Prognostic Markers of Ventricular Arrhythmia:

Is further refinement of risk stratification possible? – A prospective study of patients with Implantable Cardioverter Defibrillators and Left Ventricular Systolic Dysfunction

Thesis submitted for the degree of Doctor of Medicine at the University of Leicester

Suman Kundu

University of Leicester

April 2012

Thesis Abstract

The management and prevention of Sudden Cardiac Death remains a great challenge in modern Cardiology. Implantable Cardioverter Defibrillators (ICDs) have been shown to reduce mortality. Despite decades of research, the mechanisms are not fully understood and ICD treatment is crude, palliative and expensive. Nonetheless, outcome studies have helped to inform national and international guidance in the implantation of these devices. Patient selection is crucial to ensure correct patients are identified and appropriately treated. More refined and stringent risk stratification is needed to identify patients at high risk. This thesis examines non-invasive, readily measureable markers to see whether they can be used to assess the risk of ventricular arrhythmia in patients with cardiomyopathy who have indications for ICD implantation. Baseline data in the form of 12 lead electrocardiograms, echocardiography, 24 hour Holter monitoring and venous blood were obtained to analyse QT dispersion, Heart Rate Variability (HRV), QT Variability Index (QTVI), ECG restitution measures and NTproBNP levels in these patients.

Patients were followed up for a two year period through the ICD clinic and appropriate therapy was recorded as a surrogate marker for ventricular arrhythmia. Patients with and without appropriate therapy were then compared to look for significant differences in the examined markers. The percentage of beats with a QT/TQ ratio>1 was associated with appropriate shocks when compared with no therapy ($p=0.04$). However, the result was not significant when all appropriate ICD therapy was compared with no therapy ($p=0.06$). This possibly reflects the period of time the heart spends on the more 'unstable portion' of the restitution slope in patients at highest risk. Median BNP was non-significantly higher in patients with arrhythmia compared to those who were shock free. None of the other examined markers were predictive of appropriate therapy. There is thus promise in the use of some non-invasive markers in the refinement of patient selection with LVSD being considered for ICD therapy.

Acknowledgments

I would like to thank all the patients who kindly participated in my studies. I am also grateful to Drs Ng and Stafford not only for their support and advice with my research, but also for their support through all of my clinical work during my time in Leicester. I would also like to thank Professor Ng for his help with the BNP analysis. Mention also has to be given to my research colleagues, Drs Tuan and Jeilan. In addition there are many other people who have provided support and a shoulder to cry on.

Finally, special thanks and love to my long suffering wife Hannah for her unwavering support and love, my son Reuben and daughter Sophia, who bring light and a smile no matter what the day has brought and also my parents without whom I would not be half the person I am.

Suman Kundu

December 2012

Table of Contents

Preface

The accurate identification and prevention of sudden cardiac death has been a goal that has been and remains the subject of intensive research. The advent of the Implantable Cardioverter Defibrillator (ICD) has been shown to reduce mortality and morbidity in at-risk patients. However, they remain a crude, palliative treatment modality. In addition, treatment with these devices is not inexpensive and is not without complication. Patient selection and accurate risk stratification is thus crucial for the delivery of treatment to those likely to benefit.

The identification of accurate markers to predict those at risk of sudden death remains the goal of many researchers. As basic science mechanisms become better understood, newer non-invasive markers of risk are also developed. If such markers are found and established, ICD treatment would be better targeted and the use of this expensive treatment could be optimized with enormous cost implication.

This thesis begins with an introduction outlining the problem of sudden death and explains the rationale and indication for ICD implantation in patients with left ventricular dysfunction. The non-invasive markers are then examined. Subsequent chapters explain the methodology and present the results obtained during my period of research. Each chapter concludes with a discussion. A summary chapter concludes the thesis.

Statement of Originality and Involvement

All data collection, analysis and this thesis are entirely my own work. The methods for the thesis were designed by myself and my Principal Supervisor Dr GA Ng. I obtained ethical approval for the study and recruited all participants. The data was collected and completely analysed by myself. I also performed all of the statistical analysis. Finally, the thesis has been fully written by myself.

Abstracts

1. Kundu S, Tuan J, Jeilan M, Osman F, Mantravadi R, Ng GA; ECG Restitution Characteristics in Patients with LVSD & ICD. Europace (2008) 10 (Suppl 1): i55
   - presented at Cardiostim 2008 as Poster Presentation

2. Kundu S, Farooq M, Zaman M, Ali A, Stafford PJ, Pathmanathan RK, Ng GA; Clinical implications of adopting revised NICE guidelines on Implantable Cardioverter Defibrillators for primary prevention of sudden cardiac death. European Heart Journal (2007) 28 (Abstract Supplement), 285
   - presented at European Society of Cardiology 2007

List of figures and tables

List of abbreviations

SCD	Sudden Cardiac Death
VA	Ventricular Arrhythmia
IHD	Ischaemic Heart Disease
DCM	Dilated Cardiomyopathy
LVEF	Left Ventricular Ejection Fraction
HRV	Heart Rate Variability
NTproBNP	N terminal pro Brain Natriuretic Peptide
QTVI	QT Variability Index
QTd	QT dispersion
VF/T	Ventricular Fibrillation / Tachycardia
NYHA	New York Heart Association

1 Introduction

1.1 Epidemiology

Cardiovascular disease is the leading cause of mortality in the developed world, accounting for almost 50% of all deaths, with ischaemic heart disease (IHD) being the most prevalent underlying aetiology[1]. Mortality statistics have shown that sudden cardiac death (SCD) is the most common and often the first manifestation of IHD, with 80% cases of SCD attributable to consequences of IHD[2]. In the United States alone, SCD claims 300,000 lives annually[2].

1.2 Sudden Cardiac Death

Sudden Cardiac Death is defined as death occurring unexpectedly from a cardiac cause within one hour of onset of symptoms[2]. The majority of cases of SCD are caused by ventricular tachyarrhythmia; ventricular tachycardia (VT) or ventricular fibrillation (VF), leading to cardiac arrest[3]; the remainder of cases are due to bradycardic events.

1.2.1 Prevalence

Sudden Cardiac Death is highly prevalent in the heart failure population with 50% of deaths being attributable to this[4]. Heart failure patients have a 6 to 9 times higher incidence of SCD than the general population in addition[4]. The scale of the problem is highlighted by population based studies demonstrating an incidence up to 11.6 per 1000 population per year of new heart failure diagnoses[5,1]. Ischaemic Heart Disease accounts for over 35% of new cases[1].

1.2.2 Outcomes of SCD

Prompt defibrillation is paramount to restore cardiac output in patients with VT /VF to prevent death or cognitive and functional impairment resulting from cerebral hypoperfusion[6]. Despite a significant decline in age adjusted cardiovascular mortality primarily due to therapeutic advances, mortality due to SCD has declined less significantly due largely to the unpredictable nature of the condition[2,7]. Out of hospital cardiac arrest victims have a poor prognosis, with less than 5% of patients surviving the index event or immediate sequelae. In addition, cardiac arrest survivors have a high risk of future events[4].

1.2.3 Aetiology of SCD

Ischaemic Heart Disease accounts for 80% of cases of SCD, with dilated and hypertrophic cardiomyopathies accounting for most of the remainder (approximately 15%)[8]. The cause of SCD in the context of IHD may be due to acute myocardial infarction or sudden arrhythmia due to pre-existing infarction and scar[9]. Other cases are caused by a heterogeneous mix of pathologies including congenital cardiac anomalies, infiltrative cardiac disorders, genetically determined cardiomyopathy and ion channelopathy[8].

The incidence of SCD changes in specific populations (for example, it is higher in the cardiac failure population compared to the wider population) as does the annual numbers of sudden deaths in those populations[10]. The incidence of SCD in the whole adult population is less than 1% (US estimates in the order of 0.2%) with a rising incidence in

patients with structural heart disease and underlying coronary disease[8]. Patients who have survived cardiac arrest or those who experience ventricular arrhythmia post myocardial infarction experience the highest incidence of SCD, in comparison to a low incidence in the overall adult population[11]. Actual numbers of cases, however, are highest in the overall adult population given the much larger numbers of people in the whole population, with the converse being true in the highest risk groups (with smaller numbers in these groups). Identification of those at highest risk will thus only target a small fraction of the total numbers at actual risk[8].

1.2.4 Risk factors of SCD

Population based screening is unlikely to be cost effective, and more targeted means of risk stratification are required particularly in those at intermediate risk where accurate identification will be most beneficial particularly with regard to health economics[12]. The present cardiovascular risk factors are more geared towards identification of risk of developing structural heart disease particularly in IHD patients, which does not necessarily equate to the risk of SCD[2]. As the majority of cases of SCD are secondary to underlying IHD, it is predictable that the risk of SCD increases with age, although there is a relative decrease in the octogenarian population and above due to other competing causes of death[8]. Epidemiological studies have revealed the median age of SCD patients to be 59 years. In addition smoking, increasing age, hypertension, diabetes mellitus, raised body mass index (BMI) and hyperlipidaemia are all associated with an increased risk of SCD[13]. Smoking is a particularly important factor with a 2.5 times increased risk in smokers compared with non-smokers[8]. In addition, in a study of 310 survivors of

cardiac arrest, the recurrence rate of cardiac arrest was 27% in those who continued to smoke after the initial event, compared to 19% in those who stopped[14]. Mechanistically, this is mediated by increased platelet adhesiveness and catecholamine release. Younger individuals who experience ventricular arrhythmia and SCD typically have structural heart disease due to other underlying disease processes such as hypertrophic cardiomyopathy, or ion channelopathies such as Brugada syndrome [8,12].

Despite extensive research, the mechanisms underlying lethal ventricular arrhythmia remain incompletely understood. Arrhythmogenesis is a result of a complex interplay between the myocardial substrate and transient physiologic stimuli such as autonomic activity that contribute[15].

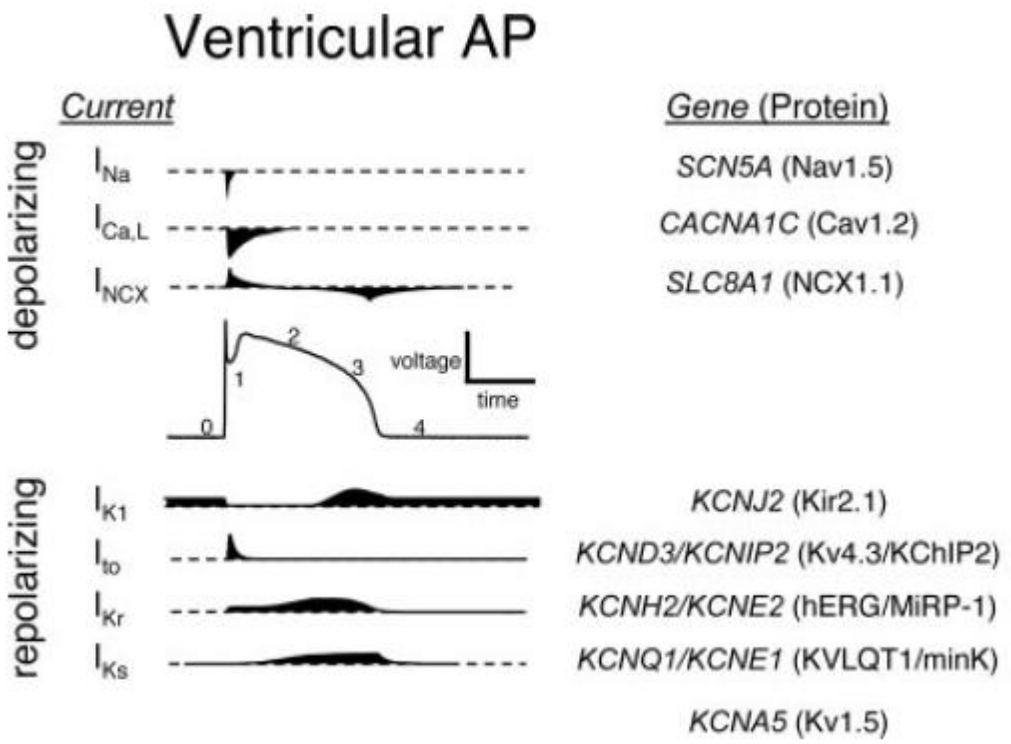
1.3 The normal cardiac action potential

Disturbance of cellular membrane function due to abnormal ion channel expression have been well described. Normal cardiac rhythm requires careful co-ordination of ion channels that allows appropriate propagation of the electrical wave front. The ventricular action potential is generated by a complex process that involves ionic currents, and the maintenance of cellular ionic balance[16–18]. The normal ventricular cell resting membrane potential is -80mV[19]. On reaching cellular activation threshold, rapid depolarisation is achieved by the inward sodium current that quickly inactivates (phase 0). This is followed by a brief interval of early repolarisation (phase 1) caused by efflux of K^+ ions through the transient K^+ I_{to} channel[18]. On reaching a membrane potential of -25mV the inward L-type calcium current activates and maintains the plateau phase of the action

potential on a background of the delayed repolarising action of the outward potassium currents IK_r and IK_s (phase 2)[18,19]. The L-type calcium current is important as cellular calcium influx triggers calcium release from the sarcoplasmic reticulum (SR) by binding to the ryanodine receptor on the SR. This is important in terms of contractile function. As the L-type calcium current declines, the repolarising potassium currents activate and start to dominate, thus restoring the resting membrane potential (phase 3)[18]. Phase 4 refers to the time when the membrane potential is back at its baseline level. In addition to the major ionic currents stated here there are other smaller currents, which also have an important role in action potential generation and ionic homeostasis[17,18].

Figure 1.1 illustrates this process and identifies some of the proteins and associated genes that are components of these ion channels[17].

Figure 1.1: Ionic contribution to ventricular action potentials & associated genes ***(reproduced from Shah et al; Molecular Basis of Arrhythmia, Circulation. 2005:112:2517-2529***[17]***, with permission from Lippincott, Williams & Wilkins)***



Disruption of these mechanisms may result in electrophysiologic changes that result in conditions favourable to arrhythmia initiation[17]. Ion channelopathies are a group of heritable diseases linked to point genetic mutations[17]. These mutations code for abnormal trans membrane protein complexes altering cardiac action potential physiology[17,18,20]. In these disease states the electrophysiologic abnormality is seen on a background of often normal cardiac structure and mechanical function[20]. A brief description of some of these conditions follows as a fuller description is beyond the remit of this thesis.

1.4 Cardiac Ion Channelopathies / Inherited cardiomyopathies

There are a number of potassium channels in the heart responsible for maintenance of the resting membrane potential, the plateau phase of the action potential, and repolarisation. Genetic disorders affecting potassium channel physiology can result in variants of long and short QT syndromes[20,21].

1.4.1 Long QT syndrome (LQTS)

Long QT syndrome (LQTS) is caused by prolonged repolarisation due to prolonged periods of intracellular positivity, resulting from genetic mutations causing loss of channel function (resulting in a reduction of 'net' repolarisation) as well as other mutations causing gain of channel function (resulting in an enhancement of depolarizing currents)[22]. Patients may present with syncope or incidentally with an abnormal electrocardiogram (ECG). They may also die suddenly due to a form of polymorphic ventricular tachycardia known as Torsades de Pointes[20,23]. To date 12 genes have been implicated, with three types accounting for more than 70% of cases (LQTS 1,2 and 3)[24].

Long QT syndrome type 1 occurs due to mutations in KCNQ1 leading to loss of potassium channel function; Long QT syndrome type 2 due to loss of function mutations in KCHN2 and LQTS 3 is caused by a mutation in SCN5A (coding for cardiac sodium channels) leading to a gain in function[22,25]. The remaining 9 genetic abnormalities cause loss of potassium channel function, gain in calcium channel function as well as mutations in other channel proteins such as ankyrin B and caveolin 3[22].

1.4.2 Short QT syndrome (SQTS)

Recently Short QT syndrome (SQTS) has also been described, characterized by a $QT_c \leq$ 330msec and a high incidence of VT/VF in infants, children and young adults[26]. Brugada and colleagues characterized the first genetic defect associated with this condition resulting in changes in the HERG channel, causing a gain of function in the IK_r channel (SQTS1)[20]. Short QT syndrome type 2 is caused by a gain in potassium channel function with a mutation in KCNQ1 and SQTS 3 is caused by mutations in KCNJ2 coding for the inward rectifier channel[25]. Two other subtypes (SQTS 4 and 5) have also been identified with mutations in genes coding for calcium channels[20,25,26].

1.4.3 Brugada syndrome

Mutations in the SCN5A gene coding for the α subunit of the sodium (Na) channel can also result in arrhythmic syndromes associated with SCD[27]. Brugada syndrome refers to electrocardiographic right ventricular precordial ST segment abnormalities and ventricular arrhythmia, predominantly fibrillation with autosomal dominant inheritance[28]. It is thought to account for 4% of all SCD cases and 20% of those cases with structurally

normal hearts with no other underlying cardiac disease[20,27]. Brugada syndrome is diagnosed on the basis of ECG and clinical criteria, such as syncope, pertinent family history and previous arrhythmia[29,30]. Although the original genetic abnormalities involved in Brugada syndrome were associated with mutations in SCN5A, recent work has suggested that rather than being a pure sodium channelopathy, Brugada syndrome may be caused by an imbalance between inward and outward currents during depolarization (phase 1)[30].

1.4.4 Catecholaminergic Polymorphic VT

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited condition transmitted in an autosomal dominant or recessive manner and as with the other inherited ion channelopathies, macroscopic cardiac structure is intact. Patients with this condition have a high risk of monomorphic and polymorphic VT and SCD[2031]. The autosomal dominant form is associated with a defect in the cardiac ryanodine receptor and the recessive form is caused by a mutation in the gene coding for calsequestrin 2[25]. This results in defective cellular calcium handling which can cause arrhythmia by delayed after-depolarisation (DAD) induced triggered activity[25,32]

These inherited syndromes are not particularly prevalent and only contribute in a small part to the overall problem of SCD. They are typically associated with a structurally normal heart. Understanding the link between the mutant gene and resulting phenotype, and the discovery of more mutations in the future may lead to more accurate risk stratification in this arena[2133].

1.4.5 Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has a prevalence of 2 in 1000 of young adults and accounts for 4 to 6% of cases of SCD[34]. It is characterized by unexplained myocardial hypertrophy and histologically by myocyte hypertrophy, disarray and interstitial fibrosis[34,35]. The condition is associated with an increased risk of ventricular arrhythmia and is the most common cause of SCD in young adults aged 35 and less. It has an autosomal dominant mode of inheritance except for those cases caused by mutations in the mitochondrial genome. There is a family history in 70% of cases, whereas the remainder of cases occur due to new sporadic genetic mutations[33–35].

1.4.6 Arrhythmogenic Right Ventricular Cardiomyopathy

Another cardiomyopathy with a genetic basis is arrhythmogenic right ventricular cardiomyopathy (ARVC). This predominantly affects the right ventricle (RV), although left ventricular (LV) involvement has been reported. This condition is progressive, and is increasingly recognised as a cause of SCD especially in the young[36]. Clinical presentation is variable including syncope, biventricular failure and SCD. Right ventricular dilatation, impairment, fibrofatty infiltration and aneurysm formation seen on echocardiography or magnetic resonance scanning (MRI) are hallmarks of this condition. It is typically inherited in an autosomal dominant manner with incomplete penetrance and variable phenotypic expression[36,37].

1.5 Heart Failure and Sudden Cardiac Death

1.5.1 Pathophysiology

The vast majority of cases of SCD occur in the setting of underlying IHD[4,10] with post mortem specimens of victims of SCD demonstrating changes associated with coronary artery disease in over 80% of cases[38]. This may manifest as acute plaque rupture leading to infarction or as myocardial scar with no evidence of an acute ischaemic event[16]. Patients with heart failure of all aetiologies are also at higher risk of SCD[10]. The remainder of cases demonstrate no anatomical abnormality[4,8]. In this study all of the patients recruited had evidence of cardiomyopathy, mostly ischaemic in aetiology, and hence this is the focus of the next portion of the introduction.

1.5.2 Aetiology

Heart failure is caused by a reduction in systolic and / or diastolic function leading to a complex syndrome caused by an inability to support the physiological circulation[39]. The most common cause of heart failure is ischaemic heart disease (IHD) secondary to coronary atherosclerosis[1]. Non ischaemic aetiologies include various infections, metabolic abnormalities, drugs and cardiac infiltration amongst other causes[1].

1.5.3 Causes of arrhythmia

In cardiomyopathy, arrhythmia occurs due to re-entry, bundle branch / intra-fascicular re-entry (disorders of conduction), and focal automaticity / triggered activity (disorders of impulse formation)[16]. Abnormal automaticity has been shown to be a mechanism for ventricular arrhythmia in ischaemic cardiomyopathy[40]. Re-entry is also important in

maintenance of arrhythmia[41]. Triggered arrhythmias occur due to abnormal depolarization resulting in further electrical activation on the background of pre-existing action potential abnormality. Early and delayed after-depolarisations fall into this category[16,41].

1.5.3.1 Re-entrant arrhythmia

Re-entrant arrhythmia is thought to be implicated in the majority of ventricular tachycardias[41]. A number of electrophysiological conditions have to be satisfied in order create conditions which will allow re-entry to occur. An area of slow conduction is a feature of re-entrant arrhythmia, most often due to structural heart disease and scar[17]. Cell to cell conduction is also dependent on satisfactory cellular coupling. Connexin proteins are important in this process. Disorganisation of cellular coupling and down regulation of connexins are commonly seen in heart failure[42]. Uni-directional block is also seen in structurally abnormal hearts which is a requirement of re-entry. Thus, heart failure conditions provide ideal substrates for arrhythmogenesis with re-entrant VT being reproducible with programmed electrical stimulation[15–18,41].

