction during the hospitalisation phase. Thirty one of 72 patients with serial data for analysis demonstrated no change in the left ventricular ejection fraction, 15 patients showed an increase of $\geqslant$5%, 15 patients showed a decrease of $\geqslant$5% and 9 patients showed a bidirectional change of $\geqslant$5%, i.e. an increase and a decrease, or vice-versa, in the left ventricular ejection fraction of $\geqslant$5%. There was no significant difference in the incidence of previous myocardial

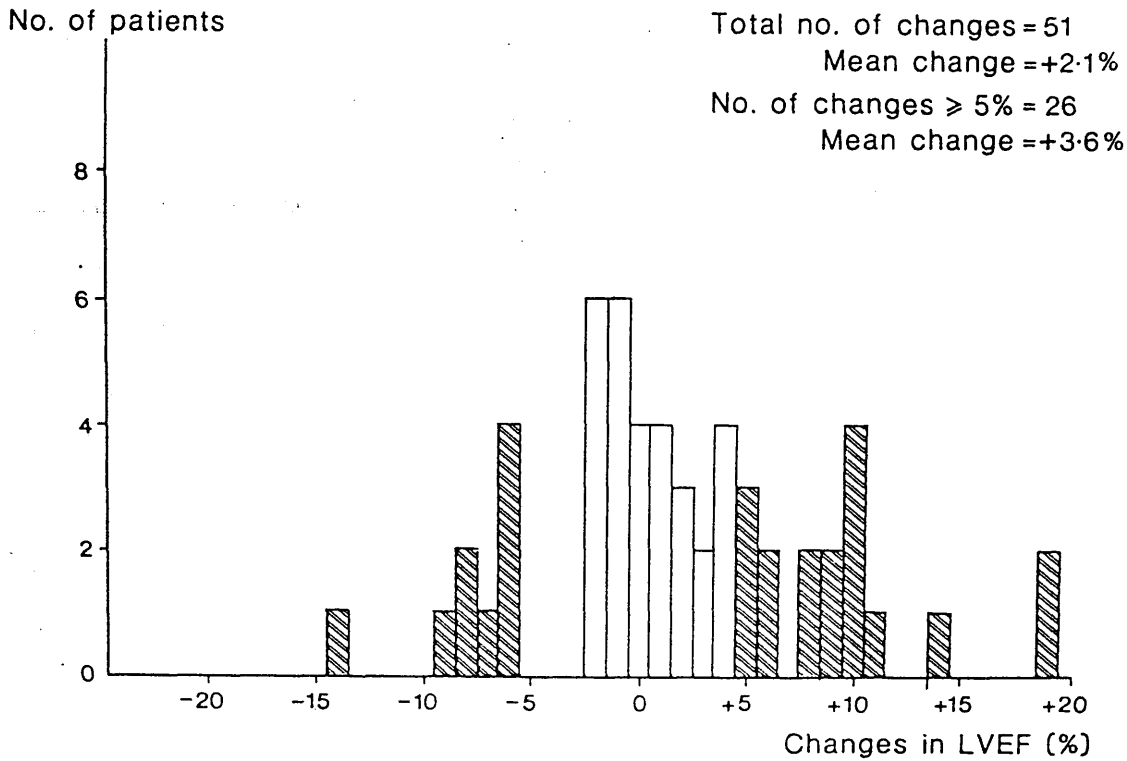

FIGURE 3. Change in left ventricular ejection fraction (LVEF) between day 3 and hospital discharge (15 ± 12 days). Hatched bars represent changes of ⩾ 5% ejection fraction units, non-hatched bars represent changes of < 5%.

infarction, site or size of the index infarction, degree of left ventricular dysfunction or to subsequent events (development of angina, coronary artery surgery or death) between any of the above groups considered either individually or in combination.

3.3 RELATIONSHIP BETWEEN THE LEFT VENTRICULAR EJECTION FRACTION AND INDICES OF MYOCARDIAL INFARCT SIZE

Two indices of myocardial infarct size were used, the peak creatine kinase level and the thallium perfusion index. No significant difference was found between the peak creatine kinase levels of patients who had sustained an anterior myocardial infarction (2004 ± 1043 IU/L) and inferior myocardial infarction (2053 ± 1621 IU/L), p = NS. However, the size of the perfusion defect was significantly larger following anterior (35.6 ± 15.1%) than following inferior myocardial infarction (31.4 ± 12.2%), $p<0.01$.

There was a weak but significant inverse correlation between the peak creatine kinase level and the left ventricular ejection fraction on day 1, Rs = -0.37, $p<0.01$. No correlation was found with the other in-hospital determinations of the left ventricular ejection fraction. Following anterior myocardial infarction there was a relationship between the peak creatine kinase level and all the estimations of the left

ventricular ejection fraction; on day 1 Rs = -0.74, $p<0.001$; on day 3 Rs = -0.44, $p<0.05$; and at hospital discharge Rs = -0.81, $p<0.001$. The left ventricular ejection fraction after 16 months was also related to the peak creatine kinase, Rs = -0.65, $p<0.01$. In contrast, the peak creatine kinase level following inferior myocardial infarction was only related to the left ventricular ejection fraction on day 1, Rs = -0.38, $p<0.05$; Table 4.

The perfusion index correlated with all the left ventricular ejection fraction estimations; on day 1 Rs = -0.50, $p<0.01$; on day 3 Rs = -0.40, $p<0.01$; at hospital discharge Rs = -0.42, $p<0.01$; and after 16 months Rs = -0.42, $p<0.01$; Table 4. No difference in the relationship between the left ventricular ejection fraction and the thallium perfusion index was observed between anterior and inferior myocardial infarction.

The exclusion of patients with evidence of previous myocardial infarction improved the correlation between the left ventricular ejection fraction and indices of myocardial infarct size. This was particularly noticeable when the peak creatine kinase level was considered and following inferior myocardial infarction, Table 5.

		LVEF1	LVEF2	LVEF3	LVEF4
ALL INFARCTS					
PEAK CK	(n)	51	57	57	55
Spearman coeff.	(Rs)	-0.37	-0.23	-0.22	-0.07
Signif. level	(p)	<0.01	n.s.	n.s.	n.s.
P.INDEX	n	51	57	57	61
Spearman coeff.	(Rs)	-0.50	-0.40	-0.44	-0.42
Signif. level	(p)	<0.001	<0.01	<0.001	<0.01
ANTERIOR INFARCTS					
PEAK CK	n	18	25	25	21
Spearman coeff.	(Rs)	-0.74	-0.44	-0.81	-0.65
Signif. level	(p)	<0.001	<0.05	<0.001	<0.01
P.INDEX	n	21	31	28	24
Spearman coeff.	(Rs)	-0.62	-0.31	-0.55	-0.41
Signif. level	(p)	<0.01	n.s.	<0.01	<0.05
INFERIOR INFARCTS					
PEAK CK	n	33	36	36	37
Spearman coeff.	(Rs)	-0.38	-0.33	-0.16	-0.05
Signif. level	(p)	<0.05	n.s.	n.s.	n.s.
P.INDEX		36	36	36	37
Spearman coeff.	(Rs)	-0.40	-0.46	-0.29	-0.33
Signif. level	(p)	<0.02	<0.01	n.s.	<0.05

TABLE 4

Relationship between left ventricular ejection fraction and infarct size

LVEF1	=	left ventricular ejection fraction on day 1.
LVEF2	=	left ventricular ejection fraction on day 3.
LVEF3	=	left ventricular ejection fraction at hospital discharge.
LVEF4	=	left ventricular ejection fraction at follow-up (mean interval 16 months).
n	=	number of patients.
PEAK CK	=	peak creatine kinase level.
P.INDEX	=	perfusion index (%) of left ventricle involved in infarct).
Spearman coeff.(Rs)	=	Spearman correlation coefficient.
Signif. level (p)	=	significance level.

		LVEF1	LVEF2	LVEF3	LVEF4
ALL INFARCTS					
PEAK CK	n	41	47	45	46
Spearman coeff.	(Rs)	-0.41	-0.27	-0.33	-0.11
Signif. level	(p)	<0.01	n.s.	<0.05	n.s.
P.INDEX	n	43	52	50	50
Spearman coeff.	(Rs)	-0.75	-0.54	-0.56	-0.41
Signif. level	(p)	<0.001	<0.001	<0.001	<0.01
ANTERIOR INFARCTS					
PEAK CK	n	14	19	18	17
Spearman coeff.	(Rs)	-0.81	-0.46	-0.90	-0.74
Signif. level	(p)	<0.01	<0.05	<0.001	<0.01
P.INDEX	n	14	22	21	19
Spearman coeff.	(Rs)	-0.88	-0.43	-0.79	-0.62
Signif. level	(p)	<0.001	<0.05	<0.001	<0.01
INFERIOR INFARCTS					
PEAK CK	n	27	28	27	29
Spearman coeff.	(Rs)	-0.63	-0.64	-0.41	-0.03
Signif. level	(p)	<0.001	<0.001	<0.05	n.s.
P.INDEX	n	29	30	29	31
Spearman coeff.	(Rs)	-0.49	-0.47	-0.14	-0.01
Signif. level	(p)	<0.02	<0.05	n.s.	n.s.

TABLE 5

Relationship between left ventricular ejection fraction and infarct size in patients without previous infarction

LVEF1 = left ventricular ejection fraction on day 1.
LVEF2 = left ventricular ejection fraction on day 3.
LVEF3 = left ventricular ejection fraction at hospital discharge.
LVEF4 = left ventricular ejection fraction at follow-up (mean interval 16 months).
n = number of patients.
PEAK CK = peak creatine kinase level.
P.INDEX = perfusion index (% of the left ventricle involved in infarct).
Spearman coeff.(Rs) = Spearman correlation coefficient.
Signif. level (p) = significance level.

3.4 THE RELATIONSHIP BETWEEN THE LEFT VENTRICULAR EJECTION FRACTION AND CLINICAL INDICES

Patients were classified according to Norris et al (49) and Killip and Kimball (51) on their admission to hospital. The mean Norris Index was 6.2 ± 2.4 (range 3.0 - 11.6) following anterior myocardial infarction and 6.3 ± 2.6 (range 2.7 ± 14.7) following inferior myocardial infarction. Following anterior myocardial infarction there was a weak correlation between the Norris Index and left ventricular ejection fraction; on day 1 $R_s = 0.49$, $p<0.05$; on day 3 $R_s = 0.38$, $p<0.05$; and at time of hospital discharge $R_s = 0.47$, $p<0.02$. Following inferior myocardial infarction there was a weak negative correlation between the Index and the left ventricular ejection fraction; on day 1 $R_s = -0.43$, $p<0.02$; on day 3 $R_s = -0.40$, $p<0.05$; and $R_s = -0.57$, $p<0.02$ at time of hospital discharge.

Using the Killip classification (51), 57 patients (71%) were in Class I, 17 (21%) were in Class 2, 4 (5%) were in Class 3 and 3 (4%) were in Class 4 on admission to hospital. There was a significant but weak correlation between the Killip Class and the left ventricular ejection fraction measured on day 3, $p<0.05$, but not with the left ventricular ejection fraction measured on day 1 or at the time of hospital discharge. As can be seen from Figure 4, although there was a

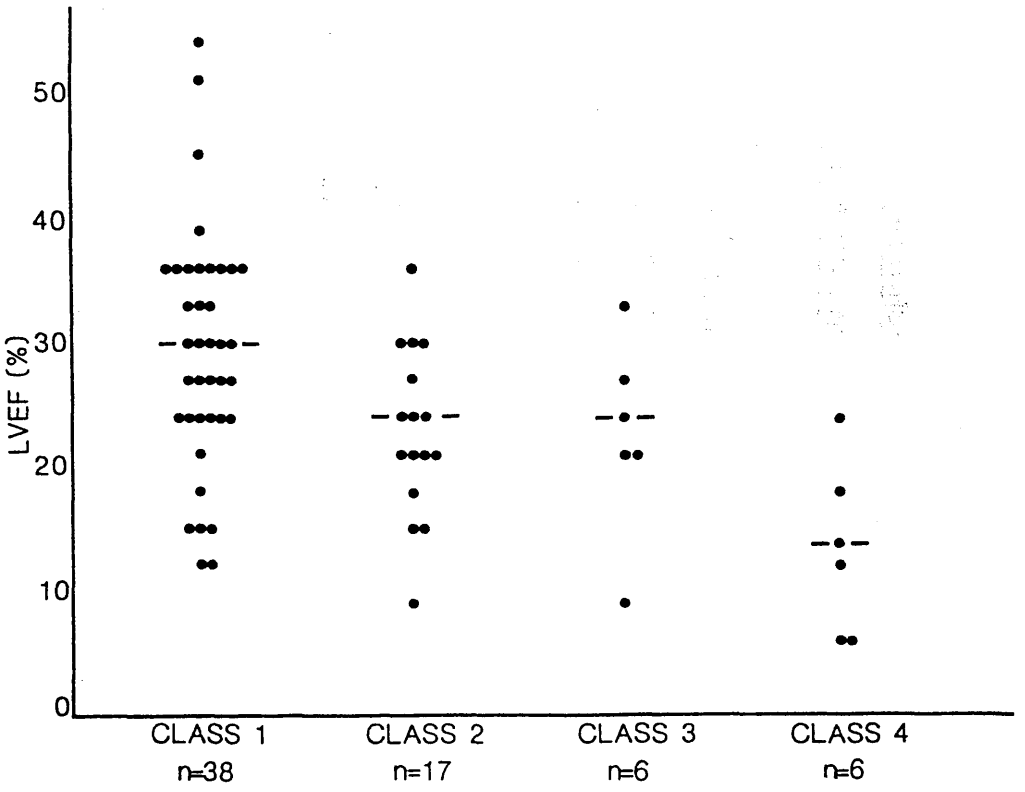

FIGURE 4. Relationship between left ventricular ejection fraction (LVEF) on day 3 and Killip Class. Mean value for LVEF is indicated by bar; Class 1 = no signs of cardiac decompensation, Class 2 = signs of heart failure, Class 3 = frank pulmonary oedema, and Class 4 = cardiogenic shock.

significant association between the Killip Class and the left ventricular ejection fraction on day 3, there were important discrepancies between the clinical classification and the left ventricular ejection fraction.

3.5 THE RELATIONSHIP OF THE LEFT VENTRICULAR EJECTION FRACTION TO MORTALITY

The cumulative mortality at the time of follow-up (mean of 18 months) was 22% (18/81 patients), with an in-hospital mortality of 10% (8/81) and an out-of-hospital mortality rate of 14% (10/81).

Using univariate statistical analysis, only the left ventricular ejection fraction on day 3 was related to in-hospital mortality, $p<0.02$. When the data was re-analysed, taking into consideration the site of infarction, only the left ventricular ejection fraction on day 3 was related to in-hospital mortality following anterior myocardial infarction. Following inferior myocardial infarction no relationship was observed between any of the estimations of the left ventricular ejection fraction and in-hospital mortality.

The left ventricular ejection fraction measured on day 3 and at time of hospital discharge correlated with the cumulative mortality after 18 months, $p<0.01$ and $p<0.05$ respectively. When the data was analysed, taking

into account the site of infarction, there was a significant correlation with all the left ventricular ejection fractions and the cumulative mortality following anterior myocardial infarction; $p<0.02$ on day 1, $p<0.01$ on day 3 and $p<0.05$ at time of hospital discharge. Following inferior myocardial infarction no relationship was found between any of the left ventricular ejection fractions and cumulative mortality.

There was a relationship between the cumulative mortality and the last recorded left ventricular ejection fraction prior to death or hospital discharge (whichever occurred first) by dichotomizing patients using a left ventricular ejection fraction of 30%. The mortality was 33% (15/45) in patients with a left ventricular ejection fraction of <30% as compared with 8% (3/36) in patients with a left ventricular ejection fraction of >30%, chi-squared = 6.03, $p<0.025$.

3.6 DISCUSSION

The characterisation of patients following myocardial infarction by left ventricular ejection fraction (31-35) is firmly established and its prognostic importance well documented (39-42,47).

The data in this thesis revealed that the site of infarction had a significant influence on the degree of left ventricular dysfunction, with lower mean left

ventricular ejection fractions being recorded in patients following anterior as compared to inferior myocardial infarcts throughout the hospitalisation period. This difference is in agreement with previous work in this field (32,35,37,41,43). The explanation for this is probably multifactorial and is discussed below.

Firstly, it is probable that anterior myocardial infarction was associated with more extensive left ventricular myocardial necrosis than inferior myocardial necrosis. The mean Thallium-201 perfusion defects following anterior infarction were significantly larger than those following inferior infarction, despite no significant difference in the peak creatine kinase levels. This apparent discrepancy between the two indices of myocardial infarct size is reconciled by the fact that a proportion of the creatine kinase released originates from the right ventricle (104-106). This would also explain the better correlation between the left ventricular ejection fraction and the peak creatine kinase levels following anterior, as compared with inferior, myocardial infarction.

A second reason for the difference in the left ventricular ejection fraction between the two groups could result from the higher incidence of topographical changes following anterior infarction which have a detrimental effect on left ventricular performance (68,69,107).

Finally, another explanation for the difference relates to a methodological error in the technique of radionuclide ventriculography. The calculation of the ejection fraction by non-geometric means makes the assumption that the change in intraventricular counts is directly proportional to change in ventricular volume. However it has been demonstrated that this is not entirely true (110). When ventricular contraction is asymmetrical the left ventricular volume either moves away from the gamma camera during systole, i.e. in the presence of infero-posterior infarction, or towards the gamma camera, i.e. in the presence of anterior infarction. This results in differences in photon attenuation such that the left ventricular ejection fraction will be underestimated following anterior myocardial infarction and overestimated following infero-posterior myocardial infarction (108,109). The magnitude of the differences between the left ventricular ejection fractions is such that it is probably a reflection of a combination of all three mechanisms.

The use of Thallium-201 imaging has been previously shown to be an accurate technique in estimating the size of both anterior and inferior myocardial infarction (110). Its prognostic predictive value has also been convincingly demonstrated (111,112). A closer correlation was found between the left ventricular ejection fraction and the size of the Thallium-201

perfusion defect than with the peak creatine kinase even after the exclusion of patients with previous myocardial infarcts.

There appeared to be little variation in the left ventricular ejection fraction during the in-hospital phase when the patients were grouped according to the site of infarction. There were no significant changes in patients with anterior myocardial infarction and only minor changes in the left ventricular ejection fraction in patients with inferior myocardial infarction. Similar findings have been reported by other workers (34,35). However, this grouping disguises significant changes in the left ventricular ejection fraction as was illustrated when patients were considered on an individual basis or subdivided according to the degree of left ventricular dysfunction.

Changes in the left ventricular ejection fraction in individual patients occurred frequently and usually without changes in the clinical status in the patient. The change in left ventricular ejection fraction did not appear to be related to the site or size of infarction (as determined by perfusion defect size or enzymatic indices), the presence of previous myocardial infarction, the degree of left ventricular dysfunction or to be predictive of subsequent cardiac events.

Wackers et al also observed wide variations in the left ventricular ejection fraction ranging from +32% to

-14% during the first 24 hours following myocardial infarction (45). Significant changes in the left ventricular ejection fraction occurred in 56% of patients and were not usually reflected by changes in the clinical status of the individual patients. Nemerovski et al examined the changes in left ventricular ejection fraction throughout the hospital phase of myocardial infarction and again reported frequent changes in the left ventricular ejection fraction (113). In the absence of any clear association with any of these parameters it has been suggested that these changes in left ventricular ejection fraction are a reflection of changes in the prevailing loading conditions of the heart rather than representing any change in the intrinsic myocardial performance (45,113).

Apparently contradictory findings have been observed by others, who have shown that patients who have evidence of transitory left ventricular dysfunction acutely following myocardial infarction, as reflected by pulmonary rales or radiological pulmonary oedema, with a near normal or normal pre-discharge left ventricular ejection fraction, constitute an at risk group of patients (39,46). Therefore, it may have been anticipated that not only patients who demonstrated a fall, but also those who demonstrated a rise in the left ventricular ejection fraction would show a poorer clinical course. However, this was not observed in this

thesis, and confirms findings of others who serially assessed the left ventricular ejection fraction following myocardial infarction (113).

This apparent discrepancy between this work and those of other workers who utilized clinical (39) or radiological (46) parameters is probably related to differences in the parameters of left ventricular function being measured and the sensitivity of these parameters. The presence of pulmonary rales or radiological pulmonary oedema signifies diastolic ventricular dysfunction which is associated with an elevation of the left ventricular filling pressure in the setting of acute myocardial infarction. The left ventricular ejection fraction is a measure of systolic ventricular function. However, it is also affected by changes in both preload and afterload and is therefore more sensitive and susceptible to changes which may not necessarily be of clinical significance. Whereas, any abnormality in ventricular function causing diastolic dysfunction of such a magnitude to produce pulmonary rales or radiological pulmonary oedema may be more specific and signify more serious and clinically important underlying pathophysiology, for example acute myocardial ischaemia in a non-infarct related vessel (46).

The degree of left ventricular dysfunction did not appear to have any consistent influence on the course of

the left ventricular ejection fraction during the hospitalisation phase of myocardial infarction. However, there did appear to be a trend for the left ventricular ejection fraction to improve following inferior myocardial infarction associated with severe (ejection fraction <25%) or moderate (ejection fraction 25-34%) left ventricular dysfunction. Only one subgroup of patients following anterior myocardial infarction showed any significant change in the left ventricular ejection fraction; patients with moderate left ventricular dysfunction showed a fall in the left ventricular ejection fraction from 28.5 ± 2.3% to 23.8 ± 6.5%, $p<0.05$. The observed changes may have been related either to alterations in loading conditions or changes in regional ventricular function. However, the small number of patients in the subgroup made interpretation of the results difficult; in addition some of the observed differences may have been a reflection of Type II statistical errors.

The use of clinically based methods of patient classification was found to be a poor indicator of left ventricular function. Although the admission Killip class was related to the left ventricular ejection fraction on day 3, it was not related to the temporally closer estimation on day 1. In addition, there were significant overlaps in the left ventricular ejection fractions between the Killip classes at this time. The

Norris Index had an interesting relationship with the left ventricular ejection fraction. In patients with anterior myocardial infarction there was a significant positive correlation between these two parameters, whereas with patients with inferior myocardial infarction there was a significant negative correlation between the left ventricular ejection fraction and the Norris Index. The reason for this latter finding is difficult to explain. It could possibly be explained in part by hypotension resulting from increased parasympathetic tone or right ventricular dysfunction. However, one would have to presuppose that the presence of hypotension following inferior myocardial infarction was inversely related to the left ventricular ejection fraction.

There have been several clinical indices developed for prognostic purposes following myocardial infarction (48-51), some using solely clinical parameters and others incorporating a combination of clinical, electrocardiographic and radiological parameters. However, their use has been found to be of limited value particularly when used on an individual patient basis (32,47).

The prognostic importance of the left ventricular ejection fraction following myocardial infarction is well known and is now generally regarded as one of the most important prognostic variables following myocardial infarction (30). The detrimental effect of left

ventricular dysfunction on prognosis following myocardial infarction was confirmed in this thesis. Patients with a left ventricular ejection fraction of less than 30% at the time of their last estimation had a significantly poorer prognosis in the subsequent eighteen months than patients with a left ventricular ejection fraction of 30% or greater.

However, the prognostic utility of the left ventricular ejection fraction did appear to be dependent upon the site of the infarction. Using univariate analysis no association was found, either with the in-hospital or the cumulative eighteen month mortality and the left ventricular ejection fraction in patients who had sustained an inferior myocardial infarction. This contrasts with the situation following anterior myocardial infarction where a significant correlation was found between in-hospital mortality and the left ventricular ejection fraction on day three, $p = 0.01$, and all the in-hospital estimations of the left ventricular ejection fraction and cumulative mortality after eighteen months $p<0.02$, $p<0.01$, $p<0.05$.

It is not possible to ascertain, from the data presented here, the aetiology of this apparent difference in the prognostic value of the left ventricular ejection fraction between patients with anterior and inferior myocardial infarction. It may have been related to uniformly higher left ventricular ejection fractions and

hence better prognosis in patients with inferior myocardial infarction. Therefore, because of the small number of patients involved, no statistically significant association between the left ventricular ejection fraction and mortality was observed following inferior myocardial infarction.

Anterior myocardial infarction was associated with a higher in-hospital and cumulative mortality than inferior myocardial infarction, as discussed in Chapter 2. Other studies have also found a poorer prognosis following anterior myocardial infarction (114-117). The MILIS Group found that, even allowing for lower left ventricular ejection fractions and larger infarct size, infarct location exerted an independent prognostic effect (117). The topographical changes that occur more commonly following anterior myocardial infarction than inferior myocardial infarction have been proposed to explain this disparity (117). Infarct expansion can be associated with ventricular rupture, left ventricular thrombus formation and left ventricular dilatation (9). Meizlish et al (71), in a study of anterior myocardial infarcts, found that those patients with evidence of early functional aneurysm formation in the infarct region had a 3-fold excess in mortality compared to patients without alterations in left ventricular topography despite similar left ventricular ejection fractions.

3.7 CONCLUSIONS

Variation in the left ventricular ejection fraction may not be apparent following acute myocardial infarction if patients are grouped together or on the basis of site of infarction. However, when the degree of left ventricular dysfunction is also taken into consideration, or when patients are examined individually, significant changes in the left ventricular ejection fraction can be identified. The aetiology of these changes is not apparent but may be related to changes in the prevailing loading conditions and/or to alterations in regional ventricular performance. This topic is discussed more fully in Chapters 8 and 9 of this thesis.

Lower left ventricular ejection fractions were found in patients with anterior, as compared with inferior, myocardial infarction. The reasons for this difference are probably multifactorial. In addition, it was observed that the left ventricular ejection fraction appeared to have more prognostic significance in patients with anterior myocardial infarction than in patients with inferior myocardial infarction; however the aetiology for this difference in the prognostic utility of the left ventricular ejection fraction remains unresolved.

These findings suggest that caution should be exercised when using this parameter in assessing left ventricular function following myocardial infarction.

This is particularly pertinent when this parameter is used in the evaluation of the efficacy of therapeutic interventions in the treatment of myocardial infarction (118-122).

CHAPTER 4

THE IMPACT OF ACUTE MYOCARDIAL INFARCTION ON RIGHT VENTRICULAR FUNCTION

4.1 INTRODUCTION

The clinical importance of right ventricular function following acute myocardial infarction has only relatively recently been realised with the description of the clinical syndrome of right ventricular infarction by Cohn et al (7), although right ventricular infarction as a pathological entity had been described some years prior to this (76,77).

