

**THE CAUSES AND SIGNIFICANCE OF  
QT DISPERSION  
AFTER MYOCARDIAL INFARCTION.**

Submitted for the degree of M.D.

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## **The causes and significance of QT dispersion after myocardial infarction.**

**J. M. Glancy.**

QT dispersion is an easily obtained measurement from the standard electrocardiogram, and is the maximum minus the minimum QT interval. QT dispersion might represent dispersion of ventricular repolarisation, and be a marker of arrhythmic substrates.

The main aim of the thesis was to explore a possible association of increased QT dispersion with death after myocardial infarction. In a preliminary study of 20 patients with acute myocardial infarction, QT dispersion was increased on day 1, increased to a maximum on day 3, and was falling by hospital discharge. A case-control study was undertaken in which 163 patients who subsequently died were drawn from the placebo arm of a large randomised trial in myocardial infarction and were matched with surviving controls. Comparison of QT dispersion measured on day 2 or 3 in patients who subsequently died and those who survived showed no association between QT dispersion and mortality. However in the subset of patients for whom later electrocardiograms were available, a significant association between mortality and late QT dispersion was observed. However these patients may represent a selected population.

The mechanism of increased QT dispersion remains unclear. QT dispersion measurements in patients undergoing angioplasty, or with dilated cardiomyopathy, indicated that neither acute ischaemia nor left ventricular size were satisfactory explanations for increased QT dispersion.

It became apparent that there were methodological problems in QT dispersion measurement. Estimates of the reproducibility of QT dispersion in the post-infarct situation were made, and problems with automated measurement of QT dispersion identified. "Lead adjustment" formulae were shown to be inappropriate. A simplified measurement protocol was proposed.

In summary, dynamic changes in QT dispersion following infarction have been confirmed, but early dispersion measurements fail to predict mortality. Failure of QT dispersion to return to normal is associated with increased mortality, but both the validity of this observation and its mechanism require further evaluation.

This work is dedicated to my son Thomas.

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CHAPTER 1.  
INTRODUCTION.

### *1.1 Introduction.*

My principal aim in this thesis has been to study the relationship of electrocardiographic QT dispersion and survival after myocardial infarction. In this introduction, I have first discussed the epidemiology of death after myocardial infarction, with emphasis on definitions of sudden death. I have then reviewed current techniques for post myocardial infarction risk stratification. Finally, I have discussed and reviewed the literature on QT interval and QT interval dispersion measurements in relation to prognosis.

### *1.2. Sudden Death after Myocardial Infarction.*

#### **1.2.1. Size of Problem ( Total Mortality ).**

Sudden, unexpected death following myocardial infarction is a major cause of mortality in patients who survive the acute phase of the infarct. The early prognosis of acute myocardial infarction has been improving steadily over the last 25 years, even during the pre-thrombolysis era (McGovern et al. 1991), although there was some doubt as to whether this improvement applied to longer term prognosis (De Vreede et al. 1991). Since these data were collected the major impact upon early mortality after myocardial infarction has been thrombolysis (ISIS-2. 1988), resulting in a dramatic improvement in 1 year mortality (Zaret et al 1995). However the long term mortality data from the GISSI study (GISSI. 1987) suggested that the benefit from thrombolysis was a reduction in mortality during the hospital phase, death rates comparing controls and cases were equal for patients who survived to hospital discharge. Therefore mortality in the post hospital phase of myocardial infarction remains a largely unresolved issue.

Absolute values for mortality after myocardial infarction are difficult to ascertain. Most data comes from clinical trials, patient selection means that it is unlikely that mortality rates quoted in trials can be generalised to the wider population. The mortality rates in the placebo arms of the ISIS-4 study (ISIS-4. 1995) were approximately 7% at 5 weeks and 12.5% at 1 year. In the LIMIT-2 study (Woods and Fletcher. 1994) the 1 year placebo mortality was 16%. The only United Kingdom observational study of mortality in the thrombolysis era (Stevenson et al. 1993) showed a 30 day mortality of 16%, and a one year mortality of 21.7%. With an annual incidence of acute myocardial infarction of 4 per 1000 total population (Petch. 1989) in the United Kingdom, the high mortality rates for patients who survive to hospital admission means that mortality following myocardial infarction remains a major public health issue.

#### **1.2.2. Size of Problem ( Sudden Death ).**

In the Framingham heart study of 4,545 healthy individuals studied for 28 years, 251 suffered sudden cardiac death (Cupples et al. 1992). It has been estimated that sudden cardiac death is responsible for between 300,000 and 400,000 deaths per year in the United States. (Hurwitz and Josephson. 1992), and between 50,000 and 100,000 deaths per year in the United Kingdom (Pye and Cobbe. 1992). These figures refer to a rather heterogeneous group of causes of mortality including primary ventricular fibrillation during the first hours of acute myocardial infarction, pump failure due to massive myocardial infarction, and miscellaneous other causes. However in some, perhaps the majority of these patients, sudden cardiac death is caused by an arrhythmic

substrate resulting from a previous myocardial infarction. This is the group of interest in this thesis.

The largest study of sudden cardiac death in the post-hospital period after acute myocardial infarction comes from the Multicentre Diltiazem Post-Infarction Trial (Sweeny et al. 1992). This is also probably the most useful study as it identified instantaneous cardiac death, implying an arrhythmic death caused by a substrate from the previous myocardial infarction, rather than death from re-infarction. During the 12 to 52 month follow-up there were 252 cardiac deaths (76%) and 81 non-cardiac deaths (24%) from 2,466 patients enrolled. Seventy-four (32%) of the patients died instantaneously. One-hundred and twenty-three patients (54%) died more than 1 hour after onset of symptoms, implying that an old arrhythmic substrate was not the cause of death in these patients. The remaining 32 deaths (14%) were between 1 and 60 minutes. The mortality rate from sudden death was highest in the first few months post-infarction, with 50% of deaths occurring by 200 days of follow-up, but there was a significant attrition rate due to sudden cardiac death throughout the period of the study. Other studies of sudden death after myocardial infarction have involved hundreds rather than thousands of patients, with the end point of sudden death measured in tens of patients (Moss et al. 1977, The Multicentre Postinfarction Research Group. 1982, Bigger et. al 1984, Mukharji et al. 1984). Their definitions of sudden death have also tended to be less rigorous. They confirm that mortality from sudden cardiac death is a high proportion of total mortality in patients who survive to hospital discharge following myocardial infarction; ranging from 37% (The Multicentre Postinfarction Research Group. 1982) to 62% (Moss et al. 1977). They also confirm that mortality

from sudden cardiac death is at its highest in the first few months post-infarction. No similar studies have been performed in the United Kingdom.

#### **1.2.2. Definitions of Sudden Cardiac Death.**

In any randomised or observational study the end-point of the study must be clearly defined if any useful information is to be obtained from that study. Definitions of the end-point of sudden cardiac death have varied widely in clinical studies. A problem is differentiating sudden death due to acute myocardial infarction or acute coronary occlusion from that caused by a previously formed arrhythmic substrate. Without post-mortem evidence such a differentiation may prove impossible on clinical grounds (Lovegrove and Thompson. 1978). Sudden cardiac death in the setting of acute myocardial infarction may well be the result of the effects of ischaemia and catecholamines upon a pre-existing arrhythmic substrate, therefore an attempt to separate sudden cardiac death resulting from acute myocardial infarction and that caused directly by an old arrhythmic substrate may well be rather artificial. The "official" definition of sudden unexpected death, endorsed by the International Society of Cardiology and the American Heart Association, remains as death occurring within 24 hours of acute onset of signs or symptoms (Paul and Schatz. 1971). This clearly will include many different causes of death, and cannot be considered a useful end-point for any study of sudden cardiac death. The most widely used definition of sudden death is unexpected death occurring within 1 hour of onset of symptoms, combined with unexpected unwitnessed death, and unexpected death during sleep. Use of this definition will still result in a proportion of deaths in which an arrhythmic substrate is not important. Other studies use instantaneous death as a definition for sudden cardiac

death. This definition has the advantage that all deaths will probably be related to an arrhythmic substrate. The disadvantage of this approach is that patients who die because of the effects of modulation of an arrhythmic substrate, for example by acute myocardial infarction, would be excluded. In addition to the problem of definitions, there are major problems with retrospective collection of information, with the majority of sudden deaths occurring outside hospital (Gillum. 1988). The best approach to the problem would seem to be to present data on total mortality alongside any data on sudden death, the latter being treated with caution.

### *1.3. Pathophysiology of Sudden Cardiac Death.*

The only direct evidence that the mechanism of sudden cardiac death in most instances is from ventricular tachycardia comes from patients wearing ambulatory electrocardiograms (ECGs) at the time of cardiac arrest (Nikolic et al. 1982, Kempf and Josephson. 1984). These patients are selected, as they were suspected to have ventricular arrhythmias, hence the reason for the ambulatory monitoring. In the largest study (Kempf and Josephson. 1984) 27 patients were studied, sudden death was associated with ventricular tachycardia or fibrillation in 20 cases. At least 3 beats of ventricular tachycardia preceded ventricular fibrillation in every case where ventricular fibrillation was the terminal rhythm. The remaining 7 patients died from bradycardias, this is in keeping with the widely quoted figure of 25% of sudden cardiac deaths being related to bradycardias. In Kempf's study most of the bradycardic deaths were in patients with heart failure, he also postulates that antiarrhythmic drugs may have caused the bradycardias in some patients.

The mechanism underlying most ventricular tachycardia is thought to involve a re-entry circuit (El- Sherif et al. 1976) and relies on an area of slow conduction, and unidirectional block.

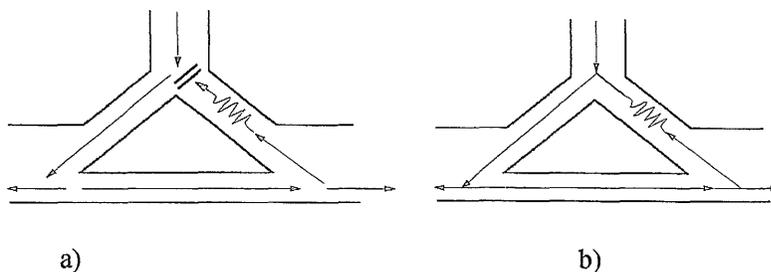


Figure 1.1 - Re-entry circuit of ventricular tachycardia (area of slow conduction is shaded).

In a) of figure 1.1 although the retrograde passage of conduction, usually generated from a ventricular ectopic beat, is slowed through the abnormal area of myocardium, it meets the anterograde conduction in a region of myocardium which is still refractory, and therefore cannot be propagated. However in b) either the timing of the retrograde conduction has altered, or the properties of the area of slow conduction have been changed. The retrograde stimulus now can enter the anterograde arm of the re-entry circuit at a point when it can be exited. A circus tachycardia is set up, and sustained ventricular tachycardia results.

Figure 1.1 illustrates the 2 requirements for ventricular tachycardia : an abnormal substrate in the myocardium, and a triggering factor for the tachycardia mediated either by inducing a ventricular ectopic beat, or by changing properties within the myocardium itself. The nature of the structural abnormality, and the functional triggering factor or factors remain the matter of considerable debate.

### **1.3.1. The Abnormal Myocardial Substrate.**

In patients with chronic coronary artery disease a number of possible structural abnormalities which could result in sudden cardiac death have been suggested. The major possibilities are acute myocardial infarction, an area of fibrosis resulting from old myocardial infarction, cardiac failure or remodelling resulting in stretch of cardiac fibres, and finally cardiac remodelling resulting not in simple mechanical stretch but in cardiac myocyte hypertrophy.

#### **◊ a) The role of acute myocardial infarction.**

Any evidence that acute myocardial infarction might play an important role in sudden cardiac death comes from post mortem studies. The largest reported series (Lie

and Titus. 1975) showed that 90-96% of patients with sudden cardiac death had chronic coronary artery disease. The incidence of acute myocardial infarction in that study ranged from 12 to 47%. Again a major problem is the definition of sudden cardiac death in studies, ranging from instantaneous death to death 24 hours after onset of symptoms. In a prospective study (Davies and Thomas. 1984) post mortem coronary angiography was performed in 100 patients who died less than 6 hours after onset of symptoms. The found evidence of coronary thrombi in 74 cases and plaque fissuring in 21 of the remaining 26 cases, implying that ischaemia plays an important role in sudden cardiac death. Only 1 study has compared post mortem studies of patients dying instantaneously with those dying suddenly (within 24 hours of onset of symptoms) (Friedman et al. 1973). From 25 instantaneous deaths only 1 acute thrombus was found at post mortem, there was no evidence in any patient of acute myocardial infarction. In contrast from 34 patients who died suddenly 28 patients had evidence of intraluminal thrombus, and 7 had suffered acute infarction. The true infarction rate may have been higher, as in some patients the histological changes of infarction may not have yet developed.

There appears to be a dichotomy between those patients dying very early after onset of symptoms, in whom ischaemia does not seem important; and those who die later, where acute myocardial ischaemia and possibly infarction plays a critical role.

◊ **b) Myocardial scarring.**

Intuitively it seems easy to understand how a scar might provide a substrate for arrhythmias. An impulse might meet an area of scar tissue, at this obstacle the impulse would divide into two. Patchy scarring in one arm might provide conditions for unidirectional block and slowed conduction, at the other end of the obstacle the

propagated impulse would enter this arm retrogradely, and a circus tachycardia result. An endocardial ultrastructure of normal Purkinje fibres and abnormal myocardial cells embedded in dense fibrous tissue at the border of healed myocardial infarcts has been described in patients undergoing myocardial resection for ventricular tachycardia (Fenoglio et al. 1983). It is felt that this border zone might provide the site of an arrhythmic substrate. There is, however, little direct evidence that myocardial scarring can provide an arrhythmia substrate.

◇ **c) Myocardial stretch.**

Poor left ventricular function is an important risk factor for sudden cardiac death. It has been postulated that simple myocardial stretch might alter the electrical properties of the left ventricle and provide a substrate for arrhythmias. Even in patients without heart failure it is possible to imagine how cardiac remodelling following myocardial infarction could provide such a substrate, with infarct expansion causing wall stress and myocardial fibre stretch. There is evidence in man that changes in ventricular volume load can alter ventricular repolarisation (Taggart et al. 1992); and in canine hearts with chronic infarctions that volume load can alter inducibility to ventricular tachycardias (Calkins et al. 1988). The most important clinical evidence comes from the V-HeFT II study (Cohn et al. 1992). This study compared treatment with enalapril and treatment with hydralazine and isosorbide dinitrate in patients with mild to moderate heart failure. Two year mortality in the enalapril arm was 18%, significantly lower than the 25% mortality in the hydralazine/nitrate arm. The difference in mortality was due to a reduction in sudden, mostly instantaneous, cardiac death. This study may suggest that the mechanism of action of enalapril is complicated,

but it is intriguing that a vasodilator drug working primarily on cardiac hemodynamics should influence sudden cardiac death.

◊ **d) Cardiac myocyte hypertrophy.**

Data from the Framingham heart study (Levy et al. 1990) showed that increased left ventricular mass is an independent risk factor for subsequent cardiovascular mortality. The well known association of sudden death with hypertrophic cardiomyopathy and aortic stenosis adds to the evidence that left ventricular hypertrophy might provide a possible arrhythmic substrate. Specifically, hypertrophied cardiac myocytes might express abnormal electrical activity through calcium channels (Hart. 1993).

**1.3.2. The Abnormal Electrical Substrate.**

The previous discussion focused on possible structural abnormalities underlying ventricular arrhythmias. However attempts at risk stratification for sudden cardiac death have tried to address the nature of the resulting electrophysiological abnormality. If anything this is an even more controversial area.

◊ **a) Dispersion of repolarisation.**

Interest in the QT interval and QT dispersion has developed following the hypothesis that abnormalities of cardiac repolarisation might be responsible for the genesis of ventricular arrhythmias. The association between nonuniform recovery of excitability and lowered ventricular fibrillation threshold was first shown clearly in the 1960's (Han and Moe. 1964). The possible arrhythmogenic role of increased dispersion of repolarisation has been demonstrated in dogs (Kuo et al. 1983). They recorded

monophasic action potentials from 6 sites in right and left ventricles, and then induced dispersion of the action potentials by a combination of generalised hypothermia followed by regional warm blood infusion. Ventricular arrhythmias did not occur spontaneously, but could be induced by a ventricular premature stimulus, but only when a critical value of dispersion of action potentials was reached. Moreover ventricular arrhythmias were only generated when the stimulus was applied at the site of a short monophasic action potential. It is easy to envisage how a propagated impulse from an area of short repolarisation would then encounter an area of long repolarisation, which would obviously still be refractory, and therefore eventually a re-entry circuit might be set up. However the experiment also demonstrates that the arrhythmias did not occur spontaneously, a triggering ventricular extrastimulus was required to generate the arrhythmias. Dispersion of repolarisation does not explain how such a trigger might arise.

Studies in humans (Vassallo et al. 1988, Yuan et al. 1995) have also demonstrated dispersion of monophasic action potentials in patients with ventricular arrhythmias. Vassallo and colleagues showed that dispersion of monophasic action potentials occurred in patients with congenital long QT syndromes and previous cardiac arrest, however in patients with coronary artery disease and ventricular tachycardia the dispersion in excitability was expressed not in dispersion of repolarisation but in dispersion of ventricular activation. The relationship between ventricular activation, monophasic action potentials, and total cardiac refractory period is shown in figure 1.2.

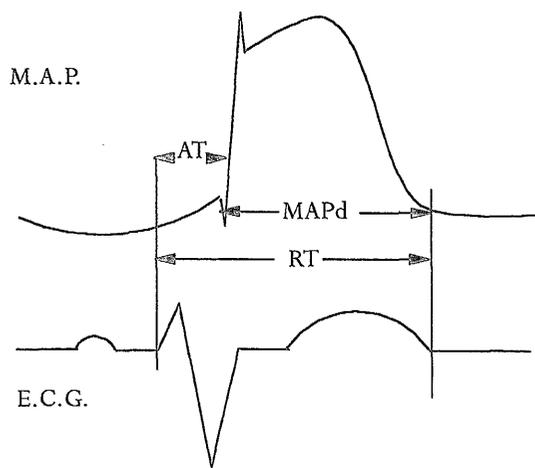


Figure 1.2 - The relationship of the ECG to the monophasic action potential.

MAPd = monophasic action potential duration. AT = ventricular activation time. RT = recovery time or total refractory period.

Figure 1.2 demonstrates that either dispersion of repolarisation or of ventricular activation could cause dispersion in total refractory period. The total period an area of cardiac tissue remains refractory is really the important factor in arrhythmia development, and although most evidence suggests that this is due in main part to cardiac repolarisation as measured by the monophasic action potential, ventricular activation and differences in the QRS complex may play a role.

The best clinical evidence that abnormalities of repolarisation are important in generating arrhythmias comes from the congenital long QT syndrome. Here right sided monophasic action potentials are markedly prolonged, probably due to an imbalance in

the autonomic nervous system. The condition predisposes to torsades de pointes, an unusual form of ventricular tachycardia defined by changing direction of the QRS axis and its association with a long QT interval (Schwartz. 1985). This tachycardia is usually precipitated by a period of bradycardia, and can be terminated and sometimes prevented by pacing at fast heart rates. Bradycardias produce relative shortening of the refractory period when compared to the total cardiac cycle, tachycardias produce the opposite result. Thus during bradycardia cardiac tissue is in an excitable state for a great proportion of the time, whereas during tachycardia cardiac tissue is refractory and unexcitable for a greater time. This is mediated through changes in the time of cardiac repolarisation (Singh and Nademanee. 1985), class III antiarrhythmic agents also probably work by this mechanism.

◇ **b) Automatic and triggered activity.**

Other possibilities exist for arrhythmogenesis. The definition of automatic activity is that it arises spontaneously in cardiac tissue, triggered activity requires a stimulus before it can occur. The best described triggered activity are afterdepolarisations, which require an action potential as their trigger. Two types have been described, early afterdepolarisations which occur during the plateau phase repolarisation of the action potential; and late afterdepolarisations, occurring after the action potential has been completed (Cranefield. 1977). Afterdepolarisations are positive potentials of only low voltage, but could reach the threshold potential to trigger inward flowing currents, and a depolarisation to be initiated. This action potential could then in turn trigger another afterdepolarisation, and a tachycardia initiated. There is experimental evidence linking early afterdepolarisations in particular to ventricular arrhythmias (Takahashi et al. 1991).

To complicate the issue further many of the conditions, both experimental and clinical, which could produce dispersion of repolarisation and favour re-entry can also produce afterdepolarisations (Surawicz. 1989). Moreover these 2 theories are not mutually exclusive.

### **1.3.3. Functional Triggers.**

In the current understanding of sudden cardiac death transient functional factors modulate the underlying structural abnormality to produce a ventricular arrhythmia, the electrical trigger being a ventricular extrasystole. It seems likely that an interaction of more than one factor may provide the functional trigger.

#### **◇ a) Myocardial ischaemia.**

The effects of acute ischaemia on cellular and regional electrophysiology has been extensively studied experimentally (Myerburg et al. 1989), and its potential role as a trigger for ventricular arrhythmias is well recognised. There are numerous theories about possible mechanisms of action including locally induced electrolyte imbalance (Gettes. 1992), acidosis (Orchard and Cingolani. 1994), or the generation of toxic compounds such as free radicals.

The high incidence of markers of ischaemic injury (Lie and Titus. 1975) and acute coronary artery thromboses (Davies and Thomas. 1984) in post mortem studies of the hearts of sudden cardiac death victims adds supporting evidence to the role of ischaemia in these deaths, however the problem of differences in the definition of sudden cardiac death, previously discussed, apply to these studies. In contrast there is a low reported incidence (12 to 26 %) of ST segment changes in patients undergoing

Holter monitoring at the time of cardiac arrest (Bayes de Luna et al. 1988), although Holter monitoring may not be a sensitive test for ischaemia.

◊ **b) The autonomic nervous system.**

There is strong experimental evidence that alterations in the autonomic nervous system may be important triggers of ventricular arrhythmias (Schwartz et al. 1992). Sympathetic activation may trigger arrhythmias and vagal activity may be protective. Furthermore myocardial infarction may alter autonomic responses in the heart, making the myocardium more susceptible to arrhythmias.

In patients following myocardial infarction abnormalities of autonomic function are associated with subsequent arrhythmic events (Farrell et al. 1991), and mortality (Kleiger et al. 1987). There is a circadian variation in sudden cardiac death with a peak between 9am and 11am (Hohnloser and Klingenhoben. 1994), with only 12% of cases occurring during sleep. It has been suggested that this variation parallels variation in the autonomic nervous system and provides further evidence for the role of autonomic activity in sudden cardiac death. The most compelling evidence for the importance of the autonomic nervous system is the effect of beta-adrenergic receptor blockers on ventricular arrhythmias, more importantly beta blockers are the only antiarrhythmic agent to consistently reduce mortality following myocardial infarction (Podrid et al. 1990).

◊ **c) Other factors.**

Electrolyte abnormalities may be important in some arrhythmias. Extracellular hypokalaemia and hyperkalaemia produce alterations in the depolarisation and repolarisation phases of the action potential, and can promote late afterdepolarisations. In patients with heart failure loop or thiazide diuretics could promote lethal

arrhythmias. Hypomagnesaemia and intracellular abnormalities of calcium and sodium may also be important factors. The arrhythmogenic mechanism of both ischaemia and the sympathetic nervous system may be modulated by local electrolyte disturbances in the myocardium (Gettes. 1992).

The potential proarrhythmic properties of antiarrhythmic agents should not be ignored. Since the CAST-1 study (CAST investigators. 1989) class I antiarrhythmic agents have been rarely used chronically following myocardial infarction, the proarrhythmic properties of newer agents may not yet be fully recognised.

#### *1.4. Risk Stratification for Sudden Cardiac Death following myocardial infarction.*

Many of the studies on risk stratification include the following terms which I shall define here for clarity:

Sensitivity is the proportion of positives that are correctly identified by the test.

Specificity is the proportion of negatives that are correctly identified by the test. Both these terms have only limited clinical application, as they do not take account of the prevalence of the abnormality in a sample, the predictive accuracy does take account of this.

The positive predictive accuracy is the proportion of patients with positive test results who are correctly diagnosed.

The negative predictive accuracy is the proportion of patients with negative test results who are correctly diagnosed. Although at first site the predictive accuracy appears much more useful, the selective nature of studies means that the prevalence of an abnormality in a sample may not reflect that in the larger population. Moreover where 2 or more diagnostic tests are applied for risk stratification in combination the statistics presented are often calculated from the proportion of patients with both tests abnormal or both tests normal. Patients with only one abnormal test may not be included in the analysis, therefore care must be taken when reading such studies.

I shall not address risk stratification for sudden death from reinfarction, but will concentrate on sudden death due to an arrhythmic substrate.

#### **1.4.1. Simple clinical methods**

Whilst in any individual study the association of variables such as site of infarction, presence of bundle branch block, presence of lung crepitations, and others have been associated with subsequent mortality these findings have not been confirmed in other studies. The only consistent findings are the association of heart failure, low ejection fraction, and ventricular premature beats with subsequent mortality following myocardial infarction.