1.5.3.2 Ischaemic Heart Disease

In animal models of IHD, ischaemia and infarction cause myocyte necrosis and if extensive, can lead to aneurysm formation[43]. In chronically ischaemic and hibernating myocardium, apoptosis and compensatory cellular hypertrophy occurs in regions remote from scar[44]. Re-entrant arrhythmia can occur in areas adjacent to scar[41]. Surviving myocytes in the peri-infarct zone constitute substrate for non-uniform anisotropy that can

promote re-entry[17]. This occurs due to remodeling of these border zones in the subacute and chronic phases. Fractionated, long duration electrograms are commonly recorded from these areas reflecting the abnormal electrophysiology[15–18].

1.5.3.3 Non ischaemic Cardiomyopathy

In non-ischaemic arrhythmia the situation is less clear. There is generally no distinct scar seen in this setting with the myocardium showing patchy areas of fibrosis, myofibril disarray, myocyte hypertrophy and atrophy[45]. The degree of non-uniform anisotropic conduction and generation of re-entrant wave fronts can be correlated with the degree of fibrosis and myofibril disarray[46]. Necropsy studies of hearts with documented *in vivo* sustained VT show a greater degree of myocardial fibrosis compared with those with only non-sustained VT. Focal initiation of VT can also arise in non-ischaemic cardiomyopathy secondary to triggered activity[46]. Electroanatomical mapping techniques have shown areas of abnormal conduction with abnormal electrograms within these areas. Bundle Branch re-entry is another mechanism of VT seen in structural heart disease. The term describes a macro re-entrant circuit involving antegrade conduction through either the left or right bundle, transeptal intra-myocardial conduction and subsequent retrograde conduction via the remaining bundle. As with other re-entrant tachycardias, conduction delay is a mandatory component to allow this to occur with an average HV interval of 80 msec[47]. This mechanism of VT is more common in non-ischaemic cardiomyopathy, but can occur in all forms of structural heart disease[4,15–18,46].

1.6 Ionic basis of arrhythmia

1.6.1 Action Potential Duration

Action potential duration (APD) prolongation and electrocardiographic QT prolongation is a feature seen in ventricular myocytes from structurally abnormal hearts independent of aetiology[4,15–18]. The precise ionic basis of this may differ depending on the mode of ventricular dysfunction. There are a number of mechanisms which account for this APD prolongation, namely downregulation of repolarising K^+ currents, alterations in intracellular calcium handling and increases in late sodium current density[17,18].

In heart failure models, functional downregulation of K^+ currents has been widely described, with all of the major K^+ currents being implicated[18]. These changes in the K^+ repolarising currents result in spatial differences in APD and alterations of resting membrane potential, which may enhance automaticity in failing ventricular myocytes[17,18].

1.6.2 Calcium

Cardiac calcium handling is critical in terms of electrical excitation as well as myocardial contraction. Cellular influx of calcium ions through L-type channels maintains the plateau phase of the action potential as well as inducing release of calcium from the sarcoplasmic reticulum[18]. Disease induced reduction of this current will shorten APD duration and suppress contractility. The degree of this depends on the stage of heart failure with an increase in the L type current in mild to moderate hypertrophy and a decrease in more advanced stages of hypertrophy and heart failure. The molecular

mechanisms behind these changes are yet to be elucidated[48]. In addition to this change, SR handling of calcium in heart failure is impaired. This leads to a reduction in the amplitude and rate of decay of the intracellular transient[18]. The cellular Na^{+}–Ca^{2+} exchanger as well as the sarcoplasmic reticulum ATPase (SERCA2a) are responsible for restoration of cytosolic calcium to diastolic levels[18]. In heart failure, SERCA2a activity is impaired. Ryanodine receptors (RyR2) are also downregulated in the failing heart[49]. This results in hyperphosphorylation of the RyR2 receptors which causes FK506-binding protein 1B to dissociate from RyR2s resulting in diastolic calcium leak that can lead to triggered activity and arrhythmia[50]. This is thought to be mediated by DADs which occur in late phase 3 or phase 4 of the action potential[17]. In susceptible hearts, catecholamine stimulation and activation of β adrenoceptors result in increased c-AMP with increased SR calcium release which can lead to DAD generation in addition[4]. Targeting these areas may provide hope in the future with regard to arrhythmia prevention and contractility[18].

1.6.3 Sodium channel function

Abnormalities in sodium channel function may also contribute to arrhythmogenesis in heart failure. Animal models of heart failure have demonstrated increases in the late component of the sodium current during phase 0 of the action potential, which will have implications on wave front propagation and arrhythmogenesis[51]. Intracellular sodium can be increased 2 to 3 times in heart failure. This can lead to reversal of function of the Na-Ca exchanger which can increase intracellular calcium and subsequent development of afterdepolarisations which can be arrhythmogenic[18].

1.6.4 Dispersion of repolarisation and repolarisation reserve

Spatial dispersion of repolarisation (DOR) refers to the repolarisation of different myocytes at different times[52]. Action potential duration increases in heart failure, which is a marker of impaired repolarisation[53]. Kuo and colleagues have shown that DOR is related to the development of sustained ventricular arrhythmia in animal models[54]. In heart failure the normal DOR seen in normal hearts is exacerbated[52,55]. Poelzing also showed that gap junctions also re-model in heart failure further exacerbating DOR[52]. DOR can occur transmurally, transseptally and apico-basally[25].

Repolarisation reserve refers to the concept of more than one cellular outward potassium current contributing to repolarisation, which can 'compensate' for each other in disease states[53]. This theory states that in heart failure and other conditions, this reserve is reduced, increasing the risk of arrhythmia[53].

1.6.5 Conclusion

In conclusion, it can be seen that ionic channels undergo complex remodeling in heart failure. The prolongation of the AP is likely to be multi-factorial. This subsequent ionic imbalance together with marked dispersion of repolarisation and reduced repolarisation reserve results in marked electrophysiological change which predispose to ventricular arrhythmia and sudden death. The specific changes are both species and disease dependent[4,17,18].

1.7 Neurohormonal factors and Cardiac Failure

Heart failure states lead to alterations in the autonomic nervous system as well as leading to activation of the renin-angiotensin-aldosterone (RAAS) system[56]. The causes of these changes will be explored in this section of the thesis. The autonomic nervous system (ANS) consists of the sympathetic and parasympathetic systems[57].

1.7.1 Sympathetic Nervous System

The sympathetic system mediates its effects via noradrenaline and adrenaline causing an increase in heart rate and myocardial contractility[56]. From origins in the stellate ganglia, the fibres travel along epicardial vascular structures with subsequent endocardial innervation. There is dense atrial innervation although ventricular innervation is present with increased basal density[57]. Cardiac adrenoceptors include α_1, α_2, β_1 and β_2 receptors[58,59]. More recently β_3 receptors have also been discovered, although their functionality has not been fully discovered[60]. Stimulation of the β_1 and β_2 adrenoceptors exert positive chronotropic and inotropic effects, and α_2 stimulation causes prolongation of the AP and suppresses β adrenergic stimulation induced DADs and is therefore protective against ischaemia induced VT *in vivo*[57,61]. Most of the ventricular β adrenergic receptors are β_1 receptors[62]. Following activation of β adrenoceptors, intracellular cyclic adenosine monophosphate (cAMP) levels are increased[61]. This ultimately leads to increased intracellular calcium levels via the L type calcium channels which will result in still higher concentrations of calcium due to release from the sarcoplasmic reticulum. This results in enhanced myocardial contractility[61]. In addition to this, enhancement of

other ionic currents (sodium, I_{Ks}) leads to the positive inotropic effects by shortening the APD and refractory period[57].

1.7.2 Parasympathetic Nervous System

The vagus nerve contains parasympathetic fibres, whose nerve endings are distributed through the heart more heterogeneously than the sympathetic nervous system[57]. The parasympathetic system uses acetylcholine as its neurotransmitter and exerts predominantly cardio-inhibitory effects by reducing sino-atrial (SA) discharge rate, via direct hyperpolarisation of sinus node cells, and atrioventricular (AV) node conduction velocity[57,63]. Parasympathetic control on heart rate is very rapid, including rapid onset and offset due to the abundant supply of acetylcholinesterase in the synaptic cleft and the fact that there is no re-uptake of acetylcholine[64]. In the ventricle, parasympathetic activation reduces intracellular cAMP, thus reducing contractility[57]. However, this is not affected when background sympathetic activity is low, but is increased with sympathetic activation[57]. Parasympathetic stimulation does not affect ventricular APD and transmural dispersion. In addition, parasympathetic tone inhibits sympathetic activation and noradrenaline release at the pre-synaptic level[57,65].

Cardiac autonomic control is dependent on the interaction between the 2 limbs of the autonomic nervous system[63]. Within the heart there is a complex interplay involving sympathetic and parasympathetic postganglionic neurons, afferent neurons and other connecting neurons[57].

1.7.2.1 Neurohumoral activity in heart failure & Sudden Cardiac Death

In heart failure neurohumoral activity increases with the aim to preserve cardiac output[61]. A description of the changes in the renin-angiotensin-aldosterone axis will follow, but the predominant autonomic changes affect the sympathetic nervous system. Whilst in early stages, increased sympathetic nervous activity may be compensatory to maintain cardiac output ultimately the adrenergic over-activity is deleterious leading to the classical symptoms and signs of heart failure through mechanisms such as renin-angiotensin activation, sodium and water retention, adverse cardiac remodeling and arrhythmia[66].

1.7.2.2 Sympathetic Nervous System in the failing heart

The sympathetic nervous system is activated in heart failure and is contributory to adverse clinical outcomes[67,68]. Cardiac adrenergic drive is increased in mild to moderate heart failure with human studies demonstrating increased cardiac noradrenaline spillover in this group[69]. In more severe heart failure, cardiac noradrenaline spillover was increased by 540%[70]. Cardiac noradrenaline synthesis is increased as evidenced by the measurable increases in the precursor dihydroxyphenylalanine and the co-transmitter neuropeptide Y[71]. Further work has revealed that there is central noradrenergic neuronal stimulation in addition with an increase in cerebral spillover of precursor molecules[71,72]. Increased cardiac noradrenergic stimulation is toxic to myocytes and causes progressive myocardial damage and dysfunction as well as adverse ventricular remodelling[61,72,73]. This also creates conditions favourable for ventricular arrhythmia[67]. Higher cardiac noradrenaline spillover rates have been shown to reduce survival in heart failure patients with 50% mortality at 2 years follow up in those with higher levels. However, plasma noradrenaline

levels are not related to survival possibly as this is not a pure measure of cardiac sympathetic activity, but reflects other factors such as plasma clearance and noradrenaline release from other organs[66,67]. The mechanisms causing these changes are related to the reflex compensatory responses to heart failure, from arterial, cardiopulmonary and skeletal baroceptors, resulting in a higher sympathetic drive[74].

Animal studies have revealed that sympathetic stimulation in the failing heart is pro-arrhythmic[75,76]. In heart failure, such as post myocardial infarction, regional sympathetic and vagal denervation and hyperinnervation occur[65,77–80]. This can cause spatial dispersion of APD mediated via changes in ionic current density that favours initiation and propagation of arrhythmia[56]. Human studies have also demonstrated that higher cardiac sympathetic activity is a risk factor for sudden cardiac death[67,81,82]. In a study by Brunner-La Rocca and colleagues, patients with high noradrenaline spillover and large noradrenaline stores were at the highest risk of SCD. This study showed that these measures, along with ejection fraction, were independent predictors of SCD in nultivariate analysis[81].

1.7.2.3 Parasympathetic Nervous System in the failing heart

In heart failure, parasympathetic activation and effects are attenuated with a reduction in central vagal activity and muscarinic receptor density being amongst the possible mechanisms[83,84]. The exact mechanisms are still not fully understood[64]. There is a reduced influence on heart rate in heart failure states compared to normal controls as a result. In addition the baroreflex control of heart rate is impaired due to a lower resting

vagal discharge rate in the presence of normal systolic pressure[63,85]. The reduction in vagal influence on the heart is thought to be multifactorial, including abnormal ganglionic function[57,63,83]. These findings have been shown by numerous groups[64]. Other studies have demonstrated that the reduction in parasympathetic activity is associated with an increased risk of sudden cardiac death. Billman and colleagues found that reductions in baroceptor reflex activity were most notable in those animals at highest risk of SCD post myocardial infarction[86]. Human studies have also supported these findings. In the Autonomic Tone and Reflexes after Myocardial Infarction study by La Rovere and colleagues, impaired baroreflex sensitivity was shown to be associated with a statistically significant increased risk of SCD[87,88]. Recovery of heart rate, which is associated with parasympathetic activity, is also associated with a higher risk of arrhythmia and SCD when impaired, further supporting the above[87,89].

Animal models of heart failure have also suggested that parasympathetic activation is antiarrhythmic[57,62,65,75–77]. A study of vagal activation in rats has shown that mortality is reduced with a statistically significant improvement in haemodynamic parameters[90]. An open label study by Ferrari et al has also shown in that vagal nerve stimulation in humans may be of benefit in the heart failure population[91]. Human studies are in progress examining this area in more detail.

1.7.2.4 Renin-angiotensin-aldosterone axis

In heart failure there is an increase in vascular resistance and sodium and water retention leading to the classical clinical features. Renal sympathetic efferent is activated which causes renin, angiotensin and aldosterone release and sodium and water retention[92].

Increased renin and aldosterone release in this setting has been well documented[93,94]. Increased renin release leads to the generation of more angiotensin I by enzymatic action. Renin is released in response to renal hypoperfusion and increased sympathetic activation. Angiotensin I is then converted to angiotensin II by the angiotensin converting enzyme (ACE). Angiotensin II leads to the physiological actions with increased blood pressure, cardiac contractility, vascular and cardiac hypertrophy, renal sodium tubular reabsorption and aldosterone synthesis[95]. Aldosterone is predominantly secreted form the adrenal gland in response to angiotensin II and potassium[96]. Hyperaldosteronism can lead to increased left ventricular mass and fibrosis even in mild states. It also causes sodium retention and vasoconstriction[96]. The increase in these factors helps to maintain arterial blood volume and renal perfusion and glomerular filtration in the early stages but leads to the clinical syndrome of heart failure ultimately[94].

Therapy with β blockers have been shown to lower renin release which demonstrates the link between renin sympathetic activity and renin-angiotensin-aldosterone levels[97]. A study using carvedilol showed a reduction in active renin by 50% with an improvement in left ventricular function in addition[98]. Other similar studies have shown the same results using metoprolol and carvedilol[99,100]. In addition, β blocker therapy blocks sympathetic pre-synaptic receptors hence reducing noradrenaline output[61]. However, aldosterone levels do not seem to be affected. Furthermore, studies in renal failure and dialysis patients have shown that there is excitatory renal afferent signals to increase sympathetic outflow further exacerbating the situation in a heart failure setting in a positive feedback cycle[97]. This is further supported by animal studies of renal denervation that have shown

improved natriuresis and diuresis in heart failure settings[92]. Hence, there is close association between the neural and humoral signaling systems.

1.8 Heart Failure Treatment, Mortality & Sudden Cardiac Death

The next section of the thesis evaluates the published evidence of pharmacological treatment of heart failure that forms the basis of current management, and the effects of these on sudden cardiac death.

1.8.1 β Blockade

The pro-arrhythmic effect of sympathetic stimulation is supported by clinical trials of beta blockade in heart failure patients. Anderson and colleagues demonstrated the antifibrillatory effects of beta blockade in a dog model[101]. These agents work by attenuating the effect of heightened sympathetic activity in disease states and can reduce the arrhythmia burden by reducing increased automaticity, as well as those due to re-entry[62].

There have been a number of randomized clinical trials looking at the effects of β blockers and SCD in heart failure. CIBIS (The Cardiac Insufficiency Bisoprolol Study) reported a 20% reduction in SCD but this, in addition to all cause mortality, was not statistically significant[102]. This study recruited 641 patients with a primary endpoint of total mortality. However, mode of death was also recorded. In CIBIS, 67 patients died in the placebo group compared with 53 deaths in the treatment arm. Twenty six patients died suddenly in the placebo arm and 19 in the bisoprolol arm. This study was not

powered for sudden death and in addition the target dose of bisoprolol (5mg) was only achieved in 50% of patients[102].

The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) was a multi-centre, double blind randomised placebo controlled trial that recruited 2647 NYHA class III and IV patients with left ventricular ejection fraction of 35% or less on optimal medical treatment at that time (diuretics and ACE inhibitors). Patients were randomised to bisoprolol and placebo aiming for a 10mg dose of bisoprolol. This trial was stopped early as patients in the bisoprolol arm showed a significant total mortality benefit[103]. In the placebo arm 228 patients died (17%) and 156 (12%) died in the treatment arm. Of these, 83 patients died suddenly in the placebo arm compared to 48 in the bisoprolol arm (4%). Comparison between the groups revealed a statistically significant reduction in sudden death in the bisoprolol arm with a hazard ratio of 0.66 (95% C.I. 0.54-0.81, $p<0.0001$). In this study there was a statistical non-significant reduction in death due to pump failure, suggesting an anti-arrhythmic action[103].

Similar studies using other agents such as metoprolol (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT HF)[104]) and carvedilol (The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS)[105]) have yielded similar results[106]. The MERIT HF trial was stopped early after 1 year due to a relative risk reduction on all cause mortality of 34%. This study recruited 3991 patients with NYHA class II-IV heart failure with left ventricular ejection fraction <40%. Of these patients 1990 patients were in the treatment arm and 2001 were in the placebo arm. In the

metoprolol group, 145 patients died with 217 deaths in the placebo arm (RR 0.66; CI 0.53-0.81;p=0.0062). Again in this study, there were fewer sudden deaths in the treatment arm (79 vs 132). The relative risk was 0.59 (CI 0.45-0.78; p=0.0002). Sudden death was more common in patients with NYHA class II heart failure[104]. The COPERNICUS study enrolled 2289 patients with NYHA class IV heart failure who were not clinically fluid overloaded and had an ejection fraction <25%. In the treatment arm 130 patients died compared to 190 on the placebo arm. There was a 35% decrease in the risk of all cause mortality (CI 19-48%, p=0.0014). In addition there was a 24% reduction in a composite endpoint of death or hospitalisation in the carvedilol arm[105,107].

The β blocker Evaluation of Survival Trial (BEST) recruited 2708 patients with NYHA III-IV heart failure and ejection fraction ≤35%. The primary endpoint was all cause mortality. Of the recruited patients, 1354 patients received the β blocker bucindolol and 1354 patients received placebo in addition to standard medical therapy. However, this study was stopped early due to the mounting evidence of β blockade in the heart failure population at the time. At this point there was no statistical significant difference in all cause mortality, but there was a statistically significant difference in the secondary endpoint of death from cardiovascular causes with 889 deaths in the placebo arm and 842 in the treatment arm (p=0.04). However, there was no statistical significance between the groups in terms of sudden death[108].

The Norwegian Multi-centre study group compared the effect of timolol to placebo in survivors of myocardial infarction. In this study, 945 patients were in the treatment arm

and 939 took placebo. In the placebo group there were 152 deaths and 98 in the timolol group. The sudden death rate was 13.9% in the placebo group compared to 7.7%, which was a statistically significant reduction of 44.6%[109]. The CAPRICORN study was another post myocardial infarction study investigating the effects on carvedilol in addition to ACE inhibition. In this study, 984 patients were in the placebo arm and 975 in the treatment arm. Of these, 38 (3.9%) experienced ventricular arrhythmia in the placebo arm compared to 9 (0.9&) in the treatment arm in a retrospective analysis. This was a statistically significant difference ($p<0.0001$). However, there was no statistically significant reduction in sudden death in the main CAPRICORN trial. The authors hypothesised that this was due to the fact that the study was not powered to detect this[110]. Authors who have performed meta analyses examining sudden death in the β blocker trials have shown a statistically significant reduction of sudden death by 38% ($p<0.001$) when β blockers are prescribed in the heart failure population[106].

The large body of evidence supporting the use of β blockers in the heart failure population with regard to all cause mortality, SCD and improved functional class, has meant that these drugs are recommended as first line treatment by NICE (National lnstitute for Clinical Excellence) in the updated 2010 Heart Failure Clinical Guidelines[39].

1.8.2 ACE inhibitors / ARBs & aldosterone antagonists

Other important treatments for heart failure include ACE (Angiotensin Converting Enzyme) inhibitors, Angiotensin Receptor Blockers (ARB) and aldosterone antagonists[39,106]. ACE inhibitors block the conversion of angiotensin to the physiologically active angiotensin II as described earlier. Hence, ACE inhibition has beneficial effects and can counteract the enhanced neurohumoral activity seen in heart failure states[106]. There have been a number of trials of ACE inhibition in heart failure and these have examined the effect of these drugs on sudden death. The initial trials were smaller studies involving captopril, enalapril and lisinopril. These trials showed total mortality benefit in those treated with ACE inhibition, but were not sufficiently powered to establish the impact of these drugs on sudden death[111,112].

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) study investigated 253 NYHA class IV heart failure patients[113]. Patients in this study received enalapril (n=127) or placebo (n=126). Hormonal levels measured in these patients included serum ACE, angiotensin II and aldosterone which were all elevated compared to controls[114]. In this study there was a 27% reduction in mortality at a 20 month follow up point. This was driven by a reduction in pump failure death, with no statistically significant difference in sudden death[113]. The CONSENSUS study also demonstrated a statistically significant correlation between aldosterone or angiotensin II and mortality, with a subsequent reduction in the levels of these hormones in the enalapril treatment arm compared with placebo[114].

