

VENTRICULAR FUNCTION FOLLOWING MYOCARDIAL INFARCTION

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The Prognostic Value of Radionuclide Ventriculography

N G Dewhurst

M.B., Ch.B., (1976) B.Sc., M.R.C.P. (U.K.)

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Department of Medicine
The Royal Infirmary
EDINBURGH

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Formal Declaration

I declare that I have written the dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observation and that, except as indicated in the thesis, the data were collected, analysed and interpreted by me.

N G Dewhurst

ABSTRACT OF THESIS (Regulation 6.9)

Name of Candidate NEIL GORDON DEWHURST

Address

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Title of Thesis VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION

..... The prognostic value of radionuclide ventriculography.

Ventricular performance was assessed in one hundred consecutive patients recovering from their first myocardial infarction using the non-invasive technique of radionuclide ventriculography. This method was successfully performed in almost 100% of cases and repeated studies had a high degree of patient acceptability; the results were reproducible and easy to interpret and quantify with relative observer independence. Gated blood pool imaging performed prior to discharge from hospital revealed significant impairment of left ventricular function in the majority of patients, often when not clinically suspected. Those patients recovering from anterior infarction had greater reduction in left ventricular ejection fraction with a higher incidence of the more severe abnormalities of regional ventricular wall motion. A system of paradox imaging proved an accurate method for the detection of ventricular dyskinesia, present in 25% of all patients recovering from infarction. Subclinical right ventricular dysfunction occurred in over 40% of those recovering from inferior infarction and the variable degree of right ventricular necrosis contributed to enzymatic indices of infarct size accounting for the relative sparing of left ventricular function. Left ventricular failure and serious arrhythmia in the acute phase were both associated with marked reduction of ejection fraction in the convalescent phase. Low resting ejection fraction at discharge failed to improve in the subsequent year and was associated with the development of left ventricular failure, ventricular arrhythmia and sudden death. Reduction in ejection fraction during exercise testing performed four weeks after discharge had greater sensitivity and specificity than conventional electrocardiographic criteria in the prediction of the development of post-infarction angina which also carried a considerable risk of sudden death. The results of radionuclide ventriculography at rest and during exercise identified as "high risk" 11 of the 13 patients who were to die in the following year and proved more accurate than the Coronary Care Indices currently in use.

The implications of these results are related to conventional clinical practice and the development of these and other radionuclide techniques to measure different parameters of ventricular function are discussed.

The Purpose of this Thesis

Over the past 40 years mortality from ischaemic heart disease has increased threefold to the extent that 40% of all deaths in middle age are now attributed to this pathology. Myocardial infarction is now second to self poisoning as the most common cause of medical admissions to hospital. The introduction of Coronary Care Units has led to a better understanding of the process of infarction and to a reduction in peri-infarction mortality but less attention has been paid to subsequent recovery and return to work and for those who survive there remains the considerable risk of the development of either angina, reinfarction, arrhythmia or sudden death. However in recent years it has been suggested that the complications occurring after discharge from hospital may be related not only to the extent of infarction but also to the function of the residual viable ventricle and its blood supply. Therefore any method employed in the assessment of survivors of infarction must determine the degree of impairment of left ventricular performance and give some indication of the vascularity of the noninfarcted ventricle. The identification of those at "high risk" would ideally occur prior to discharge from hospital and therefore the technique would preferably be noninvasive and appropriate in the screening of large numbers of asymptomatic patients. Such methodology would be suitable for serial studies and provide valuable

information regarding the natural history of left ventricular function.

Cardiac catheterisation and contrast ventriculography has in the past been the only accurate method of assessing ventricular function but because of its invasive nature this technique is usually limited after infarction to those symptomatic from angina in the late convalescent phase. However, the relatively new technique of radionuclide ventriculography, which has developed from advances in radiopharmaceuticals and nuclear medicine instrumentation, now allows the possibility of serial assessment of ventricular function in a non-invasive manner. From a single intravenous injection of a small amount of radioisotope, information can be obtained relating to global ventricular performance and regional wall movement. The method is relatively inexpensive and imparts only a small dose of radiation and avoids discomfort to the patient. It therefore affords an easy means to study ventricular function in the convalescent phase after infarction. Since the place of rehabilitation and exercise training remains controversial this thesis addresses itself to correlate the patient's ability to return to work with results of radionuclide ventriculography and to assess the prognostic value of an early exercise stress test. To assess the reliability of these techniques correlative work has been undertaken in a separate group of patients

who because of ischaemic heart disease underwent both routine cardiac catheterisation and radionuclide ventriculography.

The reproducibility of derived measurements such as cardiac output and ventricular volumes has also been validated and where possible values for cardiac output compared with those obtained by other methods such as thermal dilution. Those patients with grossly impaired ventricular function and intractable heart failure pose a difficult clinical problem and the value of inotrope therapy in this particular category of patient has been assessed.

The scope of this dissertation is thus to determine the role of radionuclide ventriculography in the assessment of ventricular function following myocardial infarction and with the use of this technique to follow the natural history of ventricular function over the ensuing year and to evaluate the efficacy of any therapeutic intervention.

In the clinical context the aim of the work presented in this dissertation is to assess the prognostic value of radionuclide ventriculography in the early identification of those patients at risk of developing angina, further infarction, ventricular arrhythmia or late sudden cardiac death after myocardial infarction. Having identified the major determinants of prognosis the technique may be of value in the assessment

of the effects of therapy on morbidity and mortality of high-risk survivors.

Plan of this Thesis

Despite the prevalence which ischaemic heart disease has now attained it was only at the end of the latter century that it formally became recognised as a clinical entity. Because of the apparent rarity of the condition it was only with great difficulty that early workers collected numbers of patients suffering either angina or myocardial infarction. However the symptoms and signs soon became well documented and with increasing recognition and a true increase in incidence myocardial infarction became a common clinical diagnosis. When sufficient numbers of patients had been studied it became evident that longevity was affected and the working lives of the middle-aged male population severely curtailed. It then became apparent that various points from the medical history together with a variety of clinical signs carried prognostic significance for later developments in the recovery or convalescent phase. In Chapter 1, the development of the concept of prognosis after myocardial infarction is discussed and the original observations and the more recent studies involving biochemical, electrocardiographical and radiological investigation are reviewed. Because of its invasive nature few studies were based upon routine angiographic assessment in the convalescent phase and it was only with advances in nuclear medicine that accurate non-invasive assessment of ventricular performance became possible. Chapter 2

summarises the historical background behind the current techniques of radionuclide ventriculography and describes the development of the modern scintillation camera and the use of improved tracers labelled with radionuclides such as technetium^{99m} which have permitted dynamic imaging of the cardiovascular system. Also discussed are improvements in data processing and the use of digital computers, allowing the first passage of a bolus of tracer through the central circulation to be visualised and recorded, permitting measurement of ventricular volumes. In addition, the incorporation of electrocardiographic gating mechanisms has meant that subsequent equilibrium studies of the cardiac blood pool allows assessment not only of ventricular volumes, cardiac output and ejection fraction but also visualisation of regional ventricular wall movement. Chapter 3 outlines the methods used in each particular area of study and where possible results have been validated by comparison with other methods such as cardiac catheterisation, contrast ventriculography and thermal dilution.

The results of radionuclide ventriculography performed at rest soon after infarction are discussed in Chapter 4 where global left ventricular ejection fraction, right ventricular size and ventricular wall motion are related to early clinical progress. The significance of acute phase heart failure and arrhythmias

together with results of routine investigation such as creatine kinase measurements, 12-lead electrocardiography and chest radiography are examined in relation to ventricular performance. Severely impaired ventricular function may be secondary either to global hypokinesis with generalised impairment of ventricular wall motion or may follow the development of localised dyskinesis which expands in paradoxical fashion during systole and thus has the propensity to form a true aneurysm. Identification of the latter abnormality is of considerable importance since with the development of modern cardiac surgical techniques the problems of intractable heart failure or recurrent arrhythmia may be cured by aneurysmectomy. The value of clinical signs and the reliability of various diagnostic methods in the detection of ventricular aneurysm will be compared to the findings of isotope studies.

At present the duration of in-hospital stay and follow-up of these patients imposes a considerable burden on resources in terms of bed occupancy and time of medical and nursing personnel. In addition the current trend towards specialist rehabilitation programmes ensures that high expenditure in the recovery phase is perpetuated. Therefore it would be of great importance to identify those individuals with a low risk of complications such as heart failure, ventricular arrhythmia or late sudden death since they would be suitable for early discharge from hospital and early

return to their previous employment. Previous studies have placed statistical weighting on the various adverse clinical, biochemical, electrocardiographical and radiological features in the acute phase in an attempt to formulate an index predictive of survival after discharge from hospital. In Chapter 5 the predictive value of serial radionuclide ventriculography will be compared with these various coronary prognostic indices and in addition with standard 12-lead electrocardiography and routine ECG monitoring. Following extensive infarction healing by fibrosis and scarring results in a grossly distorted and often aneurysmal ventricle with only limited capacity for spontaneous improvement and therefore these patients will be discussed in detail. The currently underdiagnosed clinical problem of right ventricular infarction will also be mentioned and the prognostic implications of this entity discussed.

With the modern policy of earlier mobilisation and discharge from hospital patients recovering from infarction undertake minor degrees of exercise from relatively early on in their convalescence. This theme led to the development of graduated exercise programmes being incorporated not only into their routine mobilisation but also into specific rehabilitation schemes and it was not long before the principles of electrocardiographic monitoring of formal exercise tests performed in patients with angina were applied to those

recovering from infarction. In Chapter 6 the prognostic value of early exercise stress testing combined with radionuclide ventriculography soon after myocardial infarction will be discussed in relation to the development of post infarction angina and prediction of late sudden death.

In addition to the problems of angina and reinfarction, left ventricular failure in the first year after hospital discharge is a relatively common occurrence and although occasionally due to ruptured ventricular septum or mitral regurgitation from papillary muscle damage, it usually occurs following extensive infarction and globally poor left ventricular function. Although most would agree that the modern potent loop diuretic agents are of value for acute and chronic therapy the value of the more traditional therapy of digoxin in these patients has recently been re-examined. Various workers have expressed doubt over the efficacy of digitalis glycosides in these patients since the vast majority are in a stable sinus rhythm and heart failure occurs secondary to a grossly distorted ventricle in which the infarcted area may be akinetic or dyskinetic. The value of purely inotropic drugs in these patients must be in doubt since the ventricle can no longer respond in a homogeneous fashion and although one may increase contractility of the noninfarcted area the infarcted segment may move with increasing abnormality. Radionuclide studies lend themselves admirably to the

study of therapeutic interventions since serial measurements of cardiac output, ventricular volumes and ejection fraction are possible from a single injection of tracer. In Chapter 7 the results of such studies following the intravenous and subsequent oral administration of digoxin will be discussed and in addition the effects of modern inotrope agents such as the new Beta₁ agonist, prenalterol, will be mentioned.

Chapter 8 forms a summary of the results obtained thus far in the identification of "high risk" survivors and documentation of the natural history of ventricular function after myocardial infarction. As a conclusion it draws together the results of the individual sections of this thesis and summarises the application of radionuclide ventriculography in the assessment of patients with ischaemic heart disease. In Chapter 9 the clinical implications of this work will be discussed and the relative value and practicability of this and other techniques summarised.

There has been rapid progress in the use of radionuclides in other aspects of cardiovascular investigation since the initiation of this study and there can be no doubt that isotope techniques will increase our understanding of the mechanism, effects and natural history of acute myocardial ischaemia. Since primary prevention has met with only limited success, more attention has been paid to the limitation of the

frequency, severity and duration of ischaemic episodes and this chapter concludes with a discussion of the potential role of radioisotopes in the value of intervention therapy. Special emphasis is placed upon early institution of therapy to preserve jeopardised ischaemic myocardium since a reduction in infarct size should prevent the consequences of extensive infarction: heart failure, arrhythmia and sudden cardiac death.

CHAPTER 1

PROGNOSIS AFTER MYOCARDIAL INFARCTION

Although Heberden was the first to describe anginal pain as "Pectoris dolor" (Heberden, 1768) it was not until 1912 when Herrick published his dissertation on the clinical entity of coronary thrombosis (Herrick, 1912). He described in detail the clinical symptoms and signs and in 1919 classified cases according to the mode of death but also pointed out that myocardial infarction was not necessarily fatal (Herrick, 1919). On the basis of the limited number of cases he had managed, he divided patients into four groups: those in the first two groups deteriorated rapidly and died soon after the onset of symptoms. However he also recognised two further categories of patient, those in whom death was delayed for hours, days or months with the possibility of recovery and a further group who seemed to have a better prognosis and presented with mild symptoms which he thought to be due to obstruction of the smallest branches of the coronary arteries. In that same paper he mentioned his earlier work performed with Smith on the ligation of coronary arteries in the dog and remarked that survival of the animal for days or even months after ligation was common but arrhythmias either atrial or ventricular although common immediately after ligation could persist or recur (Smith, 1918). The electrocardiographic abnormalities that Herrick alluded to

were confirmed by Pardee and thereby allowed physicians to distinguish myocardial infarction from the then well recognised syndrome of angina pectoris (Pardee, 1925). It was then that the diagnosis of coronary thrombosis became one of increasing frequency but despite White and Wood publishing their own classification of heart pain (White, 1923) the two conditions were often confused.

The first information relating the prognosis of coronary thrombosis was produced by Sir James Mackenzie and was inadvertently included in his book titled "Angina Pectoris" (Mackenzie, 1923). Then a general practitioner in England he collected 160 cases of so-called angina, of whom eighteen had in fact sustained myocardial infarction which in nine of them was confirmed at post mortem. Of these cases the mean age was 55 years and all but one had died at the time his paper was written, the average survival being about three years. However, prognosis varied considerably and although nine patients died within one year of the occlusion there were four surviving between three and four years and others who survived seven, twelve and even seventeen years. Indeed, in another report Ryle inferred from Sir Everard Hume's accounts that John Hunter lived for 20 years after a typical acute coronary occlusion (Ryle, 1928). Mackenzie's cases were reviewed by White and included in his own series from Massachusetts General Hospital in which he concluded that soft heart sounds, cardiac

failure and heart block in the acute phase added to the gravity of the prognosis and he considered age, sex, hypertension and syphilis to have little effect on prognosis but added as a postscript that in later cases the duration of fever had been an important feature and the larger the infarct the longer and perhaps higher the pyrexia (White, 1926). Despite the considerable early work by White and colleagues it was Levine, who in 1929 published from the first large series of 145 cases and concluded that no single feature seemed to be reliable as indicative of a good or poor prognosis and he remarked that "there are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis" (Levine, 1929). He noted that ventricular tachycardia and heart block in the acute phase appeared to have a higher than average mortality and commented with some surprise that even the type of change of the electrocardiogram had no influence on recovery. However, the following year Connor and Holt noted the poor prognosis associated with bundle branch block and atrial fibrillation and stressed the relatively good outlook with electrocardiographic changes confined to the T wave (Connor, 1930). They confirmed the wide variation in survival and although death was sometimes due to other causes many years after coronary occlusion, their own patients and those of White often suffered repeated occlusions and in these cases death occurred in the presence of predominantly left heart failure and was

often sudden.

Despite increasing recognition of less severe cases of myocardial infarction it had become apparent that the relatively high mortality associated with the immediate postinfarction period persisted and Bland and White confirmed that in those surviving the majority of subsequent deaths occurred in the first year (Bland, 1941). Thereafter results of large series were published by Rosenbaum and Levine (1941) and also by Billings and colleagues (1949) who examined a multitude of variables and analysed their prognostic significance not only of the immediate outcome but also in relation to long term clinical status and return to work. Both studies confirmed that the presence of shock and heart failure were most important adverse prognostic features when seen in the acute phase but Rosenbaum and Levine concluded that "weighing all the information available together with the general appearance of the patient enables the physician to make a fair estimate as to the immediate prognosis". It was following this suggestion that Schnur devised a numerical score to express the clinical state of the individual patient, but his particular mathematical index was rather complicated and employed lax criteria allowing considerable variation between individual clinicians (Schnur, 1953). Therefore Peel and colleagues produced a simplified index which could be rapidly calculated at the bedside and included age and sex of the

patient with strict categorisation of the degrees of shock and heart failure and in addition weighted adversely transmural infarction, bundle branch block and arrhythmia (Peel, 1962). Not only did this provide a reliable guide to prognosis of individual patients but also allowed assessment of the value of any therapeutic intervention and was used by Peel in his early trial of anticoagulant treatment. Thus the trend shifted from the analysis of single isolated variables which had dominated early work to the formulation of a weighted score based on the severity of a number of adverse features and thereby the concept of the Coronary Prognostic Index (CPI) developed. Thereafter the value of such an approach in the acute phase was further demonstrated by Norris who produced a similar index but one which placed greater emphasis on admission systolic blood pressure, the appearances of the initial chest radiographs and the electrocardiographic evidence of anterior infarction (Norris, 1969). On this basis the severity of infarction was assessed for each patient and their individual "scores" correlated well with their survival in hospital and on this occasion the prognostic index used to determine the effect of a coronary care unit on mortality during the acute phase. Earlier work however by Beard et al (1960) failed to show any excess early mortality following anterior infarction but the observations of Norris were later repeated by Kitchin and Pocock (1977) who confirmed the adverse prognostic implications of

anterior infarction particularly if transmural.

Thus it gradually became apparent that excess mortality during hospital stay was seen in an older age group who often had a history of a previous myocardial infarction. Other factors associated with poor prognosis in this early period included transmural anterior infarction and the presence of shock or clinical or radiological evidence of heart failure during the acute phase.

Although most authors agree upon the factors increasing the risk of hospital mortality there remains considerable debate as to the variables predictive of survival after discharge from hospital. The early reviews of Rosenbaum and Levine (Rosenbaum, 1941) and that of Bland and White (Bland, 1941) both stressed the poor long term prognostic implications of congestive cardiac failure persisting or occurring after infarction. However they could only agree on two other variables predictive of early mortality, one being increasing age, the other being atrial fibrillation a common accompaniment to heart failure, and thereafter their two views differed. Peel attempted to extrapolate his index, predictive of mortality in the first four weeks, to see whether or not it could be used as a guide to survival in the subsequent years (Peel, 1962). Unfortunately he was unable to trace all of the original population but with the limited data available it appeared as if his CPI (based on age,

previous history, shock, heart failure, rhythm disturbance and electrocardiographic changes) did bear some relationship to survival in the long term. The use of the CPI to predict long term survival was then re-examined by Norris, on this occasion using a modification of his original index for hospital mortality (Norris, 1970). The importance of each clinical variable examined was assessed using discriminant analysis and using this method survival at three years was predicted using a weighted score derived from four variables - age, previous infarction, radiological heart size and pulmonary congestion. The predictive value of the same index was later re-examined with respect to mortality at six years and once again shown to be reliable (Norris, 1974). However the same approach was used by Kitchin and Pocock who used multivariate analysis on 20 variables in an attempt to select those independently predicting mortality within five years of discharge from hospital (Kitchin, 1977). They included age and previous history but did not study the radiological changes seen in the acute phase and using this method only six of the original 20 variables significantly adversely affected prognosis - previous infarction, tachycardia, cardiac arrest (ventricular fibrillation), ventricular arrhythmia and, atrial fibrillation. Unlike the studies of Norris, increasing age was not found to adversely affect prognosis, and in addition ventricular arrhythmias, including ventricular fibrillation exerted a significant

adverse prognostic effect, a finding previously reported in only one other series (Denborough, 1968).

Yet another prognostic index was formulated by Luria and colleagues (1979) in an attempt to predict mortality within two and five years after myocardial infarction. Once again a different set of variables were used and this occasion included: systolic blood pressure on admission, highest "blood urea nitrogen" in the coronary care unit, atrial arrhythmia in the coronary care unit, angina or previous myocardial infarction and more than one ventricular premature beat (VPB) per hour recorded on an eight hour electrocardiogram during convalescence just prior to hospital discharge. The same five variables continued to be significantly predictive at five years although had to be weighted differently. In addition there were various factors that were not significant at two years but appeared significant five years after infarction and these included atrial flutter, atrial fibrillation, ventricular tachycardia and ventricular fibrillation.

From this work it is evident that although authors agree on the factors predictive of mortality in the first four weeks after infarction there is considerable dispute over the long term prognostic significance of various factors seen in the acute phase. The various coronary prognostic indices have employed different statistical methods and not always examined the same clinical

variables. Although common denominators appear in the various indices, specific attempts at cross validation have been rare. Bigger et al (1978) attempted to apply the multivariate set of predictors developed by Moss et al (1976) for mortality four months after infarction but failed to achieve any cross validation between the two hospital populations. In addition such predictive ability only applies to the final end point, death and although attempts have been made to distinguish death from cardiac causes and those sudden cardiac deaths from those occurring secondary to heart failure such an approach does not predict frequent and possibly disabling non-fatal complications of myocardial infarction such as angina or heart failure. To add to these problems such a weighted score is therefore of no value in predicting ability to return to employment in those recovering since limiting symptoms such as chest pain or dyspnoea will not be predicted.

Perhaps because of all these problems associated with the coronary prognostic indices a more fundamental approach is required. The common denominator included in the indices of Norris, Kitchin and Luria has been the past history of a previous myocardial infarction and when one considers the other variables included it becomes apparent that the majority are indirectly related to the degree of myocardial damage sustained. Perhaps therefore the single most important prognostic variable is that of residual cardiac performance which in turn is governed by

the extent of myocardial impairment or infarct size. The larger the infarct the greater the degree of myocardial impairment and clinical evidence of shock and heart failure, likewise the more severe the radiological appearances of pulmonary congestion and the greater the biochemical abnormalities that follow. Ventricular function can be more directly assessed by quantitative analysis using cardiac catheterisation and contrast ventriculography and ejection fraction has been the measurement shown to be most closely reflecting the state of global ventricular performance. Hammermeister and colleagues using univariate and multivariate analysis examined 46 variables from clinical examination, resting electrocardiogram, exercise test, coronary arteriography and quantitative left ventricular contrast angiography in a heterogeneous population of 733 medically treated patients with coronary artery disease (Hammermeister, 1979). They found that the variable most predictive of survival was left ventricular ejection fraction (EF) followed by age, number of vessels with greater than 70% stenosis and ventricular arrhythmia on resting electrocardiogram. However, routine cardiac catheterisation post-infarction cannot be justified and therefore invasive measurement of left ventricular function has previously been limited to only small populations of patients with continuing angina after infarction (Hamby, 1974).

Radionuclide ventriculography which allows accurate noninvasive assessment of left ventricular performance is therefore ideally suited to serial evaluation of myocardial function in patients recovering from myocardial infarction. The historical background and the basis of our current methodology will be discussed in the following chapter.

CHAPTER 2

RADIONUCLIDE METHODS IN ASSESSMENT OF VENTRICULAR FUNCTION

Historical Background

Until recently cardiac catheterisation and contrast ventriculography was the only accurate method to assess left ventricular performance. As an invasive technique it exposes the patient to the indisputable risks of arterial puncture and intravascular injections of hypertonic contrast media and is therefore clearly unsuitable to serial measurements or repeated studies following the effects of either exercise or drug intervention. Other methods which assess left ventricular performance such as M-mode or 2-dimensional echocardiography are dependent upon the skill of the individual operator and even then images of sufficient clarity can only be obtained in a proportion of the patients studied and clearly such techniques are unsuitable for recordings taken during exercise. Other indices which have been used include the measurement of systolic time intervals as an indirect method of assessment of left ventricular function dependent upon accurate recording of the carotid pulse wave and from which one only gains an impression of global left ventricular performance. Therefore prior to the development of radionuclide techniques there remained a

need for an accurate, noninvasive, observer-independent, reproducible method suitable for serial evaluation of global and regional ventricular function.

The first experiments using radioactive material in assessment of the cardiovascular system in man were performed by Blumgart and Weiss in 1927. In using a source of radium 226 as a generator for gaseous radon and its subsequent decay product radium C they anticipated our current radiopharmaceutical techniques by 50 years. They injected an aqueous solution of radium C and using a cloud chamber to detect activity determined transpulmonary transit time as a measure of pulmonary vascular volume. However it was 20 years later before advances in instrumentation and the discovery of artificial isotopes permitted Prinzmetal (1948) to perform more sophisticated studies and using a Geiger counter they recorded right and left ventricular volume curves during the first pass of sodium 24. In 1958 MacIntyre and colleagues (1958) realised that this radiocardiographic technique could be applied to the study of cardiac output using the principle of radiodilution based on the Stewart-Hamilton equation (Stewart, 1921; Hamilton, 1928). Using a single photo-multiplier/ scintillation crystal assembly they monitored the passage of an injected bolus of radionuclide through the heart (Figure 2.1) and were able to estimate cardiac output and pulmonary transit time. Static images of the cardiovascular system could be obtained using the then

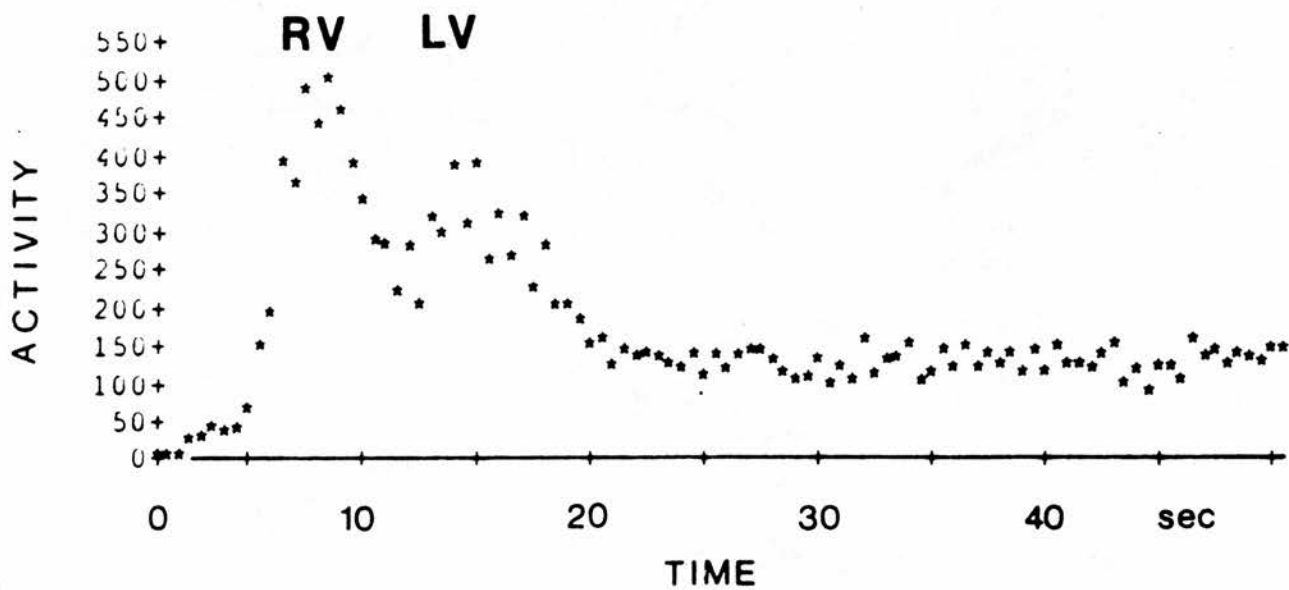


Figure 2.1 Specimen time activity curve following radionuclide bolus with a region of interest assigned over both ventricles. Two peaks are identified that represent the sequential rise and fall in counts for each 0.5 sec. sample period in the right and left ventricles (RV and LV).

available rectilinear scanner but it was not until the use of the modern scintillation camera with improved tracers labelled with radionuclides that dynamic imaging became possible.

The Radiopharmaceutical:

Historically, Blumgart and Weiss were restricted in their choice to the use of radium products, as these were the only radioactive substances then available. The tracer substance they used was the ionic form of Radium C or bismuth 214 which although has a short half life of 20 minutes is an alpha, beta and gamma emitter and thus imparts a substantial radiation burden. In contrast radionuclides in current use release only gamma photons or x-rays, all with energy sufficient to traverse overlying tissues but with no accompanying particular radiation. In addition they must have a half life sufficient to permit measurement but to decay at a rate that minimises the radiation burden to the patient. In practice the radionuclide with the desired physical properties is bound to a pharmaceutical that determines its biodistribution.

Technetium ^{99m} has physical properties that are desirable for clinical use and is one of the radionuclides most commonly used in nuclear cardiology. Technetium was the first artificially produced element and now can be separated from its parent molybdenum using a practical generator system. It has a half life of six

hours and decays emitting a single photon of 140 keV. In addition, for repeated cardiac studies, it may be confined to the intravascular space by binding it to either red blood cells (in vitro or in vivo) or perhaps more conveniently to albumin using a kit preparation (Harper, 1965). After a short period, following injection to allow for mixing of the radiopharmaceutical within the blood pool (equilibration) data acquisition may be commenced.

The Gamma Camera:

Figure 2.2 illustrates a typical modern gamma camera with 19 to 100 photomultiplier tubes located behind the camera crystal. A relatively early development was the use of a lead collimator in front of the camera assembly which acted as a type of lens allowing detection of only those gamma photons emitted parallel to the axis of the collimator holes and allowed one to one correspondence between the point of emission from the patient and the image (Figure 2.3). Outputs X and Y (Figure 2.2) indicate the X and Y position of light flashes detected by the camera crystal and used to control the horizontal and vertical deflection amplifiers of a cathode ray oscilloscope. Signal Z indicates when a light flash falls within the appropriate energy spectrum. Since the outputs from such a camera cover large voltage ranges they do not qualify as digital signals and therefore the gamma camera is connected to the computer system by analogue to digital converters, ADC's (Figure 2.4). When a Z pulse is detected the outputs of the X and Y signals are immediately sampled, held at a constant voltage and converted to digital representation, such a circuit being designated as "sample and hold". The valid events within the desired energy window have now been converted by the ADC's to digital form and can be directly processed by the computer.

Thus gamma radiation incident on the camera crystal triggers the stream of X,Y pairs into the computer from

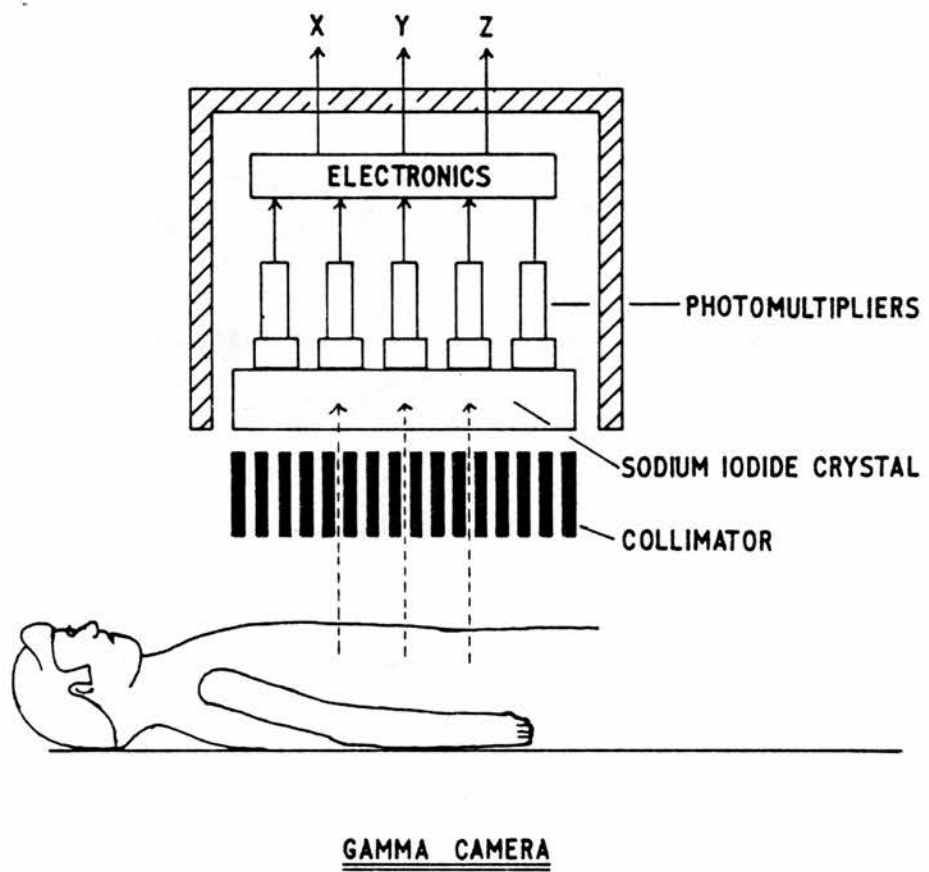


Figure 2.2 Schematic diagram of the modern gamma camera.

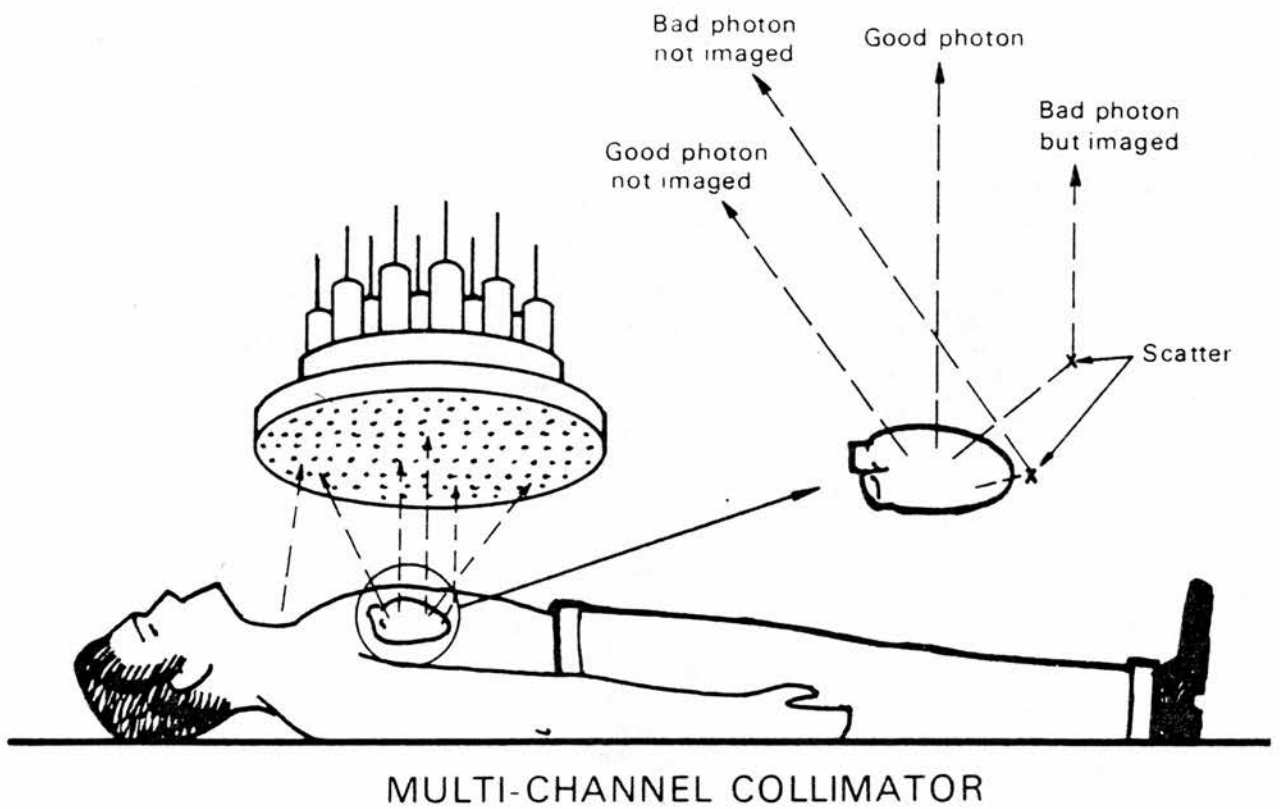


Figure 2.3 Schematic demonstration of a multichannel collimator which acts as a type of lens for photon detection.

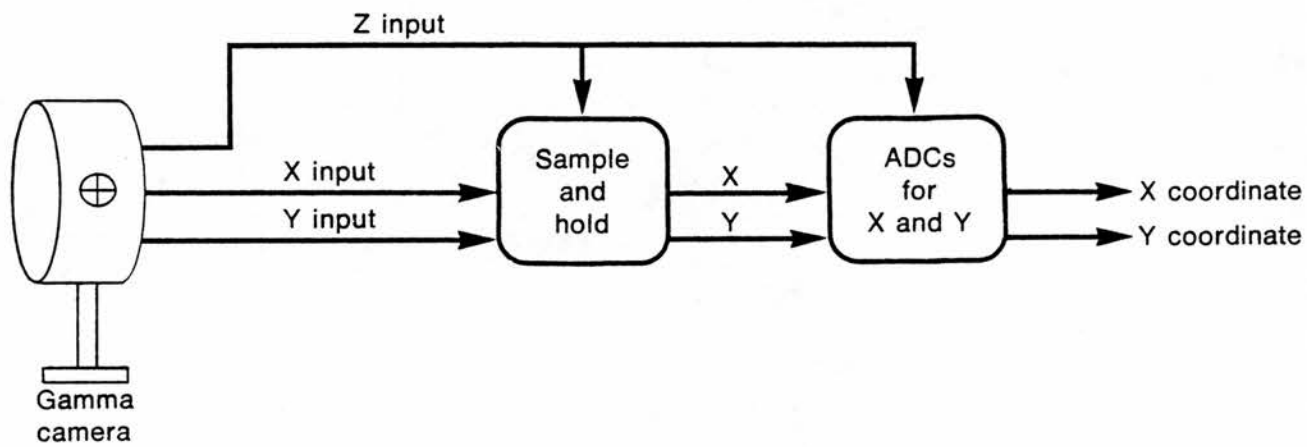
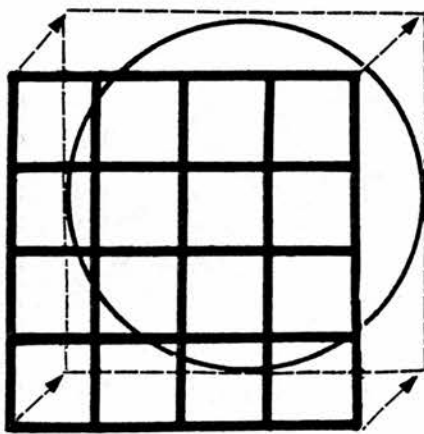


Figure 2.4 Diagrammatic representation of the gamma camera/computer interface; ADC's, analogue to digital converters.

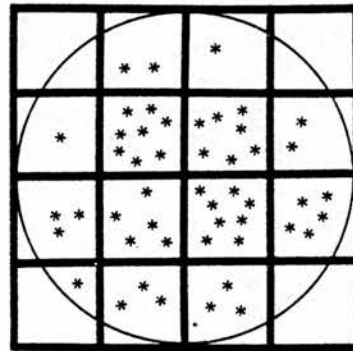
the analogue to digital converters and the coordinates are thereafter processed according to the mode of acquisition, either frame mode or list mode. Frame mode is the most widely used approach in the acquisition of nuclear medicine data and simplified merely creates a digital image of the data as the counts strike the face of the crystal. This process of digitalisation is illustrated in Figure 2.5 which shows the camera face as if partitioned by a wire grid (A). As incident gamma rays strike the crystal (B) each square has a corresponding digital value (C). In practice the camera field is usually divided into much finer portions by using larger matrix sizes and thus the net effect is to produce a small light dot on the cathode ray tube for each gamma ray detected, in the same relative position as it occurred within the subject. In contrast list mode acquisition involves transfer of the X, Y pairs directly to the computer memory and although no images result the list data can be formatted into a digital matrix when the acquisition is complete. Frame mode images are available immediately after acquisition and therefore are more economical in terms of both computer time and storage space.

The First Pass Method:

The first report of the use of the gamma/camera digital computer combination was described by Kriss et al in 1966, who were able to visualise the first passage of



A



B

0	2	1	0
1	8	7	2
3	5	8	5
1	3	3	0

C

Figure 2.5 Diagrammatic representation of the gamma camera face and the creation of a digital image.

the radionuclide labelled tracer through the central circulation and recorded the events as a photograph using the defocused oscilloscope light dot (Figure 2.6). Later the same author (Kriss et al, 1971) using similar methods made a detailed study of chamber size in a variety of congenital and acquired cardiovascular pathologies and recommended that the technique be employed as a screening test prior to formal cardiac catheterisation or indeed used preferentially in those too ill to undergo cardiac catheterisation or in those patients in who serial studies were desirable. Van Dyke and colleagues were the first to successfully apply quantitative first pass methods to the evaluation of left ventricular function (Van Dyke, 1972). Using a single crystal scintillation camera and relatively simple data processing they found that left ventricular ejection fraction could be calculated accurately from the high frequency components of the radionuclide ventriculogram. Until then calculation of ejection fraction from isotopic methods had employed the area-length method described by Dodge (1960) and originally used for contrast ventriculography (Strauss, 1971). Results from this method had been validated by Mullins using a dog model (Mullins, 1969) but as with contrast studies area-length calculations assume that the left ventricle conforms to an ellipsoid of revolution which limits its accuracy particularly in the presence of regional asynergy which is usually

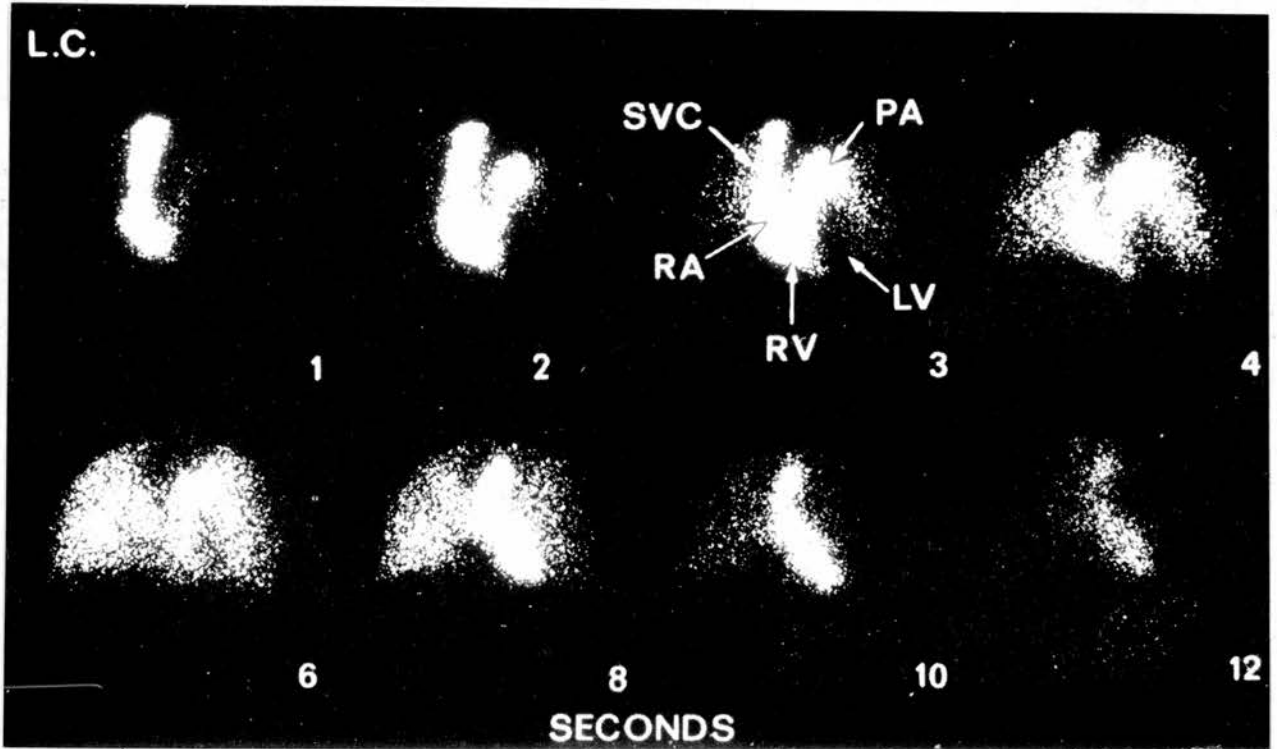


Figure 2.6 Serial images of a radionuclide bolus taken in the anterior projection, showing clear visualisation of the right and left sides of the heart and normal pulmonary transit. SVC, superior vena cava; RA, right atrium, RV, right ventricle; PA, pulmonary artery; LV, left ventricle.

present following myocardial infarction. Later it was suggested that more accurate measurement of ejection fraction could be obtained by analysis of the time activity curves generated during the first passage of radionuclide bolus and this method was shown to correlate well with biplane contrast cineangiography (Schelbert et al, 1975). The time activity curve with high temporal resolution generated from the left ventricle is made up of a series of oscillations, the peaks and troughs of activity corresponding to end-diastole and end-systole respectively. Figure 2.7 shows such a time activity curve and the highest activity peak of each cycle corresponds to end-diastole (ED) and the subsequent low value to end-systole (ES) the difference corresponding to stroke volume. The major limitation of this count based technique involves appropriate correction for background activity which in the first pass method resides mainly in the lung fields and left atrium.