#### **1.4.2. Left ventricular function.**

Left ventricular function has the strongest association with subsequent mortality following myocardial infarction of all clinical variables, and "outperforms" other more sophisticated tests as a risk stratifier (Kuchar et al. 1987). Certainly patients with normal ventricular function have a good prognosis. In a prospective angiographic study with a mean follow-up of 32 months (Sanz et al. 1982) of 79 variables examined, ejection fraction, number of diseased vessels, and the presence of cardiac failure on the coronary care unit were the only independent predictors of survival. Moreover a normal ejection fraction was associated with a 96 to 100 % survival, compared with a survival rate of only 30 to 75 % in patients with ejection fractions below 20 %. The presence of clinical heart failure confers an even worse prognosis. In a study of 972 patients (Nicod et al. 1988) the presence of clinical heart failure at any time on the coronary care unit was associated with a 26 % mortality compared to a 12 % mortality in patients without heart failure but with similar ejection fractions (less than 40%). Only 1 study has specifically addressed sudden death (Mukharji et al. 1984). Sudden death was identified in their study with an emphasis on primary ventricular tachyarrhythmia, and

patients followed-up for 2 years following infarction. Again numerous factors were examined, frequent ventricular premature beats and ejection fraction below 40 % were the only independent predictors of survival. Despite its prognostic importance, the predictive value of left ventricular ejection fraction alone is poor (Camm et al. 1994). Tests such as exercise echocardiography ,or measuring other aspects of ventricular function may prove more useful in risk stratification.

#### **1.4.3. Ventricular premature beats**

In order to identify patients who will die from ventricular arrhythmias it seems a reasonable approach to study pre-existing arrhythmias in patients following myocardial infarction. The first large study (Ruberman et al. 1981) was of 1 hour of cardiac monitoring performed on 1,739 male survivors of myocardial infarction. They found that complex ventricular premature beats (R on T, runs of 2 or more, multiform or bigeminal complexes) were associated with a threefold increase in sudden death. In a multivariate analysis they found that whilst congestive cardiac failure had the strongest influence on cardiac death, complex ventricular premature beats had the strongest influence on sudden death. Other data (Mukharji et al. 1984) concurs that ventricular premature beats have a stronger association with sudden death than that of ejection fraction. It has been suggested that the presence of ventricular premature beats is merely a marker for a low ejection fraction, but there are now many large studies showing that whilst there is some concordance between these 2 variables they do have independent predictive value (Ruberman et al. 1981, Bigger et al. 1984, Mukharji et al. 1984, Multicentre Postinfarction Research Group. 1984). The incidence of sudden death in patients with both left ventricular dysfunction and frequent ventricular

premature beats has been reported as 11 times that of patients with neither of these findings (Mukharji et al. 1984). The frequency of ventricular premature beats also appears to be important (Bigger et al. 1984, Multicentre Postinfarction Research Group. 1984). In the second study ventricular ectopic activity of greater than 10 per hour on 24 hour Holter monitoring was an independent predictor of mortality, less frequent ectopic activity was not. The 24 hour Holter monitor now seems to have become the accepted standard for risk stratification, with more than 10 premature ventricular beats per hour considered abnormal. Ventricular ectopic activity has seldom, if ever, been used alone for risk stratification, with no studies on the predictive value of this variable in isolation reported. It seems likely that its predictive accuracy alone is poor. Holter monitoring has been employed, sometimes in combination with ejection fraction, as selection criteria for more sophisticated or invasive tests. The danger of taking this strategy too far is that it may be possible to identify a population accurately who are at risk of sudden death, but whose size is so small to be meaningless in terms of both the total population and total number of sudden deaths identified.

#### **1.4.4. The resting ECG.**

Data specifically looking at the ECG as a prognostic indicator is limited, and the data inconsistent. The predischage ECG has been evaluated in 2 studies. In a study of 474 patients (Fioretti et al. 1987) QRS score (a complicated formula based on Q wave and R wave durations from all leads), and ST depression were independently predictive of cardiac mortality, however in a multivariate analysis they added nothing to information already provided by other clinical variables. In a study of 457 patients (Siltanen et al. 1985) certain aspects of the terminal P wave, ST depression and ST

elevation, QRS duration, and trifascicular block were associated with subsequent mortality. A larger study of 2,035 men (Coronary Drug Project Research Group. 1972) addressed mortality and the ECG recorded at least 3 months after myocardial infarction. Numerous abnormalities of the ECG were associated with subsequent mortality in univariate analyses, a multivariate analysis with other clinical factors confirmed many of the abnormalities to be independently predictive of an adverse prognosis, in particular "ischaemic-type" ST depression, Q waves, and left bundle branch block. The presence of T wave electrical alternans at the microvolt level on the ECG has only recently been evaluated as a predictor of arrhythmic events (Rosenbaum et al. 1994), but not specifically in patients following myocardial infarction.

#### **1.4.5. Late potentials on the signal-averaged ECG**

Over the last 2 decades, small high frequency signals have been identified near the end of the QRS complex of some ECGs. These are late potentials, and are thought to represent areas of slow conduction within the myocardium. As a result late potentials might provide some measure of potential arrhythmic substrates, and their presence has been tested as a risk stratifier in many studies. To record late potentials signal-averaging techniques are required. Usually the orthogonal leads X, Y, and Z are used. Several hundred ECG complexes are recorded, to remove noise, then band pass filtering employed to cut off the high frequency components. The low frequency signals remaining can then be magnified and used to detect late potentials. Late potentials are defined by 3 variables: the root mean square voltage of the terminal 40 ms of the signal-averaged complex, the duration of low amplitude signals less than 40 microvolts, and the duration of the total signal-averaged QRS complex. One or more abnormal

variables are used to define the presence of a late potential, however the definition of the values for abnormal variables varies with different studies. Other parameters in the measurement of the signal-averaged ECG also suffer from this lack of standardisation. Other limitations are problems of analysis of ECGs in atrial fibrillation or with bundle branch block. The timing of the signal-averaged ECG also appears to be important, with possibly the 6 to 14 day post infarct ECG being the most useful (El-Sherif et al. 1989). There are several commercially available machines available to record signal-averaged ECGs and measure late potentials.

The first major study of late potentials and prognosis after myocardial infarction was published in 1986 (Kuchar et al. 1986). One-hundred and sixty-five patients were prospectively assessed with signal-averaged ECGs recorded at hospital discharge and serially over the next year. During follow-up there were 11 patients who suffered an arrhythmic event (sudden death or sustained ventricular tachycardia). Detection of a late potential at hospital discharge predicted arrhythmic events with a sensitivity of 92 % and a specificity of 62 %. A similar study of 100 consecutive patients after myocardial infarction (Strasberg et al. 1993) resulted in very similar sensitivity (91 %) and specificity (60 %), but also reported predictive accuracy. The positive and negative predictive accuracies were 37 % and 96 % respectively. These data appear consistent with findings from others, a study of 182 patients (Steinberg et al. 1992) reported an excellent negative predictive accuracy of 95 %, but a poor positive predictive accuracy of only 15 % for late potentials in predicting 16 arrhythmic events. In a larger study of 332 patients (Odemuyiwa et al. 1992) an abnormal pre-discharge signal-averaged ECG had a positive predictive accuracy of 31 % for predicting sudden death and 13 % for predicting ventricular tachycardia at a sensitivity of 70 %. Thus on its own the

signal-average ECG appears good at identifying patients at low risk for sudden death and sustained ventricular tachycardia, but poor at predicting patients at high risk.

Two further issues have been addressed : whether late potentials added any further prognostic information to that obtained from either ejection fraction or holter monitoring, and whether the predictive accuracy of late potentials could be improved by their use in combination with other variables or by other strategies.

Data appear consistent that late potentials provide additional prognostic information to that obtained from ejection fraction (McClements et al. 1993, Kuchar et al. 1987), but that ejection fraction is probably the more powerful prognostic indicator. The presence of late potentials may to some extent reflect ventricular dysfunction (Kuchar et al. 1986), other data have shown no association (Gomes et al. 1987). There is conflicting evidence as to whether holter monitoring provides additional prognostic information further to a combination of ejection fraction and late potentials. The use of combinations of variables, particularly low ejection fraction and the presence of late potentials appears to improve predictive accuracy. In a study of 210 patients following myocardial infarction (Kuchar et al. 1987) the combination of an ejection fraction below 40 % and the presence of late potentials resulted in a 34 % probability of arrhythmic events, compared to a 4 % risk when both variables were normal. In another study (Gomes et al 1987) the combination of an abnormal ejection fraction, late potentials, and high grade ectopic activity had a subsequent arrhythmic event rate of 50 %. However combining tests undoubtedly reduces the specificity of them, in one reported study, to between 44 and 59 % (Gomes et al. 1987) for 2 abnormal tests. In this study the combination of all 3 abnormal tests gave a sensitivity of 100 %, but a specificity of only 53 % in the prediction of arrhythmic events. As more tests are

employed in combination the population identified as being at risk becomes progressively smaller.

As well as the time domain analysis of the signal-averaged ECG, attempts at risk stratification using frequency domain analysis and spectral temporal analysis (Winters et al. 1992). Neither technique has proven any superior to the traditional method, but has not been extensively tested.

Late potentials appear to have excellent predictive accuracy for predicting inducibility of sustained ventricular tachycardia at ventricular stimulation studies (Nalos et al. 1987, Nogami et al. 1991), with a reported sensitivity of 93 % and a specificity of 94 % in the first study. This questions whether ventricular stimulation studies add anything to the information already provided by the non invasive signal-averaged ECG, and also suggests that ventricular stimulation studies may be no better a predictor of events than the signal-averaged ECG.

#### **1.4.6. Heart rate variability and baroreflex sensitivity.**

The experimental evidence that abnormalities of the autonomic nervous system might provide the trigger for ventricular arrhythmias has lead to a number of clinical studies in patients following myocardial infarction (Schwartz et al. 1992). Two types of measurement have been tested. The first are based on heart rate variability from Holter monitoring. The simplest measurement is the standard deviation of R-R intervals over 24 hours, but many other time domain measures of heart rate variability have been described (Stein et al. 1994). These time domain analyses are thought to provide a reliable marker of cardiac vagal tone, a low heart rate variability might confer an adverse prognosis. In addition to the time domain analyses a number of more

complicated frequency domain analyses have been described (Stein et al. 1994). A more dynamic test is that measuring baroreceptor reflex activity. Here baroreflex sensitivity is expressed by a slope of the regression line correlating R-R interval lengthening with blood pressure increases induced by the pressor agent phenylephrine. Whereas heart rate variability is thought to reflect vagal tone, baroreflex sensitivity is probably a measure of induced vagal reflex activity.

◇ **Heart rate variability.**

Most clinical studies of autonomic function and prognosis after myocardial infarction have studied heart rate variability. The largest early study was by Kleiger and colleagues (Kleiger et al. 1987). They studied the standard deviation of R-R intervals over 24 hours in 808 patients following myocardial infarction, just prior to hospital discharge. Over a mean follow-up of 31 months the group of patients with a heart rate variability of less than 50 ms had a 5.3 times mortality rate, as compared to the group with a heart rate variability of greater than 100 ms. There was a weak association of heart rate variability with ejection fraction in this study, this finding has been confirmed by others (Odemuyiwa et al. 1991, Farrell et al. 1991). However taking into account ejection fraction, holter and other clinical variables, heart rate variability remained an independent predictor of mortality. In a similar study of 177 patients (Cripps et al. 1991) heart rate variability appeared to be the most powerful predictor of sudden death and arrhythmic events as compared to ejection fraction or the presence of late potentials, another study has also shown heart rate variability to be superior to ejection fraction in this sense (Odemuyiwa et al. 1991). However heart rate variability measured alone falls into the pitfall of other risk stratifiers, it is able to identify patients with a good prognosis, but has poor positive predictive accuracy. In Cripps and

colleague's study the negative predictive accuracy for sudden death and arrhythmic events was 98 %, but the positive predictive accuracy was only 15 %. In another study of 433 patients following myocardial infarction (Odemiuyiwa et al. 1994) the positive predictive accuracy of heart rate variability for predicting sudden death was only 12 %.

Frequency domain analyses of heart rate variability have been tested in 2 studies, and may be superior as a risk stratifier to time domain analyses (Bigger JT Jr et al. 1993). They measured several power spectral measures of heart rate variability in 715 patients 2 weeks after myocardial infarction. An advantage of their system was that only 2 to 15 minutes of ECG recordings were required for analysis. They reported positive predictive accuracies for total mortality of between 24 and 31 % for various frequency domain measures of heart rate variability. However this was no better than the positive predictive accuracy of the presence of crepitations, New York Heart Association grade of heart failure, or ejection fraction in their study. They did not report the negative predictive accuracies. Furthermore a combination of a measure of ejection fraction and a measure of heart rate variability provided an improved positive predictive accuracy, but the number of patients in a high risk category as defined by these 2 abnormal measurements was considerably reduced by this strategy. Vaishnav and colleagues (Vaishnav et al. 1992) analysed both time and frequency domain measures of heart rate variability in 226 consecutive survivors of myocardial infarction, and found an association with mortality using either parameter. They provided evidence using frequency domain analysis that the sympathetic nervous system might be important in arrhythmia production. The more complicated frequency domain method of analysis can provide information about both arms of the autonomic nervous

system, whereas time domain analysis can only provide a measure of parasympathetic tone.

Another approach is to combine the presence of late potentials with heart rate variability in risk stratification (Farrell et al. 1991). Intuitively this method has the appeal of combining a measure of the arrhythmic substrate with a measure of the functional arrhythmic trigger. Four-hundred and sixteen consecutive survivors of myocardial infarction were studied. Various clinical and other assessments were made including ventricular ectopic activity and ejection fraction. Impaired heart rate variability was the most sensitive predictor of arrhythmic events at 92 %, but its specificity was sufficiently low at 77 % to produce a significant number of false positives and a low positive predictive accuracy (17 %). The negative predictive accuracy was also fairly low at 77 %. The authors concluded that the combination of low heart rate variability and the presence of late potentials provided the best degree of risk stratification for arrhythmic events in their study. This combination produced a sensitivity of 58 %, a specificity of 93 %, a positive predictive accuracy of 33 %, and a negative predictive accuracy of 93 % for arrhythmic events. However this combination of an abnormal heart rate variability and the presence of late potentials identifies only 10 % of their patients as being at risk. Their study did not provide the raw data on numbers of patients at risk identified by each method, but it appears from their data that their "best" combination of late potentials and heart rate variability correctly identified 3 % of patients who had a subsequent arrhythmic event from the total group studied, whilst 17 % of these patients actually had an arrhythmic event.

♦ **Baroreflex sensitivity.**

There have been 2 relatively small studies of baroreflex sensitivity as a prognostic indicator following myocardial infarction, but both suggest that this measure may be at least as useful as the other methods described in this chapter. In both studies there was no association of baroreflex sensitivity with heart rate variability, suggesting they are measuring different aspects of the autonomic nervous system. Moreover there was no association of baroreflex sensitivity with ejection fraction in either study. The baroreflex sensitivity may provide a measure of the reaction of vagal activity to various stimuli, for example ischaemia or emotional stress, which may be more relevant in studying potential triggers to an arrhythmic substrate than the resting vagal tone.

In the first study La Rovere and colleagues (La Rovere et al. 1988) measured baroreflex sensitivity in 78 consecutive male patients 4 weeks after myocardial infarction. Mean follow-up was 2 years. Sixty-eight patients had a baroreflex sensitivity above 3 msec/mm Hg, and a mortality of 2.9 %. The 10 patients with a baroreflex sensitivity below this value had a mortality of 40 %. In a study of 122 patients (Farrell et al. 1992) there were 10 arrhythmic events during 1 year follow-up. Baroreflex sensitivity was recorded 7 to 10 days after myocardial infarction. Late potentials, heart rate variability, ventricular ectopic activity, and ejection fraction were also measured. A baroreflex sensitivity of less than 3 msec/mm Hg was a better prognostic indicator for arrhythmic events than any other of these variables; with a sensitivity of 80 %, a specificity of 91 %, and a positive predictive accuracy of 44 %. In another study by the same group (Farrell et al. 1990) baroreflex sensitivity was tested as a predictor of induction of ventricular tachycardia at ventricular stimulation studies, and again performed better than the other variables. One of the main disadvantages of the method

of baroreflex sensitivity measurement used in these studies is that intra-arterial cannulation was required, non invasive methods of measurement have been developed but not tested (Farrell et al. 1992).

The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) is an ongoing study of 1,200 patients measuring both various aspects of heart rate variability and baroreflex sensitivity which should provide important information about the importance of these measures after myocardial infarction (Schwartz et al. 1992).

#### **1.4.7. Ventricular stimulation studies.**

There have probably been more papers about ventricular stimulation studies as a predictor of arrhythmic events and mortality after myocardial infarction than of any of the other prognostic indicators discussed in this chapter. Moreover ventricular stimulation studies have an established clinical role in the risk stratification of patients who have survived cardiac arrest or sustained ventricular arrhythmias (Garratt. 1994). However even in that population there are limitations in the accuracy of the technique to identify patients at risk of recurrent events (Wilber et al. 1988, Forogos et al. 1992).

There are studies examining unselected survivors of myocardial infarction, but most have concentrated on "high risk" patients. Comparison between studies is often difficult due to the different populations studied. A further problem is the different protocols used for ventricular stimulation studies. In all studies an electrode catheter is passed transvenously into the right ventricle, where programmed electrical stimuli can then be applied. However the protocols then vary, with anything from 1 to 5 extrastimuli being applied before inducibility or non-inducibility of ventricular arrhythmias is decided. Also some studies provide stimuli at only the right ventricular

apex; whereas most investigators use both the apex, and if this site is non-inducible the right ventricular outflow tract. Occasionally the left ventricle has also been used (Wilber et al. 1988), or intravenous infusions given to render the heart more excitable (Forogos et al. 1992). The definition of inducibility and a positive result also varies between studies from inducibility of any short lived arrhythmia (Forogos et al. 1988) to sustained ventricular tachycardia (Buxton et al. 1984). The "best" stimulation protocol appears to use up to 3 extrastimuli at the right ventricular apex, then the right ventricular outflow tract, and possibly the left ventricular apex. The "best" definition of inducibility appears to be onset of sustained ventricular tachycardia lasting more than 10 seconds, and requiring cardioversion or overdrive pacing to terminate the induced arrhythmia.

◊ **"Unselected" survivors of acute myocardial infarction.**

From 1982 to 1986 numerous mortality studies in unselected survivors of acute myocardial infarction were published and provided conflicting data. At least 3 studies showed no association of mortality with inducibility of ventricular arrhythmias at ventricular stimulation studies (Bhandari et al. 1985, Marchlinski et al. 1983, Santarelli et al. 1985). These studies were all of less than 50 patients and each identified very few deaths, a type II error may well explain why these studies produced completely negative results. One larger study of 150 patients studied a mean 12 days after myocardial infarction (Roy et al. 1985) identified 7 patients with subsequent arrhythmic events. Ventricular stimulation studies were carried out at 2 ventricular sites, with a maximum of 2 extrastimuli applied, a fairly non-invasive protocol. A positive result was defined as induction of 6 or more beats of ventricular tachycardia which is a fairly liberal definition of a positive study. Using these criteria there was no

association for positive ventricular stimulation studies with subsequent arrhythmic events.

A much larger series was reported in 1986 (Denniss et al. 1986). Four-hundred and three well survivors were studied 1 month after acute myocardial infarction. A maximum of 2 extrastimuli were applied at a maximum of 2 ventricular sites, a positive study was defined if ventricular tachycardia or fibrillation lasting more than 10 seconds was induced. Two-year follow-up revealed that inducibility of ventricular tachycardia was positively associated with subsequent arrhythmic events. There was an association of inducibility with low ejection fraction, but both these factors were independently associated with arrhythmic events. Inducibility of ventricular tachycardia revealed a sensitivity of 52 %, a specificity of 82 %, a positive predictive accuracy of 18 %, and a negative predictive accuracy of 96 % for the prediction of instantaneous deaths and non fatal ventricular tachycardia or fibrillation. However delayed potentials on the signal-averaged ECG performed equally well as a predictor of events in this study, other data conflict with this and suggest that ventricular stimulation studies are a better predictor of arrhythmic events than late potentials, ejection fraction or holter monitoring (Richards et al. 1991). Inducibility of ventricular fibrillation was not associated with subsequent events in Denniss and colleague's study (Denniss et al. 1986), another study has also shown that inducibility of ventricular flutter or fibrillation should be considered a negative result (Bourke et al. 1995). The timing of ventricular stimulation studies may also be important (Nogami et al. 1991). Even though the numbers studied here were small, patients studied 36 days after infarction produced better results in terms of prediction, than did the same tests performed at 19 days post-infarction. Positive data has been reported by others (Cripps et al. 1989, Iesaka et

al. 1990), with positive predictive accuracies for arrhythmic events of between 36 % and 75 %, but the numbers involved in each study were relatively small.

By far the largest experience of ventricular stimulation studies in unselected survivors of myocardial infarction comes from Australia. The results of electrophysiological testing before hospital discharge in 1,209 survivors of acute myocardial infarction between 1980 and 1988 (Bourke et al. 1991) were reported. Over 3,000 patients were screened; of those then excluded 35 % refused entry to the study, 33 % had uncontrolled ischaemia or heart failure, and 29 % were over 70 years old. Sustained monomorphic ventricular tachycardia was inducible in only 75 (6.2 %) of the patients. Over a median of 28 months of follow-up 19 (25 %) of these inducible patients experienced arrhythmic events, 5 (37 %) of these events were fatal. The converse aspect of this study is that 35 (3 %) of patients who were non-inducible suffered arrhythmic events, and that 56 (75 %) of the inducible patients did not suffer subsequent arrhythmic events. A problem with the data is that the protocol for electrophysiological testing changed over the years of the study, but none the less their data do not support the use of routine ventricular stimulation studies in patients following myocardial infarction. Although ventricular stimulation studies might be the best predictor of events in this population, the performance of 2 non-invasive tests may produce equally comparable results (Viskin et al. 1994).

◇ **Ventricular stimulation studies in selected "high risk" patients.**

In Bourke and colleagues (Bourke et al. 1991) large Australian series the role of ejection fraction was examined. Where ejection fraction was measured, 30 % of the sample had an ejection fraction below 40 %, and 20 % of these patients had a positive study. The strategy of only performing ventricular stimulation studies in patients with

ejection fractions of less than 40 % would improve the positive predictive accuracy of the test from 20 % for the total sample to 28 %, with acceptable loss of sensitivity (73 % vs. 64 %), and no loss of negative predictive accuracy.

Extending this strategy 3 studies have examined the role of ventricular stimulation studies in survivors of myocardial infarction complicated by heart failure or arrhythmias during the hospital phase. Seventy patients were studied 7 to 20 days after complicated myocardial infarction (Hamer et al. 1982), using a protocol of up to 2 extrastimuli at 2 right ventricular sites, and a definition of inducibility as sustained ventricular tachycardia or more than 5 beats of self-terminating ventricular tachycardia. At 1 year follow-up there had been 12 cardiac deaths, 9 of which were sudden. Twenty of the patients had been defined as inducible, and 5 of the cardiac deaths, of which 4 were sudden, came from this group. In a similar study of 50 patients (Waspe et al. 1985) 17 patients had inducible tachycardias, 7 (41 %) of these had subsequent arrhythmic events over a mean 23 month follow-up. None of the 33 patients in the non inducible group had a subsequent arrhythmic event. However if all cardiac deaths were taken into account there was no difference between the 2 groups, the results of this study depend on the definition of sudden death, although a fairly strict criteria of witnessed instantaneous death or unexpected death during sleep was used. In a larger more recent study (Bhandari et al. 1991) 86 patients with myocardial infarction complicated by heart failure, angina, or non-sustained ventricular tachycardia were studied. To obtain this sample 416 patients with acute myocardial infarction were screened, 151 were eligible for enrolment, and 65 excluded for various reasons including emergency intervention. An aggressive protocol was used, and sustained ventricular tachycardia requiring termination used as the definition of inducibility.

Nineteen patients were inducible. In this group there were 4 sudden deaths, 2 patients with spontaneous sustained ventricular tachycardia, and 3 non sudden cardiac deaths during an average follow up of 18 months. Amongst the remaining 67 patients there were 3 sudden deaths, 2 patients with spontaneous sustained ventricular tachycardia, and 7 non sudden cardiac deaths. The sensitivity of a positive study in predicting arrhythmic events was only 55 % in this study with a positive predictive accuracy of 32 %.

Alternative strategies of pre risk stratification have been employed. As ventricular ectopic beats on Holter monitoring are a risk factor for mortality, the role of ventricular stimulation studies in patients with non-sustained ventricular arrhythmias has been explored (Kowey et al. 1990, Winters et al. 1993). In both studies inducibility of ventricular arrhythmias were poor predictors of subsequent arrhythmic events in patients with previous myocardial infarction and non-sustained ventricular arrhythmias on holter monitoring. In both studies the patients studied had remote myocardial infarction, the role of ventricular stimulation studies in such patients with recent myocardial infarction has not been examined.