The advent of non-invasive assessment of right ventricular function, using echocardiography and radionuclide ventriculography, allowed right ventricular function to be examined with greater ease and in more detail. The effects of inferior myocardial infarction on right ventricular function have been extensively investigated, particularly during the first days following the onset of infarction (82,83,88,92-98). The natural history of right ventricular function following inferior myocardial infarction over a longer period of time has not been fully elucidated. The literature tends to indicate that right ventricular dysfunction improves in the days and weeks following inferior myocardial

infarction (88,90,91) and after the acute phase is associated with a relatively benign course (89,92). However, contrary findings have been reported by other workers (93-95).

The consequences of anterior myocardial infarction on right ventricular function are less well defined. Some have found that right ventricular function is not affected (35,87) whilst other more recent studies have suggested that right ventricular dysfunction is present in 25-50% of patients following anterior myocardial infarction (88,96-98). Some have found the depression in right ventricular function to be transitory in this situation (88,96) whilst others have not (113).

The aims of this chapter are to 1) examine the changes that occur in right ventricular function; 2) determine what factors are important in determining the outcome of right ventricular function following acute myocardial infarction; and 3) determine what influence the right ventricular ejection fraction has on mortality following acute myocardial infarction.

4.2 CHANGES IN RIGHT VENTRICULAR EJECTION FRACTION DURING THE HOSPITALISATION PHASE

Right ventricular function was assessed in 57/81 patients on day 1 following the onset of symptoms (mean 29 hours), in 67 patients on day 3 (mean 3 days) and in

64 patients at time of hospital discharge (mean 15 days). Right ventricular dysfunction (right ventricular ejection fraction <35%) was identified in 14/36 (39%) patients following anterior myocardial infarction during hospitalisation, however 4 had evidence of previous inferior infarction. Following acute inferior infarction 25/45 (64%) patients showed evidence of right ventricular dysfunction during the same period.

The right ventricular ejection fraction was significantly lower in patients following inferior myocardial infarction on day 1 and day 3 as compared with patients who had sustained an anterior myocardial infarction, 28.3 ± 8.9% (n = 36) versus 38.9 ± 9.9% (n = 21), $p<0.001$ and 29.9 ± 10.2% (n = 36) versus 34.8 ± 9.9% (n = 28), $p<0.05$ respectively. However at time of hospital discharge there was no significant difference in the right ventricular ejection fractions between the two groups, 31.8 ± 10.4% in patients with anterior and 31.8 ± 8.5% in patients with inferior myocardial infarction respectively, p = NS; Table 6.

During this stage following myocardial infarction there was a trend for the right ventricular ejection fraction to improve in patients with inferior myocardial infarction. The mean was 28.3 ± 8.9% (n = 36) on day 1 rising to 32.3 ± 11.4% (n = 36) by the time of hospital discharge. However this change did not reach statistical significance. In patients with anterior myocardial

	Anterior MI	Inferior MI	p value
RVEF1	38.8 ± 9.9	28.3 ± 8.9	p<0.002
RVEF2	34.8 ± 10.1	29.9 ± 10.2	P<0.025
RVEF3	35.5 ± 8.8	32.8 ± 8.5	N.S.D.

TABLE 6

Difference in the right ventricular ejection fraction (mean ± standard deviation) between patients with anterior and inferior myocardial infarction (MI)

RVEF1 = right ventricular ejection fraction on day 1.
RVEF2 = right ventricular ejection fraction on day 3.
RVEF3 = right ventricular ejection fraction at hospital discharge.
p value = significance level (p).

infarction there was a trend for the right ventricular ejection fraction to fall over this period, right ventricular ejection fraction of 38.9 ± 9.9% (n = 21) on day 1 falling to 35.5 ± 8.8% (n = 28) by the time of hospital discharge. Again the difference was not statistically significant.

This apparent stability of the right ventricular ejection fraction in these two groups concealed wide variations in the right ventricular ejection fraction in some individuals. A change of 5% or greater in the right ventricular ejection fraction was considered outwith the reproducibility of the technique.

Twenty six patients showed a change of 5% or more in the right ventricular ejection fraction between day 1 and day 3, ranging from -20% to +23%, with a mean change of +1.2%, see Figure 5. The frequency of change was similar during the later stages of the hospital phase, from day 3 to hospital discharge, with 34 changes of 5% or greater, ranging from -17% to +20% with a mean change of +2.8%, see Figure 6. No relationship was found between the magnitude of change in the right ventricular ejection fraction and the site or size of infarction, left ventricular dysfunction, history of previous infarction, subsequent development of angina or need for coronary artery surgery or mortality.

The relationship to direction of change in the right ventricular ejection fraction was also examined.

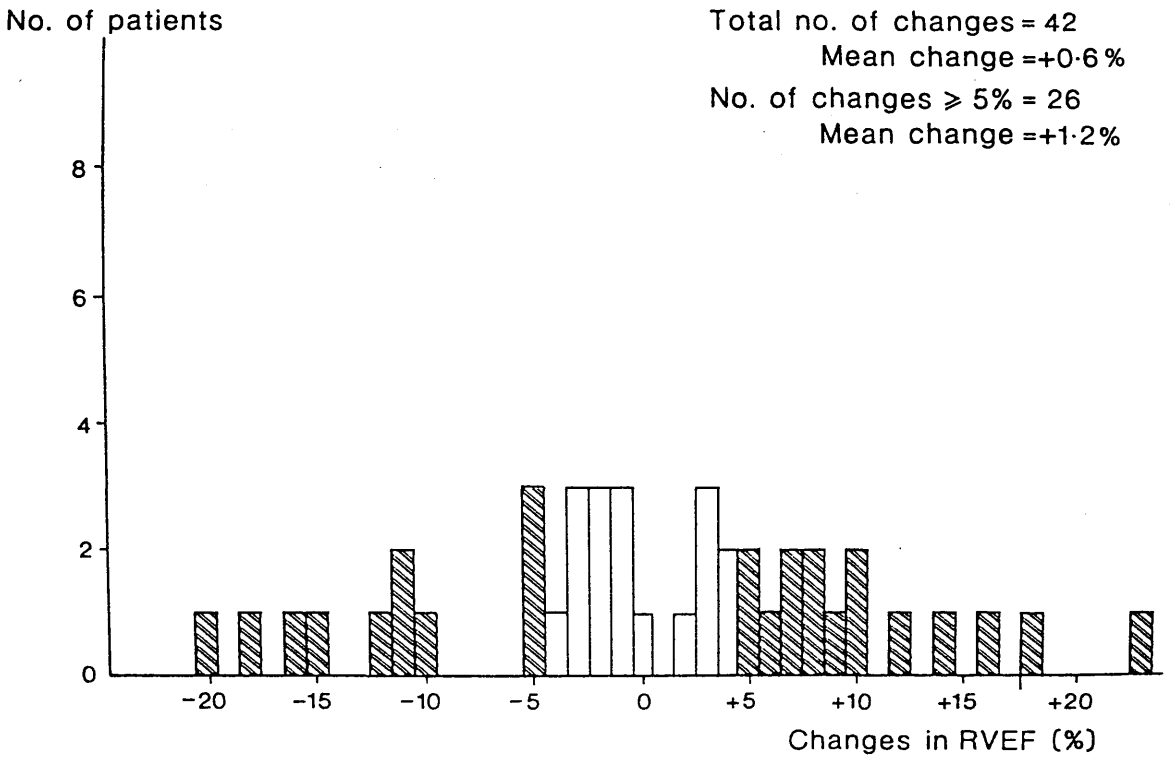

FIGURE 5. Change in right ventricular ejection fraction (RVEF) between day 1 and day 3. Hatched bars represent changes of $\geqslant$ 5% ejection fraction units, non-hatched bars represent changes $<$ 5%.

patients were subdivided into four groups according to whether the right ventricular ejection fraction increased, decreased, showed no change or bidirectional change of $\geq$5%. No association was found between direction of change and site or size of infarction, degree of left ventricular dysfunction, subsequent development of angina, the need for coronary artery surgery or mortality.

Patients were also divided according to the degree of underlying right ventricular dysfunction. Patients with a right ventricular ejection fraction <25% were considered as having severe right ventricular dysfunction, those with a right ventricular ejection fraction of between 25-34% as having moderate right ventricular dysfunction and those patients with a right ventricular ejection fraction of 35% or greater as having minimally impaired or normal right ventricular function. During the in-hospital course there were no significant trends in any of these sub-groups whether considered as one group or grouped according to the site of infarction, see Table 7.

4.3 RELATIONSHIP BETWEEN THE RIGHT VENTRICULAR EJECTION FRACTION AND INDICES OF MYOCARDIAL INFARCT SIZE

The relationship between right ventricular function and the two indices of myocardial infarct size were

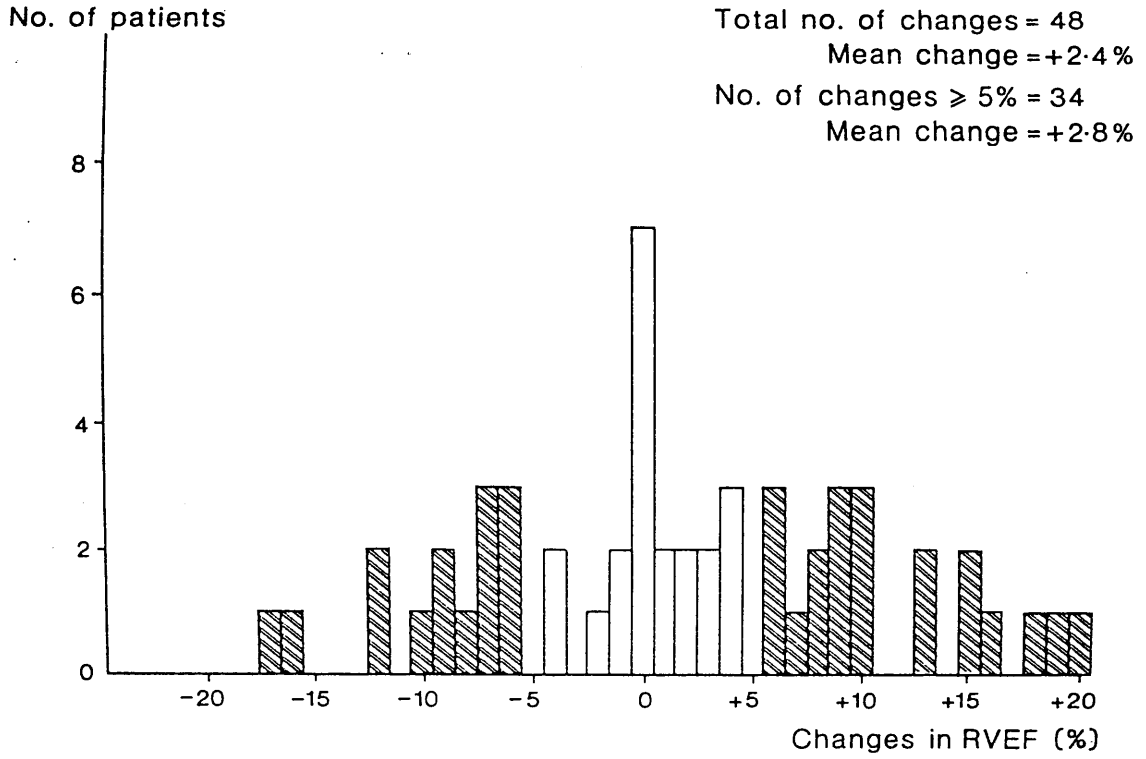

FIGURE 6. Change in right ventricular ejection fraction (RVEF) between day 3 and hospital discharge (15 ± 12 days). Hatched bars represent changes of ⩾ 5% ejection fraction units, non-hatched bars represent changes of < 5%.

A. RVEF <25%

ALL INFARCTS*	RVEF1-RVEF2	RVEF2-RVEF3
RVEF (%)	20.2 - 23.6	21.6 - 23.1
SD (%)	5.3 - 7.5	6.4 - 7.3
Number	12	7
Significance	N.S.	N.S.

B. RVEF 25-34%

ALL INFARCTS	RVEF1-RVEF2	RVEF2-RVEF3
RVEF (%)	31.1 - 34.5	28.9 - 32.8
SD (%)	2.5 - 8.9	2.6 - 9.7
Number	15	22
Significance	N.S.	N.S.
ANTERIOR MI		
RVEF (%)	32.4 - 35.6	29.4 - 33.9
SD (%)	2.4 - 7.6	2.1 - 8.3
Number	4	8
Significance	N.S.	N.S.
INFERIOR MI		
RVEF (%)	30.5 - 33.0	28.7 - 32.4
SD (%)	2.6 - 10.1	3.1 - 10.0
Number	11	14
Significance	N.S.	N.S.

C. RVEF >35%

ALL INFARCTS	RVEF1-RVEF2	RVEF2-RVEF3
RVEF (%)	42.6 - 40.0	41.7 - 39.5
SD (%)	5.4 - 10.7	5.6 - 7.4
Number	17	21
Significance	N.S.	N.S.
ANTERIOR MI		
RVEF (%)	43.1 - 38.5	41.4 - 38.7
SD (%)	6.3 - 12.4	5.7 - 7.2
Number	11	13
Significance	N.S.	N.S.

INFERIOR MI	RVEF1-RVEF2	RVEF2-RVEF3
RVEF (%)	41.0 - 42.8	42.1 - 40.8
SD (%)	3.1 7.0	5.7 8.0
Number	6	8
Significance	N.S.	N.S.

TABLE 7

Change in right ventricular ejection fraction (mean ± standard deviation) in relation to right ventricular dysfunction

RVEF (%)	=	right ventricular ejection fraction.
RVEF1-RVEF2	=	right ventricular ejection fraction on day 1 and day 3.
RVEF2-RVEF3	=	right ventricular ejection fraction on day 3 and at hospital discharge.
SD (%)	=	standard deviation.
Significance	=	significance level (p).
N.S.	=	not statistically significant.
*	=	number too small to permit division according to site of infarction.

examined. When all the patients were considered as one group there appeared to be a weak but significant inverse correlation between the right ventricular ejection fraction and the peak creatine kinase level. The association appeared to be strongest between the right ventricular ejection fractions on day 3 (RVEF2), Rs = -0.44, $p<0.001$ and prior to hospital admission (RVEF3), Rs = -0.44, $p<0.001$; Table 8.

When the site of the infarction was taken into consideration the relationship between the two variables tended to be closer in patients with inferior rather than anterior myocardial infarction. This was more apparent when patients with previous myocardial infarction had been excluded, Table 9.

The relationship between the right ventricular ejection fraction and the perfusion index was weak. During the in-hospital phase the only significant association between the two parameters was following anterior myocardial infarction at time of hospital discharge.

4.4 THE RELATIONSHIP BETWEEN LEFT AND RIGHT VENTRICULAR FUNCTION FOLLOWING ACUTE MYOCARDIAL INFARCTION

No correlation was found between the left and right ventricular ejection fractions following inferior myocardial infarction, Figure 7. However, following

		RVEF1	RVEF2	RVEF3	RVEF4
ALL INFARCTS					
PEAK CK	(n)	51	57	57	55
Spearman coeff.	(Rs)	-0.34	-0.43	-0.44	-0.32
Signif. level	(p)	<0.02	<0.001	<0.001	<0.02
P.INDEX	(n)	57	67	64	61
Spearman coeff.	(Rs)	-0.01	-0.22	-0.34	-0.42
Signif. level	(p)	N.S.	N.S.	<0.01	<0.01
ANTERIOR INFARCTS					
PEAK CK	(n)	18	25	25	21
Spearman coeff.	(Rs)	-0.51	-0.06	-0.41	-0.58
Signif. level	(p)	<0.05	N.S.	<0.05	<0.02
P.INDEX	(n)	21	31	28	24
Spearman coeff.	(Rs)	-0.12	-0.52	-0.57	-0.54
Signif. level	(p)	N.S.	<0.01	<0.01	<0.01
INFERIOR INFARCTS					
PEAK CK	(n)	33	32	32	34
Spearman coeff.	(Rs)	-0.08	-0.45	-0.46	-0.17
Signif. level	(p)	N.S.	<0.02	<0.02	N.S.
P.INDEX	(n)	36	36	36	37
Spearman coeff.	(Rs)	-0.05	-0.28	-0.24	-0.41
Signif. level	(p)	N.S.	N.S.	N.S.	<0.02

TABLE 8

Relationship between right ventricular ejection fraction and infarct size

Peak CK = peak creatine kinase.
n = number of patients.
P.Index = Perfusion Index (see text).
Spearman coeff.(Rs) = Spearman correlation coefficient.
Signif. level (p) = significance level.
N.S. = not statistically significant.
RVEF1 = right ventricular ejection fraction on day 1.
RVEF2 = right ventricular ejection fraction on day 3.
RVEF3 = right ventricular ejection fraction at hospital discharge.
RVEF4 = right ventricular ejection fraction at follow-up visit.

		RVEF1	RVEF2	RVEF3	RVEF4
ALL INFARCTS					
PEAK CK	(n)	41	47	46	46
Spearman coeff.	(Rs)	-0.36	-0.55	-0.50	-0.39
Signif. level	(p)	<0.05	<0.001	<0.001	<0.01
P.INDEX	(n)	44	53	51	51
Spearman coeff.	(Rs)	-0.17	-0.30	-0.24	-0.01
Signif. level	(p)	N.S.	<0.05	N.S.	N.S.
ANTERIOR INFARCTS					
PEAK CK	(n)	14	22	21	19
Spearman coeff.	(Rs)	-0.37	-0.37	-0.37	-0.64
Signif. level	(p)	N.S.	N.S.	N.S.	<0.02
P.INDEX	(n)	14	22	21	19
Spearman coeff.	(Rs)	-0.20	-0.28	-0.40	-0.50
Signif. level	(p)	N.S.	N.S.	N.S.	<0.05
INFERIOR INFARCTS					
PEAK CK	(n)	27	28	27	29
Spearman coeff.	(Rs)	-0.16	-0.39	-0.39	-0.23
Signif. level	(p)	N.S.	<0.05	<0.05	N.S.
P.INDEX	(n)	30	31	30	32
Spearman coeff.	(Rs)	-0.01	-0.46	-0.28	-0.05
Signif. level	(p)	N.S.	<0.02	N.S.	N.S.

TABLE 9

Relationship between right ventricular ejection fraction and infarct size in patients without previous myocardial infarction

Peak CK = peak creatine kinase.
n = number of patients.
P.Index = Perfusion Index (see text).
Spearman coeff.(Rs) = Spearman correlation coefficient.
Signif. level (p) = significance level.
N.S. = not statistically significant.
RVEF1 = right ventricular ejection fraction on day 1.
RVEF2 = right ventricular ejection fraction on day 3.
RVEF3 = right ventricular ejection fraction at hospital discharge.
RVEF4 = right ventricular ejection fraction at follow-up visit.

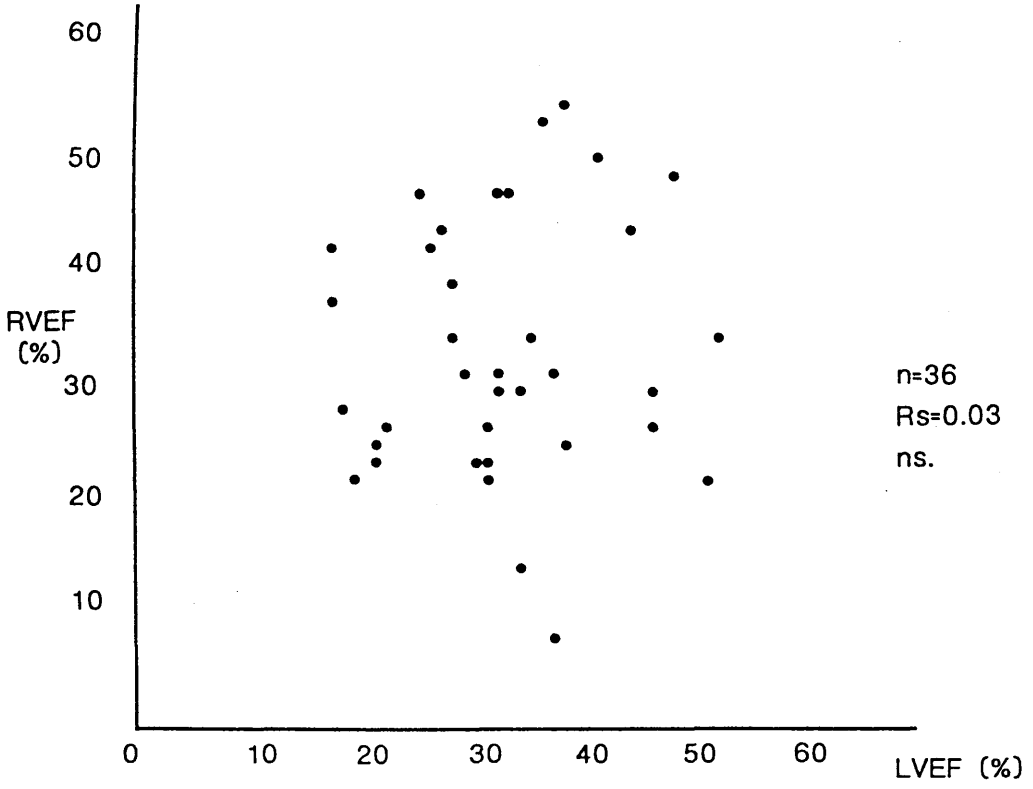

FIGURE 7. Relationship between left (LVEF) and right ventricular ejection fraction (RVEF) at time of hospital discharge following inferior myocardial infarction.

anterior myocardial infarction a significant relationship was observed between the left and right ejection fractions on day 1 Rs = 0.51, $p<0.05$, and at time of hospital discharge Rs = 0.48, $p<0.02$, Figure 8.

4.5 THE RELATIONSHIP OF THE RIGHT VENTRICULAR EJECTION FRACTION TO CLINICAL PARAMETERS AND MORTALITY

No association was found between the right ventricular ejection fraction and the Norris Index or Killip Class.

No association between the in-hospital estimations of the right ventricular ejection fractions and either the in-hospital or total cumulative mortality.

4.6 DISCUSSION

The right ventricle, which was once thought to be merely a conduit through which the systemic venous blood passed before entering the pulmonary circulation, has now been shown to form an integral part of the cardiovascular system (72,74,75). The importance of right ventricular function has been shown to be significant in many pathological conditions (72,73), including cardiac failure. In this latter condition it has been shown to be important prognostically (123) and also in determining therapeutic response to vasodilator therapy (124,125)

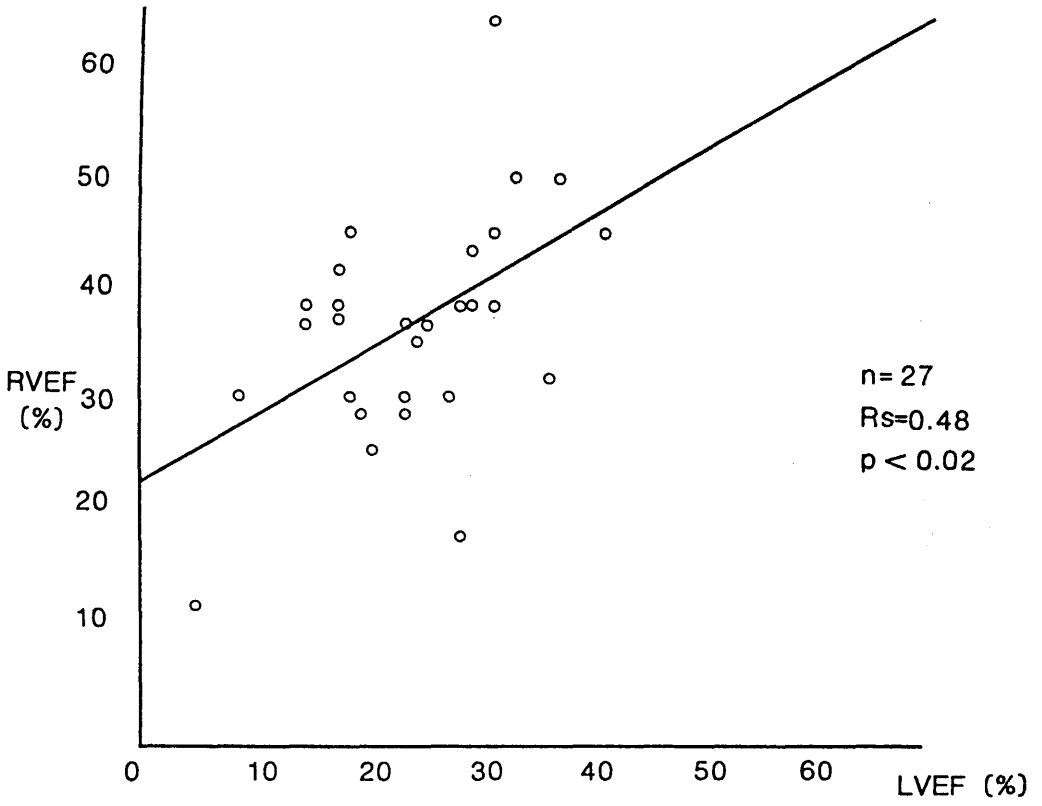

FIGURE 8. Relationship between left (LVEF) and right ventricular ejection fraction (RVEF) at time of hospital discharge following anterior myocardial infarction.

and also the functional exercise capacity of patients (126).

The incidence of right ventricular dysfunction following inferior myocardial infarction in this thesis was 64% (29/45 patients). This figure is comparable to the findings of Rigo et al (80) and Baigrie et al (8), who found an incidence of 64% and 78% respectively. These figures are much higher than those quoted in studies that use haemodynamic data for the evaluation of right ventricular function, the reason for which is probably the lower sensitivity of the latter technique (90). Right ventricular dysfunction following anterior myocardial infarction was identified in 20-30% of patients at some time during hospitalisation. Previous work relating to this subject has produced conflicting evidence. Some studies have reported no right ventricular dysfunction (35,87) whilst others have reported an incidence ranging from 25 to 50% (88,97,98,113).

The aetiology of right ventricular dysfunction following inferior wall myocardial infarction is usually related to right ventricular infarction and probably also from involvement of the interventricular septum (75,79). The pathophysiological mechanisms that underlie right ventricular dysfunction following anterior myocardial infarction remain speculative.

Two possible hypotheses have been postulated. The first hypothesis is that left ventricular dysfunction, with an elevation of the end-diastolic pressure and/or volume, results in right ventricular dysfunction either by means of ventricular interdependence and/or increased right ventricular afterload resulting from an elevation in the pulmonary arterial pressure (72,74). The second hypothesis is that the interventricular septum forms an integral component of the right ventricle and is therefore required for normal right ventricular performance (79). Therefore, infarction of the inter-ventricular septum could result in abnormal septal function which in turn leads to right ventricular dysfunction. The absence of regional wall motion abnormalities has been put forward as evidence of the former mechanism (96,98). However, Caplin et al reported the presence of regional wall motion abnormalities in the septum and therefore cite this in favour of the latter hypothesis (97).