Background Activity

Ideally, the time activity curve should be made up of counts originating exclusively from within the left ventricular cavity and should be free of activity arising from the noncardiac background structures already mentioned. In order to correct for background contributions to the ventricular time activity curve a light pen is used to draw two regions of interest (ROI) one precisely around the ventricle and a second

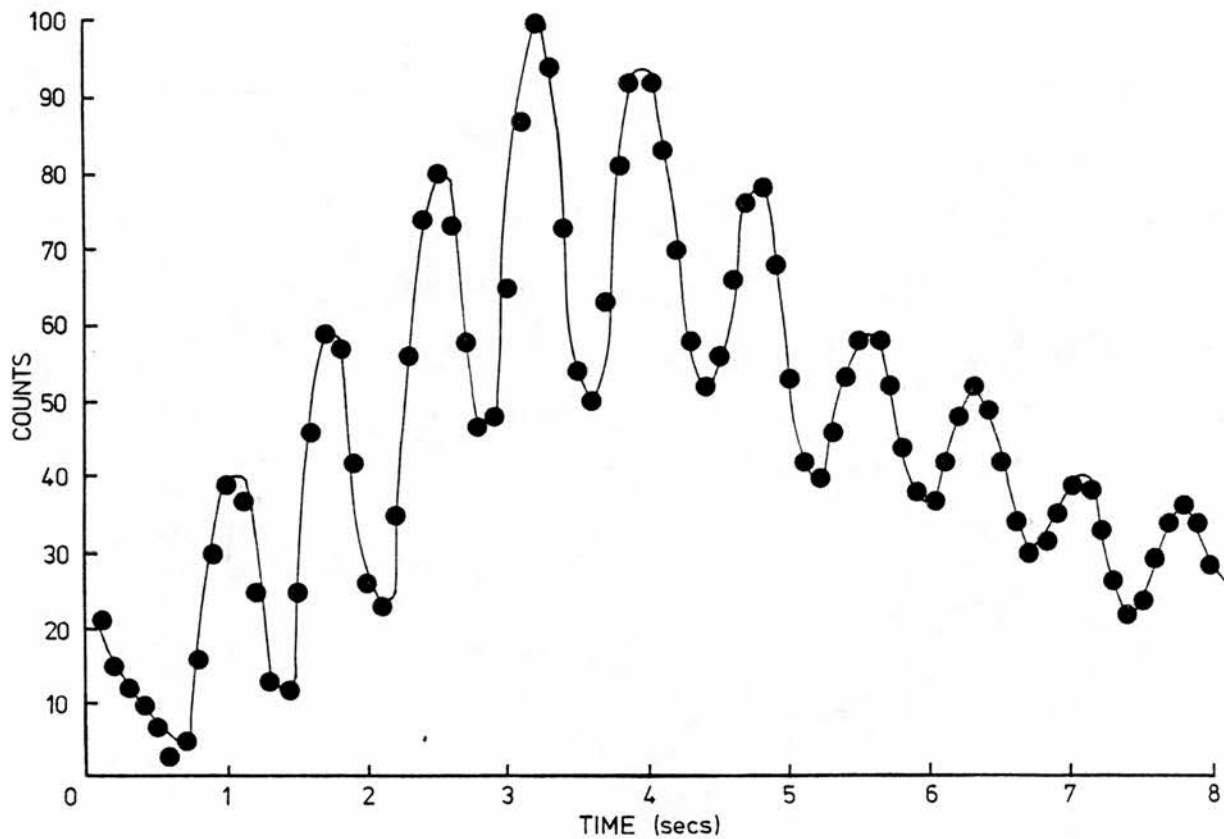


Figure 2.7 Radio-isotope dilution curve from the left ventricular region of interest showing systolic troughs and diastolic peaks of radioactivity.

accounting for the noncardiac background structures excluding the aortic root, in most instances assuming the shape of a horseshoe surrounding the ventricular ROI. From these regions of interest two simultaneous high frequency time activity curves are generated and background curve is digitally "smoothed" to minimise statistical noise and then normalised to the ventricular curve by multiplying each point on the background curve by the ratio of the area of the ventricular ROI to the area of the background ROI. Having now obtained a time activity curve corrected for noncardiac background activity the difference in count rate at end-diastole and end-systole in any one cycle is proportional to the stroke volume, which divided by the corresponding count rate at end-diastole is equal to ejection fraction: thus:-

$$EF = \frac{\text{end-diastolic counts} - \text{end-systolic counts}}{\text{end-diastolic counts} - \text{background counts}}$$

This method was first used by Parker who achieved good correlation between radionuclide and contrast methods in calculation of EF choosing as background the counts in the myocardial silhouette on the end-diastolic frame. However because end-diastole must be corrected for background in the denominator an accurate determination of background activity is essential in order to avoid varying degrees of underestimation of ejection fraction.

The main advantages of the first-pass method are as follows:

1. It allows temporal separation of the cardiac chambers, thereby permitting assessment of both right and left ventricular function (Reduto et al, 1978).
2. The short time (20 - 30 seconds) required for data acquisition in critically ill patients.
3. Studies can be performed in any projection particularly the right anterior oblique used for assessment of right ventricular wall motion.
4. It can provide assessment of the relative regional ejection fraction during maximal exercise since imaging can be performed at peak stress because of the short data acquisition time (Bodenheimer et al, 1978).

The disadvantages are:

1. Only one view is recorded with each injection thereby limiting the number of studies to two or rarely three injections because of the cumulative radiation dose effect.
2. Haemodynamic changes following various therapeutic interventions are difficult to study.
3. The technique requires a system with high count characteristics and is dependent on obtaining a good bolus injection which may at times be difficult or impossible as in severe pulmonary hypertension or in the presence of severe tricuspid regurgitation.

Gated Cardiac Studies

With the incorporation of electrocardiographic gating mechanisms to trigger repeated acquisition of data at end-systole and end-diastole, equilibrium studies of the cardiac blood pool allowed a summation of 200 - 500 heart beats and permitted serial evaluation of EF (Strauss et al, 1971). Using this method the first pass non-gated data could be analysed and thereafter a gated study could be performed and repeated if necessary following physiological or pharmacological intervention. The electrocardiogram lead with the most prominent R and T waves is usually selected for gating. The "gate" is an electronic switch which determines the intervals during which the scintillation camera records and it has two

controls. A delay control regulates the time between the triggering signal (R wave) and opening of the gate and in addition a record control regulates the time after the delay during which the gate is open and an image is recorded. In the initial studies of Strauss et al (1971) the delay in record controls was set to record only during each end-systole, that is the recording occurred only during the last 40 milliseconds of the T wave in each cardiac cycle until a count target had been reached. An end-diastolic image was then similarly produced by delaying recording until 60 milliseconds before the next R wave (Figure 2.8). In this manner an image of the mean appearance of the heart and great vessels at end-systole and another at end-diastole were obtained recording in not one but approximately 200 - 500 heart beats for each. The data could in addition be stored on magnetic disk or tape for subsequent analysis and the left ventricle displayed selectively at end-diastole and end-systole, thus permitting detection of regional myocardial dysfunction.

The haemodynamic importance of regional myocardial dysfunction as a cause of cardiac decompensation had already been emphasised (Klein, 1967; Herman, 1967) and the early noninvasive methods proved in addition to be accurate in the detection of left ventricular aneurysm (Zaret et al, 1971). End-systolic and end-diastolic volumes were initially derived from the use of long axis

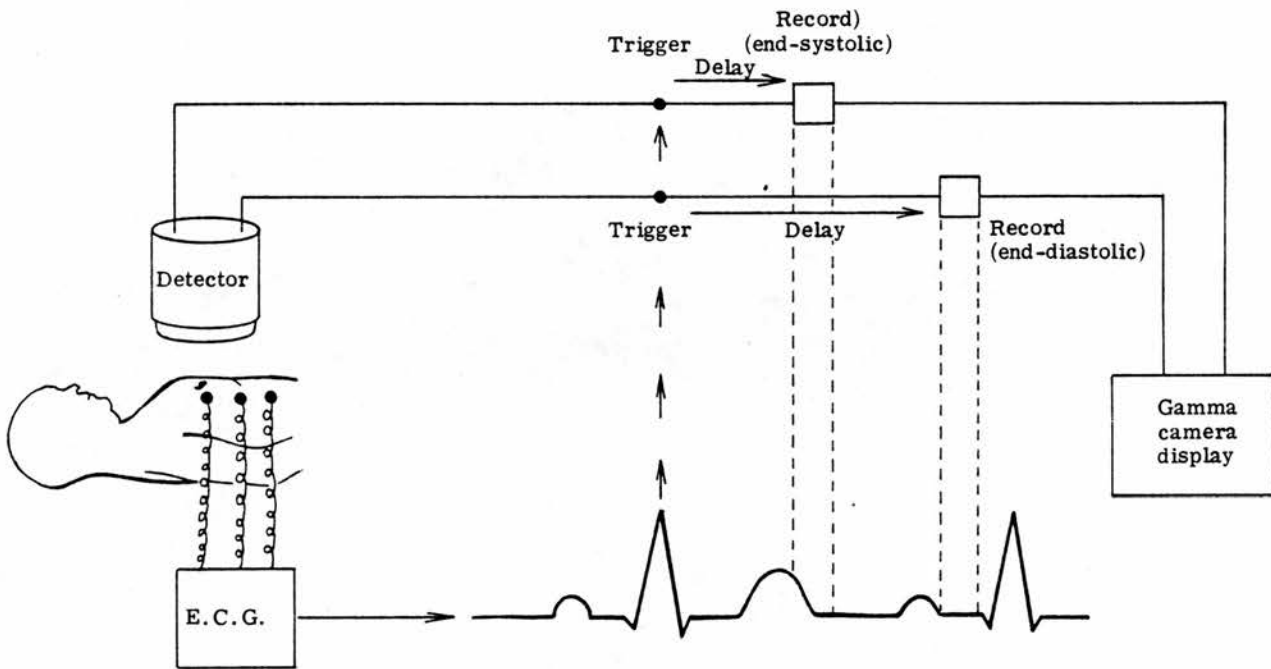


Figure 2.8 Schematic diagram of the electrocardiographic gating of the gamma camera. The R wave of the electrocardiogram triggers the gating circuit and is followed by a delay interval. After the delay interval, the gate is opened, and the gamma camera accepts data during the record interval. The setting for end-systole is on the upper line, that for end-diastole on the lower line. (After Strauss et al, 1971).

and area measurements and ejection fraction calculated from these volume measurements was shown to correlate well with values obtained by contrast ventriculography performed on the same patients (Rigo, 1974; Berman, 1976).

Multiple Gated Acquisition

Further sophistication of the gating technique allowed picture frame images to be distributed at short time intervals throughout the cardiac cycle (multiple gated acquisition gated equilibrium or blood pool imaging) and events during diastole and systole recorded over 500 heart beats, summated and viewed as a continuous-loop cine movie (Strauss, 1977; Muir, 1977). Figure 2.9 illustrates the creation of the gated image. The square waves labelled "beat 1, beat 2..." represent R wave markers which have been inserted into the scintillation data stream from continuous electrocardiographic monitoring. The X, Y coordinates of each scintillation occurring 0 - 20 milliseconds after the R marker (beat 1) specify where in the first frame (32 x 32 matrix) that scintillation count is accumulated. This process is continued for each 20 millisecond block of scintillation data until the next R wave marker (beat 2) is reached and at that point the process begins again. All the scintillation data from 500 heart beats are sorted and accumulated into the appropriate 20 millisecond frames. Figure 2.10 shows the resultant left ventricular curve and its temporal relationship to the electrocardiogram. In this case the gamma camera has been positioned in the 30° left anterior oblique projection allowing the left ventricle to be separated from other cardiac chambers. The R wave marker occurs on the upstroke and triggers data accumulation within the

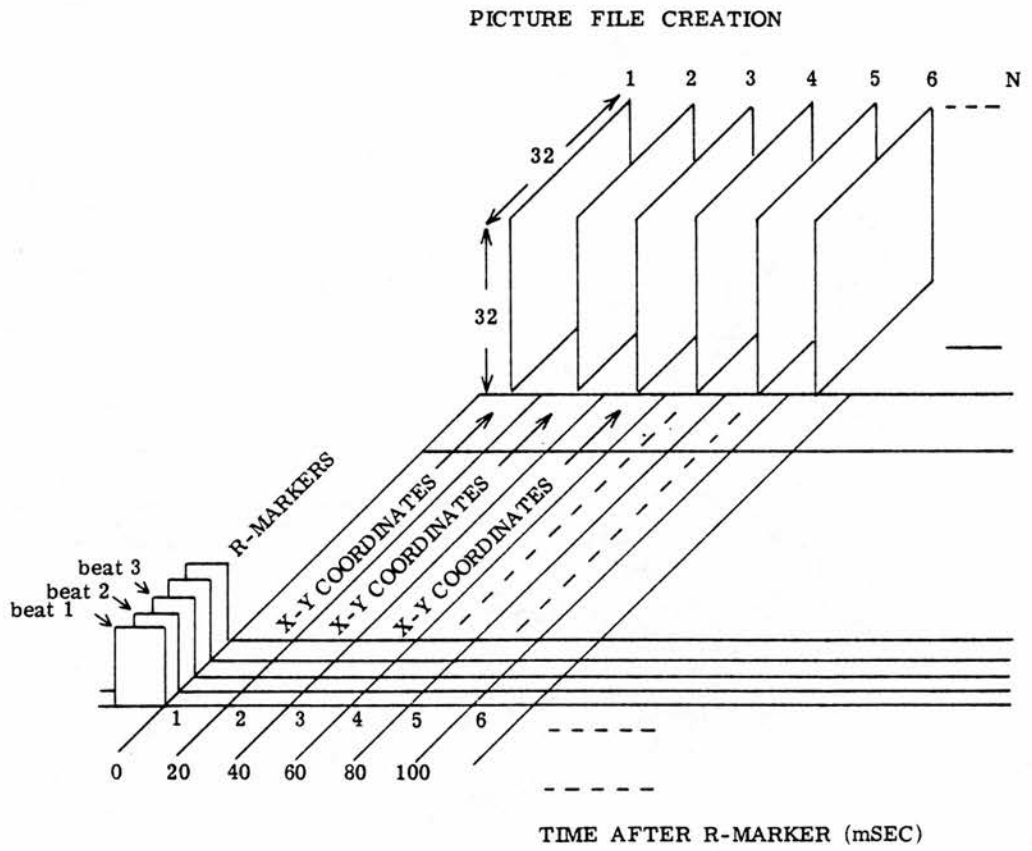


Figure 2.9 Diagrammatic representation of the creation of the gated image (see text).

ECG TRIGGERING METHOD

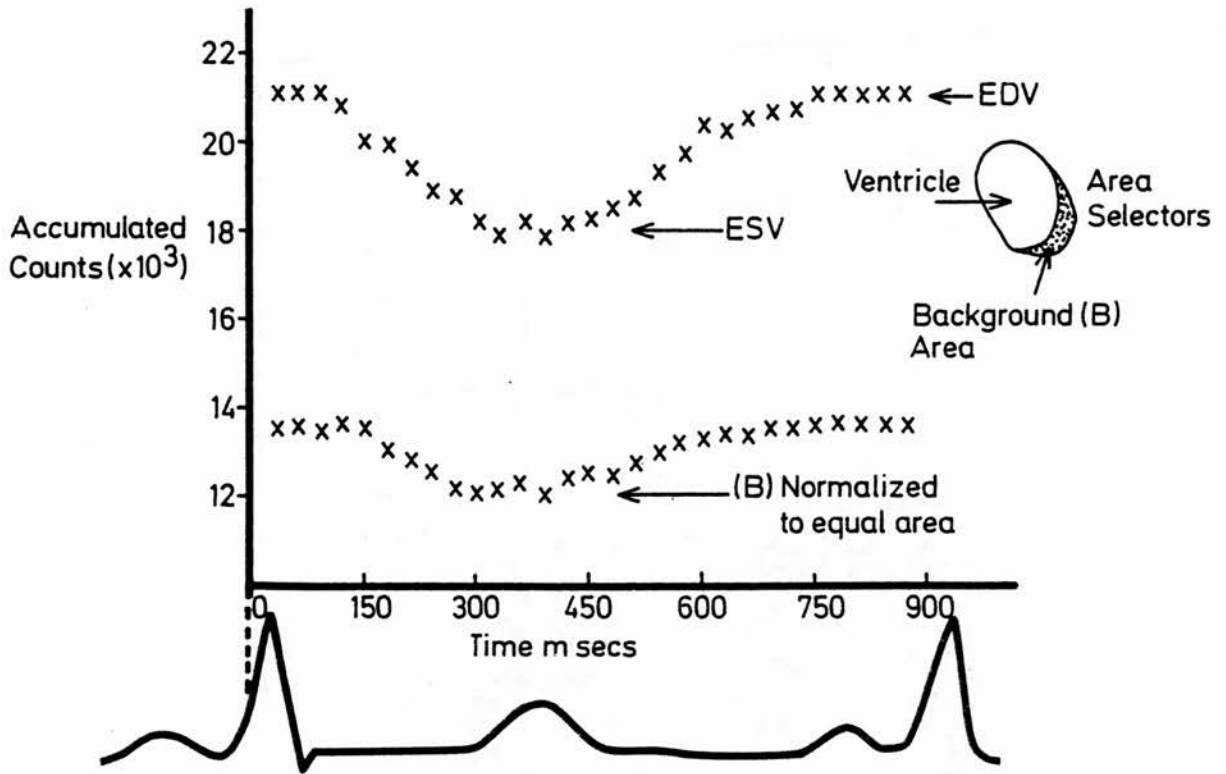


Figure 2.10 Accumulated radioactivity from the left ventricular and background (B) areas. Ejection fraction is calculated from the difference in radioactivity between end-diastole, representing end-diastolic volume (EDV), and end-systole, representing end-systolic volume (ESV), divided by the radioactivity at end-diastole. With this method the background correction has been taken from an area just inside the ventricular margin (see text).

next 20 millisecond interval and thus the first frame represents end-diastole. Since count rate is proportional to volume this frame also represents end-diastolic volume (EDV) and the same is true for each stage of the cardiac cycle and thus end-systolic volume (ESV) and ejection fraction can be measured in this way (Ashburn, 1978). As in the first pass method the left ventricular region of interest needs to be corrected for activity in the noncardiac background area (B).

The advantages of the method are as follows:-

1. It requires minimal additional instrumentation to a gamma camera installed for other purposes.
2. The safety and ease of repetitive studies allows evaluation of therapeutic interventions and differing camera projections may be used.
3. Multiple scans may be recorded over three hours. Tracer loss to the extravascular space may become significant with some preparations and border definition is severely degraded but this problem can be overcome using high quality and electrolytically labelled human serum albumin (Millar, 1979).
4. Statistically reliable data are easier to obtain because the radioactivity from the ventricle is analysed over numerous beats.
5. The need for a bolus injection is eliminated and the technique may be used in situations where a good

bolus may not be obtained.

The disadvantages are:

1. Routine imaging can only be performed in a single view - the left anterior oblique and even then separation between right and left ventricles may not be adequate and some areas of left ventricular wall motion may be visualised suboptimally.
2. The relatively lengthy acquisition time may prohibit the collection of adequate data during maximal exercise.
3. Acquisition during exercise may be limited by chest wall movement which impairs image quality.

Methodological Considerations

1. The Influence of Arrhythmias:

Border definition is adversely affected in patients with marked rhythm irregularities since during the accumulation of data over a relatively long period, heart rate should be constant with few or no ectopic beats. Persistent arrhythmias such as frequent ventricular premature beats, bigeminy or atrial fibrillation, result in significant changes in ventricular performance due to the variations in the R-R interval. Thus in such patients the results obtained will depend on the R-R interval selected, longer R-R intervals being associated with improved ejection fraction. From the patient population studied it became apparent that 10% of those individuals recovering from myocardial infarction had frequent (greater than one in twenty) extrasystoles and without some means of excluding these and the subsequent post-extrasystolic beats the calculated EF was in error. Therefore using a modified tape recorder the blood pool data were replayed into the computer and ectopic and post-ectopic beats were rejected. Using this constraining procedure, previously distorted ventricular volumes curves were effectively re-constructed, changing the end-systolic volume and EF (Brash, 1980).

2. Edge Detection

Accurate edge detection is fundamental to any

assessment of wall motion and measurement of ejection fraction. The use of selective injections of contrast in conventional ventriculography markedly enhances edge detection by avoiding overlap of specified chambers. On the other hand, in radioisotope studies, the presence of isotope in cardiac and non-cardiac structures that overlap the chamber of interest interferes with clear delineation of its wall motion. The problem of anatomical overlap is eliminated to a considerable extent using the first pass method in which the finite time required for isotope to pass through the lung fields into the left ventricle results in temporal separation. However, in gated equilibrium radionuclide studies, isotope is present simultaneously in the right and left ventricles without temporal separation. Therefore positioning of the camera is critical and the left anterior oblique view is commonly used to permit separation between right and left ventricles often with a caudal tilt to separate left atrium from the upper portion of left ventricle. The other variable which may have some effect on edge detection is the rotation of the heart which occurs during cardiac contraction.

Two common methods used for identifying the edge of the left ventricle are threshold analysis, which detects the edge of the left ventricle as a point below a percentage of the peak counts in the ventricle, or as used in our own laboratory measurement of a second derivative which places the edge of the ventricle where a

certain rate of change in counts occurs.

3. Dead Time Correction

If the camera is capable of detecting activity faster than the conversion rate of the ADC, data will be lost between the camera and the computer. The interval during which data is lost is called computer dead time. Due to higher total counting rates achieved with modern scintillation cameras, dead time losses may lead to non-linear time activity curves, and therefore a correction factor may be necessary (See Chapter 3).

4. Calculation of Ejection Fraction

Several studies discussed previously have confirmed the good correlation between measurements of ejection fraction made by radionuclide and contrast ventriculography, and this has been reported from our own laboratory (Muir et al., 1977) (Figure 2.11). Examination of the regression plots reveals however that there is a tendency to underestimate high ejection fractions and to overestimate lower ejection fractions relative to the value obtained by contrast studies. Both first pass and gated equilibrium studies correlate with each other in estimation of ejection fraction not only at rest (Wackers, 1978; Pfisterer, 1979 and Folland, 1979) but also during exercise (Pfisterer, 1979). Reproducibility of ejection fraction measurements using radionuclide ventriculography on separate days has been

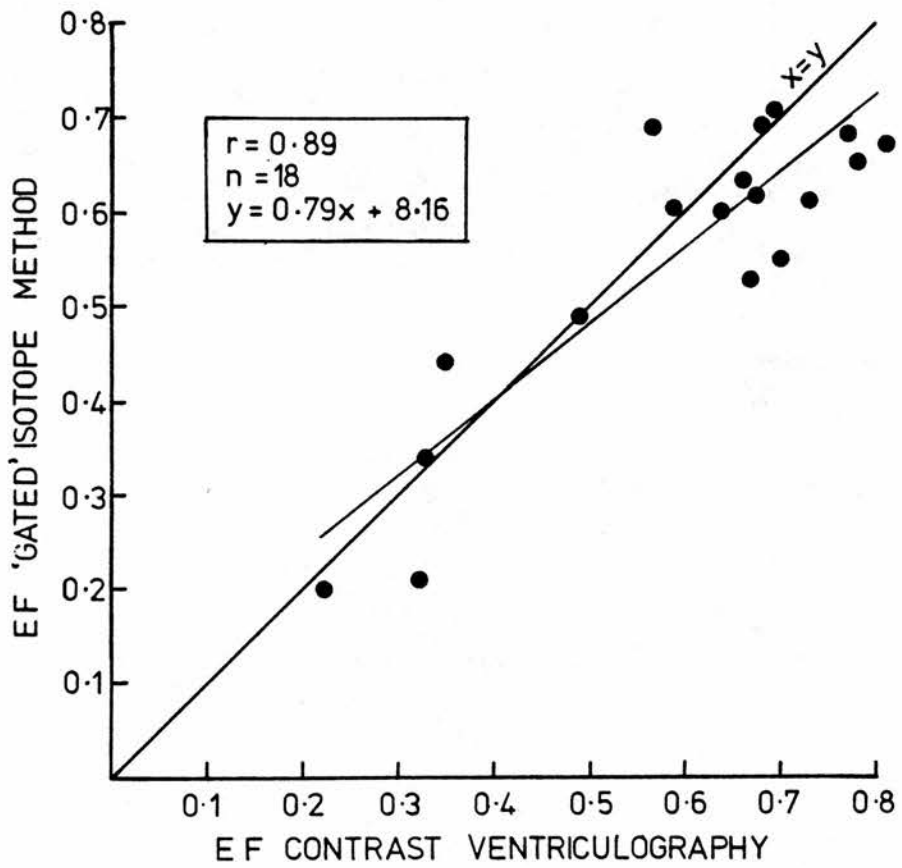


Figure 2.11 Comparison of ejection fraction (EF) measured by single plane contrast ventriculography and the gated radio-isotope method. (After Muir, 1977).

found to be surprisingly good for both methods with an average variation of approximately four percent (Wackers, 1979; Marshall, 1978) which corresponds to the variability of measurements obtained with contrast ventriculography (McAnulty, 1974). Thus despite potential methodological limitations, impressive correlations have been obtained. However, it has also been observed that if the initial ejection fraction was in the normal range, greater variability is seen (Marshall, 1979; Wackers, 1979). This has important implications when assessing the effects of interventions such as exercise on ejection fraction. But despite this Pfisterer et al (1979) found the response of ejection fraction to exercise in the supine position to be reproducible.

5. Calculation of Ventricular Volumes

Although the biplane angiographic method is reasonably accurate for measuring both ventricular volume and stroke volume the technique is not without major difficulties. The radio opaque contrast media employed are myocardial depressants that alter cardiac output and the large volumes of hypertonic contrast substances which are required for the visualisation of the cardiac chambers can change intracardiac and circulatory volume (Hilbish, 1960). Therefore conventional angiography has not been suitable for serial determination of ventricular volume. Using radionuclide methods, two basic approaches have been employed to determine end-diastolic and end-

systolic volume and thus stroke volume and cardiac output. The area-length method for determining ejection fraction is highly dependent on spatial separation of chambers and accurate edge detection. A modification of this approach uses the ejection fraction determined from the time activity curve and reduces error arising from the geometric assumptions. However this so-called "counts" technique is not completely free of geometrical considerations because of the attenuation of photons within the source at increasing depth. When the end-diastolic volume is 300 ml or less, counts perceived by the detector are linearly related to absolute volume (Bacharach, 1979). At volumes greater than 300 ml there is progressive divergence of the perceived counts and the true ventricular volume so that at 500 ml this method is no longer valid. An alternative approach is based on the use of the indicator dilution theory. If the concentration of an indicator such as a radionuclide can be determined and the administered dose is known, the volume of distribution in this case, the left ventricle, can be measured. The counts at end-diastole and end-systole are taken to reflect the concentration in the left ventricle (Hannan, 1980) however, correction for administered dose and the volume of distribution is required. This can be obtained by determining plasma volume using radiolabelled albumin with repeated blood sampling. One further criticism often levelled at the various isotopic methods, questions accurate

determination of ventricular volume, since not only do mitral and aortic valve planes move from end-diastole to end-systole but there are also slight changes in left ventricular volume and position with quiet respiration. These factors, however, do not appreciably interfere with the determination of relative change of ventricular dimensions since there is close agreement between radionuclide and conventional contrast ventriculography (Strauss, 1971; Burow, 1977).

6. Assessment of Regional Wall Motion

Although global left ventricular performance correlates well with the severity of abnormality of regional wall movement, careful assessment of segmental contractile patterns is still necessary in order to follow the natural history of coronary artery disease and to assess the effect of therapy. Of particular importance is the detection of discrete areas of ventricular dyskinesis since modern surgical techniques have provided an alternative to medical management of severe heart failure and intractable arrhythmias often associated with ventricular aneurysm. In addition to the assessment of the continuous-loop cine movie, the end-diastolic and end-systolic frames may be super-imposed using either hand or computer drawn outlines. However the three-dimensional nature of the left ventricle ideally requires multiple views in order to visualise all

areas. The right and left anterior oblique views are most commonly utilised. The right anterior oblique view permits visualisation of anterior apical and inferior zones of the left ventricle. The left anterior oblique view provides optimal delineation of the septum and posterolateral zones.

Definitions of terms used to describe wall motion abnormalities follow in the next chapter and the principles of paradox imaging, a method used in the identification of ventricular dyskinesis, will be discussed in more detail later.

7. Intervention Radionuclide Ventriculography

In recent years the concept of monitoring ventricular performance following exercise or therapeutic intervention has gained increasing acceptance. Noninvasive assessment of left ventricular function using radionuclides may be repeated after either maximal or submaximal, dynamic or isometric, supine or erect exercise and the effects of nitroglycerin or dipyridimole likewise have been monitored.

To avoid the radiation burden of repeated first pass studies our own laboratory has concentrated on the method of gated blood pool imaging and with the use of high quality electrolytically labelled human serum albumin, reliable data may be acquired for up to three hours after the injection of 20 mCi of technetium^{99m}.

In summary, since its introduction in the early

1970's, noninvasive cardiac imaging has become widely used in patients with ischaemic heart disease. The first pass studies have been used mainly in the evaluation of right ventricular function, measurement of ejection fraction and detection of wall motion abnormalities at rest and after exercise. The gated blood pool study has been found most useful in assessment of global left ventricular function, regional wall motion and right ventricular function, both at rest and during exercise and is the method of choice when serial studies following physiological or pharmacological intervention are required. The techniques are noninvasive, successfully performed in almost 100% of cases and have a high degree of patient acceptability. The results are easy to interpret and quantify and have a high degree of reproducibility with relative observer independence. Several correlative studies have now been performed and in each case significant agreement between these and the more invasive methods has been shown. Much of the information provided is new and improvements continue to be made in the techniques and their clinical applications. The particular methods and modifications of various aspects of the technique used for the work in this thesis are described in the following chapter.

CHAPTER 3

METHODS

Patient Population:

One hundred consecutive patients were studied (84 men and 16 women) of whom the majority had been transferred to a general medical unit after a variable length of stay in a coronary care unit (1 - 7 days, mean 2.3 days) between August 1978 and December 1979 following their first myocardial infarction. Nine patients were admitted to the general medical wards direct from the Accident and Emergency Department with a provisional diagnosis of myocardial ischaemia but were subsequently shown to have sustained proven myocardial infarction. Patients over the age of 70 were excluded and the mean age was 59 years (range 39 - 69). Figure 3.1 shows the age/sex distribution of the patients entered into the study. All patients satisfied the three criteria for acute myocardial infarction: myocardial ischaemic pain lasting more than 30 minutes, a rise in serum levels of two or three serum enzymes (aspartate aminotransferase, lactate dehydrogenase or creatine kinase, (CK) and electrocardiographic evidence of acute infarction. Infarct location was characterised according to established electrocardiographic criteria as anterior (including anteroseptal and anterolateral) or inferior



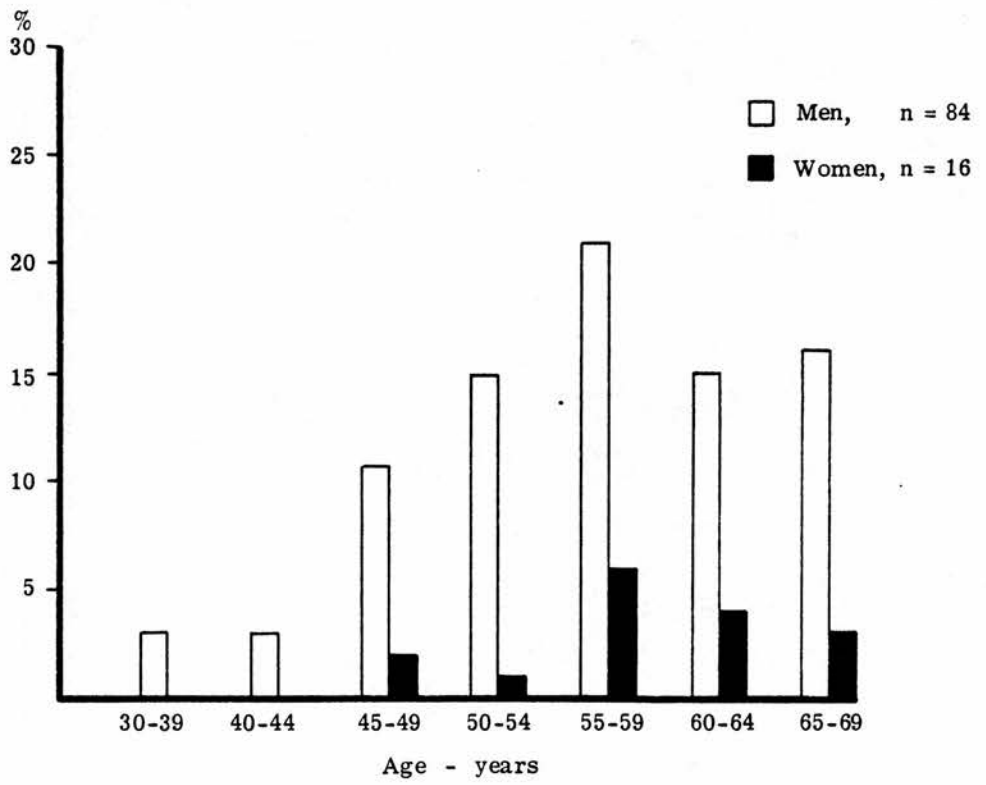


Figure 3.1 Age and sex distribution of 100 consecutive patients following their first myocardial infarction.

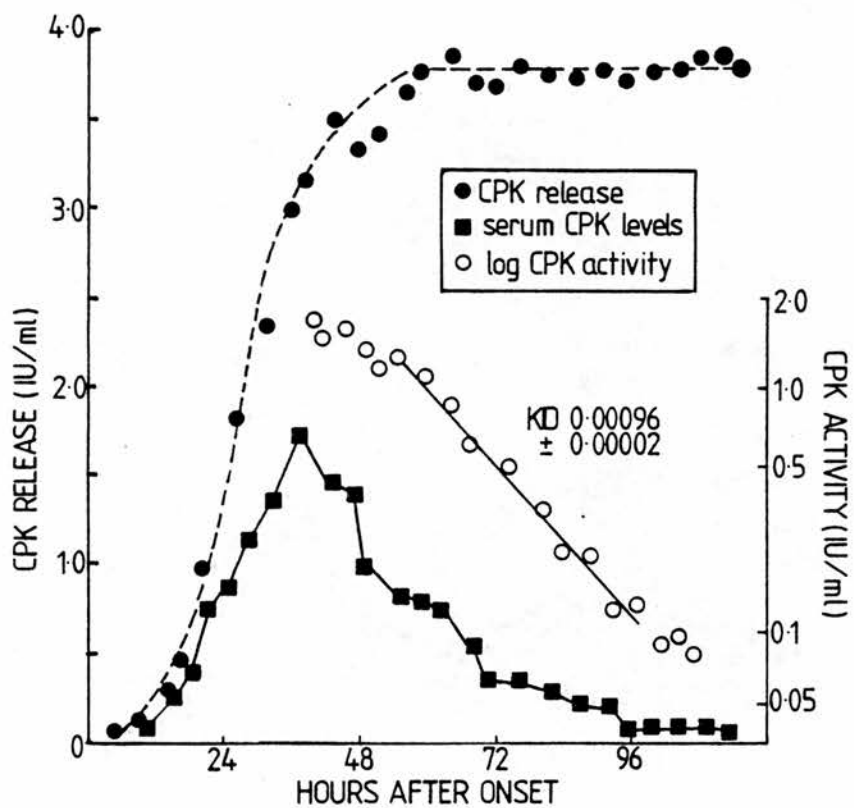
(including inferolateral and inferoposterior). The site of infarction was 'inferior' in 54 and 'anterior' in 46 patients.

Clinical progress was carefully monitored in the coronary care unit, and serious early arrhythmias defined as ventricular tachycardia, ventricular fibrillation, complete heart block or asystole, were recorded. Clinical signs of overt heart failure in the acute phase (tachycardia, gallop rhythm, and persistent crepitations) were noted. Left ventricular failure was noted separately and diagnosed radiologically as alveolar oedema. Heart size was estimated by the cardiothoracic ratio (CTR) method and expressed as the ratio of the maximal cardiac diameter to the maximal intrathoracic diameter from standard six foot chest radiograph taken on the day before discharge from hospital, values > 0.50 being considered to represent cardiomegaly.

Ninety-one individuals admitted directly to the coronary care unit (CCU) had venous blood withdrawn on admission and thereafter at 12 - 24 hourly intervals until their transfer. When possible drugs were given intravenously and timing, voltage and frequency of any cardioversion procedure noted. Total CK activity was measured by an optimised standard method (Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology, 1976) at 37° on a Rotochem IIa centrifugal analyser (American Instrument Co., Silver Spring, Maryland 8030) using kit reagents

supplied by Boehringer Corporation Ltd., Lewes, U.K. and based on a modification of the Rosalki Technique. In the laboratory using this method, between batch precision, determined from repeat assay of specimens from patients and from analysis of commercial quality control material, indicated a coefficient of variation of about 5%. The peak level of CK activity was noted for each patient. Serial enzyme values were used to construct a CK profile for individual patients and the fractional decay rate, KD of enzyme activity calculated if two or more CK levels had been measured later than 24 hours after the onset of pain. (Norris, 1975. Figure 3.2). This data was available on 47 out of the 92 patients admitted to the C.C.U. and thus an average KD value calculated for the whole population and used to estimate a theoretical peak SCK value 24 hours after the onset of pain.

Of the 100 patients, 75 were smokers at the time of admission and a further 12 had a previous history of cigarette consumption although had stopped smoking for a variable period prior to admission. Seventeen had a history of angina of effort, 11 were taking antihypertensive medication and three had diabetes mellitus. The two youngest female patients were taking oral contraceptive preparations. To characterise our patient population further the Norris, Luria and Peel Coronary Prognostic Indices were calculated for each patient producing a weighted score based on age, history



(After Norris et al, 1974)

Figure 3.2 Serial CPK activity measurements in a patient with transmural infarction. KD was calculated from the semi-logarithmic plot of the decline in CPK activity.

of infarction, radiological heart size, early arrhythmias and indices of heart failure in the early post-infarction period.

Follow-up Period

At one, four and twelve months after acute infarction, a clinical history was obtained and physical examination, 12 lead electrocardiogram and chest radiography performed. VPB frequency and morphology were noted during the resting studies and 24 hour ambulatory electrocardiographic tape recordings obtained if there was a history of either palpitation or syncope. Only one patient who moved out of Lothian region was lost to follow-up. During this period exercise tolerance, exertional dyspnoea and angina, or any change in medication were recorded. Antiarrhythmic therapy was discontinued routinely six weeks after infarction and diuretic therapy reduced or stopped provided clinical progress and chest radiography were satisfactory. No therapeutic decisions were made on the basis of measurements of ejection fraction. After intervals of one, four and twelve months radionuclide ventriculography was performed again at rest, and during supine exercise on a bicycle ergometer providing patients were free of cardiac failure, uncontrolled arrhythmias or atrioventricular block. The first 50 patients recruited were subjected to a single stage exercise test using a load of 750 kpm/min, thereafter a multistage exercise

protocol was developed and radionuclide ventriculography repeated during two or three exercise levels of exercise (Table 1). Standard chest lead V_5 was monitored throughout and blood pressure recorded at one minute intervals. The instantaneous RR interval was displayed and data collection commenced after steady state had been achieved. The exercise test was terminated if the patient developed angina, severe fatigue or dyspnoea, frequent extrasystoles (greater than 10 per minute) or depression of the ST segment greater than 5 mm.

Progress was deemed to be uncomplicated or complicated by angina, reinfarction, heart failure, arrhythmia or sudden death and death or survival confirmed for each patient without exception at the completion of the study. Death was attributed to coronary heart disease when no other cause of death was suggested by history. Timing, circumstances and certified cause of death were routinely requested from the general practitioner.

Control Subjects

A population of 26 control subjects was recruited from routine diagnostic requests. These individuals presented with atypical chest pain and had had previously entirely normal serial ECG's and one or more negative multistage exercise tests. In the majority of cases a diagnosis other than ischaemic heart disease was made eg. oesophageal spasm, hiatus hernia, biliary disease. Each

patient underwent radionuclide ventriculography and exercise testing according to the protocol used for the 100 patients recruited to the study.

Survivors of Ventricular Fibrillation:

Arrhythmias occurring in the Accident and Emergency department or in the C.C.U. were carefully documented. Ventricular fibrillation occurring in the context of myocardial infarction was classified as primary if it occurred within 24 hours of the onset of pain and in the absence of shock, heart failure or hypotension (systolic B.P. > 100 mm Hg) according to the criteria of Oliver (1967). Occurring outwith 24 hours of the development of pain or in the presence of shock, heart failure or hypotension, ventricular fibrillation was deemed to be complicating or if occurring during the course of unsuccessful resuscitation was said to be agonal. Only 10 patients of the original 100 suffered primary ventricular fibrillation and therefore to expand this patient population a further 12 consecutive survivors of this arrhythmia were recruited.

Ventricular fibrillation was self-terminating in one patient who did not require DC countershock, otherwise standard therapy was used for all patients and consisted of immediate cardioversion at 200 - 400 joules and 100 meq of sodium bicarbonate followed by a bolus intravenous injection of 100 mg lignocaine and an intravenous infusion of 3.5 g lignocaine over 36 hours. If

breakthrough ventricular tachycardia or fibrillation occurred despite lignocaine infusion a further bolus dose of 100 mg was given and the infusion rate increased. Further ventricular arrhythmia was treated with mexiletine given intravenously and classified as recurrent according to the criteria of Logan et al (1981). After 24 hours of intravenous antiarrhythmic therapy, mexiletine 750 mg per day was given orally and continued for 6 weeks. Clinical progress was carefully monitored in the coronary care unit, and further episodes of ventricular fibrillation or ventricular tachycardia were noted and the timing and frequency of DC cardioversion was recorded. Clinical signs of acute heart failure in the post primary VF phase (tachycardia, gallop rhythm and persistent crepitations) were noted and left ventricular failure diagnosed radiologically as alveolar oedema.

A control population of similar age and size of infarction (as judged by maximum creatine kinase levels) was collected consisting of 36 consecutive patients recovering from their first myocardial infarction whose acute phase progress was uncomplicated, 19 with inferior infarction and 17 with anterior infarction. Radionuclide ventriculography was performed on each of these 22 patients on the day prior to hospital discharge and as already described early C.C.U. progress and radiographical, electrocardiographical and biochemical parameters carefully documented. Follow-up (6 - 24

months) was documented via a questionnaire sent to the general practitioner and when possible repeat ventriculography performed.

Radionuclide Methods:

Ejection Fraction and Regional Wall Motion

Isotope ventriculography was performed at rest on the day immediately before discharge from hospital (mean 11 days, range 5 - 19 days), when patients were well and both clinically and radiologically clear of cardiac failure, subjects were informed of the nature of the investigation and had consented to take part.

All patients were studied in the supine position and cardiac imaging was performed in the 30° left anterior oblique projection with a 10° caudal tilt, with a Nuclear Enterprises MkV HR gamma camera (Figure 3.3). Patients were injected with 15 mCi of technetium^{99m} electrolytically labelled human serum albumin (Millar, 1979). The radioactivity counts from the praecordium were transferred and stored in 20 msec. format in a PDP 11/34 computer (Digital Equipment Corporation). The accumulation was triggered by the R wave of the patient's electrocardiogram, recorded from chest lead V₅, each 20 msec frame being updated by successive cardiac cycles until 500 heart beats had been accumulated. Each image consisted of a 32 x 32 matrix over the praecordium. By



Figure 3.3 Patient lying supine with the camera positioned in the 30° left anterior oblique projection.

accumulating only from this region it was possible to achieve a pixel size of 5 mm while using only 1024 16-bit words (IK computer memory) per frame. Up to 55 frames were available: the actual number used depended on the patient's heart rate. The use of a fixed time for each frame allowed direct quantification of rates of change of volume. At the end of the accumulation period the frames were displayed in rapid sequence or "movie" format in a purpose-built television display system. From the display the ventricular outline was selected by use of a joystick and data from within this outline were displayed to provide the uncorrected ventricular volume curve. The radioactivity counts from within this region were typically 21,000/20 msec frame at end-diastole. The ventricular region selected was checked and where necessary altered by displaying the volume curves from individual pixels. Background subtraction was made from a crescentic shell of the lateral and inferior ventricular border, corrected to provide an area equal to the left ventricle (Muir, 1977). The final volume curve was printed out with a thermal printer (Figure 3.4 and 3.5) was stored on magnetic tape for subsequent computer analysis. Left ventricular ejection fraction (EF) was calculated from the corrected time-activity curve and using this technique in 25 patients randomly selected, two observers obtained an average difference for ejection fraction of 0.01, the greatest difference being 0.04. Correlations with contrast ventriculography shown in

DEPARTMENT OF MEDICINE - ROYAL INFIRMARY

WILLIAM DICK REST LAO

EF = 53 % Cells in ROI = 145
Background counts in ROI = 25230, No. of cells in background region = 17
R-R Interval = 840 ms. Rate = 70 b/min

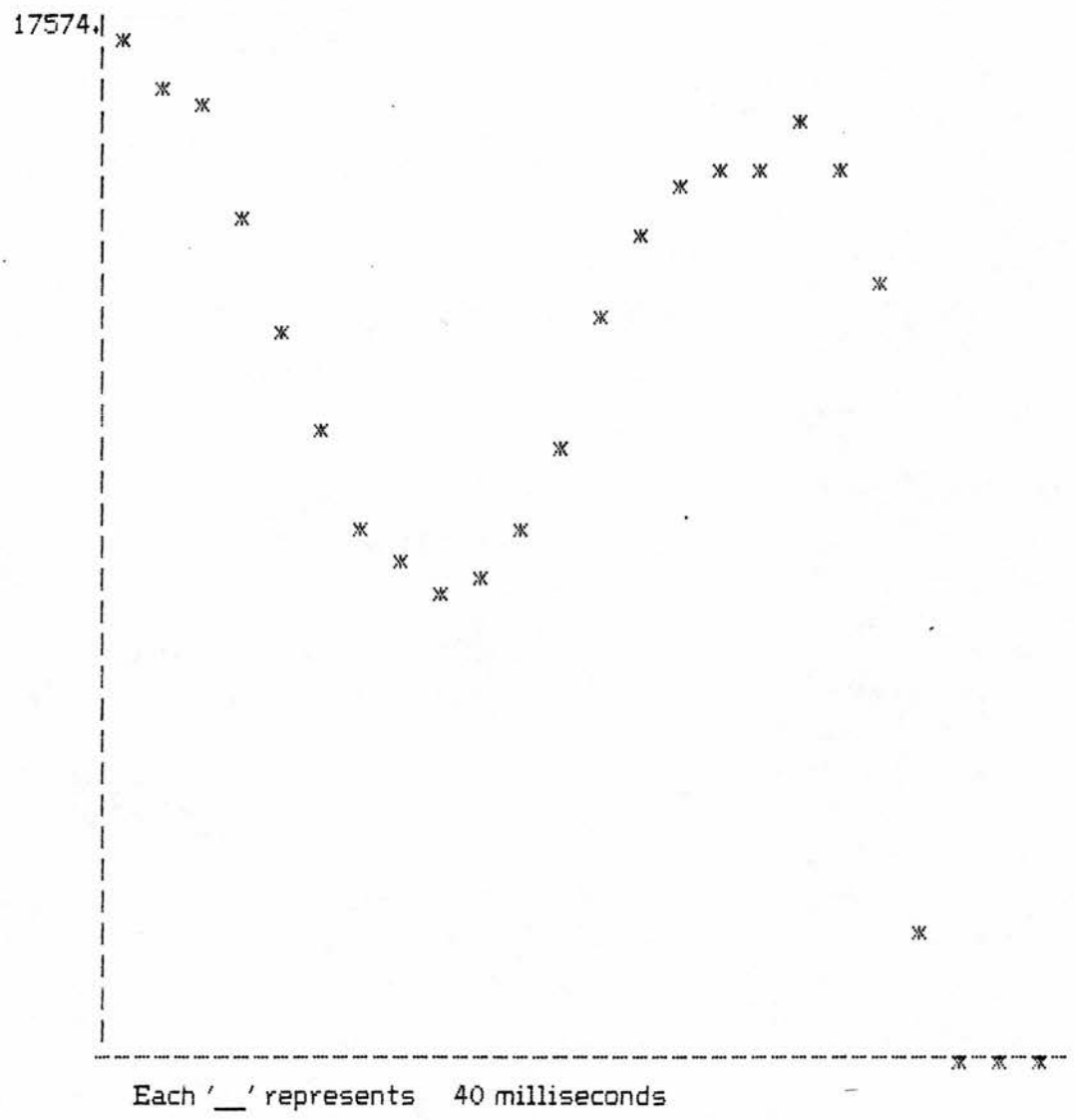


Figure 3.4 Specimen printout of a time activity curve from the left ventricular region of interest of a normal individual.