The SOLVD (Studies of Left Ventricular Dysfunction) evaluated 2569 patients with congestive cardiac failure and ejection fraction ≤35%. The patients were randomised to treatment with enalapril (n=1285) or placebo (n=1284) and 90% were NYHA class II-III. There were 452 deaths in the enalapril group and 510 in the placebo group with a 16% reduction in risk. However, this was driven by pump failure with no apparent difference between the groups in terms of sudden death[115].

A meta-analysis of 32 trials by the Collaborative Group on ACE inhibitor trials showed that the reduction in total mortality is a class effect with a reduction in mortality and heart failure hospitalization of 34%. This study pointed to a non statistical significant reduction in SCD (odds ratio 0.91,p=0.37), with the benefit in total mortality primarily due to a reduction in progressive heart failure[116] as in the SOLVD trial[115]. However, other authors have noted that as SCD is a component of cardiovascular mortality, it would be difficult to power a study to investigate this[117]. However, in the post myocardial infarction population there is evidence of a reduction in rates of sudden death in patients treated with ACE inhibition compared with placebo[118]. The authors of a meta-analysis of these trials suggested that this finding may relate to the ability of ACE inhibitors to modify sympathetic and parasympathetic activity[118]. Furthermore, ACE inhibitors have been shown to reduce the degree of ventricular remodeling in left ventricular dysfunction which may reduce the risk of sudden death[118].

Angiotensin Receptor Blockers are also recommended in the treatment of heart failure[39,119]. The Evaluation of Losartan in the Elderly Study (ELITE) compared patients

who were over 65 years with symptomatic heart failure randomising them to captopril or losartan. In this study 352 patients were in the losartan arm and 370 to captopril. In this study the primary endpoint was a persisting rise in serum creatinine, with a secondary endpoint being a composite of death and heart failure hospitalisation. The study found that losartan was well tolerated in comparison with captopril. In addition there was a 46% relative risk reduction in all cause mortality. This was as a consequence of a reduction in sudden death in the losartan arm[120]. However, the actual numbers of patients experiencing these events in the trial was low.

This led onto the larger ELITE II study. In this study, 3152 patients over 60 with NYHA II-IV heart failure and ejection fraction ≤40% were randomised to losartan or captopril. B blocker use was 20% across both groups. In the losartan group there were 1578 patients and 1574 in the placebo group. All cause mortality was the primary endpoint and there was no statistically significant difference between the 2 groups (11.7% in the losartan group and 10.4% in the captopril group). Sudden death was a secondary endpoint and again no statistically significant differences were seen. However, it was concluded that losartan was non-inferior to captopril in cases of ACE intolerance[121].

The Valsartan Heart Failure Trial (Val-HeFT) investigated NYHA class II, III and IV patients to see if there was added benefit in the addition of valsartan to standard heart failure treatment including ACE inhibitors. In this study, 5010 patients were included, with 2511 in the valsartan arm and 2499 in the placebo arm. There was no statistically significant difference in mortality but a 13.2% reduction in the incidence of the combined

endpoint of death and hospitalization for heart failure was seen using valsartan compared with placebo. This was primarily driven by a reduction in admissions. There was no significant reduction in SCD seen in this study[122].

The CHARM study evaluated candesartan in symptomatic heart failure patients including those with preserved left ventricular function. There was a group looking at candesartan instead of an ACE in those intolerant of ACE inhibition and finally there was a group where candesartan was added to ACE inhibition. In the low ejection fraction groups candesartan was shown to reduce total mortality, cardiovascular death and heart failure hospitalisation compared to placebo. These findings were statistically significant[123].

There have been 2 randomised studies demonstrating the importance of aldosterone antagonists in heart failure. The Randomised Aldactone Evaluation Study (RALES) showed a significant decrease in heart failure deaths and SCD in NYHA III and IV patients when spironolactone 25mg was added to standard treatment[124]. The RALES authors suggested that this effect on SCD was due to a direct cardiovascular effect by reducing myocardial fibrosis as well as prevention of hypokalaemia[124]. The EPHESUS study demonstrated that eplerenone 25mg in addition to standard therapy reduced mortality in patients with heart failure symptoms after myocardial infarction and an ejection fraction $\leq$ 40%[125]. A subsequent analysis of this study revealed eplerenone reduced the risk of SCD in this population by 37% within 30 days after the acute episode[126]. The 2010 NICE heart failure guidance recommends the use of an aldosterone antagonist given these findings[39]. More recently, the EMPHASIS-HF study has shown a

statistically significant benefit in the composite endpoint of total mortality and hospitalisation in patients with NYHA class II heart failure and ejection fraction ≤35%, when eplerenone was added to standard treatment compared with placebo[127].

1.8.2.1 Effects on autonomic function

As explained above, although there is no clear evidence of a reduction in sudden death in the ACE inhibitor trials of heart failure, there is a reduction when ACE inhibition is used after myocardial infarction[118]. Neurohumoral activation is a hallmark of heart failure and is a risk factor for sudden death. From patients in the CONSENSUS study elevated levels of angiotensin II, aldosterone, noradrenaline and adrenaline were significantly correlated with total mortality. In the enalapril arm, all levels were reduced except for adrenaline. This suggests that the effect of enalapril on mortality is related to its effects on this neurohumoral activation in heart failure[114]. Grassi and colleagues demonstrated that central sympathetic drive was reduced with chronic ACE inhibition as measured by muscle sympathetic nerve activity[128]The improvement in the haemodynamic state which occurs with ACE inhibition may also result in central sympathetic withdrawl[118]. In addition, as angiotensin II and aldosterone production increases the release and inhibits the uptake of noradrenaline at nerve endings, ACE inhibitors and ARB drugs would have a local reduction in sympathetic activity[61]. Central angiotensin receptor blockade in an ovine model of heart failure also reduced cardiac sympathetic activity implicating a central sympathetic modulation as well as demonstrating a possible beneficial effect of ARB medication[129]. Parasympathetic activity appears to be augmented by treatment with

ACE inhibition, reversing the effect seen in untreated heart failure, which is a further beneficial action and may explain the impact of these drugs on total mortality and sudden death[130,131].

Aldosterone also has effects on the autonomic nervous system with sympathetic activation and parasympathetic withdrawl[117]. A small human study demonstrated that spironolactone had a parasympathomimetic effect through measures of time domain heart rate variability and hence had the potential for the reduction of sudden death in the heart failure population[132]. Furthermore, a study by Barr and colleagues demonstrated that treatment of heart failure patients with spironolactone increased cardiac neuronal uptake of noradrenaline, which is then locally inactivated, and hence cardio-protective due to reduced cardiac sympathetic activity[133].

1.8.3 Other anti-arrhythmic drugs

The above described drugs, with the exception of beta blockers, have their primary effects on mortality due to pump failure. Anti-arrhythmic drugs have also been evaluated in the heart failure population to assess the impact on SCD. Amiodarone has class I, II, III and IV anti-arrhythmic properties[134]. Data from heart failure trials with amiodarone have yielded mixed results[134]. The CHF STAT trial showed no statistical significant mortality difference in heart failure patients between those on amiodarone and those on placebo. The study did demonstrate suppression in the amount of ventricular ectopy however[135]. The CAMIAT trial showed a statistically significant decrease in SCD with a 48.5% relative risk reduction in arrhythmic death and resuscitated ventricular fibrillation

in the amiodarone arm compared with placebo in patients post myocardial infarction[136]. EMIAT looked at post myocardial infarction patients with depressed ejection fractions < 40%. This study did not show any mortality benefit with amiodarone, but did reveal a 35% risk reduction in arrhythmic death[137]. Amiodarone is thus used as an effective anti-arrhythmic in patients with ventricular arrhythmia, but trials have not shown any conclusive mortality benefit in the heart failure population[106,134]. Another drug that has been evaluated is flecainide in the CAST trials. Patients who had suffered myocardial infarction were included to see if flecainide, encainide and moricizine could suppress ventricular ectopy. These trials had to be stopped early due to excess mortality in the treatment arms[138]. The Dofetilide in Patients with Congestive Heart Failure and Left Ventricular Dysfunction (DIAMOND) trial investigated the use of the class III agent dofetilide in patients admitted with worsening heart failure symptoms. This did not show any mortality benefit between patients who were in the treatment or placebo arms[139].

1.9 Implantable Cardioverter Defibrillators

Sudden Cardiac Death accounts for almost 50% of deaths in heart failure patients with the proportion of sudden deaths declining with worsening functional class[140]. Pharmacological treatment improves morbidity and has impact on mortality as demonstrated above. However, there is variable impact on SCD[106,134,138]. This has led to the development of Implantable Cardioverter Defibrillators (ICD). These are devices which monitor cardiac rhythm and are designed to detect and treat ventricular arrhythmia with anti-tachycardia pacing (ATP) or by delivering a shock. Defibrillation has been

shown to terminate ventricular tachycardia (VT) and fibrillation (VF), and hence prevent SCD[141].

1.9.1 ICD implantation

Mirowski and colleagues implanted the first ICD in dogs in 1970 and subsequently in humans in 1980[141]. ICD technology has since greatly advanced with devices now implanted with transvenous leads in a minimally invasive procedure in a pre-pectoral or sub-pectoral position[142]. Typically, local anaesthesia is used to infiltrate the deltopectoral area. A small incision is made and venous access is obtained via the cephalic, axillary or subclavian vein. The ICD lead is then introduced and positioned in the heart under fluoroscopy. Once the lead parameters are satisfactory, the device is attached and placed generally in a pre-pectoral position. The device can then be tested by inducing VF under controlled circumstances, after patient sedation, and ensuring there is a satisfactory defibrillation safety margin[143].

1.9.1.1 Potential implant complications

Implant complications are uncommon, but patients need to be consented and the risks of ICD implantation explained. Immediate complications consist of pneumothorax, bleeding (which can be catastrophic if the superior vena cava is perforated by the lead), cardiac perforation and tamponade as well as failure to adequately position the lead. Lead displacement can also occur which would require a second procedure[144]. Longer term complications consist of infection, which may necessitate device explantation, vascular

stenoses and thrombosis, and late lead failure, for example due to subclavian crush injury[145]. Inappropriate therapy is also a potential problem and can heighten patient anxiety as well as increasing the risk of clinical depression[146]. Studies have been conducted looking at appropriate and inappropriate ICD therapy. A recent study of 2471 patients with ICDs implanted showed that 32% of patients experienced appropriate therapy. This study also demonstrated that patients with secondary prevention indications experienced appropriate therapy 70% more compared with those for primary prevention[147]. In addition the study showed that 14% of patients experienced inappropriate shocks[147]. Recent problems with defibrillator leads and lead failure issues are also becoming more prevalent with associated health and cost implications[148].

1.9.1.2 Device function

Devices can be single chamber (right ventricle) or dual chamber (right atrium and right ventricle) and can be part of cardiac resynchronization devices, which have an additional lead to pace the left ventricle either via a branch of the coronary sinus, or epicardially[149]. The device monitors the heart rate for tachyarrhythmia detection and will deliver ATP or shock therapy if there is evidence of ventricular arrhythmia[143]. This is based on inherent device algorithms. The devices have a number of programmable features and these coupled with the type of device and their algorithms are designed to ensure therapy is delivered when necessary whilst reducing the incidence of inappropriate therapy, which can occur during atrial arrhythmia, for example[150].

1.9.2 Indications for ICD implantation

Implantable Cardioverter Defibrillators are implanted in patients with primary and secondary indications. Prevention of the first life threatening arrhythmia is primary prevention, whereas prevention of recurrence of life threatening arrhythmia in a patient with previous clinical events is secondary prevention[10]. There have been a number of primary and secondary prevention trials in the heart failure setting[151].

1.9.2.1 Secondary prevention

In secondary prevention the three major trials have all shown overall mortality benefit in the ICD arms[142]. The AVID (Anti-arrhythmics versus ICD) trial randomized patients who were resuscitated from near fatal ventricular arrhythmia; sustained VT with syncope or sustained VT with an ejection fraction (EF)≤40% with haemodynamic compromise between medical treatment (with sotalol or amiodarone) and ICD implantation[152]. The ICD group had a lower all cause mortality with a 31% relative risk reduction at 3 years[142,152]. The Canadian Implantable Defibrillator Study (CIDS) enrolled patients with similar criteria as in the AVID study, and randomized them between ICD and amiodarone[153]. A 20% relative risk reduction was seen with the greatest benefit seen in the highest risk groups with poor left ventricular function and poor functional status. The CASH study (Cardiac Arrest Study Hamburg) randomized survivors of patients resuscitated from cardiac arrest due to ventricular arrhythmia between ICD and drug treatment with amiodarone, propafenone and metoprolol[154]. A non significant 23% mortality reduction was seen in the ICD group with a much larger difference seen in sub group analysis looking at SCD[154]. Current NICE ICD guidance recommends implantation

for secondary indications in cardiac arrest survivors, compromising VT, and sustained VT in patients with EF<35%[155].

1.9.2.2 Primary prevention

1.9.2.2.1 Ischaemic Heart Disease

There have been a number of primary prevention ICD trials. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) investigated 196 patients with prior myocardial infarction (MI) with EF≤35%, non-sustained VT and inducible non-suppressible VT on programmed electrical stimulation[156]. Patients were randomized to medical treatment or ICD implantation. There was a 46% relative risk reduction in mortality in the ICD group with ongoing survival benefit seen at 5 years follow up (HR 0.46 CI 0.26-0.82)[156]. The Multicenter UnSustained Tachycardia Trial (MUSTT) investigated a similar population and described similar results[157]. The data from these two studies confirmed that the risk of arrhythmia and death is substantial in this population and the use of ICD significantly reduced mortality[157].

The MADIT II study investigated 1232 patients with previous MI and EF≤30%, with no additional risk stratification, randomizing them to ICD implant or conventional medical therapy[158]. There was a 31% reduction in mortality in the ICD arm (HR 0.69 CI 0.51-0.93). These studies showed a clear survival benefit with ICDs in patients with poor left ventricular dysfunction due to ischaemic heart disease. However, the CABG (Coronary Artery Bypass Grafting) Patch trial also showed no benefit if ICD implantation was

undertaken as a prophylactic measure post bypass surgery using signal averaged ECG data for risk stratification[159].

The Defibrillation in Acute Myocardial Infarction Trial (DINAMIT) investigated patients 6 to 40 days post MI, with EF≤35% and depressed heart rate variability. This study did not show a mortality benefit of early ICD implantation. Although there was a significant reduction in arrhythmic death, there was an increase in other causes of cardiovascular death which did not translate into an overall mortality benefit[160]. The cause of this was not clear according to the authors, however, this finding may have been due to the fact that a patient who is at high risk of arrhythmic death is also at higher risk of other causes of cardiovascular death[160].

1.9.2.2.2 Non ischaemic cardiomyopathy

In non-ischaemic dilated cardiomyopathy (DCM), the initial data from the Cardiomyopathy Trial (CAT) did not support prophylactic ICD implantation[161]. The larger Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) assigned 2521 patients with EF≤35% of all aetiologies to conventional treatment and placebo, amiodarone or single lead ICD implant with all cause mortality being the primary end point[162]. In this study 847 patients were assigned to conventional treatment and placebo, 845 patients to conventional treatment and amiodarone, and 829 patients to conventional treatment and ICD. Of these, 48% of patients had a non-ischaemic cardiomyopathy. There was a 23% mortality reduction in the ICD arm (HR 0.77 CI 0.62-0.96, p=0.007) with no difference between the placebo and amiodarone arms. The mortality benefits were seen regardless of aetiology[162]. Other studies of DCM and ICD include DEFINITE (Defibrillators in

NonIschaemic Cardiomyopathy Treatment Evaluation) which showed a significant reduction in SCD with ICDs and a non significant mortality benefit[163]. The AMIOVIRT (Amiodarone versus Implantable Defibrillator) study, however, did not demonstrate a survival benefit with ICD implantation in DCM patients with EF≤35% and documented non-sustained VT[164]. A pooled analysis of the primary prevention trials demonstrates a 7.9% absolute risk reduction / 25% relative risk reduction by prophylactic ICD implantation in patients with left ventricular dysfunction[165].

1.9.2.3 Guidelines

The trial evidence has led to American, European and NICE guidelines in this arena. The NICE guidelines do not cover non ischaemic DCM and states that ICD implantation on primary prevention grounds is indicated in patients with ischaemic cardiomyopathy with EF<30%, NYHA≤III, and QRS duration>120msec on resting ECG; or if the EF<35%, with evidence of non sustained VT on Holter monitoring and inducible VT on programmed electrical stimulation[155]. The American ACC/AHA/HRS 2008 guidance states that ICD implantation for primary prevention should be performed in all NYHA II/III patients with EF≤35%; or post MI, NYHA I and EF<30%; or post MI, EF<40% and inducible ventricular arrhythmia[166]. European guidelines are the same as the latter[167]. In addition to this aspect of heart failure treatment, there have been studies showing benefits of cardiac resynchronization devices[155,166]. This is an area beyond the remit of this study and was an exclusion criterion to study entry.

1.9.2.4 Impact on healthcare provision

The guidance on ICD implantation has a significant impact on healthcare provision and resources. The average cost of ICD implantation in the UK is £16250[155]. This excludes subsequent follow up costs and generator replacements. In Western European countries, the implant rate for ICD is approximately 155 per million population in 2007[168]. However, there are marked differences between countries with implant rates in the UK being 104 per million population[168]. A UK regional study estimated that if MADIT II guidelines were adopted, the implant rate would be 483 per million population[169]. This would have a serious financial and logistic impact on the health service, which already is under such pressures.

1.10 Potential non invasive markers

The prognosis of patients with cardiac failure remains poor despite modern therapeutic interventions. Within 1 year of diagnosis, estimates have shown mortality to approach 20%. Half of these deaths are sudden, predominantly due to ventricular arrhythmia. The rates of Sudden Cardiac Death (SCD) in the heart failure population are up to 9 times more than the general population[1]. The causes of this are thought to be multi-factorial. Abnormalities of cellular electrophysiology are well recognised with characterised changes in ionic currents. These lead to abnormal areas of conduction which coupled with areas of infarction and fibrosis facilitate arrhythmogenesis and propagation[17,18].

1.10.1 Autonomic Nervous System and Sudden Cardiac Death

The autonomic nervous system has been strongly implicated in sudden cardiac death in patients with left ventricular dysfunction as discussed earlier. Given these observations, there has been a great deal of interest in measurements of the ANS, how they change in pathological states as well as potential roles in arrhythmia risk prediction. There are a number of direct assessments of cardiac autonomic tone, but direct physiologic testing of the ANS is not clinically viable given its anatomic location. There are thus a number of non-invasive measurements available which have been investigated[170].

1.11 Heart Rate Variability

1.11.1 Definition

The intervals between normal sinus beats vary periodically, due to factors such as respiration, blood pressure regulation, the renin angiotensin system, circadian rhythms as well as other unknown factors[171]. Short term regulation of heart rate is predominantly governed by the ANS[172]. Heart rate variability (HRV) represents an easily measurable marker of cardiac autonomic activity. HRV is a generic term representing changes in the interval between consecutive normal heart beats, as well as changes in instantaneous heat rates[173]. It allows measurement of sympathetic and vagal activity[174,175]. Nocturnally, there is a predominance of vagal tone, with withdrawal of sympathetic input. These change on waking, with a withdrawal of parasympathetic tone and increase in sympathetic activity[176,177]. These changes are partly responsible for the increased rate of adverse cardiovascular events in the morning hours[56]. In pathological conditions, HRV alters in

an established way reflecting changes in the balance of autonomic tone[178]. This has opened the pathway for the use of this tool in clinical situations.

1.11.2 Measurement of HRV

There are a number of measurements of HRV, which reflect different changes in the cardiac autonomic state[173]. Time Domain methods of measurement utilise a continuous ECG recording, and detect the intervals between normal sinus beats (NN or RR interval). The instantaneous heart rate can be determined from this. Over a 24 hour period, more complex statistical time domain analyses can be performed. These measurements allow calculations of mean heart rate and circadian variation, amongst others. Time domain measures can also be used for shorter portions of the recording, which have allowed analyses between different physiological conditions such as tilt[173].

1.12.3 Time Domain Measurements

Time Domain measurements can be divided into those derived from direct NN interval measurement and those derived from differences in NN interval. The standard deviation of all the NN intervals in the recording (SDNN) encompasses all variations in frequency. The total variance of this measurement increases with the length of the recording, and with shorter recording times the SDNN approximates to shorter cycle lengths. Thus, recordings of similar durations should be compared when using SDNN as a measure of HRV[172]. If the recording is divided into 5 minute segments, the SDNN index and SDANN can be calculated. SDANN looks at the standard deviation of the average NN interval calculated over individual 5 minute periods. This is an estimate of changes in

heart rate due to cycles longer than 5 minutes. The SDNN Index represents the mean of the 5 minute standard deviations of NN intervals calculated over 24 hours. This measures the variability due to cycles shorter than 5 minutes[171–174,176–178].

Other Time Domain measurements look at differences in adjacent NN intervals. These are measurements of short term variation and estimate high frequency variations in heart rate and are well correlated. These include RMSSD, which is the square root of the mean squared differences of successive NN intervals; NN50, the number of successive NN intervals which differ by more than 50ms and pNN50 which represents the NN50 divided by the total number of NN intervals. 'Normal' values of time domain HRV indices have been derived from studies. In a 24 hour analysis the SDNN range is 141±39 ms, SDANN 127±35 ms and RMSSD 27±12 ms (mean±SD)[173]. Low time domain values are associated with low vagal activity and higher sympathetic activity[179].