Either of these two mechanisms would explain the correlation observed between left and right ventricular ejection fractions following anterior myocardial infarction. The larger the anterior infarct the greater the amount of interventricular septum is involved, or alternatively the greater the increase in the left ventricular pressure and/or volume, either of which could result in right ventricular dysfunction. No correlation

between the left and right ventricular ejection fractions were observed during the in-hospital phase of inferior infarction. This would be anticipated as involvement of the right ventricular free wall may occur in the absence of a large inferior wall left ventricular infarction (78).

In Chapter 3, the effects of asymmetrical contraction of the left ventricle resulting in errors in the calculation of the ejection fraction were discussed. Similarly, the presence of regional contraction abnormalities of the right ventricle could introduce errors into the calculation of the right ventricular ejection fraction. The complex geometrical shape of the right ventricle makes this a difficult problem to address, and to date there have been no published data relating to this problem.

Little change was found in the right ventricular function following either inferior or anterior myocardial infarction during the hospitalisation phase. Previous studies have reported varying accounts of the course of right ventricular function following myocardial infarction. An improvement in right ventricular function following inferior myocardial infarction has been reported by some workers (88,90,91), whilst others have reported no change (96,113). The course of right ventricular function following anterior myocardial infarction is also unclear, with some reporting a prompt

improvement towards normal function during the first few days following infarction (88,96) and others reporting no change (113). Subdivision of patients into groups according to the severity of right ventricular dysfunction did not reveal any significant differences.

However, variability in the right ventricular ejection fraction was not uncommon when the course of right ventricular function was examined in individuals. None of the demographic or prognostic variables examined were found to be associated with variability of the right ventricular ejection fraction in individual patients. These findings are similar to those reported in the preceding chapter relating to the left ventricular ejection fraction. It seems more probable that this variability in the right ventricular ejection fraction is the result of changes in the loading conditions rather than intrinsic changes in myocardial contractility. Nemerovski et al reported findings over a 25 day period which were similar to those presented here (113).

The relationship observed between the peak creatine kinase and the right ventricular ejection fraction following inferior myocardial infarction was not unexpected in view of the release of creatine kinase following right ventricular infarction. Following anterior myocardial infarction there was also a correlation between the right ventricular ejection fraction and the peak creatine kinase. The explanation

of this association may be related to the detrimental effect of left ventricular dysfunction on right ventricular performance. Hence, a large anterior myocardial infarction which is associated with a high peak creatine kinase and also left ventricular dysfunction may result, by the mechanisms discussed earlier, in right ventricular dysfunction.

The correlation between the right ventricular ejection fraction and the thallium perfusion index was tenuous. Only the discharge right ventricular ejection fraction in patients with anterior myocardial infarction was related to the size of the thallium perfusion index.

The right ventricular ejection fraction was not related to either the in-hospital or cumulative mortality over the 18 month follow-up period. Similarly, no relationship was found between the right ventricular ejection fraction and the Killip classification or the Norris Index, both of which were primarily developed to evaluate clinical evidence of left ventricular dysfunction.

4.7 CONCLUSIONS

These data reveal that the incidence of right ventricular dysfunction following both inferior and anterior myocardial infarction is relatively common. In the group of patients studied, little change was

identified in the right ventricular ejection fraction during the hospitalisation period. However, variability in the right ventricular ejection fraction in individuals was not uncommon but did not appear to have any clinical or prognostic importance. The right ventricular ejection fraction was found not to be related to mortality.

CHAPTER 5

ASSESSMENT OF RIGHT VENTRICULAR FUNCTION USING 133-XENON IMAGING

5.1 INTRODUCTION

The use of imaging techniques in the assessment of right ventricular function, as alluded to in the previous chapter, present problems because of the complex geometrical shape of the right ventricle. Therefore, the relative lack of geometrical dependence of radionuclide techniques is particularly suited to the evaluation of right ventricular function. Recent interest has been focussed on the use of inert radioactive gases for this purpose (127-131). These tracers are used using a first pass or gated first pass technique which because of the absence of left heart activity, as the tracer is excreted during first passage through the lungs, allows optimal separation of the right sided cardiac chambers without contamination from left heart activity.

The aim of this chapter is to describe the application of one of these techniques, gated Xenon-133 imaging, to assess right ventricular function during the early phase of acute inferior myocardial infarction. The results obtained were correlated to the presence of clinical features of right ventricular dysfunction. In

addition, the use of radionuclide, echocardiographic and haemodynamic assessments of right ventricular function following acute inferior myocardial infarction are also discussed.

5.2 PATIENT POPULATION

The patient population consisted of three groups: 26 patients with acute inferior myocardial infarction (all from the original population of 81 patients), 16 normal volunteers and 12 patients with coronary artery disease without previous myocardial infarction. The limited availability of the isotope for this study precluded its use in a larger group of patients or repeat evaluation in a significant number of patients.

In the group with acute inferior myocardial infarction 17 of the 26 were male. Ages ranged from 35-74 years with a mean of 57 years. All patients were examined specifically for clinical evidence of right ventricular dysfunction by the attending physicians and in particular the jugular venous pulse was assessed. The presence of either a rise in the jugular venous pressure at the end of quiet respiration (Kussmaul's sign) or the venous pressure within the internal jugular vein greater than 4 cm. above the sternal angle was considered indicative of right ventricular dysfunction.

All patients with a history of significant chronic

obstructive airways disease, pulmonary thrombo-embolic disease, pulmonary hypertension, valvular heart disease or cardiomyopathy were excluded.

Normal values were obtained from 16 healthy volunteers whose ages ranged from 23-36 years. In addition, 12 patients with arteriographically proven coronary artery disease without previous myocardial infarction, whose ages ranged from 43-61 years, were also studied for comparative purposes.

5.3 RADIONUCLIDE IMAGING

The gated Xenon-133 technique was employed to assess right ventricular function which has been previously described and validated, and has been proven to provide an accurate method for the assessment of right ventricular function. There is a good correlation between the right ventricular ejection fraction calculated using this technique and the gated equilibrium and first pass techniques using technetium-99m, with correlation coefficients of 0.92 and 0.80 respectively, over a wide range of values (131).

Data were acquired using a mobile gamma camera fitted with an ultra-high sensitivity parallel hole collimator. The camera was interfaced with a mobile computer system (Link MAPS, UK). All data were acquired in a listmode fashion to allow accurate retrospective

construction of a representative cardiac cycle.

A 5-10^{o} left anterior oblique projection with a 6^{o} caudal tilt was used to allow optimal separation of the right atrium from the right ventricle and also isolated tha activity of the right heart from the lung fields.

400-600 MBq of 133-Xenon was injected intravenously over a 20 second period with data being acquired from time of first visualisation of activity within the right heart until activity was seen to leave it. After consultation with the local Radiation Protection Officer, exhaled 133-Xenon was not routinely collected as it was advised the amount of radiation exposure from these studies was negligible. The average data acquisition time was 25 seconds. In 20 studies the average net end-diastolic counts were 3620 ± 978 in 1/16 of a cardiac cycle.

5.4 DATA PROCESSING

The Xenon images were processed in the following manner. Data were stored on a listmode file and were processed to construct a representative cycle of 16 frames for analysis. Any cycles with R-R intervals of greater than 20% outwith the running average were discarded. After standard spatial (1,2,1/2,4,2/1,2,1 matrix) and temporal (1,2,1) smoothing the end-diastolic and end-systolic frames were used to devise standard

stroke volume and paradox images, allowing definition of the tricuspid and pulmonary valve planes. The right ventricular region of interest was then extended from the valve planes to encompass the whole right ventricle. The region of interest was confirmed by superimposing the cine display and modifying it as necessary. A background region of interest was drawn three pixels wide adjacent to the right ventricular region of interest. Time-activity curves were then generated for both regions of interest, allowing the right ventricular ejection fraction to be calculated, as previously described in Chapter 2.

5.5 REPRODUCIBILITY OF TECHNIQUE

Intra-observer variation in calculating the right ventricular ejection fraction was evaluated on two occasions from 30 studies; inter-observer variation was determined from 20 studies independently by two observers. Repeatability was assessed by repeating studies within 30 minutes in five patients and five normal volunteers after 3 months.

In 20 studies the mean inter-observer difference was 2.8%, with a range of 0-9%, Figure 9. For intra-observer variation, assessed from 30 studies, there was a mean difference of 2.2% with a range of 0-6%, Figure 10. The reproducibility of the technique with repeat

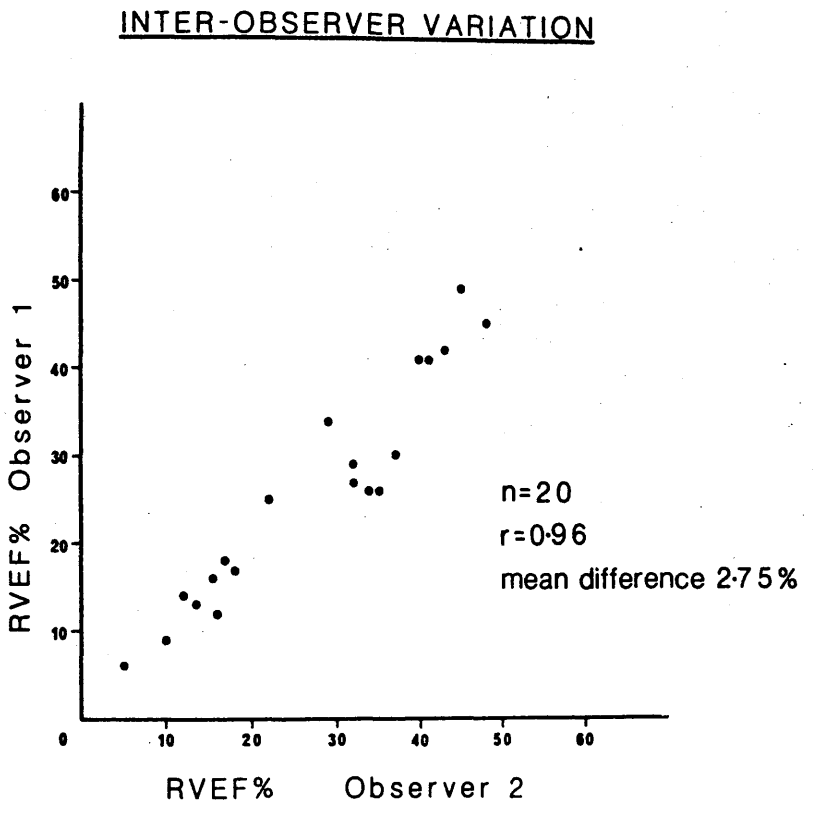

FIGURE 9. Correlation between the calculation of the right ventricular ejection fraction (RVEF) by two independent observers (n = 20; r = 0.96) with mean interobserver difference of 2.7% (range 0 - 9%).

acquisition resulted in a mean difference of 3.5% with a range of 1-14%.

5.6 RESULTS

The range of the right ventricular ejection fraction in the normal volunteers was 35-55% with a mean of 43 ± 5%, and in the patients with chronic coronary artery disease it ranged from 33-46%, mean of 39 ± 9%. There was no significant difference between the right ventricular ejection fractions between the two groups.

In patients who had sustained an acute inferior myocardial infarction, a wide range of right ventricular ejection fractions were seen. Values ranged from 7-54%, mean 30 ± 11%, which were significantly lower than those obtained from the normal volunteers $P<0.001$ and the patients with chronic coronary artery disease $P<0.001$, Figure 11.

A right ventricular ejection fraction was considered abnormal if it was less than 35%. Eighteen patients (69%) with acute inferior myocardial infarction had abnormal right ventricular ejection fractions using this criterion.

Thirteen patients (50%) showed no clinical evidence of right ventricular dysfunction at time of imaging. The right ventricular ejection fractions in this group ranged from 16-49%, mean 35 ± 9%. In the remaining patients

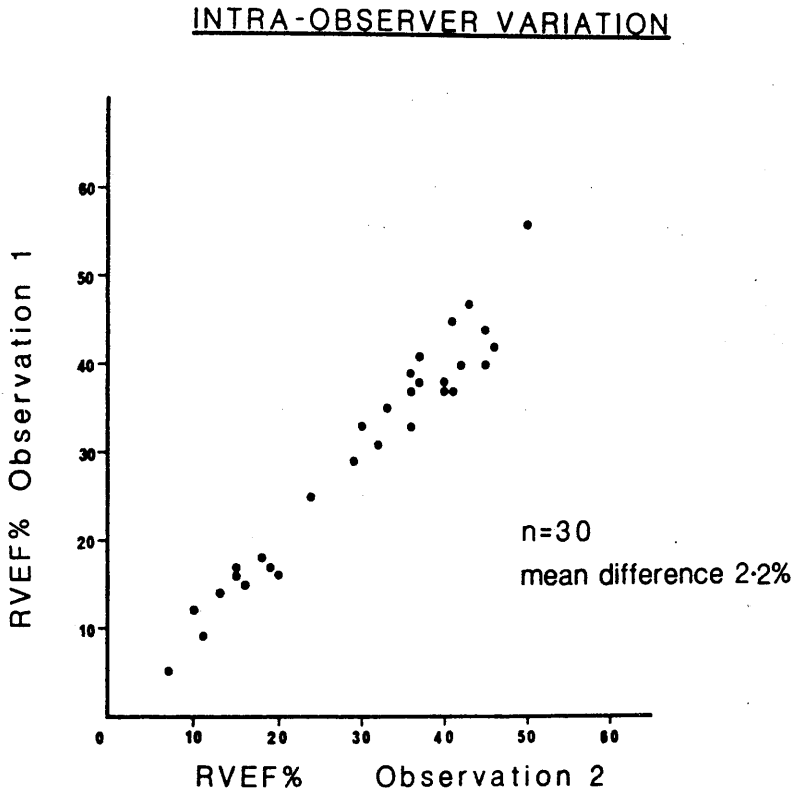

FIGURE 10. Correlation between the calculation of the right ventricular ejection fraction (RVEF) on two occasions by one observer (n = 30; r = 0.98) with mean intra-observer difference of 2.2% (range 0 - 6%).

with clinical evidence of right ventricular dysfunction, the right ventricular ejection fraction ranged from 7-54%, mean 26 ± 11%, which was significantly lower than in the group without clinical evidence of right ventricular dysfunction, $p<0.001$; Figure 12.

Figure 13 shows Xenon-133 images from a patient with normal and a patient with abnormal right ventricular function following acute inferior myocardial infarction.

The presence of clinical signs suggestive of right ventricular dysfunction had a sensitivity of 72% (13/18), a specificity of 87.5% (7/8) and a predictive accuracy of 76% (20/26) when compared to the imaging data.

5.7 DISCUSSION

These results suggest that inferior myocardial infarction has a variable impact on the right ventricle. A wide range of right ventricular ejection fraction was found, ranging from 7-54% with a significantly reduced mean value of 30% compared to normal. Eighteen patients (69%) had evidence of right ventricular dysfunction (ejection fraction <35%), which is comparable to the incidence reported by Rigo et al (80) and Baigrie et al (8), who reported an incidence of 64% and 78% respectively.

The clinical signs that indicate underlying right ventricular dysfunction were considered as being present

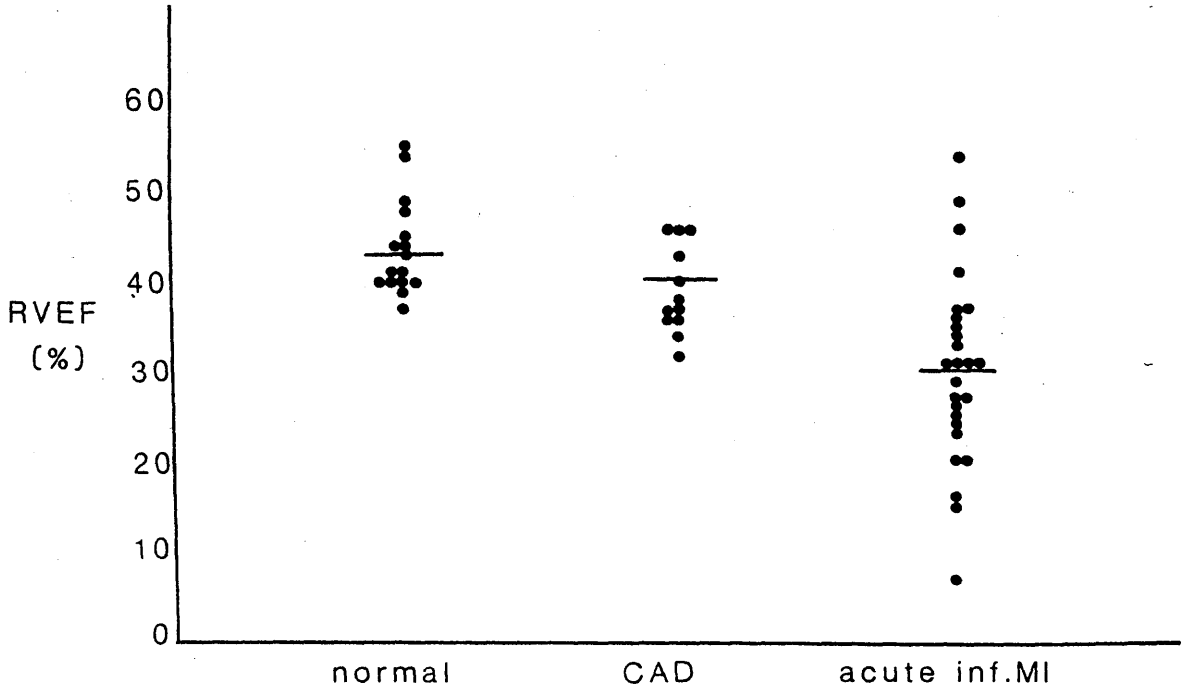

FIGURE 11. Range of right ventricular ejection fraction (RVEF) in normal volunteers, n = 16; patients with stable angina pectoris (CAD), n = 12; and patients with acute inferior myocardial infarction (inf. MI), n = 26. Mean value for RVEF in each group indicated by bar.

in 13 of the 26 patients (50%) by the attending physician. This resulted in a sensitivity of 72%, a specificity of 87.5% and predictive accuracy of 76%, when a right ventricular ejection fraction of less than 35% was taken as indicative of right ventricular dysfunction. Previous workers (132) have evaluated the accuracy of abnormalities in the jugular venous pulse in predicting right ventricular dysfunction using haemodynamics for comparison. In the setting of acute inferior myocardial infarction they reported a sensitivity and specificity of 88 and 60% for elevation of the jugular venous pressure and a 100% sensitivity and specificity for the presence of Kussmaul's sign in detecting right ventricular dysfunction. Baigrie et al (8) report somewhat poorer results and found a sensitivity, specificity and predictive accuracy of 63%, 50% and 81% respectively, employing Kussmaul's sign for the detection of right ventricular dysfunction and using two-dimensional echocardiography for comparison.

Technical considerations

Various radionuclide techniques have been employed in the assessment of right ventricular function in the setting of acute myocardial infarction. The radioisotope, technetium-99m, can be used employing either a first pass method or the gated equilibrium method. However, both of these techniques have limitations.

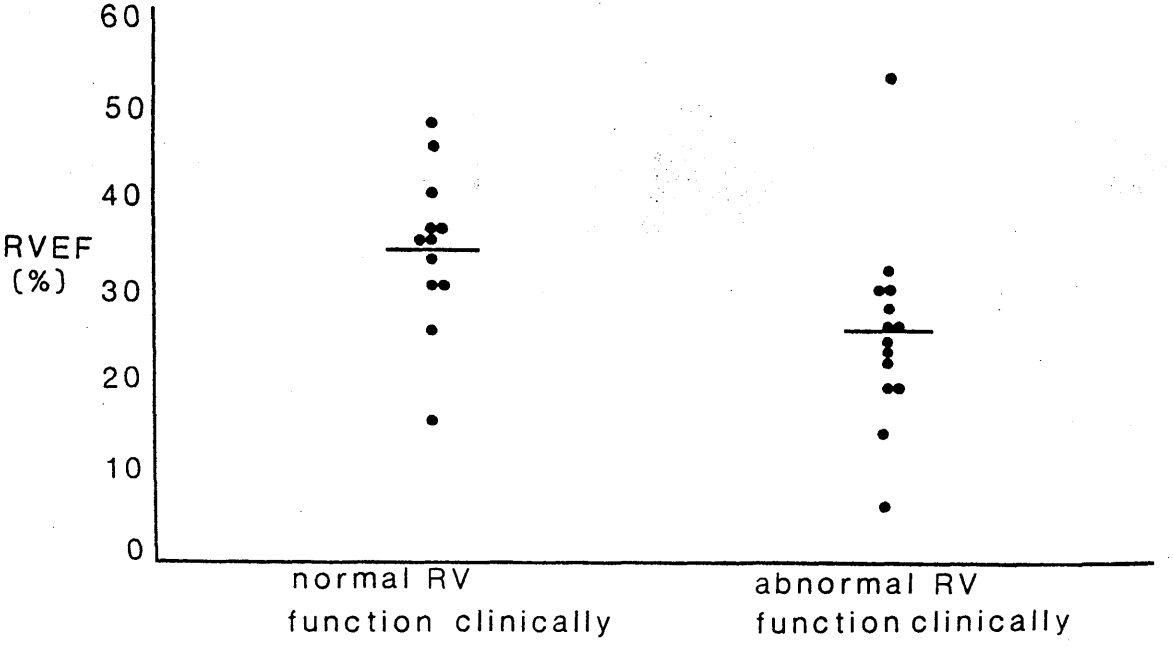

FIGURE 12. Relationship of right ventricular ejection fraction (RVEF) to presence (n = 13) or absence (n = 13) of clinical signs of right ventricular dysfunction following acute inferior myocardial infarction.

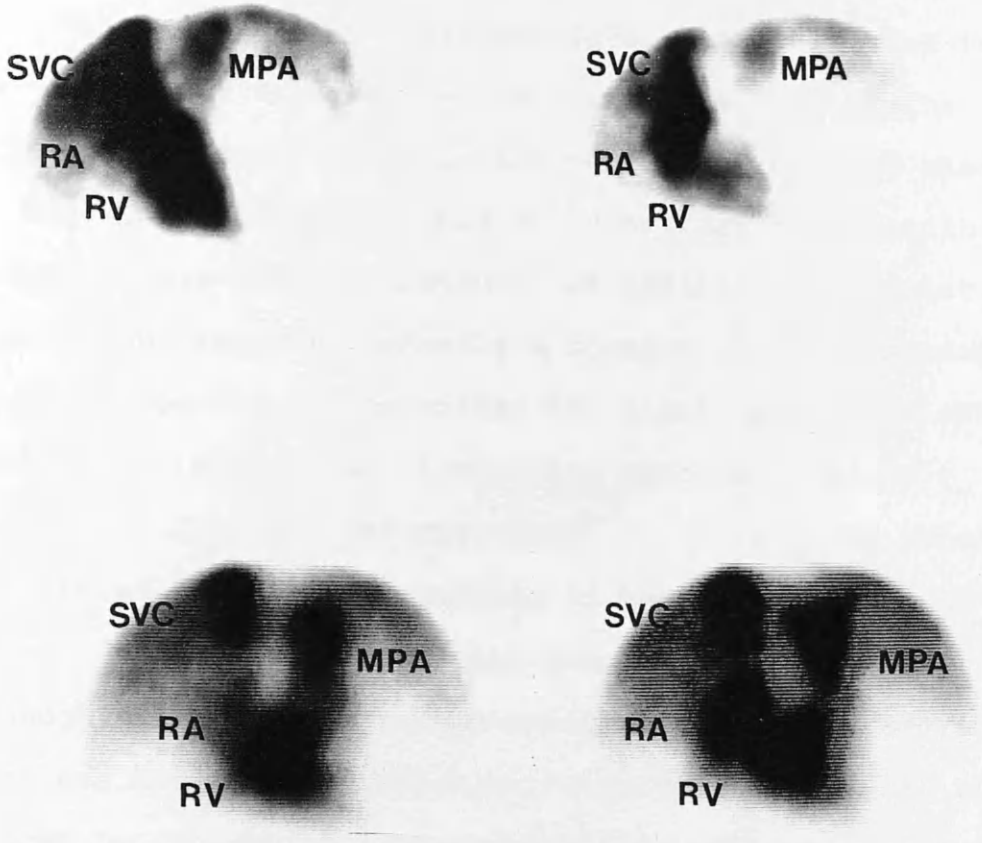

FIGURE 13. Images from a patient with normal right ventricular function (end-diastolic frame top left, end-systolic frame top right) and a patient with severe right ventricular dysfunction (end-diastolic frame lower left, end-systolic frame lower right) following acute inferior myocardial infarction. RA = right atrium, RV = right ventricle, MPA = main pulmonary artery, SVC = superior vena cava.

Using the first pass technique, one is limited to the number of studies one can perform because of the increasing exposure of radiation to the patient and also by the increasing background activity that occurs with repeated doses of technetium. In addition, the first pass method requires not only a compact bolus injection but also adequate mixing within the right ventricle; the latter can become an increasing problem as right ventricular function deteriorates. The high count rates encountered during the passage of the isotope impose severe demands on conventional single crystal cameras, although this can be overcome using multicrystal cameras, which are not widely available. High count rates can be reduced by decreasing injected activity when using single crystal cameras; however this can reduce the accuracy of the technique because of the detrimental effects on count statistics.

The main limitation of the gated equilibrium technique is the poor separation that occurs from both the right atrium and the pulmonary outflow tract from the right ventricle. The inability to exclude the right atrium and pulmonary outflow tract totally from the right ventricular region of interest resulting in systematically lower ejection fractions (102). Although the technique of gated equilibrium radionuclide ventriculography does have significant limitations this technique has been very extensively used in the

assessment of right ventricular function following myocardial infarction (87,90,91,93,96,98,113,133).

Inert gases have also been used although less extensively in the assessment of right ventricular function, namely 81m-Krypton (127,130) and 133-Xenon (128,129,131). However, although 81m-Krypton has a very short half-life of only 13 seconds it is both expensive and not readily available.

In contrast, the use of 133-Xenon does not have such limitations. The relative cost of 133-Xenon is much lower than 81m-Krypton and is comparable to that of 201-Thallium. Although it has a physical half-life of 5.3 days, its biological half-life is only 60-120 seconds, as 95% of an intravenous dose is excreted during its first passage through the lungs. However, to collect the exhaled 133-Xenon requires the patient to breathe through a mouthpiece connected to a suitable container. The radiation exposure to the patient is less than 10% of the radiation dose for a first pass study using technetium-99m (134). The rapid clearance of background activity allows repeated estimations of right ventricular function to be made. However, 133-Xenon does have the drawback of lower energy emissions in comparison with 81m-Krypton, 80 keV versus 191 keV respectively. This results in poorer resolution because of increased photon attenuation and scatter.