DEPARTMENT OF MEDICINE - ROYAL INFIRMARY

DAVID SIMPSON DIAG REST

EF = 17 %

Cells in ROI = 227

Background counts in ROI = 31553. No. of cells in background region = 18

R-R Interval = 720 ms.

Rate = 82 b/min

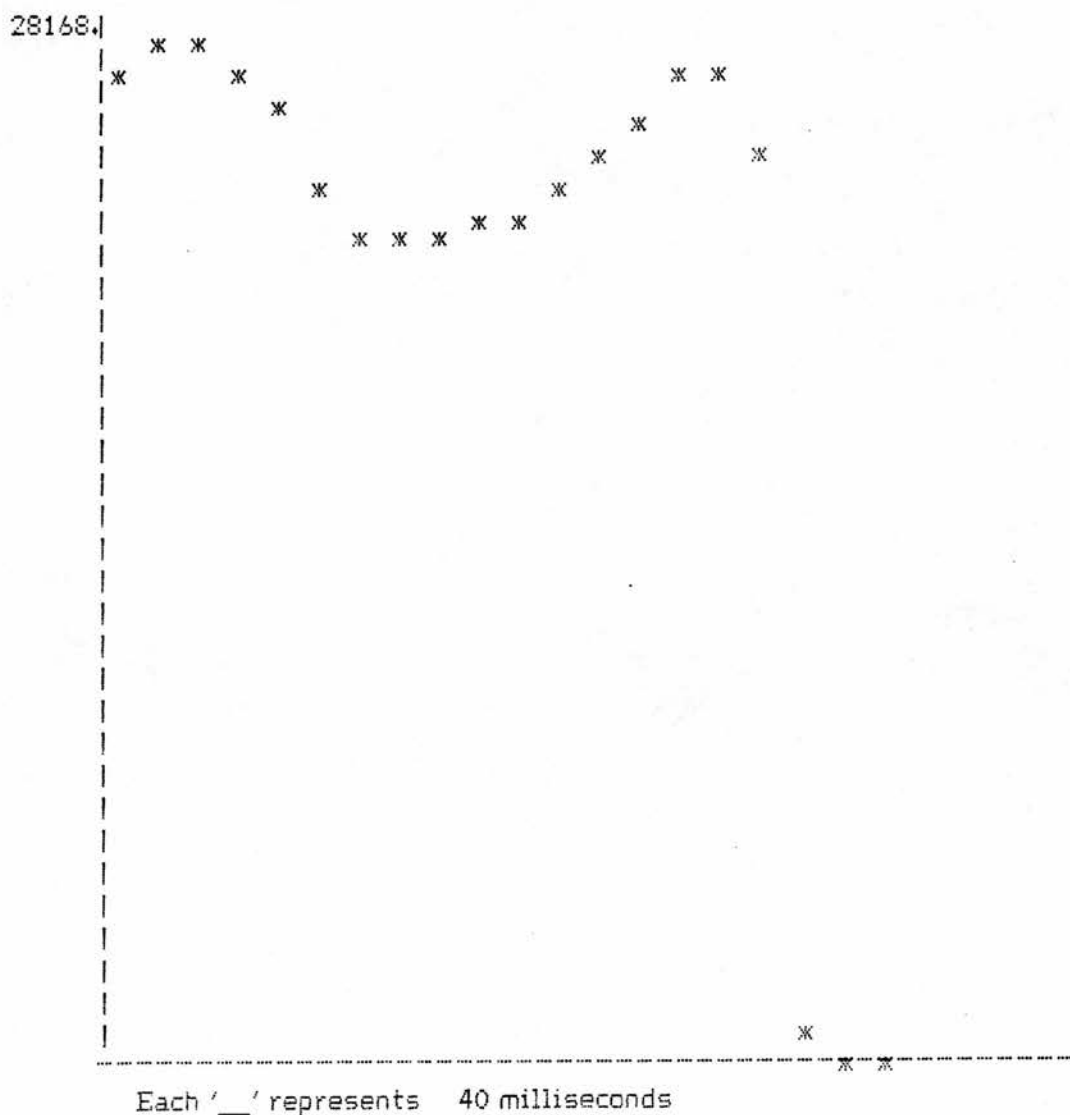


Figure 3.5 Specimen printout of a time curve from the left ventricular region of interest of a patient following transmural anterior myocardial infarction.

Figure 2.11 reveal good agreement by EF measurement made by radionuclide methods performed in our own laboratory. Left ventricular wall motion was examined from the continuous movie display with and without edge enhancement methods. Abnormalities of regional wall movement were analysed by dividing the left ventricular wall into five segments of equal length, two lateral, one apical and two septal. A regional wall movement score was formulated by two independent observers using subjective assessment of the contractility of each of the segments; normal wall motion, hypokinesia (segmental diminution of wall motion) and akinesia (no segmental wall motion) scored 0, 1 and 2 respectively. Dyskinesia was defined using a time differential method which displayed the change in volume signal by subtracting one frame from the successive frame and thus dyskinetic segments were shown as areas in which there was an increase in count rate during systole, moving out of phase relative to the remainder of the ventricular wall (Figure 3.6 and 3.7). When such areas of dyskinesia were present these were excluded from the regional wall movement score which then was used as an index of the function of the residual contractile segments. Low ejection fraction was frequently associated with ventricular premature beats and therefore a modified tape recorder was used to replay data to the computer and the ectopic and post-ectopic data rejected (Brash, 1980).

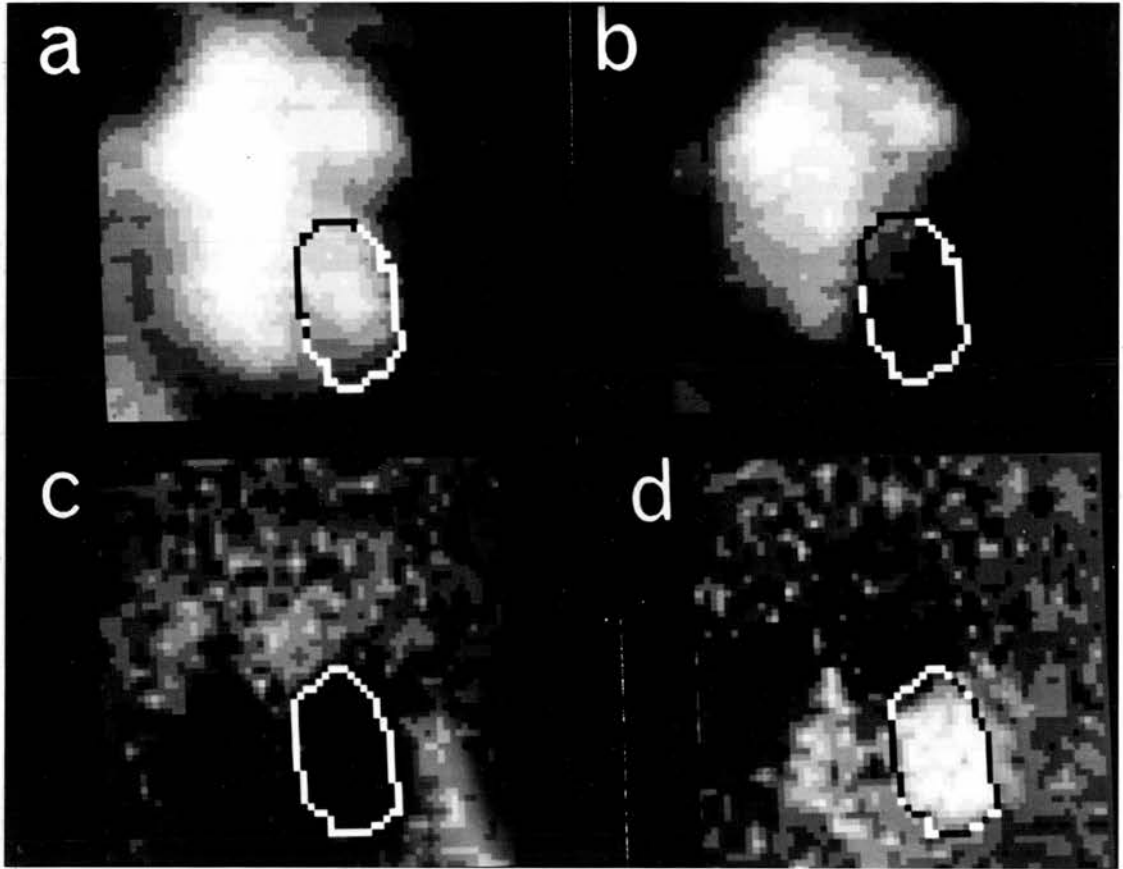
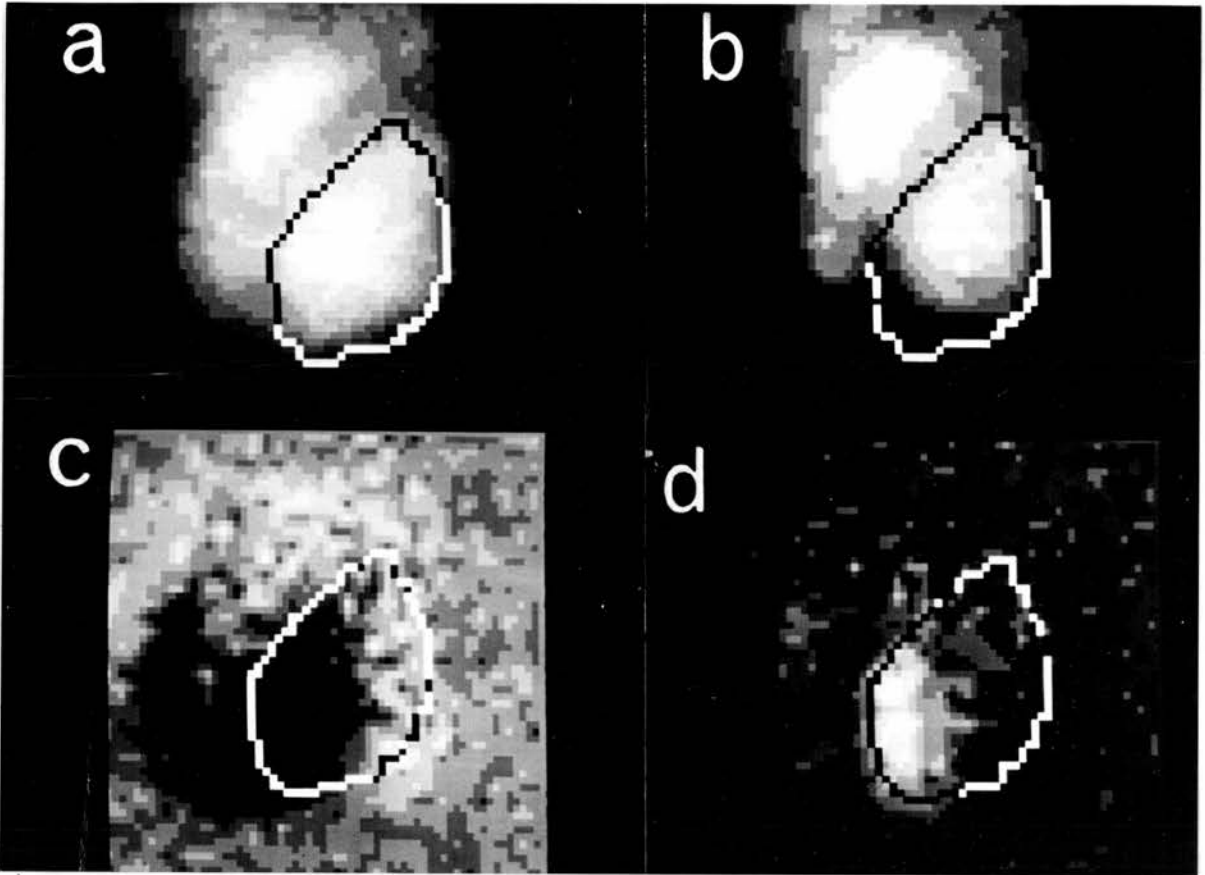


Figure 3.6 Normal left ventricular function; images taken with the left ventricle outlined in early systole (a) and early diastole (b). The corresponding time differential images (c) and (d) show uniform ventricular emptying (black) and filling (white).



- 3.7 Left ventricular dyskinesia: the large left ventricle is outlined in early systole (a) and early diastole (b), both septal segments moving normally. The apicolateral segment appears to be akinetic but is shown by the time differential images (c) and (d) to be a dyskinetic area moving out of phase, filling (white) when the remainder of the ventricle is emptying (black) and vice versa.

In order to establish the accuracy of this method for the detection of ventricular dyskinesia, radionuclide ventriculography was performed on 64 patients who underwent diagnostic cardiac catheterisation for investigation of chest pain suggestive of angina pectoris. Both investigations were performed within seven days of each other and were analysed by two sets of independent observers. Contrast cineangiography was performed in two projections (30° right anterior and 60° left anterior) and dyskinesia was defined as an expansion of any regional left ventricular wall outline at end-systole. Eight patients were adjudged to have left ventricular dyskinesia. Once again, measurements of ejection fraction correlated well between both methods and there were 16 patients with poor left ventricular function (EF < 0.30). Radionuclide ventriculography with time differential images accurately identified dyskinetic areas seen in the right contrast cineangiograms and was able to differentiate dyskinesia from generalised hypokinesia seen in the remaining eight studies.

Right ventricular size was assessed using the ratio of the right ventricular area/ left ventricular area (RVA/LVA) determined from the left anterior oblique end-diastolic frame. Selective right ventricular enlargement was said to be present when the RVA/LVA ratio exceeded the upper limit of the range observed for normal individuals (> 1.20).

Ventricular Volumes and Cardiac Output:

Assessment of pharmacological interventions such as inotropic or vasodilator agents required serial assessment of ejection fraction, ventricular volumes and cardiac output and the methods used are described below. The patient was injected with a rapid bolus of 15 mCi of Technetium^{99m} electrolytically labelled human serum albumin into an antecubital vein. The calculated radiation dose to the blood was 0.75 rad (ICRP, 1969). The activity injected was determined by comparing the syringe contents before and after injection with the count rate from a known standard, where all measurements were made at a fixed position relative to a sodium iodide scintillation detector. The passage of the bolus and subsequent four minute equilibrium period were recorded in list-mode. Four minutes after injection, approximately 2 ml of blood was withdrawn from the opposite arm to the injection site. One millilitre of this blood was accurately pipetted and the activity measured in a sodium iodide well crystal relative to a known fraction of the initial standard. By comparing the activity in 1 ml of blood with the total activity injected, the patient's blood volume was calculated. As only plasma was labelled, the true blood volume was derived by correcting the venous haematocrit to the whole-body haematocrit (ICSH, 1973).

Knowledge of the patients blood volume allowed the resting cardiac output to be measured from the indicator

dilution of the radionuclide passage through the heart (Figure 3.8). The indicator dilution curve from the left ventricle was corrected for the dead time losses for the entire field of view, as this varied significantly during the studies. The area under the peak of the indicator dilution curve (A) was determined using a gamma variate fitting technique (Starmer and Clark, 1970) to remove the effects of recirculation. This fit (solid line, figure 3.8) was performed between approximately 20% of the peak height on the upslope and about 50% of the peak height on the downslope. The equilibrium height (h) was taken as the average height between three and four minutes after injection. By analogy with conventional indicator dilution methods the cardiac output (CO) was calculated from the relationship.

$$CO = (\text{blood volume} \times h) / A$$

At the end of the four minute list mode accumulation a 32 x 32 cell matrix was positioned over the heart area and data was accumulated in 20 ms or 40 ms frames, depending on the initial heart rate. The accumulation was re-triggered by the R wave of the patient's electrocardiogram until 400 - 500 cardiac cycles had been acquired. This gave images with typically 50,000 counts in the left ventricle at end-diastole when 40 ms frames were used. For each measurement the time and total gamma

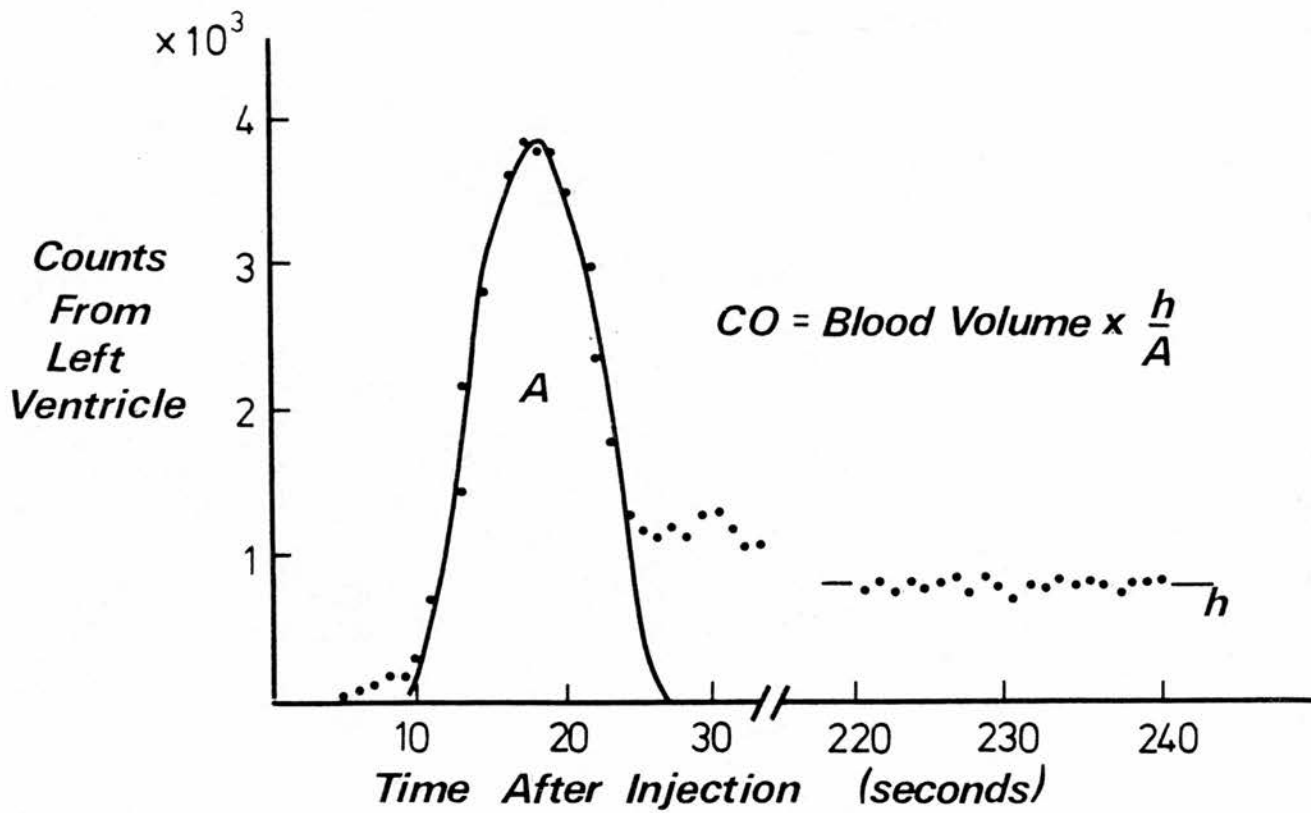


Figure 3.8 An indicator dilution curve from the left ventricle after correction for dead time losses in the gamma camera. The area (A), corresponding to the initial passage of radionuclide through the ventricle, is obtained from the gamma variate fit (solid line) to the data between approximately 20% of the peak height on the upslope and 50% of the peak height on the downslope. The equilibrium height (h) is the average count between 3 and 4 minutes post injection.

camera count rate were noted. One millilitre of blood was withdrawn and the activity measured to determine albumin clearance rate. For each study left ventricular ejection fraction was calculated from a corrected time activity curve as described previously. The average heart rate during each accumulation period was obtained from an RR interval histogram stored in the computer memory. The cardiac output (CO) determined from the indicator dilution curve was combined with the ejection fraction (EF) and heart rate (HR) measured from the initial gated blood pool study to give the end-diastole volume (EDV) during the control period:

$$EDV = CO / (EF \cdot HR)$$

End-diastolic volume was then related to the end-diastolic counts using the relationship

$$EDV = EDC (DPK/NTB)$$

where D is the dead-time correction determined from the total field of view count rate, P is the correction for physical decay, N is the number of cardiac cycles accumulated, T is the time per frame and B is the fraction of injected albumin in the circulation. The additional factor, K, depends on gamma camera sensitivity and absorption losses in the patient. For the initial

resting study the K factor is the only unknown in the above relationship, and having determined this value it may then be applied to subsequent investigations in that patient to find the new value of end-diastolic volume. The measurement of heart rate and ejection fraction in subsequent investigations allows the corresponding stroke volumes and cardiac outputs to be determined.

These radionuclide methods were used in the noninvasive assessment of various drugs on severe refractory cardiac failure persisting despite therapy with loop diuretic agents. Serial studies were performed following the intravenous administration of digoxin or prenalterol, and the protocols used in these studies will be described in Chapter 7.

Statistical Methods:

Standard statistical methods were used to calculate means and standard deviations. Results from two different populations are expressed in the text as the mean value \pm one standard deviation. If both groups of data are taken from subsets of the same population then results are expressed as the mean \pm one standard error of the mean. The Wilcoxon signed rank and rank sum tests were used to test statistical significance between grouped nonparametric data. Correlation coefficients and regression data were calculated from standard formulae and the F distribution used to test for coincidence of

two regression lines.

CHAPTER 4:
VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION

Resting Studies Before Discharge:

Our normal population consisted of 26 patients with no history of cardiopulmonary disease with recent onset of atypical chest pain associated with normal electrocardiogram and negative exercise test. The mean EF of these 'normal' subjects measured in our laboratory was 0.57 ± 0.05 (Mean \pm S.D.), none had any abnormality of regional wall motion and in each case the right ventricle was well visualised and likewise moved normally. For those patients recovering from acute myocardial infarction mean ejection fraction was significantly reduced compared with normal (0.38 ± 0.12 , $p < 0.01$).

Site of Infarction:

As a group, patients with anterior myocardial infarction had a greater reduction in EF than inferior infarction (0.32 ± 0.12 versus 0.44 ± 0.09 , $p < 0.01$) (Figure 4.1). Transmural anterior myocardial infarction ($n = 37$) resulted in a greater reduction in EF than transmural inferior infarction ($n = 46$) (0.36 ± 0.11 versus 0.42 ± 0.08 , $p < 0.01$). The same difference was apparent for subendocardial infarction, anterior ($n = 9$) having significantly lower EF than inferior infarction (n

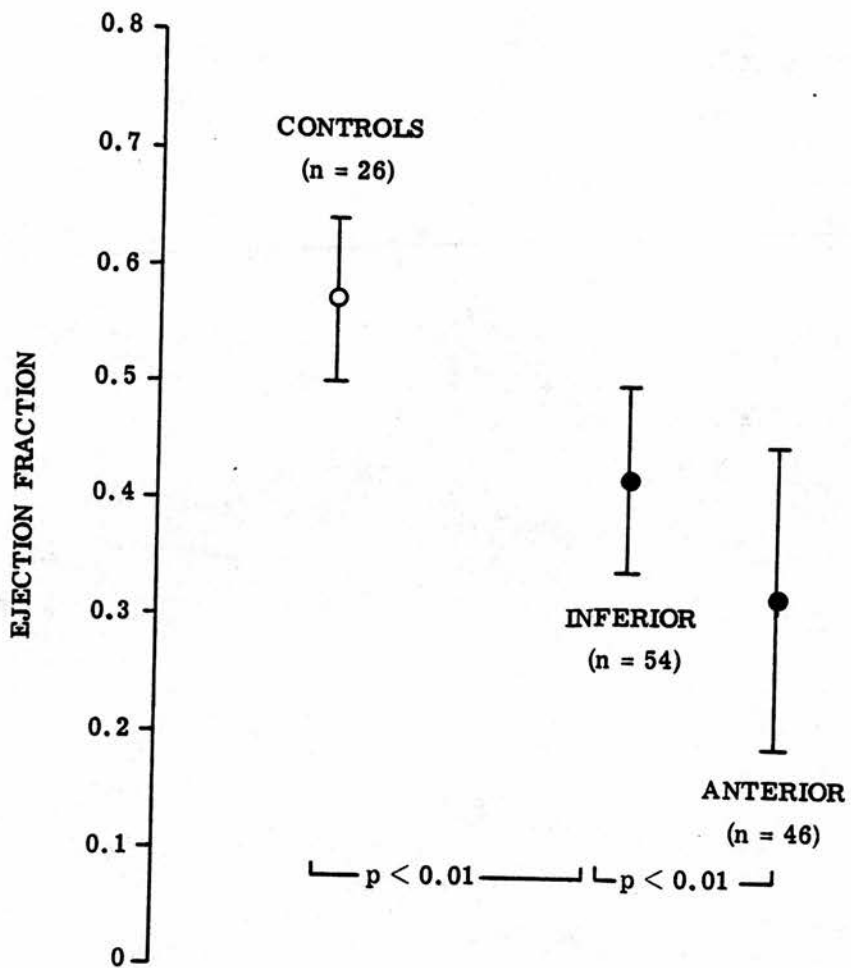


Figure 4.1 Relationship between left ventricular ejection fraction and site of infarction. Mean (\pm SD) are shown by the bars.

= 8) (0.42 ± 0.08 versus 0.53 ± 0.04 , $p < 0.01$).

Right ventricular enlargement and hypokinesis was seen in 23 patients all of whom had sustained inferior infarction which was transmural in 20 and subendocardial in the remaining three.

Size of Infarction:

Left ventricular ejection fraction correlated well with enzymatic indices of infarct size. Peak serum creatine kinase (SCK) levels were closely related to EF following anterior myocardial infarction ($R = -0.63$, $p < 0.001$) (Figure 4.2) but the relationship was less marked after inferior myocardial infarction ($R = -0.45$, $p < 0.01$) (Figure 4.3). There was no significant difference between mean peak SCK for anterior and inferior infarcts (2050 u/L versus 1786 u/L) and for an equivalent rise in SCK levels there was significant sparing of left ventricular function following inferior infarction ($f = 16.5$, $p < 0.01$).

Abnormalities of Wall Motion:

Regional wall motion appeared normal in 27 patients and abnormal in 73, abnormalities corresponding to the electrocardiographical site of infarction in 56. Segmental hypokinesis as the only abnormality was observed in 22 patients, hypokinesis affecting more than one segment was seen in 15 patients, areas of akinesis were observed in 11 patients, and dyskinetic segments seen in the remaining 25. Fourteen of the 17 patients

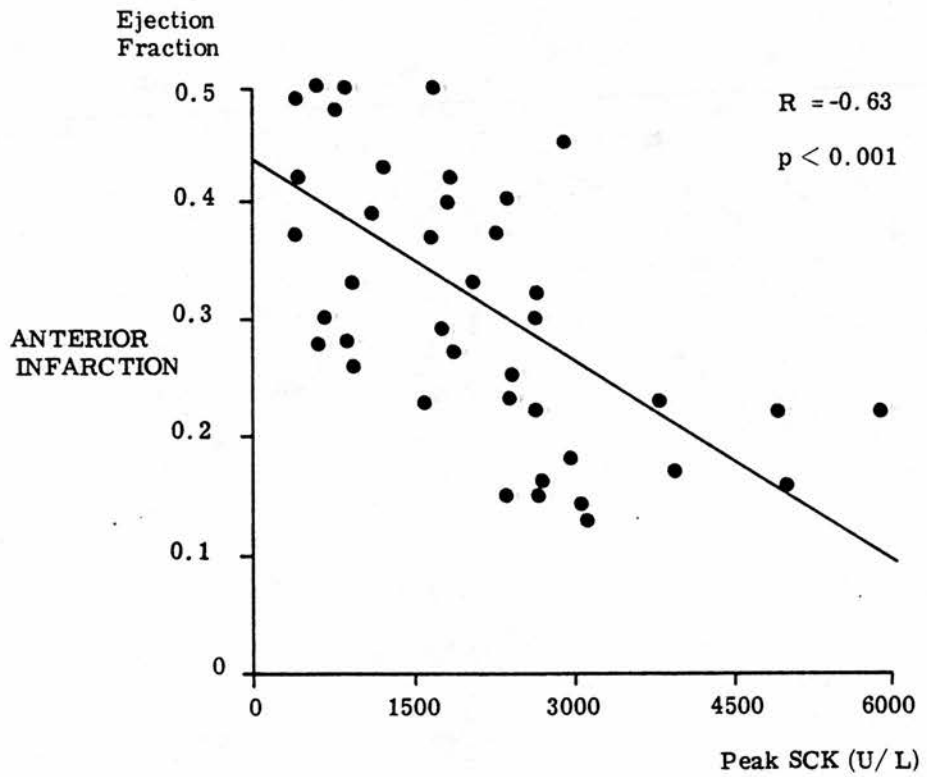


Figure 4.2 Relationship between left ventricular ejection fraction and peak serum creatine kinase (SCK) following anterior myocardial infarction.

(82%) recovering from subendocardial infarction had either normal wall motion or areas of hypokinesis; dysknetic segments were seen only following transmural infarction. Global left ventricular performance correlated well with the presence of abnormalities of regional wall movement. (Figure 4.4). Mean ejection fraction associated with normal wall motion was 0.48 ± 0.06 , with hypokinesis of one or more segments 0.41 ± 0.09 , with akinesis 0.37 ± 0.08 and with dyskinesis EF was significantly reduced at 0.23 ± 0.07 ($p < 0.001$).

Ventricular Dyskinesis:

Out of the 100 patients recovering from their first myocardial infarction, radionuclide ventriculography with time differential imaging revealed that 25 had left ventricular dyskinesis. There were 23 men and 2 women with a mean age of 60 (range 45 - 69 years). All of these patients had significant reduction in left ventricular ejection fraction below that of the remaining 75 patients with less severe abnormalities of wall motion; indeed ejection fraction was less than 0.30 in 22 patients. Apical dyskinesis was seen in 22 patients and in the remaining 3 the dysknetic area affected two segments, and was apical septal in two and apical lateral in one (Table 2). All patients with left ventricular dyskinesis had sustained transmural infarction. These included 19 patients out of a total of 46 (41%) who had

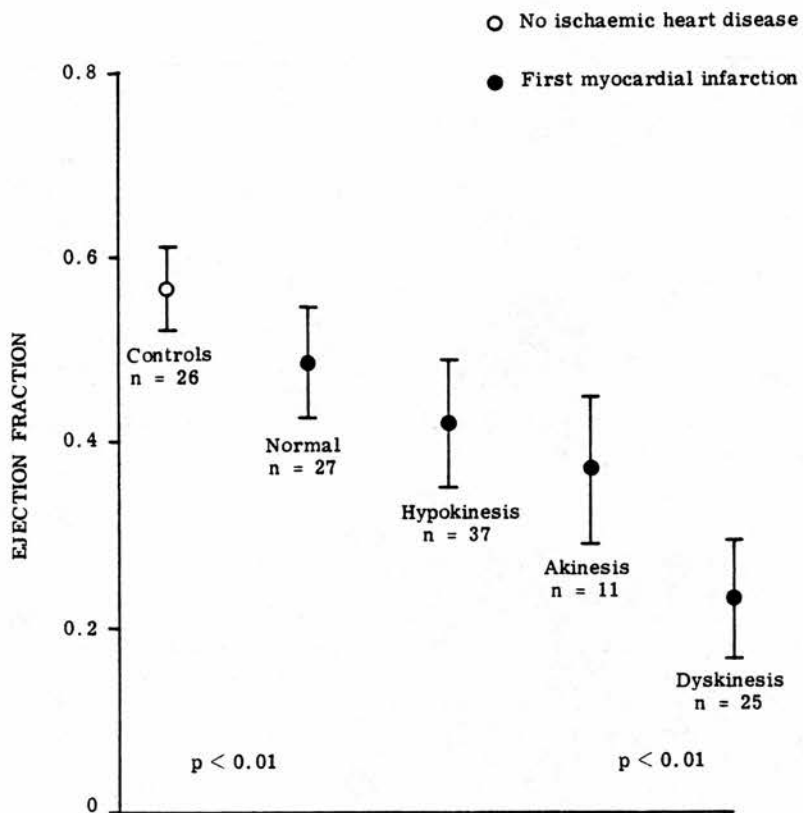


Figure 4.4 Relationship between left ventricular ejection fraction and regional wall motion abnormality. Mean (\pm SD) are shown by the bars.

sustained anterior myocardial infarction and six out of 54 (11%) following inferior myocardial infarction. The site of infarction was anterior in six, anteroseptal in four, anterolateral in nine and inferolateral in six. Major abnormalities of conduction (four bifascicular block, one complete right bundle branch block, one left bundle branch block) were seen only in patients with left ventricular dyskinesis.

ST segment elevation of one millivolt or greater persisting for longer than 28 days was seen in the anterior chest leads in a further 16 patients, but was lacking in four patients out of the six with inferolateral infarction. Moreover, similar ST segment elevation was observed in six patients who had no evidence of paradoxical wall motion. There were twelve patients with frequent ventricular premature beats on resting ECG prior to discharge from hospital and these were classified according to the modified criteria of Lown. Complicated VPB (Lown Class III - V) were seen in seven patients, all of whom had dyskinetic areas. Lown Class I - II VPB were seen in five patients with other abnormalities of regional wall motion. The chest radiograph on discharge was normal in fifteen patients and abnormal in the other ten patients who showed evidence of left ventricular enlargement but no localised protrusion of the heart border.

Early serious arrhythmia during stay in C.C.U. occurred in ten of the twenty-five patients. Ventricular

fibrillation occurred in five patients and was primary in three, and occurred in the presence of left heart failure in two. Ventricular tachycardia occurred in three patients and two others required insertion of temporary pacemakers for complete heart block. Twenty-four patients required treatment for left ventricular failure in the acute phase and 14 remained on diuretic therapy throughout their hospital stay.

Acute Phase Heart Failure:

The progress of 38 patients had been complicated by left ventricular failure (LVF) requiring treatment at the time of presentation; 13 of these had sustained inferior myocardial infarction, 25 anterior infarction. All patients were clinically and radiologically free of LVF at the time of the first study, but 21 patients had remained on diuretic therapy throughout their stay in hospital. LVF in the acute phase was associated with low EF in the convalescent phase compared with those patients whose early progress had been uncomplicated. (0.29 ± 0.11 versus 0.45 ± 0.06 , $p < 0.01$) (Figure 4.5). Disproportionate signs of right heart failure (jugular venous distension, clear lung fields and arterial hypotension) were seen in three patients all of whom had sustained transmural inferior myocardial infarction and who subsequently were shown to have right ventricular hypokinesis with preservation of left ventricular function.

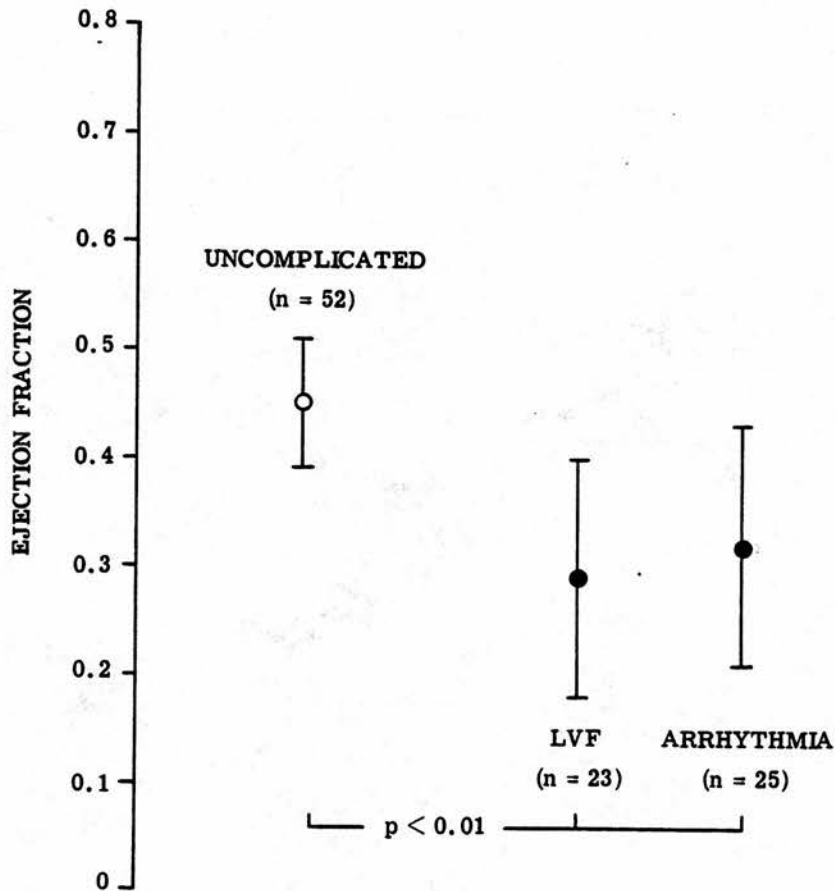


Figure 4.5 Relationship between left ventricular ejection fraction and early serious arrhythmia and left ventricular failure in the acute phase. Mean (\pm SD) are shown by the bars.

Early Arrhythmia:

Those patients with serious arrhythmia in the acute phase had low EF in the convalescent phase compared with those whose progress had been uncomplicated (0.32 ± 0.11 versus 0.45 ± 0.06 , $p < 0.01$) (Figure 4.5). There were 14 patients who survived ventricular fibrillation and a further eight had at least one documented episode of ventricular tachycardia. Those patients with primary arrhythmia ($n = 12$) and complicating arrhythmias ($n = 10$) could not be distinguished by radionuclide ventriculography and had identical mean EF which was severely reduced (0.33).

Primary Ventricular Fibrillation:

The prognosis of patients surviving this arrhythmia has been thought to be no different from those patients recovering from an uncomplicated infarction. However, preliminary analysis of the EF results above revealed significant reduction in EF below normal for the nine survivors of primary VF in our original population of 100 patients (0.32 ± 0.14 , $p < 0.01$) and therefore further patients surviving PVF had routine radionuclide ventriculography over a 2 year period from March 1979 to March 1981. Of 1086 patients admitted to a coronary care unit with the diagnosis of myocardial infarction, 97 (9%) suffered at least one documented episode of ventricular fibrillation (Table 3). There were 22 patients who survived documented primary VF occurring

within 24 hours of acute myocardial infarction in the absence of any of the clinical features of shock (cold peripheries, sweating, restlessness, confusion) or hypotension (systolic blood pressure less than 100 mm Hg).

Clinical Observations:

The mean time to ventricular fibrillation after the onset of pain was 4.3 hours (range 1 to 13.5 hours) and all but one patient had primary VF within 12 hours. Eight patients had a history of angina and four had previous myocardial infarctions (Table 4). Of the 22 patients, four were taking adrenoceptor antagonists before the event and 11 had received opiate analgesia before the onset of primary VF. Electrocardiographic recordings of the development of primary VF were available in 15 patients; seven had R on T ventricular premature beats and five had sinus bradycardia and subsequently received intravenous atropine. Complete heart block occurred in one patient and in one other an R on T VPB heralded ventricular tachycardia which progressed to ventricular fibrillation.

Primary VF was self-terminating in one patient and single cardioversion at 200 joules successful in a further 10 patients. Of the remaining eleven patients, four required more than one attempt to terminate a single episode of primary VF - two, four, five and eight cardioversions respectively. Seven patients suffered

more than one episode of primary VF requiring further cardioversion (Table 4).

Infarct location was characterised according to established electrocardiographic criteria and is shown in Table 5. Infarction was transmural with the appearance of new Q waves in 18 patients and subendocardial, with changes confined to the ST segment and T wave in three. Episodic elevation of the ST segments during pain was documented in two individuals both of whom gave a history of variant angina occurring either at rest or on exposure to cold who despite appropriate therapy sustained subendocardial infarction.

Despite antiarrhythmic therapy after the initial episode of primary VF, breakthrough ventricular arrhythmias were documented in eight of the twenty-two patients, four surviving breakthrough fibrillation and four ventricular tachycardia. Sinus tachycardia persisting for longer than 72 hours was documented in a further four patients following anterior infarction and one of these developed bifascicular block. Diuretic therapy for left ventricular failure was commenced in 15 patients and continued throughout their stay in the Coronary Care Unit.

Of the 22 patients, 18 had maximum serum creatine kinase levels of $> 1,500$ u/L and of the 10 patients who underwent only one DC cardioversion similarly high levels were seen in eight. The patient who suffered self-

terminating primary VF and did not require DC countershock had a maximum level of 2,927 u/L.

Radionuclide Ventriculography:

The results of radionuclide ventriculography are shown in Table 5. The mean ejection fraction for those patients surviving primary VF after myocardial infarction was significantly reduced (0.33 ± 0.12) compared with normal (0.57 ± 0.05 ; $p < 0.02$). In four of the twenty-two, the EF was normal (0.47 - 0.67) and in 12, each of whom had sustained anterior infarction, EF was less than 0.35 (Table 5). Mean EF for those surviving primary VF after transmural anterior infarction (0.23 ± 0.06) was reduced compared with those developing primary VF after transmural inferior infarction (0.43 ± 0.06 ; $p < 0.01$).

Normal left ventricular function after anterior infarction and primary VF was seen only in the two patients with preceding variant angina (Cases 7 and 14; EF = 0.49, 0.51 respectively) of the remaining 12 patients all had EF of less than 0.35 and nine had segmental left ventricular dyskinesis. Left ventricular function was relatively well preserved in patients with primary VF and inferior infarction, right ventricular enlargement was observed in four out of the seven patients.

Comparisons with an age-matched population of 36 consecutive patients recovering from uncomplicated myocardial infarction are shown in Figure 4.6. The mean

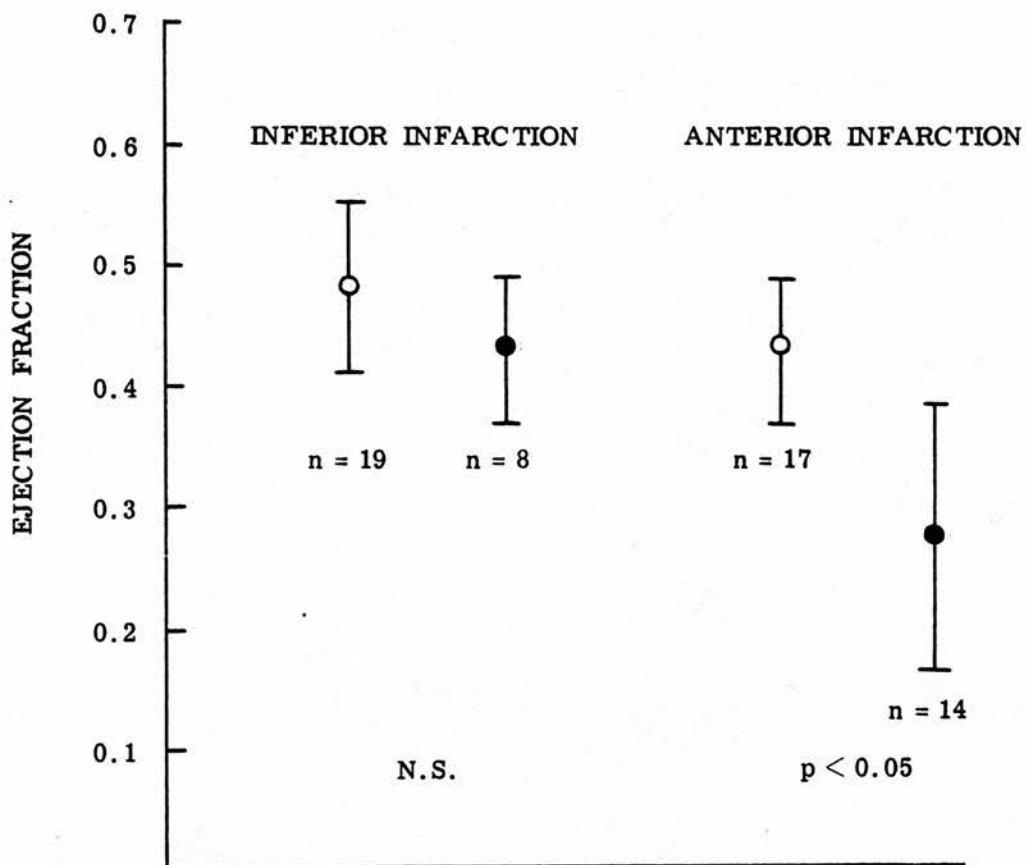


Figure 4.6 Relationship between ejection fraction and site of infarction in those patients with uncomplicated progress (o) and those surviving primary ventricular fibrillation(●).

EF for those with primary VF after anterior infarction (0.28 ± 0.11 , $n = 14$) was significantly lower than EF for those without complications (0.43 ± 0.06 , $n = 17$) ($p < 0.05$). However, there was no significant difference in EF between those patients recovering from inferior infarction and primary VF, compared with those who sustained uncomplicated inferior infarction. (0.48 ± 0.08 , $n = 19$).

All four patients with normal EF suffered no further arrhythmias following termination of primary VF and institution of antiarrhythmic therapy. Breakthrough ventricular arrhythmias occurred in eight patients and in each of these EF was reduced. Five of these patients had sustained anterior infarction and in four who developed left ventricular failure after primary VF, further episodes of ventricular arrhythmia were complicating.

DISCUSSION

Electrocardiographic and Enzymatic Correlations

The site of myocardial infarction appears to have a profound effect upon impairment of ventricular performance. Mean left ventricular ejection fraction is significantly reduced in patients recovering from anterior rather than inferior myocardial infarction. This difference which was noted by Hamby et al (1974) who reviewed cardiac catheterisation data in patients with angina and previous infarction has subsequently been shown by radionuclide ventriculography to be present within 24 hours of admission and to persist throughout hospital stay (Reduto et al, 1978). Haemodynamic studies in the acute phase by Russell, Hunt and Rackley (1973) have shown left ventricular filling pressure to be higher and stroke index to be lower in patients with anterior infarction. In an attempt to explain this difference, it was proposed from enzyme analysis that patients with anterior infarction had damaged a greater proportion of ventricular muscle mass than those recovering from inferior infarction (Sobel et al, 1972). Contrast ventriculography after infarction, however, has shown that for comparable values of total creatine kinase released, ejection fraction in anterior myocardial infarction remains lower than in those patients with inferior infarction (Hori et al, 1979) and Sammel et al

(1980) tentatively suggested that this could be the result of variable degrees of right ventricular damage in inferior infarction.