The Task Force of the European Society of Cardiology and North American Society of Pacing Electrophysiology have recommended that two estimates of HRV should be used ideally. The choice depends on the nature of the study. This report also states that different methods should not replace each other, and that distinction should be made between direct NN interval measurement and NN interval differences[173].

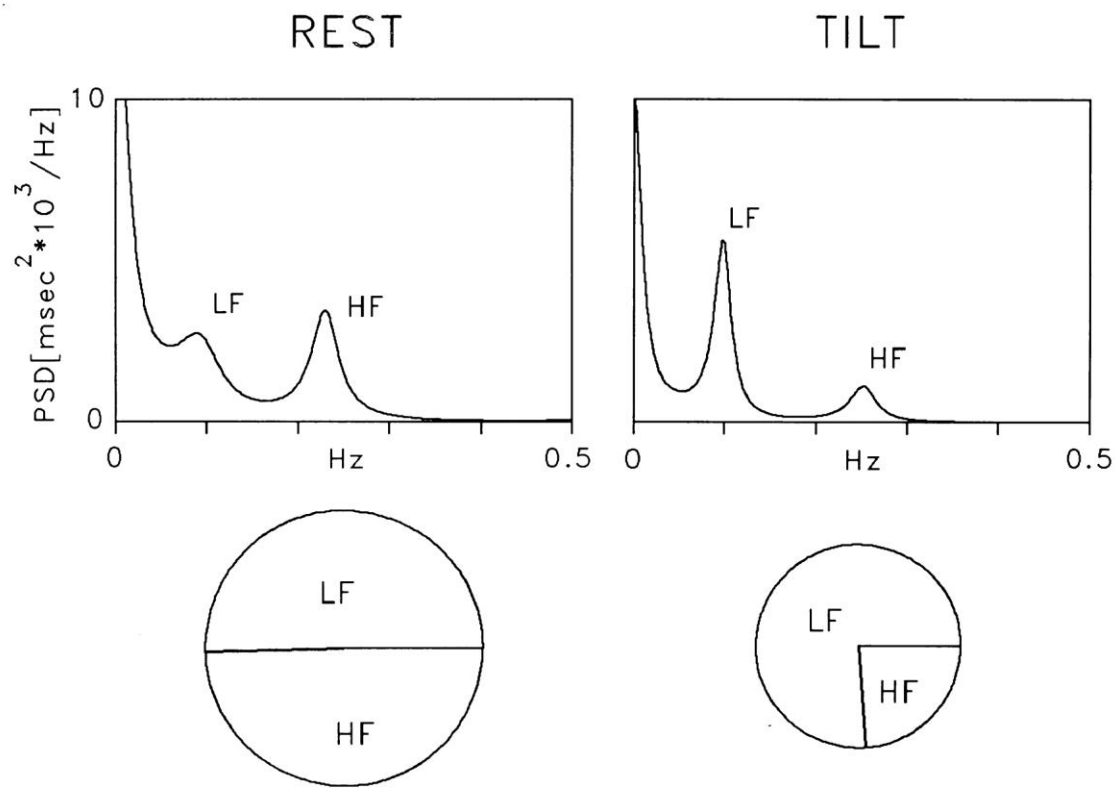
1.11.4 Frequency Domain Measurements

Analysis of the fluctuations in the frequency domain can also be used to look at heart rate fluctuation. This allows the user to break down the recording into individual frequency components that compose the overall variability. This yields information about the amount of variance (power) which occurs from periodic oscillations of heart rate at various frequencies[171]. This is expressed in milliseconds squared. This measurement will produce a Power Spectral Density (PSD) analysis (figure 1.1). Typically the Fast Fourier Transform is used to process this. By performing this, very low frequency (VLF), low frequency (LF) and high frequency (HF) components can be seen from shorter term recordings[171,172,180]. Ultra low frequency (ULF) components can also be seen in longer term recordings[174]. Low and high frequencies may also be measured in normalised units. This represents the relative value of each power component in proportion to the total power minus the VLF component. Table 1.1 shows selected frequency domain measures of HRV[173].

Table 1.1 Selected Frequency Domain Measurements of HRV[173] (reproduced from *Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use; Circulation.1996;93:1043-1065,* with permission from Wolters Kluwer Health)

Variable	Units	Description	Frequency Range
Analysis of Short-term Recordings (5 min)			
5-min total power	ms^2	The variance of NN intervals over the temporal segment	≈≤0.4 Hz
VLF	ms^2	Power in VLF range	≤0.04 Hz
LF	ms^2	Power in LF range	0.04-0.15 Hz
LF norm	nu	LF power in normalized units LF/(total power-VLF)x100	
HF	ms^2	Power in HF range	0.15-0.4 Hz
HF norm	nu	HF power in normalized units HF/(total power-VLF)x100	
LF/HF		Ratio LF [ms^2]/HF[ms^2]	
Analysis of Entire 24 Hours			
Total power	ms^2	Variance of all NN intervals	≈≤0.4 Hz
ULF	ms^2	Power in the ULF range	≤0.003 Hz
VLF	ms^2	Power in the VLF range	0.003-0.04 Hz
LF	ms^2	Power in the LF range	0.04-0.15 Hz
HF	ms^2	Power in the HF range	0.15-0.4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	≈≤0.04 Hz

Figure 1.1. Spectral analysis of RR variability in a healthy person at rest and tilt[173] (reproduced from *Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use; Circulation.1996;93:1043-1065,* with permission from Wolters Kluwer Health)



Basic science studies have revealed that the parasympathetic element predominantly determines the HF component of the frequency distribution[181]. This has been determined after experiments on vagotomised decerebrate cats, dogs as well as man with muscarinic receptor blockade[181]. Treatment with parasympathetic blockade has been shown to reduce the HF component in man[182]. A confounding factor when analysing the HF zone is respiration, which has an important effect on HRV in this area, for example with depth of respiration[172]. The interpretation of the LF component has been subject of more debate[183]. It has been thought that both components of the ANS contribute to the LF component[182]. Human studies have shown that in supine resting conditions, parasympathetic blockade predominantly influences the LF component, whereas sympathetic activity has influences in the standing position[184]. The ULF and VLF components are not fully understood in terms of their physiological correlate. There are correlates between certain time and frequency domain measures, with SDNN correlating with total power, SDANN with ULF and RMSSD, NN50 and NN50 with HF[171,173].

In normal resting conditions, the 2 main components of the frequency domain are the LF and HF components with the power of the LF component being greater than that of the HF component, with an LF:HF ratio typically greater than 1[177,180,181]. Standing or passive tilt increase the LF component with a decrease in HF[184]. In younger patients the LF:HF ratio can be markedly enhanced in this setting. Physical exercise increases sympathetic activity and is usually accompanied by a reduction in total power[173]. The opposite is true in vagal activation[173]. Ageing is thought to maintain the balance between the LF and HF components, but the physiological changes are blunted. In addition, supine HRV is

reduced reflecting a reduction in parasympathetic control of heart rate[185]. Spectral analysis of 24 hour recordings have revealed circadian patterns with higher LF values in the daytime and higher HF values at night[176,180186]. This suggests an early morning rise in sympathetic activity with a proportional reduction in parasympathetic activity[176,186]. Certain studies and Framingham population data have pointed towards a circadian variation in the incidence of cardiac events including SCD[187–189]. This suggests that these observations may reflect this change in autonomic balance.

1.11.5 Recordings

Recording of HRV NN data is typically performed with a Holter 24 hour ambulatory ECG[173]. In real world scenarios, confounding factors include noise and ectopic beats which will affect the data. There are a number of automatic algorithms which are designed to exclude unwanted data, but may also exclude important information due to their designs. Reports have suggested that time domain values may be more easily interpretable and comparable with published data, whereas frequency domain data may be prone to more error due to stationarity and the effects of other physiological factors on frequencies in the power spectrum [190].

1.11.6 HRV studies

Given the reasonable ease of HRV data acquisition and its relationship to the ANS, work has been undertaken to investigate its usefulness in different disease states. Heart failure of all aetiologies is associated with an increase in cardiac sympathetic tone and reduction in vagal tone as described earlier[191]. Plasma noradrenaline is also increased contributed

partly by a reduction in clearance due to a low output state[66]. In the short term these measures play a role in blood pressure maintenance. However, they also cause a number of disadvantageous effects, such as increasing the likelihood of ventricular arrhythmia and SCD, as well as the promotion of adverse cardiac remodelling[191].

1.11.7HRV post Myocardial Infarction

Studies have shown that HRV is decreased in patients with heart failure[192]. The Multicentre Post-Infarction Program (MPIP) showed that SDNN was an independent predictor of all cause mortality post MI[192]. In this study, 808 patients who were admitted with an acute MI had 24 hour Holter recordings. The study found that those with an SDNN < 50 ms, had a four-fold increase in mortality during the follow up phase, compared with those with an SDNN > 100ms[192]. These findings were shown to be independent of other variables.

The Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study provided further evidence supporting the prognostic value of HRV in a post MI population[88,193]. This study recruited 1284 patients with a recent MI. HRV was calculated from 24 hour Holter analysis. Patients with SDNN < 70ms were shown to be at increased risk of cardiac death compared to those with higher values (10% v 2%). This SDNN value was also a significant predictor of risk in a multivariate model with LVEF < 40% and ventricular ectopic rate > 10 / hour[88]. Subsequent analysis of this study also revealed that if depressed HRV was measured in a patient combined with the presence of non sustained ventricular tachycardia (NSVT) and depressed baroreflex sensitivity, there was

a risk ratio of 22 for cardiac mortality on multivariate analysis[194]. Bigger and colleagues looked at HRV in the frequency domain in a similar population[179]. This group found that ULF and VLF power were good univariate predictors of mortality independent of other clinical risk factors such as LVEF. LF, HF and LF:HF ratio analyses also showed an ability to predict a higher risk of mortality. Sensitivity values and positive predictive values however were low even when combined with other known clinical indicators of risk, although specificity was high[179]. The authors of both these studies commented on the importance of autonomic imbalance and adverse prognosis post MI[88,179].

1.11.8 HRV in Heart Failure

Further studies have assessed HRV in heart failure. Early studies provided conflicting data for this tool. This has been attributed to the fact that the patient population was too highly selected in these studies along with methodological considerations of HRV measurement[195,196]. In heart failure states there is evidence of autonomic dysfunction with reduced parasympathetic tone and a relative increase in sympathetic tone[57]. Nolan and colleagues demonstrated that the degree of parasympathetic dysfunction and sympathetic activation is related to the severity of left ventricular dysfunction[197]. The UK Heart study looked at time domain measures of HRV in heart failure patients who had not had a recent MI[198]. The investigators found that a depressed SDNN < 100ms was associated with all cause mortality in univariate analysis as well as progressive heart failure. It was not found to be associated with SCD in this analysis[198]. Independent predictors of SCD in this study included NSVT and left ventricular end diastolic diameter. The authors did comment that as well as autonomic imbalance, the alterations seen in HRV parameters

also reflect changes in renin-angiotensin, respiratory pattern and physical inactivity in the heart failure population[198].

There have been a number of other studies examining HRV parameters in heart failure and association with all cause mortality[199]. The SDNN is a measure which is consistently depressed and is associated with all cause mortality. Generally, this has been expressed as a dichotomised variable as can be seen in previous paragraphs. The DIAMOND-CHF study found that indexes of HRV provided prognostic information among patients with NYHA II symptoms, but not in more severe heart failure[200]. These patients had LVEF < 35%. In this study, univariate analyses provided prognostic information but not in multivariate analyses when adjusted for other variables. This study used a SDNN < 80ms as a cut off[200]. Boveda and colleagues studied 190 patients with NYHA II-IV heart failure with an LVEF < 45%. This study found that patients with SDNN values < 67ms were at a 2.5 fold increased risk of death after multivariate analysis[195]. Ponikowski and colleagues investigated 102 patients with NYHA II-IV heart failure[201]. Their population included ischaemic and non-ischaemic cardiomyopathy. They found that HRV measures which predominantly reflected vagal activity (pNN50, RMSSD and HF) did not differ between patients who died and those who survived in the study. Depressed SDNN and SDANN were found to be predictors of cardiac death, with a SDNN < 100ms used[201]. Fauchier and colleagues reported that depressed SDNN predicted mortality in a dilated cardiomyopathy (DCM) population[202]. Looking at other papers, SDNN and SDANN appear to be predictors of cardiac and all cause mortality but due to the differences

between demographic characteristics in the study populations, cut off values for these parameters can be variable[195–201 203].

1.11.9 Frequency Domain Measures and Heart Failure

Frequency Domain measures have also been studied as prognostic markers in the heart failure population. HF power does not appear to be predictive of mortality. Ponikowski and colleagues found that in their study decreased LF power was predictive[201], but this has not been borne out in all the studies[199 204]. Reduced power in the VLF frequency band does seem to be predictive[205,206], but again there are discrepant findings by other authors[199,204]. The physiological basis behind the VLF spectrum is not fully understood. Long term measures of HRV and LF power decrease with worsening heart failure class, which has been demonstrated in some of these studies. Table 1.2 outlines major studies of HRV in heart failure and their findings.

Table 1.2: Studies of HRV in heart failure (adapted from *Sandercock GRH, Brodie DA. The role of heart rate variability in prognosis for different modes of death in chronic heart failure. PACE. 2006;29(8):892-904.* With permission from John Wiley & Sons)[160]

Study	Reference	Recording	Number	NYHA	End points	Measurment	Results
Jiang et al	[203]	24 hr Holter	23	>III	Sudden death / Ventricular arrhythmia; Intractable heart failure;	SDNN, SDANN	SDNN (Event median 39.5, no event median 51) p=0.03; SDANN (Event median 30, no event median 43); p=0.02
Ponikowski et al	[201]	24 hr Holter	102	II-IV	Cardiac Death	SDNN, SDANN, LF	SDNN<100ms P=0.007; SDANN (Cardiac death 74±38, Survivors 107±39) P=0.001; ln LF (Cardiac Death 4.1±1.7, Survivors 5.0±1.0) P=0.003
Bonaduce et al	[196]	24 hr Holter	97	II-IV	Cardiac Death	SDNN, SDANN, LF:HF ratio	SDNN<120ms RR 2.08 P=0.049 SDANN<92ms RR 1.92 P=0.049 LF/HF<1.6 RR1.04
Boveda et al	[195]	24 hr Holter	190	II-IV	All cause mortality	SDNN, SDANN	SDNN<67ms; RR 2.7 P<0.0001
Bilchick et al	[207]	24 hr Holter	127	II-III	All cause mortality	SDNN	Mortality: SDNN≤65.3ms RR3.72 P=0.0001; SCD: SDNN ≤65.3 RR 2.4 P=0.088
Makikallio et al (DIAMOND CHF)	[200]	24 hr Holter	499	II-IV	All cause mortality	SDNN, VLF	SDNN<80ms RR 1.2 P<0.00; ln VLF <6.4 RR1.2 p<0.00
Aronson et al	[204]	24 hr Holter	199	III-IV	All cause mortality	SDNN, SDANN, Total Power, ULF	SDNN<44ms RR 2.2 P=0.036; SDANN<37ms RR 2.1 P=0.04; Total Power<1475ms^2 RR2.2 P=0.03; ULF<1100ms^2 RR2.6 P=0.007
Guzzetti et al	[206]	24 hr Holter	330	I-III	Cardiac event	VLF night, LF night	Pump failure: VLF night≤509ms^2 RR 2.3 P=0.0018 SCD: LF night≤20ms^2 RR2.6 P=0.012)
Hadase et al	[205]	24 hr Holter	54	II-IV	Cardiac events	VLF	VLF<6.0 ln (ms^2) 3 year event free rate 45%, 87% if VLF≥6.0 ln (ms^2)
Nolan et al (UK HEART)	[198]	24 hr Holter	433	I-III	All cause mortality	SDNN	SDNN (Survivors 116.6±39.3; Non-survivors 93.4±48.1) RR1.62 P=0.005
Fauchier et al	[208]	24 hr Holter	116	I-IV	Cardiac events	SDNN	SDNN≤100ms P=0.02

1.11.10 HRV and SCD

The relationship between HRV and SCD has also been investigated. Although some time domain measures are associated with an increased mortality including cardiac death, most studies have not shown a statistically significant relationship between the same measures and SCD / arrhythmic death[209]. Bilchick and colleagues paper showed that heart failure patients with depressed SDNN < 65.3 ms were not only at increased risk of all cause mortality but also SCD with a relative risk of 2.4, although this was only a trend and not statistically significant (p=0.088). However, those in the lowest SDNN quartile were at higher risk (P=0.016)[207]. Fauchier's group reported that in their population of patients with DCM, SDNN values < 100ms were associated with an increased of sudden death[208]. However, reference was made to the fact that the cause of sudden death might be arrhythmic or non-arrhythmic, for example pulmonary or cerebral embolism.

In other studies, these findings are not reciprocated. For instance, Galinier and colleagues found that although SDNN < 67 ms was associated with an increased mortality in their study of heart failure patients, only SDANN, RMSSD and total power and LF power during daytime were statistically significantly related to sudden death in univariate analysis[209]. Only low LF power was statistically significantly associated with sudden death in multivariate analysis. Guzzetti and colleagues demonstrated that in a study of 330 patients with heart failure in sinus rhythm, only LF power at night was predictive. Furthermore, there were no statistically significant differences between patients with ischaemic and non-ischaemic cardiomyopathy[206]. There is therefore, no consensus on HRV variables and association with sudden death, but there is compelling data

associating certain measures, for example, SDNN and VLF with all cause mortality and death from progressive heart failure. Shorter term recording measures of HRV may be more associated with SCD than 24 hour evaluations suggesting a strong role for autonomic modulation in SCD[199].

1.12 Cardiac Peptides

The 3 major natriuretic peptides are atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C type natriuretic peptide. They are involved in protecting the cardiovascular system from volume overload. A-type natriuretic peptide is mainly secreted from the atria and BNP from the ventricles[210]. B-type natriuretic peptide is released from the ventricular myocardium in states with increased volume and wall stress[211]. It begins as pre-pro BNP which is cleaved in various stages to the physiologically active BNP and the inactive N-terminal fragment (NTproBNP)[212]. The active BNP causes vasodilatation, natriuresis, and suppression of the rennin-angiotensin system counteracting the development of heart failure[212,213].

In heart failure (HF) BNP and NTproBNP levels are elevated[210]. Measurement of both is possible in plasma. However, NTproBNP has a longer half life of 1 to 2 hours and hence is more stable. It is renally excreted and hence is affected with changes in the glomerular filtration rate (GFR)[210,212].

1.12.1 Heart Failure and BNP

Population based studies of random individuals have shown that BNP measurement can be used as a prognostic and diagnostic tool in the general population [214,215]. Values of BNP above 80-100 pg/ml are thought to point towards heart failure diagnoses, but this has to be used in conjunction with other parameters such as ECG evaluation and clinical history, specifically a history of ischaemic heart disease[215–217].

There have been a number of heart failure trials demonstrating the prognostic value of BNP in cardiac failure[218]. Doust and colleagues conducted a review of the trial evidence demonstrating that for every 100ng/L rise in BNP, there was a 35% increase in the relative risk of death[216,218]. A subgroup analysis of the Val-Heft study suggested that serial measurements of NTproBNP may offer a risk stratification strategy in chronic HF patients[219]. Studies looking at dichotomous measures have varied in terms of the cut off values used, but they all show an increased risk of death or cardiovascular events with elevated BNP levels. The largest study of the prognostic value of BNP in heart failure is an analysis of the Val-Heft study. Plasma BNP was measured in 4305 patients with heart failure and left ventricular dysfunction and levels > 97pg/ml were shown to indicate an increased risk of death (HR 2.1 CI 1.79-2.42)[218,220]. The BNP levels are also used in diagnosis of heart failure and in assessing response to treatment. Studies have shown that a failure in the reduction of BNP with heart failure treatment is associated with a higher risk of death compared to patients where BNP levels improve[216].

Drugs that are well established in the treatment of heart failure have been shown to reduce BNP concentration[221,222]. Rosenberg and colleagues demonstrated a 34% reduction in BNP levels in heart failure patients treated with enalapril[223]. Treatment with spironolactone [224] has also been shown to reduce BNP levels due to a reduction in left ventricular filling pressure and remodelling. Long term beta blocker use has also shown a reduction in BNP levels in the heart failure population[225]. A small study has also suggested that amiodarone use in patients with ventricular tachyarrhythmia can reduce BNP levels[226].