A short infusion technique of 20 ml of 133-Xenon in solution over 20-25 seconds was used to avoid the difficulties encountered with a first pass technique which requires a compact bolus of tracer and adequate mixing within the right ventricle as mentioned previously. The projection used was a 5-10^{o} left anterior oblique, which allowed optimal separation of the right atrium and the pulmonary outflow tract from the right ventricle. Spatial separation of the right atrial and ventricular activity is probably optimal in the right anterior oblique projection, as is normally used in first pass technetium studies. However, the use of this projection with 133-Xenon results in superimposition of lung activity on the right heart and also increases the patient to collimator distance, degrading resolution.

Echocardiography has also been used, although less extensively, in the non-invasive diagnosis of right ventricular infarction. Sharpe et al (82) using M-mode echocardiography found a significant increase in the right ventricular end-diastolic dimensions and the ratio of right to left ventricular dimensions in patients with right ventricular involvement as compared to patients with no right ventricular involvement. D'Arcy and Nanda (83) and Baigrie et al (8), using two-dimensional echo-cardiography, showed evidence of both regional and global right ventricular dysfunction. However, to date there has been no prospective study evaluating the use of ech-

cardiography in a large number of consecutive patients which is probably a reflection of the inherent difficulties of this technique in overcoming the geometrical complexity of the right ventricle.

Haemodynamic measurements have been widely used in the detection of right ventricular involvement, and various criteria have been suggested for its diagnosis (7,84,85). However, the haemodynamic criteria are not particularly sensitive. They can be absent in the presence of right ventricular infarction if patients are volume depleted, usually as a result of prior administration of diuretics, or if there has been marked right ventricular dilatation, when haemodynamic abnormalities may only become apparent following volume expansion (8,72,80). Additionally it would appear that the use of haemodynamic techniques does not detect the less severe degrees of right ventricular dysfunction that can occur following inferior myocardial infarction (91).

It is becoming increasingly apparent, with the development of newer diagnostic techniques of radionuclide ventriculography and echocardiography, that more subtle abnormalities in right ventricular function occur following inferior myocardial infarction. These are characterised by regional wall motion abnormalities (8,91) which may not be associated with abnormalities in global right ventricular performance or the "classical" clinical syndrome (133), as initially described by Cohn

et al (7). The significance of these minor abnormalities in right ventricular function is not known. However, it may be important to identify these patients as they could constitute an "at risk" group. The use of therapy which may be detrimental, such as diuretics, could be avoided and also the identification of these patients would allow early intervention with the appropriate measures (90), before significant haemodynamic deterioration can occur.

5.8 CONCLUSIONS

In conclusion, these data show that gated 133-Xenon imaging provides a suitable method of assessing right ventricular function during the acute phase of myocardial infarction. The technique allows for repeated evaluation of right ventricular function, and would be ideally suited for the assessment of therapeutic interventions in this setting. In addition the results shown that inferior myocardial infarction can result in varying degrees of right ventricular dysfunction, which may go undetected clinically.

CHAPTER 6

THE NATURAL HISTORY OF VENTRICULAR FUNCTION IN THE SIXTEEN MONTHS FOLLOWING MYOCARDIAL INFARCTION

6.1 INTRODUCTION

The preceding three chapters have dealt predominantly with the early effects of myocardial infarction on ventricular function. This chapter deals with the effects of myocardial infarction on right and left ventricular function in the months following hospital discharge.

There is still a degree of uncertainty as to the long term effects of myocardial infarction on left ventricular function. Some workers have reported little change (35) whilst others have found an improvement in left ventricular function following myocardial infarction (33,34). Improvement in left ventricular function has been shown by some to be limited only to certain subgroups of patients (43,44).

During the in-hospital phase of acute inferior myocardial infarction the literature suggests that an improvement in right ventricular performance occurs (88,90,91), although contrary findings have been reported (93,96,113). Similar findings have been reported following acute anterior myocardial infarction (88,96,

113). However, the natural history of right ventricular function in the months following both anterior and inferior myocardial infarction still remains largely unknown.

In Chapter 4, a difference in the relationship between left and right ventricular function was identified between anterior and inferior myocardial infarction. This difference has been previously noted by others during the early phase of acute infarction (96,97, 98), however the outcome of this relationship during the months following the index infarction has not yet been determined.

Therefore, the aims of this chapter are to determine 1) the natural history of right and left ventricular function following myocardial infarction, examining what role the site of infarction and the degree of ventricular dysfunction play; 2) the relationship between right and left ventricular function in the sixteen months following myocardial infarction.

6.2 CHANGE IN THE LEFT VENTRICULAR EJECTION FRACTION IN THE SIXTEEN MONTHS FOLLOWING MYOCARDIAL INFARCTION

The patients who had sustained an anterior myocardial infarction still had significantly lower left ventricular ejection fractions after 16 ± 3 months, when compared with those who had sustained inferior myocardial

infarction, 26.1 ± 9.8% (n = 24) versus 33.0 ± 9.4% (n = 37) respectively, $p<0.01$.

The patients who had sustained an anterior myocardial infarction showed no significant difference between the in-hospital estimations and the left ventricular ejection fraction at the time of the sixteen month follow-up visit 23.4 ± 9.8% on day one, 21.4 ± 8.0% on day three, 23.5 ± 8.7% at hospital discharge and 26.1 ± 9.8% at time of follow-up (16 ± 3 months), p = NS, Figure 14.

In patients who had sustained an inferior myocardial infarction there was a trend for the left ventricular ejection fraction to improve during the sixteen months following infarction. The left ventricular ejection fraction increased from 29.9 ± 9.5% on day three to 33.0 ± 9.0% after 16 months, $p<0.02$; Figure 15.

When the degree of left ventricular dysfunction was taken into consideration, as described in Chapter 3, significant inter-group differences were observed. There was an improvement in the left ventricular ejection fraction in patients with severe left ventricular dysfunction (left ventricular ejection fraction <25%) from time of discharge to follow-up. The left ventricular ejection fraction increased from 18.9 ± 3.1% to 22.7 ± 6.2% (n = 15), $p<0.02$. This improvement was most evident in patients with inferior myocardial infarction where the

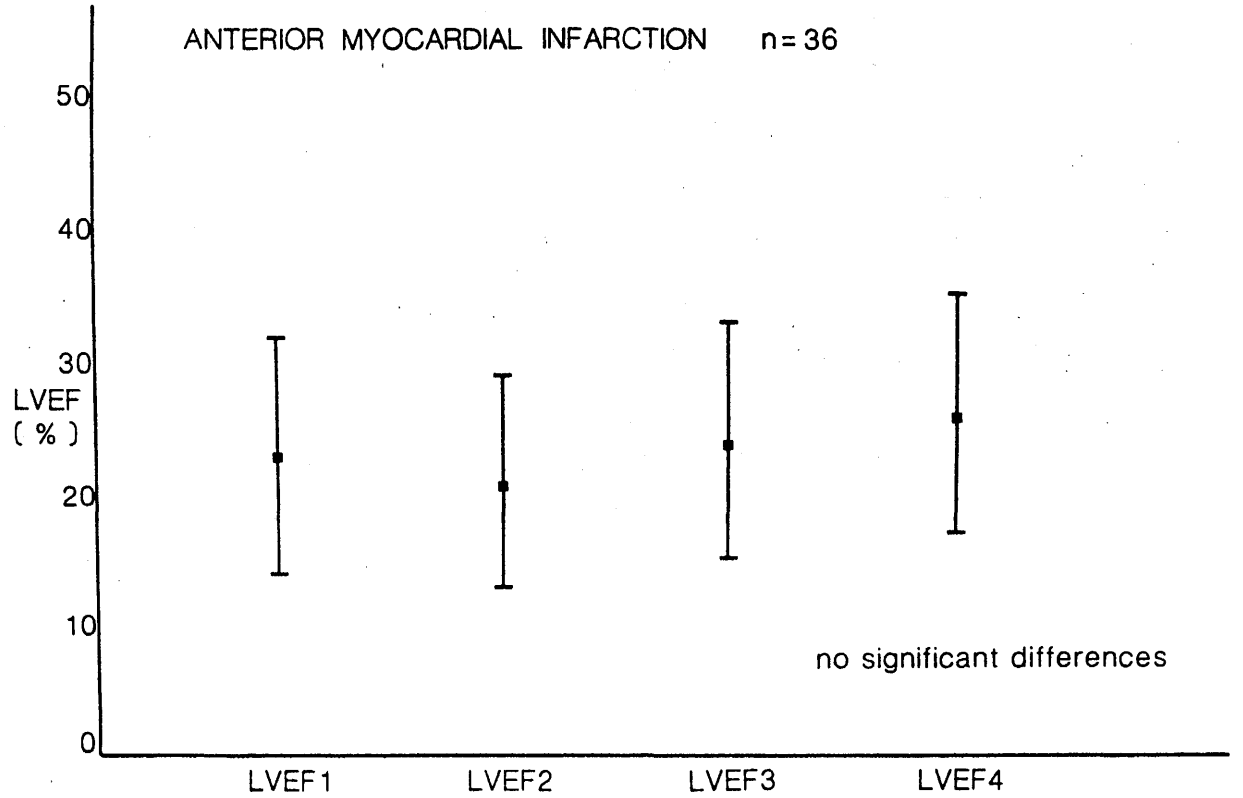

FIGURE 14. Left ventricular ejection fraction (LVEF) during the early and convalescent stages of anterior myocardial infarction. Dark square represents mean value with horizontal bar representing one standard deviation. LVEF 1-4 = left ventricular ejection fraction on day 1, day 3, hospital discharge and follow-up visit respectively.

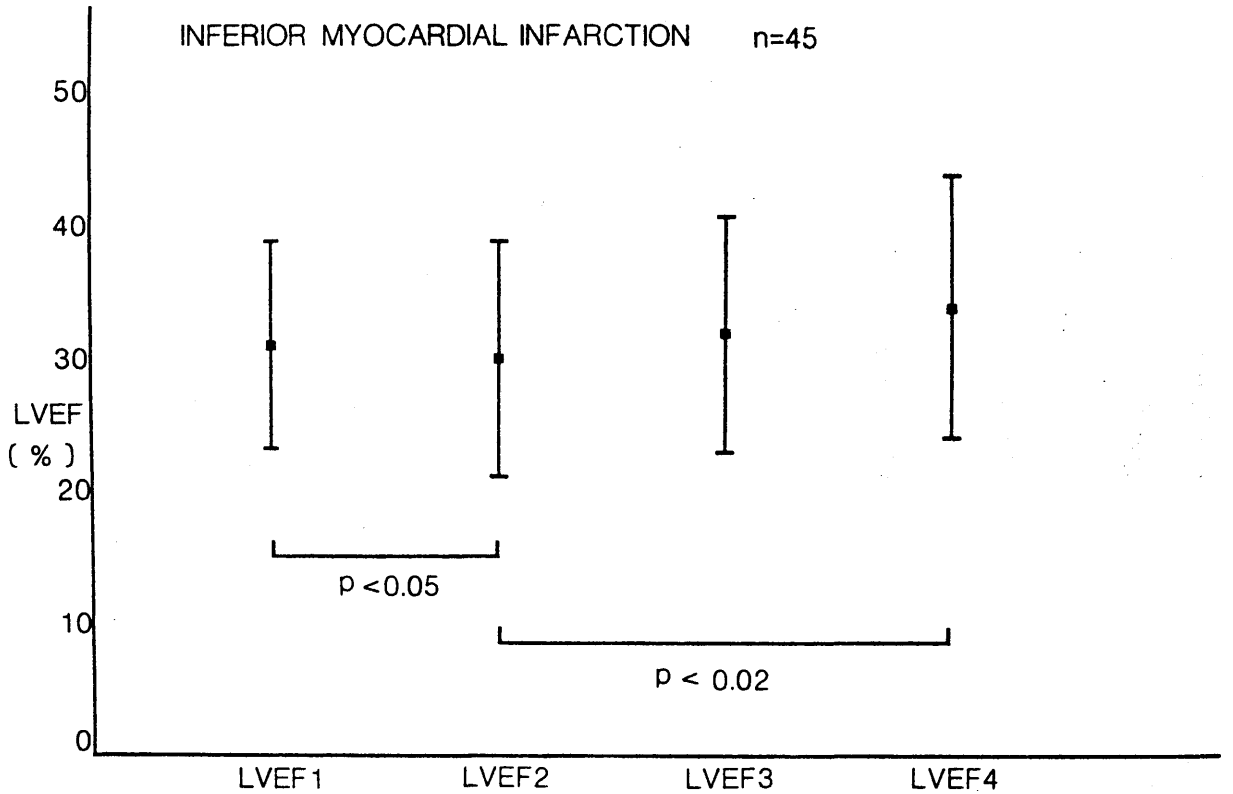

FIGURE 15. Left ventricular ejection fraction (LVEF) during the early and convalescent stages of inferior myocardial infarction. For explanation of abbreviations see Figure 14.

left ventricular ejection fraction increased from 19.2 ± 1.8% to 25.2 ± 7.0% (n = 5), $p<0.05$, whereas in patients with anterior myocardial infarction there was no statistically significant change, 18.8 ± 3.6% and 21.4 ± 5.6% (n = 10), p = NS. There were no significant changes seen in any of the other groups, Table 10.

Individual variations in the left ventricular ejection fraction were not uncommon during this period. The changes ranged from -21% to +22%, 36 of which were $\geq$5%, with a mean change of +0.6%, Figure 16. No relationship was observed between the magnitude of change and the presence of previous myocardial infarction, size or site of infarction, left ventricular ejection fraction at the time of hospital discharge or to cardiac events (development of angina or coronary artery surgery). There were sixteen patients who had a $\geq$5% decrease in the left ventricular ejection fraction (mean change 10.4 ± 4.2%). One of these patients sustained an inferior myocardial infarction following the index infarction with a resultant fall in the left ventricular ejection fraction from 25 to 10%. In the remaining patients, the perfusion index was not significantly different from that in patients in which there was no change or an increase in the left ventricular ejection fraction, 20.2 ± 5.66% versus 25.0 ± 10.9%, p = NS.

The patients were also grouped according to the direction of change in the left ventricular ejection

	Number of Patients	Hospital Discharge (15±12 days)	Follow-Up (16±3 months)
Preserved LV function (LVEF >35%)	15	41.7 ± 5.7	38.2 ± 12.1
Moderate LV dysfunction (LVEF 25-34%)	23	29.7 ± 2.7	29.8 ± 8.6
Severe LV dysfunction (LVEF <25%)	15	18.9 ± 3.1	22.7 ± 6.2*

* $p<0.02$

TABLE 10

Change in left ventricular ejection fraction (LVEF) in relationship to the degree of left ventricular (LV) dysfunction at time of hospital discharge. (see text for further details)

fraction, into those who showed no significant change in the left ventricular ejection fraction (within ±5%), those with a fall of ⩾5% and those with an increase of ⩾5%. Again no relationship was observed between direction of change in the left ventricular ejection fraction and presence of previous infarction, site or size of infarction, discharge left ventricular ejection fraction or to cardiac events (development of angina or coronary artery surgery).

6.3 CHANGE IN THE RIGHT VENTRICULAR EJECTION FRACTION IN THE SIXTEEN MONTHS FOLLOWING MYOCARDIAL INFARCTION

In the patients who had sustained an inferior myocardial infarction there was no significant change in the right ventricular ejection fraction between the in-hospital and the sixteen month follow-up visit estimations. The right ventricular ejection fraction at time of follow-up was 32.8 ± 8.5% as compared with 28.3 ± 8.9%, 29.9 ± 10.2% and 32.3 ± 11.4% on day 1, day 3 and at time of hospital discharge, p = NS; Figure 17.

In patients who had sustained an anterior myocardial infarction the right ventricular ejection fraction was significantly lower at the time of the sixteen month follow-up when compared with the in-hospital estimations. The right ventricular ejection

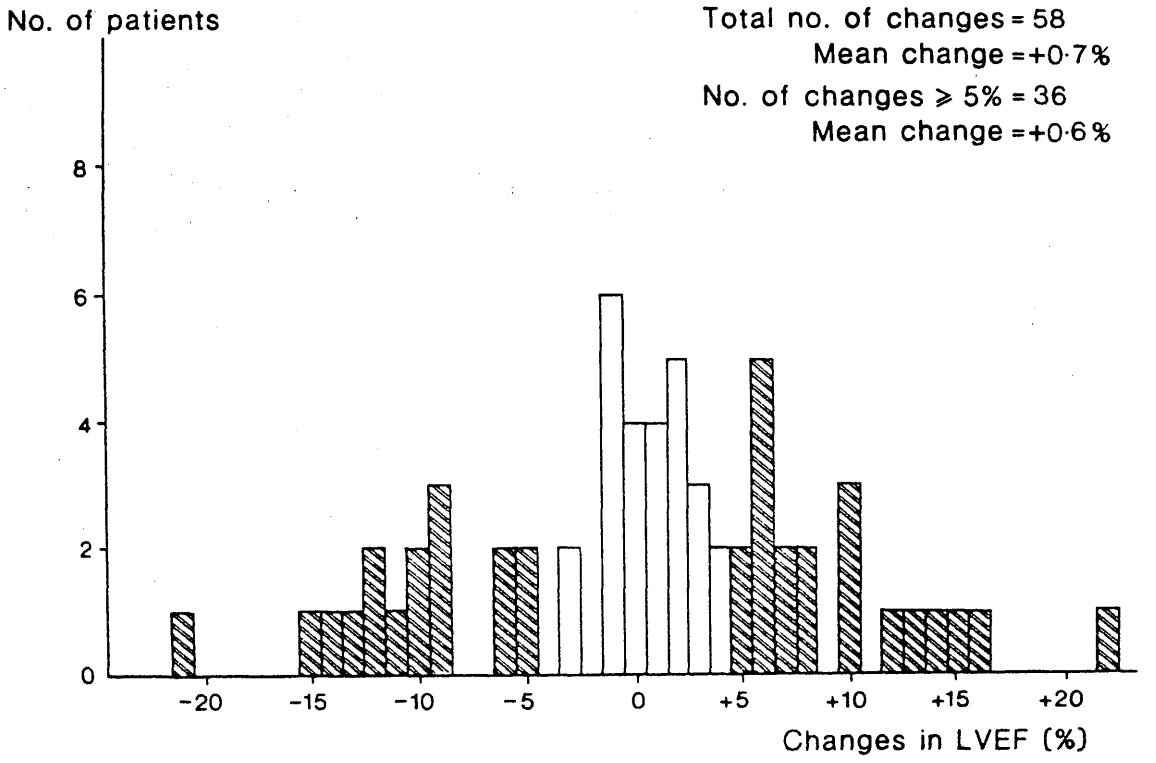

FIGURE 16. Change in left ventricular ejection fraction (LVEF) between hospital discharge (15 ± 12 days) and follow-up visit (16 ± 3 months). Hatched bars represent change of ⩾ 5% ejection fraction units, non-hatched bars represent changes of < 5%.

fraction at time of follow-up was 31.8 ± 10.4% as compared with 38.9 ± 9.9%, $p<0.01$ on day 1; 34.8 ± 10.1%, $p<0.02$; and 35.5 ± 8.8%, $p<0.01$ at time of hospital discharge; Figure 18.

Variability in the the right ventricular ejection fraction in individual patients was noted during the sixteen month follow-up period. The changes in the right ventricular ejection fraction ranged from -30% to +17%, there were 41 changes of $\geq$5% with a mean change of -0.3%, Figure 19. No statistical relationship was found between a change in the right ventricular ejection fraction and the presence of previous infarction, the site or size of infarction, the discharge left ventricular ejection fraction or to cardiac events. Patients were also grouped according to the direction of change in the right ventricular ejection fraction as described in the preceding section, again no association was found with any of the variables measured.

Patients were also subdivided according to the degree of right ventricular dysfunction, in the same manner as described in Chapter 4. In those patients with severe right ventricular dysfunction (right ventricular ejection fraction <25%) there was an increase in the right ventricular ejection fraction from 19.7 ± 6.4% to 27.9 ± 7.1% ($n = 10$), $p<0.05$. In patients with a moderate degree of right ventricular dysfunction (right ventricular ejection fraction 25-34%) there was no

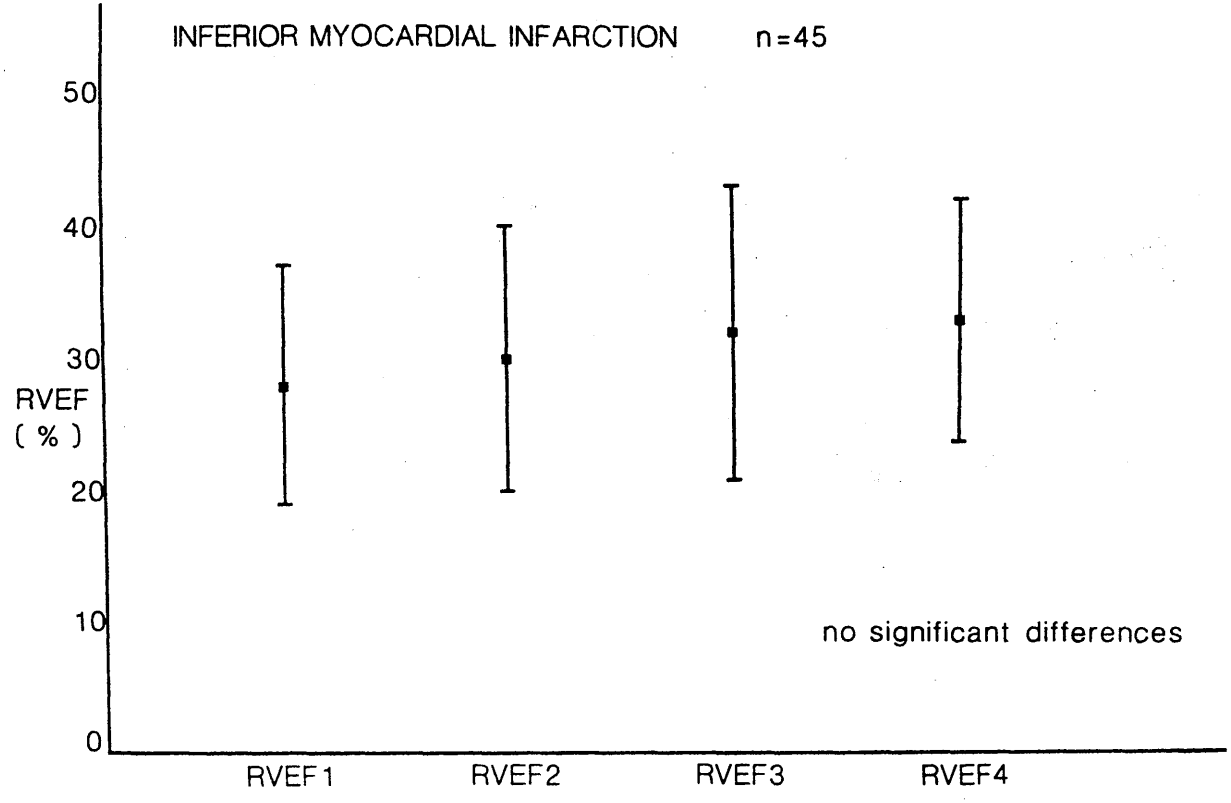

FIGURE 17. Right ventricular ejection fraction (RVEF) during the early and convalescent stages of inferior myocardial infarction. Dark square represents mean value, with horizontal bar representing one standard deviation. RVEF 1–4 = right ventricular ejection fraction on day 1, day 3, hospital discharge and follow-up visit respectively.

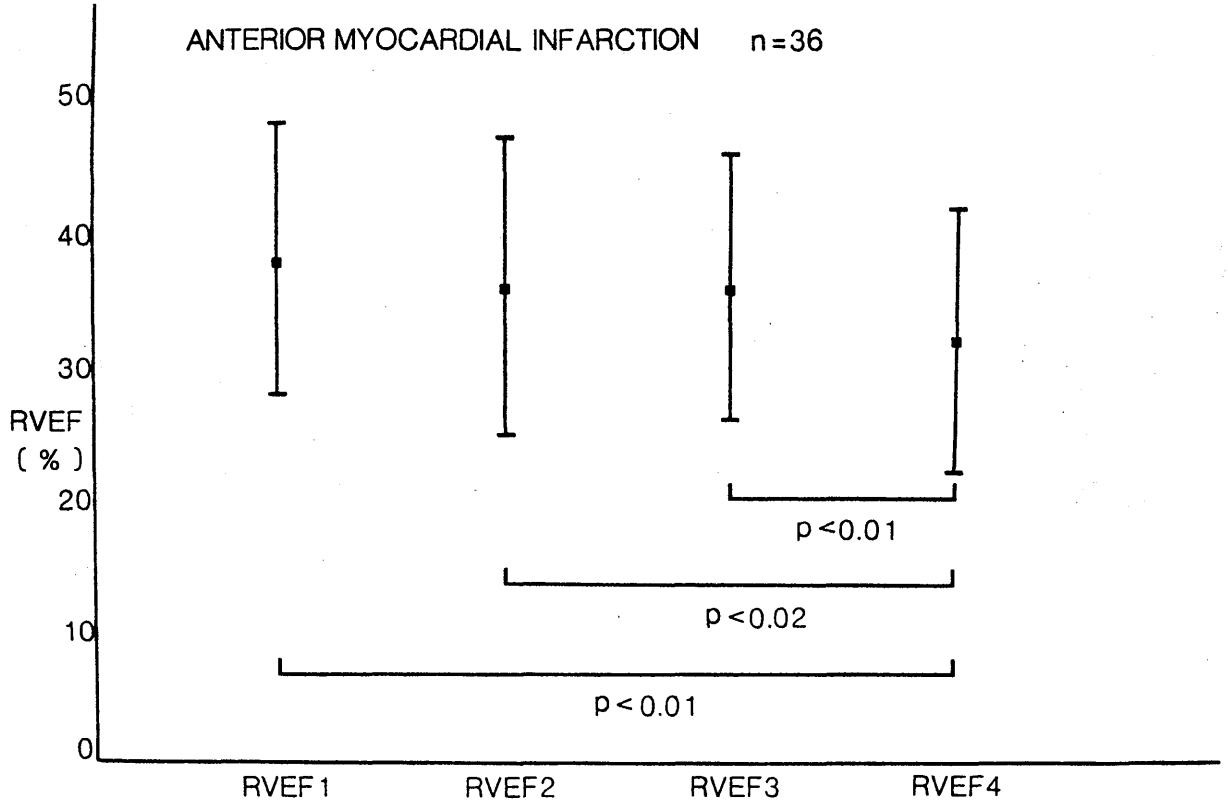

FIGURE 18. Right ventricular ejection fraction (RVEF) during the early and convalescent stages of anterior myocardial infarction. For explanation of abbreviations see Figure 17.

significant change, 29.6 ± 2.4% and 31.0 ± 9.4% (n = 17), p = NS. In those patients with preserved right ventricular function (right ventricular ejection fraction >35%) there was a fall in the right ventricular ejection fraction from 42.9 ± 6.7% to 35.0 ± 10.3% (n = 26), $p<0.001$. This fall was observed in patients with both anterior and inferior infarction, 46.2 ± 4.8% to 38.1 ± 8.1%, $p<0.02$ and 42.2 ± 7.5% to 32.8 ± 11.4%, $p<0.005$ respectively. These changes in the right ventricular ejection fraction were not accompanied by any significant changes in the left ventricular ejection fraction, Table 11.