Clinically, recognition of the syndrome of right ventricular infarction is usually only possible in the small number of patients who present with the classical signs of distended neck veins, arterial hypotension and clear lung fields following diaphragmatic wall infarction usually complicated by heart block. Until the series of Cohn et al (1974) this entity had been recognised only infrequently at post-mortem (Wartman, 1948) and descriptions in the literature had been confined to occasional case reports (Zaus, 1952; Eisenberg, 1964). This clinical diagnosis was made in only 3% of the patients Cohn studied and this incidence is similar to that of isolated right ventricular infarction documented in previous reports (Yater, 1948; Wartman, 1948). However, with the advent of gated radionuclide techniques Rigo et al (1975) reported a high incidence of right ventricular dysfunction in a small number of patients. He performed gated blood pool imaging in the 30° left anterior oblique projection soon after the patients' admission to a Coronary Care Unit and used the ratio of right ventricular area to left ventricular area from the end-diastolic frame as an index of right ventricular size. Using a similar method in this study right ventricular dysfunction was identified in 43% of those

from inferior infarction with a prevalence of 23% for all patients. These results are similar to those of Tobink et al (1977) who using the first pass method found right ventricular ejection fraction to be significantly reduced in 37% of patients recovering from inferior infarction. Using radioisotopes labelled to infarct-avid tracers such as Technetium^{99m} pyrophosphate, Sharpe et al (1976) and Wackers et al (1978) showed that in populations of patients recovering from inferior infarction 35% and 37.5% respectively had pyrophosphate images suggesting right ventricular involvement. It is concluded therefore that although the classical signs of severe right ventricular failure are usually absent, subclinical right ventricular dysfunction is common after acute inferior wall infarction. Thus, after inferior infarction, there is relative sparing of left ventricular function with a variable degree of right ventricular necrosis which contributes to enzymatic indices of infarct size.

In addition to the site of infarction, the other major factor affecting impairment of left ventricular function is, of course infarct size. Work by Sobel et al (1972) has shown that a close relationship exists between total CK release and the size of experimental infarction. More recently Hori et al (1979) demonstrated the significant relationship between total creatine kinase release and left ventricular ejection fraction, measured by contrast ventriculography two months after infarction. The work presented in this thesis confirms that a similar

close relationship may be obtained by using noninvasive methods immediately prior to the patients discharge from hospital and given the site of infarction global left ventricular ejection fraction is in close agreement with other indices of infarct size. However, despite the significant relationship between ejection fraction and peak serum creatine kinase, a given rise in CK, for example to 3000 u/L, could have been associated with either normal EF or low EF often when not suspected clinically. This variability is most likely a reflection of the method used in the derivation of peak values of SCK, since blood samples were taken in the C.C.U. merely for diagnostic purposes and not initially used as an accurate method of estimating infarct size. However, even using the frequent sampling recommended by Sobel, and quantification of the cardio-specific MB fraction of creatine kinase recommended by Rodgers et al (1977) it has been shown that there remains considerable variability in the time course of enzyme evolution between individual patients (Yusuf et al, 1981). In addition considerable doubts have been expressed regarding the validity both of the use of peak SCK results (Sobel et al, 1972) and estimation of total creatine kinase release (Roe et al, 1977) as accurate reflection of infarct size since both methods involve gross oversimplification of a complex biological system.

Nevertheless, most authors would agree that such

measurements are a useful indirect estimate of infarct size. However, as this work has shown enzymatic profiles alone are of only limited value following inferior infarction. The method is purely a reflection of the total muscle mass destroyed and although equivalent values may be obtained quantitative assessment of the variable degree of right ventricular necrosis is not possible. Therefore it follows that enzymatic methods must be substantiated by other indices of infarct size and radionuclide techniques with their ability to distinguish and quantify both right and left ventricular function are an attractive alternative.

Regional Wall Motion

Global left ventricular function correlated well with the extent and severity of abnormalities of regional wall movement. The extent of the infarcted segment contributes largely to reduction of ejection fraction in patients recovering from their first myocardial infarction since the most profound reduction in EF was observed in those patients with areas of dyskinesis. Since the detection of lesser abnormalities of wall motion relies heavily on careful edge detection and may be subject to considerable observer variation it has been suggested that biplane radionuclide ventriculography may improve accuracy. (Dymond, 1979). However, from the work presented it is evident that global ventricular function is itself an accurate reflection of regional wall motion

abnormality and recent work has confirmed that before hypokinetic zones can be accurately detected and quantified additional developments will be needed (Falsetti, 1981). In view of the potential for subsequent clinical deterioration and the possibility of surgical correction the reliable detection of ventricular dyskinesis is a more appropriate aim.

Ventricular Dyskinesis After Myocardial Infarction

The development of paradoxical left ventricular wall motion soon after coronary occlusion was first described by Tennant and Wiggers in 1935. Parmley et al (1973) confirmed that paradoxical expansion persisted for up to six days after infarction and Forrester (1972) attributed this to an early increase in compliance. Since then various authors have stressed the importance of abnormal regional wall movement in impairment of left ventricular function and Herman et al (1967) suggested persistent localised contraction abnormalities might cause heart failure.

Following the original post-mortem study by Hunter, the anatomical term aneurysm had been used to describe paradoxical wall motion, but subsequent authors failed to employ a universal definition (Klein et al, 1976; Gorlin et al, 1967; Watson et al, 1975) and the published incidence of left ventricular aneurysm after myocardial infarction varied considerably. Dubnow (1965) in his necropsy series used strict anatomical criteria and

defining an aneurysm as a localised protrusion of both internal and external aspects of ventricle, described an incidence of only 3.5% in a large number of patients who had evidence of recent or old myocardial infarction. In contrast, Mourdjinis (1969) in a prospective study using clinical, electrocardiographical and radiological evidence diagnosed ventricular aneurysm in 18 patients out of 112 consecutive admissions to a coronary care unit.

Herman et al in 1967, using contrast ventriculography, proposed a functional rather than anatomical definition and used the term dyskinesis to describe a paradoxical systolic expansion of a local portion of left ventricle. The cineangiographic study of Gorlin et al (1967) revealed evidence of ventricular aneurysm in 24% of patients undergoing contrast ventriculography because of coronary artery disease. However, their population was not confined specifically to those recovering from myocardial infarction and included patients symptomatic from either angina or heart failure. Radionuclide ventriculography, however, has advantages over the invasive methods in the study of asymptomatic patients. Regional wall movement may be analysed by superimposing end-diastolic and end-systolic images and this technique had already been shown to be a useful screening procedure for patients suspected of having localised dyskinetic areas (Rigo, 1974). However, radionuclide ventriculography provides a volume signal

independent of the geometry of the ventricle and Holman et al (1979) described a paradox image which was computer generated and displayed changes in count rates occurring between end-diastole and end-systole in those regions in which the count rate increased in systole. The work presented evaluates a similar method which in addition to producing a continuous cine image of wall motion, allowed analysis of the change of volume signal between successive frames. It proved an accurate method of detecting left ventricular dyskinesia when compared with conventional contrast cineangiography and obviates the need for careful selection of end-diastolic and end-systolic frames required by the radionuclide methods described thus far. Using this method paradoxical left ventricular wall motion was observed in 25% of all patients who had survived their first myocardial infarction. In the acute phase these 25 patients had an excessive incidence of serious arrhythmia and in addition 22 required treatment for left heart failure. Thereafter physical findings on clinical examination were poor predictors of paradoxical wall motion. In agreement with other reports, the most common abnormalities were non-specific and merely suggested left ventricular enlargement.

Assessment of routine chest radiograph prior to discharge from hospital was not helpful in determining the presence of left ventricular dysynergy; cardiomegaly

was apparent in only 40% of patients and the left heart border was suspicious in only one patient. Persisting electrocardiographic abnormalities are often present in patients with ventricular dyskinesis and the high incidence of ST segment elevation has previously been documented. However, such abnormalities are not specific for dyskinesis and this work supports the view of Gorlin et al (1967) that with dyskinesis following inferior infarction, persisting ST elevation is commonly absent. Wilson and Pantridge (1973) correlated the presence of ST segment elevation over the first 48 hours with late ventricular arrhythmias. Similarly, Schulze et al (1977), using radionuclide methods, noted the association between ST segment displacement, ventricular premature beats and low ejection fraction. From this study it is apparent that complicated ventricular beats occur in the presence of poor left ventricular performance secondary to paradoxical wall motion and are therefore associated with persisting ST segment elevation on the electrocardiogram. In addition, serious conduction defects (left bundle branch block and bifascicular block) followed extensive infarction, resulting in poor LV performance and without exception were always present with large dyskinetic areas. The prognosis of such patients must by inference be exceedingly poor but will be documented and discussed in detail in the following chapter.

Ventricular Performance After Primary Ventricular Fibrillation:

Previous studies of those suffering primary ventricular fibrillation after acute infarction have been confined to clinical observations and long term follow-up. (Lawrie, 1969; Alberti, 1979). Ritchie et al (1977) examined sixteen survivors of sudden cardiac death due to VF out of hospital using radionuclide ventriculography, reporting that in five of the sixteen EF was normal and in six EF was severely reduced (less than 0.35). The results presented describe the radionuclide findings in twenty-two survivors of primary VF following acute myocardial infarction and show that in the majority left ventricular ejection fraction is significantly below normal and severely reduced in 12.

It is therefore apparent that considerable left ventricular necrosis follows myocardial infarction and primary VF in the majority of cases and these results are supported by the enzymatic indices of infarct size. Although repeated defibrillation may significantly elevate SCK levels, other workers have shown that single DC cardioversion, effective in 10 of the patients has little effect on the peak SCK value (Mandecki, 1970), and eight of these ten had peak levels in excess of 1,500 u/L. Indeed, self-terminating primary VF was observed in one patient in whom the peak SCK level approached 3,000 u/L. Such results are in agreement with those of

Chapman (1972) and Lie (1974) who also noted significantly higher enzyme elevations in patients with primary VF. A similar relationship has been demonstrated between peak enzyme levels and the incidence of complicated VPB's and ventricular tachycardia in patients who did not require defibrillation (Roberts et al, 1975). Thus there appears to be a correlation between infarct size and all types of ventricular arrhythmia, which may occur secondary to the local release of catecholamines although potassium, lactate and other agents have also been implicated (Bigger, 1977).

Those patients surviving primary VF and anterior infarction have significantly lower EF when compared with a population recovering from uncomplicated anterior infarction. However, this difference is only apparent for those recovering from anterior infarction and it is clear once again that the site of infarction itself has a profound effect on impairment of ventricular function. Despite equivalent peak SCK levels, left ventricular performance is remarkably well preserved after inferior infarction with primary VF and this phenomenon has been referred to previously and demonstrated by Reduto et al (1978) in a population without acute phase arrhythmia.

Of those patients with anterior infarction only two had normal EF and ventricular wall motion. Both had a history of variant angina and despite appropriate therapy sustained enzymatically small subendocardial infarctions.

Prior to episodes of primary VF they experienced increasing frequency and severity of angina and may have suffered arrhythmias occurring in the reperfusion phase following prolonged episodes of coronary artery spasm. In contrast the remaining twelve patients with anterior infarction had striking reduction in EF secondary to transmural infarction and nine of these had segmental dyskinesia of the left ventricle. The association between both low EF, ventricular dysynergy and complicated Lown class III - V VPB has been referred to previously. Such an association is probably true in the earliest phase after coronary occlusion when wall motion abnormalities and changes in EF may be completed within six hours. In these patients early ventricular arrhythmia occurred during the process of extensive infarction and may have been dependent upon re-entry mechanisms within ventricular myocardium, before the 12 - 24 hour phase of increased Purkinje cell automaticity. Such electrophysiological changes may account for the lack of suppression of primary VF in five patients who received atropine because of symptomatic bradycardia since this drug will suppress benign VPB's by raising heart rate but is considerably less effective in eliminating complicated VPB's. (Epstein et al, 1973)

Recurrent ventricular arrhythmias occurred in eight patients. Logan et al (1981) have recently shown that such phenomena are not related to any of the known clinical variables, but in this study, breakthrough

ventricular tachycardia and fibrillation were seen only in patients with reduced ejection fraction and four patients with normal ventricular function suffered no further arrhythmia. Thus, as suggested by other workers, in the face of re-entrant arrhythmias associated with segmental ventricular dyskinesia the efficacy of lignocaine may be reduced (Pantridge, 1974). Despite therapy, four patients with anterior infarction went on to develop further ventricular arrhythmias and as has been suggested previously frequent repeated periods of ventricular tachycardia or VF may increase the size of an already substantial myocardial infarction. Such a progression has not previously been studied but raises the question of long term prognosis in these individuals with undoubtedly exceedingly poor left ventricular function and this will be discussed in the following chapter.

CHAPTER 5:

PROGNOSTIC VALUE OF RADIONUCLIDE VENTRICULOGRAPHY AFTER MYOCARDIAL INFARCTION

Follow-up and return to work:

Of the 100 patients only two did not have repeat radionuclide ventriculography performed at one month: one required closure of a late ventricular septal rupture and the other had developed atrial fibrillation following an inferior infarct. At 12 months a further three patients were exempt from repeat studies: one had developed intermittent bigeminal rhythm alternating with sinus rhythm with frequent VPB's, one patient had developed AV block and required a permanent pacemaker and the other had moved from the Lothian Region.

Of the 69 patients who were in full time employment prior to infarction, 60 returned to work although 10 of these were re-employed in a less physically demanding capacity. Of the nine patients who were declared medically unfit to return to work, two had severe angina despite full medical therapy, four had severe ventricular failure (N.Y.H.A. Grade III - IV) and one deemed to have angina but with an atypical history. The remaining two patients were barred from returning to work by their employing authority: one was a train driver, the other a heavy goods vehicle licence holder.

Of the seventy-five patients who were cigarette

smokers at the time of their infarct, 52 stopped smoking and remained nonsmokers throughout the follow-up period after their discharge from hospital.

The complications in the first twelve months after myocardial infarction are shown in Table 6.

Angina and Reinfarction:

Thirty-two patients developed angina and six suffered non-fatal reinfarction.

Left ventricular failure:

Twenty-three patients had documented acute phase LVF and 20 patients were taking diuretic medication at the time of their discharge from hospital. Over the 12 month follow-up period eight of these patients discontinued therapy without adverse effects, however, the remaining twelve and three others had documented episodes of left ventricular failure requiring emergency treatment by their general practitioner or readmission to hospital or both. Three additional patients developed signs of predominant right heart failure after transmural inferior myocardial infarction, one of these developing atrial fibrillation.

Ventricular Arrhythmia:

Twenty-two patients had either ventricular tachycardia or ventricular fibrillation in the acute phase and remained on prophylactic antiarrhythmic therapy throughout their hospital stay. This was discontinued

without any adverse effects in twenty patients but two who suffered recurrent late arrhythmias required readmission to hospital for reintroduction of either a single drug or drug combinations. These two patients along with ten others were indentified prior to discharge from hospital as having frequent complicated (Lown Class III - V) VPB on a resting electrocardiogram.

Deaths:

There were no deaths in the first 4 weeks after discharge, four patients had died before the 4 month follow-up and a further seven before the one year follow-up.

Changes in Ejection Fraction:

The changes in resting left ventricular ejection fraction over the first 12 months after myocardial infarction are summarised in Tables 7 and 8. The significant difference observed in ejection fraction after anterior and inferior myocardial infarction before discharge persisted throughout the first 12 months. Even one year after infarction those patients recovering from anterior infarction had significantly lower ejection fraction than after inferior infarction (0.36 ± 0.02 versus 0.43 ± 0.01 , Mean \pm SEM, $p < 0.01$) (Figure 5.1). This difference is mainly due to the excess incidence of ventricular dyskinesia and poor global left ventricular function after anterior infarction since mean EF in this

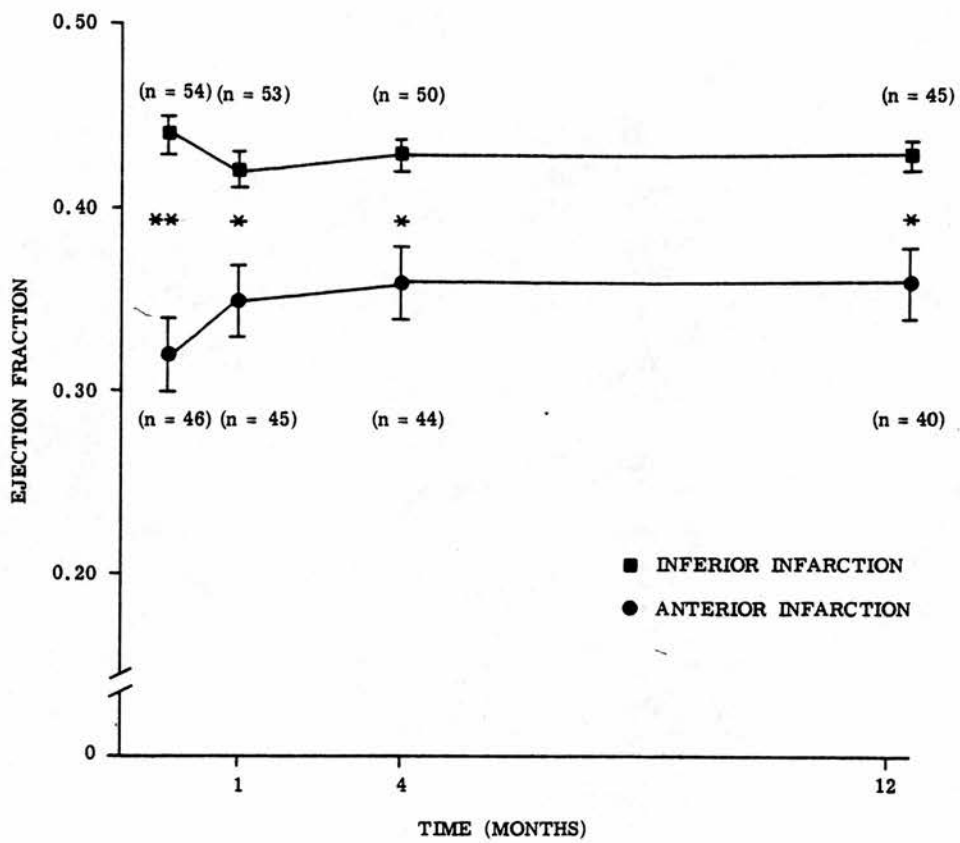


Figure 5.1 Changes in left ventricular ejection fraction at rest following discharge from hospital. Mean (\pm SEM) are shown by the bars.

** = $p < 0.01$

* = $p < 0.05$

group fails to improve significantly over the 12 month period (0.23 ± 0.01 versus 0.24 ± 0.03) (Table 8). Figure 5.2 shows the changes in ejection fraction which occurred over this period in groups of patients classified according to the initial abnormality of regional wall motion. Those patients with initial segmental hypokinesis showed a small but not statistically significant changes in EF over 12 months, whereas in those with initially normal wall motion or hypokinesis affecting more than one segment EF fell slightly but not significantly. Those patients with segmental akinesis had significant improvement in EF over one year from 0.37 to 0.44 ($p < 0.05$). The most striking difference between the individual groups however is the profound drop in EF associated with the development of segment ventricular dyssynergy (mean EF at discharge 0.23 ± 0.01) since EF fails to improve (mean EF at 1 year = 0.24 ± 0.03) and global left ventricular function 12 months later remains significantly reduced below values of those patients with less extreme abnormalities of wall motion. ($p < 0.01$) (Figure 5.2).

Ejection Fraction and Clinical Progress:

Left ventricular function as assessed by resting ejection fraction did not correlate with the patients' assessment of their own exercise tolerance or with return to full-time employment, although all four patients who were unable to resume employment of any sort had very low

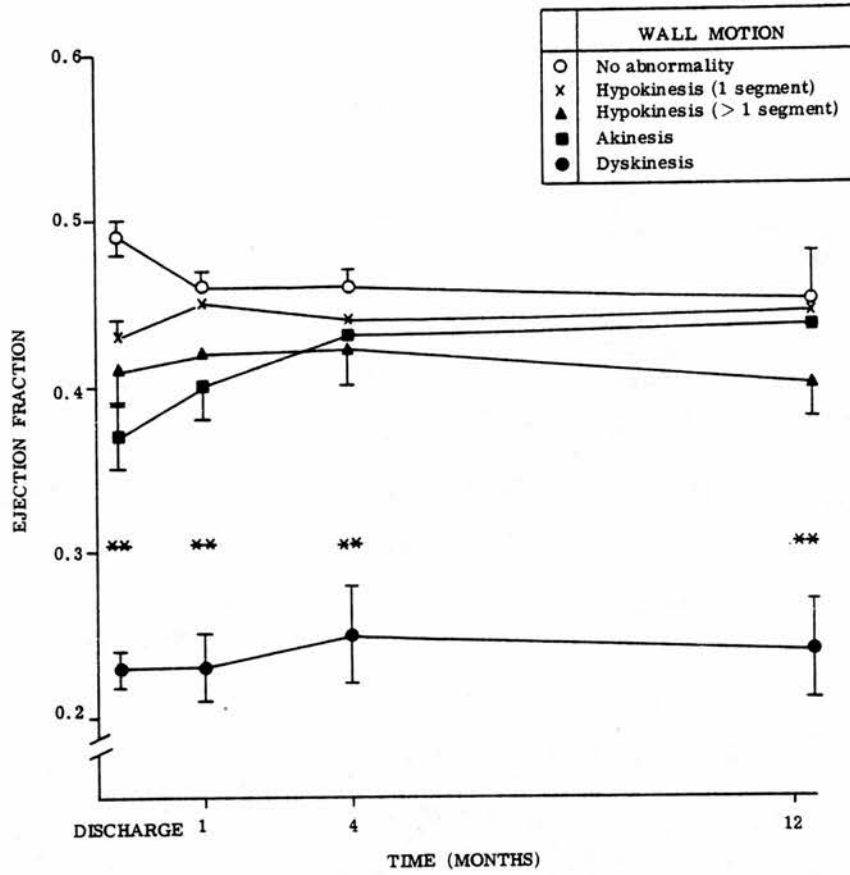


Figure 5.2 Relationship between initial abnormality of wall motion and changes in left ventricular ejection fraction following discharge from hospital. Mean (\pm SEM) are shown by the bars. ** = $p < 0.01$

ejection and segmental ventricular dyskinesis. (0.13 - 0.22, Mean 0.17). Likewise, frequency of angina pectoris did not correlate with resting ejection fraction. (Figure 5.3).

Low resting EF at discharge was associated with the development of left ventricular failure in the subsequent year. (Figure 5.3). Without exception the fifteen patients requiring maintenance or increased diuretic therapy had dyskinetic segments and severely reduced EF. Of 25 patients with dyskinesis, none died within four months of infarction and although there was no improvement in mean EF of the whole group, different patients showed striking individual changes in EF. (Table 9). All patients who developed subsequent left ventricular failure showed a further reduction in ejection fraction (Figure 5.4). Significant improvement in ejection fraction (> 0.05), however, was noted in eight patients who did not develop left ventricular failure in the follow-up period, and all of these were able to discontinue diuretic therapy. Any increase in ejection fraction was secondary to improvement in wall motion of the non-dyskinetic myocardium, but two patients (cases 15 and 25) showed apparent reduction of the dyskinetic area and the ST segment elevation previously noted also resolved. Regional wall movement score prior to discharge from hospital was predictive of clinical progress (Figure 5.5). The presence of akinesis with segmental dyskinesis was predictive of subsequent

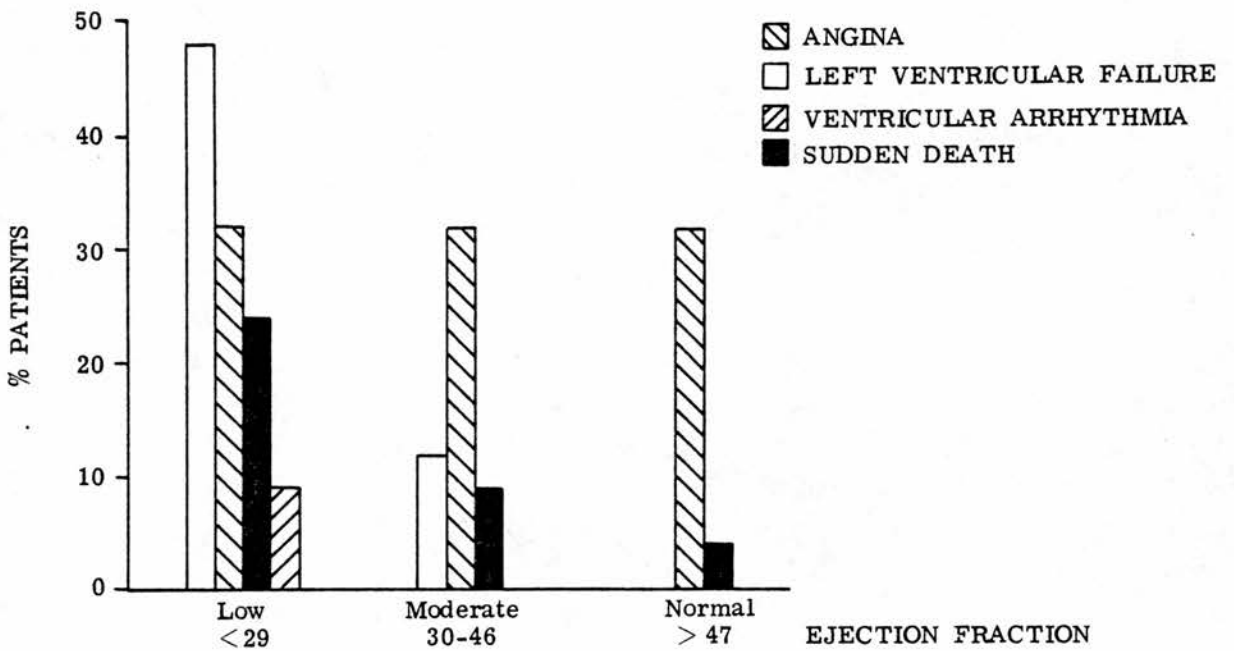


Figure 5.3 Relationship between left ventricular ejection fraction and the development of complications in the 12 month period after infarction.

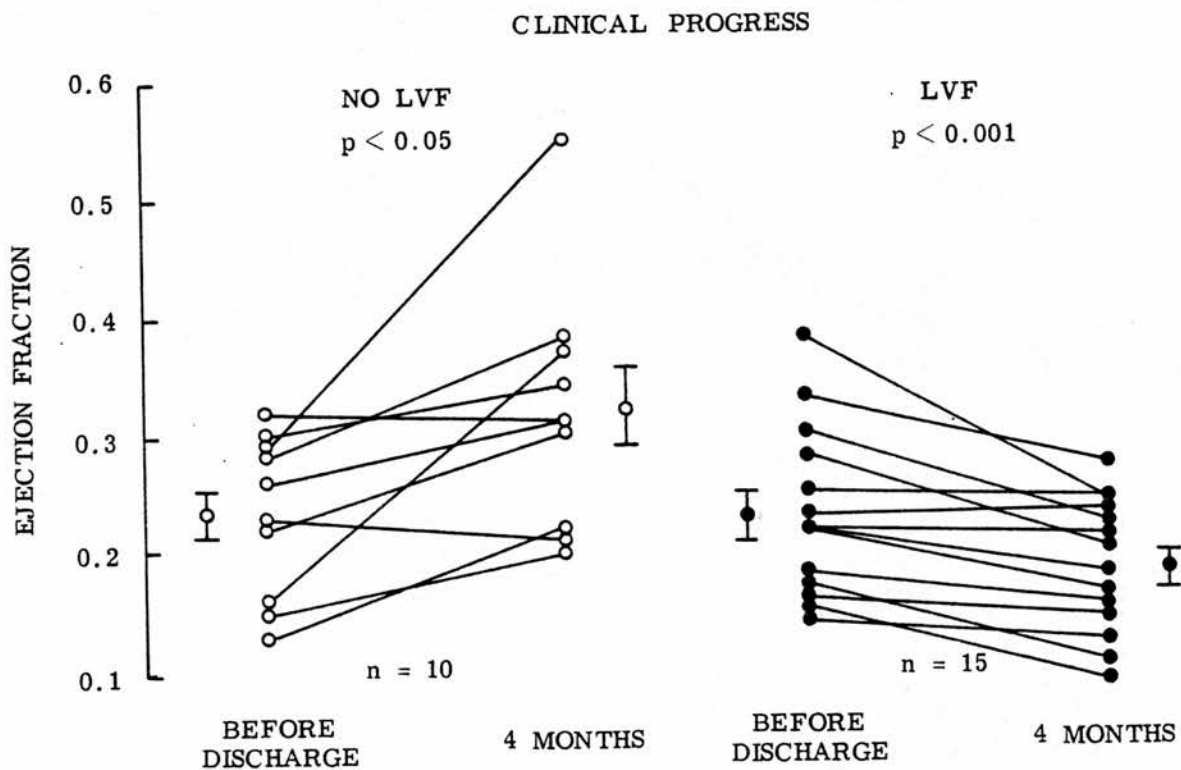


Figure 5.4 Changes in left ventricular ejection fraction at rest and the development of left ventricular failure (LVF) following discharge from hospital. Mean (\pm SEM) are shown by the bars.

LV CONTRACTILITY SCORE
BEFORE DISCHARGE

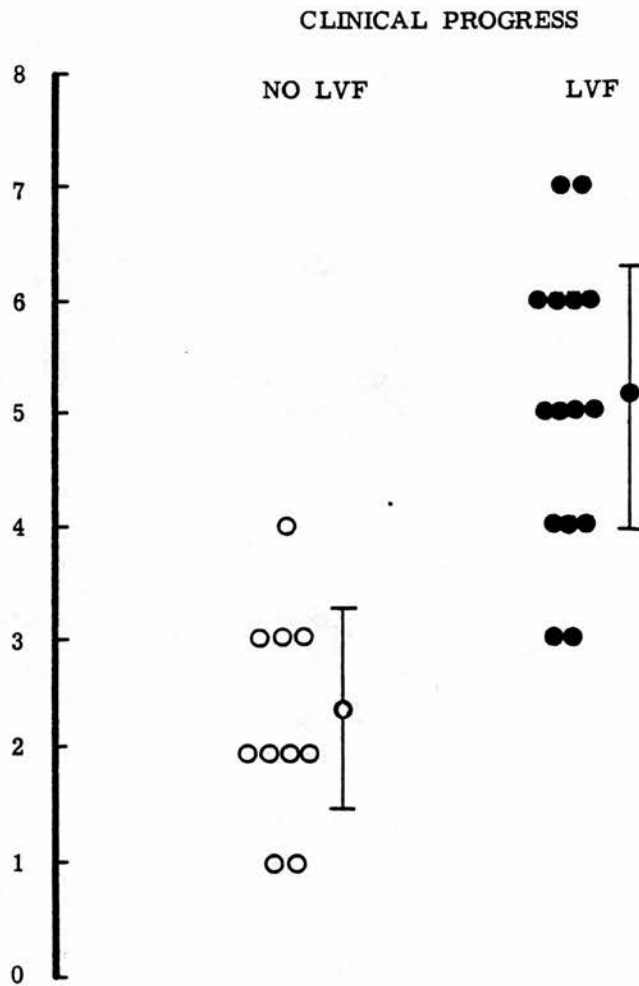


Figure 5.5 Relationship between the contractility score of the non-dyskinetic area and the development of left ventricular failure (LVF) in the subsequent four months. Mean (\pm SD) are shown by the bars.

deterioration.

The three patients who developed signs of predominant right heart failure in the follow-up period had all sustained transmural inferior myocardial infarction and at hospital discharge were noted to have dilatation and hypokinesis of the right ventricle.

The only serious arrhythmias in the follow-up period were seen in patients with dyskinetic segments and included three documented episodes of ventricular tachycardia observed in two patients (cases 22 and 23). Despite antiarrhythmic medication recommenced at four months, one patient's (case 22) complaints of lightheadedness on exertion persisted and when exercised once more developed ventricular tachycardia which degenerated into ventricular fibrillation. One patient (case 4) who required a temporary pacemaker following inferior myocardial infarction suffered intermittent sinus arrest in the follow-up period and required a permanent pacemaker.

Of the 100 patients, 11 died within the 1 year follow-up period. (Table 10). Three deaths occurred in patients who developed angina post infarction (to be discussed in the following chapter) and two other deaths were sudden and unexpected. The remaining six patients who died all had segmental dyskinesis of the left ventricle and poor global function. All these patients collapsed and died suddenly out of hospital and all but

one was found dead before medical attention could be summoned. Although myocardial infarction was the certified cause of death in all six cases, only one patient gave a history of typical ischaemic pain.

Of these six patients who died, three were given a "low risk" rating by the Peel or the Luria index and only one was deemed to be at high risk from the Norris index. In the remaining ninety-four patients there was no significant correlation between the three coronary prognostic indices used and left ventricular ejection fraction.

DISCUSSION:

Because of its noninvasive nature, radioisotope ventriculography is ideally suited to the sequential measurements of ejection fraction after myocardial infarction. Earlier work by Reduto et al (1978) has shown that ventricular performance after uncomplicated transmural myocardial infarction is reduced within 16 hours of admission and thereafter remains relatively stable during the hospital phase (13 ± 3 days). However, conflicting views have been put forward as to whether or not there is any significant improvement in ventricular function thereafter. Rodger et al (1980) who followed twelve patients six months after infarction, found that mean EF for the group fell significantly and although

there were individual variations they concluded that ejection fraction and wall motion did not improve after the early convalescent phase of myocardial infarction. Such results are in agreement with those of Kupper et al (1977) who found the main changes in left ventricular haemodynamics occurred within the first four to six weeks, there being no further significant changes in the following nine months. In contrast, however, Schelbert et al (1976), who followed 63 patients for a mean of 20 months, reported further significant improvement in over 60% of patients in the late convalescent phase. More recently Borer et al (1980) confirmed that the capacity for improvement in ventricular performance does exist but intimated that this was confined to the population with near normal ejection fractions. The work presented in this thesis supports both arguments. Despite the absence of significant changes in mean ejection fraction of the various groups (classified according to site of infarction or wall motion abnormality) there is considerable individual variation and even in the face of ventricular dyssynergy significant improvement in left ventricular function does occur and may be spontaneous in the absence of any therapeutic intervention. In addition improvement may continue beyond the initial four weeks viewed by most authors to be the critical period, although there is little change between four and twelve months after infarction.

These results support the conclusions of Rahimtoola

et al (1972) who, using haemodynamic parameters from invasive studies, noted the very poor prognosis in patients whose ventricular function failed to improve during convalescence. Without exception such deterioration follows large infarcts with dyskinesis and poor left ventricular reserve. In addition, depressed ventricular wall motion in non-infarcted areas may contribute significantly to depressed ejection fraction in the acute phase (Wyatt et al, 1976) and it would appear from the work of Mathey et al (1974) that increased contractility of these regions together with stiffening of the infarct area (Kumar et al, 1970), act as compensatory mechanisms in improving global left ventricular function. Ejection fraction is the variable most predictive of prognosis in ischaemic heart disease (Hammermeister, 1979) and most likely is related to both the extent of wall motion abnormalities and to the function of the residual contractile segment. Lee et al (1977) in pre-operative assessment found that function of the residual contractile segment was more important in determining prognosis of aneurysmectomy than the actual size of the aneurysm. A similar approach has been employed in this study in those patients recovering from myocardial infarction and careful assessment of regional wall motion prior to discharge from hospital may provide accurate information regarding the function of the residual contractile segment and in patients with

dyskinesia this is predictive of future clinical progress.

This noninvasive technique has shown that dyskinesia occurs in one quarter of all patients recovering from their first myocardial infarction and commonly persists, being associated with subsequent heart failure and serious arrhythmia. In addition these patients often exhibit increased ectopic activity in their resting electrocardiogram. These findings are supported by the work of Schulze et al (1977) who found that patients with complicated ventricular arrhythmias (multiform, couplets, ventricular tachycardia or VPB's with T wave interruption) had a greater number of proximally obstructed major coronary arteries and more extensive disease than the patients with infrequent or no ectopic activity. Such results form the basis of "The Ventricular Premature Complex Hypothesis" proposed by Lown (1979) in which he suggests that extensive cardiac disease predisposes to advanced grades of frequently recurring ventricular arrhythmia, thereby increasing the chance that sequential ectopic complexes will lower the threshold of the ventricular vulnerable period and precipitate ventricular fibrillation. Of the patients who died in the follow-up period of this study 64% had severe impairment of left ventricular function ($EF < 0.35$), and of these 86% had ventricular dyskinesia and 33% had Lown Class III - V VPB's. Calvert et al (1977) obtained similar results using contrast ventriculography

and noted increased ventricular ectopy was associated with increased ventricular asynergy and increased left ventricular end-diastolic pressure. However, it would appear that increased ventricular ectopic activity occurs independently of clinical signs of overt left heart failure since two of the six patients who died did not show clinical evidence of cardiac decompensation. It is more likely therefore that complicated VPB's and late potentially lethal ventricular arrhythmias are generated from multiple re-entrant pathways within the zone of infarction (El-Sherif, 1979), and it is of interest to note that this phenomenon may be abolished by surgical resection of akinetic and aneurysmal areas. (Ritter, 1969; Barry et al, 1972).

It would be ideal therefore for radionuclide ventriculography to be performed in all patients recovering from myocardial infarction since careful assessment of global and regional left ventricular performance is predictive of prognosis and provides a new dimension to risk stratification of the population with ischaemic heart disease. Prior to the development of these techniques, physicians relied upon the presence or absence of clinical signs associated with extensive infarction. The importance of overt left ventricular failure the acute phase on subsequent prognosis was noted by White (1976) and confirmed by Norris (1974) who examined the chest x-ray appearances of 757 patients

admitted to a coronary care unit. The work presented in this thesis is in agreement with this finding and demonstrates that left ventricular function is significantly reduced following the development of the clinical and radiological features of left ventricular failure in the acute phase. However, also included among the variables of the Norris Coronary Prognostic Index was radiological heart size (Norris 1969). In this study, although all patients with cardiomegaly had reduced EF, there was no significant correlation between EF and the Norris CPI ($r = -0.29$) and in particular EF correlated poorly with radiological heart size measured by the CTR method. Thus this work supports that of contrast ventriculography (Field et al 1974) in that the poor correlation between EF and CTR suggests that radiological heart size is a poor predictor of left ventricular function. Moreover the results demonstrate the limited accuracy of the other coronary prognostic indices in-use, notably their poor prediction of late mortality, since there was no correlation between EF and either the Peel (1962) or the Luria (1979) indices ($R = -0.33$ and -0.29 respectively).

The early reports of Lawrie (1968) and Geddes (1967) documented an excellent prognosis for the survivors of primary VF which was described as being no different from the uncomplicated infarct. However, Denborough and Lovell (1968) found arrhythmia to be predictive of late sudden death and Kitchin and Pocock (1977) found cardiac

arrest and ventricular arrhythmia in the acute phase to adversely affect survival after hospital discharge. The first attempt to categorise survivors of primary VF according to the site of infarction was made by Alberti et al (1979) who found that patients with anterior infarction and primary VF had an excess incidence of cardiac death when followed up in the long term. Thus far in the limited follow-up (6 - 12 months) of the twenty-two patients surviving primary VF there have been three sudden deaths of the original fourteen with anterior infarction and each of these had $EF < 0.35$. No deaths occurred in the eight patients with inferior infarction and primary VF.

These preliminary results indicate that survivors of primary VF following myocardial infarction show a wide range of impairment of ventricular function. Low ejection fraction is common after primary VF with anterior infarction. With the development of left ventricular dyskinesia this select population is subject to the same risk of further ventricular arrhythmias and left ventricular failure as other patients with extensive infarction. Thus long term prognosis may not be as favourable following anterior infarction and primary VF as for those who survive ventricular arrhythmias complicating inferior infarction.

Such results raise the question of whether or not early arrhythmia should be included in prognostic indices and carry adverse prognostic weighting. However,

coronary prognostic indices, previously thought to be an accurate reflection of the mortality risk, can now be replaced by a more fundamental approach using non-invasive methodology. Radionuclide ventriculography can predict those at risk from sudden death in the first year after infarction, and can do so accurately, but in addition to the prediction of the final end point it can identify those who may suffer non-fatal arrhythmia and heart failure.

CHAPTER 6

PROGNOSTIC VALUE OF EXERCISE TESTING AFTER MYOCARDIAL INFARCTION

Introduction:

Earlier mobilisation and shorter convalescent periods have been suggested for patients recovering after acute myocardial infarction, however, such patients are at a higher risk of dying than the general population. The comparative value of some of the methods available to detect high risk patients in the recovery phase have already been discussed. Such methodology has been devised on the basis of observations made in the acute phase or in the late hospital period with the patient in a resting state. However, exercise testing has now been shown to be predictive of subsequent coronary events in most populations (Ellestad, 1975; McNeer, 1978) including those patients with previous myocardial infarction (Markiewicz, 1977). The feasibility and safety of exercise testing soon after infarction have been studied (Ericsson, 1973) but the prognostic value of early testing and its usefulness in the clinical setting has not been adequately established. Early reports have suggested that a limited treadmill test performed before hospital discharge can predict mortality in the subsequent year (Theroux, 1979) but thus far only preliminary work has been published on the prognostic

value of exercise radionuclide ventriculography. (Dewhurst, 1981; Borer, 1980).

In this study, exercise tolerance was noted at each follow-up appointment and symptom limited exercise radionuclide ventriculography performed with electrocardiographic monitoring using the protocol previously outlined (Chapter 3). The next section of this thesis concerns itself with the prognostic value of exercise testing at one month in terms of morbidity and mortality over the one year follow-up period.

Results:

There were two patients excluded from repeat radionuclide ventriculography: one required surgery for late ventricular septal rupture, one other developed atrial fibrillation following inferior infarction. A further two patients were not exercised because of frequent (> 10/minute) VPB's at rest.

Tolerance and Safety:

Of 96 patients exercised four weeks after discharge from hospital, 94 were able to complete at least one level of exercise. The test was terminated prematurely in one patient because of the development of breathlessness associated with frequent VPB's and terminated in a second patient who had two episodes of self-terminating ventricular tachycardia. All four patients who did not complete one level of exercise due to ventricular arrhythmia had poor left ventricular

function and low EF (0.10, 0.15, 0.21, 0.35) and in three was secondary to extensive infarction and ventricular dyskinesia.

Of the 94 patients who completed at least one level of exercise, the test was stopped because of chest pain in 12 and in nine because of fatigue or dyspnoea. One patient who developed angina also complained of calf claudication. Apart from two episodes of self-terminating ventricular tachycardia the exercise test caused no complications. In all cases episodes of chest pain were short-lived and the increase in VPB frequency transient and no acute intervention therapy was necessary. A decrease in blood pressure did not occur in any patient during exercise.

Electrocardiographic Changes:

As shown in Table 11, 68 patients (72%) had negative exercise tests. Ventricular arrhythmia requiring premature termination of exercise occurred in eight patients; one previously mentioned had ventricular tachycardia, three developed frequent (> 10/minute) VPB's and four had transient bigemini. None of these patients had either chest pain or ST segment depression during the test. Depression of the ST segment equal to or greater than 1 mm from base line was observed in 14 (15%), three of whom had chest pain. Overall, chest pain occurred in nine patients, three of whom had depression of the ST segment.

Prognostic Value:

Of 28 patients with positive tests, 15 developed stable angina and three died during the subsequent 11 month period. The operating characteristics of the exercise test in predicting post infarction angina are shown in Table 12. Two patients who died had both developed stable angina, the other had required increased diuretic medication for heart failure. None of the six patients who reinfarcted had a positive exercise test and likewise the eight other patients who died in the first year. Five patients exhibited ST segment elevation during exercise and four of these had grossly abnormal wall motion (akinesis or dyskinesis) on radionuclide ventriculography and although two of these patients had further infarcts, none died in the follow-up period.

Exercise Radionuclide Ventriculography:

Twenty-six normal individuals subjected to an identical exercise protocol had a rise in ejection fraction from 0.56 ± 0.01 (Mean \pm SEM) to 0.64 ± 0.01 ($p < 0.01$), representing a mean rise of 14% on the resting value for the group as a whole. (Figures 6.1 and 6.2).

Site of Infarction:

During submaximal exercise at one month, EF in patients with recent transmural anterior infarction fell significantly from 0.34 ± 0.02 to 0.30 ± 0.02 (Mean change = -11.5% of resting value, $p < 0.01$), whereas for patients recovering from transmural inferior infarction

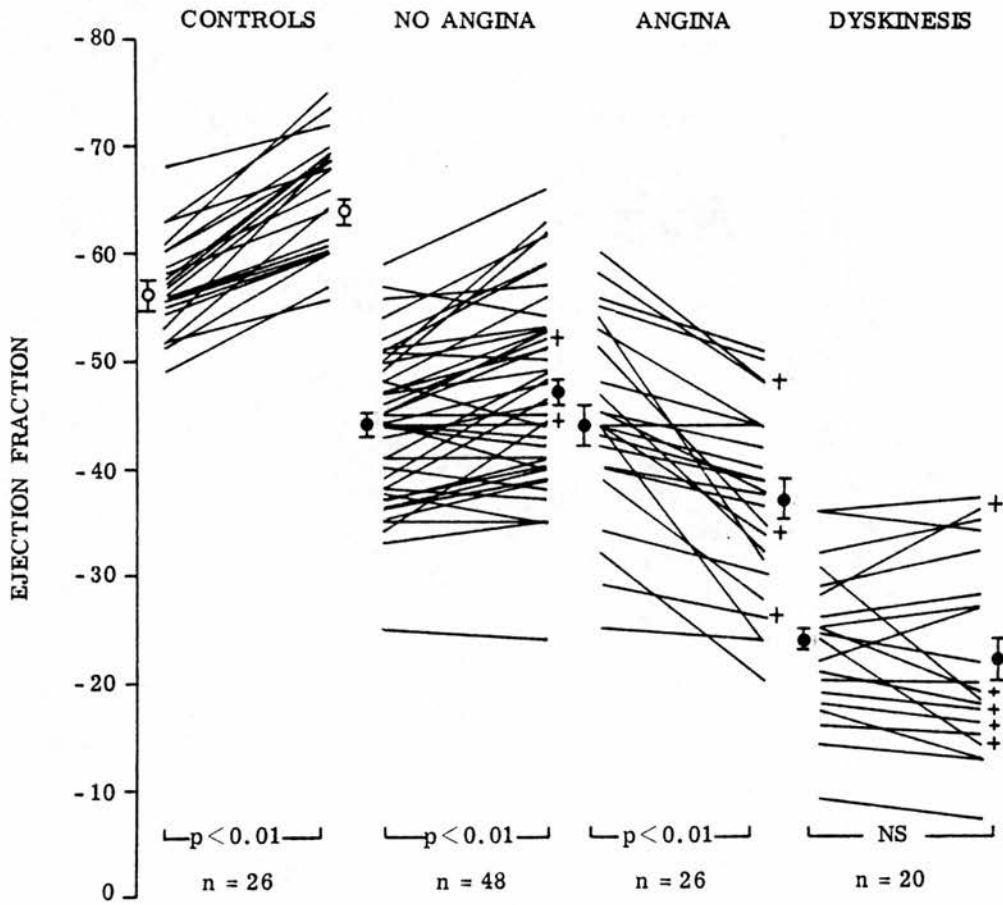


Figure 6.1 Left ventricular ejection fraction at rest and during exercise one month after infarction. Changes related to morbidity and mortality (+) in the following year. Mean (\pm SEM) are shown by the bars.