In an important study by Pedretti and colleagues (Pedretti et al. 1993) patients were preselected for ventricular stimulation studies if they had 2 or more abnormal non-invasive tests after myocardial infarction. These non-invasive variables were an ejection fraction less than 40 %, the presence of late potentials on the signal-averaged ECG, or repetitive ventricular premature complexes on Holter monitoring. Three-hundred and five consecutive patients who had survived 30 days after myocardial infarction were evaluated. Only 22 patients were excluded from the study, mean follow-up was 15 months. Sixty-seven patients had 2 or more abnormal

non-invasive tests, this strategy predicted subsequent arrhythmic events with a sensitivity of 87 %, a specificity of 88 %, a positive predictive accuracy of 30 %, and a negative predictive accuracy of 99 %. Forty seven (70 %) of these patients agreed to ventricular stimulation studies. Up to 3 extrastimuli were used, but only at 1 right ventricular site. A positive study was defined as the induction of sustained monomorphic ventricular tachycardia. Of these patients 20 (42 %) were inducible, subsequent arrhythmic events occurred in 13 of these 20 patients, compared to only 1 of the 27 patients who were non inducible. Only 6 arrhythmic events occurred in the remaining 236 patients. A positive ventricular stimulation study predicted arrhythmic events with little loss of sensitivity at 81 %, a specificity of 97 %, a positive predictive accuracy of 65 %, and a negative predictive accuracy of 99 %. Data on total and cardiac mortality is not presented. However the promising results obtained would certainly seem to merit a larger study using the same criteria.

#### **1.4.8. Conclusions.**

In conclusion there is no ideal single or combination of measures to risk stratifying patients for subsequent sudden, arrhythmic death following myocardial infarction. Whilst it is quite easy to identify patients with a good long term prognosis, it is much more difficult to identify patients at risk. The poor positive predictive accuracy of any single test could not be justified in selecting patients for implantation of a cardioverter-defibrillator device. Attempts to improve the positive predictive accuracy by combining measures of risk stratification result in reduced sensitivity, and the identification of very small numbers of at risk individuals when compared to the numbers in the total population studied.

### *1.5. The QT interval.*

The QT interval on the surface ECG represents the sum of uncanceled potential differences during ventricular depolarisation and repolarisation. There is evidence from animal and human studies that the end of the T wave approximates to the end of ventricular repolarisation (Surawicz and Knoebel. 1984). The QT interval is dependent upon many diverse factors. The ST segment is a measure of the plateau phase of the action potential. The duration of this part of the action potential appears to be dependent on heart rate, the extracellular calcium concentration, and catecholamines. The T wave corresponds to the rapid repolarisation phase of the action potential. T wave amplitude, morphology, and duration are altered by myocardial disease, the autonomic nervous system, the potassium concentration, and various drugs (Schweitzer et al. 1992). Important cardiac drugs that lengthen the QT interval are the class I agents quinidine, procainamide, and disopyramide; and the class III agents amiodarone and sotalol. Beta adrenergic blockers do not alter QT interval duration (Surawicz and Knoebel. 1984). The autonomic nervous system influences the QT interval both at the cardiac receptor level, and also by neural modulation, particularly via the cardiac stellate nerves (Rosen et al. 1992). The influence of the autonomic nervous system on cardiac repolarisation may be important in arrhythmogenesis. In this setting the QT interval might provide a measure of both an underlying arrhythmic substrate, but also of the influence of the autonomic nervous system, drugs, and other factors upon that substrate.

There are methodological problems with QT interval measurement, these will be dealt with at length in chapters 2 and 6. One important issue is the rate correction of the QT interval. The QT interval decreases with increasing heart rate. Numerous

formulae have been applied in an attempt to describe the relationship between the QT interval and heart rate (Ahnve. 1984), so that QT intervals at different heart rates can be compared meaningfully. None of the formulae tried are perfect, mainly because the relationship between the QT interval and heart rate probably varies, depending on the population studied. The formula which seems to be the most useful is that adapted from Bazett's original work in the 1920's, and is based on the square root of the R-R interval. Although this formula appears useful in most settings it does have limitations (Ward. 1988), particularly at high heart rates. The rate corrected QT interval is presented as the QTc. The upper limit of the normal QTc is often given as 440 ms. This value seems a fairly arbitrary measure with little evidence to attach any prognostic significance to it, but none the less is often used to dichotomise groups within studies. Another problem is the lack of any standard criteria of lead selection for measuring a QT interval. Different criteria include using lead II, the lead with the tallest T wave, the maximum QT interval in any limb lead, or the maximum QT interval in any lead (Cowan et al. 1988).

Renewed interest in the QT interval as a possible risk factor for sudden death came from a large study of a heterogeneous group of patients (Algra et al. 1991), a large study of healthy individuals (Schouten et al. 1991), and a study of patients following myocardial infarction (Schwartz and Wolf. 1978).

#### **1.5.1. Population studies.**

In the Rotterdam QT project (Algra et al. 1991) 6,693 consecutive patients who underwent 24 hour ambulatory electrocardiography were studied. This was a heterogeneous group of patients: 65 % having ambulatory monitoring to evaluate a

variety of symptoms, 8 % to evaluate therapy, 10 % as risk stratification after myocardial infarction, and 7 % as assessment following a transient ischaemic attack or stroke. These patients were followed for 2 years and 716 died, of whom 245 died suddenly, sudden death was defined as death within 1 hour of onset of symptoms. Patients with bundle branch block were excluded. In a case-cohort design the maximum QT interval from the limb leads of the 12 lead ECGs of 566 patients were measured. A QTc interval of greater than 440 ms was associated with a 2.3 times risk of sudden death compared to patients with a QTc interval of less than 440 ms. This only held true for patients without evidence of cardiac dysfunction. The relative risk remained the same after allowing for a number of factors including use of drugs and heart rate. In patients with cardiac dysfunction (presence of suggestive symptoms or an ejection fraction of less than 40 %) the relative risk of sudden death was 4.5 times that in patients without cardiac dysfunction. However the QTc interval, although prolonged when compared to that measured in patients without cardiac dysfunction, did not add to the risk of sudden death in this group. In an extension of their study (Algra et al. 1993) the mean QTc intervals were calculated from the 24 hour tapes of 513 patients in the cohort. A prolonged mean QTc interval of greater than 440 ms was associated with a 2.3 times risk of sudden death compared to patients with a mean QTc interval of between 400 and 440 ms, but intriguingly patients with a QTc interval below 400 ms also had a 2.2 times relative risk of sudden death. Variability in the QTc interval over short or long periods was not associated with sudden death in this study. This last finding runs contrary to suggestions that disturbances in the balance of the autonomic nervous system might be important in the pathogenesis of sudden arrhythmic death.

QT interval prolongation has also been proposed as a risk factor for mortality in apparently healthy individuals (Shouten et al. 1991). They studied 3,091 Dutch civil servants and their spouses, with 28 year follow up. As in Algra and colleagues' studies this had a case-cohort design, the ECGs of 2,053 patients at entry into the study were examined, and the maximum QT interval from the limb leads measured. QTc intervals were defined as normal below 420 ms, moderately prolonged between 420 and 440 ms, and extensive at greater than 440 ms. At 15 years the relative risk for all-cause mortality was 1.5 and 1.7 for men with moderately prolonged and extensively prolonged QTc intervals when compared to patients with normal QTc intervals. Similar relative risks for women were 1.7 and 1.6. The association at 28 years was much weaker. These risks were calculated after a multivariate adjustment for various factors, although no mention of drug therapy or heart rate is made. The only important confounder was age. The authors conclude that there are 3 possibilities that explain their data. Firstly that QT interval prolongation represents an imbalance of the autonomic nervous system and that this in itself is a risk for sudden death. Second that this imbalance may not reflect itself until the individual suffers a myocardial infarction, and develops a substrate for arrhythmic death. The third possibility is that QT prolongation may be a risk factor for the development of cardiovascular disease or may be a marker of silent ischaemia. Support for this third hypothesis comes from data from the same group (Dekker et al. 1994). In a similar study of 1,712 middle aged and elderly men from the town of Zutphen, a QTc interval of greater than 420 ms was associated not only with a high risk of sudden death, but also with coronary artery disease mortality and morbidity, and the development of acute myocardial infarction.

Conflicting data comes from evidence from the Framingham Heart Study (Goldberg et al. 1991). The baseline ECGs of all 5,125 original subjects in the study were examined, the average of 2 or 3 QT intervals from the lead with the longest QT interval was measured. Significantly longer QT intervals were recorded in females, older individuals and non-smokers. The population was divided into 5 groups depending on their QTc interval. At 30 year follow up there was no difference in total mortality, cardiovascular mortality, or sudden death between the groups. There was a trend, not statistically significant, towards increased mortality in patients with QTc intervals greater than 440 ms, or below 360 ms. There is a possibility that the differences observed between the studies in apparently healthy individuals is due to differences in the populations studied and data handling (Shouten et al. 1991, Shouten et al. 1994). However the studies appear broadly similar, in addition the fall in risk of mortality, both all cause and cardiovascular, from 15 to 28 years for patients with prolonged QTc intervals in the study of Dutch civil servants (Shouten et al. 1991) is not readily explainable.

#### **1.5.2. The QT interval and myocardial infarction.**

There is consistent evidence that QT and QTc intervals are prolonged during the hospital phase of acute myocardial infarction, and that they are maximal 24 to 48 hours after infarction (Doroghazi et al. 1977, Cinca et al. 1981, Ahnve et al. 1980). However following discharge from hospital the data is not as clear, 2 studies suggesting that after day 4 or 5 following infarction QTc intervals return to normal (Doroghazi et al. 1977, Cinca et al. 1981), other data show a progressive shortening in QTc intervals over weeks or months (Ahnve et al. 1980, Moller. 1981).

Early ventricular arrhythmias after myocardial infarction may be associated with prolonged QTc intervals. In a prospective study of 32 patients, 14 suffered early ventricular tachycardia and had longer mean QTc intervals than the other 14 patients by 50 to 60 ms, as recorded on the admission ECG (Taylor et al. 1981). These results are supported by a retrospective case control study (Ahnve et al. 1978), but other data showed no association between day 1 QTc intervals and early ventricular fibrillation (Forsell et al. 1981).

There is clear evidence that QTc intervals recorded on the discharge ECG are not associated with subsequent sudden death or mortality over long follow up periods, 3 studies each of around 500 patients producing similar negative results (Wheelan et al. 1986, Pohjola-Sintonen et al. 1986, Ahnve et al. 1980). The only positive data comes from a multicenter study of 865 patients by Ahnve and colleagues (Ahnve et al. 1984). In their total sample studied there was no association between discharge QTc interval measurement and subsequent mortality, but if patients on no medication or without pacemakers were studied a QTc value of greater than 440 ms yielded a sensitivity of 77% and a specificity of 84% for subsequent mortality. However this excluded 70% of the total sample studied, and it seems difficult to believe that these findings could be extended to clinical practice. One other positive abstract on the same theme has been published (Peters et al. 1984), but never printed as an article.

Two of the most interesting studies were published in 1978. Schwartz and Wolf studied ECGs every 2 months for 7 years in 55 survivors of myocardial infarction and 55 healthy controls (Schwartz et al. 1978). At the end of the study 28 of the patient group had died, and only 1 of the control group. In the 27 survivors mean QTc interval from all measurements taken over the 7 years was 429 ms, significantly different from

the 28 patients who died (QTc 443 ms). Heart rates were equal in both groups. Others agree that multiple QTc interval recordings may be more important than a single measurement (Ahnve et al. 1980). The other study compared QTc measurements in 125 survivors of out of hospital ventricular fibrillation with coronary artery disease and 98 ambulatory patients with previous myocardial infarction (Haynes et al. 1978). They found the mean QTc interval to be greater by 20 ms in the survivors of ventricular fibrillation, even when patients taking digitalis, diuretics, and other anti-arrhythmics were excluded. However there was a significant difference in the heart rate between the 2 groups.

There is 1 study relating QTc interval prolongation to sudden death in patients with chronic ischaemic heart disease (Puddu and Bourassa. 1986), the authors suggest that QTc prolongation might represent a simple way of monitoring patients at risk of sudden death in this population. A cohort of 1,157 patients with chronic ischaemic heart disease were available for study. Follow up over 4 years resulted in 141 deaths, and these were compared to 140 long term survivors from the same cohort. QTc interval measurements were similar between the 2 groups (423 vs. 421 ms). Sixty two patients died suddenly (death within 1 hour of onset of symptoms). There was no difference in QTc interval measurements from the ECG recorded at entry into the study in patients who died suddenly and any other group. In 33 patients who died suddenly 1 or more later ECGs were available. The mean QTc interval from these late ECGs was 444 ms, the difference in QTc dispersion measurements from early to late ECG in these patients was statistically significantly. There was no difference in QTc measurements from early to late ECG in any other group in the study, and it is on the basis of this that

the authors make their conclusions. However comparison of data in this way is not statistically valid.

Criticism of many of the positive studies of QTc intervals include the problem of lack of knowledge of drugs that could have effected the QT interval, the lack of multivariate analysis, the small numbers of patients studied, and the suggestion that the positive association of a prolonged QT interval with mortality may be more the result of differences in heart rate, leading to overcorrection by Bazett's formula (Ward, 1988). Although the data provide conflicting evidence it seems likely that an prolonged QTc interval is associated with subsequent mortality and sudden death in a number of settings. However the overlap in QTc interval measurements between groups makes it unlikely that QTc interval measurement is useful in risk stratification for a given individual. In concept the inter-lead variability of QT intervals, the QT dispersion, provides more information about regional variations in ventricular repolarisation, and therefore the potential for re-entry arrhythmias in patients following myocardial infarction.

### *1.6. QT dispersion.*

Historically QT intervals across the surface ECG have been viewed as being of uniform length. Mirvis (Mirvis. 1985), and others (Sylvén et al. 1984), measured QT intervals in multiple torso leads, and were the first to show that there was variation in QT intervals amongst these leads. This idea was later modified into the concept of QT dispersion as measured from the 12 lead standard surface ECG (Cowan et al. 1988). In this QT intervals are measured from all 12 leads and the QT dispersion calculated as the maximum minus the minimum QT interval. Data is usually presented as QT dispersion and rate adjusted QTc dispersion, although many other measurements have been described including the standard deviation of QT intervals and lead adjusted QT dispersion. Normal rate corrected values of QT dispersion are reported as between 20 ms and 50 ms, with values in the long QT syndromes rising as high as 200 ms (Higham et al. 1994). QT dispersion may reflect dispersion of ventricular repolarisation (Day et al. 1992). Any disparity in repolarisation between adjacent areas of myocardium could potentially support a substrate for re-entry tachycardias. Recent interest in QT dispersion has arisen from the possibility that this measurement might be a marker for such a substrate. Two studies in particular have suggested that QT dispersion might be an important predictor of arrhythmic events in patients with hypertrophic cardiomyopathy (Buja et al. 1993) and sudden death in patients with chronic heart failure (Barr et al. 1994). Further data suggest a less important role for QT dispersion as a predictor of events, but do reflect the view that QT dispersion might be a marker of an arrhythmic substrate (Pye et al. 1993), or may have a role in measuring drug efficacy (Hii et al. 1992, Priori et al. 1994). Others suggest QT dispersion is not a useful measurement (Davey et al. 1994, Leitch et al. 1995). The obvious advantage of QT

dispersion is that it is a non-invasive measurement, that can be simply obtained in all patients, and easily measured.

#### **1.6.1. QT dispersion and ventricular repolarisation.**

It is possible that QT dispersion is merely an artefact, reflecting inaccuracies in the measurement of T wave ends in different leads. In addition for any ECG lead the vector of repolarisation might be in the direction of that lead towards the end of repolarisation, resulting in an isoelectric terminal portion of the T wave in that lead, a short QT interval, and increased "artefactual" QT dispersion (Linker et al. 1992).

Until recently the only direct evidence that QT dispersion reflects ventricular repolarisation came from 1 published abstract (Higham et al. 1992). Monophasic action potentials were recorded from 12 ventricular sites, with simultaneous 12 lead ECGs in 8 patients undergoing cardiac surgery. QT dispersion and monophasic action potentials were compared in sinus rhythm and ventricular pacing. There was a positive correlation in the change in both parameters from sinus rhythm to pacing, but there was no data published as to whether a correlation existed at sinus rhythm or during pacing alone. Further indirect evidence for this view came from a previous study by the same group showing that QT dispersion measured in sinus rhythm was increased by ventricular pacing in 9 patients with normal ventricles, ventricular pacing would be expected to produce increased dispersion of repolarisation (Day et al. 1992). More recent supportive evidence that QT dispersion reflects dispersion of repolarisation comes from an animal study, examining the relationship of different measures of QT dispersion with monophasic action potentials in a rabbit model (Zabel et al. 1995). Ten isolated heart rabbits were studied, monophasic action potentials were recorded from 7 sites,

and an ECG closely resembling the surface ECG was also recorded. QT dispersion correlated with dispersion of action potential duration ( $r = 0.61$ ). Interestingly the T wave peak to T wave end interval, and the T wave area exhibited better correlation with dispersion of action potential, implying these variables might be a more accurate measure of dispersion of ventricular repolarisation.

#### **1.6.2. QT dispersion and the congenital long QT syndrome.**

Following the development of the concept of QT dispersion, the role of QT dispersion in a variety of conditions was studied. The congenital long QT syndrome was an obvious candidate, it had been recognised early on that QT dispersion measurements were greatly increased in these patients (Day et al. 1990). Published data on QT dispersion and risk stratification of patients with this condition illustrates the point that similar studies seem to produce diametrically opposite results and messages. This problem recurs in almost every condition in which QT dispersion has been measured. In a study of 9 patients with the congenital long QT syndrome, QT dispersion was not associated with severity of symptoms, nor influenced by beta blocking drugs, nor by left stellate ganglionectomy which is a recognised treatment in this condition (Linker et al. 1992). However ganglionectomy did produce a trend towards reduced QT dispersion, which did not reach significance probably because only 3 patients were studied.

In contrast a well-designed study of 28 patients with the Romano Ward syndrome produced very positive data (Priori et al. 1994). QT dispersion measurements were compared in 7 patients referred prior to any therapy, 10 patients rendered asymptomatic by beta blocker therapy, and 11 patients who remained symptomatic

with syncopal episodes despite beta blocker therapy. The mean QT dispersion of responders to therapy (75 ms) was significantly lower than in non-responders (133 ms), who had similar QT dispersion to patients prior to any therapy. Moreover the non-responders to therapy then underwent ganglionectomy which reduced their mean QT dispersion to 78 ms. This also one of the few studies to present data on predictive accuracy for QT dispersion measurements. In predicting patient responsiveness to beta blockade a cut-off value of QT dispersion of 100 ms gave a sensitivity of 80 %, a specificity of 82 %, a 73 % positive, and a 75 % negative predictive accuracy.

### **1.6.3. QT dispersion and hypertrophic cardiomyopathy.**

Left ventricular hypertrophy, without hypertrophic cardiomyopathy, produces an increase in QT dispersion (Davey et al. 1994). The first study of QT dispersion in patients with hypertrophic cardiomyopathy showed that amiodarone lengthens maximal QTc intervals, but reduces QTc dispersion (Dritsas et al. 1992). The only published article addressing arrhythmias in this population was by Buja and colleagues (Buja et al. 1993). Twenty-six patients with hypertrophic cardiomyopathy were studied, 13 without arrhythmias, and 13 with recent sustained or nonsustained ventricular tachycardia or fibrillation. The startling result was that all of the patients with arrhythmias had QT dispersion measurements above 60 ms, and all of the patients without arrhythmias had QT dispersion readings below this value, with no overlap between the groups. There are limitations of the data, patients were a selected sample, were not studied in the drug free state, and limited clinical or investigation data were known.

#### 1.6.4. QT dispersion during acute myocardial infarction.

All published data show that mean QT dispersion measurements are raised in the first few days after acute myocardial infarction to between 50 and 120 ms. This was first recognised in Mirvis's original study (Mirvis. 1985), which studied 30 patients on day 2 or 3 of acute myocardial infarction, and 50 controls. Here QT intervals were recorded from 150 torso leads. QT dispersion measurements using this method were equal for inferior and anterior infarction at about 100 ms, but the pattern of QT dispersion differed. Longest QT intervals in anterior infarction lay central to control readings, and those in inferior infarction were positioned more caudally.

The time course of QT dispersion during myocardial infarction is unclear. There is agreement that immediately following infarction QT dispersion measurements rise. QT dispersion may then start to fall (Higham et al. 1995), others suggest that it continues to rise, reaching a maximum at 24 hours post infarction (Cox et al. 1994). However QT dispersion certainly remains abnormal at hospital discharge, and may remain abnormal over the next few months (Day et al. 1991).

The TEAM-2 study investigators analysed factors influencing QT dispersion measured from ECGs recorded 10 days after myocardial infarction in a prospective angiographic study of 244 patients (Moreno et al. 1994). QT dispersion was not influenced by age, sex, nor by choice of leads in which minimal and maximal QT intervals were measured. The major influence on QT dispersion was the TIMI grade in the infarct related vessel. Mean QT dispersion for occluded vessels was 96 ms, compared to 58 ms where flow was normal. QT dispersion was also greater in patients with left descending coronary artery occlusion, and in patients with anterior infarction. The authors conclude that by establishing patency, thrombolytic therapy may reduce

the degree to which an abnormal electrophysiological milieu develops after myocardial infarction. However the study does not include data on ventricular function, it is possible that both the TIMI grade and QT dispersion are reflecting the degree of left ventricular dysfunction, rather than an abnormal electrical substrate.

#### **1.6.5. QT dispersion and primary ventricular fibrillation.**

Higham and colleagues studied admission ECGs from 30 patients with acute myocardial infarction prospectively (Higham et al. 1995). Four patients had an episode of primary ventricular fibrillation, and had greater QT dispersion measurements when compared to patients with an uncomplicated infarct (87 ms vs. 66 ms). Other data are in agreement with this (Van de Loo et al. 1994). In this study 11 out of 77 patients with myocardial infarction suffered primary ventricular fibrillation. Comparison of QT dispersion from the admission ECGs produced almost identical results to Higham's data. In contrast a case control study has shown no association of QT dispersion with early ventricular fibrillation (Leitch et al. 1995). The admission ECG of 24 patients with acute myocardial infarction and ventricular fibrillation within 12 hours of admission were compared to 24 patients without ventricular fibrillation, matched for site of infarction and degree of ST segment elevation. QT dispersion measurements were almost equal in each group (68 ms vs. 66 ms).

#### **1.6.6. Drug effects on QT dispersion after myocardial infarction.**

The first study of QT dispersion, measured from the 12 lead ECG, in patients with myocardial infarction looked at the effect of sotalol on QTc dispersion (Day et al. 1991). This was a randomised study comparing placebo (28 patients) to sotalol (39

patients) in the first 6 months after infarction. Over the 6 months maximal QTc intervals and lead adjusted QTc dispersion varied greatly, sotalol was associated with an increased mean maximal QTc interval and a decreased mean lead adjusted QTc dispersion. Contradictory data comes from a study of the effects of amiodarone, sotalol, and sotalol on QT dispersion in patients with previous myocardial infarction (Cui et al. 1994). For each drug 26 patients were studied, and QT dispersion compared before and during treatment. Only amiodarone significantly reduced QT dispersion. The authors could not explain the contradiction with the previous data on sotalol, but the previous study analysed lead adjusted QTc dispersion measurements, which may not be a valid measurement.

The most interesting study of drug effects on QT dispersion was not specifically in patients with myocardial infarction, but it seems likely that most patients in this study had suffered a previous myocardial infarction (Hii et al. 1992). Nine patients who developed class Ia drug induced torsades de pointes, and who subsequently received chronic amiodarone therapy were compared to 29 patients who received a class Ia anti-arrhythmic drug followed by amiodarone, without suffering from drug induced torsades. In these 29 patients neither class Ia drugs nor amiodarone therapy altered QT dispersion. In the 9 patients with class Ia drug induced torsades, QT dispersion was increased during treatment with the class Ia drug, as compared to the drug free state, but returned to former values after the class Ia drug was stopped and amiodarone instituted. The suggestion from this study is that QT dispersion may have a role in predicting drug efficacy or proarrhythmia.

#### 1.6.7. QT dispersion and chronic ischaemic heart disease.

Interest in QT dispersion was heightened by the publication of a study about sudden death in patients with chronic heart failure secondary to ischaemic heart disease (Barr et al. 1994). Forty-four patients were followed prospectively for a mean of 36 months. 21 patients survived, 12 died from progressive heart failure, and 7 died suddenly. There was a large difference in QT dispersion measurements between patients who died suddenly, and those measured from either long term survivors or patients who died of progressive heart failure. Moreover there was very little overlap between these data, suggesting that QT dispersion might be useful to risk stratify patients with chronic heart failure for sudden death. However the numbers studied were small, and the definition of sudden death always difficult. The authors defined sudden death as death within 1 hour of onset of symptoms, which will include a significant number of deaths from re-infarction rather than from a primary ventricular arrhythmia.

A further study examined QT dispersion in 18 patients with chronic heart failure and 17 controls (Davey et al. 1994). The majority of patients in both groups had ischaemic heart disease. There was a trend for QT dispersion measurements to be greater in the heart failure group, this did not reach significance. There was no association of QT dispersion with multiple ventricular premature beats on holter monitoring, and no association with measures of autonomic function, or with measurements of ventricular function from echocardiography. One other study has examined sustained ventricular arrhythmias in patients with chronic ischaemic heart disease and other groups, and compared them with similar groups without arrhythmias (Pye et al. 1993). In this study mean QT dispersion was significantly greater in patients with previous myocardial infarction and arrhythmias as compared to similar patients

without arrhythmias (82 ms vs. 38 ms). They also found a negative correlation between QT dispersion and left ventricular ejection fraction, but only in the group with arrhythmias.