6.4 ALTERATION IN MEDICATION AND CHANGE IN THE LEFT AND RIGHT VENTRICULAR EJECTION FRACTION FOLLOWING MYOCARDIAL INFARCTION

There were twenty seven patients whose medications had been changed between hospital discharge and follow-up. During the period of follow-up the mean left ventricular ejection fraction increased by +0.56 ± 8.50 compared to +1.55 ± 8.91 in patients whose medications remained unchanged, p = NS. Patients were also sub-divided on the basis on whether the left ventricular ejection fraction increased, decreased or did not change significantly, see Table 12. There were no significant differences observed between patients whose medications

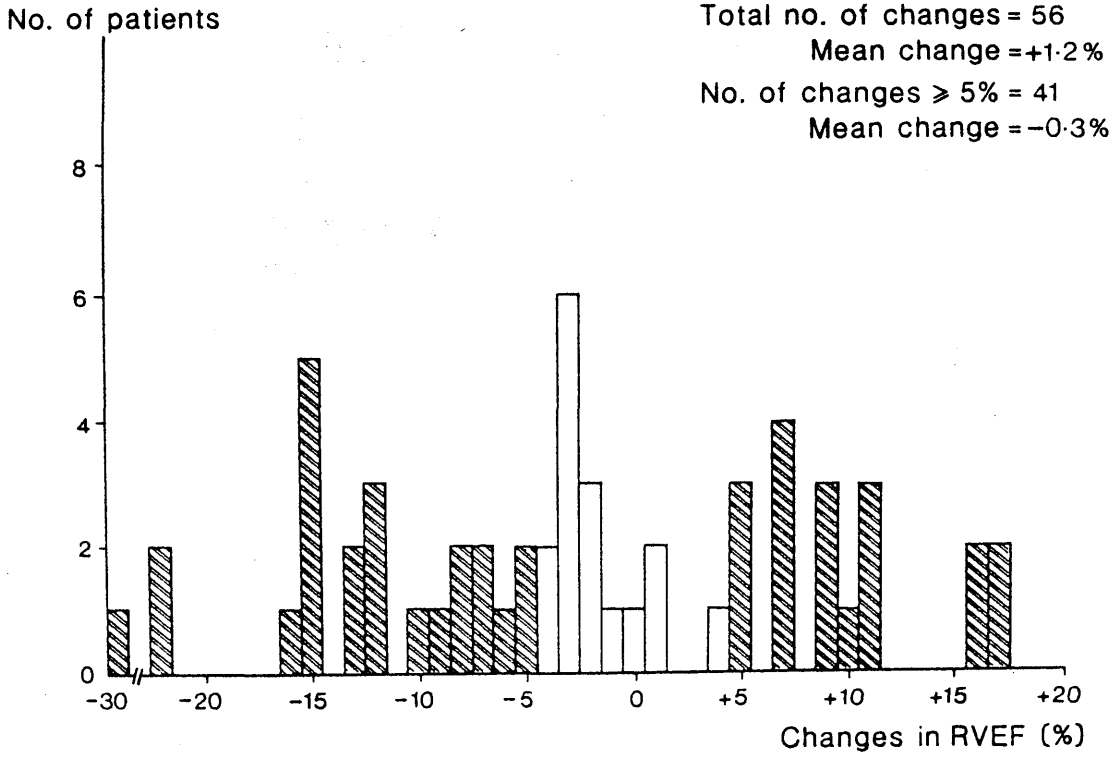

FIGURE 19. Change in right ventricular ejection fraction (RVEF) between hospital discharge (15 ± 12 days) and follow-up (16 ± 3 months). Hatched bars represent changes of $\geqslant$ 5% ejection fraction units, non-hatched bars represent changes of $<$ 5%.

	Number of Patients	Hospital Discharge (15±12 days)	Follow-Up (16±3 months)
Normal RV function (RVEF >35%)	26	42.9 ± 6.7 (28.5 ± 8.9)	35.0 ± 10.3* (30.3 ± 11.0)
Moderate RV dysfunction (RVEF 25-34%)	17	29.6 ± 2.4 (31.6 ± 9.9)	31.0 ± 9.4 (29.8 ± 11.9)
Severe RV dysfunction (RVEF <25%)	10	19.7 ± 6.4 (31.0 ± 9.1)	27.9 ± 7.1** (31.0 ± 8.4)

* p<0.001
** p<0.05

TABLE 11

Change in right ventricular ejection fraction (RVEF) in relationship to the degree of right ventricular (RV) dysfunction at time of hospital discharge; the left ventricular ejection fraction is given below the corresponding RVEF in parenthesis.

		MEDICATION UNALTERED	MEDICATION ALTERED
TOTAL GROUP	LVEF	+1.55± 8.90 (36)	+0.56± 8.50 (27)
	RVEF	-2.86±11.30 (36)	+0.30± 9.65 (27)
>5% INCREASE	LVEF	11.50± 4.95 (9)	9.25± 6.68 (8)
	RVEF	9.25± 5.68 (8)	11.60± 5.04 (8)
>5% DECREASE	LVEF	11.10± 5.15 (8)	12.80± 3.96 (5)
	RVEF	12.80± 3.96 (16)	11.10± 2.64 (8)
<5% CHANGE	LVEF	+1.21± 2.66 (19)	+0.35± 2.68 (14)
	RVEF	-0.92± 2.84 (12)	+0.36± 3.56 (11)

TABLE 12

Alteration in medication between hospital discharge and follow-up and change in the left and right ventricular ejection fraction (mean ± standard deviation)

LVEF = left ventricular ejection fraction
RVEF = right ventricular ejection fraction

Number of patients within each group are given in parenthesis. No statistically significant differences in the ejection fraction were observed between those whose medication was unaltered or altered.

remained unaltered compared to those whose medications had changed. Similar findings were seen when the changes in the right ventricular ejection fraction were examined, see Table 12.

6.5 THE RELATIONSHIP BETWEEN THE LEFT AND RIGHT VENTRICULAR EJECTION FRACTION FOLLOWING MYOCARDIAL INFARCTION

In patients who sustained an inferior myocardial infarction there was no relationship between the right and left ventricular ejection fractions at any time during their hospital admission, Table 13. However, after a mean of 16 months a weak but significant relationship was found between the right and left ventricular ejection fractions, $R = 0.44$, $p<0.01$, see Figures 7 and 20.

Following anterior myocardial infarction a different relationship between the right and left ventricular ejection fractions was observed, Table 12. Both on day 1 and at time of hospital discharge there was a weak but significant correlation between the ejection fractions, $R = 0.51$, $p<0.05$ and $R = 0.46$, $p<0.02$ respectively. By the time of the follow-up visit the correlation was even stronger, $R = 0.83$, $p<0.001$, see Figures 8 and 21.

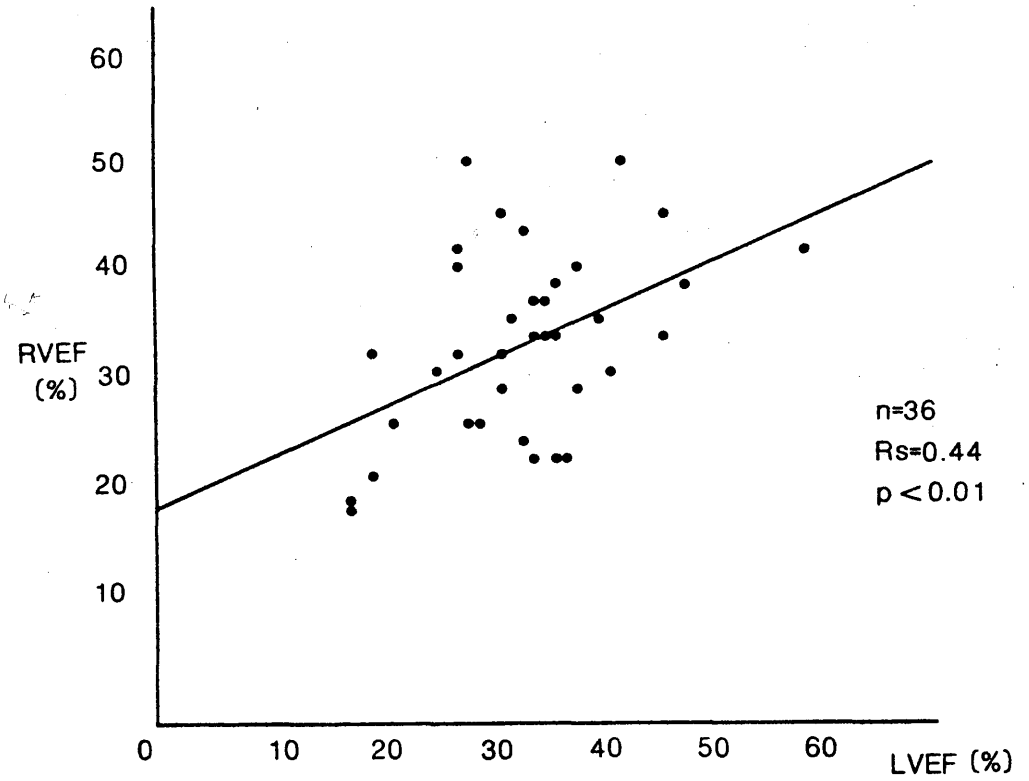

FIGURE 20. Relationship between left (LVEF) and right ventricular ejection fraction (RVEF) at time of follow-up following inferior myocardial infarction.

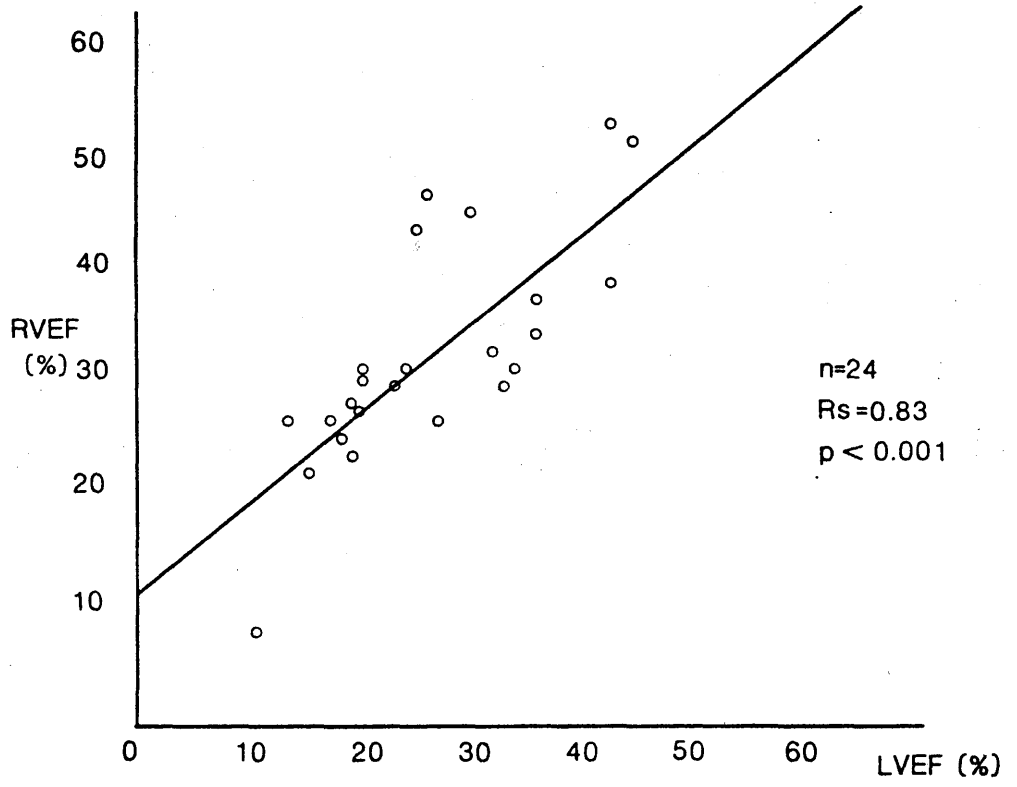

FIGURE 21. Relationship between left (LVEF) and right ventricular ejection fraction (RVEF) at time of follow-up following anterior myocardial infarction.

Site of Infarct	Day 1	Day 3	Hospital Discharge	16 month Follow-Up
Anterior	Rs = 0.51 p < 0.05	Rs = 0.09 p = N.S.	Rs = 0.48 p < 0.02	Rs = 0.83 p < 0.001
Inferior	Rs = -0.13 p = N.S.	Rs = 0.01 p = N.S.	Rs = 0.03 p = N.S.	Rs = 0.44 p < 0.01

TABLE 13

Relationship between left and right ventricular ejection fractions

Rs = Spearman correlation coefficient
p = level of statistical significance
N.S. = not statistically significant

6.6 THE RELATIONSHIP BETWEEN THE LEFT AND RIGHT VENTRICULAR EJECTION FRACTION AND MORTALITY

The effect of the functional status of both the right and left ventricles on mortality is summarised in Figure 22. Patients were sub-divided into four groups on the basis of their underlying right and left ventricular function. Group 1 (n = 25) comprised of patients with moderate to severe impairment of left ventricular function (left ventricular ejection fraction <30%) and depressed right ventricular function (right ventricular ejection fraction of <35%). Group 2 (n = 20) were patients with impaired left ventricular function (left ventricular ejection fraction <30%) and normal right ventricular function (right ventricular ejection fraction >35%). Group 3 (n = 17) patients had preserved left ventricular function (left ventricular ejection fraction of 30% or greater) with impaired right ventricular function (right ventricular ejection fraction <35%) and Group 4 (n = 19) patients had preserved left ventricular function (left ventricular ejection fraction of 30% or greater) and normal right ventricular function (right ventricular ejection fraction of 35% or greater).

After the follow-up period of 18 months there had been 10/25 (40%) deaths in Group 1, 5/20 (25%) in Group 2, 2/17 (12%) in Group 3 and 1/19 (5%) in Group 4. The mortality was significantly higher in Group 1 and

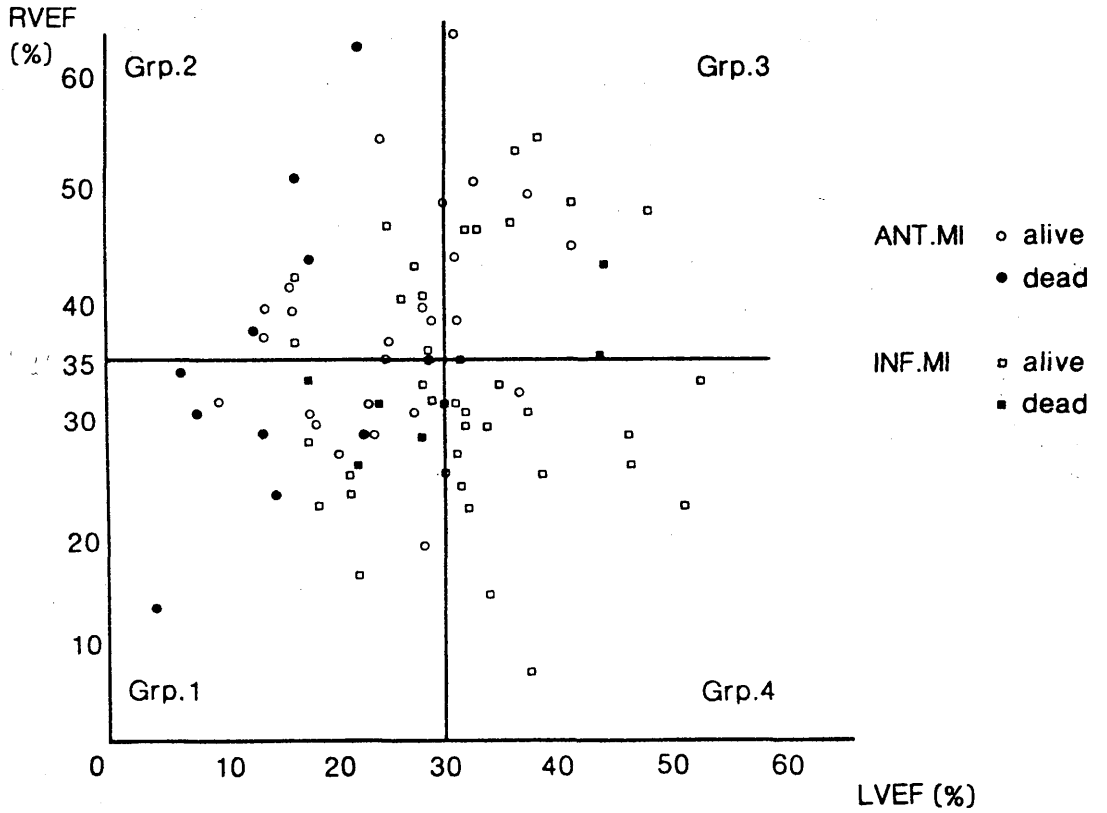

FIGURE 22. Effect of left and right ventricular dysfunction on cumulative mortality following myocardial infarction. RVEF = right ventricular ejection fraction; LVEF = left ventricular ejection fraction; ANT.MI = anterior myocardial infarction; INF.MI = inferior myocardial infarction. (see text for further details).

significantly lower in Group 4, chi-square statistic = 7.46, $p<0.01$, and chi-square statistic = 4.13, $p<0.05$ respectively.

There were no significant differences between patients with combined left and right ventricular dysfunction (Group 1) and patients in the other groups in terms of Norris Index (6.98 ± 2.43 versus 6.25 ± 2.90, p = NS); Killip Class (2.28 ± 1.06 versus 1.86 ± 1.09, p = NS); peak creatine kinase (2713 ± 1573 IU versus 2981 ± 3266 IU, p = NS) and perfusion index (28.95 ± 11.08% versus 24.55 ± 10.30%, p = NS).

6.7 DISCUSSION

Following anterior myocardial infarction no significant changes in the left ventricular ejection fraction were observed between the in-hospital estimations of the left ventricular ejection fraction and the follow-up estimations after sixteen months. Following inferior myocardial infarction there was a trend for the left ventricular ejection fraction to improve, 29.9 ± 9.5% on day 3 to 33.0 ± 9.4% at time of follow-up, $p<0.02$.

When patients were grouped according to the degree of underlying left ventricular ejection fraction there appeared to be an improvement in the left ventricular ejection fraction in the patients with severe depression of the left ventricular dysfunction (left ventricular

ejection fraction <25%). In the sixteen month period following hospital discharge these patients showed an increase in the left ventricular ejection fraction from 18.9 ± 3.1% to 22.7 ± 6.2%, $p<0.02$. Although there was an increase in the left ventricular ejection fraction following inferior and anterior myocardial infarction, the increase was only statistically significant in the former group. No significant changes in the left ventricular ejection fraction were seen in any of the other groups.

Previous work using non-invasive techniques have reported variable findings. Shelbert et al observed a slight but significant increase in the left ventricular ejection fraction in the twenty months following the index infarction (34). Others have found the increase in the left ventricular ejection fraction to be limited to certain sub-groups of patients. Dewhurst et al only found an improvement in those patients with segmental akinesis whilst those with normal wall motion, dyskinesis or hypokinesis in the region of the infarct did not (43). Borer et al found the left ventricular function improved only in those patients who attained a left ventricular ejection of >42% on exercise prior to hospital discharge (44). Reduto et al, however, found no difference in the left ventricular ejection fraction in the twelve months following myocardial infarction (35). However, this latter study only included patients who

fell into Killip classes I and II which may have influenced the results.

The short term reproducibility for the calculation of the ejection fraction was found to be good, see Chapter 2, confirming the findings of previous studies (34,35,135). There have been several published studies serially evaluating ventricular function using radionuclide ventriculography following myocardial infarction and although in some, short-term reproducibility is quoted, none have data relating to long-term reproducibility (33-35,43,44,47). There appears to be no published work addressing this issue; however, it is likely that the reproducibility would be similar to that observed during the short term as the biological variability of the ejection fraction probably relates to alterations in the preload and afterload (6).

Clinical studies using haemodynamic assessment of left ventricular function have also shown an improvement following acute myocardial infarction. Kupper et al reported an improvement in various haemodynamic parameters in patients with an abnormal pulmonary artery diastolic pressure during the acute phase (11). No change was found in patients with a normal pulmonary artery diastolic pressure. The findings in this haemodynamic study are similar to those presented in this thesis. The reason for improvement in patients with poorer ventricular function may relate to adaptive

mechanisms such as favourable changes in haemodynamics (11), an improvement in regional function (5), or possibly the introduction of drugs to treat clinical evidence of heart failure.

Little change was found in right ventricular function during the in-hospital phase in patients following either anterior or inferior myocardial infarction. However, in the sixteen months following the index infarction there was a difference in the natural history of right ventricular function between the patients with inferior and anterior myocardial infarction. In the former group there was no significant change in the right ventricular ejection fraction. However, in patients with anterior myocardial infarction significant there was a fall in the right ventricular ejection fraction during this period.

The reason for the difference in the natural history of right ventricular function between inferior and anterior myocardial infarction is not readily apparent. Possible hypotheses that could explain this difference may relate to poorer left ventricular function and/or to abnormal septal function in the patients with anterior myocardial infarction as discussed in Chapter 4.

Patients were also sub-divided on the basis of the degree of the underlying right ventricular dysfunction into those with severe right ventricular dysfunction, moderate right ventricular dysfunction and normal right

ventricular function. In patients with severe right ventricular dysfunction there was an improvement in the right ventricular function with the right ventricular ejection fraction increasing from 19.7 ± 6.4% to 27.9 ± 7.1%, $p<0.05$. This contrasted with patients with moderate right ventricular dysfunction where no change was observed, and the patients with normal right ventricular function at time of hospital discharge where there was a fall in the right ventricular ejection fraction during this period from 42.9 ± 6.7% to 35.0 ± 10.3%, $p<0.001$. Despite these changes in right ventricular function there were no significant accompanying changes in left ventricular function. In addition, there did not appear to be any significant differences between patients with anterior or inferior myocardial infarction in this subgroup of patients.

The reason for this difference in the natural history of right ventricular function following myocardial infarction remains an enigma. It may be related to differences in the underlying pathophysiological mechanisms involved. For example, severely depressed right ventricular function following myocardial infarction predominantly results from right ventricular infarction. It is possible that some of the mechanisms by which left ventricular function can improve following myocardial infarction (5) may also apply to the right ventricle resulting in enhanced right ventricular

performance. However, in patients with preserved right ventricular function during the in-hospital phase, the predominant influence on right ventricular performance appeared to be the effect of left ventricular performance; with the presence of left ventricular dysfunction leading to a progressive deterioration in right ventricular function in the subsequent sixteen months.

There is limited existing data relating the extent of right ventricular dysfunction to its subsequent course, and this predominantly relates to the first few weeks following infarction. Roderigues et al reported on a series of fifty patients with inferior myocardial infarction who were followed over an eight week period. It was found that patients with severe right ventricular dysfunction (right ventricular ejection fraction <25%) showed a fall in the right ventricular ejection fraction whilst the remaining patients showed an improvement in right ventricular performance (93). Other workers (91) have reported an improvement in the right ventricular ejection fraction in patients with a similar degree of right ventricular dysfunction following inferior myocardial infarction. However, in this latter study only patients with preserved left ventricular function were included. Starling et al reported an improvement in the right ventricular ejection fraction in patients who had haemodynamic evidence of right ventricular dysfunction following acute inferior myocardial infarction

but no change in patients without haemodynamic evidence of right ventricular dysfunction (133).

As was found during the in-hospital phase, variability in the left and right ventricular ejection fraction was not uncommon. No association was found between variability in the ejection fraction and the variables measured. One of the patients with an anterior myocardial infarction sustained an inferior myocardial infarction following hospital discharge which resulted in a fall in the left and right ventricular ejection fractions of 15% and 30% ejection fraction units respectively.

Alterations in medication during the follow-up period may have resulted in changes in the ejection fraction. There was a trend for a higher percentage of patients to be receiving beta adrenoreceptor antagonists, calcium-channel blocking agents and long-acting nitrate preparations, see Section 2.2. There were twenty seven patients whose medication had altered during this period. However, no obvious effect on either the right or left ventricular ejection in these patients when compared with patients whose medications were unaltered, see Table 12. Nevertheless, alterations in medication may have produced alteration in the ejection fraction, in either direction, in individual patients.

During the in-hospital phase of myocardial infarction no correlation was found between the right and

left ventricular ejection fractions in patients who had sustained an inferior myocardial infarction. However, by the time of the follow-up evaluation there was a weak but significant correlation between the left and right ventricular ejection fractions, $R_s = 0.44$, $p<0.01$. In patients who had sustained an anterior myocardial infarction a significant correlation was found between the right and left ventricular ejection fractions during the in-hospital phase and also at the time of follow-up. However, the relationship appeared to be at its strongest after sixteen months, with a correlation coefficient of 0.83 at that time as compared with 0.51 and 0.48 on day 1 and at time of hospital discharge, respectively.

The mechanism by which this relationship changes during the sixteen months following myocardial infarction probably relates to the changes observed in right ventricular function during this period of time. In the patients with predominantly right ventricular dysfunction there is an improvement in right ventricular performance whilst in patients with left ventricular dysfunction there is a progressive deterioration in right ventricular function. Both of these trends would result in a closer correlation between right and left ventricular function with time.

The presence of both right and left ventricular dysfunction in a patient following myocardial infarction was an adverse prognostic factor, resulting in a

cumulative mortality after 18 months of 40% as compared with 14% in the other groups, $p<0.01$. The existence of right ventricular dysfunction in the absence of severe or moderate left ventricular dysfunction was associated with a relatively benign prognosis with a mortality of 5% and as compared to a combined mortality of 27% in the other groups. Identification of these patients was not possible on the basis of clinical classification, i.e. Killip Class or Norris Index or the size of infarction as determined by either enzymatic means or size of perfusion defect.

The adverse prognostic significance of the combination of right and left ventricular dysfunction following acute myocardial infarction has also been observed by Shah et al (98). The importance of the functional status of the right ventricle has also been demonstrated to be important in patients with coronary artery disease and cardiac failure prognostically (123). In addition, right ventricular performance also affects the therapeutic response to vasodilator therapy (124,125) and the exercise capacity (126) in patients with heart failure.

6.8 CONCLUSIONS

The results presented in this chapter suggest that changes in ventricular function do occur in the sixteen

months following myocardial infarction. There is some improvement in left ventricular function, however these changes are small and are limited to certain sub-groups of patients. The natural history of right ventricular function is more variable and relates to the site of infarction and also the extent of right ventricular dysfunction. The relationship between right and left ventricular function changes during this period with a closer correlation existing between the right and left ejection fractions.