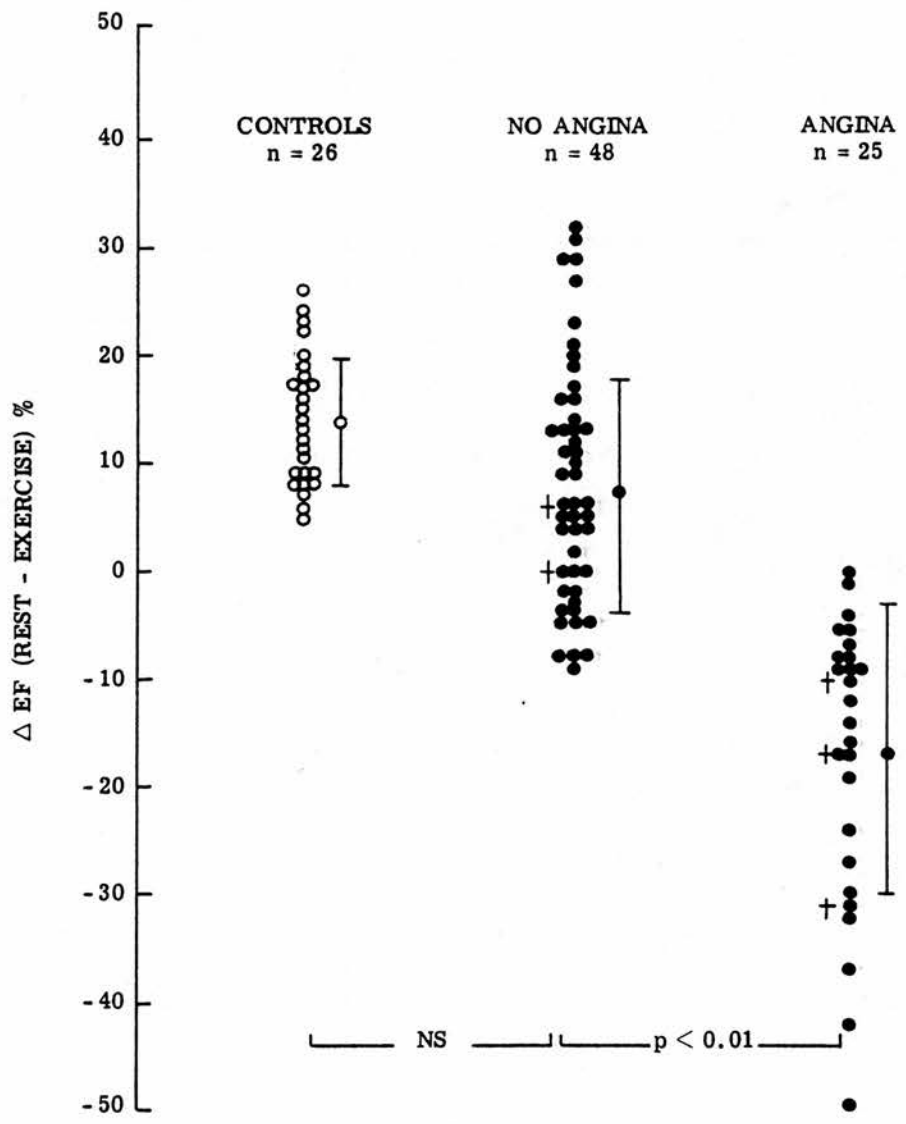


Figure 6.2 Relationship between change in ejection fraction on exercise and the subsequent development of post-infarction angina. Mean (\pm SD) are shown by the bars.

there was no significant change (0.49 ± 0.02 to 0.48 ± 0.04). Likewise, there was no significant change in EF on exercise following subendocardial infarction (Table 13)

Wall Motion:

The twenty-five patients with dyskinesia had been identified as high risk survivors on the resting study. Of twenty patients who completed at least one level of exercise, only nine could increase EF on exercise (Figure 6.1). For the group mean EF fell (mean change = -6%) and in 11 patients the fall was related to an increase in paradoxical movement of the dyskinetic segment. In these patients the results of exercise testing were of no further value in predicting outcome and therefore were excluded from further statistical analyses.

Post-infarction Angina:

Of the remaining 74 patients, the 26 who were to develop post-infarction angina had significant reduction in mean EF on exercise from 0.44 ± 0.02 to 0.37 ± 0.02 ($p < 0.01$). Those 48 patients who did not develop angina showed a significant increase in mean EF on exercise from 0.44 ± 0.01 to 0.47 ± 0.01 ($p < 0.01$). (Figure 6.1 and 6.2). No patient who developed angina was able to increase EF on exercise. Individual reduction in EF was often profound and related to increasing degree of wall motion abnormality. Although the size of the affected

segment commonly increased and normal or hypokinetic wall became more hypokinetic or akinetic the progression to exercise-induced dyskinesia was never observed.

Changes in EF expressed as percentage of resting EF are shown in Figure 6.2. Reduction of greater than 5% was seen in 27 patients, and of these, 23 developed post-infarction angina; the operating characteristics are shown below (Table 14).

Six patients had already developed angina at the time of the exercise test one month after discharge but the test was predictive in the remaining 17 patients who were to develop angina in the subsequent 11 months.

Correlation between EF and Electrocardiographic Changes:

No significant differences existed in the absolute values of ejection fraction at rest or during exercise in the subgroup with ST segment depression of 0.1 mV or greater compared with the subgroup lacking such depression. (Figure 6.3). Although absolute values were not significantly different, the subgroup with ST depression manifested a reduction in ejection fraction of 11.5% during exercise compared with the value at rest. This exercise induced reduction was significantly greater ($p < 0.05$) than the average reduction of 2% in the group lacking ST segment depression (Figure 6.4).

Reinfarction

Of six patients who suffered recurrent infarction, three were unable to increase EF on exercise. Four

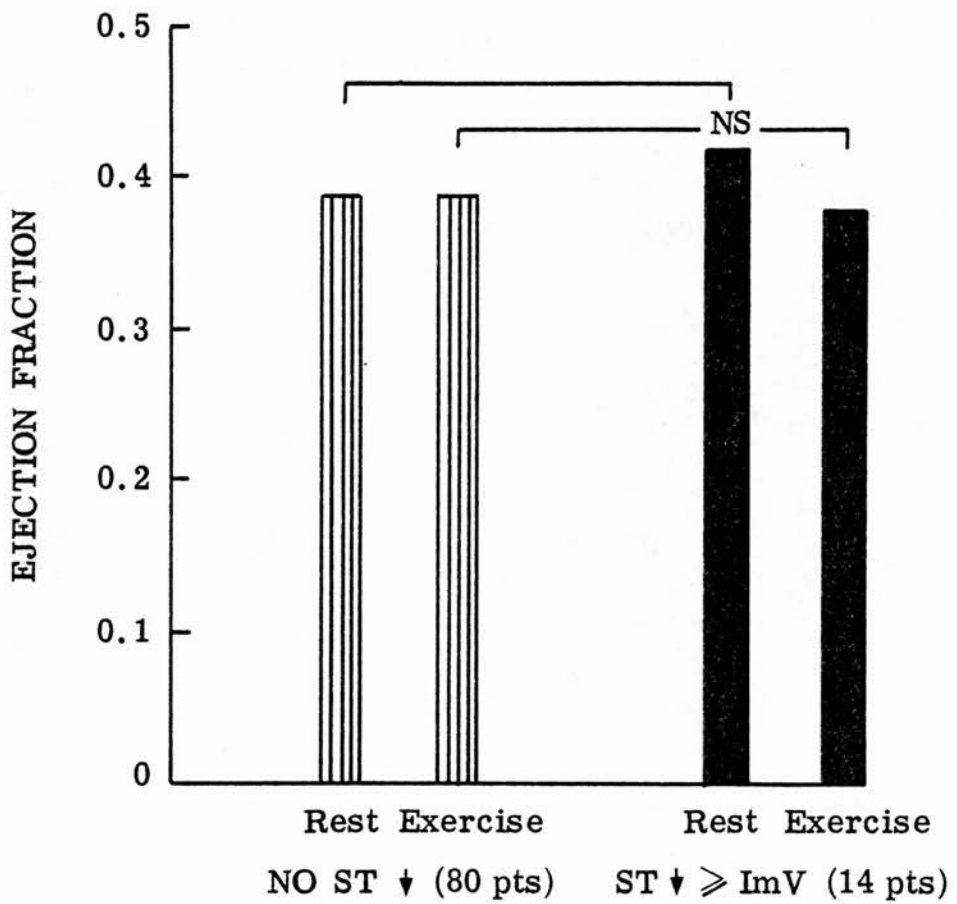


Figure 6.3 Average left ventricular ejection fraction in 94 patients with and without exercise induced ST-segment depression of 0.1 mV or greater in magnitude.

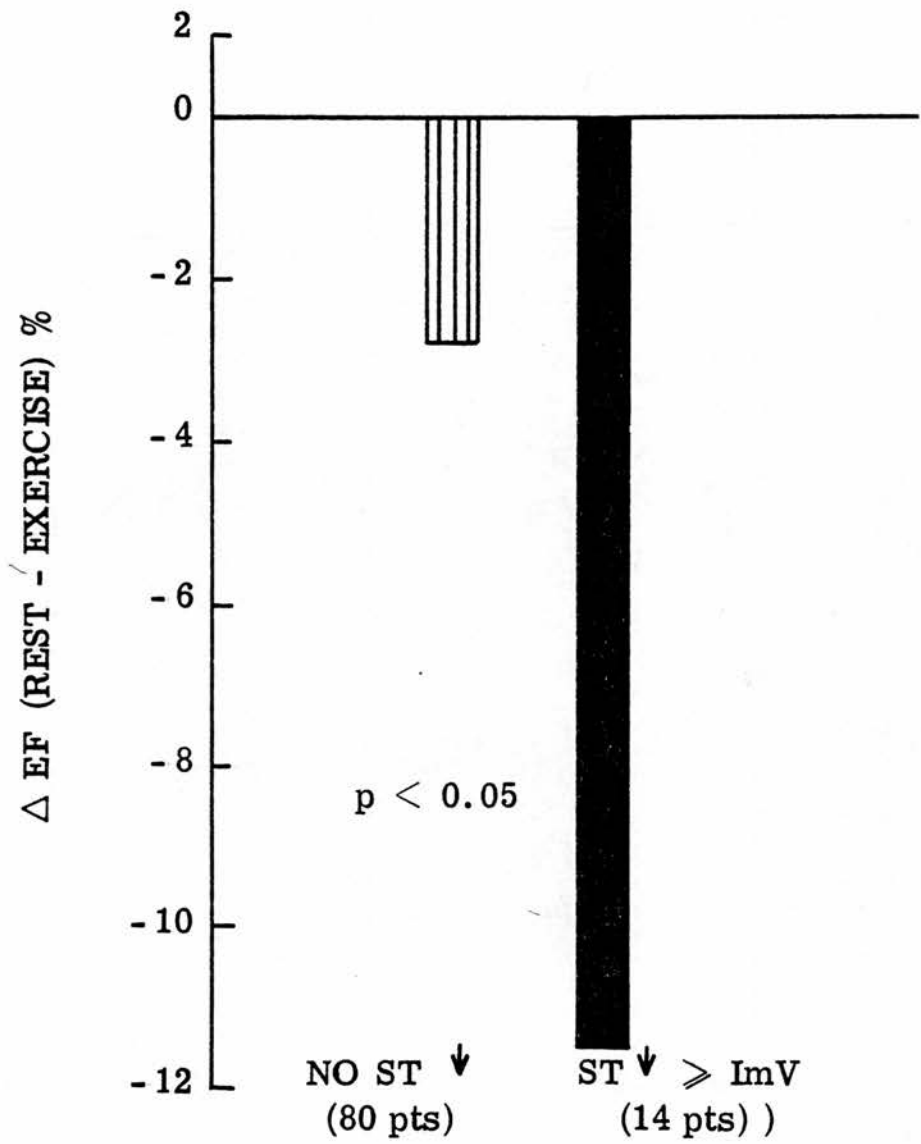


Figure 6.4 Magnitude of change in ejection fraction from rest to exercise (ΔEF) in patients with and without exercise-induced ST-segment depression of 0.1 mV or greater in magnitude.

patients showed significant reductions in EF on exercise but did not develop angina and of these, one has reinfarcted. When exercise testing was repeated at four months, one patient was subsequently able to increase EF, the other two were both unable to increase EF but thus far have remained well. In the other patients the results of exercise testing at one month were reproducible at four months and individual responses appeared consistent.

Sudden Death:

Six patients with poor left ventricular function consequent upon segmental dyskinesia died in the first year and have been discussed in detail previously. Three other deaths occurred in the twenty-six patients (12%) with moderate or good left ventricular function who developed angina and only one of these was predicted by conventional coronary prognostic indices.

Two deaths occurred in the group of 48 patients (4%) with moderate or good left ventricular function who did not show reduction of EF on exercise. These deaths which were sudden and not predicted by exercise radionuclide ventriculography were also not predicted by either of the three Coronary Prognostic Indices used and occurred in allegedly "low risk" survivors.

DISCUSSION:

Although the safety of exercise testing has been well documented a small risk of associated morbidity and mortality exists. A survey of 170,000 exercise tests reported by Rochmis and Blackburn (1971) revealed a mortality of approximately 0.01% and morbidity requiring admission to hospital occurred in 0.2%. Of the 16 deaths reported, all occurred within one week of stress testing and eight were immediate. In another study of 15,000 tests reported by Bruce (1975) there were no fatalities but two patients experienced postexercise cardiac arrest. Such observations prompted Fortuin and Weiss (1977) in a review of the topic to list recent myocardial infarction as one of the contraindications to any form stress test and advised that exercise testing should not be performed within three weeks of infarction. Until recently this "three week rule" was universally accepted.

The first observations regarding routine exercise testing three weeks after myocardial infarction were published by Atterhog et al (1971). Since 1968 bicycle ergometry had been part of their routine management and they observed both ST segment depression and elevation which they regarded as being of possible prognostic value and variable changes in T wave amplitude which they felt were non-specific. However, their observations were limited to a small number of patients all of whom were selected after anterior infarction. In 1973, Ericsson et

al reported on the value of treadmill testing three weeks after infarction. They concluded that it was a sensitive method for demonstrating a tendency to increased VPB frequency in patients with recent infarction and in their small group of only 16 patients did not report any arrhythmia or reinfarction induced by the test. They noted that the VPB frequency on exercise was higher in those patients with complications in the acute phase but could provide no evidence for the prognostic value of either VPB frequency or ST segment shift.

The first prospective study which provided such evidence was reported by Markiewicz et al (1977). They studied 46 patients using repeated treadmill testing at three, five, seven, nine and eleven weeks after myocardial infarction and found that ST segment depression which occurred in 45% of patients was associated with a significant increase in the incidence of subsequent coronary events. They also concluded that the presence of exercise-induced ventricular ectopic activity provided little independent prognostic information. Although there were no serious complications in the 210 tests performed they studied a highly selected group of patients. Only 9% of their population had a Norris Coronary Prognostic Index score of over 6, whereas this value was present in 40% of Norris' unselected patients and 30% of the population in this study.

Following this preliminary report it was felt that

should the test be of such predictive value then to be most useful it would if possible be best performed before the patient left hospital, since it had been suggested that much of the first year mortality occurred soon after discharge (Moss, 1977). Accordingly, Theroux and colleagues (1979) published the results of a limited treadmill exercise test performed one day before hospital discharge. They exercised 210 consecutive patients at a mean of 11 days (range 7 to 20 days) after myocardial infarction. Although they were exercised to a higher target heart rate or workload sooner after infarction than patients studied previously they reported no adverse effects. However, they excluded 31% of survivors who had either persisting sinus tachycardia or third heart sound and only 19% of the patients studied had a Norris score of 6 or greater.

Although there is little doubt that an exercise stress test is of some prognostic value, it would appear that there remains considerable uncertainty concerning the ideal timing of such an event after infarction and its exact value in a clinical context. The theoretical basis for exercising soon after infarction must also be challenged. Much of the support for the institution of routine early exercise tests based on the papers of Moss et al (1977) and Schulze et al (1977) which document a high mortality in the initial 6 months and particularly in the first month after infarction. However, in the

Edinburgh population of 100 patients recovering from their first infarct none of the 11 deaths occurred in the first 6 weeks after infarction. Schulze et al (1977) documented a first month mortality of 4% but 20 of his 81 patients had a history of previous infarction and these patients contributed disproportionately to mortality. Moss et al (1977) reported that 38% of all cardiac deaths in the first 6 months occurred in the first posthospital month. Although they did not document the proportion of patients with previous infarction, 70% were taking digoxin and 50% diuretic and thus by inference the population was biased toward those with a history of heart failure and poor left ventricular function. It is therefore apparent that high mortality in the first month post infarction only follows infarction complicated by heart failure or recurrent infarction. These observations which were made in the original report of Norris et al (1979) may be derived from the history and documented early clinical progress and therefore an early exercise test for these patients appears to be of no further benefit to either themselves or their physician.

In addition patients must be selected as being suitable for an early exercise test and for the purposes of safety those with continuing signs of heart failure or frequent VPB's at rest must be excluded. The papers of Markiewicz (1977) and Theroux (1980) both report considerable predictive value from exercise tests, however, these favourable results which were obtained

from selected groups of patients should not be extrapolated to the whole population surviving myocardial infarction. Indeed Markiewicz et al gave no indication of the proportion of patients excluded on the basis of either frequent VPB's or heart failure but of the 326 patients screened by Th eroux et al 31% were not exercised. Of the population in this study there were two patients with > 10 VPB's at rest were prohibited from performing the exercise test and this is in close agreement with the paper of Atterhog et al (1971) which documents a prevalence of 3% of such patients who were not exercised seen after infarction. In two other patients exercise was terminated prematurely; in one developed increased VPB frequency but the other developed ventricular tachycardia. Although ventricular tachycardia was self-terminating on the first occasion the latter patient was exercised again to evaluate the efficacy of combined antiarrhythmic therapy and on this second occasion developed ventricular tachycardia which degenerated into ventricular fibrillation. This may have been an isolated incident but represents a complication rate of 1% and, moreover, occurred in a patient clinically free from heart failure with normal sinus rhythm at rest. Such exercise induced arrhythmias may be more common in the late hospital phase (Vismara, 1975) and illustrate the potential dangers of the adoption of routine exercise testing on an unselected population soon

after myocardial infarction. As discussed previously poor left ventricular function often occurs when not apparent clinically and to select patients for exercise on the basis of the presence or absence of clinical signs may expose a minority to unnecessary risk.

Another argument which has been put forward in favour of early stress testing centres on the rehabilitation of patients surviving myocardial infarction. In 1977 Marciewicz et al concluded that treadmill testing provided objective information concerning the capacity to resume physical activity, including return to work. In this study ability to return to work did not correlate with either resting ejection fraction or any of the parameters monitored during exercise. However, since the work loads tolerated differed between patients and since oxygen consumption was not directly measured, definitive conclusions concerning changes in physical working capacity cannot be drawn from this study. Fifteen of the 100 patients were recruited to a supervised exercise programme lasting two months as part of a rehabilitation scheme for patients with ischaemic heart disease. Over this period there were no significant changes in N.Y.H.A. classification or regional or global left ventricular function but there was a small but not significant reduction in resting heart rate. Such results are in agreement with those of Detry et al (1971) who showed that the increase in maximal oxygen uptake after physical training in patients

with coronary heart disease resulted mainly from an increase in arteriovenous oxygen difference; stroke volume remaining unchanged. In a further study using invasive techniques Lee et al (1979) failed to identify any significant change in cardiac index, stroke index or left ventricular end-diastolic pressure, volume and ejection fraction following exercise training. Despite the lack of impairment of resting ventricular function, physical work capacity however improved.

In the selected populations studied thus far it has been shown that exercise-induced ST segment depression and chest pain are predictive of subsequent cardiac events whether exercise is performed before hospital discharge (Thérout, 1979) or three weeks after infarction (Sami, 1979; Davidson, 1980). In the largest series of male and female patients Thérout and colleagues reported increased frequency of angina and sudden death following exercise induced ST segment depression. Davidson and DeBusk confirmed these original observations in the 195 male patients they studied but in addition concluded that clinical characteristics and exercise-induced ectopic activity were of no further predictive value. The work presented in this thesis confirms that ST segment depression on exercise is associated with the development of angina but with the exercise protocol and electrocardiographic monitoring system employed, although of high specificity the test has low sensitivity (48%)

with a high false negative rate. These results are similar to those of Castellonet et al who described a comparably low sensitivity (52%) for the detection of significant coronary artery stenosis in noninfarcted regions two months or more after anterior myocardial infarction. The authors attributed this low sensitivity to the opposing effects of anterior ventricular aneurysm on the exercise-induced vector. In their patients with inferior infarction, aneurysm was less frequent and the sensitivity of exercise testing for the detection of coronary lesions corresponding higher. However, in the Edinburgh population, the site of infarction or the presence of dyskinesia did not significantly influence the occurrence or degree of ST segment depression and this is in agreement with the results of Davidson (1980). It would be pertinent at this point to mention some of the other factors which may affect the results and reproducibility of exercise testing such as drug effects or metabolic disturbance and the exercise protocol or electrocardiograph lead system employed. These factors are discussed in detail in a review of the topic by Fortuin and Weiss (1977) and illustrate the problems in the development of a universally acceptable exercise test.

The predictive value of early exercise radionuclide ventriculography after myocardial infarction has thus far not been widely reported and the preliminary results of this study (Dewhurst 1981) were among the first to appear

in the literature. To date only one other paper, that of Borer et al (1980) included the results of exercise stress testing performed with routine radionuclide ventriculography soon after myocardial infarction. Using an upright submaximal treadmill test and a two-lead monitoring system they found that changes of ejection fraction on exercise were of no value in predicting mortality, but did not examine their data to determine any prognostic value in the prediction of angina pectoris. Moreover in their study, no relation was noted between ST segment depression and mortality but they comment that other investigators had employed a more stressful protocol which could have accounted for the greater predictive value. In addition it may be significant that they performed exercise testing prior to discharge from hospital since it is well documented that exercise tolerance spontaneously improves between one and four weeks after discharge from hospital (Markiewicz, 1977).

Supine exercise equilibrium radionuclide ventriculography for the detection of coronary artery disease was first described by Borer et al in 1976. They demonstrated that patients with coronary artery disease were unable to increase their ejection fraction with maximal exercise and also exhibited new regional wall motion abnormalities induced by exercise. Berger et al (1979) examined the inter-relationships between changes

in ejection fraction, wall motion and ischaemic ST segment responses in 60 patients 30% of whom had suffered recent myocardial infarction (less than three months before testing). Of 30 patients who developed ST segment depression, all showed either a decrease or no increase in ejection fraction. Of the remaining 30 patients with negative tests 15 had normal ventricular contraction at rest and the stress test had to be discontinued because of fatigue, with only seven patients demonstrating abnormal left ventricular reserve. The other 15 patients had abnormal left ventricular function at rest and after exercising to fatigue, 11 were found to have abnormal left ventricular reserve despite a negative ST segment response. Similar results were obtained by other authors and Slutsky (1979) demonstrated that the normal increase in ejection fraction with exercise is due primarily to a decrease in end-systolic volume, whereas the exercise-induced decrease in ejection fraction in patients with angina is due primarily to an increase in end-systolic volume. Patients with coronary artery disease who do not experience angina may have no change in ejection fraction with exercise presumably because there is no significant change in end-systolic volume but responses to suboptimal exercise levels must obviously be interpreted with caution.

Thus, an important aspect of this form of testing is to attain adequate levels of stress. Although the loads used may differ between the various studies

Caldwell et al (1979) have shown that supine ergometry produces a maximal left ventricular stress which equals that obtained during upright exercise and the ability of the two methods to produce an ischaemic ST segment response is equivalent. Table 15 summarises the reported experience with exercise radionuclide ventriculography for the detection of significant coronary stenosis (> 50 or > 70%) in 427 patients of whom approximately one third had either documented previous myocardial infarction or abnormality of regional wall motion at rest. Failure to increase ejection fraction with exercise had a sensitivity of 87% and a specificity of 93%. The electrocardiographic exercise test had a sensitivity of 64% and a specificity of 98%. Exercise radionuclide ventriculography was significantly more sensitive ($p < 0.0001$) than the exercise electrocardiographic changes when analysed by the chi-squared test.

In this study stricter criteria were applied to the exercise induced changes in ejection fraction since small increases, falling within observer error, must be interpreted with caution. However, the results demonstrate that a fall in ejection fraction of greater than 5% of the resting value is predictive of angina and these patients do carry an increased risk of mortality. The results are in agreement with the other studies presented in Table 15 and demonstrate the higher sensitivity of exercise radionuclide ventriculography

compared with electrocardiographic exercise testing. This is most likely due to electrical changes occurring at a higher ischaemic threshold than the contractile changes as shown by Scheuer and Brachfeld (1966). To support this argument, Upton et al (1979) using serial exercise radionuclide imaging have demonstrated that ejection fraction changes precede electrocardiographic changes in patients with coronary artery disease.

The response of ejection fraction to exercise at one month and four months appeared to be reproducible in the majority of cases and such results are in agreement with the work of Upton et al (1980) who studied normal individuals. However, a longer follow-up period will be necessary before the significance of a change in exercise response becomes apparent. Likewise the exercise response following anterior infarction requires further study. The results of this study confirm the observations of Pulido et al (1978) who noted the different functional response to submaximal exercise between transmural anterior and inferior infarction. It is possible that this is merely a reflection of the excess prevalence of ventricular dyskinesia and poor left ventricular function which follows anterior infarction. An exercise induced fall in ejection fraction following anterior infarction may be related to the site and extent of myocardial necrosis or alternatively may be evidence of significant disease of the left coronary system. Larger studies using both radionuclide and

electrocardiographic techniques will be required to determine the relative prognostic significance of these changes. Such an approach could also elucidate the origin of exercise induced ST segment elevation. In this study such changes were only apparent following extensive transmural infarction with either akinetic or dyskinetic segments and there is now good evidence that ST segment elevation may represent either left ventricular aneurysm or exercise-induced dyskinesia (Weiner et al, 1978; Waters et al, 1980).

In the summary, this work has shown that, radionuclide ventriculography at rest is an accurate non-invasive method of detecting patients with poor left ventricular function prior to their discharge from hospital since clinical features of cardiac decompensation are commonly absent. Gross impairment of left ventricular function was detected in six of the eleven patients who were to die in the year following infarction. However, in those individuals without significant left ventricular dysfunction, prognosis is significantly influenced by the number of diseased coronary arteries. It is therefore important to identify the survivors of myocardial infarction who have multivessel disease since one may identify those at risk from further ischaemic episodes, ventricular tachyarrhythmias and sudden death.

In this chapter we have reviewed the techniques

currently available to detect ischaemia of the residual noninfarcted myocardium and it would appear that exercise radionuclide ventriculography is superior to other methods since it combines a high sensitivity and specificity. Electrocardiographic changes only identify 50% of high risk patients and myocardial perfusion scanning is not suitable for routine screening of large numbers. Resting radionuclide ventriculography can select those patients in whom an exercise test would be of no further prognostic value and prevent them being exposed to an inappropriate stress test soon after infarction. In the remaining individuals an exercise induced fall in ejection fraction of greater than 5% correctly predicted 88% of patients who were to develop post infarction angina and of these a further three patients died suddenly in the first post infarction year.

The technique however did not predict the deaths of two individuals who had been assigned to a low risk category by all three coronary prognostic indices and who did not develop exercised induced ST segment depression or complain of post infarction angina. We have already discussed the limited value of response to submaximal exercise but in both cases there was a significant increase in heart rate of between 25-50% of resting rate. The small changes in ejection fraction observed may have been within observer error but repeat analysis of these results was of no further value. Other authors have implicated different pathogenetic mechanisms in sudden

cardiac death such as irreversible coronary artery spasm or psychological stress but any relevance of these factors to the above cases is speculative.

Using current methods, radionuclide determined changes in ejection fraction both at rest and during exercise soon after myocardial infarction predict the vast majority of patients who will develop left ventricular failure and angina in the first post infarction year. However, a longer period of observation is necessary to determine whether recurrent infarction can be related to the results of exercise ventriculography. The technique identified as high risk survivors, 82% of all those who were to die in the first year and therefore although death was classified as "sudden" it could be predicted in the majority within one month of discharge from hospital.

CHAPTER 7:

RADIONUCLIDE ASSESSMENT OF INOTROPIC THERAPY FOLLOWING MYOCARDIAL INFARCTION.

DIGOXIN:

Introduction:

Some preparation of the foxglove plant has had a place in domestic and medical therapy for centuries. It was, however, a Birmingham physician, Withering, who in 1785 identified *Digitalis purpurea* as the diuretic agent in a Shropshire woman's herbal brew and published his "Account of the foxglove" to record the first reliable observations on its therapeutic efficacy. Although he was most impressed with its diuretic properties and it was to demonstrate this effect that he published his book, he also commented upon cases of heart failure, in which digitalis had good effect. Withering knew of no other agent with comparable properties, and he succeeded where many others had failed by adopting a reliable dose regimen and using an experimental approach in each case. However, the indications for its use remained ill defined and with more widespread prescription many patients with little prospect of improvement, were at serious risk from toxic side-effects. With little else to offer from the therapeutic armamentarium, Herrick (1912) in his original description of acute coronary occlusion, recommended its use after myocardial infarction. He noted the grave

prognosis which followed the development of "dyspnoea, cyanosis, weak pulse and basal rales" and concluded that "digitalis or strophanthus by increasing the force of the heart's beat, would tend to help in this direction more than the nitrites. The prejudice against digitalis in cases in which the myocardium is weak is only partially grounded in fact." His latter phrase referred to controversy at the end of the eighteenth century regarding the efficacy of the drug, however, McKenzie (1911) reintroduced digitalis in cardiovascular therapeutics because of its atrioventricular nodal blocking properties. With Lewis (1942) he developed the concept that heart failure was caused by "fatigue" of the ventricular muscle and both authors considered atrial fibrillation as the specific indication for digitalis and were convinced that few other cases benefited from it.

Comparisons of the action of digitalis in sinus rhythm and in atrial fibrillation were made by Christian (1922), Luten (1924) and Marvin (1927). These authors reported a total of over 130 patients and showed that digitalis was associated with some improvement in about half the cases in which it was used and they proposed that patients with sinus rhythm benefited as much as those with atrial fibrillation. However, the modern loop diuretics are very potent agents for the relief of salt and water retention and will improve symptoms in the majority of patients. These drugs are now the first line treatment of cardiac failure and the use of digoxin as an

inotropic agent to produce further symptomatic improvement is being questioned with increasing frequency (Guz, 1978; Johnston, 1979).

The following study was undertaken to evaluate the cardiovascular effects of intravenous and oral digoxin in patients with sinus rhythm in chronic cardiac failure (despite diuretic therapy) following myocardial infarction.

Protocol:

Patient Population:

Nine patients with ischaemic heart disease were studied: all had sustained a myocardial infarction and were known from previous radionuclide ventriculography to have poor left ventricular function (ejection fractions 0.13 - 0.37). These included six cases from the original 100 patients and individual patient details are summarised in Table 16. Despite at least 80 mg frusemide, each of the nine patients was in chronic left ventricular failure as judged by clinical and radiological examination. No patient had been prescribed digoxin therapy previously and none had biochemical evidence of impaired renal function. All therapy was continued unchanged during a three day in-hospital assessment period and diuretic agents were given at 0600 hours on the day of the study. The study commenced in each case at 1400 hours and heart rate, ejection fraction

and end-diastolic volume were determined in the resting state using the method previously described.

The protocol employed the regime recommended in this Institute for urgent digitalisation of patients with left ventricular failure and consisted of 0.5 mg digoxin administered intravenously over 30 minutes. Measurements of heart rate, ejection fraction, relative end-diastolic volume and relative cardiac output were repeated at hourly intervals thereafter for three hours. In addition, the derived ventricular volume curves were used to examine changes in the weighted mean ejection time. This variable describes changes in the shape of the systolic portion of the curve and is shortened by increased contractility (Muir, 1980).

After a subsequent oral dose of 0.5 mg digoxin, patients were placed on a maintenance dose of 0.25 mg digoxin daily and three weeks later clinical status was reviewed and radionuclide ventriculography repeated.

Results:

No patient complained of adverse effects of the drug. Before digoxin, five patients were N.Y.H.A. Class III and four patients Class IV. After three weeks oral digoxin therapy one patient had deteriorated, one improved and one had died. (Table 16).

Intravenous Digoxin:

The effects of intravenous digoxin on ventricular performance at rest are shown in Table 17. Over the

three hour study period there was a significant fall on heart rate from 86 ± 3 (Mean \pm SEM) to 78 ± 4 ($p < 0.05$). Absolute values for ejection fraction did not change significantly (0.22 ± 0.02 versus 0.20 ± 0.02). The mean ejection time (ts), normalised by left ventricular ejection time (LVET) was identical before and three hours after the intravenous administration of digoxin (0.53 ± 0.03 versus 0.53 ± 0.02). There was no significant overall change in relative end-diastolic volume and the relative cardiac output fell to 0.83 ± 0.05 of the control value. (Figure 7.1).

The effects of intravenous digoxin on ventricular performance at rest and exercise are shown in Table 16. The five patients in N.Y.H.A. Class III who were exercised before digoxin achieved a significant increase in heart rate (86 ± 3 to 112 ± 5) but there was no significant change in cardiac output (108 ± 0.07). The changes in ejection fraction (0.22 ± 0.04) likewise were not significant.

On exercise after intravenous digoxin despite a significant increase in heart rate there was no significant change in either ejection fraction or cardiac output. However, in three of four patients in whom data was available cardiac output after exercise increased and patient 2 with the highest ejection fraction at rest increased cardiac output by 38% of the resting value.

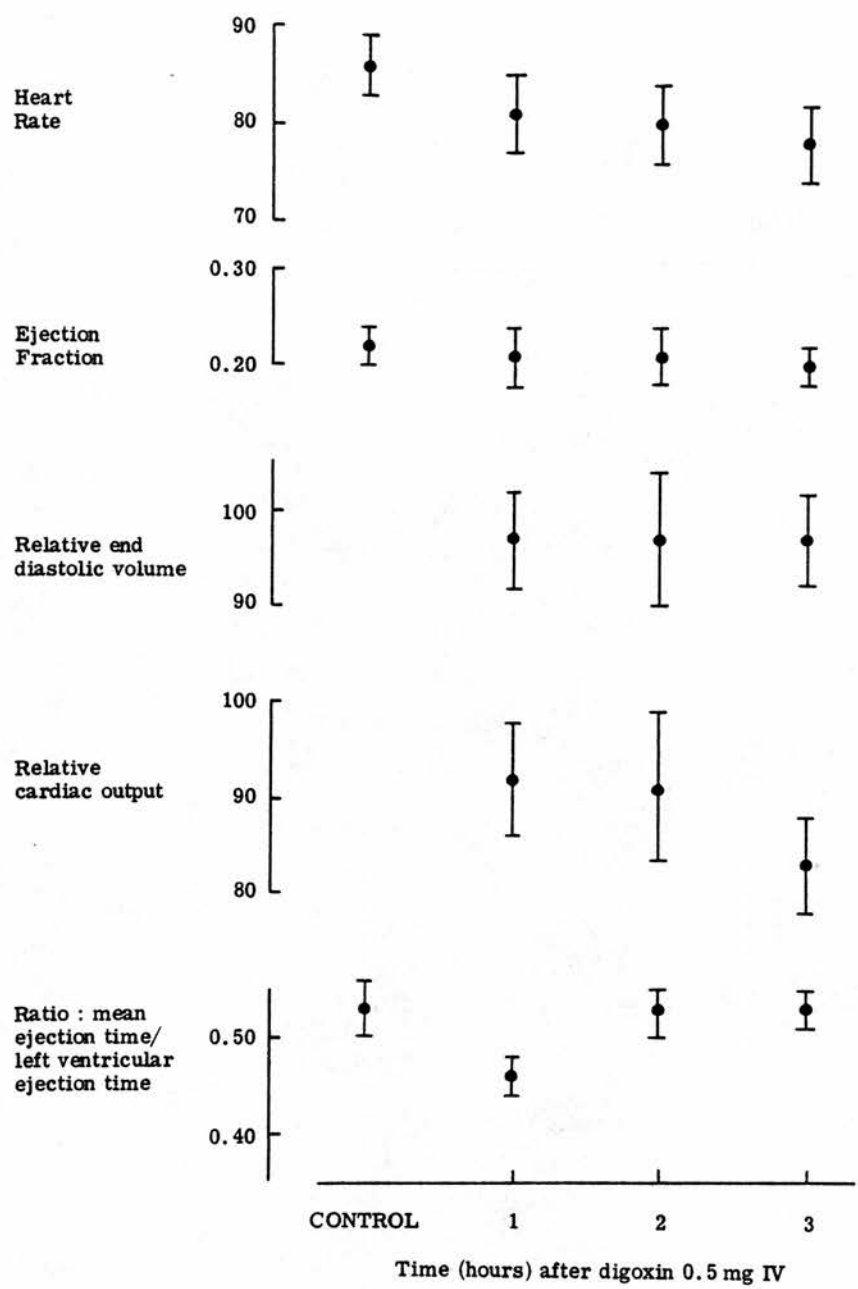


Figure 7.1 The effects of intravenous digoxin on haemodynamic variables of nine patients in chronic heart failure with sinus rhythm.

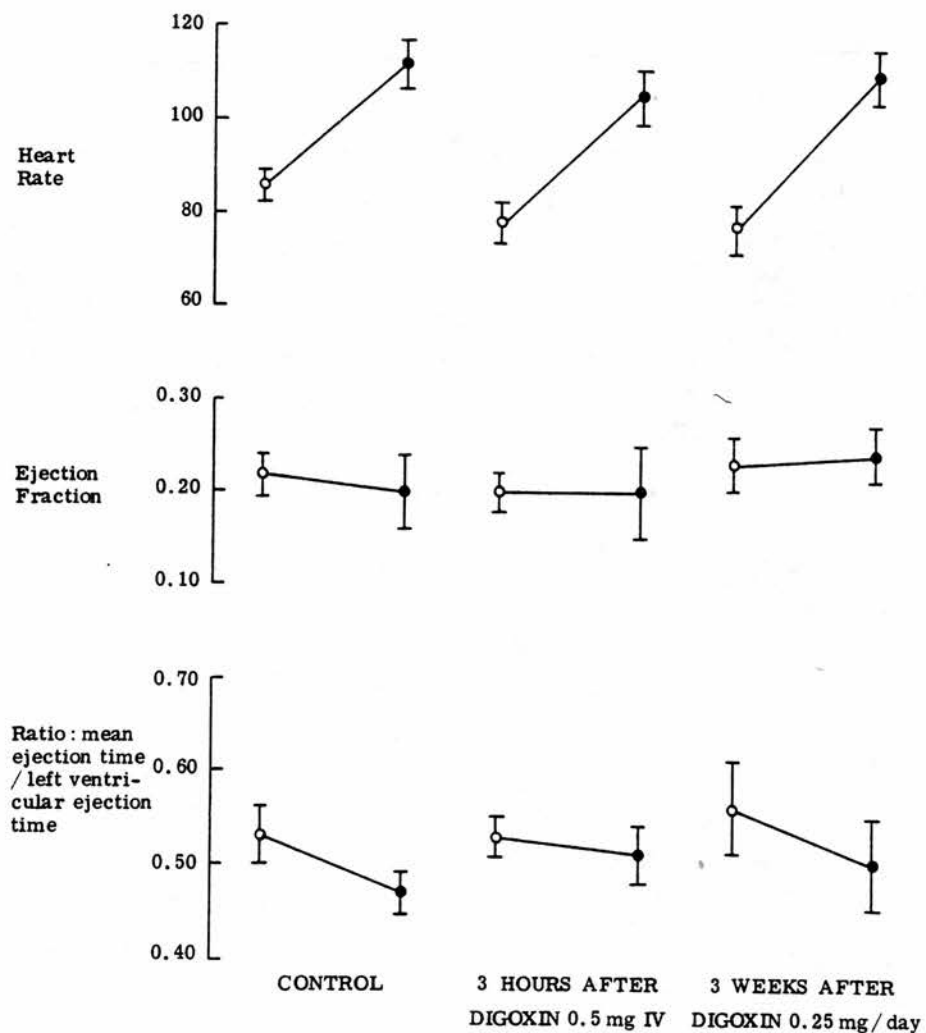


Figure 7.2 The effects of intravenous and oral digoxin on haemodynamic variables at rest and during supine exercise in patients with chronic heart failure and sinus rhythm.

Oral digoxin:

The effects of prolonged oral digoxin therapy on ventricular performance are shown in Table 18. The significant reduction in resting heart rate achieved during intravenous digitalisation persisted (86 ± 3 versus 77 ± 5) but there was no significant improvement in ejection fraction over control values (0.22 ± 0.02 versus 0.23 ± 0.03). (Figure 7.2).

DISCUSSION:

Digoxin administration in patients with sinus rhythm and chronic left ventricular failure pre-treated with diuretics failed to achieve any significant improvement in either clinical status or ventricular performance as assessed by radionuclide ventriculography. Despite observing a significant reduction in heart rate both intravenous and oral digoxin therapy apparently failed to improve either ejection fraction or cardiac output at rest. Although more favourable results were obtained during exercise, the improvements in left ventricular performance did not achieve statistical significance.

In 1952, McMichael experienced considerable difficulty in showing that digoxin had a positive inotropic effect with the techniques then available and he concluded that "digitalis has no measurable effect on the contractile force of a normally functioning myocardium." However, the development of more sensitive

techniques such as strain gauge measurements at cardiac surgery allowed Braunwald to demonstrate an inotropic effect albeit in patients with no evidence of heart failure (Braunwald, 1961). Using ventricular markers to study myocardial force-velocity relations, Sonnenblick (1966) also demonstrated a positive inotropic effect again in patients who had undergone surgery for correction of congenital cardiac shunts but had no evidence of heart failure. The measurement of systolic time intervals and the ball travel time of an aortic Starr - Edwards valve also reflect the contractile state of the left ventricle in man and using these methods Davidson and Gibson (1973) demonstrated a beneficial effect following acute administration of digoxin. However, of the nine patients they studied, five had no evidence of heart failure and only four were taking diuretics. Moreover they concluded that the response was variable and transient and that the inotropic effect was relatively weak being approximately one-third of that produced by mild supine exercise.

Therefore it is apparent that the results thus far obtained have depended on the sensitivity of the techniques available and the clinical status and therapeutic regime of the patients studied. Details of the method used in this study and its reproducibility have been published (Hannan, 1980). However, there are several potential sources of error in this technique. The

first lies in the determination of cardiac output. Several investigators have used the radionuclide method for the determination of cardiac output and in general have found good agreement, with invasive methods provided the initial bolus is of good quality (Fouad, 1979). Alazraki et al (1975) also used a gamma variate curve-fitting method when calculating cardiac output from a bolus of $^{99}\text{Tc}^{\text{m}}$ - labelled albumin. They found that cardiac output measured in this way was in good agreement with that measured by dye dilution. In the present study it was not possible to measure simultaneously cardiac output by invasive techniques but subsequently it has been possible to compare the value of cardiac output by the radionuclide method and thermal dilution in three patients. In each case the two methods agreed within 0.5L min^{-1} .

A second potential source of error lies in the definition of the ventricular region of interest as this defines the end-diastolic counts. Using our method, which inspects volume-time curves from individual pixels on the border of the left ventricle, the inter-observer variation was 4% for ejection fraction and 3.8% for end-diastolic volume. Successive measurement of end-diastolic volume is not only affected by the region of interest, but also by the corrections for physical decay, gamma camera dead-time and blood clearance of the tracer. Blood volume was determined from 15 mCi of $^{99}\text{Tc}^{\text{m}}$ electrolytically labelled to human serum albumin and

using this preparation 90% remains within the vascular space at one hour (Millar, 1979). Estimation of blood volume using this method agreed closely with that determined by ^{125}I labelled albumin which was also used in four of the patients studied. In addition, a reproducibility study of successive measurements of end-diastolic volume revealed an average difference of 5%, representing a coefficient of variation of only 2.4%. However, the reproducibility study was performed in patients with relatively normal ventricular function (ejection fraction greater than 0.40) and although for patients with gross impairment of ventricular performance the same correction factors may be applied with confidence the identification of significant changes of ejection fraction presents considerable difficulty. For example a change in ejection fraction from 0.20 to 0.24 represents an increase of 20% but unfortunately could be accounted for purely by observer error. Small changes from such low values for EF may be significant but cannot be detected reliably and obviously the accuracy of the radionuclide method requires further validation in patients with poor left ventricular function and cardiac failure.

In addition it could be argued that a significant haemodynamic response could not be expected from the relatively small dose of digoxin used or indeed could be expected within the three hour study period. In the

present study the initial bolus of 0.5 mg digoxin intravenously was chosen to avoid any toxic reaction and remains the dose recommended by many authors (Moe and Farah, 1975). Indeed a significant fall in heart rate was observed within three hours of the intravenous infusion. Cardiac slowing is not a significant feature of digitalis action in normal man, but it commonly attends the use of digitalis in congestive heart failure. Congestive failure in patients with normal sinus rhythm is accompanied by tachycardia, as well as vasoconstriction, as part of the reflex compensation for a reduction in cardiac output. Should there be improvement in cardiac output following digoxin one would expect a reduction in heart rate. This indeed was observed, not as a primary therapeutic action of the drug but presumably secondary to an improvement in the haemodynamic state which was too small to be detected by the method used.

Using digoxin intravenously the onset of action is said to occur within minutes but the peak effect may be delayed up to several hours (Smith, 1973). Unfortunately, the study time using radioisotope methods could not be extended to greater than three hours after injection since there is significant clearance of the labelled tracer and significant physical decay of the radionuclide.

The oral maintenance dose of 0.25 mg was derived using body weight and renal function from the nonogram of

Jelliffe and Brooker (1974). For the nine subjects studied the recommended dosage ranged from 0.22 - 0.28 mg and therefore each was prescribed 0.25 mg daily and compliance checked by tablet counting. However, experimental studies have indicated that the positive inotropic action of cardiac glycosides increases progressively until toxic arrhythmias appear (Klein, 1971) and such studies in the future may need to be repeated using increasing doses of drug. Digoxin serum levels were not determined routinely in every patient since although levels accurately reflect a toxic state the therapeutic range is wide (Huffman et al, 1976).