#### **1.6.8. QT dispersion, myocardial infarction, and long term prognosis.**

Two abstracts relating to long term prognosis have been published. Seventy patients had QT dispersion measured on day 1, 3, 21, and 6 months after myocardial infarction (Potratz et al. 1993). Day 3 QT dispersion was increased in the 13 patients who died suddenly or suffered ventricular arrhythmias during follow up as compared to the other 57 patients. A QTc dispersion recorded on day 3 of greater than 85 ms had a 42% positive predictive accuracy, and an 89% negative predictive accuracy for subsequent arrhythmic events. The second study was reported following completion of the work presented in this thesis. In a prospective study of 512 patients (Kautzner et al. 1995), 23 patients suffered ventricular arrhythmias or died suddenly during 1 year follow up. There was no association of QT dispersion recorded from the pre-discharge ECG with subsequent arrhythmic events in that study.

#### **1.6.9. QT dispersion in other conditions.**

Numerous abstracts ranging from QT dispersion as a predictor of patients dying on a cardiac transplant waiting list to QT dispersion in patients with primary autonomic failure have been published. Three published articles have appeared to date, 2 studying arrhythmias. In the first 13 male athletes with symptomatic ventricular tachycardia were studied, and compared to control groups of 15 road cyclists, 10 basketball players, and 15 sedentary healthy individuals (Jordaens et al. 1994). The study is interesting

because it compares the discriminant value of the signal-averaged ECG with QT dispersion. Mean QT dispersion was greater in the group with arrhythmias than in all other groups, but the signal averaged ECG showed a difference only between the arrhythmia group and sedentary controls. Certainly in this study the signal-averaged ECG performed more poorly than QT dispersion. In the other study (Tieleman et al. 1995) QT dispersion was shown to be greater in patients with ventricular arrhythmias and mitral valve prolapse than in age and sex matched controls, suggesting that dispersion of refractoriness might be the arrhythmogenic mechanism in this population.

### *1.7. Aims of the thesis.*

The methods used for QT interval and QT dispersion measurement are described in chapter 2. Chapter 3 examines the time course of QT dispersion after myocardial infarction. The main work of the thesis, a case control study of QT dispersion in patients from the LIMIT-2 study who died following myocardial infarction, and in age and sex matched survivors, is described in chapter 4. Chapter 5 explores possible associations of QT dispersion with other variables, derived from the data in chapter 4, and describes studies on QT dispersion in patients during coronary angioplasty and in patients with impaired left ventricular function. Chapter 6 examines the reproducibility of QT dispersion measurements and the automatic measurement of QT dispersion. Chapters 7 and 8 re-evaluate methods of measuring and expressing QT dispersion in the light of experience gained in the course of this work. Chapter 9 summarises results and discusses future possibilities.

**CHAPTER 2.**  
**METHODS OF ECG ANALYSIS.**

### *2.1. Introduction.*

Before the 1980's QT intervals were usually measured manually. The growing interest in the QT interval called for as accurate measurement of QT intervals as possible. The usual approach now employed for measuring QT dispersion uses ECGs recorded at 50 mm/sec. QT intervals are then analysed using a digitising tablet, sometimes with a magnifying glass, interfaced with a personal computer. The digitising technique gives a repeatability error of about 3 ms (Murray et al. 1994).

An accurate automatic measurement of QT dispersion would be highly desirable as it would eliminate both observer error and bias. A computerised system would also have the advantage of being able to handle digital images directly, without the need for paper hard copy. The accuracy of measuring QT intervals automatically from normal ECGs has been verified in 2 studies using different computer programs (O'Donnell et al. 1981, Puddu et al. 1992). However the accuracy of these programs has not been tested in abnormal ECGs, and the definition of the T wave end used in these studies differs. Computer programs from both studies also relied on signal averaging several ECG complexes to remove background noise. QT intervals will vary over these complexes, therefore the programs' measurement of QT dispersion would be different from that obtained traditionally.

The software for the computer measurement of QT intervals and dispersion throughout all the studies described in this thesis were designed by Dr H. K. Bhullar, Department of Engineering, University of Leicester. The system allows for totally automated measurement of QT intervals, and a user-interactive method. The method has been validated previously (Bhullar et al. 1993), and gives a repeatability error of 4 ms (1 pixel). I shall now describe the method in detail.

### *2.2. The User - Interactive and Automated Computer Measurement of QT Intervals and QT Dispersion.*

In all studies 12 lead standard ECGs were recorded at 25 mm/sec. Most ECGs were recorded using the Hewlett Packard page writer which records all leads simultaneously. A small proportion of ECGs were recorded by machines analysing only 3 leads simultaneously (Marquette inkwriter, FCP- 4101U, Cambridge 3038), resulting in a short time delay between sets of leads recorded. The analysis system consisted of a flatbed scanner (Hewlett Packard Scanjet Plus) interfaced with a personal computer (Elonex 386 + math coprocessor).

An ECG is covered with an appropriately coloured filter to mask the background grid, and effectively remove it. The method is not suitable if the background grid is very close in colour, for example blue ECG tracing on a green background, or for black and white photocopies. The ECG is scanned to produce a .PCX computer file (Scangal software, Hewlett Packard) at 300 dots per inch resolution. A graphics editor (HP Brush, Hewlett Packard) is used to cut the file into 12 .PCX subfiles corresponding to the 12 leads of the ECG. Using the same editor any background noise is removed and any gaps in the image joined up.

Specially designed software is then applied to the 12 .PCX subfiles. This software ensures all background noise is removed and the gaps filled in, then thins the image, and extracts digital information from this thinned image. The extracted digital information can then be displayed on a computer screen.

At this stage user-interactive measurements of QT intervals can be made using a computer mouse. Each ECG lead is presented in turn on the computer screen, and

different magnifications can be applied both vertically and horizontally for optimal QT interval measurement.

When analysing the ECG by computer it is important to view the original 12 lead ECG at the same time, as the end of the T wave from other leads give important clues in deciding the end of an ambiguous T wave.

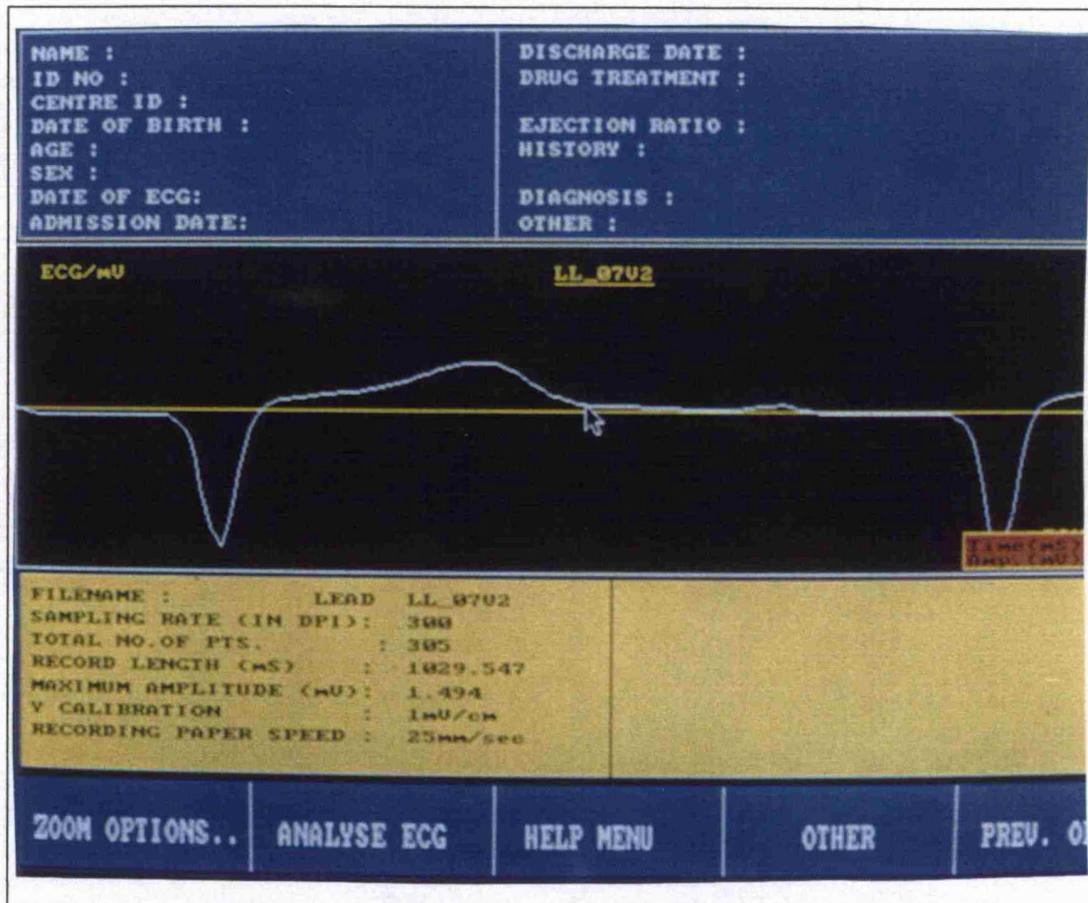


Figure 2.1 - The QT interval presented for user- interactive measurement.

In all studies QT intervals were measured using the definitions of Lepschkin and Surawicz (Lepschkin and Surawicz. 1952). This paper states the importance of

examining the complete ECG to differentiate T from U waves, particularly when the T wave in one or more leads is notched or biphasic. If this was not helpful, their observation that the distance between the summits of a notched or biphasic T wave never exceeds 40% of the distance between the beginning of the QRS complex and the second summit was employed. The converse of this "rule" is that the distance between summits of T and U waves exceeds 40% of the distance between QRS and U wave summit. When there was a notch between T and U wave the nadir of the notch was used to define the QT interval, although such a notch appeared to be a rare occurrence. QT intervals were rate corrected by Bazett's formula: QT interval divided by the square root of the RR interval. The methodological problems of QT dispersion measurement will be presented in more detail in chapters 6 and 7.

Alternatively the automated measurement of QT intervals can be used at this stage. This again uses specially designed software, but this runs within the Matlab software package (The Mathworks Inc. South Natick, MA 01760). The automatic algorithm relies on the creation of area maps for each ECG waveform, and the application of a series of rules to determine the QRS onset, and T wave offset. The rules were specifically designed to identify most common T wave morphologies. Each ECG lead is analysed in turn, and the system is monitored visually at each stage. The software was designed to allow visual monitoring at all stages of the automated program, an automatic measurement can be substituted with a user-interactive measurement if it is felt necessary.

### *2.3. Measures of QT Dispersion.*

The software calculates and presents the following measures of QT interval and dispersion :

1. Uncorrected and rate corrected (Bazett's formula) QT intervals from all leads measured.

2. The mean uncorrected and rate corrected QT interval.

3. The standard deviation of QT intervals

4. QT dispersion is the maximum minus minimum QT interval.

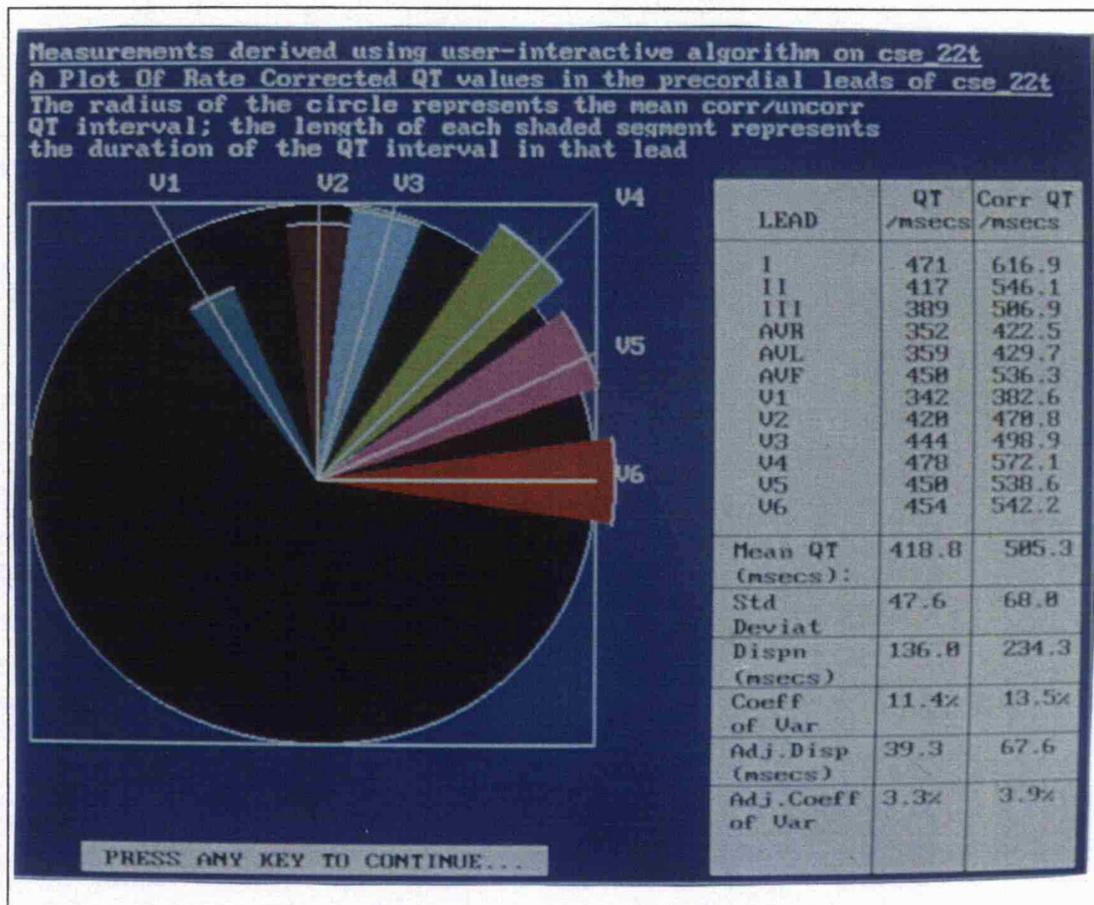
5. QTc dispersion is the rate corrected QT dispersion.

6. The adjusted QT dispersion is the is the QT dispersion divided by the square root of the number of leads in which a QT interval was measured (Day et al. 1991).

This measure was designed to allow for any effect that the number of leads measured might have on QT dispersion itself. It can be presented rate corrected or uncorrected.

7. The coefficient of variation of QT intervals is the standard deviation of the QT intervals divided by the mean QT interval (Bhullar et al. 1993). This formula attempts to automatically correct for the number of leads measured, and also for any effect that heart rate might have on QT dispersion.

Figure 2.2 - Presentation of measures of QT dispersion by the computer program.



**CHAPTER 3.**  
**TIME COURSE OF QT DISPERSION**  
**FOLLOWING MYOCARDIAL INFARCTION.**

### *3.1. Introduction.*

To determine which ECGs should be examined in the mortality study it was necessary to determine the variability of QT dispersion during the hospital phase of acute myocardial infarction. Data on the time course of QT dispersion following myocardial infarction is limited, and therefore a small cohort of consecutive patients admitted to Leicester Royal Infirmary with acute myocardial infarction was studied prospectively.

### *3.2. Patients and methods.*

Ten patients with acute anterior infarction and an equal number of patients with acute inferior infarction were studied. No patients had suffered previous myocardial infarction, and none were taking drugs known to effect the QT interval or QT dispersion. All patients gave typical histories, had ECGs at entry into the study showing classical changes of acute infarction, and subsequently had a rise in serum creatinine kinase to at least twice the upper limit of normal. All patients received intravenous magnesium, were thrombolysed with streptokinase on admission to the coronary care unit, and were subsequently treated with aspirin.

The ECG on admission to the coronary care unit was designated as the day 1 ECG. Day 1 was defined as being from midnight to 24 hours later. The day 2 ECG was recorded between 8 and 10 am on the following day, and was therefore an ECG recorded between 8 and 34 hours after admission. The day 3 ECG was recorded at a similar time to the previous day, and was therefore recorded between 32 and 58 hours after admission. All patients had an ECG recorded on day 6 at between 8 and 10 am prior to discharge from hospital. All ECGs were recorded using the Hewlett Packard

page writer, recording all 12 leads simultaneously. Both QT intervals and QT dispersion are approximately normally distributed, measurements were compared by unpaired T tests.

### **3.3. Results.**

Seventeen of the patients subsequently developed pathological Q waves. Fourteen patients were started on Beta blockers, initiated no earlier than day 4, and usually commenced from day 5 onwards. One patient with chronic angina was taking atenolol and diltiazem on admission and these drugs were continued. Two patients developed clinical and radiological evidence of heart failure, and were treated with diuretics. One of these patients died on day 7.

Compared to historical controls from other studies of individuals without myocardial infarction all measures of QT dispersion were raised, from admission to hospital through to hospital discharge. Maximal QT dispersion was seen on day 3 of myocardial infarction, and then fell towards values recorded on the admission ECG. However by day 6 mean QT dispersion measurements had not yet fallen to those recorded on admission. At all stages of infarction there were large variations in QT dispersion measurements. Both mean QT and QTc intervals paralleled the changes in QT dispersion. Measures of QT intervals and QT dispersion on days 1,2,3, and 6 of infarction are shown in table 3.1, the time course of QTc dispersion is shown in figure 3.1.

Table 3.1 - QT dispersion and QT intervals from days 1, 2, 3, and 6 of acute myocardial infarction.

	<i>Day 1</i>	<i>Day 2</i>	<i>Day 3</i>	<i>Day 6</i>
QT interval (ms)	404 (44)	415 (44)	440 (68)	394 (47)
QTc interval (ms)	457 (38)	479 (54)	499 (61)	436 (27)
R-R interval (ms)	798 (196)	762 (101)	780 (126)	827 (175)
QT dispersion (ms)	93 (35.4)	124.2 (43.5)	145.4 (55.9)	106.2 (70.7)
QTc dispersion (ms)	107 (44.8)	141.8 (44)	162.3 (64.8)	117.4 (67.4)
Lead adjusted QTc dispersion (ms)	31.9 (13.1)	43.1 (13.4)	49.3 (19.1)	34.8 (19.7)
Coefficient of variation of QT intervals (%)	7.42 (2.98)	9.51 (2.55)	11.19 (5.21)	8.65 (5.74)

All data mean (SD)

For QTc dispersion the differences measured between ECGs recorded on different days reached statistical significance at  $p < 0.01$  for day 1 vs. day 3;  $p < 0.05$  for day 1 vs. day 2 and for day 3 vs. day 6. For QT dispersion similar results were seen at  $p < 0.05$  for day 3 vs. day 1 and day 2; for lead adjusted QTc dispersion  $p < 0.001$  for day 1 vs. day 3,  $p < 0.05$  for day 1 vs. day 2 and for day 3 vs. day 6; and for coefficient of variation of QT intervals  $p < 0.01$  for day 1 vs. day 3, and  $p < 0.05$  for day 1 vs. day 2.

There were no statistically significant differences seen between heart rates. For mean QTc intervals the differences measured between ECGs recorded on different days reached statistical significance at  $p < 0.001$  for day 3 vs. day 6;  $p < 0.01$  for day 2 vs. day

6, and  $p < 0.05$  for day 1 vs. day 3. For mean QT intervals a significant difference was seen only between the day 3 and day 6 ECGs ( $p < 0.05$ ).

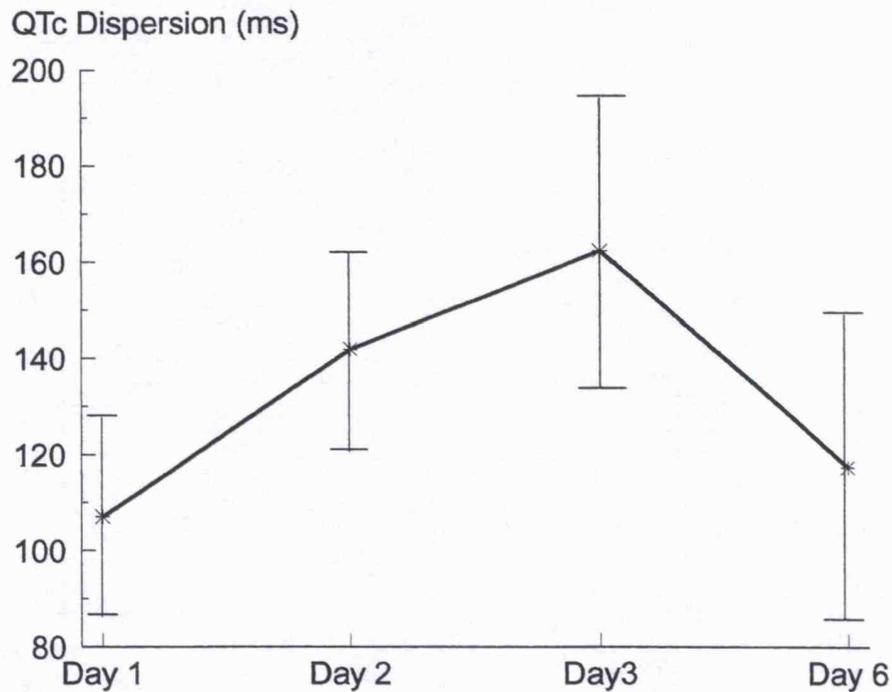


Figure 3.1 - Time course of mean QTc dispersion measurement during the hospital phase of acute myocardial infarction (error bars are 95 % confidence intervals of means).

#### **3.4. Discussion.**

The evolving changes in QT dispersion and QT interval duration over the first few days of myocardial infarction seem to reflect the changing morphology of the ST segment and T wave. In the first few hours of infarction the ECG tends to show marked ST segment elevation, with much less in the way of T wave changes. Over the next 24

hours as the ST elevation settles deep T wave inversion predominates. The deepest T wave inversion seen in the ECGs of the patients studied seem to occur at between 24 and 48 hours after infarction, before starting to normalise. The most deeply inverted T waves appear to be associated with the longest QT intervals. In addition the disparity between areas of the ECG with marked T wave inversion and those with T waves of normal appearance seems to cause the greatest QT dispersion. Thus the time course of QT dispersion in the first few days after myocardial infarction appears to be, at least to a large part, to be merely a reflection of changing ECG morphology.

A similar time course in QT interval changes to that observed here has been shown by others. In a retrospective study of 63 patients (Doroghazi et al. 1978) QTc interval duration was reported as normal immediately after infarction, became abnormal over the next 4 days, reaching a maximum at 48 hours after infarction, and had returned to normal levels by 14 days post infarction. In a prospective study of 21 patients (Cinca et al. 1981) an initial shortening in QT interval duration was observed immediately after infarction, followed by a very marked lengthening in the QT interval, associated with T wave inversion, which reached a maximum 12 to 24 hours after infarction. By 4 to 6 days post infarction the QT interval was returning to normal.

The pathophysiology underlying the time course of T wave inversion after myocardial infarction remains to be fully elucidated. In an experimental model in dogs (Mandel et al. 1967) acute ischaemia caused relative shortening in refractory periods, whilst chronic ischaemia resulted in lengthening of refractory periods at 24 to 72 hours after coronary ligation. These refractory periods were then used to derive theoretical T wave morphologies. The theoretically derived T wave from refractory periods associated with chronic ischaemia showed the characteristic T wave inversion that

occurs after the first few hours of infarction. As well as by a direct effect on the action potential, the effects of local ischaemia on repolarisation could be modulated through a number of other mechanisms including local hypothermia, stimulation of cardiac sympathetic nerve endings by localised hyperkalaemia, or direct ischaemic damage to these nerve endings (Doroghazi et al. 1978). The theory with most supporting evidence is that ischaemic damage may cause local extracellular hypocalcaemia, resulting in QT interval prolongation. In an experimental model of ischaemic damage followed by reperfusion, damaged myocardial cells take up large amounts of calcium (Shen and Jennings. 1972), which would result in subsequent local extracellular hypocalcaemia. There is evidence from radionuclide uptake in dogs with experimental myocardial infarction (Buja et al. 1975) that calcium uptake by damaged myocardial cells is maximal at 48 hours after infarction, which would be consistent with the time course of QT interval changes seen here and in other studies.

There are limited data concerning the time course of QT dispersion in the early days of myocardial infarction. Only 1 abstract has specifically addressed this issue (Cox et al. 1994), and is in broad agreement with the data presented here. They studied 58 patients treated with thrombolytic therapy. Mean QTc dispersion in 57 age and sex matched controls was 65 ms. In the patients with myocardial infarction on the day of admission mean QTc dispersion was 106 ms, increased to 109 ms the next day, and 48 hours later had fallen to 98 ms, ( $p < 0.01$ ). However the differences seen in QT dispersion over the first few days of infarction in that study were small, and were statistically significantly different only because of the very small standard deviations seen in QTc dispersion measurement of between 3 and 6 ms. The data presented here

show large variation in QT dispersion measurements between individuals, which appears to be the case in almost all published studies.

One study shows conflicting data to that seen here (Higham et al. 1995), suggesting that QT dispersion is highest in the first 6 hours after infarction, and is falling by the next day. They studied QT dispersion in 30 patients following myocardial infarction within 6 hours of onset of symptoms. For 27 of these patients a further ECG was recorded the next day. Four of the later ECGs were excluded from analysis, as 2 were recorded during chest pain which increased the QTc dispersion by 30 ms, and 2 patients developed right bundle branch block. The ECG pairs were a mean 5 and 19 hours apart. QTc dispersion fell in 18 patients, stayed the same in 3 patients, and rose in the remaining 3 patients. The mean fall in QTc dispersion was a statistically significant 24 ms. The differences in the data presented here and Higham and colleagues data may be partly explained by their exclusion of 2 patients with chest pain. Furthermore QTc dispersion measurements in their study were markedly lower than those seen here and by others (Cox et al. 1994), suggesting the patients studied may have been different in other respects. They did not study ECGs from subsequent days.