1.12.2 BNP and SCD

Given the prognostic utility of BNP in HF in terms of mortality, efforts have been made to investigate whether there are any relationships between BNP levels and SCD, and whether it may be used as a method of risk stratification. There have been 2 types of study that have assessed this. Firstly, there are studies examining BNP and SCD in patients without ICDs, and secondly, studies examining BNP and its ability in predicting arrhythmia in ICD populations[211]. Bayes-Genis and colleagues[227] showed that NTproBNP was a statistically significant univariate and multivariate risk marker for SCD. In this study 494 patients with NYHA II-IV heart failure were enrolled and NTproBNP levels were measured at baseline. Fifty patients experienced sudden death at the 3 year follow up point. The study found that NTproBNP levels >908ng/L was statistically significantly higher in those who experienced sudden death in univariate analysis (HR 4.6 CI 2.2-9.5). Other statistically significant univariate factors included indexed left atrial size, history of nyocardial infarction and atrial fibrillation. In multivariate analysis NTproBNP >908ng/L

was a statistically significant marker of sudden death (HR 3.1 CI 1.5-6.7% p=0.003) independent of clinical variables and ejection fraction[227]. Similar results have been demonstrated by groups led by Tapanainen, Tigen and Berger[228–230]. These studies were analysed using dichotomous BNP levels based on each individual analysis. The study by Berger and colleagues recruited 452 patients with left ventricular ejection fraction ≤35% with 44 sudden deaths over a 3 year period. Univariate risk factors of sudden death included log BNP (p=0.0006), LVEF (p=0.0054), log NTproBNP (p=0.0057) and NYHA class (p=0.00375). In multivariate analysis the only independent predictor of sudden death was log BNP (p=0.0006). Further analysis showed that BNP levels above 130pg/ml conferred the highest risk in this population[229].

Analyses of BNP have also been conducted in patients with ICDs. There have been mixed results in these trials. However, a recent meta-analysis by Scott and colleagues, suggested that BNP is a predictor of SCD risk independent of LVEF. This meta-analysis found that in patients without ICDs there was a four-fold increase in the risk of sudden death in patients with raised BNP levels compared with lower BNP levels. In the ICD population there was a two-fold increase in the risk of ventricular arrhythmia in patients with raised BNP levels. However, the authors suggested that the evidence did not mandate routine clinical use in this arena. Reasons for this include the heterogeneity of the cut off values for BNP given the different patient populations in the trials and the fact that raised BNP is not specific for SCD, in that it can also predict other modes of death such as pump failure[211]. Verma and colleagues investigated 345 consecutive new ICD patients. This group suggested that raised pre-implant plasma BNP above the 50th centile

was an independent predictor of subsequent ICD therapy (573 vs. 243 pg/ml, p=0.0003)[231]. Blangy and colleagues also showed that a BNP level above the median value in their study (64ng/L) was an independent predictor of VT in an ICD population with ischaemic cardiomyopathy[232]. Another study of 50 ischaemic heart failure patients also identified an elevated BNP above 2536 pg/ml as an independent predictor of appropriate ICD therapy[233].

Despite these positive studies, there are other studies which do not support these findings. The PROFIT study showed that left ventricular ejection fraction, permanent AF and QRS duration were independent predictors for VT / VF therapy in a cohort of 250 ICD patients with any underlying aetiology[234]. However NTproBNP was not an independent predictor of therapy in this analysis. More recently, an Italian study of 42 ICD patients (with ischaenic and non-ischaemic cardiomyopathy) did not demonstrate any significant difference in BNP levels between those that received appropriate therapy and those who were arrhythmia free[235]. The authors of this study did comment that given the small numbers of patients, the findings needed to be confirmed in larger populations.

The table below (1.3) lists studies investigating BNP or NTproBNP as markers of ventricular arrhythmia in varying ICD populations. As can be seen there is no consensus as to whether these biomarkers are predictive or not. In addition, in the studies where there is an association, the study designs and populations vary. Furthermore, the cut off measurement varies between the studies. Despite this, measurement of BNP does have clinical use as evidenced by its inclusion in the 2010 National Institute for Clinical

Excellence guidelines for Heart Failure. Firstly, measurement of BNP is advocated in the algorithm for the diagnosis of heart failure. The authors recommend measurement in suspected heart failure and if levels are normal (BNP <100pg/ml and NTproBNP <400pg/ml) then the diagnosis is unlikely. Furthermore, given the fact that high levels of BNP are associated with worse prognosis, in suspected primary care cases with high levels (BNP >400pg/ml and NTproBNP >2000pg/ml) specialist referral is recommended on an urgent basis[39].

Table 1.3 Studies demonstrating the utility of BNP / NTproBNP in prediction of arrhythmia occurrence in ICD populations[211](adapted from *Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: a meta-analysis. Scott et al; European Journal of Heart Failure, 2009:11,958-966; with permission from Oxford University Press)*

Authors	Population	Number	Hormone measured	Measurement	Result
Budeus et al [236]	Ischaemic	93	BNP	>265pg/ml	p=0.015;predicted ICD therapy
Blangy et al[232]	Ischaemic	121	BNP	>64ng/L	p=0.014; Raised BNP predicts VT in ICD patients (odds ratio 3.75)
Klein et al[234]	Any	250	NTproBNP	>405ng/L	p=0.49; No significant difference in ICD patients (multivariate)
Klingenberg et al[233]	Ischaemic	50	NTproBNP	>2536pg/ml	p<0.0001;Predicted shocks in ICD patients
Verma et al[231]	Any	345	BNP	>283ng/L	p=0.04;single pre-implant BNP predicts ICD therapy
Battipaglia et al[235]	Ischaemic / DCM	42	NTproBNP	Not significant	p=0.91; no significant difference (ICD patients)
Manios et al[237]	Ischaemic	35	NTproBNP	>880pmol/L	P=0.001; sensitivity 73%, specificity 88% for ICD events
Nagahara et al[238]	Any	54	BNP	>187pg/ml	p=0.012; predicted ICD shock
Yu et al[239]	Ischaemic	99	NTproBNP	>497ng/L	p=0.036; predicted VT/VF
Konstantino et al[240]	Heart Failure	50	BNP	Not significant	p=0.9; no difference between VA & no VA

VA-ventricular arrhythmia

1.13 QT Dispersion

1.13.1 Definition

Measurement of the QT interval on the resting 12 lead ECG has been used to assess ventricular repolarisation[241]. The difference between the longest QT interval and shortest QT interval on the resting ECG is known as QT dispersion (QTd)[242]. This has been associated with the inhomogeneity of myocardial repolarisation and as such has been studied in a variety of areas[243]. In resting healthy individuals, QTd varies from 30-60ms. In patients with coronary artery disease it is increased to 60-80ms[242]. Population studies have revealed that healthy individuals with a QTd≥90ms compared to those with a Qtd<30ms have a four-fold rise in cardiac death[244].

1.13.2 Physiology

Kuo along with other authors have demonstrated the link between the dispersion of ventricular recovery times and ventricular arrhythmia, stating that a large dispersion of repolarisation facilitates the development of conduction delay which is required to sustain arrhythmia[54,242]. QT dispersion is thought to reflect the dispersion of ventricular repolarisation and hence, there have been studies conducted investigating this as a prognostic tool. Basic science studies previously demonstrated the correlation between monophasic action potential recordings of dispersion of repolarisation and ECG QT dispersion[245]. However, further studies demonstrated that there is probably no clear mechanistic link between QTd and the dispersion of ventricular recovery times. In addition QT measurement can be compounded further by measurement difficulties in cases of abnormal T wave morphology. Thus, although it is not correct to state that QTd

is a direct measurement of repolarisation inhomogeneity, it may still represent a useful tool as an approximate expression of repolarisation abnormalities[241,246].

1.13.3 Measurement

Measurement of QTd is hampered by the unreliability of QT measurement in individual leads[246]. A study by Glancy and colleagues examined 70 patients' ECGs after they had been admitted with acute myocardial infarction. Measurements of QT intervals were conducted manually and using automatic algorithms. In this study, QT dispersion measurements had large errors, with an intra-observer error of 17.3%, inter-observer error of 22% and an error of 30% between manual and automatic measurements[247]. This occurs given the difficulty in assessment of the exact point at which the T wave ends[248]. Automatic measures of this have not proved to be superior to manual estimations[241,248]. Difficulties arise due to morphological considerations as well as separation of the end of the T wave from the U wave. However, other studies have reported smaller errors of less than 5% in the measurement of QTd[246]. Despite these potential errors, studies looking at the use of QTd do suggest that it may be a useful ECG measure[248].

1.13.4 Clinical Studies

In myocardial disease, ventricular arrhythmia can occur due to electrical heterogeneity in different areas of the heart[249]. In light of this, studies have been conducted to explore the potential use of QTd. In arrhythmogenic right ventricular cardiomyopathy (ARVC) studies looking at QTd have yielded mixed results[249]. Heart failure is associated with a significant increase in the risk of sudden arrhythmic death and QTd is increased in this

population[250]. Barr and colleagues demonstrated that an increased QTd was associated with a statistically increased risk[251]. Pye and colleagues showed similar findings with a greater mean QTd in patients with sustained ventricular arrhythmia compared to controls[252]. However, Galinier and colleagues demonstrated that aetiology may be important. This study separated patients with ischaemic cardiomyopathy and those with dilated cardiomyopathy (DCM). QT dispersion was significantly raised and was an independent predictor of sudden death and arrhythmic events in patients with DCM but not in patients with ischaemic heart disease[250]. Grimm and colleagues conducted a prospective study that demonstrated that there was a significant increase in QTd in DCM patients with arrhythmic events compared to those who were arrhythmia free[253]. Fu and colleagues studied 163 patients with congestive cardiac failure secondary to DCM and myocardial ischaemia[254]. In this study, 24 patients experienced sudden death and a further 10, ventricular arrhythmia. QT dispersion was noted to be statistically significantly higher in these patients compared to those who were arrhythmia free (95±19ms vs 54±21, $p<0.001$) in univariate but not multivariate analysis. Other repolarisation parameters measured did reach significance in multivariate analysis. These were JT dispersion (the dispersion of the time between the J point of each QRST complex and the end of the T wave) and the coefficients of variation of the QT (QTrd) and JT (JTrd) interval. The authors stated that QTrd ≥ 5.5 had a positive predictive accuracy of 56.6% and negative predictive accuracy of 95.2%[254].

Despite these results, there have been other studies that have not demonstrated any statistically significant difference in QTd in heart failure patients. In a study of 135 DCM patients, Fei et al showed that there was no significant difference in QTd between patients with and without arrhythmia[255]. Pedretti's study also supported this[256]. The conflicting results may in part relate to the difficulties in QT measurement mentioned above, which is compounded by abnormal electrocardiograms in the heart failure population, making measurement more difficult[250].

Table 1.4 below summarises some of the published trials examining QTd as a prognostic marker.

Table 1.4 Studies demonstrating QT dispersion values in studies (patients v controls)

Authors	Population	Number	Method	QTd value	Result
Pedretti et al[256]	IHD	547	Manual & Automated	NA	QTd not different between post MI patients who died / had VA
Davey et al[257]	CCF	18	Manual	NA	Not significantly raised in patients with VA on Holter
Perkiomaki et al (1995)[258]	IHD	70	Manual	104±41	p<0.001; increased QTd in patients with VT/VF
Perkiomaki et al (1997)[259]	IHD	94	Manual	103±37	p<0.001; increased risk of VT/VF
Fu et al[254]	CCF	163	Manual	95±19	p=0.01; Increased risk of SCD / VA
Grimm et al[253]	DCM	107	Manual	NA	QTd increased in VA vs. no VA, but large overlap
Fauchier et al[260]	DCM	169	Manual	NA	No prediction of cardiac death
Fei et al[255][159]	DCM	135	Manual	NA	No difference in QTd between survivors/death/transplant

IHD Ischaemic Heart Disease; DCM Dilated cardiomyopathy; NA non applicable

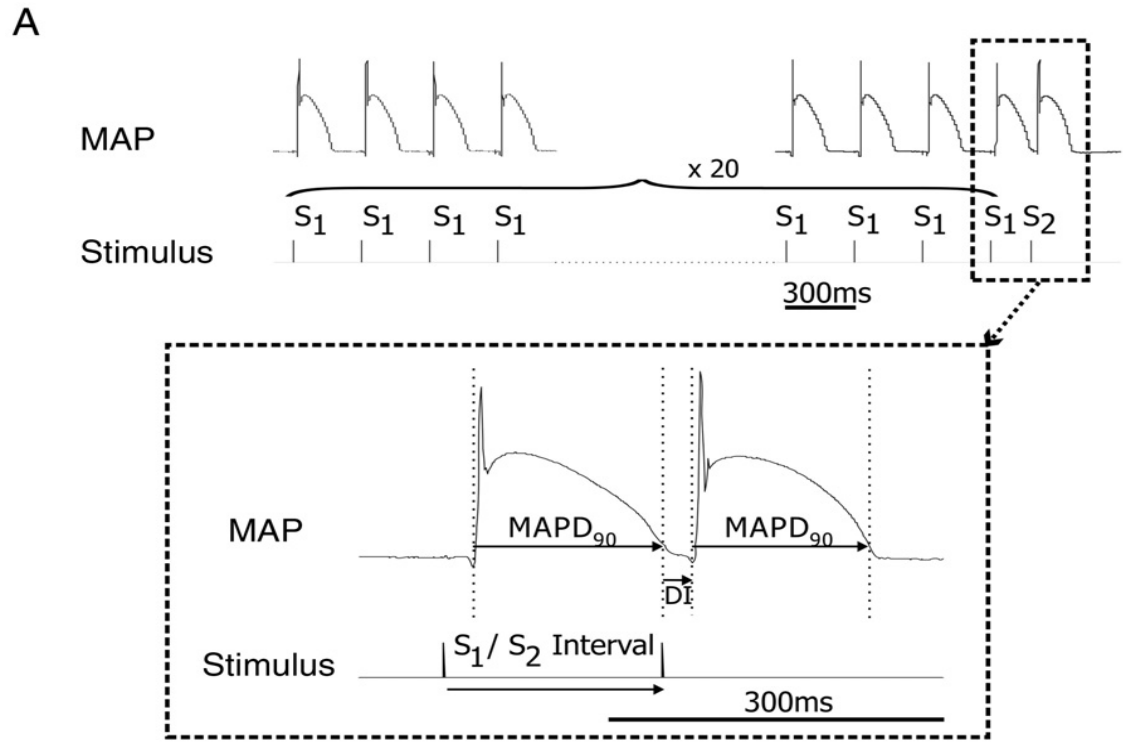
1.14 ECG restitution

1.14.1 Definition

Regional variation in action potential duration (APD) is important in re-entry and arrhythmogenesis. Electrical restitution refers to the changes in APD following changes in the preceding diastolic interval (DI) and was first described in 1975[261]. Cardiac APD duration depends on the duration of the previous diastolic interval which is the period between repolarisation and the next excitation[262]. This property is known as restitution. The standard restitution curve is produced by adding an extra stimulus (S2), of decreasing cycle length, to a steady state drive train (S1). The S1-S2 coupling interval is decreased until there is loss of capture (figure 1.3)[263]. The relationship between the APD to its preceding DI (S1-S2 coupling interval – S1 APD) forms the restitution curve[264]. The restitution hypothesis states that when the slope of this curve is greater than 1, consecutive changes in cycle length at fast rates induce oscillations in APD (alternans) which will increase in magnitude with successive beats that can result in wave break and fibrillation[265]. This occurs as small differences in DI are amplified into larger changes in APD in this setting. This leads to alternans and can lead to action potential failure. If cardiac excitation is viewed as a wave, the wave front corresponds to depolarisation. If there is an anatomic obstacle for instance, such as scar, the wave can break and ultimately multiple re-entrant waves can be created causing ventricular arrhythmia. A steep restitution slope facilitates this phenomenon [262,266]. If the slope is less than l, then the oscillations dampen progressively until a new steady state is achieved. This protects against the development of fibrillation[267]. At fast rates a steep restitution slope can also result in spatial gradients of repolarisation which may increase the risk of arrhythmia[267].

These spatial heterogeneities in APD restitution have been documented in predominantly animal studies as well as using non contact mapping techniques in humans[262,264].

Figure 1.3. Illustration of Ventricular Monophasic Action Potentials and the method of generating a restitution curve in an animal model[263](reproduced from *Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. Cardiovascular Research. 2007 (73) Issue 4,750-760; with permission from Oxford University Press)*



1.14.2 Physiology

The basic premise of the steepness of the restitution slope and subsequent vulnerability to arrhythmia has been documented in biological studies. Drugs which flatten the restitution slope can convert VF into a more stable VT[262]. Conversely, the restitution hypothesis may explain why rapid VT may degenerate into VF compared with slower VT with shorter cycle lengths leading to a steeper position on the restitution slope, subsequent APD alternans, wave break and VF[264]. In the failing heart there are changes in autonomic activity, as described earlier, with sympathetic stimulation on the heart being pro-arrhythmic. Ng and colleagues have documented that sympathetic stimulation steepens the restitution slope, whereas vagal stimulation flattens it [268]. In addition to this, the same group also showed that VF threshold was reduced with sympathetic stimulation and vice versa[263]. Similar results have been shown elsewhere in a human study by Taggart et al[264].

1.14.3 Human Studies

Data also exists in human studies which have revealed differences in electrical restitution between normal and structurally abnormal hearts. Alternans of APD can be induced in normal hearts at rapid heart rates if the restitution slope is steep but this feature is seen at lower heart rates in patients with steep slopes and underlying structural heart disease. In addition to this, patients with cardiomyopathy will have an earlier onset of APD alternans with increased magnitude compared to normal individuals. Experimental mathematical work has also suggested that the spatial heterogeneity seen in heart failure increases the risk of wave break if sufficiently large[263].

1.14.4 Non invasive assessments

Restitution analyses in the cited studies above are invasive assessments, and thus interest has grown into the feasibility and accuracy of non-invasive techniques. Fossa and colleagues have described techniques using 24 hour Holter recordings to analyse ECG restitution[265,269]. The dynamic beat to beat method of analysis uses 24 hour Holter analysis to collect all QT intervals from the recorded period[270]. The TQ interval can be calculated from the data, and QT/TQ relationships can be assessed. These can be used to approximate to the recognized APD / DI relationship in normal restitution[271]. When the ratio is greater than 1, the heart is working more per cycle (QT (action potential duration)>TQ (diastolic interval)) increasing vulnerability to ventricular arrhythmia[272]. Fossa described this in humans in 2007[265]. This study examined a few parameters. Firstly, the percentage of beats with QT/TQ ratio >1 was examined, citing this to reflect the relative time on the restitution curve where stability was uncertain. The TQ 5^{th} quantile was also looked at, given the fact that there is an increase in the likelihood of re-entry as the relative refractory period approaches zero. Finally, the upper 98% quantile was assessed to reflect the magnitude of the slope. This study compared normal individuals before and after sotalol looking at the restitution parameters. In addition to this, a patient with coronary disease and Torsades de Pointes was evaluated. The authors found that in this patient, the median TQ interval was below healthy subjects. In addition, there was a lower TQ 5^{th} quantile, an increase in the QT/TQ 98^{th} quantile and increase in the percentage of beats with a QT/TQ ratio >1[265]. To date, there is no work looking at

whether, these parameters measured of 24 hour Holter analyses can be used to predict the risk of ventricular arrhythmia in humans.

1.15 QT Variability Index

1.15.1 Definition and Calculation

The QT variability index (QTVI) represents the relationship between QT and RR variability and expresses temporal dispersion of cardiac repolarisation as opposed to spatial dispersion measured with QT dispersion[273]. It has been studied in congestive cardiac failure, ischaemia and in normal states[274]. Berger et al described the QTVI in 1997[273,274]. The QT and RR mean (QTm and RRm) and variances (QTv and RRv) are calculated for the epoch in question. The following formula then calculates the QTVI:

$$QTVI=log_{10}((QTv)/(QTm)^2)/((RRv)/RRm)^2))^{275}.$$

1.15.2 Studies

Piccirillo et al demonstrated that QTVI was elevated in heart failure states compared with matched population controls[273]. Berger et al also showed similar findings in a DCM population[275]. The rationale for this is that in structurally normal myocardium, all myocardial cell repolarisations are of similar duration, and hence variance and QTVI will be low. However, in structurally abnormal myocardium, variance and QTVI will be raised[275]. Murabayashi et al demonstrated increased QTVI in acute ischaemia[276]. Furthermore, analysis of the MADIT II population showed an increase in QTVI in those who experienced VT/VF compared to those who did not[277]. The authors concluded that

this was driven by an increase in QTv as the RRv was not different between the two groups. A QTVI>-0.52 was thought to be an independent risk factor in this study, although the negative predictive value was thought to be low. Another study of stable NYHA class I heart failure patients with previous myocardial infarction and an EF between 35 and 40% showed that QTVI≥80th percentile had a higher risk of SCD with an odds ratio of 4.6[278].

2 Study aims

2.1 Rationale of study

Implantable Cardioverter Defibrillators (ICDs) have been shown to improve mortality in patients at risk of sudden cardiac death (SCD) from malignant ventricular arrhythmias[152–160]. Despite decades of research, the mechanisms underlying lethal arrhythmias such as ventricular fibrillation are poorly understood and ICDs remain a crude, palliative treatment modality which is not inexpensive[143]. Patient selection is crucial so that treatment may be delivered to those who are most likely to benefit in order to maintain high cost-effectiveness of the therapy. In addition studies have shown that over 50% of patients who receive ICD therapy never require therapy from the device. Hence, more refined and stringent risk stratification is clearly needed to identify patients who are most likely to benefit from this expensive treatment and also to exclude those who are at lower risk.

2.2 Study aims

The aims of this study are to examine whether some easily measureable non invasive parameters can be used to predict arrhythmia risk in a real world ICD population with left ventricular systolic dysfunction. The main measures being assessed are plasma NTproBNP, heart rate variability (as a marker of autonomic function), QT dispersion, QT variability index (QTVI) and QT/TQ analyses from 24 hour Holter recordings (ECG restitution).

The following hypotheses will be examined:

1. Plasma natriuretic peptide levels are higher in patients treated with an ICD who experience ventricular arrhythmia

2. QT dispersion restitution measurements are associated with ventricular arrhythmic events in patients treated with an ICD.

3. Assessment of autonomic nervous system activity by heart rate variability is associated with ventricular arrhythmic events in patients treated with an ICD.