Changes in haemodynamic variables, to be of any significance in a clinical context, must of course be accompanied by the relief of dyspnoea or fatigue. The beneficial effects of the potent diuretic agents cannot be in doubt but whether digoxin therapy is of further value remains controversial. In the present study there was no significant improvement in symptoms using the subjective N.Y.H.A. classification. Appropriate studies however, must involve the continuation of sufficient diuretic therapy to produce a 'dry' basal weight. Such an approach was used by McHaffie and his colleagues (1978) who studied patients in heart failure in sinus rhythm on diuretic therapy and could not identify any change in symptoms, exercise capacity, or respiratory quotient after withdrawal of digoxin treatment.

Johnston and McDevitt (1979) have also withdrawn digoxin from a group of patients in sinus rhythm in whom the pre-ejection period/ left ventricular ejection time ratio was measured as an index of left ventricular function. In only two of the seventeen patients who remained in sinus rhythm was there any evidence of reduced left ventricular performance after stopping digoxin.

Studies thus far have been confined to the resting state but recently, Murray and co-workers (1981) using radionuclide and thermodilution measurements examined haemodynamic variables during rest and exercise. They failed to identify any significant changes at rest following intravenous ouabain but ejection fraction increased during exercise and the significance of this result was supported by a corresponding increase in stroke volume index determined by thermodilution. However, no changes could be detected either at rest or during exercise after maintenance oral digoxin. The results of the present study would tend to support these findings although the significance of the changes determined by radionuclide ventriculography require further validation by invasive methods and even then they must be accompanied by symptomatic improvement to be of value in the clinical context.

Thus, in the acute situation the inotropic effect of digoxin is relatively weak and in most patients in sinus rhythm digoxin has no long term stimulatory action on the heart. Hence a rational recommendation is to give

adequate diuretic treatment as the first approach to patients with heart failure who are in sinus rhythm. Digoxin could then be administered and withdrawn as required, to ascertain whether the use of this drug further improved the clinical state.

Other Inotropic Agents:

Catecholamines and other sympathomimetic amines exert potent inotropic effects by interacting with myocardial (beta -1) adrenergic receptors. For many years attempts were made to utilise these properties in the treatment of heart failure, but these efforts were largely unsuccessful because of the other effects of these agents, namely the production of peripheral vasoconstriction and tachycardia. Two agents introduced relatively recently, dopamine and dobutamine, produce less tachycardia and fewer peripheral vascular effects and are being used increasingly in the treatment of acute heart failure but have the disadvantage in that both require to be given intravenously.

Prenalterol, (S-(-)-1-(4-hydrophenoxy)-3-isopropyl-amino-propranolol-2 hydrochloride) is a new selective beta1 adrenoceptor agonist, and studies in animals have shown a more marked effect on myocardial contractility than on heart rate. As prenalterol is readily absorbed after oral administration, it might prove a useful adjunct to the management of refractory heart failure. Therefore as part of a larger study,

three patients who had not been improved by digitalisation, were studied to evaluate the cardiovascular effects of prenalterol in patients with impaired ventricular function. The three patients were all in chronic left ventricular failure despite diuretic therapy and had resting ejection fractions of 0.30, 0.14 and 0.18 with segmental ventricular dyskinesia. Each was given 1.0 mg prenalterol intravenously over 10 minutes and measurements of haemodynamic variables repeated using radionuclide ventriculography as described previously 10 minutes after the injection had been completed. Each patient then received a further injection of 2.0 mg of prenalterol and all variables were again re-measured 10 minutes after this injection had been completed. Although this dose produced a significant increase in ejection fraction in normal individuals, in the three patients in cardiac failure there was no change in EF, relative end-diastolic volume or relative cardiac output. Thus any beneficial effect of this agent could not be detected and in two patients dyskinesia increased after prenalterol. Increased dyskinesia has been reported with inotropic agents and described in detail after the administration of digoxin (Kleiman, 1979). Such changes which may be due to increased contractility of viable nonischaemic muscle could theoretically be alleviated by afterload reduction thus further enhancing global left ventricular

performance and providing a more satisfactory means of dealing with the problem of refractory heart failure. The benefit of such an approach is now being examined using pirbuterol - a beta-agonist which combines vasodilator and inotropic properties (Dawson, 1981).

However, despite limitations, radionuclide ventriculography remains an attractive noninvasive means of assessing changes in ventricular performance following drug intervention and has been used by other workers to follow the effects of various inotropes. Indeed, Cheesbro and colleagues (1980) have used the technique to examine the effects of amrinone - the latest in the series of inotropic agents. Their results once again stress the importance of simultaneous invasive measurements of haemodynamic parameters since although ejection fraction measured by the radionuclide technique remained unchanged the drug resulted in significant improvement in cardiac index.

With the advent of mobile gamma camera systems a combined approach is now possible. A Searle LEM camera has now been acquired and pilot studies are in progress with simultaneous radionuclide and invasive haemodynamic measurements (Figure 7.3) following combined therapy using an inotropic agent - prenalterol and vasodilator - hydralazine. It is hoped that this approach will validate results obtained by radionuclide ventriculography and determine the role of this technique in non-invasive assessment of therapeutic intervention.



Figure 7.3 Simultaneous invasive and non-invasive measurement of haemodynamic variables. Thermodilution catheter in situ in the left antecubital fossa and cardiac output computer to the left of the patient. On the right, microprocessor, videodisplay unit and the Searle LEM camera (positioned in the left anterior oblique projection).

CHAPTER 8: SUMMARY

8.1 Ventricular function after myocardial infarction

1. Radionuclide ventriculography permitted non-invasive assessment of global and regional left ventricular performance. The technique was successfully performed in almost 100% of cases and repeated studies had a high degree of patient acceptability. The results were easy to interpret and quantify and had a high degree of reproducibility with relative observer independence.

2. The first pass study was used in the determination of cardiac output and ventricular volumes whereas the gated blood study was the method of choice in assessment of global left ventricular function and regional wall motion, at rest and during exercise or pharmacological intervention.

3. Increased frequency of ventricular premature beats commonly occurred following extensive infarction resulting in error in the calculated ejection fraction. A modified tape recorder was employed to reject ectopic and post-ectopic beats and permitted reconstruction of the previously distorted ventricular volume curves.

4. Patients recovering from myocardial infarction had impairment of global left ventricular function and mean left ventricular ejection was significantly reduced below

the normal range.

5. Patients with anterior myocardial infarction had a greater reduction in ejection fraction than those who had suffered inferior infarction and this difference was significant following both transmural and subendocardial infarction.

6. Peak serum creatine kinase levels correlated well with ejection fraction following anterior infarction but for an equivalent rise in enzyme plasma concentration there was significant sparing of left ventricular function following inferior infarction.

7. Although clinical recognition of the syndrome of right ventricular infarction was infrequent, right ventricular enlargement and hypokinesis was observed exclusively after inferior infarction and occurred in 43% of these patients. Thus, subclinical right ventricular dysfunction is common after inferior myocardial infarction and the variable degree of right ventricular necrosis which contributes to enzymatic indices of infarct size accounts for relative sparing of left ventricular function.

8. Global left ventricular performance correlated well with the presence of abnormalities of regional wall movement and progressive reduction in ejection fraction was observed with increasing hypokinesis or akinesis determined by accurate edge detection of the ventricular

border in end-diastole and end-systole.

9. A system of paradox imaging proved an accurate method for the detection of ventricular dyskinesia. Present when often not clinically apparent, this abnormality was detected in 25% of all patients recovering from infarction and was much more common after anterior infarction being located in the majority of cases at the apex of the heart.

10. Ventricular dyskinesia was associated with severe impairment of global left ventricular function and increased frequency of ventricular premature beats and conduction disturbances. In these cases persisting ST segment elevation on the electrocardiogram was occasionally absent (usually after inferior infarction) and chest x-ray was frequently normal at the time of discharge from hospital.

11. Left ventricular failure in the acute phase was associated with low ejection fraction in the convalescent phase compared with those patients whose early progress had been uncomplicated.

12. Those patients with serious arrhythmia in the acute phase had low ejection fraction in the convalescent phase compared with those whose progress had been uncomplicated. Patients with primary and complicating ventricular fibrillation could not be distinguished by radionuclide ventriculography and had identical mean

ejection fraction which was severely reduced.

13. Patients surviving primary ventricular fibrillation and anterior infarction had significantly lower ejection fraction compared with either those recovering from uncomplicated anterior infarction or inferior infarction with primary VF.

14. Recurrent ventricular arrhythmias after the initial episode of primary VF were more common after anterior infarction and occurred on the background of poor global left ventricular function consequent upon segmental ventricular dyskinesis. Such arrhythmias were not observed in patients subsequently shown to have normal or near normal ventricular function.

8.2 Prognostic value of radionuclide ventriculography after myocardial infarction.

1. Left ventricular function as assessed by resting ejection fraction did not correlate with the patients' assessment of their own exercise tolerance or with return to full-time employment.

2. Frequency of angina pectoris did not correlate with resting ejection fraction.

3. Low resting ejection fraction at discharge was associated with the development of left ventricular failure in the subsequent year.

4. Any increase in ejection fraction was secondary to improvement in wall motion of the non-infarcted myocardium but in addition even severe abnormality of wall motion such as akinesis was occasionally seen to resolve. In particular, cases were observed in whom the dyskinesis area, along with the associated ST segment elevation, resolved spontaneously and completely.

5. Those patients who developed predominant right heart failure in the follow-up period had all sustained transmural inferior myocardial infarction and at hospital discharge were noted to have dilatation and hypokinesis of the right ventricle.

6. Documented serious arrhythmias (VT or VF) in the follow-up period were seen only in patients with dyskinetic segments and poor global left ventricular function.

7. Of eleven patients who died within the one year follow-up period, six had segmental dyskinesis of the left ventricle and poor global function. All collapsed and died suddenly out of hospital and although the certified cause of death in all six was myocardial infarction only one patient gave a history of typical ischaemic pain.

8. Of these six patients who died each was shown by radionuclide ventriculography to have very poor left ventricular function, but three were given a "low risk"

rating by the Peel or Luria indices and only one was deemed to be at high risk from the Norris index.

9. In the remaining ninety-four patients there was no significant correlation between the three coronary prognostic indices used and left ventricular ejection fraction.

8.3 Prognostic value of exercise testing after myocardial infarction.

1. Of the one hundred patients, ninety-four were able to complete at least one level of exercise four weeks after discharge from hospital.

2. Those in whom exercise was terminated prematurely had poor global left ventricular function: three patients had increasing frequency of ventricular premature beats and the remaining patient developed exercise induced ventricular tachycardia.

3. Of the patients who developed a significant ST segment depression 54% developed postinfarction angina and 11% died suddenly.

4. The sensitivity of the exercise-induced electrocardiographic changes for the development of subsequent postinfarction angina was 48% with a specificity of 80% and a false negative rate of 52%.

5. ST segment elevation during exercise was seen in patients with grossly abnormal wall motion at rest with either extensive akinetic or dyskinetic segments.

6. All normal subjects were able to achieve an exercise-induced increase in ejection fraction without the appearances of any ischaemic ST segment shift on the electrocardiogram.

7. The patients with segmental dyskinesia and poor left ventricular function were unable to increase ejection fraction on exercise. They were correctly identified by resting studies as being high risk subjects and exclusion of their exercise data permitted a reduction in the false positive rate with a corresponding increase in specificity.

8. In the remaining individuals an exercise-induced fall in ejection fraction of greater than 5% correctly predicted 88% of patients who were to develop post-infarction angina and of these 13% died suddenly in the first post-infarction year.

8.4 Radionuclide assessment of inotropic therapy following myocardial infarction.

1. In patients with sinus rhythm in heart failure despite diuretics an intravenous dose of 0.5 mg digoxin resulted in a significant fall in resting heart rate.

2. Absolute values for ejection fraction did not change significantly and the mean ejection time normalised by left ventricular ejection time was identical before and three hours after the intravenous administration of digoxin.

3. There was no significant overall change in relative end-diastolic volume and the relative cardiac output fell.

4. On exercise after intravenous digoxin despite a significant increase in heart rate there was no significant change in either ejection fraction or cardiac output.

5. Prolonged oral digoxin therapy resulted in the persistence of a significant reduction in resting heart rate but this was not accompanied by any significant improvement in symptoms or by any change in radionuclide determined ejection fraction.

6. Preliminary studies with a new selective beta-1 adrenoceptor agonist (prenalterol) have revealed a significant increase in radionuclide determined ejection fraction in patients with moderate impairment of left ventricular function (N.Y.H.A. Class II - III) but in three patients with very low EF and severe heart failure (N.Y.H.A. Class IV) there was no increase in EF.

7. Analysis of regional wall motion following

inotropic intervention revealed increasing dyskinesia consequent upon increased contractility of viable non-ischaemic muscle. It has therefore been proposed that combined inotropic and vasodilator therapy could result in further enhancement of global ventricular performance. However, because of the poor sensitivity of the radionuclide technique with low ejection fractions simultaneous radionuclide and invasive haemodynamic studies have been recommended.

CHAPTER 9

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

From the work presented in this thesis it is apparent that radionuclide ventriculography both at rest and during exercise can provide valuable information concerning global and regional ventricular function following myocardial infarction. Although in the work for this dissertation, the technique was used primarily for research purposes, if employed in routine clinical practice it would have far-reaching implications and be of considerable value in patient management. Because it is a non-invasive technique it has a high degree of patient acceptability and since all the information is collected within minutes of an antecubital venous injection, the technique is cost effective in terms of doctor, nurse and technician time and is suitable for screening large numbers. Since the computer software is now being incorporated into many of the commercially available multipurpose gamma camera systems, the equipment is widely available and with the already established centralised radiopharmaceutical laboratories which are now a feature of our larger teaching centres, the additional cost of such a "package" could fall within the budget of even the district general hospital. Such a system would not of course be used exclusively for cardiac imaging but would in addition serve as a gamma

camera capable of imaging brain, bone, lung, liver etc.

The studies which have been presented illustrate the potential value of routine radionuclide ventriculography in all survivors of myocardial infarction since the technique can accurately predict those at risk from heart failure, angina, arrhythmia and sudden death. A resting study performed prior to discharge from hospital would give the physician valuable information concerning not only the impairment of both right and left ventricular function but also could provide details of the contractility of the residual non-infarcted ventricle. Although the acute phase complications of heart failure or arrhythmia are hallmarks of extensive infarction the technique has been shown to reveal poor residual ventricular function surprisingly frequently often when not clinically suspected. Transient, mild heart failure in the acute phase may be not be recognised clinically, and even if apparent, may only be treated in the short term with diuretic agents on the assumption that there will be significant spontaneous improvement in ventricular performance. However, this work has shown that there is only limited potential for improvement in global ventricular function and any efforts to reduce or discontinue therapy directed against heart failure must only follow an accurate assessment of ventricular performance and contractility of the non-infarcted ventricle. In those patients who have continuing

clinical signs of cardiac decompensation the technique has shown that ventricular performance rarely improves spontaneously and often there is a steady downward progression. In such patients diuretic therapy must be given life-long often in increasing doses but in isolated cases the technique can accurately identify individuals with localised dyskinetic segments who might acquire symptomatic relief from surgical intervention.

In addition the work presented has shown that the incidence of acute phase ventricular arrhythmia, both primary and complicating, is a reflection of the size of the infarct and such patients are also at risk from the development of heart failure and further potentially lethal late ventricular arrhythmias. The incidence of both these complications in the late convalescent phase reached considerable proportions in those with very poor ventricular function but such problems were not apparent in those with normal or near normal ejection fractions. It would therefore be a rational approach to defer discharge from hospital in those patients with extensive infarction (whether apparent clinically or not) and to carefully assess the need for diuretic, vasodilator or positive inotropic therapy. In addition such patients form a select population in whom ambulatory 24 hour electrocardiographic monitoring prior to discharge could yield valuable results since it has been shown that poor ventricular function is often consequent upon ventricular dyskinesia which may, through re-entry mechanisms,

predispose these patients to paroxysmal life-threatening ventricular tachycardia. If indeed such arrhythmia was detected then specific antiarrhythmic therapy could be introduced. Alternatively if arrhythmia were detected in patients already on treatment then the efficacy of such antiarrhythmic agents would need to be reconsidered. The duration of such therapy remains a controversial topic and often antiarrhythmic drugs are prescribed merely for an arbitrary period of a few weeks since prophylactic long-term antiarrhythmic therapy for all survivors of infarction has been shown to have no effect on survival and is often accompanied by significant and sometimes intolerable side-effects. However, long-term prophylactic antiarrhythmic agents may justifiably be recommended to those who on radionuclide studies and ambulatory monitoring are shown to have poor ventricular function and a tendency to arrhythmia since the potential benefit could outweigh any side-effects which the patient might experience.

With the current trend to earlier mobilisation, exercise testing and training programmes it is important to identify those patients who stand to benefit from this more active approach to rehabilitation. Certainly it must be stressed that although all patients may benefit from such an approach since the majority gain in self confidence, this is not accompanied by any improvement in intrinsic cardiac function. Moreover, exercise testing

all patients to identify those at high risk from subsequent coronary events is potentially dangerous and should be confined only to a selected population and preferably delayed for several weeks after infarction. In this study radionuclide ventriculography identified a surprisingly large number of patients who recovering from only their first infarct had exceedingly poor ventricular function and of these individuals almost 30% died in the following year. Their risk of subsequent sudden death was seven times as great as patients with normal ventricular function and radionuclide ventriculography identified these individuals before discharge from hospital without the need for early stress testing. The results of radionuclide ventriculography had greater predictive value than the various coronary prognostic indices currently in use and since these "high risk" individuals contribute excessively to the total first year mortality ideally gated blood pool imaging should be performed on all survivors of myocardial infarction before they are discharged from hospital.

This approach would obviate the need for exercise testing those individuals shown to be at high risk from a resting study and in addition would provide a suitable basis for the "risk-stratification" of therapeutic trials. The results of radionuclide studies would provide observer independent assessment of ventricular function and together with clinical parameters would ensure that populations treated with either drug or

placebo are indeed matched for comparable risk. Thus any significant beneficial effects of antiarrhythmic, vasodilator or inotropic therapy could more reasonably be related to a true effect rather than a bias in the selection of the original population groups.

In addition the results of routine radionuclide ventriculography would identify those patients with moderate or normal left ventricular function in whom an exercise test may be of predictive value in the identification of those who are at risk of the development of postinfarction angina with the attendant risk of sudden death. A resting study would exclude many of those likely to give false positive results on exercise and correspondingly increases the specificity of an exercise induced fall in ejection fraction. Such a response presumably is a reflection of vessels with significant stenoses supplying further potentially ischaemic though non-infarcted myocardium. Thus continuing mild angina after a small anterior infarction may occur on a background of an isolated but severe lesion of the left anterior descending coronary artery: a lesion with a poor prognosis if managed medically but eminently suitable for surgical intervention. Routine coronary arteriography after myocardial infarction is at present not recommended in this country. However, this work has shown that post-infarction angina carries a small but significant risk of sudden death, independent

of the severity of symptoms, and therefore such a development may merit early definition of the coronary anatomy.

Most would agree that the institution of antianginal drugs is usually followed by symptomatic benefit to those who develop post-infarction angina, however, there remains considerable debate about the value of prophylactic therapy with beta-1-adrenoceptor antagonists. It has been suggested that long-term beta-adrenergic blockade may reduce mortality in patients surviving acute myocardial infarction. However, in clinical trials reported to date there has been failure to show any overall benefit (Reynolds, 1972; Wilcox, 1980) or the effects claimed have not been sufficiently convincing (Wilhelmsson, 1974; Multicentre International Study, 1975).

However, the most recently published (Norwegian Multicentre Study, 1981) concluded that long-term treatment with timolol maleate reduced mortality and the rate of reinfarction. Previous trials had been criticised on the composition of the placebo treated groups since patients with a previous history of heart failure could not be justifiably treated with beta adrenoceptor antagonists. Therefore the timolol trial was designed as a double-blind randomised study with division of both treated and placebo populations into groups stratified according to equal risk. Unfortunately the placebo group once again contained patients who had

more previous diuretic therapy, heart failure, cardiomegaly and acute phase serious arrhythmia and such a discrepancy could adequately explain the apparent benefit of the drug. The results of this trial are now under close scrutiny and the potential problems with this and similar trials have recently been reviewed in detail by Mitchell (1981). What is needed is an observer independent accurate non-invasive method to ensure that like is compared with like and in the future it seems inevitable that radionuclide ventriculography will be employed in the risk stratification for such trials to ensure that treated and placebo populations contain patients of equivalent cardiac status.

Since the risks of sudden cardiac death vary widely between patients and now may to some degree be predicted by radionuclide ventriculography, results of routine screening of survivors of infarction may be of considerable value in determining the need for rehabilitation and regular follow-up. Patients with normal or near normal ejection fraction are suitable for early discharge to the care of the general practitioner. Indeed, since these patients are at low risk of subsequent sudden death the strict regulations currently in force regarding driving and employment may need to be reconsidered.

There can be no doubt that poor prognosis follows extensive infarction and since primary preventive

measures have met with only limited success our next aim must be the early institution of therapeutic measures to limit infarct size. Since the incidence of ventricular arrhythmia is also a function of the size of the infarct this greatly expands the horizon for what could potentially be accomplished by techniques to prevent myocardial necrosis before the completion of the infarct. Many agents have now been used in acute therapeutic intervention and of these beta-adrenoceptor antagonists, nitrates, hyaluronidase and other anti-inflammatory agents have proved the most popular. The effects of such agents may be relatively small and therefore to detect any benefit estimation of infarct size must be accurate. A variety of methods have been proposed and include analysis of electrocardiographic changes, ST segment mapping and the total release of cardiac enzymes, but none has found universal acceptance. Radio-isotope methods provide a further dimension to quantification of myocardial ischaemia. Gated blood pool imaging has already become an established method in the quantification of wall motion abnormalities and determination of global residual left ventricular function. The use of infarct-avid radiopharmaceuticals was initially promoted as an attractive method for estimation of the location and size of myocardial infarction, however, further experience has revealed considerable limitation (Maisey et al, 1980). Perhaps one of the most exciting developments has appeared with

the advent of positron-emitting radionuclides and Weiss et al (1977) have demonstrated that both ventricular anatomy and myocardial infarction are readily delineated in tomographic images of the entire left ventricle. In addition using this technique the same authors have in the experimental situation been able to demonstrate some of the metabolic sequelae of ischaemia. However, any clinical application of positron emission tomography remains to be established.

The work presented in this thesis has shown that prognosis after myocardial infarction is dependent upon the degree of impairment of left ventricular function and the vascularity of the residual non-infarcted ventricle. Radionuclide ventriculography is able to predict those patients who are at risk of the development of angina, heart failure or serious arrhythmia. Although death out of hospital is usually sudden it too can be predicted by results of gated blood pool imaging and usually follows extensive infarction. Since primary preventive measures have met with only partial success, limitation of infarct size must now be the prime aim and the use of radionuclides provide attractive methodology with which to assess the effects of early therapeutic intervention (Figure 9.1).

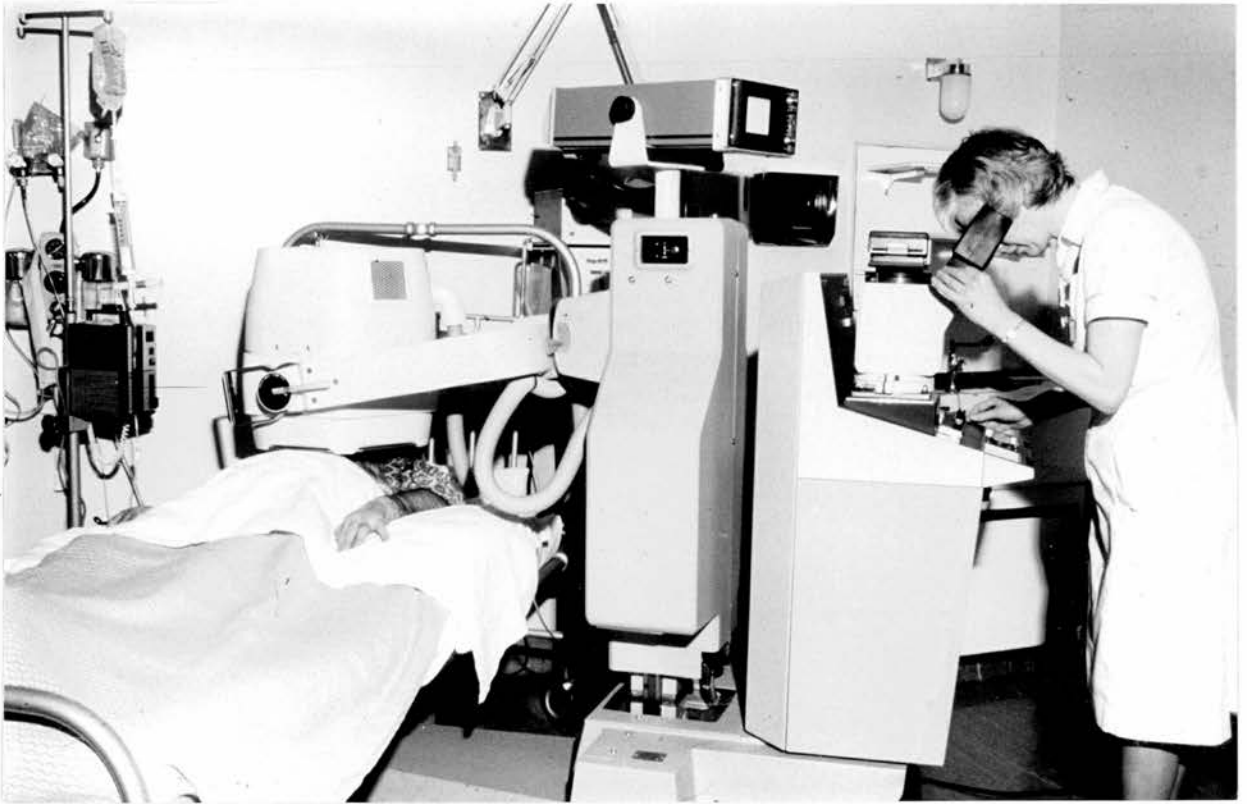


Figure 9.1 The Searle LEM camera in operation in the Coronary Care Unit, within minutes of this patient's admission following the development of ischaemic pain.

TABLES

TABLE 1: PROTOCOL FOR EXERCISE TESTING (Using Bicycle Ergometer with the supine position)

	<u>Setting (KG)</u>	<u>Watts</u>	<u>KPM (approx)</u>
<u>MEN</u>			
LOAD 1	0.7	25	250
2	1.4	50	500
3	2.1	75	750
<u>WOMEN</u>			
LOAD 1	0.5	20	200
2	1.1	40	400
3	1.7	60	600

TABLE 2: Clinical Details and Investigations of Patients with Ventricular Dyskinesis

Patient	Age/Sex	Infarct Site	Peak SCK	Conduction Defect	Acute Phase Arrhythmia	LVF
1	49 M	Inferolateral	3126	-	CHB	+
2	57 M	Inferolateral	4802	-	-	+
3	69 M	Inferolateral	3087	-	VF	+
4	66 M	Inferolateral	3294	-	CHB	+
5	61 M	Inferolateral	1465	LBBB	VT	-
6	66 F	Inferolateral	4176	-	-	+
7	58 M	Anterolateral	3058	-	-	+
8	55 F	Anteroseptal	2406	-	-	+
9	45 M	Anterior	2628	-	-	+
10	59 M	Anterolateral	2656	-	-	+
11	69 M	Anteroseptal	1580	LAD + RBBB	VT	+
12	47 M	Anterior	5876	RAD + RBBB	VF	+
13	52 M	Anterolateral	2677	-	-	+
14	63 M	Anterolateral	2981	RAD + RBBB	-	+
15	58 M	Anterolateral	2703	-	-	+
16	61 M	Anterolateral	4970	-	-	+
17	68 M	Anteroseptal	918	-	VF	+
18	64 M	Anterolateral	3808	-	-	+
19	53 M	Anterolateral	2643	-	-	+
20	63 M	Anterior	3143	RAD + RBBB	-	+
21	64 M	Anteroseptal	2382	RBBB	VF	+
22	62 M	Anterior	4929	-	VF	+
23	63 M	Anterior	3966	RBBB	VT	+
24	55 M	Anterolateral	2438	-	-	+
25	69 M	Anterior	591	-	-	+

Abbreviations:

- CHB Complete heart block
- VF Ventricular Fibrillation
- VT Ventricular Tachycardia
- CTR Cardiothoracic Ratio
- SCK Serum Creatine Kinase

TABLE 2 (continued)

<u>Patient</u>	<u>Paradoxical impulse</u>	<u>Added heart sound or gallop rhythm</u>	<u>ST segment elevation</u>	<u>CTR > 0.5</u>	<u>Site Dyskinesis</u>	<u>LVEF</u>
1	-	-	+	-	Apical	0.26
2	-	+	-	-	Inferoapical	0.38
3	-	-	-	+	Inferoapical	0.28
4	+	-	+	+	Apical	0.30
5	+	+	-	-	Apical	0.22
6	+	+	-	-	Apical	0.28
7	+	+	+	+	Apical	0.14
8	-	+	+	-	Apical	0.23
9	-	+	+	-	Apical	0.30
10	+	+	+	-	Apicolateral	0.15
11	-	+	+	+	Apical	0.23
12	-	-	+	-	Apical	0.22
13	-	-	+	+	Apical	0.32
14	+	+	+	-	Apical	0.18
15	-	-	-	+	Apical	0.16
16	-	+	+	-	Apical	0.16
17	+	-	+	-	Apical	0.33
18	+	+	-	+	Apical	0.23
19	-	-	+	-	Apical	0.22
20	+	+	+	-	Apical	0.13
21	-	-	+	-	Apical	0.15
22	+	-	+	-	Apical	0.22
23	+	-	+	+	Apical	0.17
24	-	+	+	+	Apical	0.25
25	-	-	-	+	Apical	0.28

TABLE 3: Ventricular Fibrillation in 1086 Patients with Myocardial Infarction
 Admitted to C.C.U. (March 1979 - March 1981)

<u>Type of VF</u>	<u>No of Patients</u>
Primary	22
Complicating	49
Agonal	23
Pacemaker induced	1
Drug induced	2
Total	97

TABLE 4: Clinical Details of patients surviving primary ventricular fibrillation

Patient	Age	Previous Angina	History Infarction	Time from Pain to VF (hours)	Preceding Arrhythmia	Episodes of Primary VF	Number of DC shocks	SCK Max
1	43	-	-	4½	R on T	1	-	2927
2	69	+	-	13½	R on T/Brady Couplets	2	2	940
3	45	-	-	1½	-	1	5	13869
4	57	-	-	3½	-	1	4	4000
5	54	+	+	9	-	1	1	2313
6	66	+	-	4	R on T/Tachy	2	1	2541
7	65	+	+	11	-	1	1	802
8	57	-	-	3½	Brady	1	1	1706
9	61	+	-	7½	R on T/Brady	2	2	1944
10	62	+	+	1	-	2	2	2796
11	64	-	-	4½	R on T/Tachy	1	1	2366
12	64	-	-	4½	-	1	1	1898
13	57	+	-	1	Brady	2	2	2592
14	48	+	-	3	R on T/VT	1	1	395
15	38	-	-	4	-	2	2	1818
16	59	-	-	1½	-	1	8	2166
17	53	-	-	2	-	1	1	3612
18	65	+	-	3	R on T	2	1	2512
19	60	-	-	3	CHB	3	3	2000
20	53	-	-	2½	R on T/Brady	2	2	2240
21	58	-	-	3	-	1	1	2264
22	67	-	+	4½	-	1	2	2102

Abbreviations: R on T = R on T VPB
 CHB = Complete heart block

TABLE 5: Investigations and Results of Radionuclide Ventriculography of Survivors of Primary Ventricular Fibrillation

Patient	Site of Infarct	Transmural = TM Subendocardial = SE	Ejection Fraction	Wall Motion	Post Primary VLF	Post Primary VF Arrhythmia
1	Anteroseptal	TM	0.25	Apical dyskinesia	+	-
2	Anteroseptal	TM	0.33	"	+	VF
3	Anteroseptal	TM	0.25	"	+	VT
4	Anterolateral	TM	0.17	"	+	-
5	Anterior	TM	0.30	Apical hypokinesia	+	-
6	Anterior	TM	0.21	Apical dyskinesia	+	-
7	Lateral	SE	0.51	Normal	-	-
8	Anterolateral	TM	0.24	Apical dyskinesia	+	-
9	Anteroseptal	TM	0.27	Apicolateral hypokinesia	-	VF
10	Anteroseptal	TM	0.22	Apical dyskinesia	+	VF
11	Anteroseptal	TM	0.15	"	+	-
12	Anterolateral	SE	0.33	Apicolateral akinesia	-	-
13	Anterolateral	TM	0.14	Apical dyskinesia	+	VT
14	Anterolateral	SE	0.49	Normal	-	-
15	Inferior	TM	0.46	Inferior hypokinesia	-	VT
16	Inferior	TM	0.44	Lateral hypokinesia	+	-
17	Inferior	TM	0.51	Normal	-	VF
18	Inferior	TM	0.37	Inferior hypokinesia	+	VT
19	Inferior	TM	0.37	Apical hypokinesia	-	VF
20	Inferolateral	TM	0.35	"	+	-
21	Posterolateral	TM	0.52	Normal	-	-
22	Inferior	TM	0.44	Normal	+	-

TABLE 6: Complications in the first 12 months after myocardial infarction.

<u>Clinical Progress</u>	<u>number</u>
Uncomplicated	46
Angina	32
Reinfarction	6
Left ventricular failure	15
Right ventricular failure	3
Atrial fibrillation	1
Ventricular tachycardia	2
AV block	1
Deaths	11

TABLE 7: Changes in Ejection Fraction over 1 year after Anterior and Inferior Myocardial Infarction

Site of Infarction	Ejection Fraction				
	Predischarge	1 month	4 months	12 months	
ANTERIOR	Mean	0.32	0.35	0.36	0.36
	SD	+0.12	+0.14	+0.13	+0.14
	SEM	+0.02	+0.02	+0.02	+0.02
	n	46	45	44	40
INFERIOR	Mean	0.44	0.42	0.43	0.43
	SD	+0.09	+0.09	+0.10	+0.09
	SEM	+0.01	+0.01	+0.01	+0.01
	n	54	53	50	45

TABLE 8: Changes in Ejection Fraction of Patients Categorised According to Initial Abnormality of Regional Wall Motion

Abnormality of Wall Motion		Ejection Fraction			
		Predischarge	1 month	4 months	12 months
NIL	Mean	0.49	0.46	0.46	0.45
	SD	±0.06	±0.07	±0.07	±0.09
	SEM	±0.01	±0.01	±0.01	±0.02
	n	27	27	27	27
HYPOKINESIS (1 segment)	Mean	0.43	0.45	0.44	0.44
	SD	±0.06	±0.06	±0.06	±0.07
	SEM	±0.01	±0.01	±0.01	±0.02
	n	22	21	19	18
HYPOKINESIS (> 1 segment)	Mean	0.41	0.42	0.42	0.40
	SD	±0.09	±0.10	±0.08	±0.08
	SEM	±0.02	±0.03	±0.02	±0.02
	n	15	15	14	13
AKINESIS	Mean	0.37	0.40	0.43	0.44
	SD	±0.08	±0.07	±0.10	±0.08
	SEM	±0.02	±0.02	±0.03	±0.03
	n	11	11	10	9
DYSKINESIS	Mean	0.23	0.23	0.25	0.24
	SD	±0.07	±0.09	±0.10	±0.11
	SEM	±0.01	±0.02	±0.03	±0.03
	n	25	24	24	18

TABLE 9: Progress Over 4 Month Follow-Up Period in 25 Patients with Ventricular Dyskinesis

Patient	N.Y.H.A. Grade	LVF	Arrhythmia	Lown Class	LVEF	
					At discharge	4 months
1	I	-	-	-	0.26	0.31
2	II	+	-	-	0.38	0.24
3	I	-	-	-	0.28	0.38
4	III	+	2° AV block	III	0.30	0.22
5	III	+	-	IV	0.22	0.16
6	III	+	-	-	0.28	0.20
7	III	+	-	-	0.14	0.12
8	III	+	-	-	0.23	0.24
9	I	-	-	-	0.30	0.34
10	II	+	-	III	0.15	0.09
11	III	+	-	IV	0.23	0.22
12	I	-	-	-	0.22	0.30
13	I	-	-	-	0.32	0.31
14	II	+	-	-	0.18	0.16
15	I	-	-	-	0.16	0.37
16	III	+	-	III	0.16	0.14
17	II	+	-	-	0.33	0.27
18	III	-	-	IV	0.23	0.21
19	II	+	-	-	0.22	0.21
20	III	-	-	-	0.13	0.22
21	I	-	-	-	0.15	0.20
22	III	+	VT + VF	III	0.22	0.18
23	II	+	VT	-	0.17	0.10
24	II	+	-	-	0.25	0.24
25	I	-	-	-	0.28	0.55

TABLE 10: Details of 11 patients who died within 12 months of discharge from hospital

Patient Initials	Age(yrs)	Site of Infarct	Coronary Prognostic Index			Ejection Fraction (at discharge)	Wall Motion Abnormality	Survival (months)
			Peel	Norris	Luria			
AW	60	Inferior	4	3.7	4.7	0.46	Hypokinesis	2
MH	67	Inferior	20	9.7	7.1	0.29	Akinesis	3
AN	62	Inferior	4	2.9	4.6	0.44	Hypokinesis	3
JC	49	Inferior	3	2.7	9.4	0.26	Dyskinesis	4
WG	59	Anterior	5	2.0	6.8	0.50	Hypokinesis	4
RK	64	Anterior	9	9.7	6.0	0.17	Dyskinesis	5
JD	62	Inferior	9	2.9	9.3	0.22	Dyskinesis	6
WM ^C N	54	Anterior	9	2.0	5.4	0.22	Dyskinesis	7
TN	69	Inferior	8	4.5	8.6	0.33	Dyskinesis	7
WR	69	Anterior	5	4.6	6.9	0.23	Dyskinesis	11
ES	57	Inferior	5	2.0	5.5	0.47	Hypokinesis	11

— Denotes high risk categorisation

TABLE 11: Exercise Test Results

	<u>Number</u>
Negative Test	68
ST segment depression alone	11
Angina alone	6
Angina with ST segment depression	3
Ventricular arrhythmia	8
TOTAL	96

TABLE 12: Operating characteristics of the exercise test in the prediction of post-infarction angina.

		Angina		TOTAL
		Occurrence	Non-occurrence	
Exercise Test	Positive	15	13	28
	Negative	16	52	68
TOTAL		31	65	96

Sensitivity for subsequent post-infarction angina = 48%

Specificity = 80%

False negative rate = 52%

False positive rate = 20%

Predictive value = 54%

TABLE 13: Changes of ejection fraction on exercise following inferior and anterior myocardial infarction

SITE OF INFARCT	REST EF	EXERCISE EF
Inferior (Subendocardial)	Mean 0.52 SD 0.05 SEM 0.02 n 8 _____ N.S. _____	Mean 0.56 SD 0.07 SEM 0.03 n 8
Inferior (Transmural)	Mean 0.41 SD 0.08 SEM 0.01 n 44 _____ N.S. _____	Mean 0.42 SD 0.11 SEM 0.02 n 44
Anterior (Subendocardial)	Mean 0.49 SD 0.05 SEM 0.02 n 8 _____ N.S. _____	Mean 0.48 SD 0.10 SEM 0.04 n 8
Anterior (Transmural)	Mean 0.35 SD 0.13 SEM 0.02 n 34 _____ p < 0.01 _____	Mean 0.30 SD 0.12 SEM 0.02 n 34

TABLE 14: Operating characteristics of exercise radionuclide ventriculography in the prediction of post-infarction angina.

EF change	Angina		
	Occurrence	Non-occurrence	TOTAL
> 5%	23	4	27
+, 0 or < -5%	26	48	74

Sensitivity for subsequent post-infarction angina = 84%
 Specificity " " " " = 92%
 False negative rate = 12%
 False positive rate = 8%
 Predictive value = 85%

TABLE 15: Reported results of blood pool angiographic exercise test

Year	Principal Investigator	Method	Patients (n)	EF		Ex ECG	
				Sens	Spec	Sens	Spec
1978	Rerych	Erect first pass	60	29/30	27/30	23/30	—
1979	Borer	Supine Gated	84	56/63	21/21	43/63	20/21
1979	Berger	Supine of erect first pass	73	44/60	13/13	33/60	13/13
1979	Jengo	Erect first pass	19	11/11	8/8	7/11	—
1979	Caldwell	Supine + erect gated	39	31/33	4/6	—	—
1979	Borer	Supine gated	53	—	—	—	—
1979	Verani	Supine gated	38	—	—	—	—
1980	Kirshenbaum	Supine gated	61	—	—	32/50	11/11
Total			427	171/197 0.87	73/78 0.93	138/214 0.64	44/45 0.98

EF = failure to increase ejection fraction by 5% with exercise;

Ex ECG = abnormal exercise electrocardiogram;

Sens = sensitivity;

Spec = specificity;

— = data not reported

TABLE 16: Clinical details of nine subjects given intravenous digoxin.

Patient	Age (years)	Site of infarction	Abnormality of Wall Motion	Time of Study after infarct (weeks)	N.Y.H.A. Class	
					Before digoxin	After digoxin
1	64	Anterolateral	Dyskinesis	6	III	IV
2	59	Anterolateral	"	16	III	III
3	56	Anterolateral	"	20	III	III
4	59	Anterior	Akinesis	4	IV	DECEASED
5	55	Anteroseptal	Dyskinesis	32	III	III
6	67	Inferolateral	"	6	IV	IV
7	65	Anterolateral	"	2	IV	III
8	62	Anterolateral	"	20	III	III
9	75	Anterolateral	"	2	IV	IV

TABLE 17: The effects of intravenous digoxin on ventricular performance in 9 subjects at rest.

Patient	State	Heart Rate (beats/min)	Ejection Fraction	Relative EDV	ts (ms)	ts/LVET	Relative CO
1	Control	83	0.13	100	169	0.43	100
	1 hr after digoxin	79	0.12	102	162	0.55	91
	2 " "	79	0.14	73	171	0.52	76
	3 " "	79	0.14	88	157	0.65	88
2	Control	94	0.37	100	136	0.57	100
	1 hr after digoxin	100	0.37	100	131	0.43	106
	2 " "	83	0.36	98	128	0.53	84
	3 " "	75	0.33	79	152	0.54	56
3	Control	83	0.19	100	121	0.50	100
	1 hr after digoxin	65	0.20	74	149	0.46	55
	2 " "	65	0.24	82	149	0.46	81
	3 " "	62	0.19	91	114	0.48	68
4	Control	83	0.12	100	120	0.50	100
	1 hr after digoxin	79	0.12	109	148	0.46	104
	2 " "	79	0.09	105	147	0.61	75
	3 " "	83	0.11	91	148	0.62	84
5	Control	75	0.26	100	154	0.55	100
	1 hr after digoxin	71	0.30	77	187	0.52	84
	2 " "	68	0.27	98	179	0.64	92
	3 " "	65	0.25	111	168	0.52	93
6	Control	75	0.22	100	152	0.63	100
	1 " "	75	0.21	118	156	0.35	113
	2 " "	79	0.21	145	177	0.63	146
	3 " "	68	0.20	130	163	0.51	107
7	Control	94	0.20	100	126	0.45	100
	1 hr after digoxin	83	0.21	95	130	0.41	84
	2 " "	83	0.22	77	115	0.41	75
	3 " "	83	0.20	81	113	0.47	72

TABLE 17: (continued)

<u>Patient</u>	<u>State</u>	<u>Heart Rate</u> (beats/min)	<u>Ejection</u> <u>Fraction</u>	<u>Relative EDV</u>	<u>ts</u> (ms)	<u>ts/LVET</u>	<u>Relative CO</u>
8	Control	100	0.21	100	108	0.68	100
	1hr after digoxin	100	0.14	100	99	0.49	100
	2 "	107	0.14	106	85	0.53	113
	3 "	100	0.13	99	100	0.50	92
9	Control	83	0.24	100	130	0.46	100
	1hr after digoxin	79	0.25	96	120	0.43	95
	2 "	79	0.26	85	129	0.46	81
	3 "	83	0.22	99	125	0.52	91

TABLE 18: The effects of intravenous and oral digoxin on ventricular performance at rest and during exercise.

Patient	State	Heart Rate (beats/min)	Ejection Fraction	Relative EDV	ts (ms)	ts/LVET	Relative CO
1	A Rest	83	0.13	100	169	0.43	100
	Exercise	107	0.10	103	121	0.47	99
	B Rest	79	0.14	88	157	0.65	88
	Exercise	115	0.09	94	128	0.53	88
	C Rest	79	0.12	—	112	0.56	—
	Exercise	—	—	—	—	—	—
2	A Rest	94	0.37	100	136	0.57	100
	Exercise	125	0.29	84	87	0.44	88
	B Rest	75	0.33	79	152	0.54	56
	Exercise	115	0.33	83	97	0.48	91
	C Rest	94	0.31	—	101	0.36	—
	Exercise	115	0.31	—	89	0.37	—
3	A Rest	83	0.19	100	121	0.50	100
	Exercise	107	0.17	89	101	0.42	115
	B Rest	62	0.19	91	114	0.48	68
	Exercise	100	0.18	85	105	0.43	70
	C Rest	59	0.22	—	135	0.56	—
	Exercise	107	0.19	—	119	0.59	—

TABLE 18: (continued)

<u>Patient</u>	<u>State</u>	<u>Heart Rate</u> (beats/min)	<u>Ejection Fraction</u>	<u>Relative EDV</u>	<u>ts</u> (ms)	<u>ts/LVET</u>	<u>Relative CO</u>
5	A Rest	75	0.26	100	154	0.55	100
	Exercise	94	0.31	88	139	0.50	132
	B Rest	65	0.25	—	168	0.52	—
	Exercise	79	0.28	—	151	0.63	—
	C Rest	71	0.31	—	157	0.56	—
	Exercise	83	0.28	—	150	0.47	—
6	A Rest	75	0.22	100	152	0.63	100
	Exercise	—	—	—	—	—	—
	B Rest	68	0.20	145	177	0.63	146
	Exercise	—	—	—	—	—	—
	C Rest	68	0.24	—	172	0.54	—
	Exercise	—	—	—	—	—	—

TABLE 18: (continued)

<u>Patient</u>	<u>State</u>	<u>Heart Rate</u> (beats/min)	<u>Ejection Fraction</u>	<u>Relative EDV</u>	<u>ts</u> (ms)	<u>ts/LVET</u>	<u>Relative CO</u>
7	A Rest	94	0.20	100	126	0.45	100
	Exercise	—	—	—	—	—	—
	B Rest	83	0.20	81	113	0.47	72
	Exercise	—	—	—	—	—	—
	C Rest	79	0.23	—	138	0.69	—
	Exercise	115	0.22	—	109	0.45	—
8	A Rest	100	0.21	100	108	0.68	100
	Exercise	125	0.14	105	125	0.53	105
	B Rest	100	0.13	99	100	0.50	92
	Exercise	118	0.13	103	109	0.48	94
	C Rest	100	0.15	—	105	0.69	—
	Exercise	125	0.18	—	107	0.62	—
9	A Rest	83	0.24	100	130	0.46	100
	Exercise	—	—	—	—	—	—
	B Rest	83	0.22	99	125	0.52	91
	Exercise	—	—	—	—	—	—
	C Rest	71	0.24	—	144	0.51	—
	Exercise	—	—	—	—	—	—

A = Control period

B = 3 hours after 0.5 mg digoxin intravenously

C = 3 weeks after 0.25 mg digoxin orally/day

Note: Patient 4, who was in N.Y.H.A. Class IV, died before the 4 week follow-up study.