The rapid changes in QT dispersion over the first few days after myocardial infarction have important implications in the design of any study of QT dispersion and prognosis, arrhythmia prediction, or drug efficacy after myocardial infarction. Comparison of studies of QT dispersion after myocardial infarction must also be treated cautiously, with careful account taken of the timing of the ECGs recorded.

**CHAPTER 4.**  
**QT DISPERSION AND MORTALITY**  
**FOLLOWING MYOCARDIAL INFARCTION.**

#### *4.1. Introduction.*

If QT dispersion is a measure of variability in ventricular recovery time and this variability is important in arrhythmogenesis, QT dispersion may be a means of identifying patients at risk of arrhythmias and sudden death after acute myocardial infarction.

This hypothesis was tested using ECGs recorded on day 2 or 3 of infarction, and (when available) ECGs recorded at least 4 weeks later. The reason for studying these 2 populations of ECGs was to evaluate the importance of QT dispersion at its peak value post infarct, and also when it had reached a steady state. The rationale for choosing a 1 month gap was to hopefully ensure that this steady state had been reached, in addition few patients had a second ECG available before 1 month post infarct.

#### *4.2. Patients and Methods.*

Patients with confirmed acute myocardial infarction were drawn from the placebo arm of the LIMIT-2 study (Woods et al. 1992), they were admitted to Leicester Royal Infirmary between September 1987 and February 1992. All patients were 'flagged' in the National Health Service Central Register, with complete mortality follow-up to the censoring date in January 1994. Criteria for the diagnosis of acute myocardial infarction were at least two of the following: typical history; rise in serum creatinine kinase to at least twice the upper limit of normal; evolving ECG changes consistent with acute infarction. Thirteen deceased patients were excluded due to chronic atrial fibrillation, or complete heart block, which made QT interval measurement impossible. Twenty-seven patients who

died on the day of admission were also excluded. Twenty-five sets of case notes could not be traced.

A total of 163 patients who died between 24 hours and 61 months after myocardial infarction were compared with an equal number of age and sex matched patients who survived to the censoring date. ECGs and clinical records were analysed retrospectively. From the data in chapter 3 it seems likely that QT dispersion is maximal on day three of acute myocardial infarction. Consequently day 3 ECGs were analysed if possible, or if this was not available the ECG from day 2. The last available ECG from later in life was also studied, providing it had been recorded at least 28 days post infarct. Fifty-three (late) ECGs were recorded in the death group, and 82 for the survivors.

QT interval analysis was performed by the author, unblinded to the outcome. Repeatability of the QT measurements was tested by an independent observer blindly analysing a random sample of 23(5%) of the ECGs.

Four measures of QT dispersion are presented : the QT dispersion, QTc dispersion, adjusted QTc dispersion, and the coefficient of variation of QTc intervals. Mean global uncorrected and rate corrected QT intervals for ECGs without bundle branch block are also shown.

For the analysis of QT dispersion and mode of death, definite sudden death or death from progressive heart failure could be confirmed where detailed case notes were available for those deaths. Probable sudden death was defined as death outside hospital with the general practitioner registering the cause of death as myocardial infarction.

In the study all measures of QT intervals and dispersion were approximately normally distributed, therefore paired and unpaired t-tests were used in their analysis.

Other data were analysed using a Mann-Whitney test for continuous variables. Discrete data are presented as counts, percentages, and odds ratios with 95% confidence intervals (CI). Continuous data are presented as means, standard deviations, differences with 95% CI, and p values.

#### **4.3. Results.**

##### **Reproducibility**

Repeat measurements on 23 ECGs (234 leads) showed a mean, non significant, difference of 6ms (SD 11ms, Coefficient of variation 1.4) for QTc dispersion measurements between the two observers.

##### **Early ECGs**

Time from acute myocardial infarct to death is shown in figure 4.1. The death rate was highest early after infarction, as would be expected, with over half the deaths occurring in the first year.

Patient characteristics are shown in Table 4.1. The major differences between patients that died and those that survived were in the greater incidence of heart failure, arrhythmias and their treatment, prior myocardial infarction, presence of bundle branch block, and lack of thrombolysis in the death group. There was a higher proportion of inferior myocardial infarction in the survivors group. The difference in mean age between patients who subsequently died and survivors is explained by a small number of very elderly patients in the former group (17 patients over 80 years), for whom only younger controls could be found.

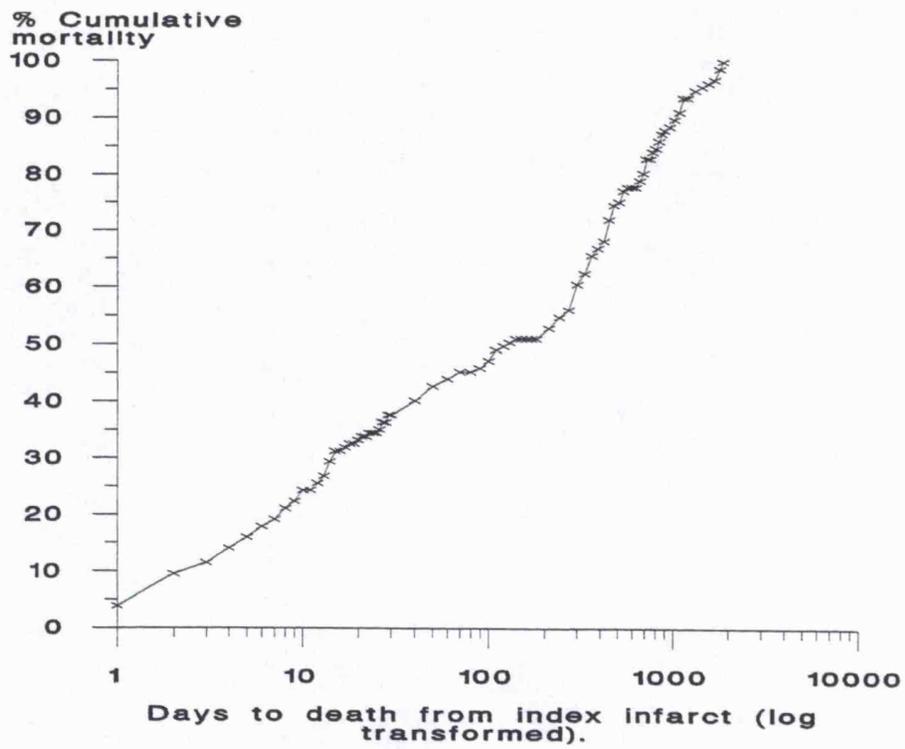
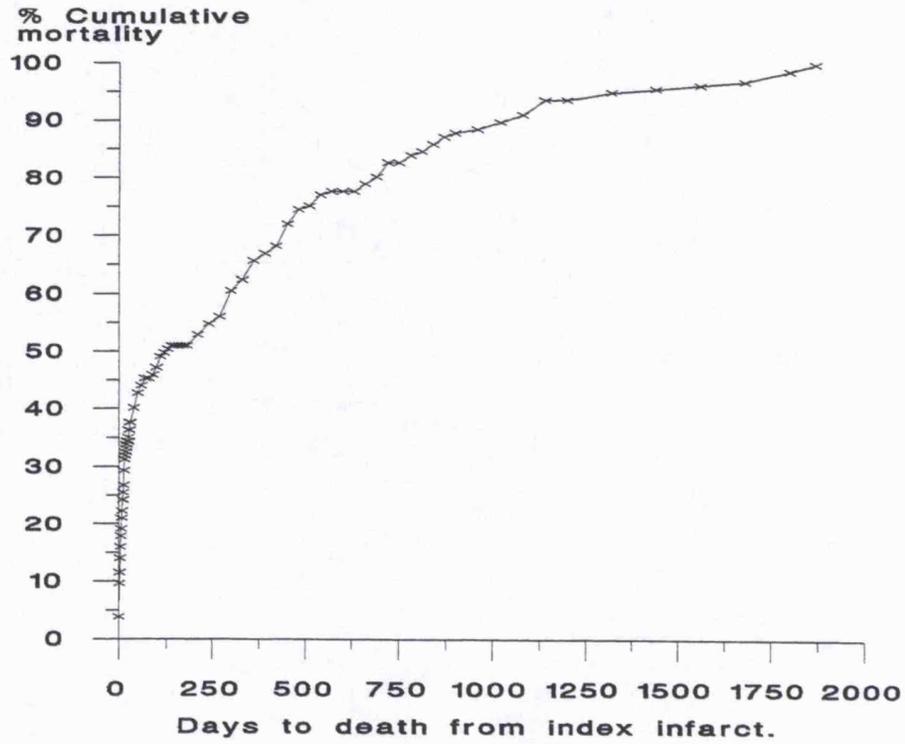


Figure 4.1 - Cumulative mortality in death group.

Table 4.1 - Patient characteristics at early ECG recording

	Deaths n = 163	Survivors n = 163	Difference	95% CI of Differences
Mean age(SD) yrs	68.4 (11)	66.4 (9.4)	2 yrs	- 4.73, - 0.64
Males	110 (68%)	110 (68%)		<b>Odds ratios (95% CI)</b>
Females	53 (32%)	53 (32%)		
Previous myocardial infarct	53 (32%)	15 (9%)	72%	4.75 (2.54, 8.87)
Hypertensive	37 (23%)	41 (25%)	8%	0.87 (0.52, 8.87)
Diabetic	29 (18%)	19 (12%)	33%	1.64 (0.88, 3.06)
Current heart failure	76 (47%)	39 (24%)	49%	2.77 (1.73, 4.46)
Current ventricular arrhythmias	25 (15%)	10 (6%)	60%	2.77 (1.73, 4.46)
Current anti-arrhythmic therapy	34 (21%)	6 (4%)	81%	6.9 (2.81, 16.94)
Anterior infarct	71 (44%)	66 (40%)	9%	1.13 (0.73, 1.76)
Inferior infarct	45 (28%)	67 (41%)	32%	0.55 (0.34, 0.87)
Q wave	108 (66%)	116 (71%)	7%	0.79 (0.50, 1.27)
Thrombolysis given	55 (34%)	99 (61%)	44%	0.33 (0.21, 0.52)
Bundle branch block	28 (17%)	7 (4%)	76%	4.62 (1.96, 10.92)
Day 2 ECG recorded	61 (37%)	72 (44%)	16%	0.76 (0.48, 1.18)
Day 3 ECG recorded	102 (63%)	91 (56%)	11%	1.32 (0.85, 2.06)

Table 4.2 - Early QT dispersion.

<i>All patients</i>	Deaths n = 163	Survivors n = 163	Difference between means (95% CI)	p
QT dispersion(ms)	93.6 (41.0)	94.2 (39.7)	0.6 (- 9.4, 8.2)	0.89
QTc dispersion (ms)	112.1 (44.4)	109.9 (42.7)	2.2 (- 7.2, 11.7)	0.64
Adjusted QTc dispersion(ms)	36.6 (14.7)	35.2 (13.9)	1.4 (- 5.2, 4.3)	0.84
Coefficient of QT variation(%)	7.7 (3.2)	7.7 (3.1)	0 (- 0.7, 0.7)	1
Mean QT(ms)	413 (56)	410 (49)	3 (- 8.5, 14.4)	0.61
Mean QTc(ms)	484 (41)	469 (36)	15 (6.5, 23.6)	0.0006
<i>Patients without bundle branch block</i>	n = 135	n = 156		
Mean QT(ms)	409 (55)	409 (48)	0 (- 12.6, 11.4)	0.92
Mean QTc(ms)	479 (41)	469 (36)	10 (1.0, 18.9)	0.03

Data Mean (SD)

There was no difference in early QT dispersion between the 2 groups, as shown in table 4.2. There was a small difference in mean QTc intervals between the 2 groups.

#### Late ECGs

Fifty-five patients died before 28 days, making them ineligible for study in our later ECG group. Patient characteristics and the reason for a second ECG being recorded are presented in table 4.3. The last ECG available from the case notes was studied, therefore there was a wide range in the timing of the late ECGs. However most late ECGs were

recorded within the first 6 months after myocardial infarction. Figure 4.2 shows the timing of the late ECGs and the relationship of QT dispersion to that timing.

Table 4.3 - Patient characteristics at late ECG recording.

	Deaths n = 53	Survivors n = 82	Difference	95% CI of difference
Median days to late ECG (inter-quartile range)	154 (53 - 447)	86 (44 - 632)	68 days	- 84, 210
Mean age (SD) yrs	67.2 (9.6)	65.4 (7.5)	1.8 yrs	- 1.3, 4.93
				<b>Odds ratios (95% CI)</b>
Males	39 (74%)	59 (72%)	3%	1.09 (0.50, 2.36)
Females	14 (26%)	23 (28%)	7%	0.92 (0.42, 2.00)
Hypertensive	14 (26%)	21 (26%)	0%	1.04 (0.47, 2.29)
Diabetic	13 (24%)	10 (12%)	50%	2.34 (0.94, 5.82)
Current heart failure	27 (51%)	15 (18%)	65%	4.64 (2.13, 10.09)
Current ventricular arrhythmias	3 (6%)	1 (1%)	83%	4.86 (0.49, 48.01)
Current anti-arrhythmic therapy	9 (17%)	8 (10%)	41%	1.89 (0.68, 5.26)
Anterior infarct	23 (43%)	31 (38%)	12%	1.26 (0.62, 2.55)
Inferior infarct	16 (30%)	37 (45%)	33%	0.53 (0.25, 1.09)
Q wave	35 (66%)	59 (72%)	8%	0.76 (0.36, 1.60)
Thrombolysis given	18 (34%)	50 (61%)	44%	0.32 (0.16, 0.68)
Bundle branch block	10 (19%)	4 (5%)	74%	4.53 (1.34, 15.33)
<b>Reason for late ECG</b>				
Exercise ECG	11 (21%)	47 (57%)	63%	0.19 (0.88, 0.43)
Routine follow up	17 (32%)	20 (24%)	25%	1.46 (0.68, 3.15)
Admitted with heart failure	14 (26%)	4 (5%)	81%	7.00 (2.16, 22.68)
Admitted with angina	5 (9%)	6 (7%)	22%	1.32 (0.38, 4.56)
Others	6 (11%)	5 (5%)	45%	1.97 (0.57, 6.80)

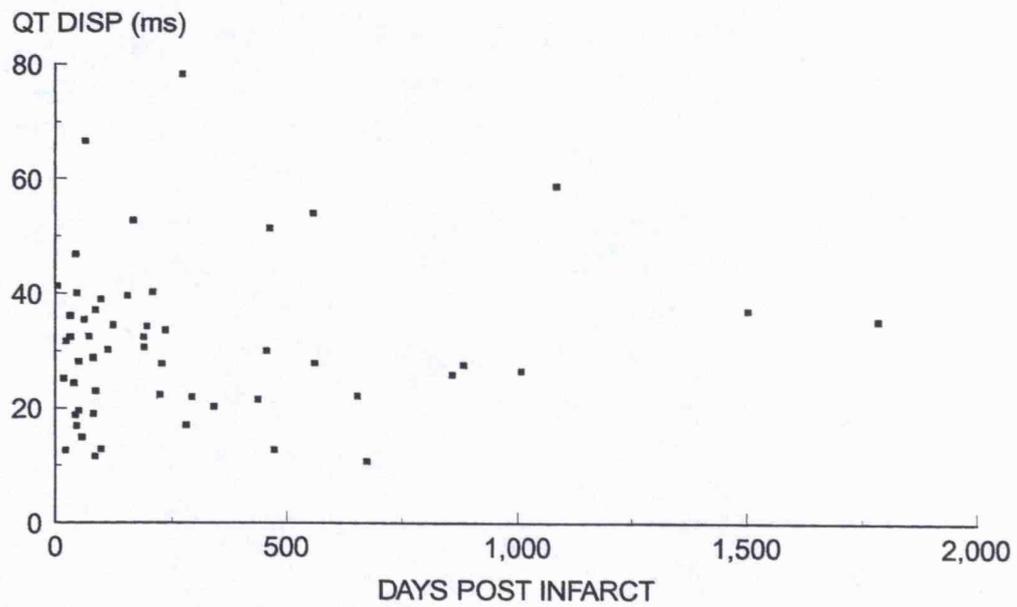
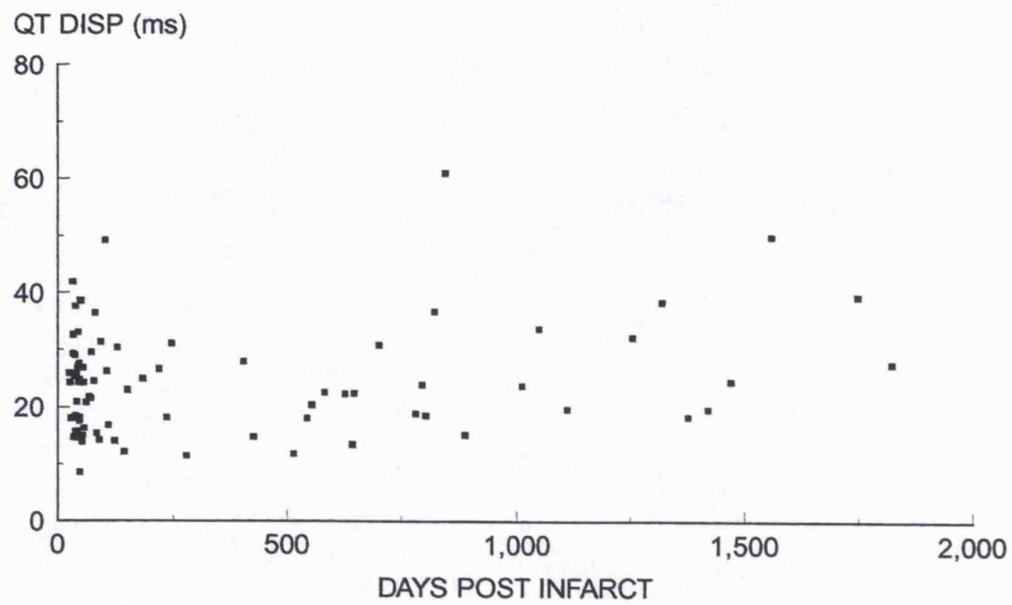
**DEATHS****SURVIVORS**

Figure 4.2 - QT dispersion and timing of late ECG.

There was a mean fall of 34.4 ms (95% CI 22.3, 46.5) in QTc dispersion from early to late ECG for long term survivors (early QTc dispersion 110.9[SD 48.5]ms, late QTc dispersion 76.5[28.8]ms). For patients who subsequently died there was a fall of 9.1 ms (95% CI - 8.0, 25.8) in QTc dispersion from early to late ECG (108[51]ms vs. 98.9[43.1]ms). These data are for paired comparison of the early ECG with the late ECG for the same subject. Table 4.4 shows QT dispersion measurements in early and late ECGs, table 4.5 compares the differences between early and late QT dispersion in patients who died and in those who survived.

Table 4.4 - Paired data from early to late ECGs

Data mean (SD)

	Early ECG	Late ECG
<b>DEATHS, n = 53</b>		
QT dispersion (ms)	90.2 (40.8)	87.6 (40.8)
QTc dispersion (ms)	108 (51)	98.9 (43.1)
Adjusted QTc dispersion (ms)	35.4 (16.9)	31.2 (13.9)
Coefficient of variation of QT intervals (%)	7.6 (3.6)	6.9 (3.0)
Mean QT (ms)	410 (59)	407 (57)
Mean QTc (ms)	482 (41)	465 (44)
<i>Bundle branch block excluded, n = 43</i>		
Mean QT (ms)	407 (57)	402 (47)
Mean QTc (ms)	475 (40)	457(41)
<b>SURVIVORS, n =82</b>		
QT dispersion (ms)	97.3 (44.4)	69.6 (26.0)
QTc dispersion (ms)	110.9 (48.5)	76.5 (28.8)
Adjusted QTc dispersion (ms)	35.5 (15.8)	24.5 (9.5)
Coefficient of variation of QT intervals (%)	7.8 (3.6)	5.8 (2.3)
Mean QT (ms)	412 (51)	401 (46)
Mean QTc (ms)	467 (40)	438 (33)
<i>Bundle branch block excluded, n = 78</i>		
Mean QT (ms)	413 (51)	402 (46)
Mean QTc (ms)	467 (39)	437 (32)

Table 4.5 - Differences between early and late ECGs for survivors and patients who subsequently die, with mean changes of the differences.

<i>All patients</i>	<b>Deaths</b> n = 53	<b>Survivors</b> n = 82	<b>Difference between change scores (95% CI)</b>	<b>p</b>
QT dispersion(ms)	2.6 (57.1)	27.7 (49.7)	25.1 (6.2, 44.2)	0.01
QTc dispersion (ms)	9.1 (60.8)	34.4 (55.2)	25.3 (4.8, 45.8)	0.016
Adjusted QTc dispersion(ms)	4.3 (20.3)	14.6 (37.3)	10.3 (0.5, 20.1)	0.04
Coefficient of QT variation(%)	0.7 (3.9)	2.1 (3.9)	1.3 (- 0.03, 2.7)	0.054
Mean QT(ms)	2 (65)	10 (59)	8 (-13.7, 30)	0.46
Mean QTc(ms)	17 (54)	22 (45)	12 (- 5.9, 29.5)	0.19
<i>Patients without bundle branch block</i>	n = 43	n = 78		
Mean QT(ms)	4 (65)	11 (59)	7 (- 16.9, 30.4)	0.57
Mean QTc(ms)	18 (55)	30 (45)	12 (- 7.1, 32.1)	0.21

Data Mean (SD)

Descriptive statistics of QTc dispersion for patients with clinical evidence of heart failure are presented in table 4.6, and for mode of death in table 4.7. In view of the small numbers involved, and the nature of subgroup analysis, no further statistical inferences are drawn.

Table 4.6 - QTc dispersion in patients with heart failure.

<i>Early ECG</i>	Deaths n =76	Survivors n =39
QTc dispersion(ms)	110.6 (42.3)	109 (39.4)
Late ECG *	<i>Early ECG</i>	<i>Late ECG</i>
QTc dispersion(ms)		
Deaths, n = 27	100 (43.3)	105.8 (28.2)
Survivors, n = 15	102.7 (41.3)	78 (25.9)

\* Paired data from early to late ECG, patient with evidence of heart failure at 2nd ECG  
Data Mean (SD)

Table 4.7 - QTc dispersion and mode of death.

Early ECG	Definite sudden death n =16	Definite and probable sudden death n = 39	Death from progressive heart failure n = 41
QTc dispersion(ms)	118.5 (53.3)	112.2 (42.6)	112.7 (41.1)
Both early and late ECGs available	n = 5	n = 12	n = 9
QTc dispersion(ms)			
Early ECG	160.4 (68.8)	126.8 (58.4)	101.1 (52.4)
Late ECG	120.5 (81.5)	117 (61.9)	109 (35.5)

Data Mean (SD)

Scatter graphs of QTc dispersion for all patients in the study are shown in figures

4.3 and 4.4.

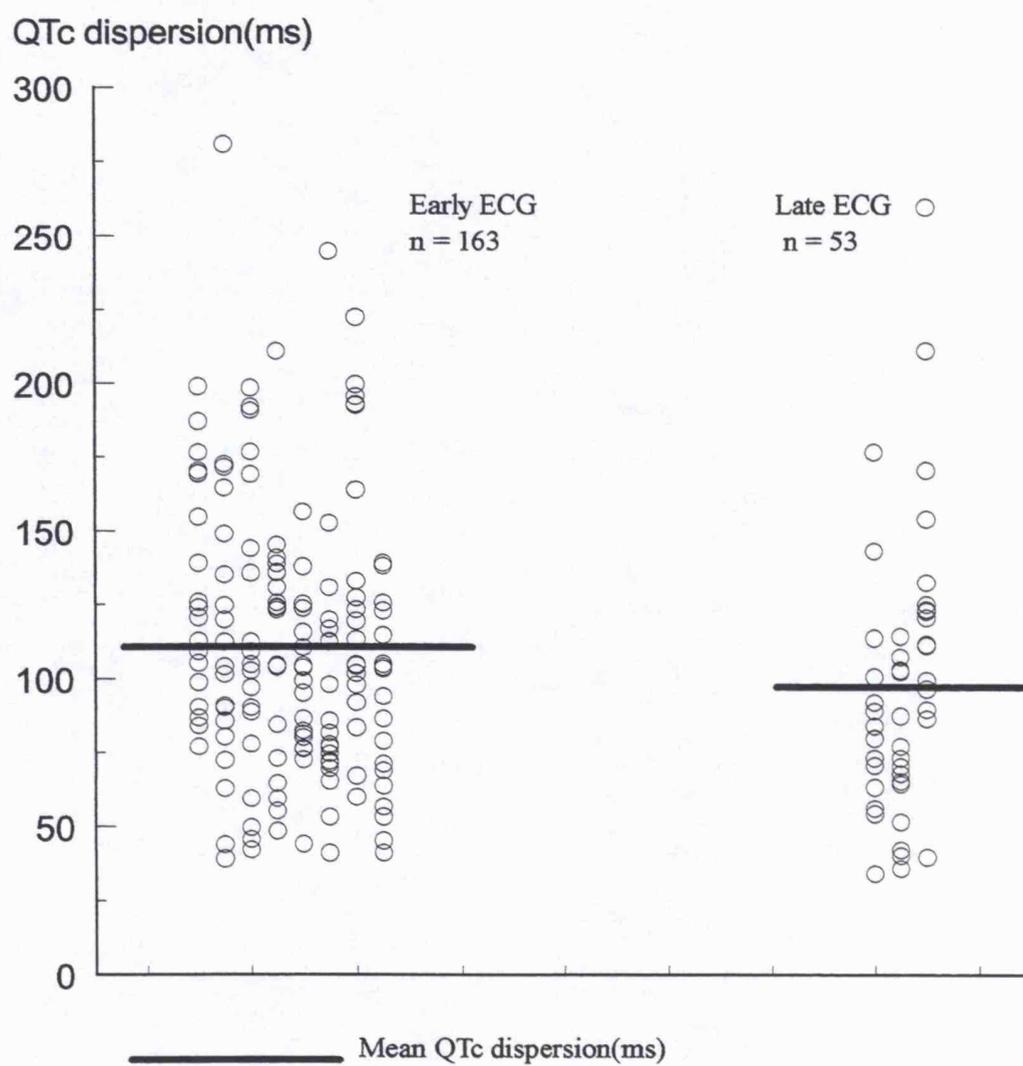


Figure 4.3 - Early and late QTc dispersion in patients who died.