4. QTVI and ECG restitution measurements are associated with ventricular arrhythmic events in patients treated with an ICD.

2.3 End points

The primary end point of this study is appropriate ICD shock. This is used for the purpose of this study as a surrogate for sustained, potentially life threatening ventricular arrhythmia. The secondary end point is a combination of appropriate ICD shock and ATP therapy.

2.4 Thesis Layout

The results chapters have thus been laid out as follows:

Chapter 5: NTproBNP analysis

Chapter 6: QT dispersion analysis

Chapter 7: Analysis of Holter data, which includes HRV, QTVI and measures of ECG restitution.

The final chapter gives an overall summary and the limitations of the study.

3 Methods

3.1 Ethical approval

The study was approved after consideration by the University Hospitals of Leicester (UHL) NHS Trust R&D department (UHL 10,053) and the Leicestershire Research Ethics Committee (LREC)(06/Q2502/35) in May 2006 after application using the online NRES (formerly COREC) website.

3.2 Overview

Patients who underwent ICD implantation between August 2006 and April 2008 at Glenfield Hospital were approached for inclusion into the study. Patients were approached with the permission of the supervising clinician who was responsible for their clinical care. I was the single investigator who recruited the patients and performed all of the necessary investigations. Patients were initially approached 24 hours prior to recruitment. The study was explained at this stage and a Patient Information Sheet was left with the patient. If patients agreed to participate, signed consent was then obtained.

3.3 Data Collection

I was the sole investigator in this study and collected all of the data myself. The demographic data of patients who agreed to be included in the study, and who met the entry requirements (see below) were collected. A baseline 12 lead ECG was obtained which was recorded at paper speeds of 25mm/s and 50 mm/s to allow for measurements of QT dispersion. A Delmar Reynolds 3 channel Holter recorder was fitted, which was removed after 24 hours recording. A 20ml venous blood sample was also taken at this initial assessment. The blood was taken after a 15 minute period of rest. The sample was

then immediately transferred to 2 EDTA lined tubes and placed on ice pending transfer to the laboratory. Echocardiography was then performed to allow estimation of left ventricular ejection fraction. If a recent satisfactory echocardiogram was available, this was used for the required data collection. Echocardiography was performed using Phillips Sonos and IE33 machines.

3.4 Inclusion and Exclusion criteria

3.4.1 Inclusion criteria

Patients being considered for new ICD implantation with NYHA class I-III symptoms of heart failure and documented left ventricular dysfunction were approached for inclusion into the study. The decision for device implantation was at the discretion of the supervising clinician. When the decision for device implantation was made, I screened the notes to assess suitability for inclusion. If the patient fulfilled the entry and exclusion criteria, I then approached the patient to obtain consent.

3.4.2 Exclusions

As persistent ventricular pacing and biventricular pacing may affect cardiac function and future arrhythmia occurrence, patients with high grade AV block and those requiring cardiac resynchronisation therapy (biventricular pacing) were excluded from the study. For similar reasons, patients with unstable coronary disease requiring revascularisation were also excluded. The following patients were not considered for inclusion into the study:

- Unstable coronary heart disease, likely to have needed percutaneous or surgical intervention

- Requirement for cardiac resynchronization therapy
- Recent coronary artery bypass graft surgery and percutaneous coronary intervention (within 3 months)
- Recent valvular surgery (within 3 months)
- Recent myocardial infarction (as documented by appropriate ECG & biochemical analysis) (within 3 months)

3.5 Recruitment

Given the methods described above, the numbers of patients included into each analysis varies. Recruitment occurred between July 2006 and April 2008. I was the sole person responsible for recruitment. In this period,

A more detailed description of the numbers of patients included into each analysis will follow in the subsequent chapters. The total number of patients recruited was limited by the fact that recruitment was being conducted by a single individual at a single site. Cross site recruitment was considered, but could not be undertaken due to practical and logistical considerations. In addition the exclusion criteria, particularly the exclusion of patients with recent acute coronary syndromes and subsequent revascularisation resulted in a small cohort recruited. The exclusion of patients needing cardiac resynchronisation also reduced the cohort as seen in the Consort Diagram (Figure 3.1).

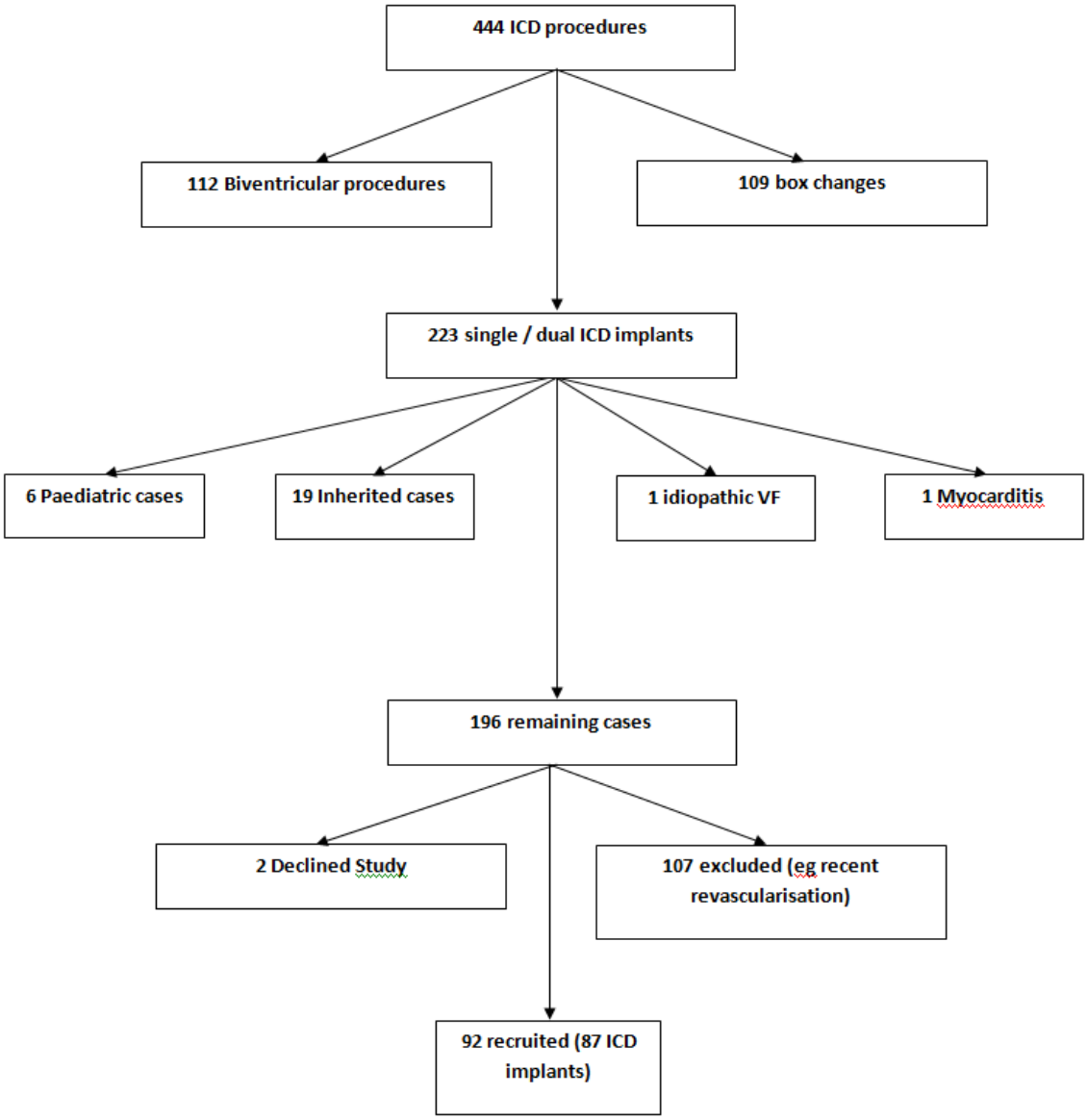


Figure 3.1. Consort diagram of patient recruitment

3.6 Follow up

The majority of patients were followed up in the Glenfield device clinic. Data were collected up to 2 years post initial implant by review of the device notes. The first patient was recruited in August 2006, and the final patient in April 2008. Appropriate ICD therapy was recorded in the form of anti-tachycardia pacing and shock. These were used as surrogate markers of sustained ventricular arrhythmia. As Glenfield Hospital is the regional tertiary cardiology centre encompassing Leicestershire, parts of Linconshire, Derbyshire and Northamptonshire, some patients were followed up at other centres. The data for these patients were obtained by contacting the appropriate centre.

3.7 Data Analysis

3.7.1 NTproBNP

The blood samples collected before ICD implantation were placed in EDTA lined bottles and taken on ice to the laboratory for storage. The samples were then centrifuged and the EDTA plasma was obtained. These samples were then stored at -80ºC. All of the samples were then analysed in 1 batch to obtain NTpro BNP levels using the ELISA technique previously described by Ng and colleagues[279]. I collected and processed all of the blood samples to obtain the NTproBNP data.

3.7.2 QT Dispersion

QT dispersion was calculated from the recorded 12 lead electrocardiograms. ECGs were measured at 50mm/s paper speed. Patients not in normal sinus rhythm were not included for this part of the analysis. QT and RR intervals were recorded. Three consecutive sinus

beats were used to obtain a mean QT interval for that particular lead. The ECG parameters were measured using an ECG ruler manually. I measured all of the ECGs to obtain the data. The end of the T wave was determined visually, as the point of return to the isoelectric line. I measured all of the ECGs as the single operator. Once all 12 leads were obtained, QT dispersion was calculated by the following formula:

$$QT_{(disp)}=QT_{(max)}-QT_{(min)}.$$

3.7.3 Heart Rate Variability (HRV)

The 24 hour tape data was collected on 3 channel Delmar Reynolds Holter recorders. These are the standard Holter recorders used clinically in our centre. The recordings were then initially analysed on Delmar Reynolds Pathfinder software. Patients who were in sinus rhythm were included in this part of the analysis. The recordings of those included were then checked by me to ensure appropriate labelling of beats by the automated software. If there was a high proportion of ectopic activity, the patient was not included in the final analysis. The data was then transferred in a '*.dat'* format to the Delmar Reynolds HRV tools software to calculate the measures of HRV used in the study. I collected and analysed all of this data.

3.7.4 QT Variability Index (QTVI)

The 24 hour Holter data obtained in those patients who had their HRV analysed was also used to calculate QTVI. The Pathfinder software records QT and RR data in text files. These can then be opened in Microsoft Excel, to calculate the components of the QTVI equation:

$$QTVI: QTVI=log_{10}((QTv)/(QTm)^2)/((RRv)/RRm)^2)) \quad (195)$$

3.7.5 ECG restitution

The 24 hour Holter data used above was also used to calculate various parameters of ECG restitution. The QT and RR text files were opened in Microsoft Excel and the markers of ECG restitution were calculated.

A fuller explanation of some of the techniques used for data collection and analysis will be presented in Chapter 6, the Holter Measurements section.

3.8 Statistical analysis

Around 120 new ICDs were implanted at Glenfield Hospital each year at the time of the study (in line with the 50 per million population implant rate that was laid down by the NICE guidelines)[155]. Considering an arrhythmia occurrence rate of 30% per annum, it was estimated that there would be around 30 events over the 2 year study period and that

around 80 patients would be required for the study. This is assuming a power of 80%. This was considered to be adequate for the purposes of this study.

The data was analysed using SPSS 18 software. Continuous variables were compared using the Student's t-test once normality was confirmed. They are reported as mean (SD). The Mann Whitney U test was used to compare non-parametric data. Categorical data was analysed by the chi-squared test and are presented as absolute numbers and percentages. NTproBNP data are expressed as median with interquartile range. Binary logistic regression was used for univariate analyses in terms of the outcome data. A P value<0.05 was considered statistically significant. Data that was statistically significant was planned to be further analysed in a multivariate model. Receiver Operating Characteristic curves were constructed to demonstrate the predictive accuracy of each test. The null hypothesis was retained if the Area Under the Curve (AUC) was not statistically significantly different from 0.5.

4. NT pro BNP

4.1 Synthesis

Brain Natriuretic Peptide is released from the ventricular myocardium in response to increased volume and wall stress. It is one of three cardiac peptides involved in protecting the vascular system from volume overload. NTproBNP is synthesized as a by-product when the active BNP molecule is made. This is more stable in plasma and hence more readily measured[210–212].

4.2 BNP and heart failure

Studies have demonstrated that both BNP and NTproBNP are both elevated in heart failure states[210]. BNP is sympathoinhibitory and leads to a reduction in circulating renin, angiotensin II and aldosterone. This causes vasodilatation with a reduction in blood pressure and increased sodium and water excretion[216]. Levels are higher in women and increase with age. In addition, levels can also be increased with derangement of renal function[210]. Genetic influences have also been shown to alter circulating BNP levels in individuals. Furthermore, the reference ranges for assays can vary depending on the population studied and the assay used[216,280,281]. These factors have had a bearing in the utility of BNP as a marker in the heart failure population.

4.3 Studies

There have been a number of studies looking at BNP and NTproBNP in terms of risk stratification for heart failure and SCD as well as the potential diagnostic ability in larger populations.

There have been several large prospective trials that have established the role of BNP in acute decompensated heart failure diagnosis[281]. The Breathing Not Properly study looked at 1586 patients with breathlessness who presented to the emergency department. The investigators found that a BNP level of 100pg/ml and above gave a sensitivity of 90%, specificity of 76% and diagnostic accuracy of 83% in the diagnosis of acute heart failure. The PRIDE (ProBNP investigation of Dyspnoea in the Emergency Department) study showed similar findings using NTproBNP. The authors found that NTproBNP levels <300pg/ml had a negative predictive value of 99% in the exclusion of acute heart failure[282,283]. Similar reports have been made when investigated in primary care.

There have been a large number of studies looking at the ability of BNP and NTproBNP to predict cardiovascular outcomes and death. In a systematic review of the literature, Doust and colleagues concluded that BNP was a consistent significant predictor in the heart failure population[218]. The American National Academy of Clinical Biochemistry recommends the use of BNP and NTproBNP as a useful adjunct in risk stratification to routine established clinical assessment (class IIa). Trends in BNP levels have also been shown to be useful to assess changing risk profiles[218,281].

BNP has also been investigated to assess its usefulness in SCD prediction in heart failure and ICD populations. A more in depth analysis of the literature is presented elsewhere in this thesis, but there are several trials pointing towards a predictive capability, with others not demonstrating this. A previous meta-analysis did not recommend BNP or NTproBNP

as a routine clinical marker in the assessment of patient suitability for ICD implantation[211]. However, work is still ongoing to assess this further.

4.4 Aims & Methods

The aims of this study were to investigate a range of non-invasive markers to see if there are any predictors of ventricular arrhythmia (VA) in patients who are due to undergo ICD implantation. Patients who were admitted to Glenfield Hospital, Leicester and who had been assessed to need an Implantable Cardioverter Defibrillator (ICD) were invited to participate in the study. If they consented to take part and met the inclusion and exclusion criteria they were recruited.

For the peptide analysis, a 20ml venous blood sample was obtained after a 15 minute period of rest. The sample was divided into 2 EDTA lined bottles and placed immediately on ice for transport. The samples were then centrifuged. The plasma was extracted and divided into 8 aliquots. These were stored at -80ºC until they were analysed. All the patients recruited in the study had their NTproBNP samples examined in 1 batch. The final result was obtained after an ELISA assay, as previously described by Ng and colleagues[279]. I performed all of this work. If a recent echocardiogram documenting left ventricular function was not available, this was performed. I then analysed the data to calculate the left ventricular ejection fraction of each patient.

ICD follow up took place at device clinics as per usual clinic practice at 1 month post implant and then every 3-6 monthly. All arrhythmia occurrence and appropriate device

therapy for sustained tachyarrhythmias including antitachycardia pacing and defibrillation was recorded. Patients were followed up for 2 years post implant or until their first appropriate ICD shock (which was assumed to be a surrogate for sustained ventricular arrhythmia), whichever was sooner.

4.5 Statistical analysis

Continuous variables were compared using the Student's t-test once normality was confirmed. The Mann Whitney U test was used for non parametric data. Categorical data was analysed by the chi-squared test. Binary logistic regression was used for univariate and multivariate analyses in terms of the outcome data. A P value<0.05 was considered statistically significant. NTproBNP levels were compared in patients who had experienced shocks and those that had not. A comparison was also made between those patients with all appropriate therapy, and those who had experienced no therapy.

4.6 Results

4.6.1 Demographics

In total 92 patients were initially recruited into this study. Patients were inpatients at Glenfield Hospital, Leicester, UK between October 2006 and June 2008. This was the only site recruitment took place. Of these, three patients had to be withdrawn after initial recruitment as the supervising clinician decided not to implant an ICD, and a further 2 patients were lost to follow up as they had moved region, and their data could not be obtained. NTproBNP analysis was thus conducted in 87 patients. The limitations regarding patient recruitment have been described earlier in Chapter 3.

The baseline characteristics of these patients are outlined in Table 4.1. There was a higher proportion of males recruited into the study with a higher ischaemic to non ischaemic ratio. Mean EF was 27.7±11.8%. There was a high percentage use of beta blockade (89.7%) and ACE / angiotensin II blockers (90.8%), as would be expected in an optimally treated heart failure population. All medications were continued throughout and clinical management was not influenced by study participation. The majority of patients fell into the secondary prevention category.

Table 4.1 Clinical characteristics of study patients (n=87)

Age	65.0±11.4
Gender (M/F)	67/20 (76.7/23.3)
NYHA class	
I	40 (46.0)
II	32 (36.8)
III	15 (17.2)
Aetiology	
Ischaemic	64 (73.6)
Non ischaemic	23 (26.4)
Ejection Fraction (%)	27.7±11.8
Primary / Secondary prevention	39/48 (44.8/55.2)
QRS durations (msec)	98.3±33.2
Hypertension	32 (36.8)
Diabetes Mellitus	21 (24.1)
Smoking	65 (74.7)
Drugs pre implant	
Beta blockade	78 (89.7)
Amiodarone	16 (18.4)
ACE / Angiotensin II blockers	79 (90.8)
Digoxin	4 (4.6)
Serum creatinine	121.7±80.9
SR	73 (83.9)
AF	11 (12.6)

*expressed as mean±SD, figures in () represent % of sample size

ICD interrogation within the 2 year follow up time revealed that 16 (18.6%) patients experienced appropriate ICD shocks for ventricular arrhythmia. There were 7 (8.1%) deaths within the 2 year follow up, of which 2 patients had previously experienced shocks. The remainder of the patients did not experience appropriate shock therapy. No inappropriate shocks were recorded.

4.6.2 Appropriate Shocks v no shocks

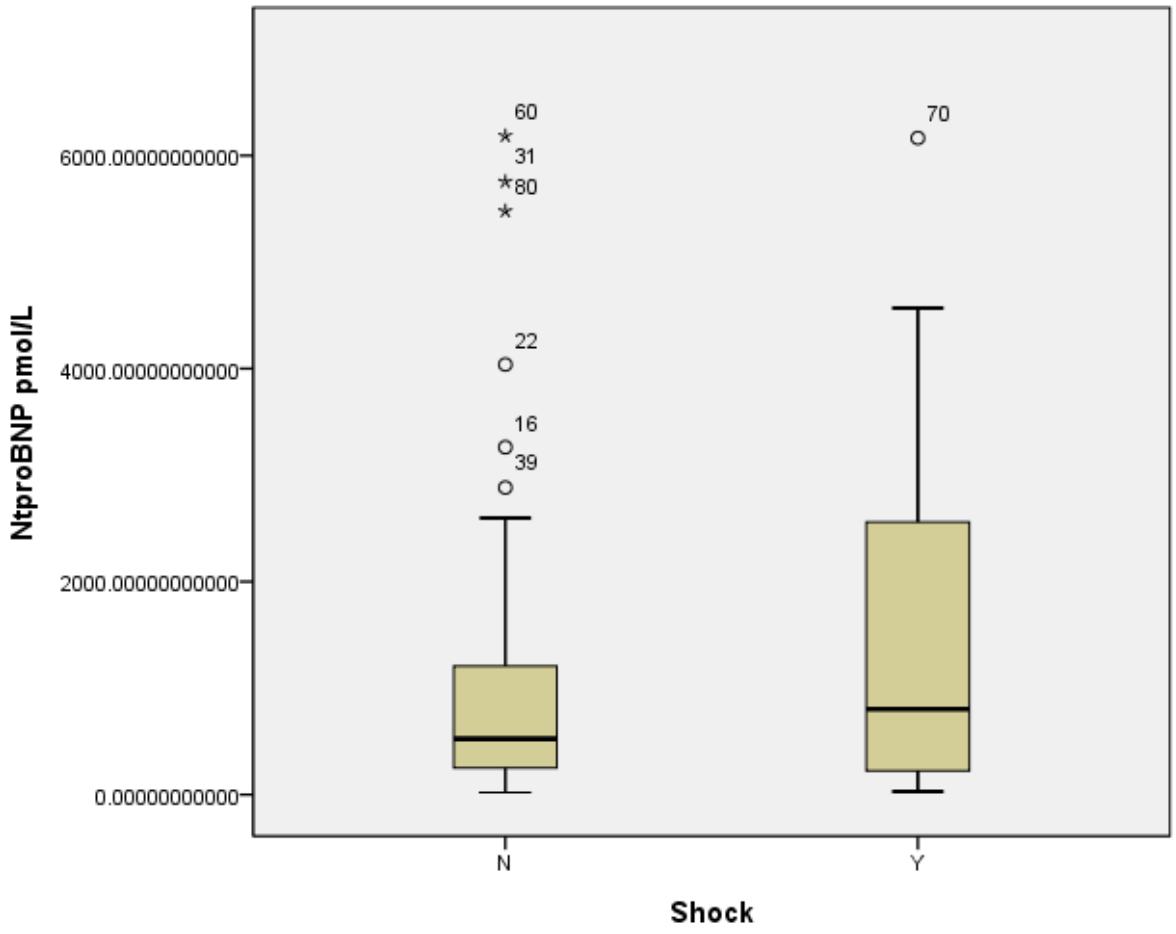
The main clinical characteristics of the patients who experienced appropriate shocks compared to those who remained shock free are outlined in Table 4.2. Age, gender, LVEF, NYHA class and medications did not differ between the two groups. Baseline NTproBNP levels showed a skewed distribution. Although the median values of NTproBNP appeared higher in the patients with appropriate shocks (figure 4.1), this did not reach statistical significance. Similarly, there was no significant difference between the groups when performing univariate analysis using binary logistic regression methods. Amiodarone use was significantly lower in the shock group (p=0.04).