APPENDIX I:

At the time of writing there have been a further three deaths in the second follow-up year making a total mortality of 14% over a period of mean patient follow-up of 21 months. The eleven deaths occurring within twelve months of infarction have been discussed in detail in the previous chapters. Of the three later deaths, two occurred in patients identified as "high risk" by radionuclide ventriculography. Both these patients had extremely poor left ventricular function consequent upon segmental dyskinesia, with ejection fractions of 0.15 and 0.22 respectively. One died in hospital following refractory ventricular fibrillation and the other died suddenly out of hospital, the certified cause of death being myocardial infarction. The third patient died in hospital following a long illness and although permission for post mortem examination was refused a firm clinical diagnosis of metastatic bronchogenic carcinoma had been made.

Thus far, radionuclide ventriculography has predicted 85% of all individuals (11 out of 13) who have died suddenly in the late convalescent period after their first myocardial infarction. The majority of these patients had poor left ventricular function and although the effect of infarct size on mortality has been said to be confined to the first few months of convalescence (Geltman et al, 1979) it is evident that the associated

excess incidence of sudden death may continue into the second post-infarction year.

APPENDIX II:

The work for this dissertation was carried out entirely within the Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh under the supervision of Dr. A. L. Muir, Reader, Department of Medicine and the practical work was performed entirely by myself. A second observer was used in the assessment of regional wall motion studies and Dr. W.J. Hannan, Lecturer in Medical Physics and Engineering assisted in the calculation of ventricular volumes and cardiac output. My appointment during the time of preparation of this thesis has been Lecturer in General Medicine, Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh.

Part of the work presented has appeared in published form:

1. Brash HM, Wraith PK, Hannan WJ, Dewhurst NG, Muir AL. The influence of ectopic heart beats in gated ventricular blood-pool studies. J Nucl Med 1980; 21: 391-3.
2. Hannan WJ, Vojacek J, Dewhurst NG, Muir AL. The

sequential measurements of ventricular volumes and cardiac output by radionuclides. Clin Phys Physiol Meas 1980; 1: 125-34.

3. Hannan WJ, Brash HM, Wraith PK, Muir AL, Dewhurst NG. Reconstruction of ventricular volume curves distorted by variations in heart rate. Clin Phys Physiol Meas 1980; 1: 221-7.

4. Dewhurst NG, Hannan WJ, Muir AL. Prognostic value of radionuclide ventriculography after myocardial infarction. Q J Med 1981; 49: 479-90.

5. Dewhurst NG, Hannan WJ, Brash HM, Wraith PK, Muir AL. The prevalence and prognosis of ventricular dyskinesis after myocardial infarction using radionuclide ventriculography. Eur Heart J (In Press).

6. Dewhurst NG, Muir, AL. Prognostic value of radionuclide ventriculography after first myocardial infarction. B Heart J 1981; 45: 611p.

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Prognostic Value of Radionuclide Ventriculography After Myocardial Infarction

N. G. DEWHURST, W. J. HANNAN AND A. L. MUIR

From the Department of Medicine and Department of Medical Physics, University of Edinburgh, Royal Infirmary, Edinburgh

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SUMMARY

We have studied 50 consecutive patients who had sustained their first myocardial infarction. Using the noninvasive technique of radionuclide ventriculography, ventricular performance, as assessed by left ventricular ejection fraction (EF), was measured at rest just before discharge from hospital when patients were well and free from cardiac failure and then at one and four months after infarction, at rest and during submaximal supine exercise. Left ventricular ejection fraction was below normal in 42 patients (normal range 0.43-0.71). Mean EF for those patients recovering from inferior infarction was 0.43 ± 0.09 (mean \pm 1 S.D.), whereas for those who had sustained anterior infarction mean EF was significantly lower, 0.33 ± 0.13 ($p < 0.01$). EF was significantly reduced ($p < 0.01$) in those patients whose early progress was complicated either by serious arrhythmia or left ventricular failure. There was only poor correlation between EF and radiographically determined heart size but global left ventricular performance correlated well with the presence of abnormalities of regional wall movement.

Over the first four months low EF failed to improve in seven patients with areas of dyskinesia (EF < 0.30) and despite diuretic therapy five suffered further episodes of cardiac failure. Excluding those with dyskinesia there were 18 patients who were unable to increase EF on exercise one month after infarction. Of these four already had symptoms of angina but a further 10 patients developed angina in the subsequent three months.

Poor left ventricular performance is common after anterior myocardial infarction, complicated in the acute phase by serious arrhythmia or left ventricular failure. Patients with persistently low EF had an increased risk of further episodes of cardiac failure, whereas a fall in EF on exercise was associated with subsequent angina.

INTRODUCTION

Prognosis after myocardial infarction has been shown to depend upon a number of variables related indirectly to the mass of ventricular muscle destroyed. The larger the infarct the more frequent will be the development of clinical signs of shock and heart failure and the greater the radiological and biochemical abnormalities that

follow. Various mathematical indices have been formulated with weighting placed on the factors known to be predictive of survival or mortality. The early work by Peel, Semple, Wang, Lancaster, and Dall (1962) was based on retrospective data analysis and stressed the importance of those factors (age, previous history, shock, heart failure, arrhythmias) which were associated with a poor prognosis within the first four weeks after infarction. Norris, Brandt, Caughey, Lee, and Scott (1969) constructed an index predictive of hospital mortality based on material collected immediately after the patient's admission and made similar observations, but also noted the significance of cardiac enlargement and pulmonary congestion determined radiologically. Of the six factors investigated only four—age, heart size, pulmonary congestion and previous ischaemia were relevant to three and six year survival (Norris, Caughey, Deeming, Mercer, and Scott, 1970; Norris, Caughey, Mercer, and Scott, 1974). Other coronary prognostic factors have been formulated by Kitchin and Pocock (1977) and also by Luria, Knoke, Wachs, and Luria (1979) and likewise their predictive value confirmed after a five year follow-up period. Although the variables incorporated in all these studies are similar, cross-validation of results between two centres has not been possible (Bigger, Heller, Wenger, and Weld, 1978), and therefore it would appear that a more fundamental approach is indicated. From the clinical, radiological and biochemical factors incorporated into the various indices, it becomes apparent that the single important determinant in cardiac function is the extent of myocardial impairment. Recent work has shown that left ventricular ejection fraction is in itself most predictive of survival in patients with angina and coronary artery disease (Hammermeister, DeRouen, and Dodge, 1979). Accurate measurement of left ventricular performance has, in the past, required cardiac catheterization and contrast ventriculography and therefore has been limited to only small populations of patients with continuing angina after infarction (Hamby, Hoffmann, Hilsenrath, Aintablian, Shanies, and Padmanabhan, 1974). Ejection fraction may be determined noninvasively by radionuclide ventriculography and using this technique we have studied the progress of 50 patients recovering from their first myocardial infarction.

METHODS

Patient population

We studied 50 consecutive patients (36 men and 14 women) who had been transferred to a general medical unit after 48 hours in a coronary care unit between August 1978 and March 1979 following their first myocardial infarction. Patients over the age of 70 were excluded and the mean age was 59 years (range 39–69). All patients satisfied the three criteria for acute myocardial infarction: myocardial ischaemic pain lasting more than 30 minutes, a rise in serum levels of two or three enzymes (aspartate aminotransferase, lactate dehydrogenase or creatine kinase) and electrocardiographic evidence of acute infarction. Infarct location was characterized according to established electrocardiographic criteria as anterior (including anteroseptal and anterolateral) or inferior (including inferolateral and inferoposterior). The site of infarction was 'inferior' in 26 and 'anterior' in 24

patients. Clinical progress was carefully monitored in the coronary care unit, and serious early arrhythmias defined as ventricular tachycardia, ventricular fibrillation, complete heart block or asystole, were recorded. The early progress of 11 patients was complicated by serious arrhythmia within six hours of the onset of pain. Six suffered arrhythmia following inferior myocardial infarction (two ventricular fibrillation, one ventricular tachycardia, two complete heart block and one asystole) and five following anterior infarction (three ventricular fibrillation and two ventricular tachycardia). Eight patients were taking oral mexiletine at the time of the first study. Clinical signs of overt heart failure in the acute phase (tachycardia, gallop rhythm and persistent crepitations) were noted. Left ventricular failure was noted separately and diagnosed radiologically as alveolar oedema. Heart size was estimated by the cardiothoracic ratio (CTR) method and expressed as the ratio of the maximal cardiac diameter to the maximal intrathoracic diameter from standard six foot chest radiograph taken on the day before discharge from hospital, values >0.50 being considered to represent cardiomegaly. Of the 50 patients, 35 were smokers at the time of admission, six had a history of angina of effort, six patients were taking antihypertensive medication and the two youngest female patients were taking oral contraceptive preparations. To characterize our patient population further the Norris Coronary Prognostic Index was calculated for each patient, producing a weighted score based on age, history of infarction, heart size and signs of heart failure on the admission chest radiographs.

Radionuclide methods

Isotope ventriculography was performed at rest on the day immediately before discharge from hospital (mean 11 days, range five to 19 days), when patients were well and both clinically and radiologically clear of cardiac failure. Subjects were informed of the nature of the investigation and had consented to take part.

All patients were studied in the supine position and cardiac imaging performed in the 30° left anterior oblique projection with a 10° caudal tilt using the Nuclear Enterprises Mk 5 HR gamma camera. Following an intravenous injection of 15 mCi of technetium 99 m electrolytically labelled human serum albumin. The counts from the precordium were transferred and stored in 20 msec frame format in a PDP 11/34 computer (Digital Equipment Corporation). The accumulation was triggered by the R wave of the patient's electrocardiogram, recorded from chest lead V5, each 20 msec frame being updated by successive cardiac cycles until 500 heart beats had been accumulated. At the end of the accumulation period the frames were displayed in rapid sequence or 'movie' format on a purpose built television display screen. From the display the ventricular outline was selected using a joy-stick and data from within this outline was displayed to produce the uncorrected ventricular volume curve. The ventricular region selected was checked and where necessary were altered by displaying the volume curves from individual pixels. Background subtraction was made from a crescentic shell of the lateral and inferior ventricular border, corrected to provide an area equal to the left ventricle and left ventricular ejection fraction was calculated from this corrected time activity curve. Left ventricular wall motion was examined from the continuous movie dis-

play with and without edge enhancement methods. Abnormalities of regional wall movement were analysed by dividing the left ventricular wall into four segments of equal length, two lateral, one apical and one septal. Dyskinetic segments were identified using a time-differential method which displayed the change in volume signal by subtracting frame n from frame $n + 1$, and displayed areas of dyskinesia moving out of phase relative to the remainder of the ventricular wall. Normal values for EF were measured in a group of 16 individuals with no history of cardio-pulmonary disease.

Follow-up period. At one and four months after acute infarction, a clinical history was obtained and physical examination, 12 lead electrocardiogram and chest radiography performed. No patient was lost to follow-up. During this period exercise tolerance, exertional dyspnoea and angina, or any change in medication were recorded. Antiarrhythmic therapy was discontinued routinely six weeks after infarction and diuretic therapy reduced or stopped provided clinical progress and chest radiography were satisfactory. No therapeutic decisions were made on the basis of measurements of ejection fraction. After intervals of one and four months radionuclide ventriculography was performed again at rest, and during supine exercise on a bicycle ergometer using a single stage load of 750 kpm/min. Standard chest lead V5 was monitored throughout and blood pressure recorded at one minute intervals. The instantaneous RR interval was displayed and data collection commenced after steady state had been achieved. The exercise test was terminated if the patient developed angina, severe fatigue or dyspnoea, frequent extrasystoles or depression of the ST segment greater than 5 mm.

The Wilcoxon Rank Sum and Signed Rank tests for non-parametric data were used in all statistical analyses.

RESULTS

Before discharge

The mean EF of 16 normal subjects measured in our laboratory was 0.57 ± 0.07 . In those patients recovering from their first myocardial infarction EF was reduced (0.38 ± 0.12 , $p < 0.01$). Anterior myocardial infarction resulted in a greater reduction in EF than inferior infarction (0.33 ± 0.13 versus 0.43 ± 0.09 , $p < 0.01$) (Fig. 1). When we related EF to the early progress of patients serious arrhythmia in the acute phase was associated with low EF in the convalescent phase (0.28 ± 0.08 versus 0.42 ± 0.10 , $p < 0.01$) (Fig. 2).

The progress of 19 patients had been complicated by left ventricular failure (LVF) requiring treatment at the time of presentation; seven of these had sustained inferior myocardial infarction, 12 anterior infarction. All patients were clinically and radiologically free of LVF at the time of the first study, but 12 patients had remained on diuretic therapy throughout their stay in hospital. LVF in the acute phase was associated with low EF in the convalescent phase (0.29 ± 0.11 versus 0.44 ± 0.08 , $p < 0.01$) (Fig. 4).

Regional wall movement appeared normal in 12 patients and abnormal in 38 patients, abnormalities corresponding to the site of infarction in 29. Segmental

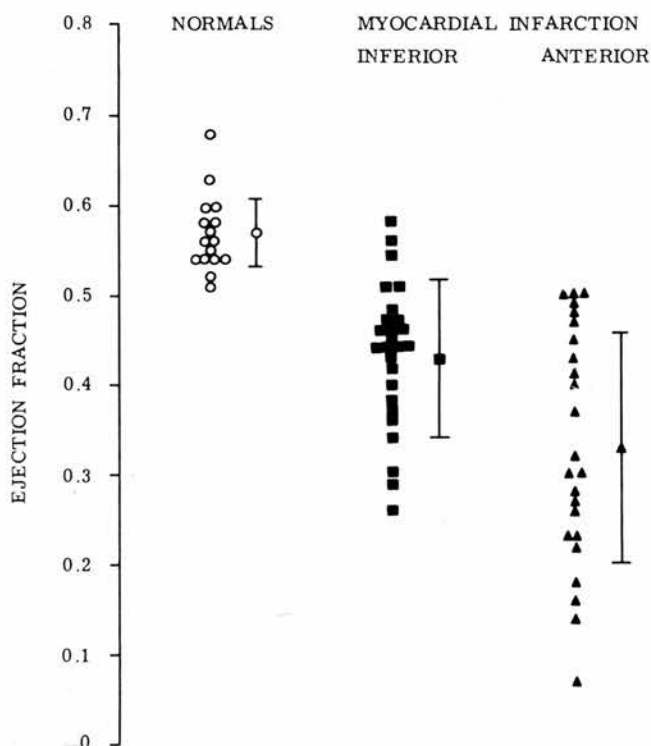


FIG. 1. Relationship between left ventricular ejection fraction and site of infarction. Mean (\pm S.D.) are shown by the bars.

hypokinesia as the only abnormality was observed in 10 patients, hypokinesia affecting more than one segment seen in eight patients and areas of akinesia were observed in five patients. Dyskinetic segments were identified in 15 patients and of these 11 (73 per cent) were subsequently found to have persisting ST elevation on ECG at 30 days, whereas only five (33 per cent) showed cardiac enlargement radiologically. Global left ventricular performance correlated well with the presence of abnormalities of regional wall movement. Mean ejection fraction, associated with apparently normal wall motion, was 0.47 ± 0.05 , with hypokinesia of one segment 0.44 ± 0.08 , with hypokinesia affecting more than one segment 0.42 ± 0.09 , with akinesia 0.38 ± 0.11 and with dyskinesia 0.27 ± 0.10 (Fig. 4).

Excluding patients with a history of hypertension, radiological heart size (CTR) correlated poorly with EF ($r = -0.29$). Although EF was depressed in all patients with cardiomegaly, normal heart size was often associated with depressed LV function even when not clinically apparent. EF correlated poorly with the Norris Coronary Prognostic Index predictive of long term survival ($r = -0.29$, $p > 0.05$).

Follow-up. Two patients were excluded from study; one patient required surgical closure of a late ventricular septal defect and the other was found to be in atrial fibrillation following inferior infarction. Seven patients remained on oral mexiletine, nine were taking diuretic therapy and five had developed angina controlled by

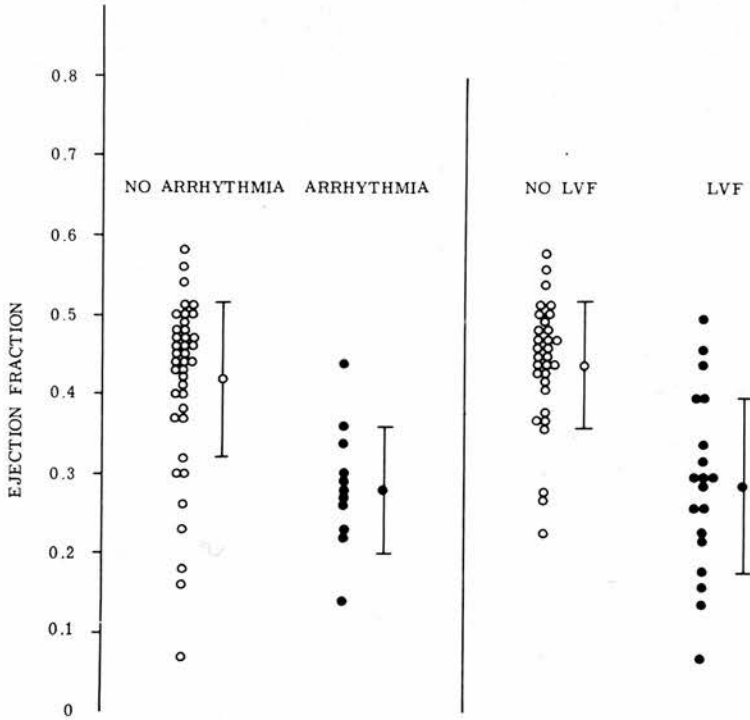


FIG. 2. Relationship between left ventricular ejection fraction and early serious arrhythmia and left ventricular failure in the acute phase. Mean (\pm S.D.) are shown by the bars.

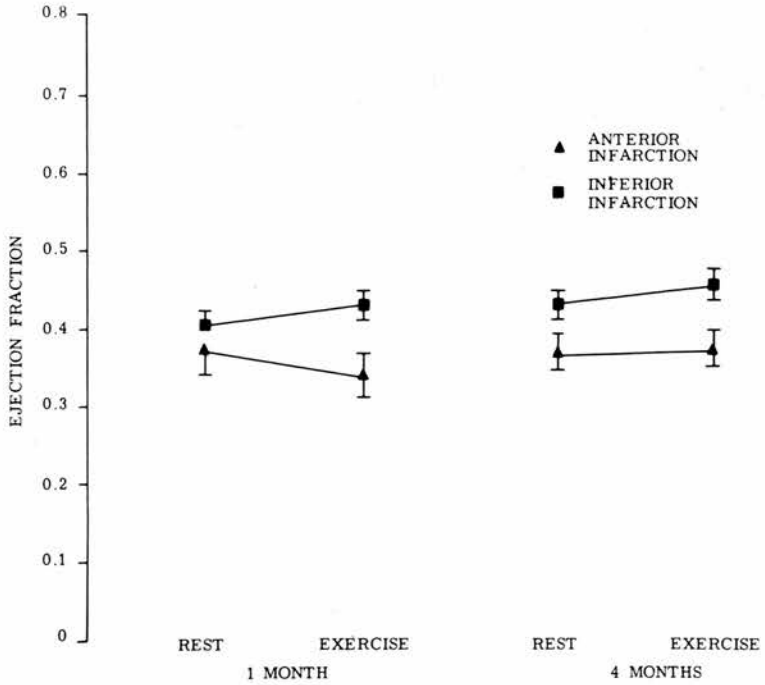


FIG. 3. Left ventricular ejection fraction at rest and during exercise one and four months after infarction. Mean (\pm S.E.M.) are shown by the bars.

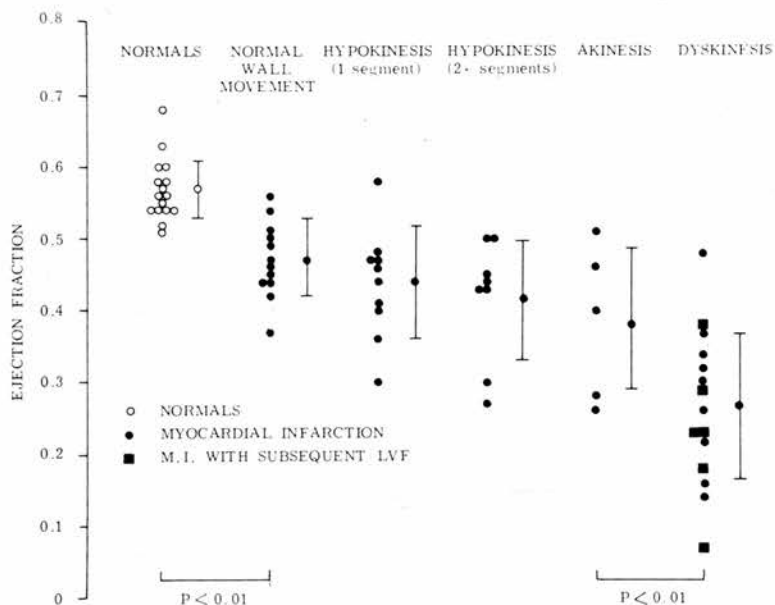


FIG. 4. Relationship between left ventricular ejection fraction and regional wall abnormality. Mean (\pm S.D.) are shown by the bars.

trinitrin alone. There were no patients taking either digoxin or beta adrenergic blockers. In the four month period after infarction a further 10 patients had developed angina, six had episodes of cardiac failure, three suffered non-fatal reinfarction and two had died. Diuretic therapy was continued in nine patients and two patients had been digitalized. Treatment with beta adrenergic blocking agents was commenced in seven patients and four received other antianginal drugs. There was relatively little change in EF over the first month, EF after anterior infarction increased (mean change = +11.3 per cent, $p < 0.05$), whereas EF in those recovering from inferior infarction fell (mean change = -8.0 per cent, $p < 0.01$) (Fig. 5). In the three month period between follow-up appointments there was no significant change in resting EF in either group. Left ventricular failure in the convalescent phase was associated with low resting EF. Over the first four months after infarction low EF ($p < 0.30$) failed to improve in seven patients with areas of dyskinesia and despite diuretic therapy five suffered further episodes of cardiac failure (Fig. 4). The other patient with further left ventricular failure had a global EF of 0.38 but in addition to a small dyskinetic segment had mitral regurgitation following papillary muscle rupture.

Exercise studies (Fig. 6). During submaximal exercise at one month, EF in patients with recent anterior infarction fell significantly (mean change = -9.5 per cent, $p < 0.01$), whereas for patients recovering from inferior infarction EF increased on exercise (mean change = +7.8 per cent, $p < 0.05$). Four months after infarction both groups were able to increase EF on exercise. Patients with dyskinesia at rest were unable to increase EF on exercise (mean change = -5.2 per cent) and were excluded from further statistical analyses. Of the remaining 34 patients, 18 were unable to increase EF on exercise at one month and 14 of these

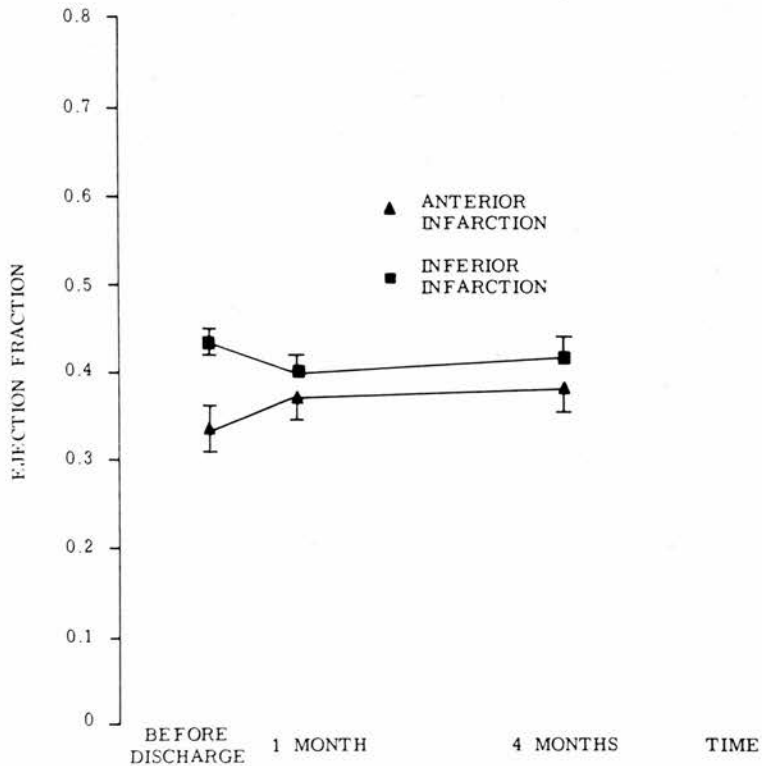


FIG. 5. Changes in left ventricular ejection fraction at rest following discharge from hospital. Mean (\pm S.E.M.) are shown by the bars.

developed angina. No patient who developed angina was able to increase EF on exercise. Reductions of greater than 5 per cent were seen in 12 patients all of whom subsequently developed angina ($p < 0.01$). Three of these patients already had angina at one month, but the remaining nine patients developed angina in the subsequent three months. Therefore a reduction in EF of greater than 5 per cent on exercise one month after myocardial infarction was predictive of subsequent angina.

Of the 15 patients who developed angina, four were poorly controlled on drug therapy, two were unable to complete the exercise test at four months and one who showed the greatest reduction in EF ($\Delta 34$ per cent) died. Three patients had a further infarction and only one was able to increase EF on exercise. One death was sudden and was not predicted.

DISCUSSION

The site of myocardial infarction appears to have a profound effect upon impairment of ventricular performance. Mean left ventricular ejection fraction is significantly reduced in patients recovering from anterior rather than inferior myocardial infarction. This difference which was noted by Hamby *et al.* (1974) who reviewed cardiac catheterization data in patients with angina and previous infarction has subsequently been shown by radionuclide ventriculography to be

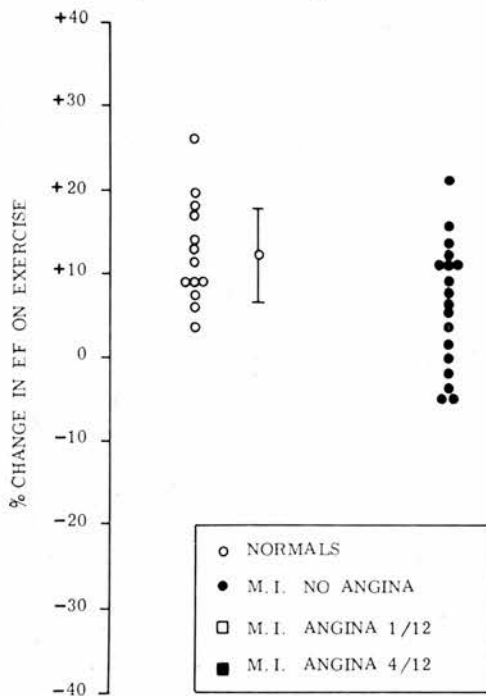


FIG. 6. Relationship between change in ejection fraction on exercise and the subsequent development of post-infarction angina. Mean (\pm S.D.) are shown by the bars.

present within 24 hours of admission and to persist throughout hospital stay (Reduto, Berger, Cohen, Gottschalk, and Zaret, 1978). Haemodynamic studies in the acute phase by Russell, Hunt, and Rackley (1973) have shown left ventricular filling pressure to be higher and stroke index to be lower in patients with anterior infarction. In an attempt to explain this difference, it was proposed from enzyme analysis that patients with anterior infarction had damaged a greater portion of the ventricular muscle mass than those recovering from inferior infarction (Sobel, Breshnahan, Shell, and Yoder, 1972). Contrast ventriculography after infarction, however, has shown that for comparable values of total creatine kinase (CK) released, ejection fraction in anterior myocardial infarction remains lower than in those patients with inferior infarction (Hori, Inoue, Fukui, Shimazu, Mishima, Ohgitani, Minamino, and Abe, 1979). This difference persisted even after the exclusion of those patients with proximal right coronary artery lesions who might have had right ventricular necrosis, confirming that left ventricular function after infarction depends in part on the site of the infarct. Although this difference between resting EF in anterior and inferior myocardial infarction is significant before discharge from hospital, statistical significance is lost in the subsequent four month period. Such changes in EF with time may explain why the initial excess mortality associated with anterior infarction in the hospital phase does not persist (Weinberg, 1976).

In addition to the site of infarction, the other major factor affecting the impairment of left ventricular function, is, of course, infarct size. Work by Sobel,

Bresnahan, Shell, and Yoder (1972) has shown that a close relationship exists between total CK release and the size of experimental infarction. More recently Hori *et al.* (1979) demonstrated the significant relationship between total CK release and left ventricular EF, measured by contrast ventriculography two months after infarction. We have not attempted in this study to repeat detailed enzyme analysis, but in a select number of patients it was possible to produce a similar relationship between EF calculated by the radio-isotope method and peak SCK measured as a projected value 24 hours after the onset of pain ($r = 0.57$, $p < 0.01$). Although a significant relationship was demonstrated, a rise in SCK (for example to 2000 u/l) was associated with either normal EF or low EF, often when not suspected clinically.

The importance of the radiological appearances of LVF in the acute phase on subsequent prognosis has been demonstrated (Norris *et al.*, 1974). In our own population poor LV performance was associated with LVF in the acute phase despite apparent well-being just before discharge from hospital. The Norris Coronary Prognostic Index (CPI) also incorporates amongst its variables radiological heart size (Norris *et al.*, 1969). In our own population, although all patients with cardiomegaly had reduced EF, there was no significant correlation between EF and CPI ($r = -0.29$) and in particular EF correlated poorly with radiological heart size measured by the CTR method. Our own work would support that of contrast ventriculography (Field, Russell, Moraski, Soto, Hood, Burdesmaw, Smith, Maurer, and Rackley, 1974) in that the poor correlation between EF and CPI suggests that radiological heart size is a poor predictor of LV function.

Similar prognostic significance has been placed upon serious arrhythmia both in the acute phase (Denborough, Lovell, Nestel, and Goble, 1968) and also in the late hospital phase (Schulze, Struss, and Pitt, 1977). In our own population those with serious arrhythmia had significantly lower EF than those whose early progress was uncomplicated. Although all arrhythmias occurred within six hours of the onset of pain, seven of the 11 patients also had radiological evidence of LVF at the time of presentation and the arrhythmias in these may have been complicating rather than primary. There were, however, two patients with early serious arrhythmia (ventricular tachycardia) who remained free of LVF, and EF before discharge was greatly reduced (0.27, 0.23). Therefore arrhythmias in the absence of LVF may also be associated with marked impairment of left ventricular function in the convalescent phase.

Global left ventricular ejection fraction correlated well with the extent and severity of abnormalities of regional wall movement, the greatest reduction in EF being observed in those patients with areas of dyskinesis. Radionuclide studies have been shown to be reliable in the identification of apical and anterior dyskinesia (Friedman and Cantor, 1979), although more recent work recommends the use of biplane radionuclide ventriculography in the quantification of wall motion abnormalities (Dymond, Stone, Elliot, Britton, Banim, and Spurrell, 1979). Field, Russell, Dowling, and Rackley (1972), using quantitative biplane contrast ventriculography, noted the importance of regional wall abnormalities in relation to

heart failure and found this to be more common in patients with $EF < 0.3$. We have shown, however, that without exception patients who develop left ventricular failure in the four months after first infarction had areas of dyskinesia and all, except one, had $EF < 0.3$. Therefore any reduction in diuretic therapy must be carefully monitored in this selected population where cardiac failure remains the most common cause of death (Dubnow, Burchell, and Titus, 1965).

Because of its noninvasive nature, radioisotope ventriculography is ideally suited to the sequential measurements of ejection fraction after myocardial infarction. Earlier work by Reduto *et al.* (1978) has shown that ventricular performance (after uncomplicated transmural myocardial infarction) remains relatively stable during the hospital phase (13 ± 3 days). Our own work demonstrates that there is not only little change in ventricular performance in the immediate one month period, but also that the changes during the first four months are very small, there being only slight improvement. In those patients who were readmitted with LVF, resting EF failed to improve and remained very low over the four month period after infarction. Such results support the conclusions of Rahimtoola, Digilio, Ehsani, Loeb, Rosen, and Gunnar, (1972) who, using haemodynamic parameters, noted the very poor prognosis in patients whose ventricular function failed to improve during convalescence. Although all our patients in this group have required increasing diuretic therapy, none has died. Without exception, such deterioration follows large infarcts with dyskinesia and the poor LV reserve.

Exercise studies early after myocardial infarction were performed by Pulido, Doss, Twig, Blomqvist, Faulkner, Horn, DeBates, Tobey, Parkey, and Willerson (1978), who noted the different functional ventricular response between patients with anterior and inferior infarction. Our own results confirm these initial observations and that in the first month EF on exercise tends to increase following inferior and decrease following anterior infarction. This difference, however, does not persist and four months after infarction, mean EF of both groups increases on exercise. However, this data must exclude patients with large dyskinetic segments who as a group were unable to increase EF. A fall in EF on exercise was also noted in patients who developed angina within the follow-up period and was associated with the development of new regions of wall dysfunction (Borer, Bacharach, Green, Kent, Epstein, and Johnston, 1977) and an overall increase in end systolic volume (Slutsky, Karliner, Ricci, Schuler, Pfisterer, Peterson, and Ashburn, 1979). Excluding those patients with dyskinesia, a fall in EF on exercise at one month was predictive of subsequent angina. Of 15 patients with angina, two were unable to complete the exercise test at four months, two had reinfarcted, and one, showing the greatest reduction in EF on exercise, had died.

In conclusion, low EF is common after anterior myocardial infarction, complicated in the acute phase by either left ventricular failure or serious arrhythmia. Subsequent changes in EF, both at rest and during exercise testing one month after infarction, are predictive of the development of left ventricular failure and angina. A longer period of observation is necessary to determine whether recurrent infarction or death can be related to the results of radio-isotope ventriculography at rest and during exercise after myocardial infarction.

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The sequential measurement of ventricular volumes and cardiac output by radionuclides

W J Hannan, J Vojacek, N J Dewhurst and A L Muir

Department of Medical Physics and Medical Engineering, and Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh EH3 9YW Scotland

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Abstract. A method is described which allows sequential measurements of absolute ventricular volumes from a single intravenous injection of $^{99}\text{Tc}^m$ -labelled human serum albumin. The indicator dilution curve detected by a gamma camera is used to make the initial determination of cardiac output and stroke volume, and to calibrate the left ventricular end-systolic and end-diastolic volumes determined from subsequent gated blood pool imaging. Further changes in left ventricular end-diastolic volume can be related to changes in the end-diastolic counts. Thus each measurement of ejection fraction can be used to determine absolute changes in ventricular volume, stroke volume and cardiac output. In 12 patients resting, repeat measurements of end-diastolic volume showed no significant difference (coefficient of variation 2.4%). In 6 normal subjects the infusion of isoprenaline ($2\ \mu\text{g}\ \text{min}^{-1}$) caused a significant increase ($P < 0.01$) in cardiac output and ejection fraction and a significant decrease ($P < 0.01$) in end-diastolic volume. Propranolol ($0.14\ \text{mg}\ \text{kg}^{-1}$) caused a significant decrease in stroke volume and cardiac output. The relationship between stroke volume and end-diastolic volume was depressed.

1. Introduction

The assessment of cardiac performance by radionuclides was first introduced by the pioneering work of Blumgart and Yens (1927). However, the recent rapid rise in the use of radionuclides in cardiological investigation owes much to the introduction of modern gamma camera/computer systems. Most attention has centred on the measurement of left ventricular ejection fraction using either a first pass method (Hannan *et al* 1977, Marshall *et al* 1977), or by the gated blood pool imaging method (Ashburn *et al* 1978).

However, the ejection fraction expresses only changes in relative volume and neither of its two determinants, end-systolic volume and end-diastolic volume, are measured. In theory, ejection fraction, end-diastolic volume, end-systolic volume and stroke volume can all be determined from the injection of a bolus of radioactive material. However, the relatively high activity required for the initial determination of ejection fraction makes second and subsequent measurements difficult. The administration of sequential injections would have an accumulative effect on gamma camera deadtime until a saturation count rate was finally reached and would also result in a corresponding increase in the radiation dose to the patient. In contrast, the gated blood pool method lends itself to sequential measurements of ejection fraction without imposing any further radiation burden on the patient. With a high background activity, however, it is difficult to make further measurements of cardiac output by the indicator dilution method. Thus in detailed physiological and pharmacological studies changes in

ejection fraction may be measured (Sapru *et al* 1980), but these directional changes may be influenced by the end-diastolic volume which is unknown.

We report a method for making sequential measurements of end-diastolic volume and cardiac output using the gated blood pool imaging method. Initially cardiac output is determined from a bolus of radionuclide and from this the stroke volume is derived. The ejection fraction is calculated from the changes in counts between systole and diastole in the region over the left ventricle. However, these counts are proportional to volume; thus if stroke volume is known, the end-diastolic volume can be calculated. Initial counts from the left ventricle can be used to calibrate subsequent changes in counts. We report the reproducibility of this method in sequential measurements made in patients undergoing routine radionuclide ventriculography and changes in end-diastolic volume, stroke volume and cardiac output produced by a beta adrenoceptor agonist (isoprenaline) and a beta adrenoceptor antagonist (propranolol).

2. Methods

Investigations were carried out with the patient lying supine beneath a Nuclear Enterprises Mark V gamma camera with a high-sensitivity parallel-hole collimator. A 30° left anterior oblique view with a 10° caudal tilt was used to optimise the separation of right and left ventricles and left atrium. The heart rate was derived from the electrocardiogram, which was monitored continuously throughout the study. The patient was injected with a rapid bolus of 555 MBq (15 mCi) of $^{99}\text{Tc}^m$ -labelled albumin into an antecubital vein. This electrolytically labelled human serum albumin is suitable for sequential studies since 90% remains within the vascular space at one hour (Millar *et al* 1979). The calculated radiation dose to the blood is 7.5 mGy (0.75 rad) (ICRP 1969). The activity injected was determined by comparing the syringe contents before and after injection with the count rate from a known standard, where all measurements were made at a fixed position relative to a sodium iodide scintillation detector. The passage of the bolus and subsequent four minute equilibration period were recorded in list mode on a PDP 11/34 (Digital Equipment Corporation) computer. Four minutes after injection, approximately 2 ml of blood was withdrawn from the opposite arm to the injection site. One millilitre of this blood was accurately pipetted and the activity measured in a sodium iodide well crystal relative to a known fraction of the initial standard. By comparing the activity in 1 ml of blood with the total activity injected, the patient's blood volume was calculated. As only plasma was labelled, the true blood volume was derived by correcting the venous haematocrit to the whole-body haematocrit (ICSH 1973).

Knowledge of the patient's blood volume allowed the resting cardiac output to be measured from the indicator dilution curve of the radionuclide passage through the heart (figure 1). The indicator dilution curve from the left ventricle was corrected for the dead-time losses for the entire field of view, as this varied significantly during the study. These dead-time losses are also a function of the energy spectrum. In this study we used dead-time corrections measured from known activities of $^{99}\text{Tc}^m$ with 8 cm of tissue-equivalent material placed between the sources and the collimator surface. The area under the peak of the indicator dilution curve (A) was determined using a gamma variate fitting technique (Starmer and Clark 1970) to remove the effects of recirculation. This fit (solid line, figure 1) was performed between approximately 20% of the peak height on the upslope and about 50% of the peak height on the downslope. The equilibrium height (h) was taken as the average height between 3 and 4 min after

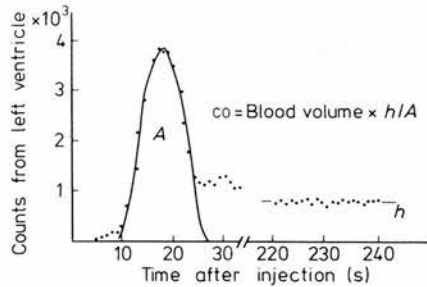


Figure 1. An indicator dilution curve from the left ventricle after correction for dead-time losses in the gamma camera. The area (A), corresponding to the initial passage of radionuclide through the ventricle, is obtained from the gamma variate fit (solid line) to the data between approximately 20% of the peak height on the upslope and 50% of the peak height on the downslope. The equilibrium height (h) is the average count between 3 and 4 min post injection.

injection. By analogy with conventional indicator dilution methods, the cardiac output (CO) was calculated from the relationship:

$$CO = (\text{blood volume} \cdot h) / A.$$

At the end of the four minute list mode accumulation a 32×32 cell matrix was positioned over the heart area and data was accumulated in 20 ms or 40 ms frames, depending on the initial heart rate. By 'zooming in' on only this region it was possible to achieve a pixel size of 4 mm while using only 1k words per frame. The accumulation was re-triggered by the R-wave of the patient's electrocardiogram until 400 to 500 cardiac cycles had been acquired. This gave images with typically 50 000 counts in the left ventricle at end-diastole when 40 ms frames were used. For each measurement the time and total gamma camera count rate were noted. One millilitre of blood was withdrawn and the activity measured to determine albumin clearance rate.

After each complete study the images were replayed in movie format on an interpolated 64×64 cell display. A region of interest around the left ventricle at end diastole was selected using a joystick, and the counts detected in this region during successive frames were displayed as a volume-time curve (Muir *et al* 1980). The volume-time curves from individual cells around the border of the selected region were displayed and inspected so that individual cells could be added to or removed from the original region. Extracardiac radioactivity was corrected for using an automatic background correction; this correction was derived from the counts within a region one cell wide inside the lateral and inferior edge of the region of interest, taken at end systole, and scaled to an equal number of cells to the left ventricle (figure 2). Ejection fraction ((EF) was calculated from the relationship

$$EF = (EDC - ESC) / EDC$$

where EDC and ESC are the end-diastolic and end-systolic counts respectively. The average heart rate during each accumulation period was obtained from an RR interval histogram stored in the computer memory. The cardiac output (CO) determined from the indicator dilution curve was combined with the ejection fraction (EF) and heart rate (HR) measured from the initial gated blood pool study to give the end-diastolic volume (EDV) during the control period:

$$EDV = CO / (EF \cdot HR).$$

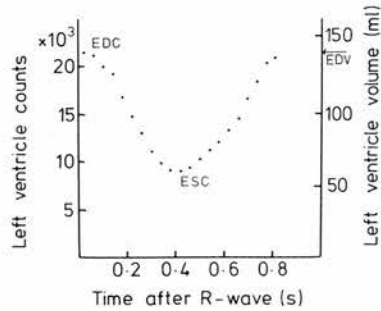


Figure 2. A background corrected activity-time curve from the left ventricle. The calibration in absolute volume units has been obtained by relating the ventricular counts to the stroke volume measured from the first pass indicator dilution curve.

End-diastolic volume was then related to the end-diastolic counts using the relationship

$$EDV = EDC \cdot (DPK/NTB)$$

where D is the dead-time correction determined from the total field of view count rate, P is the correction for physical decay, N is the number of cardiac cycles accumulated, T is the time per frame and B is the fraction of injected albumin in the circulation. The additional factor, K , depends on gamma camera sensitivity and absorption losses in the patient. For the initial resting study the factor K is the only unknown in the above relationship, and having determined this value, it may then be applied to subsequent investigations in that patient to find the new value of end-diastolic volume. The measurement of heart rate and ejection fraction in subsequent investigations allows the corresponding stroke volumes and cardiac outputs to be determined.

3. Patient studies

3.1. Reproducibility

In 12 patients with coronary artery disease referred for routine radionuclide ventriculography, measurements of ejection fraction, end-systolic and diastolic volumes, stroke volume and cardiac output were made during an initial control period and then 45 min later, the patient having remained supine on the examination couch.

3.2. Pharmacological study

In six patients with non-cardiac pain, measurements were made at rest and then 10 min after the start of an infusion of isoprenaline given at a constant rate of $2 \mu\text{g min}^{-1}$. Twenty minutes after the isoprenaline infusion had ceased, an intravenous injection of propranolol (0.14 mg kg^{-1}) was given and 20 min after the injection had been completed, ejection fraction, ventricular volumes and cardiac output were remeasured.

All patients were informed of the nature of the investigations and agreed to take part. These investigations had the approval of our hospital ethical committee. No patient had received a beta adrenoceptor antagonist for at least one week prior to the study.

4. Results

4.1. Reproducibility study

In the 12 patients with ischaemic heart disease the mean cardiac index (cardiac output per unit body surface area) was 3.8 ± 0.2 (SE) $l \text{ min}^{-1} \text{ m}^{-2}$. The mean ejection fraction was 0.43 ± 0.03 (SE) in the first measurement period and was 0.42 ± 0.03 in the second period (coefficient of variation 3.2%). The mean end-diastolic volume was 215.1 ± 17.3 ml in the first period and 216.3 ± 16.5 ml in the second period (figure 3) (coefficient of variation 2.4%). As both measurements can be influenced by the region of interest selected for the ventricle, the same observer re-selected the region of interest one week later. Two other trained observers also selected regions of interest around the ventricle and measured ejection fraction and end-diastolic volume. The mean intra-observer error was 2.8% for ejection fraction and 3.4% for the end-diastolic volume. The mean inter-observer error was 4.0% for ejection fraction and 3.8% for end-diastolic volume.

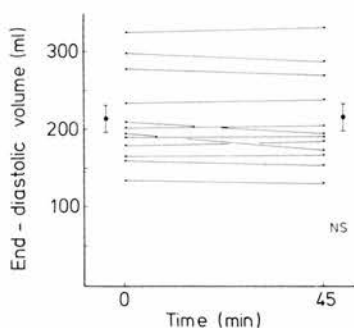


Figure 3. End-diastolic volume measured on two occasions on 12 patients. The mean values and standard errors are also shown. The average difference between successive measurements was only 5% (coefficient of variation 2.4%). NS: not significant.

The successive measurement of end-diastolic volume is not only affected by the region of interest, but is also affected by the corrections for physical decay, gamma camera dead-time, blood clearance of the tracer, and the number of cardiac cycles collected. To test the validity of the corrections we made for these factors, we also normalised the counts in the left ventricle at end diastole by the total counts in the end-diastolic frame. This total count is also affected by these same factors and provided the patient has not moved and the cardiac function has not been changed by physiological or pharmacological means (as in this part of the study), then the corrected end-diastolic volume should be the same. The coefficient of variation when end-diastolic volume was corrected in this way was 2.1%, which is not significantly less than that obtained for the correction procedure described previously. It is apparent therefore that the corrections may be applied with confidence in situations where ventricular volume is altered. Since neither ejection fraction, heart rate nor end-diastolic volume varied significantly, there was no change in stroke volume or cardiac output.