CHAPTER 7

ASSESSMENT OF REGIONAL VENTRICULAR FUNCTION FOLLOWING MYOCARDIAL INFARCTION

7.1 INTRODUCTION

The impact of myocardial infarction upon ventricular function is primarily a regional phenomenon of profound and immediate onset (1,2).

It is therefore not surprising that regional ventricular function has been shown to be important in determining the impact on global ventricular function and prognosis following myocardial infarction (9,36,53, 54).

The ability of global parameters to adequately characterize left ventricular function has been called into question, particularly in the setting of myocardial infarction. This results in an abnormality in ventricular function which is primarily regional, thus the effect of an area of akinesis in the zone of infarction may be masked by an area of hyperfunctioning myocardium outwith the infarct zone. There is the additional limitation when using global parameters, of susceptibility to changes in the prevailing loading conditions of the heart (6).

Particularly with the increasing use of interventional techniques in the management of acute myocardial infarction there is a requirement for the availability of a technique that can accurately assess left ventricular performance (136). This requires a method which can provide an accurate quantitative measurement of both regional and global ventricular function. Not only does this provide important prognostic information but can also be used to assess the efficacy of a particular intervention in preserving left ventricular function.

The generally accepted technique which is used as the "gold standard" against which other methods of assessing ventricular function are judged is contrast ventriculography. Qualitative assessment of regional ventricular function in routine clinical practice has been widespread. However, this has been shown to lack objectivity and reproducibility in the assessment of regional ventricular function (137-139). As a consequence, several methods have been developed to quantitatively assess regional ventricular function. These can be broadly classified into those techniques that use axii (140,141) or radii (142,143) and those that use endocardial wall motion (136,144).

Many of these techniques have been adapted and applied to radionuclide ventriculography (65,66,145). However, this has been criticised because these

techniques depend on the relatively high spatial resolution provided by contrast but not radionuclide ventriculography (63,64). This has in turn led to the development of techniques to assess regional ventricular function from radionuclide ventriculography which are relatively independent of geometry and do not require a high degree of spatial resolution (62-64).

The objective of this chapter is to describe the method used in this thesis by which regional left ventricular function was evaluated. This chapter describes the methodology, validation and application of the technique. In addition, other methods of assessing regional ventricular function are discussed.

7.2 METHODOLOGY

The methodology of the technique of radionuclide ventriculography has been previously described in Chapter 2. The method employed to assess regional left ventricular function is described below.

A stroke volume image was obtained by subtraction of the end-systolic from the end-diastolic frame. The end-systolic frame was defined as the frame at which the intraventricular activity was at a minimum and the end-diastolic the frame when it was at a maximum. This image was interpolated from a 64 by 64 to a 128 by 128 matrix. A regional ejection fraction image was then produced by

dividing the stroke volume image on a pixel by pixel basis (63) which was then normalised to 100%. A schematic diagram of a normal regional ejection fraction image is illustrated in Figure 23. A crescent of activity forming a left ventricular shell with an inner core is seen in the presence of normal regional ventricular function with an adjacent area of activity originating from the right ventricle. Figure 24 shows a schematic diagram of a regional ejection fraction image from a patient who has sustained a large anterior and apical myocardial infarction. No activity, representing akinesis, is noted in the region of infarction. There is an area of reduced activity at the lateral edge of the infarct area indicating hypokinesis.

The regional ejection fraction image was analysed quantitatively by dividing the image into 12 equal sectors in the following manner. A long axis was drawn from the left ventricular apex to the bisection of the aortic valve plane and the image was then rotated until the long axis was vertical. A region of interest was drawn around the outside of the regional ejection fraction image. The position of this region of interest was confirmed by superimposition of the region on the end-diastolic frame from the representative cardiac cycle. Following this the region of interest was divided into twelve 30 degree sectors from a point that bisected the long axis of the left ventricle. The value in each

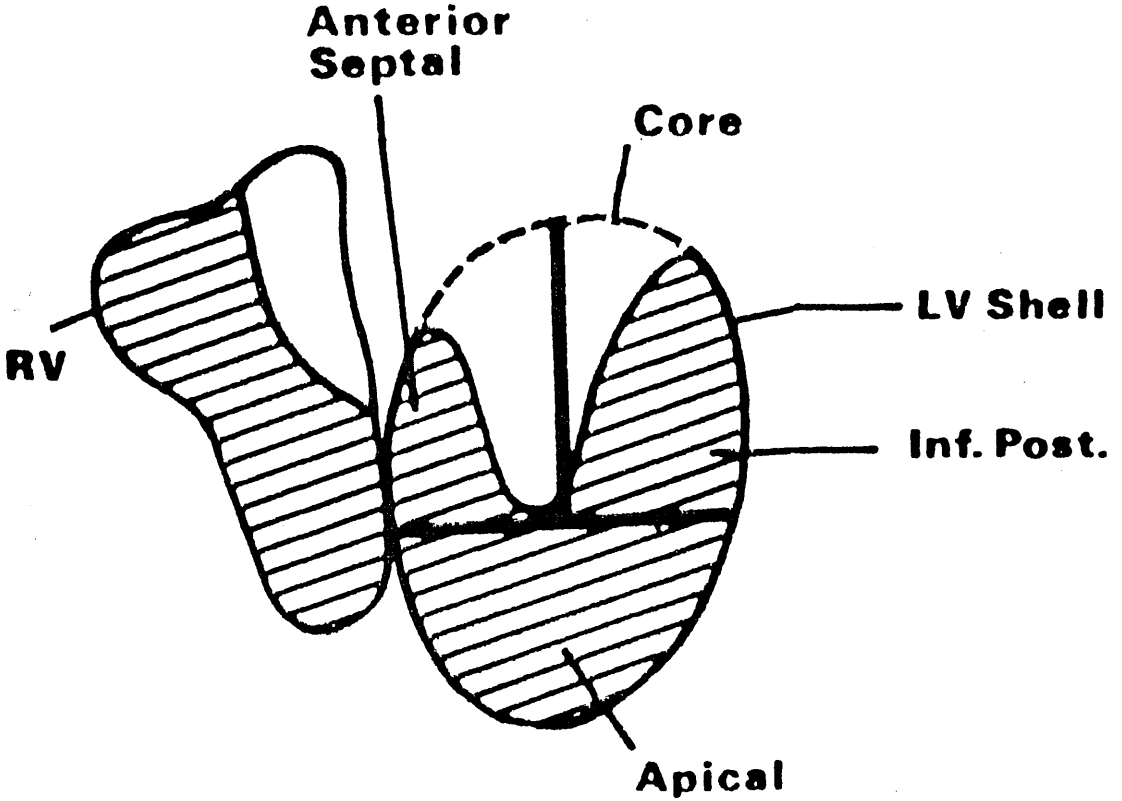

FIGURE 23. Schematic diagram of a normal regional ejection fraction image. Illustrates crescent of activity produced by the left ventricle - left ventricular (LV) shell; Inf. Post. = inferior posterior; RV = right ventricle.

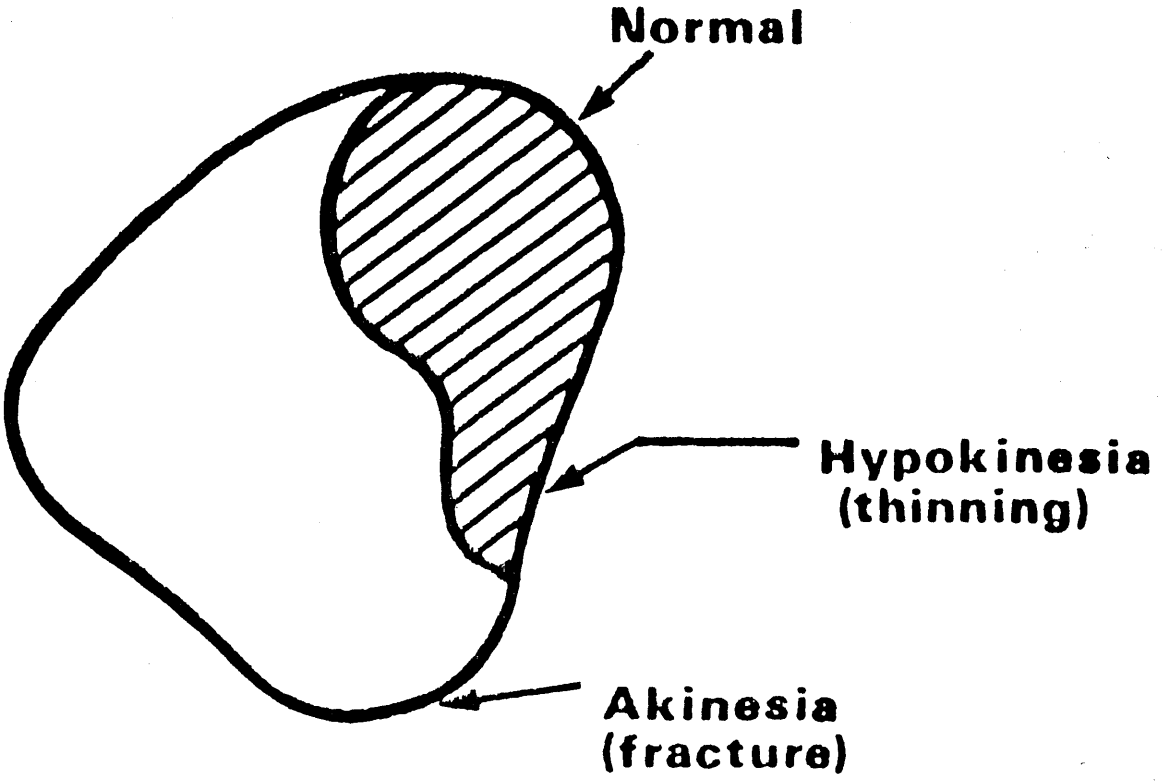

FIGURE 24. Schematic diagram of an abnormal regional ejection fraction image from a patient with a large anterior myocardial infarction. Absent activity is found in the antero-septal and apical regions, indicating akinesis, with reduced activity + thinning laterally indicating hypokinesis.

sector was expressed as a percentage of the total image.

Normal values for each sector were obtained from the 10 patients that served as normal controls for the global parameters of ventricular function (Chapter 2). These values, along with the patients with myocardial infarction, excluding those with a history of previous myocardial infarction, were analysed. The values from the data acquisitions from the patients with myocardial infarction were grouped together and used for comparison with the normal values. The intra-observer variation was determined from repeat analysis of the data on three separate occasions. The reproducibility of the technique was obtained from repeat data acquisitions from five patients with 30 - 60 minutes between data acquisitions. The five patients which made up this group all had coronary artery disease documented by arteriography. All had resting regional wall motion abnormalities evident both on cine display of the representative cardiac cycle and the regional ejection fraction image. The left ventricular ejection fraction ranged from 23-42% with a mean value of 31.5 ± 8.3%.

7.3 RESULTS

The normal values (mean ± standard deviation) for each of the twelve sectors are shown in Table 14. Sectors X, Y, Z, O and P correspond to the septal region;

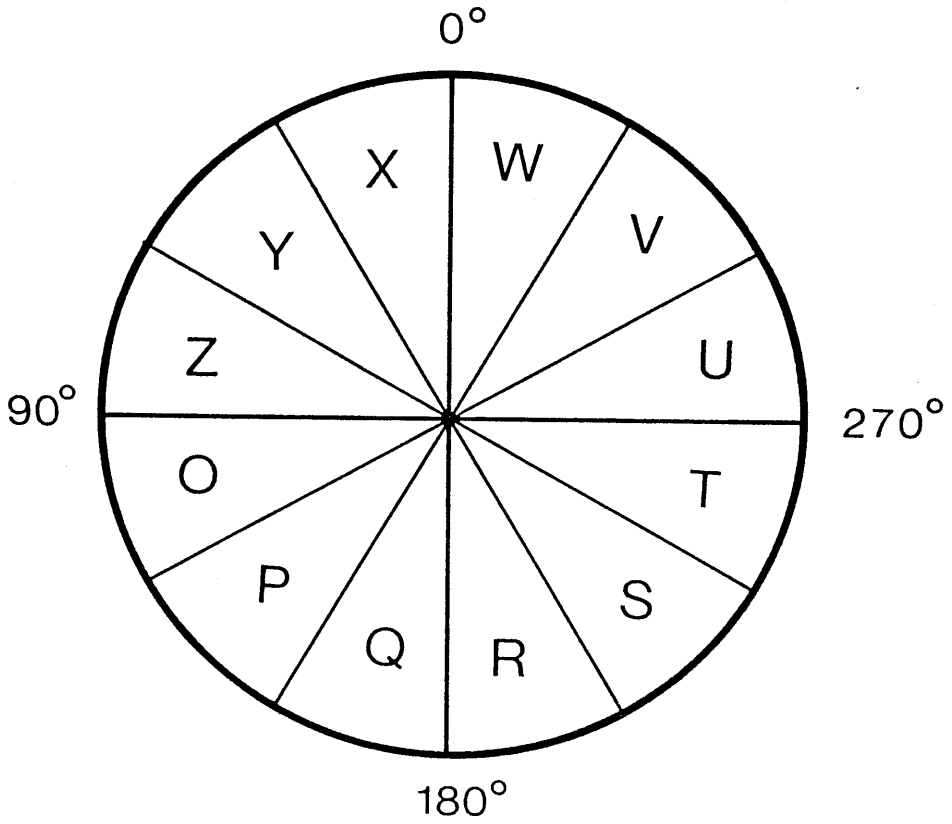

FIGURE 25. Anatomic location of sectors used in the analysis of the regional ejection fraction image. Sectors X–P correspond to the anterior and septal region; Q, R and S correspond to the apical region; and T–W correspond to the posterior and lateral regions of the left ventricle.

SECTOR	DEGREES	NORMALS	ANTERIOR MI	SIGNIFICANCE (p)	INFERIOR MI	SIGNIFICANCE (p)
X	0 - 30	5.7(0.6)	4.0(2.1)	0.005	7.0(2.5)	N.S.
Y	31 - 60	7.1(0.5)	4.3(2.5)	0.005	7.6(2.5)	N.S.
Z	61 - 90	8.4(1.0)	5.5(2.3)	0.001	8.5(2.6)	N.S.
O	91 - 120	9.3(0.6)	6.5(2.8)	0.002	8.8(3.1)	N.S.
P	121 - 150	9.6(0.7)	6.9(3.4)	0.02	8.6(2.7)	N.S.
Q	151 - 180	9.8(0.5)	7.2(3.6)	0.05	7.6(2.8)	0.02
R	181 - 210	9.8(0.6)	8.8(3.2)	N.S.	6.9(2.8)	0.001
S	211 - 240	9.7(0.3)	11.4(3.5)	0.9	7.2(3.4)	0.02
T	241 - 270	9.3(0.9)	12.6(4.4)	0.02	8.0(3.3)	N.S.
U	271 - 300	8.4(1.2)	11.7(3.7)	0.01	8.8(2.6)	N.S.
V	301 - 330	6.9(0.6)	9.5(3.3)	0.01	8.1(2.5)	N.S.
W	331 - 360	5.7(0.2)	5.9(2.3)	N.S.	7.4(1.9)	0.005

TABLE 14

Sector values (mean +/- standard deviation) in normals and patients with myocardial infarction (MI); see text for details.

sectors Q, R and S correspond to the apex; and sectors T, U, V and W corresponded to the lateral wall of the left ventricle, Figure 25.

There were inter-sector variations in the contribution to the total left ventricular output. The highest contributions were found in sectors Q, R, S in the apical region of the left ventricle contributing 9.8%, 9.8% and 9.7% respectively to the total left ventricular output. Moving from the apex to the base of the left ventricle there was a decrease in the contribution from each sector, Table 14.

Figure 26 is a normal regional ejection fraction image displaying a normal left ventricular crescent of activity to compare with Figures 27 and 28. Figure 27 shows images from a patient following an extensive anterior and apical myocardial infarction. The top left and right panels are the end-diastolic and endsystolic frames respectively. The lower panel shows the corresponding regional ejection fraction image, similar to the schematic diagram seen in Figure 24. Figure 28 shows a regional ejection fraction image of a patient who has sustained a large infero-lateral myocardial infarction. The left ventricular region of interest has been drawn in red, the centre of region of interest is marked in green, and the whole image is rotated to bring the valve plane to be at twelve o'clock. The values are seen in each corresponding sector; values are expressed

SECTOR	DEGREES	INTRAOBSERVER VARIATION (EF units %)	REPEATABILITY (EF units %)
X	0- 30	0.09 ± 0.10	0.33 ± 0.21
Y	31- 60	0.12 ± 0.10	0.27 ± 0.12
Z	61- 90	0.11 ± 0.10	0.55 ± 0.24
O	91-120	0.15 ± 0.16	0.54 ± 0.20
P	121-150	0.14 ± 0.14	0.42 ± 0.57
Q	151-180	0.16 ± 0.15	0.55 ± 0.28
R	181-210	0.16 ± 0.15	0.45 ± 0.39
S	211-240	0.16 ± 0.17	0.39 ± 0.46
T	241-270	0.14 ± 0.11	0.62 ± 0.42
U	271-300	0.08 ± 0.08	0.27 ± 0.18
V	301-330	0.10 ± 0.09	0.33 ± 0.30
W	331-360	0.09 ± 0.07	0.59 ± 0.51
Mean		0.12	0.44
SD		±0.03	0.32

TABLE 15

Reproducibility of quantitative analysis of the regional ejection fraction image.

Values are expressed as the mean difference ± the standard deviation (ejection fraction (EF) units %) between the two evaluations. A mean value and standard deviation (SD) is quoted at the bottom of both columns; (see text for further details).

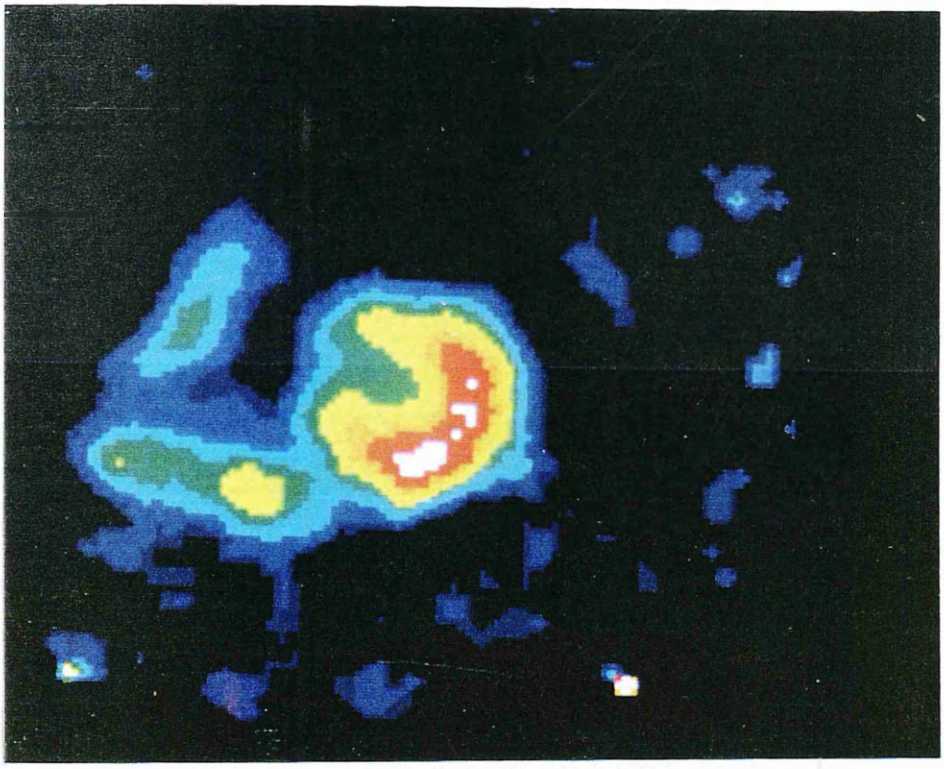

FIGURE 26. Regional ejection fraction image from a patient with normal ventricular function. Differences in colour represent differences in the regional ejection fraction; with the areas with the highest regional ejection fraction being white or red, and areas with the lowest regional ejection fraction being blue and intermediate values coded in yellow and green (compare with Figure 27).

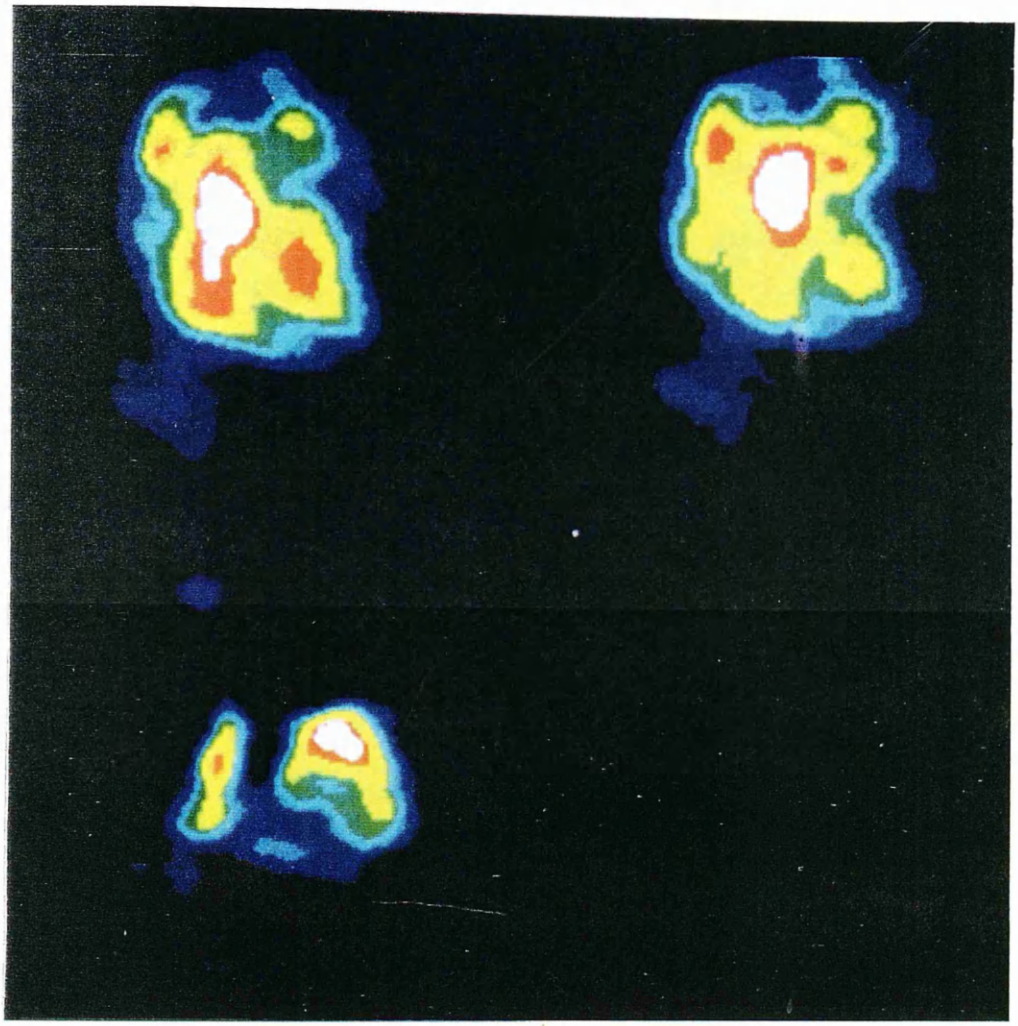

FIGURE 27. Corresponding images from a patient following extensive anterior myocardial infarction. Top left panel shows the end-diastolic frame and top right the end-systolic frame with the regional ejection fraction image in the lower left panel.

Following anterior myocardial infarction there was a significant reduction in comparison with normals in the percentage contribution from sector X through to sector Q, 5.7 ± 0.6 vs 4.0 ± 2.1% for sector X, $p<0.005$, 7.1 ± 0.5 vs 4.3 ± 2.5% for sector Y, $p<0.005$, 8.4 ± 1.0 vs 5.5 ± 2.3% for sector Z, $p<0.001$, 9.3 ± 0.6 vs 6.5 ± 2.8% for sector O, $p<0.002$, 9.6 ± 0.7 vs 6.9 ± 3.4% for sector P, $p<0.02$ and 9.8 ± 0.5 vs 7.2 ± 3.6% for sector Q, $p<0.05$ for normal and anterior myocardial infarction respectively, Table 14.

Following inferior myocardial infarction there were significant reductions in the percentage contributions from sectors Q, R and S in comparison with normals; namely, 7.6 ± 2.8% vs 9.8 ± 0.50% in sector Q, $p<0.02$; 6.9 ± 2.8% vs 9.8 ± 0.6% in sector R, $p<0.001$; and 7.2 ± 3.4% vs 9.7 ± 0.3% in sector S, $p<0.02$, respectively.