Table 4.2 Baseline Characteristics in patients with appropriate shocks and those shock free

	Free of shock (n=71)	Appropriate shocks (n=16)	p value
Clinical Variables			
Age (years)	64.1±11.6	69.3±9.8	0.10
Gender (male / female)	55/16 (77.5/22.5)	12/4 (75/25)	0.83
Aetiology (Ischaemic / Non ischaemic)	50/21 (70.4/29.6)	14/2 (87.5/12.5)	0.16
Primary/Secondary	34/37 (47.9/52.1)	5/11 (45.4/54.6)	0.23
NYHA I	34 (47.9)	6 (37.5)	0.61
II	26 (36.6)	6 (37.5)	
III	11 (15.5)	4 (25)	
EF (%)	27.8±12.0	27.4±11.4	0.74
Serum creatinine	124.6±88.7	109.2±25.1	0.26
Hypertension	26 (36.6)	6 (37.5)	0.95
Diabetes Mellitus	18 (25.4)	3 (18.8)	0.58
Smoking	53 (74.6)	12 (75)	0.98
QRS durations	98.9±30.4	95.4±11.2	0.70
Drugs pre implant			
Beta blockade	64 (90.1)	14 (87.5)	0.75
Amiodarone	16 (22.5)	0 (0)	0.04
ACE / Angiotensin II blockers	65 (91.5)	14 (87.5)	0.63
SR	60 (84.5)	13 (81.3)	0.75
AF	10 (14.1)	1 (6.3)	0.39
NTproBNP (pmol/L)	524.8	803.4	0.38
Interquartile range	965.13	2335.01	

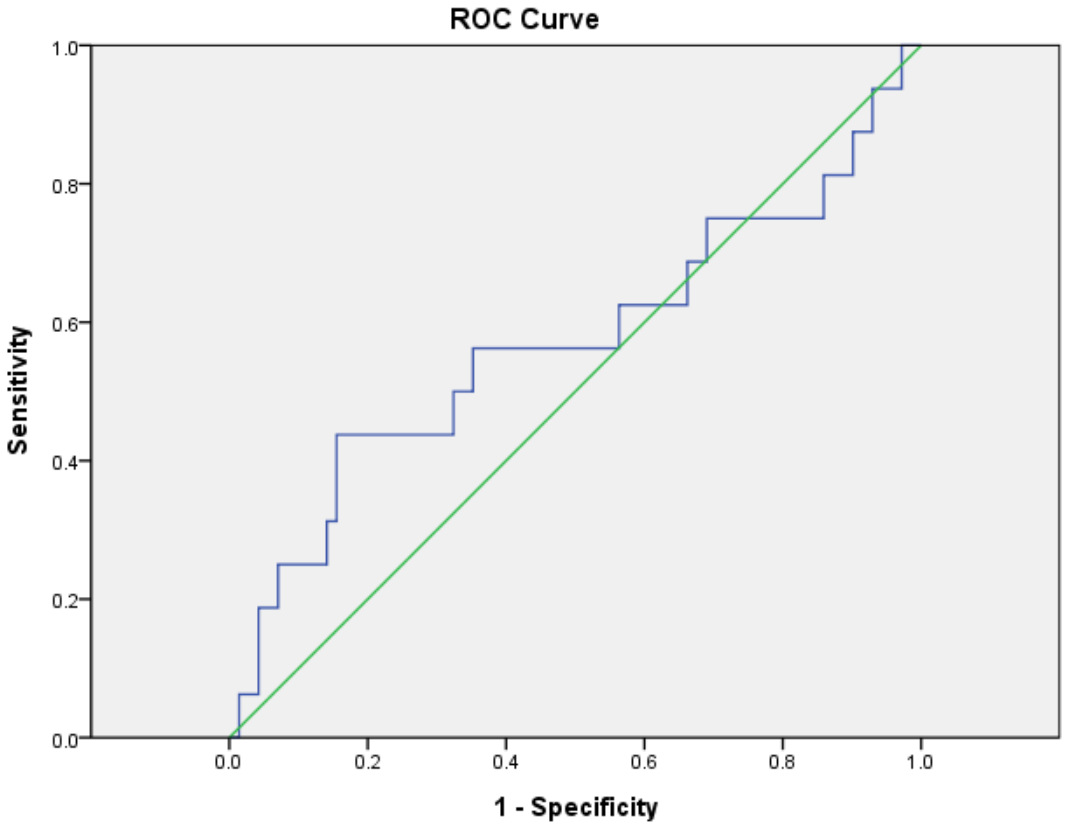
Data presented in mean ± SD or number of patients, except NTproBNP (expressed as median); figures in () represent % of sample size

Figure 4.1: Box and Whisker plot comparing NTproBNP levels in both groups



The median NTproBNP levels from the 2 groups (no shock versus shock) are shown. Median NTproBNP levels are non-significantly higher in the group with shocks. The numbered points represent 'outlier' patients within each group. The ROC curve for this population is shown in Figure 4.2. The area under the curve was 0.57 suggesting low predictive ability for NTproBNP and shocks in this population.

Figure 4.2: ROC curve (NTproBNP; shocks vs. no shocks)



4.6.3 Appropriate therapy v no therapy

NTproBNP levels were then compared in patients who received any form of appropriate therapy (ATP or shock) and those that were completely therapy free. From the 87 patients analysed, 34 experienced therapy and 53 did not. The table (4.3) below illustrates the baseline demographics between the 2 groups and the median NTproBNP in those who experienced therapy and those that did not. There were no significant differences between the 2 groups in any of the parameters. In addition, NTproBNP had a low positive predictive value for appropriate therapy with an AUC of 0.50 on ROC curve analysis.

Table 4.3 Baseline Characteristics in patients with appropriate therapy & those arrhythmia free

	Free of therapy (n=53)	Appropriate therapy (n=34)	p value
Clinical Variables			
Age (years)	63.6±11.6	67.2±10.9	0.86
Gender (male / female)	40/13 (75.5/24.5)	27/7 (79.4/20.6)	0.67
Aetiology (Ischaemic / Non ischaemic)	38/15 (71.7/28.3)	26/8 (76.5/23.5)	0.62
Primary/Secondary	23/30 (43.4/56.6)	16/18 (47.1/52.9)	0.74
NYHA I	25 (47.2)	15 (44.1)	0.80
II	20 (37.7)	12 (35.3)	
III	8 (15.1)	7 (20.6)	
EF (%)	29.1±12.6	25.7±10.6	0.92
Serum creatinine	125.5±101.1	116.1±30.0	0.14
Hypertension	20 (37.7)	12 (35.3)	0.82
Diabetes Mellitus	13 (24.5)	8 (12)	0.92
Smoking	39 (73.6)	26 (76.5)	0.76
QRS durations	98.5±27.8	98.0±40.7	
Drugs pre implant			
Beta blockade	46 (86.8)	32 (60.4)	0.27
Amiodarone	12 (22.6)	4 (7.5)	0.20
ACE / Angiotensin II blockers	47 (88.7)	32 (94.1)	0.32
SR	44 (83.0)	29 (85.3)	0.78
AF	8 (15.1)	3 (8.8)	0.39
NTproBNP (pmol/L)	524.88	522.16	0.92
Interquartile Range	1007.98	1221.12	

Data presented in mean ± SD or number of patients, except NTproBNP (expressed as median); figures in () represent % of sample size

4.6.4 Appropriate shocks v no therapy

This section compares patients who experienced appropriate shocks (n=16) and those that that did not experience any form of therapy (n=53). The AUC was 0.57 in this analysis, demonstrating low predictive accuracy in this setting.

Table 4.4 Baseline Characteristics in patients with appropriate shocks and those therapy free

	Free of therapy (n=53)	Appropriate shocks (n=16)	p value
Clinical Variables			
Age (years)	63.6±11.6	69.3±9.8	0.20
Gender (male / female)	40/13 (75.5/24.5)	12/4	0.97
Aetiology (Ischaemic / Non ischaemic)	38 (71.7)	14 (87.5)	0.20
NYHA I	25 (43.4/56.6)	6 (37.5)	0.62
II	20 (37.7)	6 (37.5)	
III	8 (15.1)	4 (25)	
EF (%)	29.1±12.6	27.4±11.4	0.98
Serum creatinine	125.5±101.1	109.2±25.1	0.22
Hypertension	20 (37.7)	6 (37.5)	0.99
Diabetes Mellitus	13 (24.5)	3 (18.8)	0.63
Smoking	39 (73.6)	12 (66.7)	0.91
Primary / Secondary	23/30 (43.4/56.6)	5/11 (31.3/68.7)	0.39
QRS durations	98.5±27.8	95.4±44.7	0.74
Drugs pre implant			
Beta blockade	46 (86.8)	14 (87.5)	0.85
Amiodarone	12 (22.6)	0 (0)	0.09
ACE / Angiotensin II blockers	47 (88.7)	14 (87.5)	0.69
SR	44 (83.0)	13 (81.3)	0.87
AF	8 (15.1)	1 (6.3)	0.36
NTproBNP (pmol/L)	524.88	803.4	0.73
Interquartile Range	1007.98	2335.34	

Data presented in mean ± SD or number of patients, except NTproBNP (expressed as median); figures in () represent % of sample size

There were no significant demographic differences between the groups, nor was there a difference in median NTproBNP levels.

4.6.5 Ischaemic Heart Disease

Patients with an underlying ischaemic aetiology were separated from those who had a non-ischaemic cardiomyopathy and the median NTproBNP levels were compared. There were 64 patients in this portion of the analysis, of which 26 patients experienced appropriate therapy. The median NTproBNP in the therapy category was 498.16pmol/L and in the no therapy category was 674.91pmmol/L. This was not a significant difference (p=0.20). Baseline characteristics were also not significantly different. Table 4.5 illustrates this data.

Table 4.5 Baseline Characteristics in IHD patients with appropriate therapy & those therapy free

	Free of therapy (n=38)	Appropriate therapy (n=26)	p value
Clinical Variables			
Age (years)	67.03±8.04	68.92±10.17	0.41
Gender (male / female)	35/3 (92.1/7.9)	23/3 (88.5/11.5)	0.62
NYHA I	17 (44.7)	12 (46.2)	0.90
II	15 (39.5)	9 (34.6)	
III	6 (15.8)	5 (19.2)	
EF (%)	25.77±8.91	24.96±10.91	0.76
Serum creatinine	140.74±116.17	113.54±24.44	0.25
Hypertension	15 (39.5)	10 (38.5)	0.94
Diabetes Mellitus	12 (31.6)	6 (23.1)	0.46
Smoking	32 (84.2)	21 (80.8)	0.72
Primary / Secondary	19/19 (50/50)	12/14 (46.2/53.8)	0.76
QRS durations	100.29±29.42	102.76±30.47	0.75
Drugs pre implant			
Beta blockade	34 (89.5)	24 (92.3)	0.70
Amiodarone	9 (23.7)	3 (11.5)	0.22
ACE / Angiotensin II blockers	37 (97.4)	24 (92.3)	0.38
SR	30 (78.9)	24 (92.3)	0.15
AF	8 (21.1)	2 (7.7)	0.15
NTproBNP (pmol/L)	674.91	498.46	0.20
Interquartile Range	716.56	1121.92	

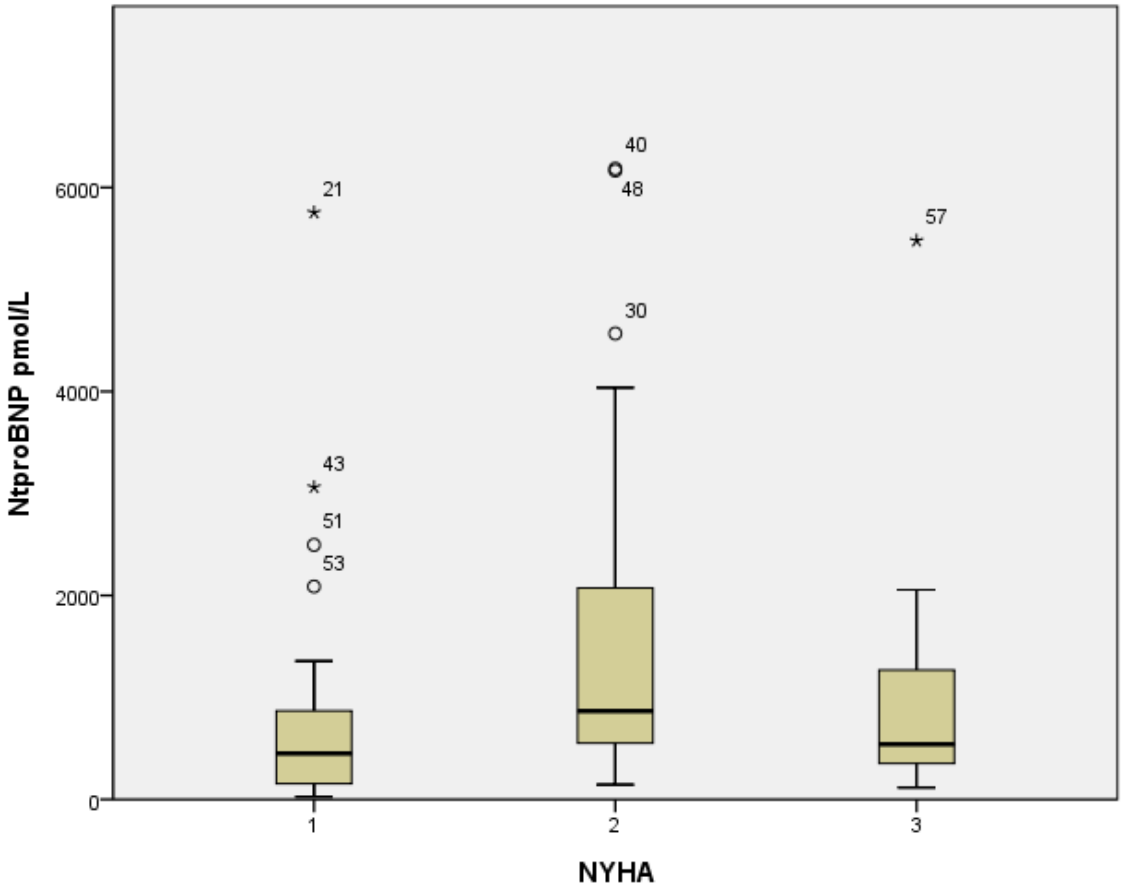
Data presented in mean ± SD or number of patients, except NTproBNP (expressed as median); figures in () represent % of sample size

4.6.6 NYHA class and NTproBNP

Given the fact that NTproBNP levels have been shown to be higher with worsening heart failure symptoms and higher NYHA class[284], levels of NTproBNP were analysed according to NYHA class for the whole population. In addition univariate analysis was undertaken to see if there was any association between NYHA class and event (appropriate therapy).

Figure 4.3 illustrates the comparison of NYHA class and NTproBNP level. As can be seen, there does appear to be an increase in NTproBNP levels between NYHA class I and II, but the levels appear lower in class III. Furthermore, there was no association between NYHA class and appropriate therapy.

Figure 4.3 NTproBNP levels and NYHA class in the study population



4.7 Discussion

This was a study of patients in an NHS hospital with underlying cardiomyopathy and a clinical indication for ICD implantation. The only statistically significant difference between the groups was that those treated with amiodarone did not experience appropriate ICD therapy. This might be explained by the small number of patients involved. When looking at appropriate shocks compared to no shock, the median NTproBNP level was higher in the appropriate shock group, but this did not achieve a statistically significant level. In addition the interquartile range was wide**.** There was no predictive accuracy of NTproBNP in the analyses also. There were no significant differences in LVEF between the groups suggesting that the raised NTproBNP in those at risk of shocks, and by inference, sustained ventricular arrhythmia, may be raised independent to LVEF. However, when all therapy was compared to no therapy, no such difference was seen. This may point to the fact that pre-implant NTproBNP levels are higher in those who are at risk of more 'dangerous' arrhythmia requiring termination by cardioversion, although this cannot be proven conclusively given the lack of significance, and the fact that susceptibility to shock is also governed in part by device programming. In this study the NTproBNP levels did not vary across NYHA class also. In addition, there did not seem to be an evident trend across worsening class of heart failure. The high percentage of heart failure medication may have influenced these results.

Previous studies have investigated the utility of BNP to predict SCD in heart failure in both patients with and without ICDs. Individual studies and subsequent systematic reviews have demonstrated that raised BNP levels are predictive of higher mortality in

heart failure populations. Furthermore, treatment of heart failure reduces BNP levels[216,218,219,221,223,224,226]. In heart failure patients with ICDs, there are mixed results when investigating the role of BNP and prediction of arrhythmic events. The largest study by Verma and colleagues demonstrated that a single pre-implant BNP above the 50th centile (573ng/L) was predictive of future appropriate therapy with a hazard ratio of 2.19 (95% CI 1.07-4.71,p=0.04)[231]. This study looked at all patients with cardiomyopathy. A smaller more recent study of ischaemic patients also showed similar results[285]. A meta-analysis of studies in ICD populations concluded that BNP was a predictor of arrhythmia, but issues regarding cut-off points due to study heterogeneity were raised[211]. The results of the current study would not support routine use of BNP as a risk stratification tool to exclude patients with LVSD for ICD treatment. However, based on these results, there may be utility in terms of using more intensive anti-arrhythmic therapy in those with higher NTproBNP levels to try and reduce shock frequency. Overall, there is conflicting data about BNP use in this arena. Based on this study, coupled with observations from previous studies, it appears that BNP may have some role in stratification of risk, but will not be the tool with which to determine whether implantation should take place, or can safely not.

The study is limited in part by the numbers recruited as explained earlier. In a larger population, it is possible that significance may have been reached. In addition, a longer follow up phase may yield more arrhythmic events which would influence the final results. However, the frequency of events seen is comparable with other studies. Patients awaiting biventricular implants were also excluded, as has been done in previous similar

studies. The rationale for this is the inability to assess the potential impact of biventricular pacing on future appropriate ICD therapy.

5 QT Dispersion

5.1 Definition

QT dispersion (QTd) refers to the difference between the longest and shortest QT intervals on the resting ECG[242]. It is associated with the inhomogeneity of myocardial repolarisation[243]. Interest into QTd as a marker for ventricular arrhythmia and SCD has been established following basic science work that correlates this with dispersion of repolarisation[245]. Kuo and colleagues have shown that a large dispersion of repolarisation is required to sustain arrhythmia[54]. Further work has demonstrated regional differences in QT duration between areas of ischaemia, normal heart and infarction[242]. In the arena of SCD prediction, there have been mixed results. Perkiomaki and colleagues have demonstrated that there is a larger QTd in patients who have a history of arrhythmia post myocardial infarction compared to those who do not[258]. However, Pedretti and Galiner did not find a similar association in their respective studies[250,256]. In non ischaemic patients, the results are similarly mixed[250,253–255]. A fuller discussion on this topic can be found earlier in this thesis.

5.2 Aims and Methods

The aims of this current study are to identify whether more accurate prognostic information can be obtained in an ICD population with cardiomyopathy, specifically whether QTd can be used to predict shocks, which are being used as surrogate markers of ventricular arrhythmia and sudden cardiac death.

Patients who were admitted to Glenfield Hospital, Leicester and who had been assessed to need an Implantable Cardioverter Defibrillator (ICD) were invited to participate in the study. Inclusion and exclusion criteria have been stated earlier in this thesis.

Patients who agreed to be included in the study and met the entry requirements (see below), had a baseline ECG prior to ICD implantation, to allow analyses of PR, QRS and QT intervals, as well as QT dispersion. If a recent echocardiogram documenting left ventricular function was not available, this was performed.

ICD follow up took place at device clinics as per usual clinic practice. All arrhythmia occurrence and appropriate device therapy for sustained tachyarrhythmias including antitachycardia pacing and cardioversion or defibrillation was recorded. Patients were followed up for 2 years post implant or until their first appropriate ICD shock, whichever was sooner.

For this portion of the study, patients were included if they were in stable sinus rhythm. Patients who were in atrial fibrillation and who were in a paced rhythm were excluded. All measurements were made on conventional 12 lead electrocardiograms which were recorded with a paper speed of 50mm/sec. The QT intervals were measured manually by the author. The QT interval is defined between the beginning of the QRS complex and the end of the T wave. . The end of the T wave was determined visually, as the point of return to the isoelectric line. QT intervals were measured in all 12 leads. Three consecutive cycles were measured and the mean value of the QT interval was obtained.