4.2. Isoprenaline and Propranolol

For the six normal subjects who received infusions of isoprenaline and propranolol, the mean heart rate at rest was 77.2 ± 2.9 (SE) beats per minute. This increased to

106.2 ± 7.2 beats per minute during the infusion of isoprenaline ($P < 0.01$). Following treatment with propranolol, the heart rate was 68.5 ± 2.6 (figure 4). The resting ejection fraction was 0.55 ± 0.03. This increased to 0.74 ± 0.04 during the isoprenaline infusion and was 0.51 ± 0.03 following injection of propranolol. The resting end-diastolic volume (figure 5) was 159.3 ± 9.1 ml and fell to 131.5 ± 4.7 ml following isoprenaline ($P < 0.01$). Following propranolol the end-diastolic volume was not significantly different from that of the control period with a mean of 156.2 ± 10.3 ml. From these measured values the calculated cardiac output was derived. At rest the cardiac output was 6.7 ± 0.4 l min⁻¹ and increased to 10.5 ± 1.0 l min⁻¹ during isoprenaline ($P < 0.01$) and following propranolol the calculated cardiac output fell to 5.4 ± 0.4 l min⁻¹ (for propranolol against rest $P < 0.05$, figure 5).

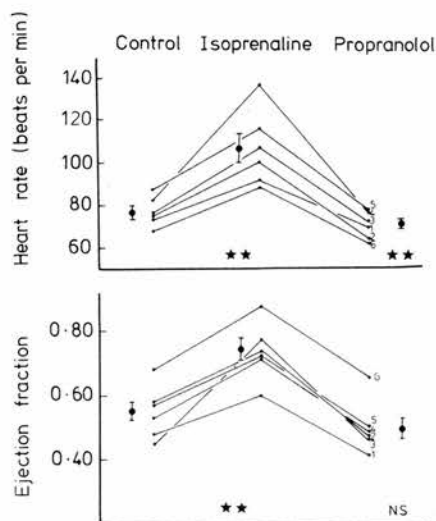


Figure 4. Heart rate and left ventricular ejection fraction measured in six patients during a control period, after infusion of isoprenaline ($2 \mu\text{g min}^{-1}$) and after an intravenous injection of propranolol (0.14 mg kg^{-1}). The mean values and standard errors are also shown. Results were compared by student's paired t-test. NS: not significant; *: $P < 0.05$; **: $P < 0.01$.

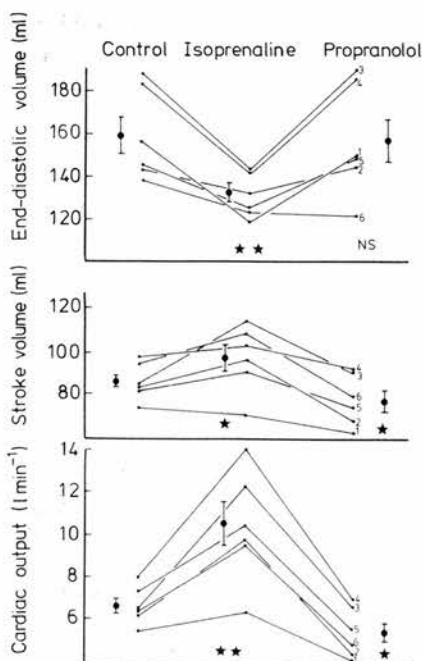


Figure 5. End-diastolic volume, stroke volume and cardiac output measured in the six patients during the control period, after infusion of isoprenaline and after propranolol. The mean values and standard errors are shown. Significance levels are the same as in figure 4.

5. Discussion

Ventricular volumes may be derived by contrast angiography or echocardiography, but both methods assume that the ventricle is a prolate ellipsoid. No such assumption is needed for radionuclide methods, making them particularly valuable in the study of ischaemic heart disease where geometrical assumptions may be invalid. Several workers have proposed the use of radionuclides to measure ventricular volumes. Early

work was based on a single-probe detector (Kuikka *et al* 1975). However, more recently Kuikka and colleagues (Kuikka *et al* 1979) have re-examined their methods using a gamma camera. In this they measured cardiac output from the passage of a bolus of $^{113}\text{In}^m$, but they derived ejection fraction from the mean disappearance rate of tracer from the ventricle, rather than the more conventional modern methods using gated or bolus techniques. The clearance rate measured from the left ventricle is dependent on the rate of arrival and it would have to be deconvolved with the input function before the true clearance could be obtained. They obtained sequential measurements during exercise by giving successive injections of $^{113}\text{In}^m$. In addition to the problem of further radiation burden with successive injections, the relatively high gamma ray energy of $^{113}\text{In}^m$ results in an undesirable reduction in gamma camera resolution and sensitivity.

Slutsky *et al* (1979) measured ventricular volumes by the gated blood pool method, expressing their results in dimensionless units. They obtained a general equation relating ventricular counts to cardiac volumes measured by contrast angiography. Whilst rightly criticising the geometrical assumptions of contrast ventriculography, their absolute calibration relied on measurements made by that technique.

Our own approach contains elements of both these methods. Our absolute calibration is made from the initial cardiac output determination. Ventricular volumes are then obtained from the gated blood pool study. Subsequent measurements of ventricular volume are obtained from the end-diastolic counts. There are several potential sources of error in this approach. The first lies in the determination of cardiac output. Several investigators have used the radionuclide method for the determination of cardiac output and in general have found good agreement, provided the initial bolus is of good quality (Berman *et al* 1974, Fouad *et al* 1979). Alazraki *et al* (1975) also used a gamma variate curve-fitting method when calculating cardiac output from a bolus of $^{99}\text{Tc}^m$ -labelled albumin. They found that cardiac output measured in this way was in good agreement with that measured by dye dilution. In the present study we were unable to measure simultaneously cardiac output by invasive techniques, but we have subsequently been able to compare values of cardiac output by the radionuclide method and thermal dilution in three patients. In each case the two methods agreed with 0.5 l min^{-1} .

A second potential source of error lies in the definition of the ventricular region of interest as this defines the end-diastolic counts. Using our method, which inspects volume-time curves from individual pixels on the border of the left ventricle, our inter-observer variation was less than 4%.

Other errors relate to the corrections for dead-time, physical decay and blood clearance. Our normalisation of ventricular counts by the total field counts, where the patient did not move and there was no physiological or pharmacological change, confirmed that these corrections may be applied with confidence.

An alternative approach in assessing the value of this method is to examine changes produced by pharmacological intervention. In this study we choose to examine the changes produced by intravenous infusion of isoprenaline and propranolol. Both drugs produced clear changes, with isoprenaline producing the increase in heart rate and ejection fraction which we have documented in previous studies (Sapru *et al* 1980). The end-diastolic volume fell by a mean of 27 ml following isoprenaline. Isoprenaline caused an increase in both stroke volume and heart rate and thus the cardiac output increased from a mean of 6.7 l min^{-1} to 10.5 l min^{-1} . Previous investigations have shown that following similar doses of isoprenaline cardiac output increases between 11

and 147% (Rosenblum *et al* 1968). The increase in cardiac output is partly brought about by an increase in heart rate and partly by an increase in stroke volume (Krasnow *et al* 1964). They were able to measure end-diastolic volume in eight patients, four of them with aortic stenosis. As long as the aortic valve was not critically tight, the infusion of isoprenaline brought about a decrease in the end-diastolic volume. This is similar to a detailed study on the effects of changes in preload, afterload and inotropic state on ventricular function in conscious dogs (Mahler *et al* 1975) where isoprenaline caused an increase in heart rate, a decrease in left ventricular end-diastolic pressure and a decline in left ventricular end-diastolic diameter. The haemodynamic changes after beta adrenoceptor antagonist therapy are usually small at rest and maximal effects are noted after exercise (Epstein *et al* 1965). Similarly only small changes in end-diastolic volume occur in patients with good ventricular function after propranolol (Coltart *et al* 1975), although the study by Mahler *et al* (1975) in conscious dogs showed propranolol ($0.25\text{--}0.5\text{ mg kg}^{-1}$) to cause an increase in end-diastolic pressure and dimensions. Our own observations show that after propranolol changes in left ventricular volumes are small but when stroke volume is plotted against end-diastolic volume (figure 6) the 'ventricular function' curve (Sarnoff and Mitchell 1962) is shifted downwards. Isoprenaline causes an increase in stroke volume for a given end-diastolic volume.

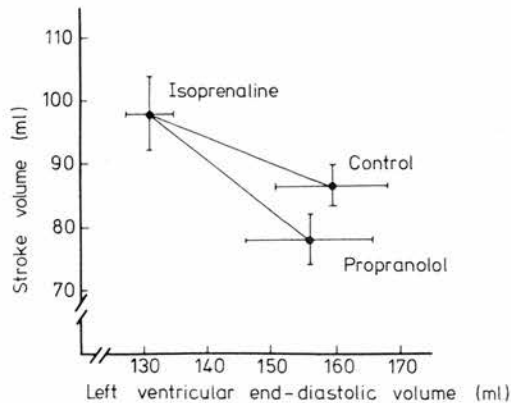


Figure 6. Plot of end-diastolic volume and stroke volume in six normal subjects. Treatment with isoprenaline shifts upwards to the left the stroke volume/end-diastolic volume relationship. Propranolol causes this relationship to be shifted to below that of the control state.

6. Conclusion

This study has shown that, in addition to the measurement of ejection fraction, by using both the bolus and gated blood pool methods in combination, cardiac output, stroke volume and end-diastolic volume can be obtained for serial studies without additional radionuclide injections. The assessment of ejection fraction alone, although helpful in defining ventricular performance, is inadequate in assessing contractility. Probably there is no single measure which can be used for the assessment of left ventricular performance in man. Nevertheless, by being able to relate the changes in ejection fraction to changes in end-diastolic volume, further information about ventricular performance is obtained without any additional patient intervention.

Résumé

La mesure séquentielle du volume ventriculaire et de la puissance cardiaque par radionuclides.

Une méthode est décrite qui permet les mesures séquentielles des volumes ventriculaires absolus par une injection intraveineuse simple de $^{99}\text{Tc}^m$ -marqué albumine de sérum humain. La courbe de dilution de l'indicateur détectée par une caméra gamma est utilisée pour effectuer la détermination initiale de la puissance cardiaque et volume de coup, et pour calibrer les volumes de fin systolique et de fin diastolique du ventricule gauche déterminés précédemment par imagerie de plaque de sang. Des changements supplémentaires de volume de fin diastolique du ventricule gauche peuvent être rapportés aux changements des comptages de fin diastolique. Par conséquent, chaque mesure de fraction d'éjection peut être utilisée pour déterminer les changements absolus de volume ventriculaire, de volume de coup et de puissance cardiaque. Sur 12 patients au repos, des mesures répétées de volume de fin diastolique ne montrèrent aucune différence importante (coefficient de variation 2,4%). Sur 6 sujets normaux, l'infusion d'isoprénaline ($2 \mu\text{g min}^{-1}$) causa une augmentation importante ($P < 0,01$) de la puissance cardiaque et de la fraction d'éjection et une réduction importante ($P < 0,01$) du volume de fin diastolique. Le propranolol ($0,14 \text{ mg kg}^{-1}$) causa une réduction importante du volume de coup et de puissance cardiaque. Le rapport entre le volume de coup et le volume de fin diastolique fut réduit.

Zusammenfassung

Stufenweise Messung des Herzkammervolumens und der Herzleistung mit Hilfe von Radionukliden.

Es wird ein Meßmethode beschrieben, die die Durchführung von Sequenzmessungen des absoluten Ventrikulärvolumens von einer einzigen intravenösen Einspritzung von menschlichem Serumalbumin mit $^{99}\text{Tc}^m$ -Indikator aus gestattet. Die Indikator-Verdünnungskurve, die von einer Gamma-Kamera bestimmt wurde, diente zur anfänglichen Bestimmung der Herzförderleistung und des Schlagvolumens sowie zur Kalibrierung der durch anschließende Blutpfützenabbildung mit Torschaltung bestimmten systolischen und diastolischen Blutvolumina der linken Herzkammer jeweils am Ende. Weitere Veränderungen des finaldiastolischen Volumens auf der linken Herzkammerseite können auf Änderungen der diastolischen Zählwerte am Ende zurückgeführt werden. Folglich kann jede Messung der Ausstoßfraktion zur Bestimmung der absoluten Veränderungen des Herzkammervolumens, des Schlagvolumens und der Herzleistung verwendet werden. Bei 12 ruhenden Patienten ergaben wiederholte Messungen des End-Diastolvolumens keinen bedeutsamen Unterschied (Variationskoeffizient 2,4%). Bei 6 normalen Versuchspersonen führte die Einspritzung von Isoprenalin ($2 \mu\text{g min}^{-1}$) zu einem bedeutsamen Anstieg ($P < 0,01$) der Herzleistung und der Ausstoßfraktion sowie einer bedeutsamen Abschwächung ($P < 0,01$) des End-Diastolvolumens. Propranolol ($0,14 \text{ mg kg}^{-1}$) führte zu einer signifikanten Verminderung des Schlagvolumens und der Herzleistung. Die Beziehung zwischen dem Schlagvolumen und dem End-Diastolvolumen war deprimiert.

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Reconstruction of ventricular volume curves distorted by variations in heart rate

W J Hannan, H M Brash, P K Wraith, A L Muir and N G Dewhurst

Department of Medical Physics and Medical Engineering, and Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh EH3 9YM, Scotland

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Abstract. Variations in heart rate or frequent ectopic beats may seriously distort the results obtained from ECG-gated radionuclide ventriculography. A method is described for measuring the effective acquisition time for each frame from the patient's R-R interval distribution stored in computer memory. Normalising factors calculated from this R-R interval histogram are applied to each image frame. A computer simulation has been used to assess the effectiveness of the method in removing distortions in ventricular volume curves. In 95 consecutive patient studies five showed unacceptably large variations in heart rate and six patients had frequent ectopic beats. These studies were re-analysed using our reconstruction technique. A significant improvement in image quality was obtained which allowed ventricular wall motion to be observed throughout the cardiac cycle. Values of left ventricular ejection fraction derived from the reconstructed images always agreed within 0.03 with those obtained from a modified video recorder which allowed heart beats outside chosen limits to be excluded.

1. Introduction

Radionuclide ventriculography using a gamma camera and computer system has become an established procedure in the non-invasive assessment of cardiac function. The most common method of measuring left ventricular ejection fraction (EF) is by gated blood pool imaging of the praecordium (Ashburn *et al* 1978). In this method a sequence of images corresponding to different phases of the cardiac cycle is held in computer memory and these are updated by re-triggering off the R-wave of the patient's electrocardiogram until several hundred heart beats have been detected. An important requirement in this method is that the patient's heart rate must remain constant throughout the study, with few ectopic beats.

We have previously investigated the effects of variations in heart rate on gated blood pool studies (Brash *et al* 1980) and have described a method of modifying a video recorder by replacing the video erase head with an extra audio record/replay head to exclude data from heart beats outside selected limits, along with the succeeding beat. Studies which showed an unacceptable variation in heart rate were recorded and subsequently replayed with the audio track, including the ECG signal, advanced by 2 s relative to the video signal. The ECG signal and the output of the ADCs of the camera were realigned with respect to time. The 'time advanced' signal was used by the computer to decide whether each heart beat fell within chosen acceptance limits.

Although this method proved satisfactory in excluding the distortions caused by ectopic beats, its wider application was limited by the fact that a video recorder does not

form part of the conventional gamma camera and computer configuration. The effect of an ectopic beat is to update only those frames up to that point, resulting in an excessive number of beats contributing to the early systolic frames. If the exact number of beats which contribute to each frame could be determined, it should be possible to calculate a series of normalising factors to apply to these frames.

2. Methods

2.1. Theory

The effect of a variation in heart rate is to generate a sequence of images which have been acquired for different effective times. Even if the ventricular ejection fraction remains constant for these different heart beats the overall ventricular volume curve may be distorted and the measured ejection fraction underestimated. In practice, the distortions caused to the ventricular volume curve depend on the actual shape of the patient's R-R interval histogram. If a significant number of beats occur in the region of the histogram corresponding to the systolic portion of the average volume-time curve then the measured ejection fraction may be seriously overestimated because the effective acquisition time for the end-diastolic frame is greater than that for the end-systolic frame.

If a patient's R-R interval histogram is known, we may then calculate from this the effective acquisition time for each frame. In calculating these times we may assume that each beat has contributed for the entire frame time to each image except the last associated with that beat. It contributes to this frame, on average, for only half the frame time before the accumulation is re-triggered and it makes no further contribution to frames beyond this time. The counts in each pixel of each frame may therefore be multiplied by a series of correction factors (C_i) given by the relationship

$$C_i = N / \left[N - \sum_{i=1}^{i-1} N_i - (N_i/2) \right]$$

where N is the total number of beats and N_i is the number of beats in the i th interval of the R-R interval histogram. Thus, in the above relationship, the summation term corrects for the fact that beats of duration less than a particular frame time have failed to contribute to the counts in that frame. The term $N_i/2$ indicates that the average time during which a beat has contributed to the final frame associated with that beat is only half the frame time. The number of correction factors required is equal to the number of frames and each pixel in a frame is normalised by the same correction factor.

2.2. Computer simulation

To investigate the possibility of reconstructing ventricular volume curves distorted by variations in sinus rhythm or by ectopic beats we developed a computer model based on summing together known curves in a given proportion and then determining the appropriate series of correction factors to apply to the resultant distorted curve. An example of a study to simulate the effect of a variable heart rate on the generated 'ventricular' volume-time curve is shown in figure 1. The composite curve (figure 1(a)) was computed by summing together a series of curves each of different duration and weighted by the number of beats shown in the R-R interval histogram (figure 1(b)). Each curve was a modified cosinusoidal shape with an 'ejection fraction' of 0.6 and an

isovolumic period of 80 ms immediately prior to the start of the next beat. The large reduction in counts in the later phase of the composite curve is typical of the distortion observed in the ventricular volume curve from a patient whose heart rate is varying during the accumulation period. From the R-R interval histogram it is apparent that each heart beat has contributed to every point up to and including that time. The total number of beats contributing to each point was calculated and the series of normalising factors was applied to the composite curve to generate the reconstructed curve (figure 1(c)).

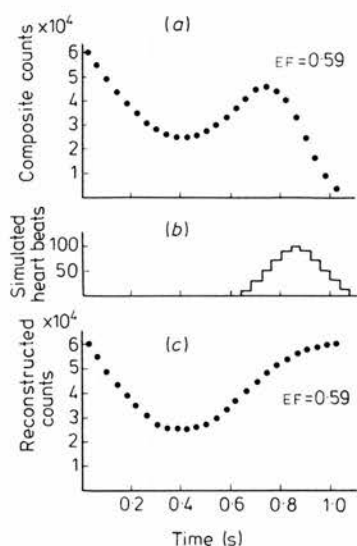


Figure 1. A computer simulation of the effect of a varying heart rate on the measured 'ventricular' volume curve. A series of modified co-sinusoidal curves, with ejection fraction (EF) of 0.6, were summed to give the distorted composite curve in (a). Corrections derived from the 'heart rate' distribution shown in (b) were used to obtain the reconstructed curve in (c).

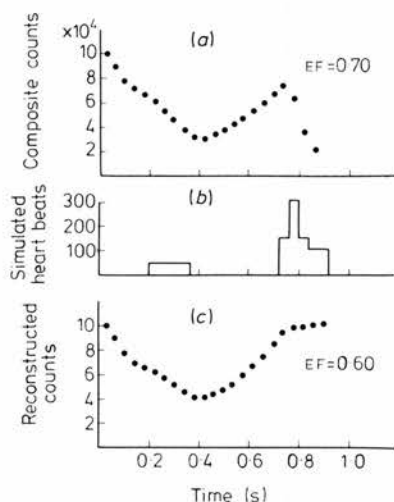


Figure 2. A computer simulation of the effect of frequent ectopic and post-ectopic beats on a ventricular volume curve. The composite curve in (a) significantly overestimates the mean weighted ejection fraction. Corrections based on the known 'heart rate' distribution of (b) gave the smoothly varying curve in (c) with an ejection fraction in good agreement with the mean value of 0.58.

The composite volume-time curve shown in figure 2(a) was generated from the R-R interval histogram of figure 2(b). In this example the sinus, ectopic and post-ectopic beats were all considered to be a modified cosinusoidal shape with isovolumic periods of 80 ms immediately prior to the start of the next beat. The main population, consisting of 60% of the total beats, had R-R intervals between 720–840 ms and had an ejection fraction of 0.6. An ectopic group between 200–360 ms were considered to have an ejection fraction of 0.4 and an equal number of post-ectopic accentuated beats were included between 840–920 ms with an ejection fraction of 0.7. The series of normalising factors derived from the R-R interval histogram was applied to the composite curve to give the smoothly varying curve shown in figure 2(c).

2.3. Patient studies

Ninety-five consecutive patients referred for routine radionuclide ventriculography were studied. Each patient lay supine beneath a Nuclear Enterprises Mk 5 HR gamma

camera connected on-line to a PDP11/34 (Digital Equipment Corporation) computer. The camera was positioned in a 30° left anterior oblique view with a 10° caudal tilt to give optimum separation of left and right ventricles and left atrium. 555 MBq (15 mCi) of technetium-99m labelled to human serum albumin was administered via an ante-cubital vein and after equilibration in the blood pool a region was positioned on the computer display to accept events from only the praecordium. By zooming in on this region only, it was possible to use no more than 1 K words per frame while maintaining a pixel size of only 4 mm. Images were accumulated in fixed 20–40 ms frames depending on the average heart rate and were re-triggered by the R-wave of the patient's electrocardiogram until 500 beats had been accumulated. The R-R interval histogram was accumulated into time bins. On the arrival of each R-wave the elapsed time since the previous R-wave was noted and the corresponding bin was incremented by one. At the end of the study each bin contained the number of heartbeats which had R-R intervals falling within the time limits of that bin. The computer interface, including the zoom facility, ECG-trigger circuit and all software, were provided by the authors.

Five patients who were in sinus rhythm had unacceptably wide variations in heart rate (coefficient of variation >10%) and a further six patients had frequent (>5%) ectopic beats. These studies were recorded on video tape along with the electrocardiogram for subsequent replay.

3. Results

For the computer simulation in which the ejection fraction was kept at 0.6 while the heart rate varied (figure 1) both the composite and reconstructed curves had an ejection fraction of 0.59 but the serious distortion in the 'diastolic' portion of the curve was removed. It should be noted that the reconstruction technique will only alter the measured ejection fraction if the total acquisition time for the end-diastolic frame is greater than that for the end-systolic frame. However, even in the relatively extreme example where the coefficient of variation of the R-R interval was 12% the measured value was within 0.01 of the true ejection fraction. From our computer simulations it is apparent that variations in heart rate when the patient is still in sinus rhythm should normally result in only small errors in the measured ejection fraction but may cause serious distortions to the diastolic phase of the volume curve. These distortions should be satisfactorily removed by normalising for the different acquisition times.

In the simulated ectopic study (figure 2) the mean weighted ejection fraction was 0.58 and the values from the composite and reconstructed curves were 0.70 and 0.60 respectively. The effect of ectopic beats on the measured ejection fraction depends on the actual shape of the R-R interval histogram. In the example illustrated, where the ectopic population was in the 'systolic' portion of the composite curve, the ejection fraction was significantly over-estimated and the diastolic phase of the curve badly distorted. The reconstructed curve removed the distortion and gave an ejection fraction in good agreement with the mean weighted value.

When the patient studies that showed a wide variation in heart rate or frequent ectopic beats were displayed in movie format on the computer TV, each sequence of images contained several frames during the diastolic phase that had been accumulated for total times shorter than the other frames in the sequence. The resultant reduction in counts in these frames caused the display to 'flash' when shown in the loop formation. This made it difficult for the observer to follow the ventricular wall motion and prohibited measurements of ventricular filling rate from the generated volume-time

curve. Application of the correction factors determined from the measured R-R interval distribution resulted in a significant improvement in image quality.

An example of a ventricular volume-time curve from a patient with a widely varying heart rate is shown in figure 3. The coefficient of variation of the R-R interval was 15% and the measured ejection fraction was 0.39. In the reconstructed curve (figure 3(c)) the ejection fraction was not significantly altered but a significant improvement was obtained in the quality of the movie images. This improvement is reflected in the recovery of the distorted diastolic phase of the volume curve.

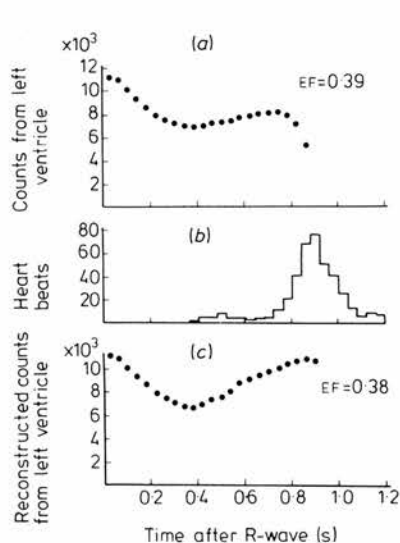


Figure 3. (a) The ventricular volume-time curve from a patient with a widely varying heart rate. The effective acquisition time for each frame was determined from the measured R-R interval histogram (b). The reconstructed curve in (c) has only a minimal difference in ejection fraction but shows a significant improvement in the diastolic phase.

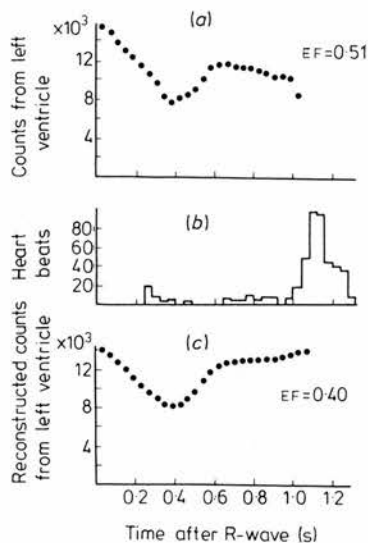


Figure 4. (a) The ventricular volume-time curve from a patient with frequent ectopic beats. Correction factors derived from the R-R interval histogram (b) were applied to the individual frames to produce the reconstructed curve in (c). Pile-up of counts in the early frames had resulted in a significant overestimate of ejection fraction.

The serious distortion which may be caused to a ventricular volume-time curve by ectopic and accentuated post ectopic beats is illustrated in figure 4. In this case the movie images proved inadequate for satisfactory interpretation and the curve shown (figure 4(a)) was in fact obtained from the original data using the ventricular region selected from the reconstructed images. The distortions were therefore not caused by failure to select the appropriate ventricular region, but because adequate signal averaging had not been achieved. The computed ejection fraction from the original curve (figure 4(a)) was 0.51 whereas the value for the reconstructed curve (figure 4(c)) was 0.40.

In general, even relatively large variations in heart rate (coefficient of variation 15%) only underestimated the ejection fraction by up to 3% provided the patient was in sinus rhythm. However, distortions during the diastolic phase of the movie images, which often made wall motion difficult to interpret, were satisfactorily removed by the correction process. In contrast, frequent ectopic beats (>5% of total) resulted in significant errors in the measured ejection fraction. The effect of the ectopic beats

depended on the frequency and time relationship of these and the post-ectopic beats to the sinus beats.

We have previously shown that our method of calculating the ejection fraction from the same data gives an average reproducibility of ± 0.01 (Muir *et al* 1980). The values of the ejection fraction determined from the reconstructed images always agreed within 0.03 (average 0.02) with the corresponding measurements made from our modified video tape recorder when this was used to accept only those beats within ± 40 ms of the average sinus beat.

4. Discussion

We have previously investigated the importance of excluding ectopic heart beats from ECG-gated ventricular blood pool studies (Brash *et al* 1980) and have shown that when premature beats represent more than 5% of the total, the measured ventricular curve may be seriously distorted. Our experience suggests that 7% of patients with chronic ischaemic heart disease have frequent extrasystoles and in studies following acute myocardial infarction this proportion will increase. Unwanted beats may be excluded using a dedicated computer as a buffer between the gamma camera and the main computer (Douglas *et al* 1976) but this solution is expensive and is not generally available in clinics. Alternatively the study may be accumulated in list mode using a computer with a very large and fast memory store, the size of which presents the ultimate limitation on the statistical quality of the images. Direct memory access may also be used to examine each heart beat in a buffer before entering it into list or frame mode (Bacherach *et al* 1977). All of these methods depend on a particular hardware configuration being available and therefore do not offer a general purpose solution to departments with small dedicated computers. Differences in accumulation times could be normalised by counts in the lung region but inclusion of a sufficient lung area would either degrade the image quality by increasing the pixel size or would require a significant increase in computer memory. We have now developed a method which may be used in the 'zoom' acquisition mode. By accepting events from only the praecordium the image pixel size may be kept small while using only 1 K words per frame. The method determines the total effective acquisition time for each frame by using the standard physiological measurement technique of storing the patient's R-R interval histogram in computer memory.

Imaging the cardiac blood pool by ECG-gating necessarily results in a volume-time curve which at best is the average over the study period. Thus even if the heart rate and volume curve shape remain the same during this time the measured ejection fraction, end-diastolic volume and stroke volume are only average values. These may well be more indicative of the physiological state of the patient than those derived from only a few heart beats following the injection of a bolus of radionuclide. Variations in the shape of the volume curve will of course result in a certain smearing of the overall curve even when the heart rate remains constant. However, the major distortion to the overall curve results from the purely physical effect of each frame being accumulated for different times. This may be confirmed by the fact that values of ejection fraction determined by our present technique agreed well with those obtained using our modified video recorder to exclude unwanted beats. We therefore believe that this method may be used to correct for the major cause of distortion in the majority of cases where the patient's heart rate is varying and may also improve the results obtained during stress examinations or pharmacological intervention. It may be readily implemented on existing systems without the addition of further instrumentation.

Résumé

Technique de reconstruction des courbes de volume ventriculaire perturbées par des variations du rythme cardiaque.

Les résultats obtenus par ventriculographie isotopique avec 'multi-gating' peuvent être perturbés par des variations du rythme cardiaque ou par des extra-systoles fréquentes. Nous décrivons une méthode permettant de mesurer le temps d'acquisition effectif de chaque image, à partir de la distribution des intervalles R-R stockée dans la mémoire de l'ordinateur. Un facteur de normalisation, calculé à partir de cet histogramme des intervalles R-R, est appliqué à chaque image. Nous avons utilisé une simulation sur ordinateur pour apprécier l'efficacité de la méthode pour supprimer les perturbations des courbes de volume ventriculaire. Parmi les études effectuées chez 95 patients consécutifs, 5 avaient des variations trop importantes du rythme cardiaque et 6 des extra-systoles fréquentes. Ces études ont été réanalysées en utilisant notre technique de reconstruction. Nous avons obtenu une amélioration significative de la qualité des images, ce qui a permis d'étudier les mouvements de paroi au cours du cycle cardiaque. Les valeurs de la fraction d'éjection ventriculaire gauche, obtenues à partir de ces images reconstruites, ont toujours été en accord, dans une limite de 0,03, avec celles obtenues à partir d'un enregistreur video modifié permettant d'exclure les cycles cardiaques situés en dehors des limites choisies.

Zusammenfassung

Rekonstruktion von Ventrikelvolumenkurven bei Störungen durch Veränderungen der Herzfrequenz

Veränderungen der Herzfrequenz können die Ergebnisse einer EKG-getriggerten Radionuklid-Ventriculographie verfälschen. Es wird eine Methode beschrieben zur Messung der effektiven Acquisitionszeit jeder im Computer gespeicherten Matrix. Aus diesen R-R-Intervall-Histogrammen werden Normierungsfaktoren berechnet und auf jede Bildmatrix angewandt. Eine Computer-Simulation diente der Beurteilung der Anwendbarkeit dieser Methode zur Beseitigung von Störungen der Ventrikelvolumenkurven. Bei 95 aufeinander folgenden Untersuchungen zeigten 5 unakzeptabel große Variationen der Herzfrequenz und 6 Patienten ectoische Schläge. Diese Untersuchungen wurden neu analysiert mit Hilfe der beschriebenen Technik. Eine signifikante Verbesserung der Bildqualität wurde erzielt, die die Beobachtung der ventrikulären Wandbewegung über den gesamten Herzzyklus erlaubte. Werte der linken Ventrikel Ejektionsfraktion, die aus den so rekonstruierten Bildern gewonnen wurden, stimmten immer innerhalb von 0,03 mit denen überein, die mit Hilfe eines Video-Rekorders ermittelt wurden, der den Ausschluß von Herzschlägen außerhalb wählbarer Grenzen erlaubte.

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The Influence of Ectopic Heart Beats in Gated Ventricular Blood-Pool Studies

H. M. Brash, P. K. Wraith, W. J. Hannan, N. G. Dewhurst, and A. L. Muir

Royal Infirmary, Edinburgh, Scotland

Direct data collection from ventricular blood-pool studies were stored in frame mode in a computer and by means of a modified tape recorder, the blood-pool image and ECG were recorded on tape. At the end of the study the tape data were replayed into the computer. The ECG signal was passed through a trigger circuit that detected the R wave which was sampled by the computer once every msec. Contractions outside of the desired range could be rejected along with the subsequent contraction. Of seven patients whose calculated ejection fractions were changed by more than 0.03, all had frequent (one in 20) ectopic contractions. The distorted ventricular volume curves were effectively restructured by the constraining procedure, changing the end-systolic volume and EF. Computer modeling showed a linear relationship between the percent of ectopic contractions and the underestimate of ejection fraction. One ectopic beat in ten led to a 5% underestimate of EF.

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Ventricular function can be assessed by a variety of radionuclide methods. Probably the most widely used is the blood-pool method that incorporates the multiple acquisition of images gated to the patient's electrocardiogram over several hundred heart beats. An implicit assumption underlying a method involving accumulation over a relatively long time interval is that the heart rate is constant, with few or no ectopic beats. Alternatively, such ectopic beats (and the postectopic accentuated beat) must be excluded from the analysis. This can be achieved in several ways. First, a dedicated computer can be used as a buffer between the gamma camera and the main computer to exclude unwanted cardiac beats (1). Second, in systems with access to computers with very large and fast memory stores, the entire study may be accumulated in "list mode". Alternative approaches are to predict the RR intervals from the patient's heart rate and to accept into the frame mode only those beats occurring within these preset intervals, or to use direct memory access (DMA) to examine each heart beat in a buffer before entering it into frame or list mode (2). To determine the importance of changes in heart rate and the presence of ectopic beats in gated imaging, we have devised a simple delay system for eliminating unwanted heart beats, and have examined the effects of such data treatment on the calculated ejection fraction (EF).

METHODS

We studied 100 consecutive patients undergoing angiography. Each patient was injected with 15 mCi of technetium-99m human serum albumin and, after equilibration, imaging commenced in a modified 30° left anterior oblique projection. Activity from the precordium was detected by a gamma camera, and the data analysis was carried out "on line" to a laboratory computer. In addition to direct data collection in frame mode by the computer, the blood-pool image and the patient's electrocardiogram were recorded on a modified videotape recorder. At the end of data collection, the data were replayed from the tape recorder into the computer.

The original video erase head of the tape recorder was removed and replaced by a spare audio record/replay head mounted on an adjustment plate. A well-screened switch was used to select either the new or the original audio head of the VTR. To prevent possible damage to the erase oscillator, the video erase head, located elsewhere, was wired across the oscillator.

After careful positioning and alignment of the new head, audio recordings made with the new head could be replayed, either in correct time or with the audio track, including ECG signal, advanced by 2,010 msec relative to the video signal. This advance time was determined experimentally and depended on the tape speed and the tape distance between the two audio heads. Tape speed depended largely on the local 50-Hz power-line frequency, normal fluctuations of which result in a variation of the delay of less than ± 10 msec.

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For reprints contact: Dr. A. L. Muir, Dept. of Medicine, Royal Infirmary, Edinburgh, Scotland.

TABLE 1. CALCULATED EJECTION FRACTION BEFORE AND AFTER ADDITION OF CONSTRAINT TO REMOVE ECTOPIC BEATS

Patient No.	% Ectopic beats	EF unconstrained	EF constrained	% error
1	19	0.65	0.59	+10%
2	12	0.21	0.26	-19%
3	14	0.60	0.55	+9%
4	8	0.51	0.58	-12%
5	21	0.27	0.35	-23%
6	7	0.43	0.39	+10%
7	13	0.56	0.64	-13%

The ECG signal replayed from the tape recorder was passed through a trigger circuit that detected the R wave, and the output of this was sampled by the computer once every millisecond. The computer was arranged to have stored in it at any time the last 2,010 samples. By associating the data coming from the gamma camera, not with the current sample from the trigger circuit, but with the one taken 2,010 msec earlier, the trigger signal and the output of the camera's ADC's could be realigned in time. But

because the "time-advanced" signal was also available to the computer, it could sense, when it came to start on a new beat, how long that beat was actually going to last. Thus the data from beats with periods outside the desired range could be rejected, as could the data from the beat immediately following each out-of-range beat. Since rejection of ectopic and postectopic beats could cause loss of 10 to 40% of all recorded beats where frequent ectopic beats were noted, the standard 500-cycle collection was extended to approximately 800 beats to give an adequate number for subsequent analysis.

Computer model studies. As a complementary study, we simulated the data acquisition in the computer, assuming that the ventricular volume-time curve for each individual beat is co-sinusoidal. We allowed for up to three populations of beats, each having its own ejection fraction and RR-interval histogram. The net volume-time curve was displayed and the apparent ejection fraction calculated.

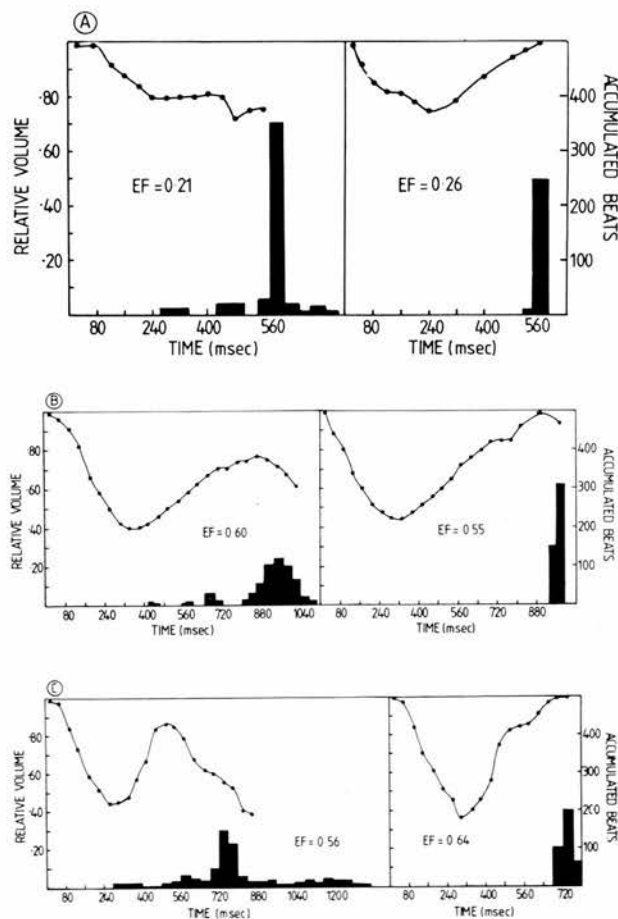


FIG. 1. Left-hand panels show generated ventricular volume curves in three patients with frequent ventricular ectopic beats, these being reflected in the wide spread of the RR-interval histogram. After filtration (right-hand panels), RR-interval histogram is narrow and ventricular volume curves are restored to normal shape. Effect of frequent ventricular ectopics is variable, causing either apparent underestimation (A and C) or apparent overestimation (B) of ejection fraction. (Bin width = 40 msec).

RESULTS

Patients. Replay of the data through the delay system, but without imposing any acceptance criteria, caused no change in the calculated EF.

In 93 of the 100 patients, replaying the data and sampling only the data from the principal frame of the RR-interval histogram caused EF to change by less than 0.02 if the same region of interest and background region of interest were selected. This applied to patients with quite wide, but normally distributed histograms (coefficient of variation up to 10%) who were in sinus rhythm with few, if any, ectopics. Although this could imply a significant percentage error in patients with a low EF, such small changes are of little clinical significance.

Of the seven patients whose calculated EFs were changed by more than 0.03 all had frequent (i.e., >1 in 20) ventricular or supraventricular ectopic beats (Table 1). The resultant ventricular volume curve appeared distorted, particularly in the diastolic phase. This is illustrated in Fig. 1, where three patients with widely varying ventricular function were chosen to show examples of such data treatment. The wide RR-interval histograms (left-hand panels) indicate the spread of ectopic and postectopic beats in the original data-collection period. The constraining procedure produces a narrow histogram of RR-intervals (right hand panels) and has the effect of restructuring the ventricular volume curve, and as end-systolic volume is changed, so is the calculated EF. The effects of varying the sampling window were also examined; the RR-interval sampling period could be widened by 100–200 msec without changing the calculated EF as long as the ectopic beats were not included in the sampling period.

Computer model. We constructed two models. In the first we used a single population and held the ejection fraction constant, but allowed an increasing spread in RR interval, noting the per-

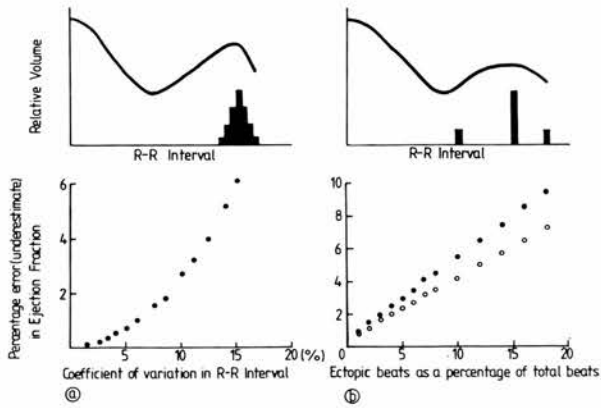


FIG. 2. Computer predictions of errors in measured ejection fraction that would result from either increased variation in heart rate (a) or increasing frequency of ectopic heart beats (b). Top left-hand panel simulates generated ventricular volume curve with equally, but widely distributed, RR-interval histogram. Below it, percentage underestimate in ejection fraction is plotted against coefficient of variation in RR interval. CV must be greater than 10% before there are serious errors in calculated ejection fraction. Top right-hand panel simulates a ventricular volume curve generated from a population of ectopic beats, postectopic beats, and normal beats. Below are plotted underestimates relative to ejection fraction associated with sinus beats (●), and underestimates using weighted mean of the values associated with the sinus, ectopic, and postectopic beats (○).

centage underestimate of the ejection fraction and the coefficient of variation in the RR interval (Fig. 2A). In the second model we tested the effects of increasing the frequency of ectopic beats on the calculated ejection fraction. The following assumptions were made: (a) The EF of the 'ectopic' beat should be 0.67 of the 'normal' beat and occur at 0.67 of the normal cardiac cycle; and (b) the EF of the postectopic beat should be 1.2 times the normal beat and should occur after a time interval 1.2 times the normal cardiac cycle to account for the normal compensatory pause. The results show a linear relation between the number of ectopic beats as a percentage of total beats, and the percentage underestimate in ejection fraction. One ectopic beat in ten would lead to a 5% underestimate of ejection fraction.

DISCUSSION

The evaluation of ventricular function by radiotracer has been of particular value in ischemic heart disease. For multiple gated acquisition methods, 200–500 cardiac cycles are required, and although the majority of patients with chronic ischemic heart disease are in sinus rhythm, the nature of the condition means that some will have extrasystoles. Our own studies suggest that in chronic ischemic heart disease, 7% have frequent extrasystoles, and without some means of excluding these and the subsequent post-extrasystolic beats, the calculated EF is in error. In studies following acute myocardial infarction, the proportion of patients with extrasystolic beats will increase. Exclusion of these ectopic beats also enhances the quality of the movie image format and allows better assessment of ventricular wall movement. It could be argued that the overall ventricular function and EF during the period of study is important and that the original curve allows this

to be calculated. However, our computer model shows clearly that the 'original' curve is not the arithmetic mean of normal, ectopic, and postectopic beats. Our clinical studies suggest that one ectopic beat in 20 is enough to alter the ventricular volume curve seriously. Our computer model deals with a very special situation with three distinct populations of cardiac cycles, producing different stroke outputs. This is rarely the case in patients, where there is a greater spread of time intervals and force of contraction among ectopic beats, normal beats, and postectopic beats. Where ectopic beats occur early in the cardiac cycle, model experiments also show that the accumulation of counts detected from the normal beats contribute to only the first few time 'bins' before accumulation is restarted by the ectopic beat. The increased number of counts in the early time bins results in overestimation of ejection fraction. This overestimation was also seen in some of the patient studies. Our model suggests that one ectopic beat in ten will cause considerable underestimation of EF, but it is difficult to predict the precise number of ectopic beats that will cause errors in estimation of EF, since this will depend on the varying time intervals and force of contraction caused by these and the subsequent postectopic beats. However, where inspection of the histogram of the RR-interval for the acquired multiple images shows more than 5% of the total beats accumulated occurring in a 'premature' frame, then these data should be re-examined with some technique that excludes the ectopic beats. In contrast, the coefficient of variation in the RR-interval histogram has to be greater than 10% before data distortion takes place for patients in sinus rhythm with a varying RR interval.

Our own method of excluding ectopic beats merely requires modification of a standard VTR system. A disadvantage is the additional 10 min replay time for a patient study, but in practice this is needed only for the relatively few patients with frequent ectopic beats. Apart from having to bulk erase, the only practical difficulty has arisen with heavily used, stretched tapes when the much lower tape tension at the site of the new head can allow the distorted tape to leave the surface of the head. This was overcome by a felt pressure pad to maintain tape-to-head surface contact. Other systems have been devised to exclude unwanted cardiac beats, but they have their own disadvantages. Acquisition in list mode requires very extensive memory storage if the image quality is to be maintained. In a typical study we accumulate 7 million counts from the precordium. A further disadvantage of list-mode acquisition is the invariable delay required for frame up at the end of the acquisition period. Another solution is to use a dedicated computer as a buffer between gamma camera and the main computer, but to date this is expensive. Buffer stores require direct memory access. Predictions of the RR interval from the patient's observed ECG and preselected limits on the computer acquisition time intervals provides a system that is less flexible if the patient's heart rate changes in an unpredictable way, as it will during exercise or other physiological and pharmacological maneuvers. Our studies do show that some method of excluding frequent ectopic beats is required if radionuclide ventriculography is to be available for all patients.

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