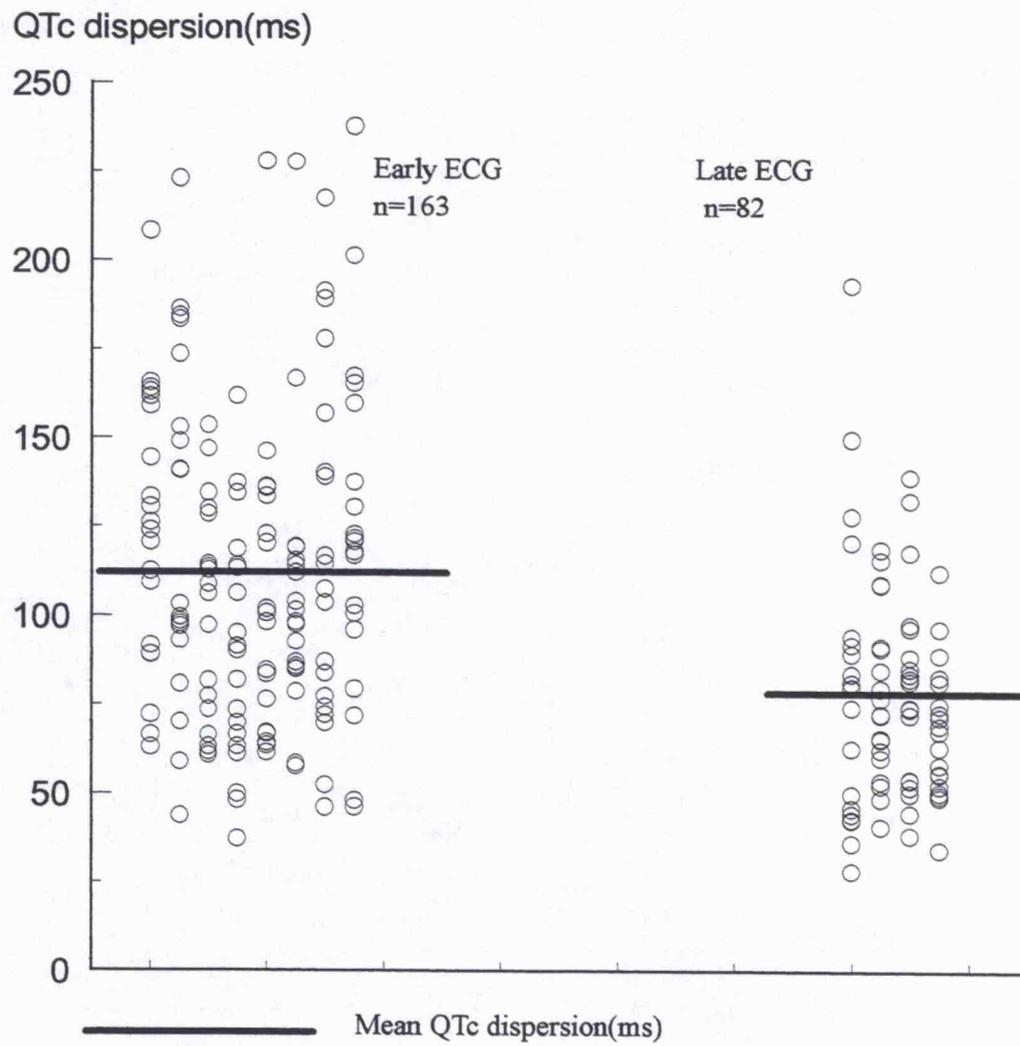


Figure 4.4 - Early and late QTc dispersion in survivors

#### *4.4. Discussion.*

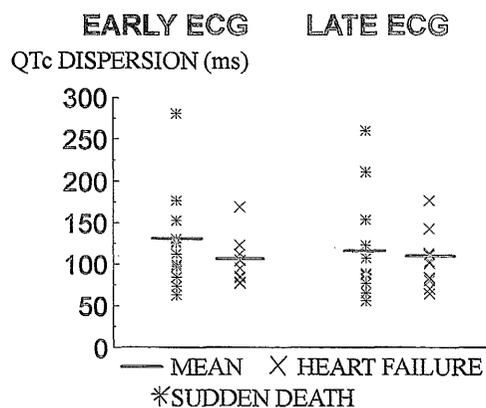
The principal finding of this study is that QT dispersion measured from ECGs recorded on day 2 or 3 of acute myocardial infarction did not predict subsequent mortality in a large patient population followed for a mean of 4.1 years. Amongst those patients who underwent repeat electrocardiography following hospital discharge, however, there was an association between persistence of increased QT dispersion and subsequent death over the follow-up period.

There are a number of possible explanations for the lack of association between QT dispersion measured early after infarction and subsequent mortality. QT dispersion in this setting may not be a marker of subsequent life-threatening arrhythmias, either because of limitations inherent in the technique of measurement or because other processes related to acute infarction mask the relevant repolarisation changes. Possible factors underlying the changes seen in QT dispersion in the first few days after infarction have been discussed in the previous chapter. Alternatively it may be that QT dispersion is a marker of arrhythmic death but that relatively few deaths in this study were arrhythmia-related. This would seem unlikely, as a number of previous studies have suggested that arrhythmic death contributes approximately one third of total post-infarct mortality after hospital discharge (Multicentre Postinfarction Research Group. 1983, Mukharji et al. 1984).

Owing to the retrospective nature of the study, assessment of the precise mode of death (arrhythmic or non-arrhythmic) was possible in only a limited number of patients, and we would draw limited inference from their pooled results. However the wide overlap in QT dispersion (early or late) between patients who died suddenly and those who died of

progressive heart failure (figure 4.5) means that QT dispersion is unlikely to be useful in predicting sudden death after myocardial infarction.

Figure 4.5 - Early and late QTc dispersion and mode of death.



Failure of QT dispersion to decrease late after infarction (in those in whom it was measured) was associated with subsequent all-cause mortality. This finding is consistent with the development of a substrate for life-threatening arrhythmias after the first few days post-infarction, perhaps associated with the ventricular remodelling process. Ventricular remodelling starts early after myocardial infarction but any infarct expansion is progressive for at least 14 days (Zardini et al. 1993). Thrombolysis appears to be important in limiting infarct expansion and it is of interest that nearly twice as many patients in the survivors group received thrombolysis as did those that subsequently died. Previous work has shown that there is no difference in late potentials measured at 48 hours between patients treated with or without thrombolytics, but at 7 days post-infarction a difference does emerge (Eldar et al. 1990). Ventricular remodelling may determine the development of QT dispersion as well as late potentials and might explain why early QT dispersion is not a

useful marker for late mortality. It is clear, however, that alternative explanations exist for the apparent association between "late" QT dispersion and subsequent mortality seen in this study. Due to the retrospective nature of this study, "late" ECGs were available in less than half of the patients, and it is possible that the association is related to patient selection. For instance, many of the late ECGs recorded from patients who subsequently died were taken because of the development of heart failure: the relationship between persistent QT dispersion and subsequent death could be explained by its dependence on ventricular function. Other workers have shown an association between QT dispersion and ejection fractions in different settings (Davey et al. 1994, Pye et al. 1993). The fact that QT dispersion decreased in patients with heart failure who subsequently survived (table 4.6) would suggest that "late" QT dispersion may be independently associated with death but the numbers involved are too small to be confident of this.

A further possibility is that QT dispersion is merely a surrogate marker of a morphologically abnormal ECG. In the first few days after acute myocardial infarction all ECGs are grossly abnormal, and therefore QT dispersion measurements are large. After a period some ECGs will become more normal in appearance, and as a result QT dispersion falls. The ECGs which remain grossly abnormal may have greater values of QT dispersion, and a worse prognosis. However studying these ECGs in more detail reveals that the major difference between the 2 groups of later ECGs is in the ST segment rather than the T wave, which would not be expected to alter QT dispersion measurements.

A prolonged single lead QT measurement has been proposed as a risk factor for mortality following myocardial infarction (Ahnve et al. 1984, Wheelan et al. 1986). Criticism of previous papers suggested that this effect may be more the result of

differences in heart rate, leading to overcorrection by Bazett's formula (Ward, 1988). This would be consistent with our data, since there is no difference between non-survivors and survivors when the QT interval is not rate corrected. QT dispersion, and particularly coefficient of QT variation, is less sensitive to rate adjustment. Previous studies have varied in the timing of the ECG measured after myocardial infarction, the rapid change in QT intervals during the early days of myocardial infarction also helps to explain the lack of consistency in the results of these studies.

In conclusion, QT dispersion measured on an ECG recorded on day 2 or 3 of acute myocardial infarction is not a predictor of subsequent mortality over a 5 year follow-up period. Increased QT dispersion on ECGs recorded after this period may be associated with subsequent mortality. It is unlikely that QT dispersion is a useful predictor of sudden, arrhythmic, death after myocardial infarction.

**CHAPTER 5.**  
**MECHANISMS AND POSSIBLE**  
**CAUSES OF QT DISPERSION.**

### *5.1. Associations and possible causes of QT dispersion after myocardial infarction.*

A limited amount of clinical and therapeutic categorical data was available from the case notes of the patients studied in the previous chapter. I have examined possible associations of these factors with QT dispersion from the pre-discharge ECGs. The late ECGs represent a much smaller group and are possibly a selected sample, analysis of possible associations with QT dispersion measured from these ECGs is probably not valid.

Univariate analysis showed no association of any of the categorical factors shown in table 5.1 with an increase or decrease in QT dispersion. In particular the presence of early heart failure was not associated with increased QT dispersion, and patients who were thrombolysed did not have decreased QT dispersion. There was a trend towards decreased QT dispersion in patients receiving antiarrhythmic therapy, surprisingly a similar trend towards decreased QT dispersion was seen in patients who subsequently died, who had ventricular arrhythmias. This may be explained by the fact that most of these patients were receiving antiarrhythmic therapy, 10 were receiving amiodarone. For continuous data there was no significant correlation of QT dispersion with either age or level of creatinine kinase.

Table 5.1 - Categorical data and QT dispersion measured from an "early" ECG following myocardial infarction.

	<i>DEATHS</i>			<i>SURVIVORS</i>		
	<i>n</i>	Mean QT dispersion	Mean QTc dispersion	<i>n</i>	Mean QT dispersion	Mean QTc dispersion
Total	163	93.6	112.1	163	94.2	109.9
Males	110	94.3	113.8	110	96.3	111.1
Females	53	92.1	108.7	53	89.8	107.4
Previous myocardial infarction	53	94.2	114.6	15	98.3	112.2
Hypertensive	37	94.8	115.7	41	94.4	109.1
Diabetic	29	83.2	101.8	19	106.5	119.7
Smoker	49	97.6	113.2	53	97.5	112.8
Antianginal therapy	43	103.6	117.8	31	106.5	122
Diuretic therapy	82	92.1	112.2	35	86.1	102.8
Antiarrhythmic therapy	34	84	101	6	92.8	105.5
Anterior infarction	71	94.4	112.6	66	98	119
Inferior infarction	45	92.2	110.6	67	89.4	100.5
Presence of Q waves	108	95.9	114.2	116	93	108.3
Patients thrombolysed	55	94	115.1	99	93.9	109.4
Ventricular arrhythmia	25	81.2	102.6	10	95.8	106.1
Presence of heart failure	76	89.1	109.6	39	93.6	112.9

### 5.2. QT dispersion during coronary angioplasty.

Ten patients with stable angina were studied during percutaneous coronary angioplasty. QT dispersion was measured from continuous ECG recordings during the procedures. The ECGs were all simultaneous 12 lead recordings. QT dispersion was measured prior to the start of the procedure, during balloon inflation, and after balloon deflation, ranging from 2 to 10 minutes post-angioplasty. There was no difference in mean QT dispersion before, during, or after angioplasty, as shown in table 5.2.

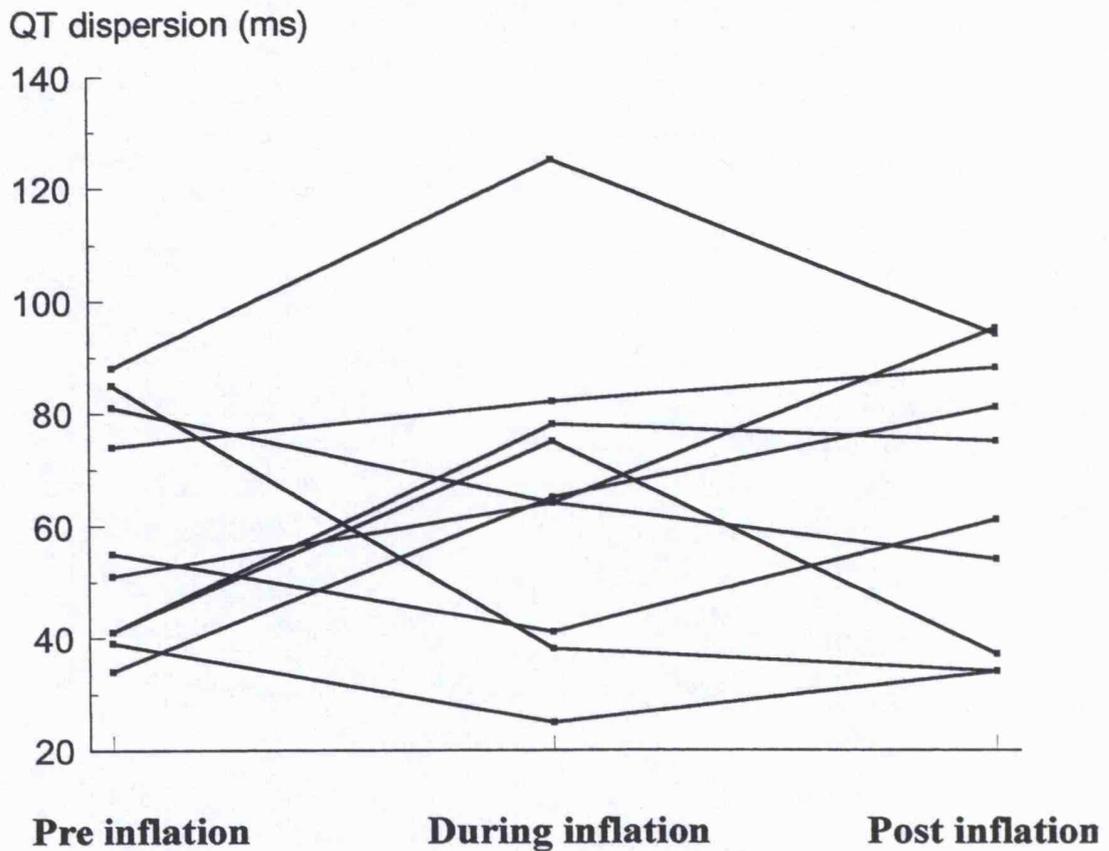
Table 5.2. - QT dispersion during coronary angioplasty.

	Pre-procedure	During angioplasty	Post-procedure
QT dispersion (ms)	58.9 (21)	65.7 (28)	69.4 (29.9)
QTc dispersion (ms)	63 (25)	72 (33)	71 (30.6)
Adjusted QTc dispersion(ms)	19.4 (7.4)	21.9 (9.5)	21.5 (8.9)
Coefficient of QT variation(%)	4.38 (1.59)	4.91 (1.91)	5.18 (1.94)

Data Mean (SD)

However in 5 of these patients there were marked changes in QT dispersion during balloon inflation. In 4 patients there was a rise of over 30 ms in QT dispersion during balloon inflation. In 2 of these patients this rise was followed by a fall in QT dispersion towards pre-procedure values, in the other 2 patients QT dispersion increased further after balloon deflation. In one patient there was a fall of nearly 50 ms in QT dispersion during balloon inflation. These data are shown in figure 5.1.

Figure 5.1. QT dispersion in each of the 10 patients during coronary angioplasty.



Amongst the 5 patients with a change of over 30 ms in QT dispersion measurements during angioplasty there were marked ECG changes during coronary angioplasty in 4 cases, 3 of which showed gross ST segment elevation. In the other 5 patients who had little change in QT dispersion measurements only 1 patient developed marked ECG changes during angioplasty.

There are 2 explanations of these data. It is possible that QT dispersion is increased during acute ischaemia induced by coronary angioplasty. The 5 patients who had little change in QT dispersion also had little change in ECG morphology during

balloon inflation, and may not have been rendered ischaemic during the procedure. The fall in QT dispersion during balloon inflation as seen in 1 patient is less readily explained. An alternative explanation is that the rise in QT dispersion is merely a marker of the change in morphology of the ECGs. Certainly the gross ST segment changes induced by coronary angioplasty in some patients makes the T wave end more difficult to measure, and this might result in a degree of artefactual increase in QT dispersion measurements.

There are no published articles about QT dispersion during coronary angioplasty, 1 published abstract shows data consistent with that presented here. In a study of 48 patients an equal number of individuals were randomised to receive either propafenone or placebo (Faber et al. 1994). Experimental ischaemia was induced by coronary angioplasty. The authors reported a mean increase of 41 ms in QT dispersion with angioplasty in the propafenone treated group, and a mean increase of 27 ms in the placebo group.

The data presented justify a much larger study of QT dispersion during coronary angioplasty, including measurement of biochemical and other markers of ischaemia.

### *5.3. QT dispersion in patients with dilated cardiomyopathy.*

QT dispersion was measured in 17 patients with a clinical diagnosis of dilated cardiomyopathy. These patients are all of Omani origin, from Dr Ajit Agarwal's series. These patients were all admitted to hospital with a diagnosis of congestive cardiac failure of unknown aetiology. Ischaemic heart disease was excluded by a combination of exercise testing, with coronary angiography in selected patients. Characteristic echocardiographic appearances of dilated cardiomyopathy were obtained in all cases.

Their ECGs are all abnormal, mostly with left ventricular hypertrophy and strain pattern, ST segment and T wave abnormalities. Mean (SD) QT dispersion in these patients is 62.8 (33.6) ms, QTc dispersion is 74.7 (35.5) ms, adjusted QTc dispersion is 24.8 (11) ms, coefficient of QT variation is 5.5 (2.5) %. The relatively low values of QT dispersion observed in these patients is in keeping with other data on QT dispersion measurements in patients with chronic heart failure (Pye et al. 1993, Barr et al. 1994, Davey et al. 1994), and suggest that left ventricular dysfunction is not a cause of increased QT dispersion. However the data presented here does have major limitations, with little information available about the patients. The most important conclusion is that markedly morphologically abnormal ECGs are not necessarily associated with increased QT dispersion measurements.

**CHAPTER 6.**  
**REPRODUCIBILITY OF QT DISPERSION.**

### **6.1 Introduction.**

For any clinical measurement to be useful, particularly as a predictor of events, it must be reproducible. In normal ECGs the reproducibility of QT dispersion has been questioned, with large relative errors for both interobserver, and intrasubject measurements (Kautzner et al. 1994). This may have been partly the consequence of the absolute values for QT dispersion measurements being small in normal subjects, and therefore small absolute errors would convert into large relative errors. Reproducibility of QT dispersion from abnormal ECGs has not previously been properly addressed. Therefore 70 of the late ECGs from the study in chapter 4 were reanalysed, both for intraobserver and interobserver error. An answer to the problem of reproducibility would be a 100% accurate automated system. The 2 observers' measurements were compared with the automatic algorithm, previously described.

### **6.2. Methods.**

From the previous study of QT dispersion and mortality 135 patients had ECGs available from at least 28 days post infarct. Seventy of these ECGs were randomly chosen for analysis. Sixty of the ECGs had inverted or biphasic T waves. Of the remaining 10 ECGs 8 had Q waves, and 8 had prominent U waves. Two ECGs looked morphologically normal.

The author (observer 1) re-analysed the ECGs at least 6 months after the first measurement, a second observer experienced in QT interval measurement also determined QT dispersion in all 70 ECGs. The fully automated algorithm was also used to measure QT dispersion from the ECGs. Visual monitoring of the automatic algorithm very occasionally revealed gross misinterpretation of a QT interval, such a

lead was excluded from analysis. The 20 ECGs with greatest error for QTc dispersion measurements between the automatic system and observers were re-analysed automatically. Observer 1 monitored the re-analysis and substituted his measurement of a QT interval if he felt the automatic system to be markedly wrong. Mean RR interval, uncorrected mean QT interval, and QTc dispersion for each ECG analysed were calculated. Statistical analysis were by methods described by Bland and Altman, with log transformation of data if necessary (Bland and Altman 1986). The repeatability coefficient is the expected value below which 95% of the differences will fall for intrasubject and interobserver reproducibility. For comparison between the two methods of measurement 95% of expected differences will fall within the limits of agreement.

### **6.3. Results.**

Mean absolute errors, relative errors, and repeatability coefficients or limits of agreement for RR intervals, uncorrected QT intervals, and rate corrected QT dispersion are shown for intrasubject and interobserver variability in table 6.1 and for comparison between the user-interactive and automatic systems in table 6.2.

Table 6.1 - Intrasubject and interobserver errors of mean RR intervals, mean QT intervals, and QTc dispersion.

	<u>Intrasubject</u> <u>Measurements</u>			<u>Interobserver</u> <u>Measurements</u>		
	RR interval	QT interval	QTc dispersion	RR interval	QT interval	QTc dispersion
Mean absolute difference (ms)	4	6	12	4	7	15
Relative difference (%)	0.5	1.4	17.3	0.5	1.8	22.1
Coefficient of repeatability (ms)	2	16	28	2	20	37

Table 6.2 -Errors between observers and automatic measurement for mean RR intervals, mean QT intervals, and QTc dispersion.

	<u>Observer 1</u>			<u>Observer 2</u>		
	RR interval	QT interval	QTc dispersion	RR interval	QT interval	QTc dispersion
Bias (ms)	0	2	22	0	8	17
Mean absolute difference (ms)	3	10	30	3	11	28
Relative difference (%)	0.3	2.5	35.4	0.3	2.8	31.9
Limits of agreement (ms) [% for log transformed data]	- 16, 16	- 15, 19	- 64%, 63%	- 10, 10	- 11, 27	- 86%, 63%

There was close agreement for RR interval measurements between both observers and the automatic system. Figures 6.1 and 6.2 are Bland-Altman plots for interobserver and intrasubject errors of mean QTc intervals. Figure 6.3 is a similar plot combining the data from both observers vs. the automatic system for mean QT interval measurements.

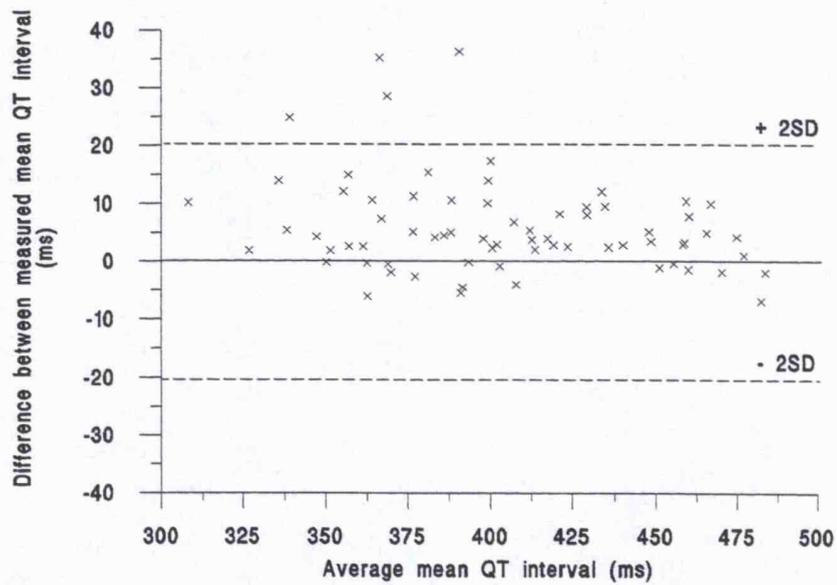


Figure 6.1 - Interobserver error of mean QT intervals.