In addition to reductions in the contribution from infarcted regions there were relative increases in the contributions from the sectors not involved in the infarction. Following anterior myocardial infarction there was an increase in the relative contribution from the lateral wall of the left ventricle, sectors S through to V. The contribution from sector S increased from 9.7 ± 0.3% to 11.4 ± 3.5%,$p<0.01$; sector T from 9.3 ± 0.9% to 12.6 ± 4.4%, $p<0.02$; sector U from 8.4 ± 1.2% to 11.7 ± 3.7%, $p<0.01$; and sector V from 6.9 ± 0.6% to 9.5 ± 3.3%, $p<0.01$. Following inferior myocardial infarction only

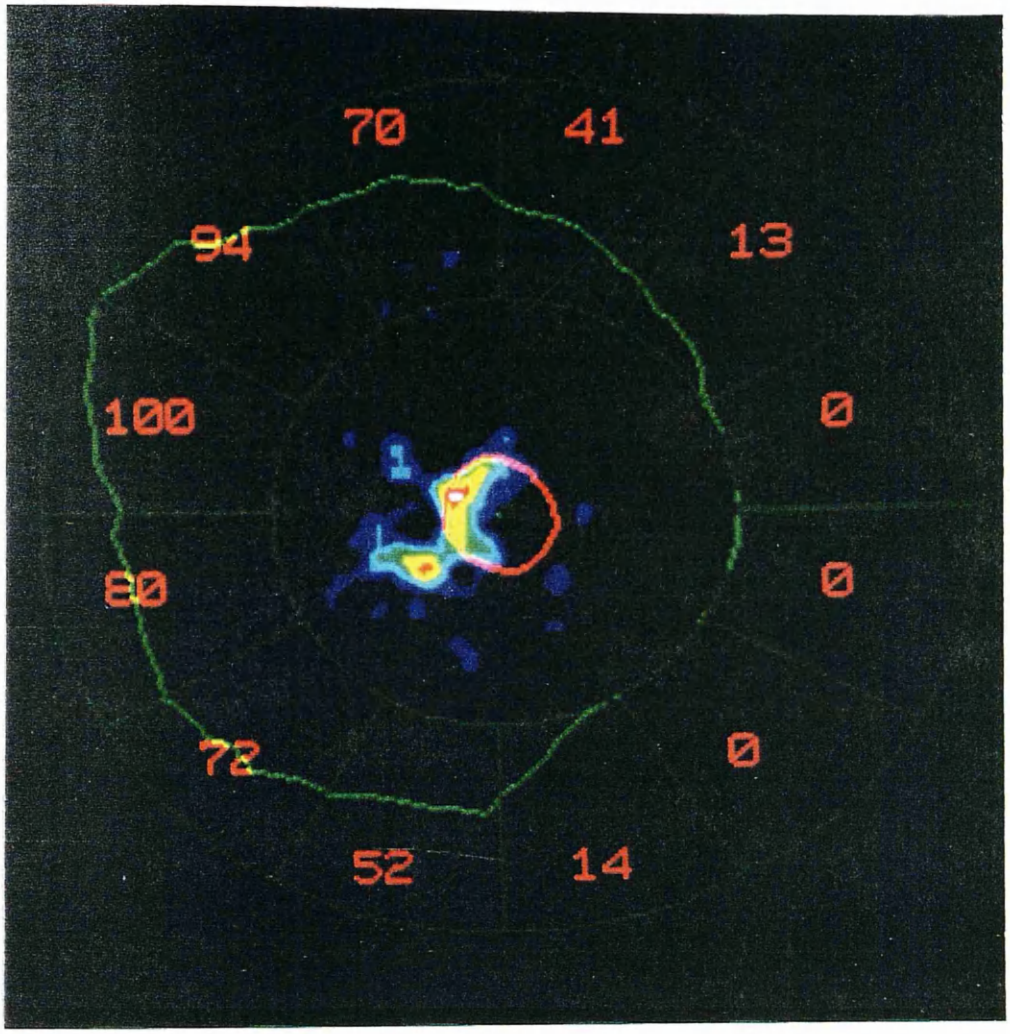

FIGURE 28. Quantitative analysis of a regional ejection fraction image from a patient following extensive infero-lateral myocardial infarction. A region of interest is drawn around the left ventricle (in red).

one sector showed a significant increase in its contribution. Sector W increased its contribution from 5.7 ± 0.2% to 7.4 ± 1.9%, $p<0.005$.

The intra-observer variation was calculated from repeat analysis of data from the ten normal patients and ten of the infarct patients selected at random. Values are expressed as a difference, 0.08 to 0.16%, mean 0.12 ± 0.03. The reproducibility from repeat acquisition of data resulted in a mean difference of 0.44 ± 0.32% (range 0.27-0.62), Table 15.

7.4 DISCUSSION

Assessment of regional ventricular function from qualitative visual analysis of contrast ventriculograms has been shown to lack objectivity and reproducibility (137-139). This has resulted in the development of quantitative methods. The existence of the large number of available techniques is a testament to the many inherent difficulties in quantifying regional ventricular function.

Some methods have utilised hemi-axii evenly spaced along the long axis of the left ventricle between the aortic valve plane and the apex (140,141). These methods have been criticised because of the assumption that shortening along the long axis is homogeneous, which it is not during myocardial ischaemia (18,146). The use of

radii to measure the extent of wall motion has also been used (142,143) however, the assumption that motion proceeds to a single point may be invalid (143,147,148). Additional criticism of the above approaches is that many of the methods require location of the left ventricular apex which has been shown to be the most difficult landmark of the endocardial outline to locate (149,150).

The centerline method is another method which has been developed which obviates many of these problems. This method employs 100 chords constructed perpendicular to centerline drawn midway between the end-diastolic and end-systolic contours and normalised for heart size (136). Although it does overcome many of the problems encountered with other techniques it still does not correct for translational movement of the heart within the thorax.

Slager et al developed a technique for assessing ventricular wall motion by tracking the path of endocardial landmarks during the cardiac cycle using contrast ventriculography (144). This technique was validated using an animal model and has been subsequently successfully applied to clinical studies of regional ventricular function (121). This technique provides a quantitative method of analysis which is similar to the subjective assessment of the contrast ventriculogram. However, this technique requires the identification of endocardial landmarks which may prove difficult in the presence of

extensive endocardial scarring which can occur following myocardial infarction. An additional limitation is that this technique can only be applied to contrast ventriculography, which restricts its use in clinical practice.

Many of the above techniques have been applied to radionuclide ventriculography (65,66,145,151). However, these techniques rely upon high spatial resolution which is provided by contrast ventriculography.

Radionuclide ventriculography does not afford a high degree of resolution and therefore the application of these techniques is limited by the spatial resolution of the image and by the constraints of two-dimensional imaging. However, it does have the advantage over contrast ventriculography of being relatively independent of geometry. To take advantage of this techniques have been developed to evaluate regional ventricular function which depend on change of counts in a particular left ventricular region rather than attempting to measure the extent of wall motion (62-64).

Schad evaluated regional ventricular performance using a regional stroke volume image by subtracting the end-systolic frame from the end-diastolic frame, thereby providing a representative image of the regional change in ventricular volume (62). Later, Maddox et al qualitatively assessed regional ventricular performance by producing an ejection fraction image which was

produced by dividing the stroke volume image by the background corrected end-diastolic frame. The technique was found to have an excellent correlation with contrast ventriculography, greater accuracy than the stroke volume image and to have good reproducibility and repeatability (63).

This was subsequently developed to provide quantitation of regional ventricular function by creating ejection fractions for each region of the left ventricle (64). The regional ejection fraction therefore, allowed quantitation of regional ventricular function which was not limited by spatial resolution and edge definition. The relative independence from geometry allows left ventricular activity to be assessed in three dimensions and does not require assumptions to be made about left ventricular shape. This technique was found to provide an accurate, sensitive and reproducible means of assessing regional ventricular performance.

Fourier phase analysis has been applied to radionuclide ventriculograms for quantitative analysis of regional ventricular function (152-156). Phase analysis consists of mathematically fitting sine and cosine waves to time-activity curves generated for each pixel over time. The data can be presented in three ways: phase and amplitude images, phase histograms, and a continuous cine-loop display. These can be used to objectively evaluate regional ventricular function. However, there

are reservations concerning the sensitivity, particularly in serial analysis, of this technique in the assessment of regional ventricular function (156).

The technique used in this thesis provided a quantitative evaluation of regional ventricular performance using a computer-assisted analysis of the regional ejection fraction, providing an index of the relative contribution of each particular region to the total left ventricular output. Therefore, regional performance is expressed as a percentage of the total output of the left ventricle rather than in absolute terms as originally described by Maddox et al (64). It was decided to express the performance of a particular region in relative terms, ie. as a percentage of the total left ventricular output, to allow serial changes in regional ventricular function to be viewed independent of the prevailing loading conditions. There was concern that the use of an absolute value for the regional ejection fraction may also be liable to change from alterations in preload or afterload.

From the data obtained from the normal patients it is apparent that there is difference between the sectors in the relative contributions to the total left ventricular output. The highest contributions came from the sectors at the apex of the left ventricle, sectors Q, R, and S which contributed 9.8 ± 0.5%, 9.8 ± 0.6% and 9.7 ± 0.3% respectively. The relative contribution of the

sectors decreased for the apex towards the base of the heart. A similar pattern was found by other workers using the regional ejection fraction image (64).

Anterior myocardial infarction resulted in significant reductions in the contributions from five septal (X, Y, Z, O, P) and one of the apical sectors (Q). The most significant reductions were seen the two apical-septal sectors Z and O contributing 5.5 ± 2.3% and 6.5 ± 0.6% versus 8.4 ± 1.0% and 9.3 ± 0.6% when compared with normal patients, $p<0.001$ and $p<0.002$ respectively.

A significant decrease in the contributions from two apical sectors, P and Q was also identified, 6.9 ± 3.4% and 7.2 ± 3.6% versus 9.6 ± 0.7% and 9.8 ± 0.5% in normals, $p<0.02$ and $p<0.05$ respectively. The involvement of this region following anterior myocardial infarction is possibly a reflection of topographical changes which commonly involve the left ventricular apex. The left ventricular apex is particularly prone to topographic change because of reduced myocardial thickness and lack of supporting structures in this region (9).

Significant increases in the contribution from the lateral left ventricular wall (sectors S-V) were noted following anterior myocardial infarction. This was anticipated as this technique provides a relative and not an absolute index of regional ventricular performance.

Following inferior myocardial infarction there were significant reductions in the contributions from the

three apical sectors: Q, 7.6 ± 2 .8%; R, 6.9 ± 2.8%; S, 7.2 ± 3.4%; when compared with normals; 9.8 ± 0.5%, 9.8 ± 0.6%, 9.7 ± 0.3%, $p<0.02$, $p<0.001$ and $p<0.02$, respectively. There was no evidence of ventricular dysfunction in any other regions. One basal-lateral sector (W) showed an increase in its contribution, 7.4 ± 1.95 versus 5.7 ± 0.2%, $p<0.005$.

Although this technique does provide a computer-assisted means of quantitative assessment of the relative performance of regional ventricular performance it does have limitations. It does not provide an absolute index of regional ventricular performance and therefore it will not allow discrimination as to whether the contribution of a particular region is changing because of intrinsic changes in the performance of that region or because of change in another region. The ventricle was sub-divided into 12 equal sized sectors. This number is a compromise. A larger number of sectors may have optimised evaluation of regional ventricular function (157). However, it was felt the 12 sectors used would represent a significant improvement on three zones as used by some (53,54) without running into problems of data management and statistical analysis that would occur with a larger number of sectors with the limited resources available. The division of the left ventricle into sectors requires selection of a central point within the left ventricle, in this instance the mid-point of the

long axis connecting the mid-point of the aortic valve plane and the left ventricular apex. The limited spatial resolution of the technique has already been discussed as has the difficulties in locating the left ventricular apex. The latter is particularly pertinent when considering serial analysis of regional ventricular performance following myocardial infarction where changes in anatomical reference points due to alterations in left ventricular topography occur (158).

7.5 CONCLUSIONS

Despite the limitations mentioned above, this technique allowed a reproducible and quantitative method for the serial assessment of the relative contributions from different regions of the left ventricle. Therefore, this technique allows the identification of changes in regional ventricular performance occurring after myocardial infarction and also the determination of the relationship that exists between changes in regional and global ventricular function. In the subsequent chapter this technique is applied to the serial evaluation of regional ventricular function following myocardial infarction.

CHAPTER 8

THE RELATIONSHIP BETWEEN THE LEFT VENTRICULAR EJECTION FRACTION AND REGIONAL VENTRICULAR FUNCTION

8.1 INTRODUCTION

It was demonstrated in earlier chapters that although there was little variation in the left ventricular ejection fraction when patients were grouped according to site of infarction there was significant variability in the ejection fraction when patients were evaluated either as individuals or grouped according to the degree of left ventricular dysfunction. Variability in the left ventricular ejection fraction did not appear to have any bearing on the clinical status, prognosis or other demographic variables.

The underlying aetiology of these changes in the left ventricular ejection fraction are not known. They may result from changes in regional ventricular function or from changes in the prevailing loading conditions on the heart. Understanding the underlying pathophysiological mechanisms involved in these changes might be important as the left ventricular ejection fraction is currently a widely used parameter not only in the characterisation of patients following myocardial infarction but also in assessment of the efficacy of

interventions used in the management of acute myocardial infarction (118-123).

The aim of this chapter is to apply the technique described in the previous chapter to serial data obtained from the patients following myocardial infarction. It was anticipated that this technique would help identify the mechanism(s) that underlying the changes in the left ventricular ejection fraction. In addition, it may also provide an insight to the natural history of regional left ventricular function in the sixteen months following myocardial infarction.

8.2 REGIONAL VENTRICULAR FUNCTION FOLLOWING ANTERIOR MYOCARDIAL INFARCTION

During the in-hospital phase following anterior myocardial infarction there were no significant changes in the relative contributions from either the infarcted or non-infarcted regions of the left ventricle, Table 16. Similarly, there were no significant changes in the global left ventricular ejection fraction during this period.

In the sixteen months following hospital discharge there were increases in the relative contributions from two of the twelve left ventricular sectors. The contribution from sector X (the most basal septal sector) increasing from 3.30 ± 1.64% to 4.58 ± 1.45%, $p = 0.026$.

SECTOR	DEGREES	LVEF1-2 (n = 18)	LVEF2-3 (n = 24)	LVEF3-4 (n = 22)
X	0 - 30	4.92(1.11) - 4.11(0.93)	4.19(2.29) - 3.67(1.64)	3.30(1.64) - 4.58(1.45)**(1)**
Y	31 - 60	4.46(1.29) - 5.11(2.18)	5.34(2.42) - 4.85(3.46)	4.08(1.87) - 4.17(1.35)
Z	61 - 90	5.44(1.67) - 5.76(2.11)	5.99(2.22) - 6.36(3.18)	5.79(1.86) - 5.34(1.60)
O	91 - 120	6.84(3.47) - 6.40(2.03)	7.69(3.14) - 7.30(2.72)	6.73(2.29) - 6.71(2.57)
P	121 - 150	7.44(2.44) - 6.47(2.65)	7.97(3.72) - 8.35(4.02)	7.75(3.50) - 7.71(3.36)
Q	151 - 180	7.07(3.54) - 7.35(3.14)	8.13(3.62) - 8.95(4.16)	8.45(3.40) - 8.55(3.23)
R	181 - 210	8.62(3.29) - 8.88(4.11)	8.81(4.11) - 10.55(2.86)	10.43(2.16) - 9.75(2.82)
S	211 - 240	11.88(2.95) - 11.93(2.87)	11.58(3.36) - 11.56(4.01)	13.10(2.63) - 12.52(2.67)
T	241 - 270	13.34(2.69) - 13.63(3.06)	12.97(4.72) - 12.69(4.10)	13.43(3.04) - 13.25(3.74)
U	271 - 300	11.48(2.72) - 13.45(3.05)	12.28(4.38) - 11.52(4.17)	11.98(3.28) - 11.04(2.97)
V	301 - 330	10.98(3.26) - 10.80(2.65)	9.69(4.40) - 8.67(2.30)	9.18(2.64) - 9.53(2.96)
W	331 - 360	7.26(1.81) - 6.27(1.97)	5.42(2.38) - 5.51(1.38)	5.80(2.18) - 6.91(2.25)**(2)**

(1) p = 0.026
(2) p = 0.034

TABLE 16

Changes in regional ventricular function following anterior myocardial infarction

LVEF1-2 = change in the left ventricular ejection fraction (LVEF) between day 1 and 3
LVEF2-3 = change in LVEF between day 3 and hospital discharge
LVEF3-4 = change in LVEF between hospital discharge and follow-up.

All values are expressed as a mean (standard deviation) in per cent (see text for further details).

Sector W (the most basal lateral sector) also increased from 5.80 ± 2.18% to 6.91 ± 2.25%, p = 0.034. There was no significant change in the global left ventricular ejection fraction during this period, 23.5 ± 8.7% and 26.1 ± 9.8%, p = NS.

No significant changes were identified in regional left ventricular function when patients were sub-divided according to the severity of the depression of the left ventricular ejection fraction during the 16 months following anterior myocardial infarction.

8.3 REGIONAL VENTRICULAR FUNCTION FOLLOWING INFERIOR MYOCARDIAL INFARCTION

Following inferior myocardial infarction changes in the relative contributions were observed during both the in-hospital and out of hospital phases, Table 17. During the in-hospital period there was a decrease in the contribution from sector Q in the apical region; decreasing from 8.80 ± 2.38 to 7.24 ± 2.76%, p = 0.027 between day 1 and 3. During this same period there was a slight fall in the left ventricular ejection fraction from 31.0 ± 8.4 to 29.9 ± 9.5%, $p<0.05$. Between day 3 and hospital discharge there were further alterations in regional contributions. There was a decrease in the contribution from two septal sectors; sector X and Y decreased from 8.54 ± 2.49 and 9.04 ± 2.68 to 6.92 ± 2.81

SECTOR	DEGREES	LVEF1-2 (n = 27)	LVEF2-3 (n = 29)	LVEF3-4 (n = 31)
X	0 - 30	7.49(2.24) - 8.54(2.36)	8.54(2.49) - 6.92(2.81)**(2)**	7.72(2.16) - 7.04(1.87)
Y	31 - 60	8.42(2.13) - 8.88(2.67)	9.04(2.68) - 7.95(2.70)**(3)**	8.14(2.40) - 7.97(1.89)
Z	61 - 90	9.13(3.20) - 9.18(2.70)	8.89(3.17) - 8.85(3.07)	9.14(2.91) - 9.19(1.53)
O	91 - 120	9.64(3.96) - 9.23(3.32)	9.31(4.08) - 9.00(2.87)	9.88(3.71) - 9.86(2.18)
P	121 - 150	9.21(2.88) - 9.15(3.29)	8.67(3.80) - 8.38(2.87)	9.59(2.59) - 9.27(2.23)
Q	151 - 180	8.80(2.38) - 7.24(2.76)**(1)**	7.33(2.63) - 7.60(3.13)	9.00(2.35) - 7.76(2.44)**(6)**
R	181 - 210	7.36(2.76) - 6.82(2.53)	6.65(3.02) - 7.08(3.41)	7.61(2.78) - 7.00(2.51)
S	211 - 240	7.67(3.21) - 7.41(3.24)	6.95(4.03) - 7.56(3.30)	7.09(3.06) - 7.77(2.63)
T	241 - 270	8.42(3.67) - 7.95(3.41)	7.67(3.97) - 9.16(3.42)**(4)**	7.79(3.47) - 8.96(2.35)
U	271 - 300	8.18(2.88) - 9.00(2.68)	9.46(3.42) - 10.46(2.78)**(5)**	7.92(2.64) - 9.53(1.99)**(7)**
V	301 - 330	8.12(1.79) - 8.34(2.53)	8.49(4.07) - 9.24(2.97)	8.25(1.70) - 8.38(2.07)
W	331 - 360	7.57(1.35) - 8.19(1.71)	8.71(2.85) - 7.76(2.01)	7.97(1.79) - 7.25(1.53)

(1) p = 0.027
(2) p = 0.015
(3) p = 0.009
(4) p = 0.024
(5) p = 0.022
(6) p = 0.001
(7) p = 0.01

TABLE 17

Changes in regional ventricular function following inferior myocardial infarction.

All values are expressed as a mean (standard deviation) in per cent (see text for further details).

LVEF1-2 = change in the left ventricular ejection fraction (LVEF) between day 1 and 3
LVEF2-3 = change in LVEF between day 3 and hospital discharge
LVEF3-4 = change in LVEF between hospital discharge and follow-up.

and 7.95 ± 2.70, p = 0.015 and p = 0.009 respectively. This was associated with an increase in the contribution from two of the sectors in the lateral wall. Sector T and U increased from 7.67 ± 3.97 and 9.46 ± 3.42 to 9.16 ± 3.42 and 10.46 ± 2.78, p = 0.024 and p = 0.022 respectively.

Following hospital discharge there was a further decrease in the contribution from sector Q, 9.00 ± 2.35% to 7.76 ± 2.44%, p = 0.001. During this period there was an increase in the contribution from sector U, located in the lateral wall which increased from 7.92 ± 2.64 to 9.53 ± 1.99, p = 0.01, Table 17. A small statistically significant increase in the global left ventricular ejection fraction was noted between day 3 and the follow-up visit following inferior myocardial infarction, 29.9 ± 9.55 on day 3 to 33.0 ± 9.0%, $p<0.02$.

Significant changes in the left ventricular ejection fraction occurred both during the in-hospital and the follow-up period following inferior myocardial infarction in patients with severely depressed left ventricular function. The left ventricular ejection fraction increased from 16.6 ± 4.6% to 23.4 ± 7.0% between day 3 and hospital discharge, $p<0.05$ and from 18.9 ± 3.1% to 22.7% ± 6.2% between hospital discharge and the follow-up visit, $p<0.02$. There were no significant alterations in regional ventricular function associated with these changes.

8.4 RELATIONSHIP BETWEEN REGIONAL VENTRICULAR PERFORMANCE AND CHANGES IN THE LEFT VENTRICULAR EJECTION FRACTION IN INDIVIDUAL PATIENTS

In individuals, it was observed in Chapter 3 that variation in the left ventricular ejection fraction occurred not uncommonly; in addition these changes were at times quite large. However, no significant changes were identified in the relative contributions from any of the left ventricular regions to account for this, Tables 18-20.

8.5 DISCUSSION

These results indicate that changes in the left ventricular ejection fraction often occur without identifiable alteration in regional ventricular function. In addition, the converse was also observed, namely, that changes in regional left ventricular function can occur without any change being reflected in the left ventricular ejection fraction.

There were no significant changes identified in either regional or global ventricular function during the in-hospital phase of anterior myocardial infarction. In the subsequent 16 months there were significant increases in the relative contributions from the basal aspects of the left ventricle which were not associated

SECTOR	DEGREES	LVEF ≥ 5% (n = 6)	LVEF ≤ -5% (n = 15)	-5% < LVEF < 5% (n = 23)
X	0 - 30	6.82(2.24) - 7.14(3.33)	6.28(2.01) - 6.19(1.92)	6.67(3.0) - 7.41(3.58)
Y	31 - 60	7.32(2.55) - 8.26(2.26)	5.88(1.70) - 6.78(1.93)	7.21(3.56) - 7.32(4.25)
Z	61 - 90	7.09(2.80) - 8.86(3.39)	7.04(2.80) - 6.91(3.09)	7.93(4.46) - 8.32(4.01)
O	91 - 120	10.08(4.24) - 9.05(3.04)	6.88(3.11) - 6.77(2.75)	8.60(4.76) - 7.68(3.88)
P	121 - 150	7.85(3.86) - 9.35(1.57)	7.37(2.96) - 6.59(3.21)	7.75(3.87) - 7.36(4.17)
Q	151 - 180	7.04(4.95) - 6.51(2.26)	8.11(3.40) - 7.10(2.81)	6.89(2.80) - 6.29(3.38)
R	181 - 210	5.85(3.70) - 5.04(2.71)	8.28(3.11) - 7.96(3.12)	6.38(3.16) - 6.51(3.37)
S	211 - 240	8.95(4.43) - 7.88(1.81)	9.65(3.26) - 8.99(4.30)	8.33(3.84) - 7.98(4.33)
T	241 - 270	10.20(6.31) - 10.66(4.89)	11.32(4.22) - 10.27(2.95)	11.19(5.48) - 10.52(5.15)
U	271 - 300	9.35(3.80) - 10.64(4.66)	11.26(4.11) - 12.20(5.14)	11.33(6.72) - 11.82(5.56)
V	301 - 330	11.50(3.70) - 8.55(1.76)**(1)**	9.95(4.44) - 11.26(6.92)	9.92(4.51) - 10.42(4.72)
W	331 - 360	8.38(2.16) - 8.02(2.36)	7.82(2.23) - 8.95(4.20)	7.81(2.00) - 8.36(2.40)

(1) p = 0.07

TABLE 18

Relationship between change in left ventricular ejection fraction (Δ LVEF) and alteration in regional left ventricular function between day 1 and day 3.

All values are expressed as a mean with standard deviation in parenthesis in percentage (see text for further details).

SECTOR	DEGREES	LVEF ≥ 5% (n = 17)	LVEF ≤ -5% (n = 9)	-5% < LVEF < 5% (n = 25)
X	0 - 30	6.16(3.86) - 5.50(2.60)	7.90(3.50) - 8.05(4.28)	6.39(3.25) - 5.06(2.43)**(3)**
Y	31 - 60	6.92(3.61) - 6.64(3.26)	9.19(3.65) - 8.27(5.00)	6.69(3.20) - 6.38(3.22)
Z	61 - 90	7.01(3.90) - 8.04(3.64)	9.65(3.30) - 8.07(5.01)	7.10(3.17) - 7.49(3.38)
O	91 - 120	8.79(4.90) - 6.62(3.79)	7.21(3.34) - 5.77(4.38)	7.96(2.80) - 7.72(2.80)
P	121 - 150	8.34(4.75) - 8.46(3.42)	6.39(2.79) - 3.78(3.71)**(1)**	7.86(3.76) - 8.34(3.03)
Q	151 - 180	6.84(3.63) - 7.98(3.07)	6.57(3.16) - 5.54(3.60)	7.39(3.24) - 8.04(4.19)
R	181 - 210	8.18(4.30) - 8.57(3.92)	5.47(3.06) - 7.21(3.89)	6.94(3.59) - 7.80(3.91)
S	211 - 240	9.47(5.33) - 8.79(3.78)	6.29(3.54) - 9.31(5.60)**(2)**	8.85(4.45) - 9.56(4.61)
T	241 - 270	10.29(4.22) - 10.38(3.27)	9.45(5.17) - 11.36(7.07)	10.61(5.50) - 11.41(4.99)
U	271 - 300	10.92(5.26) - 11.05(3.88)	11.71(4.54) - 12.58(5.11)	11.99(5.81) - 11.76(4.00)
V	301 - 330	9.18(6.76) - 8.81(3.84)	11.74(4.90) - 11.01(2.29)	10.25(4.92) - 9.72(2.75)
W	331 - 360	7.82(3.42) - 7.04(1.69)	8.25(2.16) - 8.46(2.97)	7.99(3.79) - 6.70(2.07)**(4)**

(1) p = 0.04 (3) p = 0.03
(2) p = 0.04 (4) p = 0.04

TABLE 19

Relationship between change in left ventricular ejection fraction (Δ LVEF) and alteration in regional left ventricular function between day 3 and hospital discharge.

All values are expressed as a mean with standard deviation in parenthesis in percentage (see text for further details).