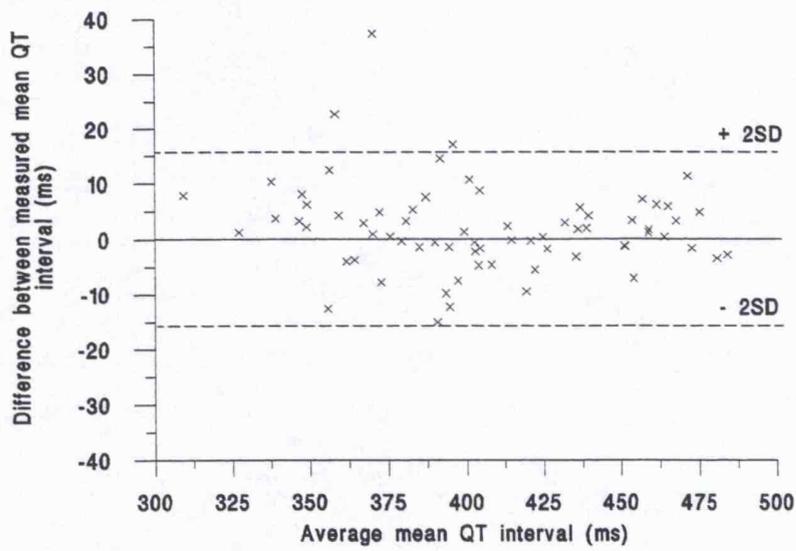


Figure 6.2 - Intrasubject error of mean QT intervals.

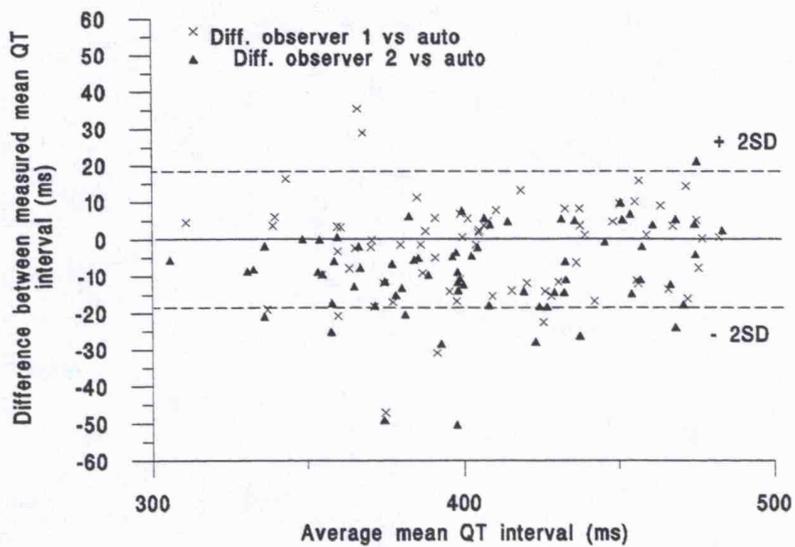


Figure 6.3 - Difference between observers and automatic algorithm for mean QT interval measurements.

Figures 6.4 and 6.5 are Bland-Altman plots for interobserver and intrasubject errors of QTc dispersion. Figure 6.6 is a similar plot combining the data from both observers vs. the automatic system for QTc dispersion measurements.

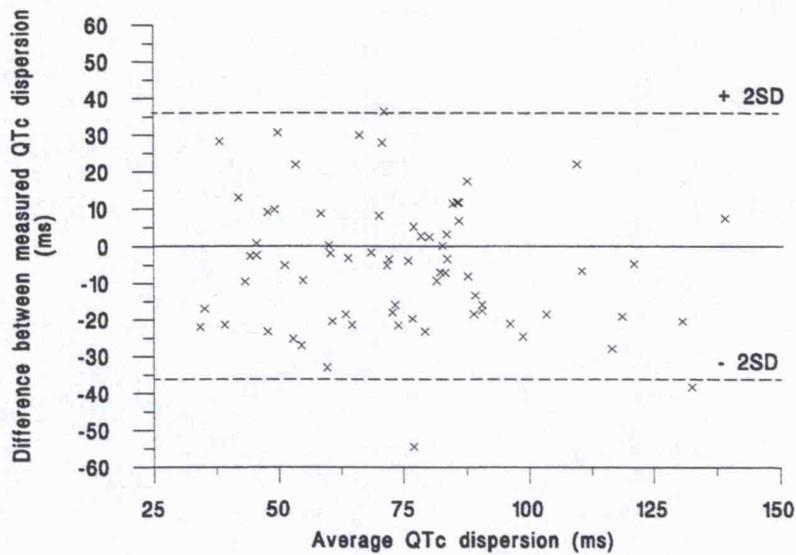


Figure 6.4 - Interobserver error of QTc dispersion.

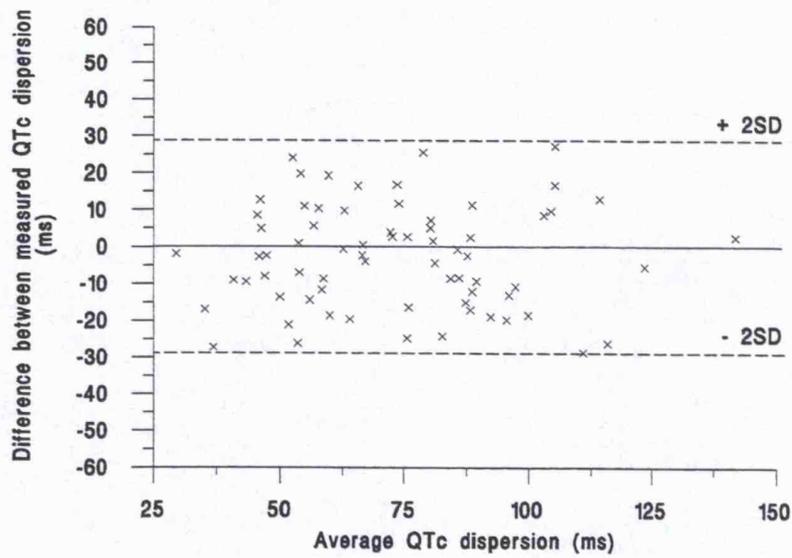


Figure 6.5 - Intrasubject error of QTc dispersion.

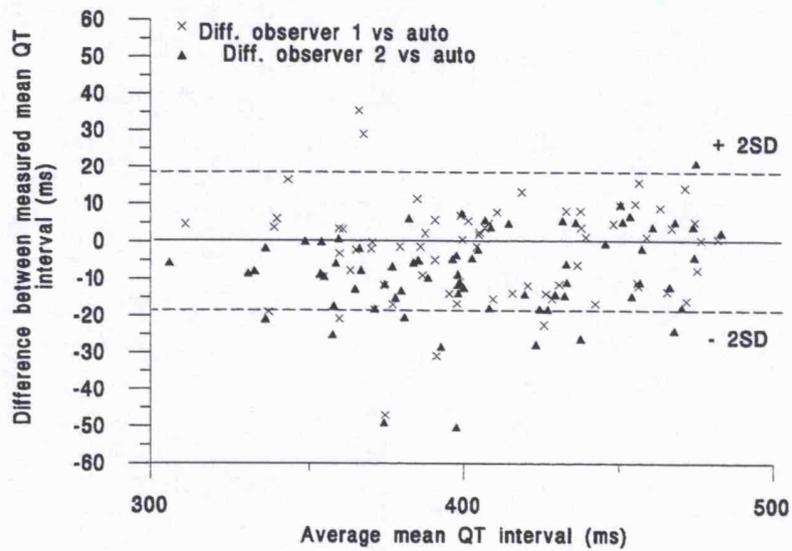
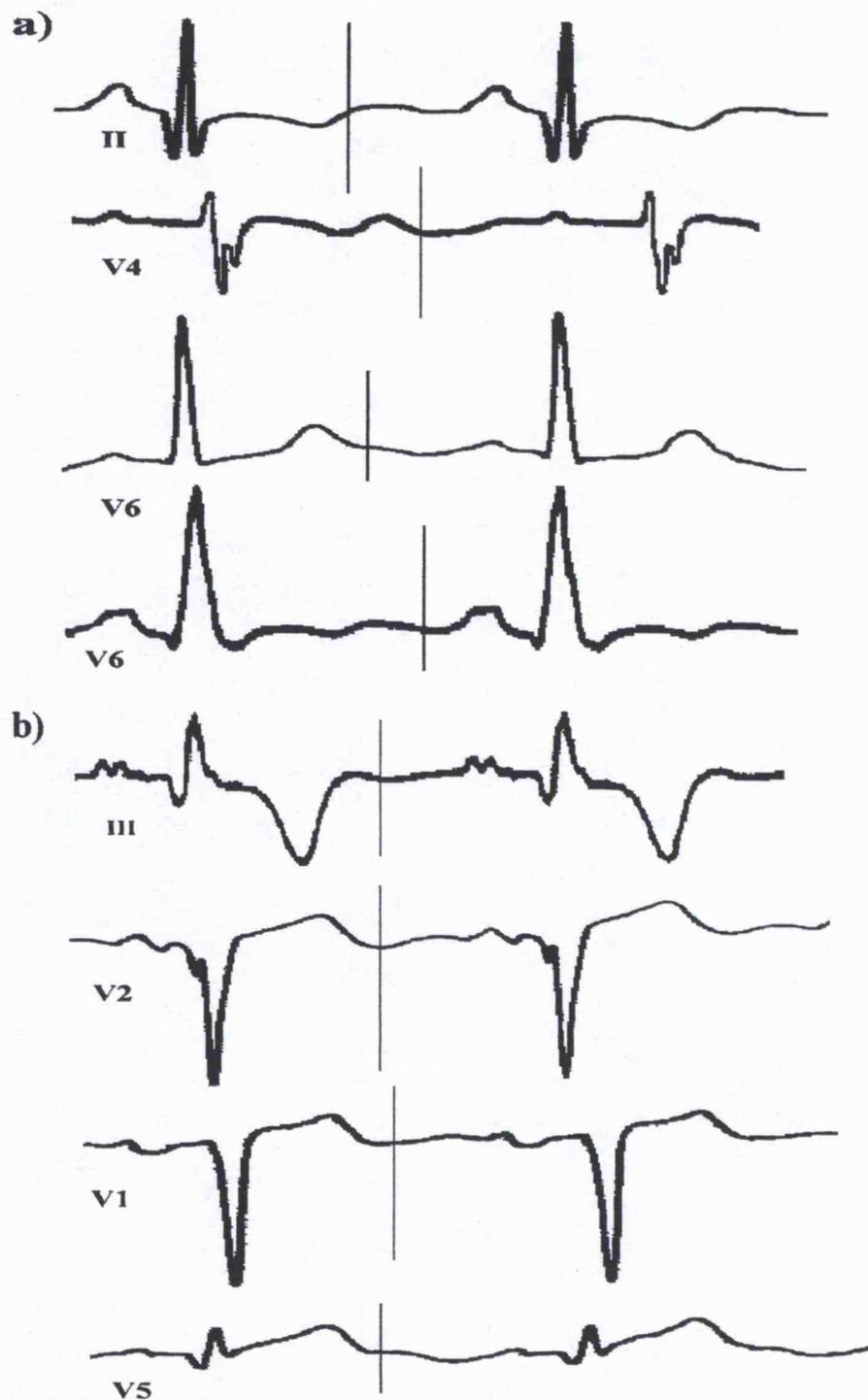


Figure 6.6 - Difference between observers and automatic algorithm for QTc dispersion measurements.

There was a small bias of 6 ms for observer 2 to measure shorter mean QT intervals, compared to observer 1. There was bias for the automatic system to measure both longer mean QT intervals and higher QTc dispersion than either observer. Greater errors of QTc dispersion measurement between the automatic system and observers existed at higher average QTc dispersion values.

For the 20 ECGs re-analysed automatically observer 1 detected and corrected marked errors of QT interval measurements in 1 lead for 18 ECGs, 2 leads for 2 ECGs, and 3 leads for 1 ECG. Repeatability of the automatic system was confirmed as 100%. In 9 leads a part of the T wave was misinterpreted as a U wave, for 4 leads the converse error was seen. In 6 leads the automatic system attempted to measure T waves too flat for accurate measurement, and in 2 leads misinterpreted baseline wander as a T wave. The remaining 4 leads had errors in the measurement of the QRS onset. Correction of these leads by observer 1 reduced the absolute error (relative error) in QTc dispersion measurements between observer 1 and the automatic system for these 20 ECGs from 53 ms (53%) to 14 ms (14%). Figure 6.7 shows examples of leads causing greatest error for a) the automatic system, and b) between observers.



**Vertical lines are T wave ends as defined by observer 1  
Based on definitions by Lepschkin**

Figure 6.7 - Examples of ECG leads causing greatest error a) for the automatic system, and b) between observers.

#### *6.4. Discussion.*

Definitions of reproducibility can be confusing. This chapter concentrates on reproducibility of QT dispersion measurement from many ECGs containing different T wave morphologies, and not on the reproducibility of measuring QT dispersion from a single ECG on several different occasions. Using the first definition reproducibility of QT dispersion appears to be a major problem. In normal subjects Kautzner and colleagues found relative errors between observers of between 26.8% and 33.2% for measures of QT dispersion (Kautzner et al. 1994). Others have shown absolute interobserver errors of up to 20 ms for QT dispersion in normal subjects, and suggested poor reproducibility (Fei and Statters. 1994). The data presented concurs with those studies. In contrast van de Loo and colleagues studied 77 ECGs from 120 patients during acute myocardial infarction (43 patients were excluded from the study), in combination with 50 ECGs from age and sex matched normal controls (Van de Loo et al. 1994). They reported a mean interobserver error of only 7 ms for QTc dispersion, and a mean intrasubject error of 6 ms for QT dispersion in the total group studied. Unfortunately errors within each group were compared by correlation coefficients, making comparison of their population of abnormal ECGs with the data presented here difficult. They concluded their reason for good reproducibility was that ECGs were recorded at 50 mm/sec and not 25 mm/sec. They compared a small subgroup of ECGs at different recording speeds again by correlation coefficients to try to confirm this hypothesis.

If the problem of reproducibility was due to paper speed recording, and therefore problems of resolution, then one would expect poor reproducibility for all QT intervals. These data and others do not show this (Kautzner et al. 1994). Improved

reproducibility of mean QT interval measurement has been shown with faster paper speeds in small numbers of ECGs, however the interobserver error of mean QT intervals reported here of 7 ms is less than that study's reported error in ECGs recorded at 100 mm/sec (Murray et al. 1994).

Large errors in the determination of QT intervals during acute myocardial infarction have been reported between observers not specifically experienced in QT interval measurement (Ahnve. 1985). Accurate QT interval measurement requires some experience, the end of a T wave can be difficult to determine. The definitive paper by Lepeschkin and Surawicz in 1952 remains as the only benchmark for accuracy and repeatability of QT interval measurement (Lepeschkin and Surawicz. 1952), and its criteria for determining a T wave end must be adopted strictly. Even here there are problems. Some of their methods used to define T wave ends rely on the synchronicity of all T waves across a surface ECG, an idea contrary to the concept of QT dispersion. The greatest potential source for error is the analysis of a T-U interval. If a notch or kink is present between a T and U wave then the measurement is easier. The often misquoted phrase "if a U wave was present we defined the end of the T wave as the nadir between the T and U wave" in fact refers to the nadir of a notch if it is present. This misinterpretation from Lepeschkin's paper may be responsible for considerable error. The use of the nadir of the notch to define a T wave end was used in these difficult waveforms to produce a reproducible measurement of the T wave end. However there is no electrophysiological basis for using the nadir of the notch as a measurement of cardiac repolarisation. The use of the nadir of the notch in these difficult ECGs may produce a reproducible but inaccurate measurement of QT dispersion. In the abnormal ECGs we studied an inverted T wave often flowed

smoothly into a U wave, without any obvious notch, resulting in difficulty in determining the T wave end. When a U wave is superimposed on a T wave, for example the final waveform in figure 4, phonocardiography was used by Lepschkin and Surawicz to define the T wave end. The method of extrapolating the downslope of the T wave to the baseline would seem to be the best method of analysing such leads (Cui et al. 1994). Where problems with T and U waves are encountered, interlead variability of QT intervals is significantly decreased by excluding such leads (Sylvén et al. 1984). However if these leads were ignored in analysis, a falsely low value of QT dispersion would be obtained. From the data presented here it is likely that these difficult to measure QT intervals are those most likely to contribute to QT dispersion.

The advantage of a fully automated system of QT dispersion measurement is 100% reproducibility. This automatic algorithm was designed to recognise most common T wave morphologies. To this extent it appears quite successful, repeatability for mean QT intervals between this system and the 2 observers appear acceptable. However recognition of rarer T wave morphologies appears poor, resulting in inaccurate measurements of QT dispersion. Methods of designing most automatic computer algorithms for QT interval measurement rely on recognising common T wave morphologies, and have been validated using normal ECGs (O'Donnell et al. 1981, Puddu et al. 1992). The specific problem encountered here with the automated measurement system is probably a general one. Increasing the repertory of algorithms available to automatic systems is feasible, but some form of "operator monitoring" remains desirable. Simple improvements to the automatic system tested here could be applied. A filter to exclude T waves from measurement if the T wave peak fell below a certain voltage would exclude the near isoelectric T waves from measurement. A

similar filter set at say 200 ms from the QRS complex introduced to prevent the system measuring an impossibly early T wave end would provide a further improvement. At present, particularly in ECGs early after myocardial infarction, the system occasionally interprets a grossly elevated ST segment as a T wave end. No system, whether automated or manual, will cope with the completely isoelectric T wave.

The poor reproducibility of QT dispersion measurement limits its usefulness. With an intrasubject coefficient of repeatability of 28 ms, reported differences of this order in QTc dispersion measurements in the same study for one observer should be treated with caution. Comparisons of QT dispersion measurements between either different observers or across studies call for even greater care.

CHAPTER 7.

ARE LEAD ADJUSTMENT FORMULAE OF  
QT DISPERSION APPROPRIATE AFTER  
MYOCARDIAL INFARCTION ?

### *7.1. Introduction.*

A potential confounding factor in QT dispersion measurement is the number of leads in which a QT interval can be accurately measured. For abnormal ECGs, in one or more leads the end of the T wave may be difficult to define because of flattening of the waveform, or a U wave may interrupt the T wave end. Such leads may have to be omitted from QT dispersion analysis for a given ECG. QT dispersion depends on the two extreme values of QT interval measured. In normal subjects, as leads are removed from QT dispersion analysis the mean QT dispersion of that population falls, dependent on the number of leads removed. To adjust for this, the formula QT dispersion divided by the square root of the number of measurable leads was devised by Day and colleagues (Day et al. 1991). An alternative approach to a lead adjusted formula is a formula based on the standard deviation or coefficient of variation of QT intervals for all measured leads (Priori et al. 1994). As well as potentially allowing for differences in the number of measured leads, this approach may have the advantage of providing information about QT dispersion from the entire ECG.

Hnatkova and colleagues have recently observed that the application of different lead adjustment formulae causes a large variation in QT dispersion estimates obtained from 27 electrocardiograms of healthy subjects (Hnatkova et al. 1994). In this chapter QTc dispersion is evaluated in ECGs following myocardial infarction, to ascertain if lead adjustment formulae are appropriate in this population.

### *7.2. Methods.*

All ECGs from the study of mortality and QT dispersion (chapter 4) were studied. A total of 461 ECGs were examined. Each ECG had at least 5 leads in which a QT interval could be accurately measured.

Leads had been excluded from QT dispersion analysis if the T wave, or its terminal portion, were too flat to determine accurately the T wave end; or if a U wave so interfered with a T wave end that the end of the T wave could not be accurately identified. There were no formal criteria for excluding a lead from measurement, this being decided by simple observation by the author. QT intervals were rate corrected using Bazett's formula. QTc dispersion is presented, with 2 formulae that attempt to correct for number of leads measured :

- a) Lead adjusted QTc dispersion (QTc dispersion divided by the square root of the number of leads in which a QT interval was measured).
- b) Coefficient of variation of QTc intervals (standard deviation of QTc intervals divided by the mean QTc interval).

Statistical analyses were by correlation coefficients and simple regression for the comparison of lead adjustment formulae against QTc dispersion, and Mann-Whitney tests for comparison of inter-lead measurements.

### 7.3. Results

Table 7.1 shows the contribution of individual leads to QTc dispersion measurements. Lead aVR was by far the most commonly omitted lead from QT interval measurement, in marked contrast to leads V2 or V3 which were rarely omitted. The contribution of individual leads as maximum or minimum QT intervals was more evenly spread, lead V4 was over twice as likely to supply a maximum rather than a minimum QT interval, in contrast to lead V1 which showed the opposite trend.

Table 7.1 - Leads omitted from QT interval analysis, and contribution of leads to QTc dispersion measurement.

	aVR	aVL	aVF	I	II	III	V1	V2	V3	V4	V5	V6
Number of omitted leads	176	111	63	79	95	63	72	19	13	40	67	109
Longest QTc interval	15	31	46	24	43	37	20	32	48	72	53	38
Shortest QTc interval	29	30	30	38	47	31	67	32	40	30	52	33

Table 7.2 shows QTc dispersion measurements and lead adjustment formulae for ECGs with different numbers of leads in which QT intervals could be measured. There was a small, non significant, increase in unadjusted QTc dispersion from 12 to 8 leads, followed by a fall in QTc dispersion from 8 to 7 leads. There were differences in unadjusted QTc dispersion measurements ( $p < 0.05$ ) between ECGs where 7 leads could be measured, and where 8, 9, or 11 leads were analysed. However the number of ECGs in which only 7 leads had a measurable QT interval were small, and for 6 leads very small. There were large, significant, increases in lead adjusted QTc dispersion and

coefficient of variation of QTc intervals from 12 through to 8 leads, and then a fall from 8 to 7 leads, which reached significance only for lead adjusted QTc dispersion. For lead adjusted QTc dispersion the differences measured between ECGs with different numbers of measurable QT intervals reached statistical significance at  $p < 0.001$  for 12 vs. 8 leads;  $p < 0.01$  for 12 vs. 10 and 9 leads, 8 vs. 10 and 11 leads; and  $p < 0.05$  for 7 vs. 8 leads. For coefficient of variation of QTc intervals similar results were seen at  $p < 0.01$  for 12 vs. 9 and 8 leads; and  $p < 0.05$  for 8 vs. 10 and 11 leads.

Table 7.2 - QTc dispersion, lead adjusted QTc dispersion, and coefficient of variation of QTc intervals for ECGs in which between 6 and 12 leads had a measurable QT interval.

Number of measurable leads	12	11	10	9	8	7	6
Number of ECGs	68	103	125	72	50	28	8
QTc dispersion (ms)	100 (35.5)	105.4 (46.3)	103 (40.1)	110.1 (45.5)	109.5 (47.9)	89.5 (39.3)	93.5 (54)
Lead adjusted QTc dispersion (ms)	28.9 (10.3)	32.2 (13.8)	32.6 (12.7)	36.6 (16)	38.7 (16.1)	33.8 (14.9)	38.2 (22.4)
Coefficient of QTc intervals (%)	6.43 (2.19)	7.15 (2.92)	7.12 (2.9)	7.84 (3.22)	8.45 (3.94)	7.29 (3.12)	8.01 (4.76)

The relationship of lead adjusted QTc dispersion and coefficient of variation of QTc intervals with unadjusted QTc dispersion is shown in figures 7.1 and 7.2, for ECGs in which QT intervals were measured in 8, 10, and 12 leads.

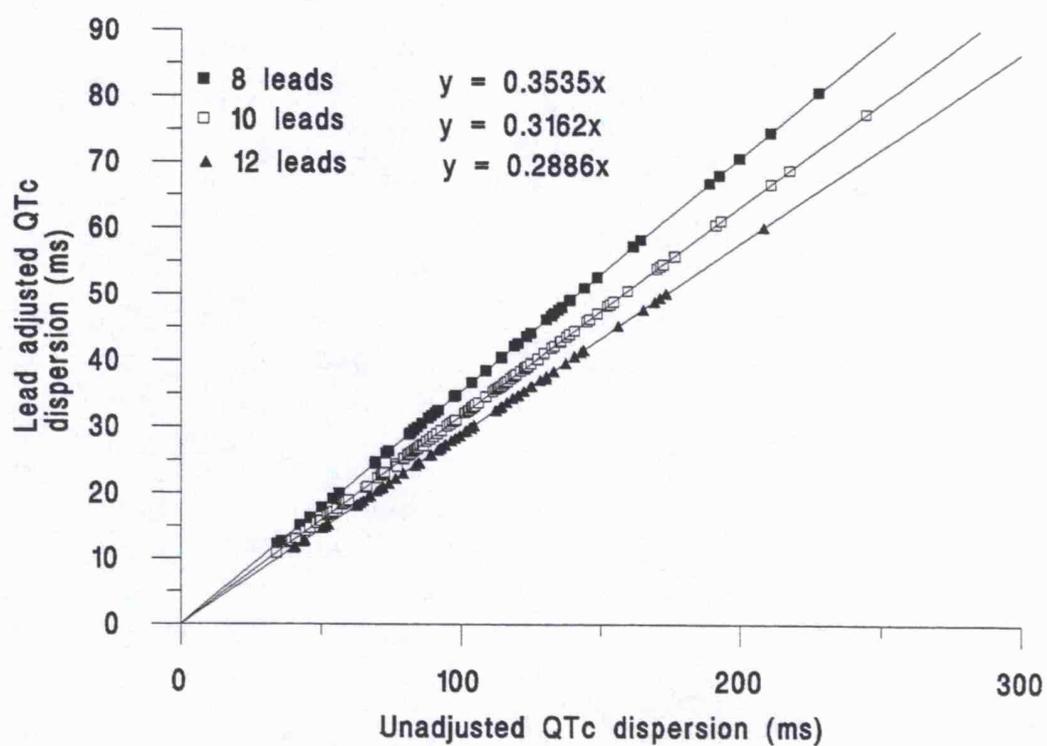


Figure 7.1 - Relationship of lead adjusted and unadjusted QTc dispersion for 8, 10, and 12 leads.

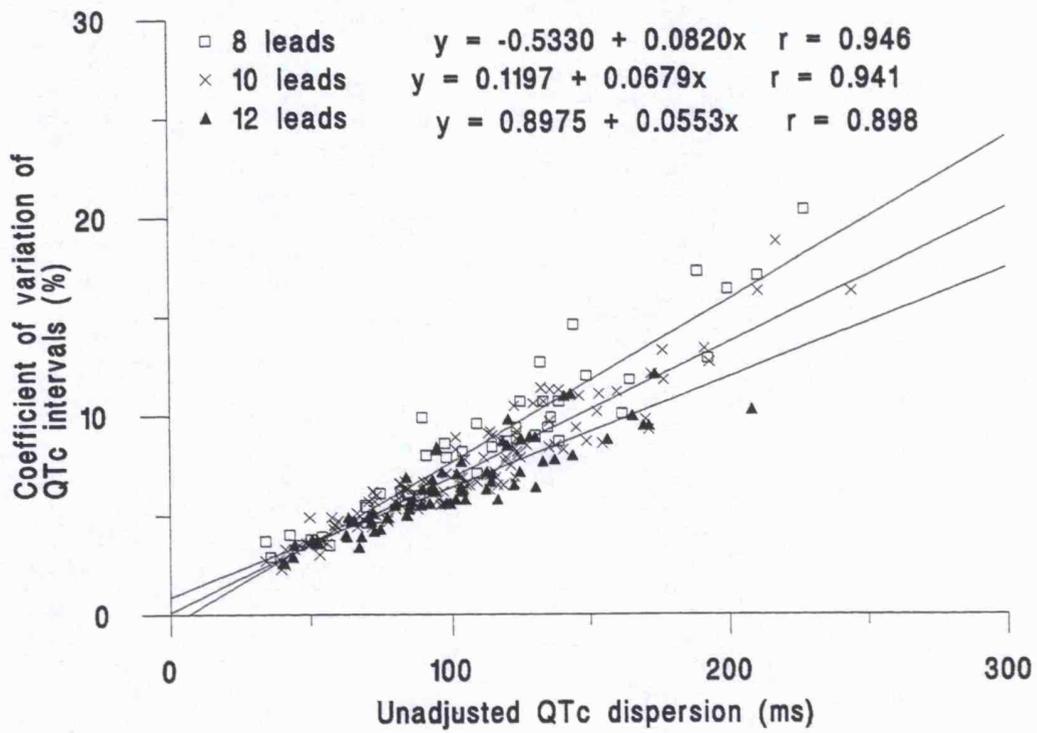


Figure 7.2 - Relationship of coefficient of QT intervals and unadjusted QTc dispersion for 8, 10, and 12 leads.

#### *7.4. Discussion.*

When measuring QT dispersion from a 12 lead ECG, failure to measure the QT interval in all available leads increases the likelihood that a lead containing a maximum or minimum QT interval will be omitted, and tends to lead to an apparent reduction in the measured QT dispersion. Day and colleagues showed that this effect could largely be compensated for by dividing the QT dispersion by the square root of the number of measurable leads.

Application of a valid correction formula to QT dispersion measurements from a large number of patients would be expected to produce a homogeneous distribution of adjusted QT dispersion measurements. In fact, in these ECGs whilst little change was observed in unadjusted QTc dispersion in patients for whom between 8 and 12 leads could be measured, the application of the adjustment formula caused a consistent and highly significant increase in "adjusted" QTc dispersion in patients for whom fewer leads could be measured.

One possible explanation is that patients with increased QT dispersion are more likely to have "unusual" ECGs and thus more likely to have one or more leads in which the QT interval is not measurable. An alternative explanation is that in the post myocardial infarct situation the leads whose QT measurement are most likely to be omitted are in fact those least likely to show either a maximum or minimum QT value. This would not only explain the apparent overcompensation of the Day formula, but would also explain why coefficient of QTc variation, which in concept should include information from all measured leads, also shows a consistent bias towards a higher value in ECGs for which less than 12 leads have been measured. This hypothesis is

difficult to substantiate, as by excluding a lead from measurement it is impossible to know if it would have included an extreme QT interval.

Lead adjusted QT dispersion and coefficient of variation of QT intervals may be useful measurements in normal subjects, but are not appropriate in patients following myocardial infarction. Moreover any simple arithmetical correction factor could be appropriate only if the removal of leads from QT interval measurement in this study were a random process, as would probably be the case in normal ECGs. The data presented show that there was a systematic bias in the removal of leads from QT interval measurement.

These data contrast with the work of Day and colleagues (Day et al. 1991). In their study of patients treated with sotalol after the acute stage of myocardial infarction QTc dispersion increased in proportion to the square root of the number of leads. They studied a smaller number of ECGs, and the population studied was restricted to patients able to take a beta blocker. From the data presented most of the ECGs were recorded on day 2 or 3 of acute infarction. Half of the patients in this study subsequently died, and a high proportion had heart failure. Some of the differences in the data between the studies could be based on the difference in the nature of the populations studied.

Small changes in QTc dispersion produces large changes in either lead adjustment formula, e.g. a 9.5% increase in QTc dispersion from 12 to 8 leads is associated with a 33.9% increase in lead adjusted QTc dispersion and a 31.4% increase in the coefficient of variation of QTc intervals. Rather than adjusting for leads these formulae are producing results biased by the number of leads measured. Simple regression slopes for lead adjusted QTc dispersion are the reciprocal of the square root of the number of leads measured. For different numbers of leads measured in absolute

terms greater error is introduced at high values of QTc dispersion, but in relative terms the errors are equal at all values. Similar regression comparing the correlation of variation of QTc intervals to QTc dispersion reveals greater absolute and relative error at high values of QTc dispersion. However the regression lines for different numbers of leads crosses at a QTc dispersion of between 50 and 60 ms, suggesting that around this value the coefficient of variation of QTc intervals may be a very good lead adjustment factor. Hnatkova and colleagues have studied the effect of systematically eliminating leads from QTc dispersion analysis in ECGs from healthy subjects (Hnatkova et al. 1994). In this population they found that both lead adjusted QTc dispersion and unadjusted standard deviation of QTc intervals were stable methods of lead adjustment, and removed the bias introduced by omitting leads. Their major finding was that the coefficients of variance, of any method of QTc dispersion analysis employed, for incomplete ECGs were surprisingly large when compared to electrocardiograms in which all 12 leads were measured, and became greater as more leads were removed. From this they concluded that although on average lead adjustment formulae may work for a population of normal ECGs, they would not be successful in an individual example.

A potential limitation of the data presented is that all measurements were by a single observer, resulting in possible systematic bias. However the vast majority of studies of QT dispersion have been by a single observer, blinded to other data about the studies. It seems unlikely that the author could have anticipated the result obtained, and in that sense was "blinded". If the observer here encountered a problem with lead adjustment formulae, then it is likely that a similar conclusion would be reached by others.

The data presented suggest that neither lead adjustment formulae based on the square root of the number of measurable leads nor the measurement of the coefficient of variation of QT intervals are valid in patients following myocardial infarction. The best current option is to present QT dispersion as unadjusted QT or QTc dispersion, stating the mean (SD) of the number of leads in which a QT interval was measured.

CHAPTER 8.  
THREE LEAD MEASUREMENT  
OF QT DISPERSION.

### **8.1. Introduction.**

An answer to the problem of lead adjustment formulae would be to measure QT dispersion from a small standardised subset of leads (Hnatkova et al. 1994). It is possible that alternative, quicker methods using fewer than 12 leads could be used to provide the same information as the traditional measurement.

The difference in QTc dispersion from the "late" ECGs recorded at least 1 month after myocardial infarction between patients who subsequently die and long term survivors was used to test this hypothesis. There was a difference in the fall in QTc dispersion from early to late ECG between the groups (9.1[SD 60.8]ms for deaths vs. 34.4[55.2]ms for survivors,  $p = 0.016$ , using the standard 12 lead measurement of QTc dispersion. These ECGs were reanalysed using 4 methods to determine if the difference observed was maintained when QTc dispersion is measured from different subsets of leads.

### **8.2. Methods.**

QTc dispersion was recalculated in the 135 late ECGs, and their early paired ECGs by 4 methods:

- a) with the 2 extreme QTc intervals excluded.
- b) from the 6 precordial leads
- c) from the 3 leads most likely to contribute to QTc dispersion (aVF, V1, V4).
- d) from the 3 quasi-orthogonal leads (aVF,I,V2).

The decision to examine QTc dispersion based on the 3 leads most likely to contribute to QTc dispersion was based on examination of the contribution of leads to QT dispersion from all ECGs in this study. Lead aVR was by far the most commonly omitted lead from QT interval measurement (176 times), in marked contrast to leads V2 or V3 which were rarely omitted (32 times). The contribution of individual leads as

maximum or minimum QT intervals was more evenly spread, lead V4 was over twice as likely to supply a maximum rather than a minimum QT interval, in contrast to lead V1 which showed the opposite trend.

Assessment of agreement between each method and the traditional 12 lead measurement is by correlation coefficients and by mean differences (Bland and Altman, 1986). QTc dispersion is approximately normally distributed, and therefore predictive value of methods were compared by t-tests.

### **8.3. Results.**

All methods used for calculating QTc dispersion correlated well with QTc dispersion calculated by the traditional method: quasi-orthogonal leads  $r = 0.752$ , 3 "likeliest" leads  $r = 0.765$ , precordial leads  $r = 0.761$ , extreme leads removed  $r = 0.851$ ;  $p < 0.0001$ .

Both 3 lead methods showed less agreement with the traditional 12 lead method as compared to the other 2 methods assessed. The mean difference in QTc dispersion measurements between the 12 lead method and the quasi-orthogonal leads method was 39 ms (SD 30), and using the "likeliest leads" method 35 ms (31). For the precordial lead method the difference was 26 ms (30), and the ten lead method 29 ms (24). A Bland-Altman plot of the differences between QTc dispersion calculated from the quasi-orthogonal leads and the traditional 12 lead method for all ECGs studied is shown in figure 8.1

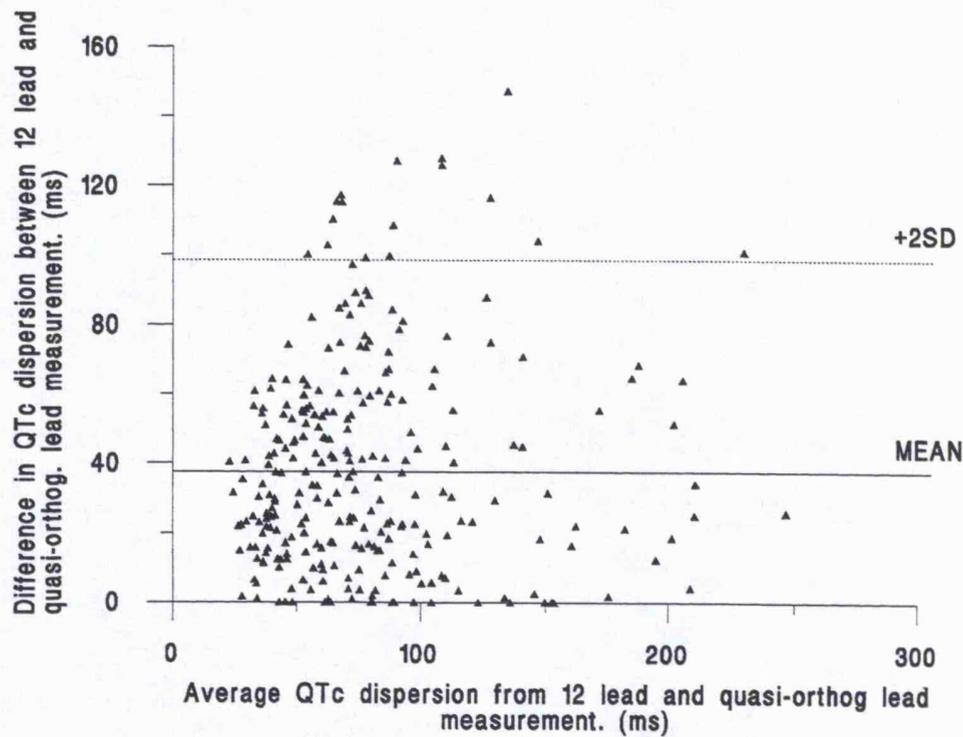


Figure 8.1 - Bland-Altman plot of the differences between QTc dispersion calculated from the quasi-orthogonal leads and the traditional 12 lead method for all ECGs studied

Table 8.1 shows QTc dispersion measurements using all methods for both "early" and "late" ECGs in patients who subsequently died and long term survivors. Table 8.2 compares the differences between the early and late ECGs for both groups. The predictive value of QTc dispersion measurements and the difference between groups was maintained using either 3 lead method, but not when the other 2 methods were employed.

Table 8.1 - Early and late QTc dispersion.

<i>Survivors</i>	QTc dispersion.	Three "likeliest" leads	Quasi-orthogonal leads	Precordial leads	Extreme leads removed
Early ECG	110.9 (48.5)	74.4 (49)	70.2 (47.1)	77.7 (45)	75.6 (40.7)
Late ECG	76.5 (28.9)	44.9 (28.3)	43.3 (29.5)	55.7 (28.8)	53.9 (23.3)
<i>Deaths</i>					
Early ECG	108 (51)	71 (51.5)	61 (47.7)	88.2 (50.4)	78.9 (44.4)
Late ECG	98.9 (43)	62.5 (40.9)	63.6 (45)	69.2 (36.4)	69.6 (34.9)

Data Mean (SD). Units - ms.

Table 8.2 - Comparison of differences between early and late ECGs for patients who died and survivors.

Mean change early to late ECG				
	Survivors	Patients who died	Difference (95% CI) between groups	p
n	82	53		
QTc dispersion.	34.4 (55.2)	9.1 (60.8)	25.3 (4.8, 45.8)	0.016
Three "likeliest" leads.	29.5 (50.2)	8.6 (64.9)	20.9 (0, 47.1)	0.05
Quasi-orthogonal leads.	26.9 (54.3)	- 2.6 (56.2)	29.5 (10.2, 49)	0.003
Precordial leads.	22 (50.8)	19.1 (55)	2.9 (- 15.9, 21.7)	0.76
Extreme leads removed.	21.8 (42)	9.2 (50.1)	12.6 (- 4, 29)	0.13

Data Mean (SD). Units - ms.

Scatter graphs of QTc dispersion calculated from 12 leads and the quasi-orthogonal leads are shown for patients who subsequently died in figure 8.2, and for long term survivors in figure 8.3.

Figure 8.2 - Scatter graph of QTc dispersion from early and late ECGs for patients who subsequently died, calculated from the 12 lead ECG, and from the quasi-orthogonal leads.

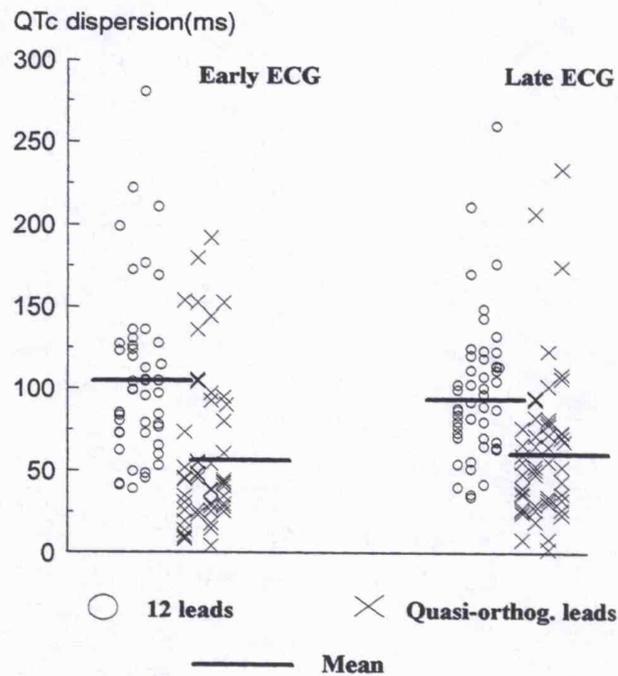
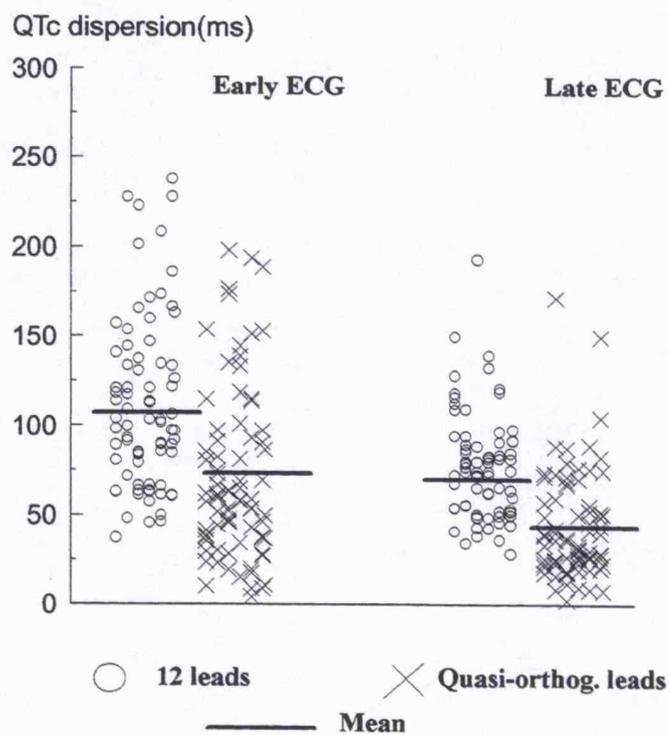


Figure 8.3 - Scatter graph of QTc dispersion from early and late ECGs for long term survivors, calculated from the 12 lead ECG, and from the quasi-orthogonal leads.



#### *8.4. Discussion.*

The data presented suggest that QT dispersion measured from a subset of leads of a standard ECG, and in particular from 3 leads, may provide similar information to that derived from the measurement of QT intervals in all 12 leads.

The predictive value of QTc dispersion measurements presented appear to be maintained when either 3 lead method are employed, but not when either the 10 lead or precordial lead method are used. Despite this the latter 2 methods agree more closely with QTc dispersion calculated from the traditional method. It is likely that this difference in agreement is simply a factor of the number of leads employed in measurement. As more leads are analysed for each ECG, QTc dispersion measurements are likely to be closer to the traditional 12 lead method. The 10 lead method tested deliberately excludes the leads most likely to contribute to QTc dispersion, and probably explains why this method agreed less well with the 12 lead method than measurements from the 6 precordial leads. Although QT or QTc dispersion calculated from 12 leads of a standard ECG has become the traditional method of measurement it may not be the "gold standard" measurement (Hnatkova et al. 1994). Many alternative methods have been used including methods based on the standard deviation of QT intervals; using JT or T wave apex dispersion; or even weighting differences between leads (Pye et al. 1992), postulating that adjacent QT dispersion is more important than distant QT dispersion. Although comparisons of agreement of any other method with the traditional 12 lead method provides useful information, good or poor agreement does not imply the new method would fare any better or worse as a predictor.

If QT dispersion were to prove a clinically useful tool, this approach would have the advantage of speed and ease of calculation as compared to the 12 lead method. Using the method described, analysis and calculation of QT dispersion from a single 12

lead ECG takes 30 minutes or more. Moreover the analysis of QT intervals can be difficult and the application of a number of rules may be required to accurately define a difficult T wave end (Lepeschkin and Surawicz. 1952). Poor reproducibility of QT dispersion measurements greatly limits its role as a potentially clinically useful tool. The time saved by analysing only 3 leads to measure QT dispersion, could be used in a more rigorous evaluation of T wave ends, and might result in an improvement in reproducibility.

Intuitively, it would seem that the correct approach would be to measure QT dispersion from the maximum number of leads available, as this would give the greatest chance of detecting a possible substrate for re-entry dysrhythmias. Mirvis's method of using multiple torso leads showed that the site of infarction could be mapped using QT intervals from these leads (Mirvis. 1985). This method of mapping QT dispersion more precisely than from a 12 lead ECG has not been tested as risk stratification for dysrhythmias, and requires further evaluation. It may be that QT or QTc dispersion measured from either 12 or 3 leads are equally poor at detecting potential arrhythmia substrates, rather than equally good.

All the methods of calculating QTc dispersion used here correlate well with QTc dispersion calculated from 12 leads. The rationale for excluding the 2 extreme QT intervals from QT dispersion measurement is to make the measurement more stable and less prone to error (Davey et al. 1992). The fact that the difference in QTc dispersion between the 2 populations of ECGs studied was eliminated using this method suggests that this is not a useful measurement. The problem of measuring QT dispersion calculated from only the 6 precordial leads has been described previously (Van de Loo et al. 1994); ignoring other vectors and surfaces of the heart might explain the weakness of this method.

The quasi-orthogonal leads have the obvious advantage of viewing the heart in all 3 planes. The other 3 lead formula also tested nearly satisfies this requirement. This 3-dimensionality might explain why the 3 lead formulae tested appear successful in QTc dispersion measurement.

At first sight the data presented suggest that QTc dispersion measured from the quasi-orthogonal leads to be the "best" measure in our study. However this is partly explained by the "early" QTc dispersion in the death group being lower than that for survivors. This would seem unlikely, and is a limitation of the data.

QT dispersion calculated from 3 selected leads may be as useful a measurement as QT dispersion calculated from all leads of a standard ECG. Its advantages are simplicity and the lack of need of adjustment for missing leads.

**CHAPTER 9.**  
**CONCLUSIONS AND FURTHER STUDIES.**

The major finding from this work is that QT dispersion recorded on day 2 or 3 of acute myocardial infarction was not associated with subsequent total mortality. The overlap in QT dispersion measurements between patients who subsequently died and long term survivors means that QT dispersion is unlikely to be useful as a predictor for mortality or sudden death. This statement holds true for both the early ECG, but also the late ECGs, recorded at least 1 month post infarction. The observation that QT dispersion measured from these late ECGs was associated with subsequent mortality is interesting, suggesting that an arrhythmic substrate based on increased dispersion of cardiac repolarisation might be an important mechanism of subsequent mortality and sudden death in patients following myocardial infarction. However the retrospective design of the study meant that late ECGs were available in only a proportion of patients, and the positive result obtained could merely have been caused by patient selection.

The only solution to this problem is a prospective study of consecutive patients following myocardial infarction. ECGs would be recorded in all patients prior to discharge (day 6) and at 6 week review; and early, late, and early minus late QT and QTc dispersion calculated. As most arrhythmic deaths occur in the first six months post infarction 1 year mortality would be the primary end point. The secondary end point would be sudden death: defined as unexpected death occurring within 1 hour of onset of symptoms, combined with unexpected unwitnessed death, and unexpected death during sleep. A sample size of 600 patients would result in approximately 120 deaths in total, and possibly 30 to 40 sudden arrhythmic deaths.

Variables such as the signal averaged ECG and ventricular stimulation studies have been tested in combination for risk stratification. It is possible that QT dispersion

in combination with other variables might be useful in risk stratification, this has never been tested. A study combining QT dispersion (arrhythmic substrate) with heart rate variability and baroreflex sensitivity (arrhythmic trigger) would be an interesting approach. If current studies, for example the European Myocardial Infarction Arrhythmia Trial (EMIAT) study, show a role for antiarrhythmic drug therapy in patients following myocardial infarction the role of QT dispersion in predicting drug efficacy also requires testing.

Part of the aim of this thesis was to examine causes of QT dispersion. This has been possible to only a very limited degree. The data from the patients studied with cardiomyopathy and those undergoing angioplasty suggests that left ventricular dysfunction may not be an important mechanism in QT dispersion, but that acute ischaemia might cause an increase in QT dispersion. Both these data sets have limitations. The cause of the rapidly changing QT dispersion over the first few days of acute myocardial infarction remains obscure. The categorical data from the retrospective mortality study also adds little to any understanding of underlying mechanisms. Further studies are required: in particular examining the relationship of QT dispersion with ejection fraction, whether ACE inhibitors modify QT dispersion, QT dispersion during ischaemic stress testing, and the relationship of QT dispersion to measures of autonomic function both in controls and in patients following myocardial infarction.

The methodological limitations of QT dispersion measurement, and particularly its poor reproducibility are major problems. The data presented indicate that lead adjustment formulae should be abandoned. QT and QTc dispersion measured from the 3 quasi-orthogonal leads needs to be tested against the traditional 12 lead measure in a

variety of settings before its usefulness can be decided. The issue of whether QT dispersion should be presented rate corrected or not also needs addressing. The reproducibility problem is more difficult. Solutions might include measuring the T wave area, QU dispersion, QT apex dispersion, or defining the T wave end from the maximal gradient of the final T wave upslope or downslope extrapolated to the baseline. Automatic algorithms based on any of these methods would be possible, and the accuracy of an automatic measurement of QT dispersion would almost certainly be improved. Better reproducibility of a meaningless measurement might result from all these strategies, however they all merit further assessment.

Given the data presented, and other information available, measurement of QT dispersion cannot be recommended for routine clinical use in patients following myocardial infarction. QT dispersion is an important research tool, providing insight into mechanisms of cardiac arrhythmias using an easily obtained simple measurement. Even if further studies were to suggest a more important clinical role for QT dispersion, its poor reproducibility is a major limitation.

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## 10.2. Published work from the thesis.

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