SECTOR	DEGREES	LVEF ≥ 5% (n = 20)	LVEF ≤ -5% (n = 16)	-5% < LVEF < 5% (n = 22)
X	0 - 30	6.22(3.05) - 6.48(1.85)	5.33(2.50) - 6.47(2.14)	6.00(2.81) - 5.97(2.81)
Y	31 - 60	6.85(3.41) - 6.38(2.17)	6.24(3.00) - 6.70(2.69)	7.26(3.48) - 6.03(3.30)**(1)**
Z	61 - 90	8.18(3.00) - 7.91(3.15)	7.23(2.83) - 7.87(2.91)	8.49(3.72) - 7.26(3.03)
O	91 - 120	7.91(2.96) - 8.97(2.96)	7.99(2.04) - 7.88(2.49)	7.53(3.66) - 8.02(3.05)
P	121 - 150	7.56(3.63) - 8.88(2.59)	8.36(2.66) - 7.78(2.50)	7.16(3.96) - 7.69(3.72)
Q	151 - 180	7.74(3.58) - 7.99(3.56)	8.75(2.95) - 7.69(3.06)	7.02(3.42) - 6.78(3.34)
R	181 - 210	8.43(4.04) - 8.04(3.86)	8.63(2.31) - 7.46(3.02)	7.13(3.66) - 7.03(3.63)
S	211 - 240	9.86(5.08) - 9.09(3.75)	9.70(3.34) - 9.35(3.68)	8.57(4.30) - 9.44(3.89)
T	241 - 270	10.64(4.96) - 10.33(4.01)	10.78(3.73) - 10.52(4.10)	10.13(3.99) - 11.89(3.90)**(2)**
U	271 - 300	10.49(2.85) - 9.80(2.58)	10.76(3.71) - 10.75(3.28)	12.11(3.70) - 11.56(3.72)
V	301 - 330	8.79(1.98) - 8.75(2.68)	9.46(3.33) - 10.03(2.99)	10.67(3.54) - 10.08(3.56)
W	331 - 360	7.29(2.63) - 7.35(1.75)	6.83(1.70) - 7.85(2.27)	7.68(2.50) - 8.05(2.50)

(1) p = 0.016
(2) p = 0.025

TABLE 20

Relationship between change in left ventricular ejection fraction (Δ LVEF) and alteration to regional left ventricular function between hospital discharge and follow-up.

All values are expressed as a mean with standard deviation in parenthesis in percentage (see text for further details).

with any change in the left ventricular ejection fraction.

Following inferior myocardial infarction there was a decrease in the contribution from the apical region of the left ventricle during both the in-hospital and out of hospital phases. The contribution fell from 8.80 ± 2.38% to 7.24 ± 2.76% and 9.00 ± 2.35% to 7.76 ± 2.44%, respectively. This former change was associated with a small but significant decrease in the left ventricular ejection fraction. Between day 3 and hospital discharge there were significant alterations to the total output from the septal and lateral aspects of the left ventricle, with a decrease from the former and an increase in the latter. This alteration was not associated with change in the left ventricular ejection fraction.

Previous work relating to the natural history of regional ventricular function has reported conflicting results. Tamaki et al serially evaluated regional ventricular function in the ten days following myocardial infarction (151). In normal, non-infarcted segments they reported a decrease in chord shortening. In akinetic segments there was a significant improvement in chord shortening during the same period. These changes in regional ventricular function were not reflected by changes in left ventricular ejection fraction. Other workers have also reported changes in the regional

ventricular function without any change in the left ventricular ejection fraction (54). The changes were not found to be related to the site, size, type (non-Q or Q wave) infarction or to the initial ejection fraction.

Ramanathan et al found an improvement in both regional ventricular function both in the region of infarcted and non-infarcted regions which was associated with an increase in global parameters in left ventricular performance (65).

Data relating to regional changes in ventricular function in the year following myocardial infarction is limited. Dewhurst et al, using qualitative analysis of regional function, reported an increase in the left ventricular ejection fraction in patients with segmental akinesis, but not in patients normal wall motion, segmental hypokinesis or dyskinesis at time of hospital discharge (43). Reduto et al found no significant changes in either regional or global ventricular performance in the twelve months following anterior or inferior myocardial infarction (35). Regional function was also assessed qualitatively in this latter study.

Studies evaluating left ventricular function in patients with acute myocardial infarction treated with coronary thrombolysis have shown that although no change in the left ventricular ejection fraction was observed, improvement in regional ventricular performance occurred often, frequently in the region of infarction (121,162-

165).

Various pathophysiological changes have been shown to result in alterations in regional ventricular function following acute myocardial infarction; some of which predominately involve the infarcted region whilst others primarily take place in the non-infarcted areas.

1) Spontaneous or therapeutic reperfusion and collateral flow can result in limitation of the area of infarction by sparing the sub-epicardium which undergoes infarction later than the sub-endocardium (166,167). The myocardium in this epicardial "border zone" fulfils the criteria for "stunned myocardium" as described by Braunwald and Kloner (159). Collateral flow has been shown to decrease the transmural extent or even prevent the occurrence of myocardial infarction (168-171). Several studies have observed improvement in regional ventricular function following reperfusion with the administration of a thrombolytic agent (121,162-165). The effect of spontaneous reperfusion of the infarct related vessel is less well defined. There is growing evidence to suggest that even "late" reperfusion, i.e. after 6 hours, can have a beneficial effect on ventricular function. There have been a few studies (172-176) that have observed that patients with Q wave infarction associated with a patent infarct-related artery have better left ventricular function than those whose infarct-related vessel remains occluded. It is

difficult to explain this on the basis of myocardial salvage; spontaneous reperfusion, resulting from normal intrinsic thrombolytic mechanisms, usually occurs outwith the accepted time-frame for myocardial salvage. The importance of a patent infarct-related coronary artery was also identified in the Western Washington trial which compared the efficacy of intracoronary streptokinase with placebo (175). In this trial the time between onset of symptoms and treatment was relatively late, mean of 5 hours. No improvement in global or regional ventricular function or infarct size was observed, presumably relating to the relatively late initiation of thrombolytic therapy. However, despite this, there was a lower mortality in those patients treated with thrombolysis compared with placebo (176); subsequent analysis of the data found that patency of the infarct-related coronary artery was an independent predictor of survival (177). Similar findings have been reported by the TIMI investigators (178-180). The efficacy of streptokinase and aspirin, both alone or in combination, was evaluated in the ISIS-2 trial, used as late as 24 hours following the onset of symptoms (181). A significant reduction in mortality was still observed even in patients who were treated as late as 12-24 hours after the onset of infarction. There is also experimental evidence showing a beneficial effect on left ventricular performance following coronary reperfusion which appears to be

independent of myocardial salvage, which probably results from the attenuation of detrimental alterations in left ventricular topography (182). Different mechanisms by which reperfusion alters ventricular topography have been suggested. The haemorrhage, oedema, cell swelling and contraction band necrosis that occurs following reperfusion (182) decreases the compliance in the infarcted myocardium thereby limiting the amount of infarct expansion and subsequent aneurysm formation and ventricular dilatation. Another possible mechanism that has been postulated is that the patent infarct-related coronary artery and vascular bed is filled with blood which provides support to the subtended myocardium, analogous to a "scaffolding" effect, which limits expansion of the necrotic myocardium.

2) A decrease in the circumferential extent of the area of ventricular dysfunction following myocardial infarction also results in improved regional ventricular function in these regions. The circumferential border of an infarct zone is a mixture of normal and infarcted tissue with a discrete interface, possibly with abnormal function extending into the normally perfused myocardium (183-185). There is experimental work, using a canine model, to suggest return of regional ventricular function of the border zone (3). An alternative explanation of this apparent return of function is that this may reflect a change in anatomical reference base as the infarcted

area begins to scar and contract resulting in infarct "shrinkage" (158).

3) Beneficial alterations in the compliance of infarcted myocardium as a result of reperfusion injury were discussed in relation to patency of the infarct-related artery. These changes have also been shown to occur without apparent reperfusion and is another postulated mechanism by which regional ventricular function in the region of the infarct may occur (2,12,14-16). Conversely, infarct expansion resulting from thinning and stretching of the infarcted myocardium results in worsening regional ventricular function in the area of infarction (67,68).

4) Alteration in the performance of remote, non-infarcted myocardium also occurs following acute myocardial infarction. Ischaemia in the territory of the non-infarcted area can result in decreased function in that area (186); conversely resolution of ischaemia will result in improved regional performance and has been suggested as an explanation of the transitory acute phase ventricular dysfunction following myocardial infarction (39,46). Increased function in areas distant from infarction have been observed by several workers (12,28, 60). The interaction between different vascular territories can be complex with occlusion in one territory leading to ischaemia in another (187-189).

5) The effects of variation in the loading conditions on the natural history of regional ventricular function are largely unknown. A decrease in ventricular pressure may reduce the pressure at the collateral head, this may be balanced or reduced by the fact that the lower ventricular filling pressure will reduce the intra-myocardial resistance to collateral flow. In addition, lower intraventricular pressure may have beneficial effects by reducing the incidence and extent of detrimental alterations in left ventricular topography.

An additional finding in this thesis was that when patients were grouped according to the degree of underlying left ventricular dysfunction no association was found between changes in the left ventricular ejection fraction that occurred and alterations in regional ventricular function. The reason for this lack of an association may imply that these changes occurred as a result of haemodynamic changes leading to favourable alterations in preload and/or afterload, rather than regional improvement in ventricular performance. This is consistent with the findings Kupper et al reported an improvement in several haemodynamic parameters following acute myocardial infarction in patients with moderate to severe impairment of left ventricular function (11). Alternatively, no statistically significant relationship may have been apparent because of the small number of patients in each subgroup.

Variability in the left ventricular ejection fraction was relatively common and sometimes large in individual patients. These were not accompanied by corresponding changes in regional ventricular function. The lack of association between change in the left ventricular ejection fraction and changes in regional ventricular function suggest that these changes are the result of changes in the prevailing loading conditions of the heart rather than intrinsic changes in the performance of the myocardium. Nemerovski et al who assessed regional ventricular function qualitatively during the first 25 days following infarction also found no significant changes in regional ventricular function to parallel the changes in the left ventricular ejection fraction that were observed in individual patients (113). The implications of the variability in the left ventricular ejection fraction in individuals which occur without alteration in relative regional ventricular performance and apparently of little consequence to the clinical status or outcome of the patient raises questions as to its use following myocardial infarction. It would appear that serial evaluation of left ventricular performance following myocardial infarction using the left ventricular ejection fraction alone is of limited value.

There are limitations in the data presented in this chapter. As discussed in the preceding chapter, the

technique employed in evaluating regional ventricular function does have certain drawbacks. Firstly, it only provides a relative measurement, although this has the advantage of being less susceptible to changes in loading conditions it does not allow the determination of whether change has occurred because of an inherent change in that region or whether this a reflection of change in another area or areas. In addition, it is possible that if an increased number of sectors were employed the technique would be more sensitive and more changes may have been identified. The size of many of the groups are small and therefore it is possible that with larger numbers of patients relationships may have become apparent. The large number of statistical analyses performed also increases the potential for Type 1 statistical errors. Despite these potential limitations the data does provide an insight to regional ventricular function following myocardial infarction and its relationship to the left ventricular ejection fraction.

8.6 CONCLUSIONS

These results suggest that changes in the left ventricular ejection fraction, whether in individuals or in groups of patients often occur without any change in the relative contribution of different left ventricular

regions. This suggests that these changes may occur as a result of changes in the prevailing loading conditions of the heart rather than an inherent alterations in intrinsic myocardial function.

In addition, it has been shown that changes in regional ventricular function occur in the days and months following myocardial infarction, and that these changes often are not associated with any change in the left ventricular ejection fraction.

CHAPTER 9

THE IMPACT OF MYOCARDIAL INFARCTION ON VENTRICULAR FUNCTION

9.1 INTRODUCTION

The aim of this chapter is to briefly review the subject of ventricular function following myocardial infarction with reference to the data presented in this thesis. The main findings from different chapters are combined and reviewed in the context of previous work. In addition, possible future avenues of investigation are discussed. The effects of acute myocardial infarction on the left and right ventricles are considered separately.

9.2 THE IMPACT OF MYOCARDIAL INFARCTION ON THE LEFT VENTRICULAR FUNCTION

Acute myocardial infarction results in loss of contractile myocardium; as the extent of this loss increases the more severe is the resulting left ventricular dysfunction and consequent mortality (12).

However, the size of infarction is not the only parameter which determines the degree of left ventricular dysfunction following myocardial infarction (9).

The site of infarction appeared to have a significant effect on both the size of infarction and also the degree of left ventricular dysfunction. The infarct size in this thesis was estimated by both an enzymatic method and myocardial scintigraphy. Despite no significant difference in the enzymatically determined infarct size between anterior and inferior myocardial infarction, anterior sited infarction was associated with larger Thallium-201 perfusion defects and lower left ventricular ejection fractions.

The larger perfusion defects found following anterior myocardial infarction may have been the result of more extensive myocardial infarction and also possibly the result of topographical changes resulting in expansion of the area of infarction, which occurs more frequently following anterior infarction (67-70). The release of creatine kinase from the right ventricle associated with inferior myocardial infarction may explain the apparent disparity between the enzymatically determined infarct size and Thallium-201 perfusion defect size, since the latter does not include right ventricular perfusion. Right ventricular release of creatine kinase is postulated to be the aetiology of the poorer correlation that is observed between the peak creatine kinase level and left ventricular ejection fraction following inferior myocardial infarction (104-106).

Lower left ventricular ejection fractions were observed following anterior myocardial infarction, and have been reported by others (32,35,37,41,43,47). This may be explained by more extensive infarction and/or detrimental changes in left ventricular topography. In addition, a methodological error in the calculation of the ejection fraction using radionuclide ventriculography due to differences in photon absorption by the intra-ventricular blood pool may also contribute to this difference (108,109).

Variability in the left ventricular ejection fraction in individual patients was not uncommon. It was not usually associated with any change in the patient's clinical status and was not found to be associated with site or size of infarction, the presence of previous infarction, the degree of associated left ventricular dysfunction or prognosis. The variability in the left ventricular ejection fraction has been previously reported during the early stages of infarction and has been hypothesised to be the result of changes in the prevailing loading conditions of the heart, however regional ventricular was either not assessed (45) or only assessed qualitatively (113). The data presented in this thesis obtained from serial quantitative assessment of the regional contribution to left ventricular output suggest that there is no relationship between alteration in regional ventricular performance and variation in the

left ventricular ejection fraction in individual patients. This supports the hypothesis that the variability is a reflection of change in the haemodynamic milieu, rather than change in the intrinsic myocardial performance.

These findings appear to be in direct conflict with others, who have found that the presence of transitory ventricular dysfunction early following acute infarction, reflected as by clinical (pulmonary rales) or radiological evidence of left ventricular failure is an adverse prognostic event (39,46). However, the presence of pulmonary rales and radiological evidence of pulmonary oedema results from major diastolic dysfunction and therefore probably signifies significant reversible left ventricular dysfunction, such as ischaemia in another coronary vessel (186). This contrasts with changes in the ejection fraction which occur frequently without change in clinical status; probably occurring as a result of change in the loading conditions. It is possible that larger changes in the left ventricular ejection fraction may have more clinical and prognostic significance.

Little change in the left ventricular ejection fraction was observed when patients were grouped according to the site of infarction. However, when the degree of associated left ventricular dysfunction was also taken into account significant changes were

identified. Patients with severe ventricular dysfunction following myocardial infarction showed an improvement in the left ventricular function, this increase in the left ventricular ejection fraction which was most noticeable following inferior myocardial infarction. However, this increase in the ejection fraction was not associated with any relative alteration in regional ventricular performance. This again tends to imply that this change was related to beneficial alterations in haemodynamics. Conversely, changes in the relative contribution from left ventricular regions were identified following both anterior and inferior myocardial infarction which were not associated with any change in the global left ventricular ejection fraction.

The left ventricular ejection fraction was found to be important prognostically. However, the prognostic utility appeared to be dependent on the site of infarction; the left ventricular ejection fraction was associated with mortality following anterior but not inferior myocardial infarction. The true significance of this finding is uncertain because of the relatively smaller number of patients studied.

Additional important prognostic information can be obtained following acute myocardial infarction by coupling radionuclide ventriculography with exercise (43, 44,52,194-195). The normal left ventricular response to exercise is characterised by an increase in the left

ventricular ejection fraction by at least 5 per centage units, a decrease in the left ventricular end-systolic index, an increase in the left ventricular systolic pressure/volume index, and more vigorous segmental contraction (197,198). These studies have found significant alterations in global and regional left ventricular function frequently occur during submaximal exercise following myocardial infarction (43,44,194,195, 199); however, the response to exercise has been found to be heterogeneous (43,47,194,195). This is due, at least in part, to the effects of exercise-induced myocardial ischaemia with its detriment effect on left ventricular performance. Exercise studies of left ventricular function were not included in the thesis because the underlying coronary anatomy in the majority of patients was unknown. The availability of exercise data would have been interesting, however without results of coronary arteriography the conclusions that could be drawn from the exercise studies would have been limited; particularly when the main objective was to examine the functional effects of myocardial infarction rather than identification of prognostic indicators.

The assessment of the functional status the left ventricle following myocardial infarction is a complex and multi-faceted problem. The use of left ventricular ejection fraction is widely used in the evaluation of left ventricular function following myocardial infarction

(30,32,39-42).

The data presented illustrate important limitations of using the left ventricular ejection fraction following myocardial infarction in the assessment of left ventricular function. The importance of ventricular volumes following myocardial infarction are increasingly being realised (190,191). White et al in a study of 605 survivors of myocardial infarction found that the end-systolic volume to be more important in determining survival following myocardial infarction than the ejection fraction. Therefore, the measurement of ventricular volumes provides important and complimentary information to that obtained from calculation of the ejection fraction alone.

Not only were changes in the left ventricular ejection fraction not associated with alterations in regional ventricular performance, the converse was also true. Namely, that changes in regional ventricular function frequently occurred without identifiable change in the left ventricular ejection fraction. Previous work has also demonstrated alterations in regional ventricular performance not reflected by change in the ejection fraction following myocardial infarction (54,65,151). However, there does not appear to be an identifiable pattern to the natural history of regional ventricular function following myocardial infarction.

The importance of assessing regional ventricular function for the accurate characterisation of left ventricular function is becoming increasingly obvious. Not only does it provide a more sensitive and accurate assessment of left ventricular function (5,36, 53,61) it is also important prognostically (43,47,68,71). It also provides important data relating to the beneficial effects of thrombolytic therapy in the management of acute myocardial infarction were the improvement in ventricular function may only occur within the region of infarct, and not reflected by improvement in the left ventricular ejection fraction (121,162-164). Therefore, some means of assessing regional ventricular function should be employed in studies of left ventricular function following myocardial infarction.

The detrimental effects of topographical changes of the left ventricle following myocardial infarction are well known. The adverse effect on morbidity and mortality relate to the increase in ventricular volumes and an increased incidence of ventricular rupture, left ventricular thrombus and aneurysm formation (67-71,107). The evidence that these detrimental changes in left ventricular topography may be attenuated by thrombolytic therapy (182) or by the use of angiotensin converting enzyme inhibitors (24,192,193) has resulted in renewed interest in this subject; including the techniques for evaluating left ventricular topography.

Two-dimensional echocardiography has been the most widely used technique to evaluate changes in left ventricular topography. However, the technique of gated tomographic radionuclide ventriculography is particularly suited to the assessment of ventricular function (200-203). The sampling of the ventricular volume in three dimensions by the tomographic technique overcomes many of the geometrical limitations of two-dimensional echocardiography and planar ventriculography. Until recently the practicality of this technique has been restricted by the limited capabilities of the computers used to process the vast amounts of data generated. However, recent developments in computer software and also imaging hardware have resulted in the resurgence of interest in this technique for assessing left ventricular function (204,205). Preliminary results using gated radionuclide with a dedicated 3-detector tomograph have shown that this can provide a sensitive technique for the assessment of alterations in left ventricular topography following myocardial infarction (203), and therefore will be useful in the evaluation in the efficacy of interventions at limiting change in ventricular topography.

The availability of new technetium-99m labelled myocardial perfusion agents appears to be on the horizon which offer advantages over current used agents (206-208). The isonitrile analogue, 2-methoxy-isobutyl-isonitrile (MIBI) has radiation dosimetry and myocardial

stability that permit gated myocardial imaging with tomography. Preliminary studies with this agent have demonstrated the ability to assess both myocardial perfusion and global and regional left ventricular function simultaneously (209-211). The ability to assess these simultaneously in three dimensions appears to have substantial potential.

Although the assessment of regional function is important following myocardial infarction, it does present problems. Firstly, there are the specific limitations pertaining to whichever method is being used to evaluate regional ventricular function, as previously discussed in Chapter 7. There is the additional problem of alterations in left ventricular topography resulting from cardiac remodelling following myocardial infarction which leads to difficulties in serial evaluation of regional ventricular performance resulting from a changing anatomical reference base (147).

9.3 THE IMPACT OF MYOCARDIAL INFARCTION ON THE RIGHT VENTRICULAR FUNCTION

The effects of acute myocardial infarction on right ventricular function were found to be dependent upon the site of infarction. Thereafter, the natural history of right ventricular function appeared to be dependent both on the site of infarction and the degree of right

ventricular dysfunction.

Depression of right ventricular function occurred in 64% of patients following acute inferior myocardial infarction. The presence of right ventricular dysfunction following inferior infarction is a relatively common finding (8,80), and relates to infarction of the right ventricular free wall which is often associated with infarction of the inferior wall of the left ventricle (69,78,82,86).

Following anterior myocardial infarction depression of right ventricular function also occurred and was identified in 28% of patients. The presence of right ventricular dysfunction following anterior myocardial infarction is a somewhat controversial topic, however the evidence is increasingly in favour of its presence (88, 96-98). The aetiology has been postulated to be related either to global left ventricular dysfunction (96,98) or abnormal function of the interventricular septum (97).

Determination of the natural history of right ventricular function following acute anterior and inferior myocardial infarction was one of the main objectives of this thesis. Following inferior myocardial infarction there was a trend for the right ventricular ejection fraction to increase. This contrasted with the fall in the right ventricular ejection observed in the sixteen months following anterior myocardial infarction. The natural history also appears to be related to the

degree of right ventricular dysfunction present during the in-hospital period. Patients with severe depression of the right ventricular ejection fraction (<25%) showed an improvement, whilst those with moderate depression (25-34%) showed no change, and those with an initially normal right ventricular ejection fraction (>35%) showed a fall in the sixteen months following hospital discharge. Previous data relating to the natural history of right ventricular function following myocardial infarction has presented conflicting evidence, and is largely confined to the in-hospital or to the first few weeks following infarction (88,90,91,93,96,113). There is no published data as to the long term effect of anterior myocardial infarction on right ventricular function.

The postulated pathophysiological mechanisms for the observed changes in the right ventricular ejection fraction are probably related to differences in the underlying aetiology of the right ventricular dysfunction. Severe right ventricular dysfunction occurred only following inferior left ventricular wall infarction and presumably resulted from right ventricular infarction. This is usually associated with a propensity to improve over subsequent days (88,90,91). Patients with initially normal right ventricular function the presence of associated left ventricular dysfunction is the predominating factor which resulted in a progressive

deterioration in right ventricular function. The underlying aetiology in this situation relates to ventricular interdependence as discussed in Chapter 6.

Another previously unreported finding was the changing relationship between the right and left ventricular ejection fractions that was observed. Following anterior sited infarction there was a correlation between the left and right ejection fractions which was closest 16 months following the index infarction. Following inferior myocardial infarction no relationship existed between the left and right ventricular ejection fractions during the in-hospital period. However, after 16 months a weak but significant correlation between the two parameters was observed. The explanation for the closer relationship between the left and right ventricular ejection fraction in the 16 months following the index infarction presumably relates to an increase in the right ventricular ejection in those patients with predominately right ventricular dysfunction resulting from right ventricular infarction and a fall in the right ventricular ejection fraction resulting from co-existent left ventricular dysfunction.

Variability in the right ventricular ejection fraction in individual patients, as was found with the left ventricular ejection fraction, was not an uncommon finding. The variability was not usually associated with change in the patient's clinical condition, and was not

related to the site or size of infarction, presence of previous infarction or with the left ventricular ejection fraction and did not appear to have any prognostic significance. These findings are similar to those reported by Nemerovski et al (113), and presumably occur as a result of alterations in loading conditions of the right ventricle.

The functional status of the right ventricle per se did not appear to be important prognostically. However, the presence of left and right ventricular dysfunction in a patient did appear to be associated with an even poorer prognosis than with left ventricular dysfunction alone. This finding reinforces the prognostic importance of considering the functional status of both ventricles in patients with coronary artery disease (98,123).

The complex geometrical shape of the right ventricle makes functional assessment difficult. Radionuclide techniques using inert gases, for example Xenon-133 and Krypton-88, have been developed to overcome the limitations of other radionuclide and imaging modalities. Gated Xenon-133 imaging was used in a subgroup of patients with inferior myocardial infarction to assess right ventricular function during the early phase of myocardial infarction. The findings obtained from the 133-Xenon imaging were related to clinical evidence indicative of right ventricular dysfunction.

The accuracy of clinical assessment of right ventricular function in this setting was evaluated using the results obtained from this technique. Although the presence of clinical signs of right ventricular dysfunction, i.e. an elevated jugulo-venous pressure or a rise in the jugulo-venous pressure on quiet inspiration, were relatively specific, the sensitivity and resulting predictive accuracy were limited.

Xenon-133 imaging was found to be an ideal technique for the evaluation of right ventricular function in the setting of acute myocardial infarction which can be performed easily and repeated as necessary with a relatively low radiation exposure to the patient. The technique allows excellent definition of the tricuspid and pulmonary valve planes and absent activity in the region of the left ventricle providing an accurate and reproducible means of quantitating right ventricular function.

APPENDIX

THE EFFECT OF USING ONE REGION OF INTEREST AND TWO REGIONS OF INTEREST ON THE REPRODUCIBILITY IN CALCULATING THE EJECTION FRACTION

The effect of using one region of interest and two regions of interest on the repeatability of calculation of the ejection fraction was evaluated in twenty eight patients. The left ventricular ejection fraction ranged from 30 - 58%, mean 42.7 ± 8.7%, and the right ventricular ejection fraction from 21 - 49%, mean 34.4 ± 6.9%. The method employed to calculate the ejection fraction using one region of interest is as described in Section 2.3 of the Methods Chapter. When using two regions of interest, an end-diastolic region of interest was drawn around the ventricle as described previously. After identification of the end-systolic frame, i.e. the point at which the activity within the ventricle reached a minimum, a second end-systolic region of interest was manually drawn around the ventricle. Verification of correct assignation of regions of interest and drawing of the background regions of interest was performed as previously described for the single region of interest technique. The formula used to calculate the ejection fraction for both methods is as given in Figure 1.

		INTRA-OBSERVER VARIABILITY	INTER-OBSERVER VARIABILITY
LVEF :	1 ROI	2.53 ± 1.29	1.75 ± 2.55
LVEF :	2 ROI	4.29 ± 2.99 (1)	7.03 ± 5.88 (3)
RVEF :	1 ROI	2.71 ± 1.90	3.54 ± 3.47
RVEF :	2 ROI	5.50 ± 3.80 (2)	11.60 ± 8.42 (4)

(1) - (4) $p<0.001$

TABLE 21

Reproducibility of calculating the left ventricular (LV) and right ventricular (RV) ejection fraction (EF) using one and two regions of interest (ROI). Values are expressed as mean differences ± standard deviations in ejection fraction units (%). See text for further details.

The results are tabulated in Table 21, and reveal that the use of a single region of interest drawn in end-diastole results in both significantly better intra-observer and inter-observer variability.

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