The QTd was then calculated from the following equation: QT(max)-QT(min). The standard deviation of the QT interval across all 12 leads was also calculated. The patients were then divided into those who met the arrhythmia endpoint and those who had remained event free.

5.3 Statistical analysis

Continuous variables were compared using the Student's t-test once normality was confirmed. The Mann Whitney U test was used for non-parametric data. Categorical data was analysed by the chi-squared test. Binary logistic regression was used for univariate and multivariate analyses in terms of the outcome data. A P value<0.05 was considered statistically significant.

5.4 Results

5.4.1 Demographics

Of the 92 patients recruited into this study 68 patients were included into the QTd analysis. Five patients were withdrawn from the entire study. The supervising clinician decided not to implant an ICD in 3 patients, and 2 patients were lost to follow up as they had moved region. Other reasons for exclusion included AF (n=11) and paced rhythm (n=3). Five patients' ECGs were not suitable for measurement.

The baseline characteristics of the patients are outlined in Table 5.1. Of the 68 patients analysed here, 12 (17.6%) patients received appropriate ICD shocks for sustained VA. Four patients died (non-arrhythmic), of which 1 had received shocks following implant.

Fifteen different patients received appropriate ATP therapy. The remaining patients were therapy and sustained VA free at the 2 year follow up mark. There was a male predominance and more patients had ischaemic heart disease as the underlying aetiology. Use of heart failure medication was of a high percentage as can be predicted in this kind of population. There were no significant differences in QT dispersion across the 3 NYHA classes.

Table 5.1 Clinical characteristics of study patients (n=68)

Age*	62.94±11.65
Gender (M/F)	51/17 (75/25)
NYHA class	
I	33 (48.5)
II	26 (38.2)
III	9 (13.2)
Aetiology	
Ischaemic	49 (72.1)
Non ischaemic	19 (27.9)
Ejection Fraction (%)*	27.34±12.76
Primary / Secondary prevention	31/37 (45.6/54.4)
QRS durations (msec)	102.5±23.5
Hypertension	26 (38.2)
Diabetes Mellitus	16 (23.5)
Smoking	51 (75)
Drugs pre implant	
Beta blockade	61 (89.7)
Amiodarone	13 (19.1)
ACE / Angiotensin II blockers	61 (89.7)
Serum creatinine*	119.49±88.59

*expressed as mean±SD; figures in brackets represent % of sample size

5.4.2 Appropriate Shock vs no shock

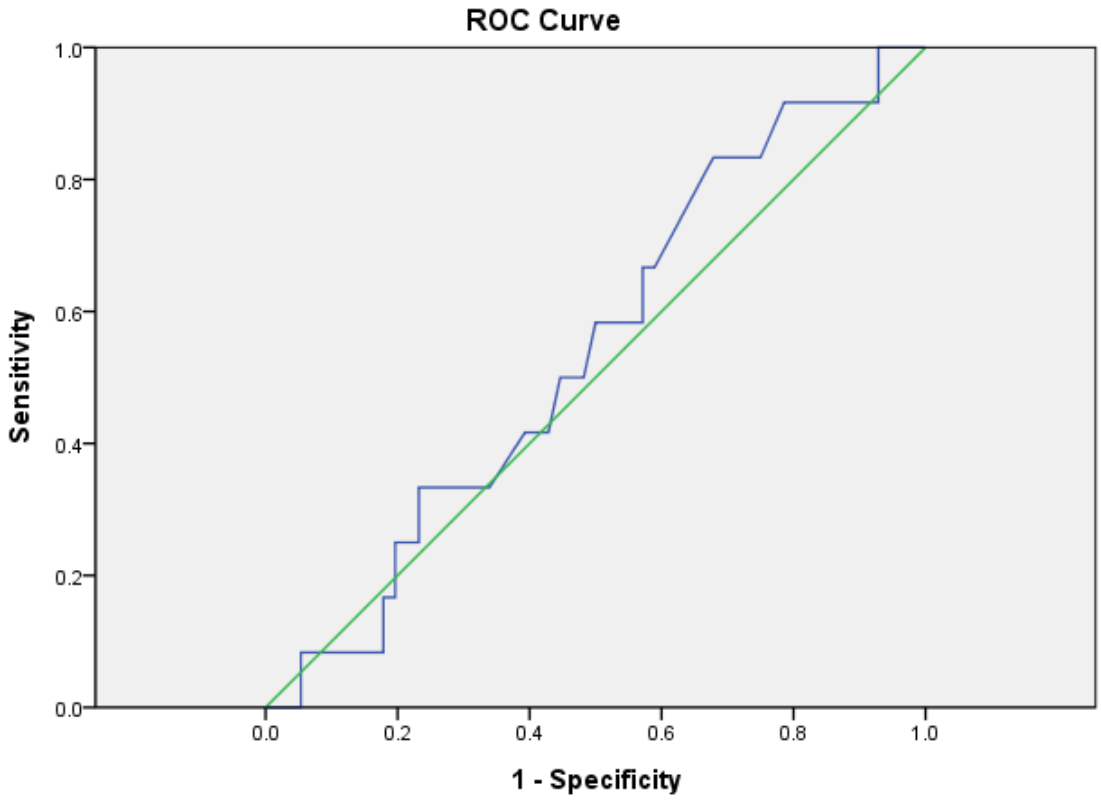
Table 5.2 shows the baseline characteristics and QT dispersion values in patients with and without appropriate shocks (n=12). Patients who were older tended to experience more shocks, although this did not reach significance. Patients with ischaemic heart disease were significantly more likely to experience shocks, but this may be a reflection of absolute numbers and the study population rather than a true finding. The other baseline parameters were not significantly different between the groups. QT dispersion values were also not significantly different between patients with and without shocks. On ROC curve analysis (figure 5.1), the AUC was 0.54 suggesting the null hypothesis should be retained (QTd does not have predictive accuracy in the prediction of shocks in this population).

Table 5.2 Characteristics in patients with appropriate shocks and those shock free

	Free of shock (n=56)	Shocks (n=12)	p value
Clinical Variables			
Age (years)	61.75±11.56	68.5±10.81	0.07
Gender (male / female)	41/15 (73.2/26.8)	10/2 (83.3/16.7)	0.46
Aetiology (Ischaemic / Non ischaemic)	37/19 (66.1/33.9)	12/0 (100/0)	0.02
NYHA I	27 (48.2)	6 (50)	0.85
II	21 (37.5)	5 (41.7)	
III	8 (14.3)	1 (8.3)	
EF (%)	27.47±13.14	26.83±11.72	0.88
Serum creatinine	121.13±97.03	111.83±25.51	0.74
Hypertension	22 (39.3)	4 (33.3)	0.70
Diabetes Mellitus	14 (25)	2 (16.7)	0.54
Smoking	41 (73.2)	10 (83.3)	0.46
Primary / Secondary	27/29 (48.2/51.8)	4/8 (33.3/66.7)	0.35
QRS durations (msec)	100.84±22.55	110.49±27.33	0.20
Drugs pre implant			
Beta blockade	50 (89.3)	11 (91.7)	0.81
Amiodarone	13 (23.2)	0 (0)	0.06
ACE / Angiotensin II blockers	51 (91.1)	10 (83.3)	0.65
QT Dispersion	0.09±0.03	0.093±0.029	0.86

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

Figure 5.1 ROC curve analysis (QTd and shocks)



5.4.3 Appropriate Therapy vs no therapy

QT dispersion was then compared in patients who received any form of appropriate therapy (ATP or shock) and those that were completely therapy free. From the 68 patients analysed, 27 experienced therapy and 41 did not. The table below illustrates the baseline demographics between the 2 groups and the mean QT dispersion in those who experienced therapy and those that did not. There were no significant differences between the 2 groups in any of the parameters except for QRS duration, where the mean value was greater in the therapy group. QT dispersion was not significantly different between the 2 groups. The ROC curve analysis revealed that the AUC was 0.54 in keeping with a low predictive accuracy of QTd for appropriate therapy.

Table 5.3 Characteristics in patients with appropriate shocks / ATP and those event free

	Free of shock/ATP (n=41)	Appropriate shock/ATP (n=27)	p value
Clinical Variables			
Age (years)	61.41±11.93	65.26±11.01	0.19
Gender (male / female)	29/12 (70.7/29.3)	22/5 (81.5/18.5)	0.32
Aetiology (Ischaemic / Non ischaemic)	27/14 (65.9/34.1)	22/5 (81.5/18.5)	0.16
NYHA I	20 (48.8)	13 (48.1)	0.89
II	15 (36.6)	11 (40.7)	
III	6 (14.6)	3 (11.1)	
EF (%)	28.76±14.35	25.54±10.43	0.34
Serum creatinine	125.12±112.41	110.93±25.64	0.52
Hypertension	16 (39)	10 (37)	0.87
Diabetes Mellitus	10 (24.4)	6 (22.2)	0.84
Smoking	29 (70.7)	22 (81.5)	0.32
Primary / Secondary	23/18 (56.1/43.9)	14/13 (51.9/48.1)	0.73
QRS durations (msec)	97.81±20.10	109.73±26.78	0.04
Drugs pre implant			
Beta blockade	35 (85.4)	26 (96.3)	0.15
Amiodarone	9 (22.0)	4 (14.8)	0.46
ACE / Angiotensin II blockers	36 (87.8)	25 (92.6)	0.80
QT dispersion	0.091±0.038	0.092±0.03	0.92

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

5.4.4 Appropriate shock vs. no therapy

This part of the study examined QT dispersion measures in study patients who experienced appropriate shocks and compared them to study patients who were therapy and hence sustained ventricular arrhythmia free. There were 53 patients in this analysis. Table 5.4 illustrates baseline characteristics and the mean QT dispersion in these groups. Older patients tended to experience more shocks compared to those who were therapy free. This, however, was not statistically significant. Patients who experienced shocks all had ischaemic heart disease. In the statistical analysis this was significant, but given the relatively small population, and the low number of non-ischaemic patients, the result cannot be extrapolated to the wider population without a larger study. In this analysis, there was no significant difference in mean QT dispersion. The AUC in ROC curve analysis was 0.55 showing that there was no predictive accuracy in this analysis.

Table 5.4 Characteristics in patients with appropriate shocks and therapy free

	Free of shock/ATP (n=41)	Appropriate Shocks (n=12)	p value
Clinical Variables			
Age (years)	61.41±11.93	68.5±10.81	0.07
Gender (male / female)	29/12 (70.7/29.3)	10/2 (83.3/16.7)	0.38
NYHA I	20 (48.8)	6 (50)	0.84
II	15 (36.6)	5 (41.7)	
III	6 (14.6)	1 (8.3)	
EF (%)	28.76±14.35	26.8±11.7	0.68
Serum creatinine	125.12±112.41	111.83±25.5	0.69
Aetiology (Ischaemic / Non ischaemic)	27/14 (65.9/34.1)	12/0 (100/0)	0.02
Hypertension	16 (39)	4 (33.3)	0.72
Diabetes Mellitus	10 (24.4)	2 (16.7)	0.57
Smoking	29 (70.7)	10 (83.3)	0.38
Primary / Secondary	23/18 (56.1/43.9)	4/8 (33.3/66.7)	0.51
QRS durations (msec)	97.81±20.10	110.49±27.33	0.08
Drugs pre implant			
Beta blockade	35 (85.4)	11 (91.7)	0.72
Amiodarone	9 (22.0)	0 (0)	0.17
ACE / Angiotensin II blockers	36 (87.8)	10 (83.3)	0.80
QT dispersion	0.091±0.038	0.093±0.029	0.87

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

5.4.5 QT Dispersion in IHD

Given the possible myocardial inhomogeneity associated with ischaemic cardiomyopathy, QT dispersion was also calculated for the patients with an ischaemic aetiology, excluding the others. This left 49 patients in the analysis. Of these, 22 patients experienced appropriate therapy, including 12 patients with appropriate shocks. In this sub-group analysis, there were no statistically significant differences in the baseline characteristics between those with and without appropriate therapy. In addition, there was no significant difference in QT dispersion between IHD patients with and without therapy ($p=0.79$). This is illustrated in Table 5.5.

Table 5.5 Characteristics in ischaemic patients with appropriate shocks / ATP and those event free

	Free of shock/ATP (n=27)	Appropriate shock/ATP (n=22)	p value
Clinical Variables			
Age (years)	64.8±8.2	67.2±10.1	0.35
Gender (male / female)	24/3 (88.9/11.1)	19/3 (86.4/13.6)	0.79
NYHA I	12 (44.4)	10 (45.5)	0.89
II	10 (37.0)	9 (40.9)	
III	5 (18.5)	3 (13.6)	
EF (%)	24.9±9.1	25.2±11.1	0.90
Serum creatinine	143.7±135.0	110.9±23.7	0.27
Hypertension	11 (40.7)	9 (40.9)	0.99
Diabetes Mellitus	9 (33.3)	4 (18.2)	0.23
Smoking	23 (85.2)	18 (81.8)	0.75
Primary / Secondary	14/13 (51.9/48.1)	10/12 (45.5/54.5)	0.66
QRS durations (msec)	102.34±21.07	106.90±23.05	0.47
Drugs pre implant			
Beta blockade	24 (88.9)	21 (95.5)	0.40
Amiodarone	7 (25.9)	3 (13.6)	0.29
ACE / Angiotensin II blockers	26 (96.3)	20 (90.9)	0.65
QT dispersion	0.090±0.045	0.093±0.32	0.79

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

5.5 Conclusions

This analysis did not reveal any significant differences in QT dispersion between groups of ICD patients with cardiomyopathy recruited in this study. This was the case even in a sub group analysis looking at patients with ischaemic heart disease. The groups were well matched in terms of their baseline characteristics and represent patients that are seen by Cardiologists on a daily basis. Despite a relatively small sample size, the rates of arrhythmia and appropriate therapy appear consistent with published data[147].

QT dispersion measurements in this population are higher than those recorded in normal groups in earlier studies with an average QTd of 102msec compared to 30-60msec in control groups[242,244]. This reflects the spatial inhomogeneity in myocardial repolarisation in the study population due to the underlying structural abnormalities. Recruitment of a control group (cardiomyopathy patients not meeting ICD implant criteria) would have been ideal, however was challenging due to logistical reasons. Furthermore, the high risk nature of the study group meant that ECGs were often abnormal exacerbating measurement difficulties. The current study would not support the use of this measure in arrhythmia prediction in terms of risk stratification for identification of potential ICD patients or assessment of arrhythmia/shock risk in current ICD patients. Previous studies have also yielded mixed results with some studies suggesting an association with QTd and ventricular arrhythmia and others not. Galinier and colleagues investigated QTd in congestive cardiac failure, and found that the marker could identify those at higher risk of arrhythmia in dilated cardiomyopathy but not in ischaemic patients[250]. However, other authors have not found similar associations in their studies[253,255]. In ischaemic

cardiomyopathy similar mixed results are seen. Periomaki and colleagues showed that QTd was significantly increased in patients post MI with documented arrhythmia compared with similar patients with no propensity to arrhythmia[258]. However, Pedretti and colleagues showed no association in a retrospective study of patients with previous myocardial infarction[256]. The negative result in this study is therefore in keeping with previous observation. However, given the relatively small number of non-ischaemic patients, it is difficult to comment on the use of this marker solely in this population.

The study is limited by its relatively small sample size. The reasons for this have been presented earlier. In addition, manual measurement of QT interval is subject to some degree to individual interpretation, which may introduce an element of error and potential bias. Difficulties with the reproduction of QT measurement and intra-observer variability have also been cited by various authors as problems with this test[241]. These issues may limit the use of this tool as a predictor of arrhythmia. However, a small sample (n=10) of patients' ECGs were re-analysed by the same analyst in a blinded fashion. The patients were selected randomly and the same technique of measurement was used. The QTd values were compared with the original measurements and the coefficient of repeatability was calculated as described by Altman and colleagues. This is calculated by firstly squaring the measurement differences, adding them up, dividing this value by the number of observations and taking the square root to obtain the standard deviation of the differences. This value is then doubled to obtain the coefficient of repeatability. In this analysis the coefficient of repeatability of QTd was 34.51 milliseconds. This demonstrates the difficulties with manual measurement of QTd and shows and confirms

the fact that this measure can be affected by intra-observer and by inference inter-observer variability.

6 Holter measurements

6.1 Heart Rate Variability

Heightened sympathetic activity has been shown to be pro-arrhythmic, with increased vagal tone being protective in the abnormal heart[286]. These findings have been demonstrated in both animal and human models[80]. The mechanisms underpinning this have been discussed earlier. Adrenergic blockade with beta blockers have been shown to reduce arrhythmia and SCD burden in various clinical studies[103,104]. Given these observations, there has been a great deal of interest in measures of the ANS, how they change in pathological states as well as potential roles in arrhythmia risk prediction.

There are a number of direct assessments of cardiac autonomic tone, but direct physiologic testing of the ANS is not clinically viable given its anatomic location. The intervals between normal sinus beats vary periodically, due to factors such as respiration, blood pressure regulation, the renin angiotensin system, circadian rhythms as well as other unknown factors[170]. Short term regulation of heart rate is predominantly governed by the ANS[171]. Heart rate variability (HRV) represents an easily measurable marker of cardiac autonomic activity. HRV is a generic term representing changes in the interval between consecutive normal heart beats, as well as changes in instantaneous heat rates. It measures the balance between sympathetic and parasympathetic mediators of heart rate[173,174]. Measurement of HRV has been discussed in more detail in an earlier chapter.

Studies have shown that HRV is decreased in patients with heart failure. The Multicentre Post-Infarction Program (MPIP) showed that SDNN was an independent predictor of all cause mortality post MI[179,192]. The Autonomic Tone and Reflexes after Myocardial

Infarction (ATRAMI) study recruited 1284 patients with a recent MI. HRV was calculated from 24 hour Holter analysis. Patients with SDNN < 70ms were shown to be at increased risk of cardiac death compared to those with higher values (10% v 2%). This SDNN value was also a significant predictor of risk in a multivariate model with LVEF < 40% and ventricular ectopic rate > 10 / hour[193]. The UK Heart study looked at time domain measures of HRV in heart failure patients who had not had a recent MI. The investigators found that a depressed SDNN < 100ms was associated with all cause mortality in univariate analysis as well as progressive heart failure. It was not found to be associated with SCD in this analysis[198]. Further studies have confirmed the finding of depressed HRV in heart failure states[195,200–202]. The available data looking at HRV and SCD is unclear. A recent study showed that depressed SDNN<44msec and LF amplitude<13msec were associated with a higher incidence of ICD shocks in a small cohort of patients with ICDs and left ventricular dysfunction[235]. Other studies have also shown an association with depressed SDNN and SCD but other studies have not shown an association[207–209]. Currently there is no agreement as to the use of HRV in this setting.

6.2 QT Variability Index

The QT variability index (QTVI) represents the relationship between QT and RR variability and expresses temporal dispersion of cardiac repolarisation as opposed to spatial dispersion measured with QT dispersion[273,274]. The following formula is used to calculate the QTVI:

$$QTVI: QTVI=log_{10}((QTv)/(QTm)^2)/((RRv)/RRm)^2))^{275}$$

QTv–QT variance; QTm–QT mean; RRv -RR variance; RRm-RR mean

In normal hearts the QTVI is low, but in structural abnormalities, such as heart failure states, the QTVI is raised. The data can be calculated over varying time periods. This has been shown in studies, including a sub group analysis if the MADIT II population[273–277]. There are no trials looking at the ability of QTVI to predict ventricular arrhythmia in an ICD population.

6.3 ECG restitution

Electrical restitution refers to the changes in APD following changes in the preceding diastolic interval (DI)[261]. The relationship between these form the restitution curve[265]. The formation of the standard restitution curve has been described earlier. The restitution hypothesis and the increased risk of arrhythmia arise when the gradient of the curve is greater than 1[267]. Basic science work has shown an increased restitution slope and lower arrhythmia threshold when sympathetic conditions predominate such as in heart failure[263]. Fossa et al have illustrated a non-invasive method of ECG restitution analysis in humans[265]. Some of these methods are used in this study to examine whether there are any ECG restitution parameters which are predictive of ventricular arrhythmia.

6.4 Aims and methods

The aims of this present study are to investigate a range of non invasive markers to see if there are any predictors of ventricular arrhythmia (VA) in patients who are due to undergo ICD implantation. We are interested in:

1 Investigating markers of the autonomic nervous system and their association with VA

2 Investigating whether there is a difference in QTVI between heart failure patients who have ICD implants in terms of appropriate therapy vs. no therapy.

3 Investigating whether there are any ECG restitution parameters that may differ between ICD patients who experience appropriate therapy and who do not.

Patients who were admitted to Glenfield Hospital, Leicester and who had been assessed to need an Implantable Cardioverter Defibrillator (ICD) by their Cardiologist were invited to participate in the study if they met the entry requirements (see chapter 3). Out of this group, patients who were in a paced rhythm and those not in continuous sinus rhythm were excluded from this part of the study. A Delmar Reynolds 3 channel 24 hour tape was fitted prior to ICD implantation, which is the standard clinical Holter used at our centre. The Holter was removed 24 hours after placement. Most patients were awaiting ICD implantation as inpatients, and were thus mainly sedentary during the recording. Normal clinical care continued throughout the monitoring with no change to prescribed medication, which was under the control of the patient's cardiologist. The data was then analysed as described below to investigate the HRV, QTVI and ECG restitution

parameters. ICD follow up took place at device clinics as per usual clinic practice at 1 month post implant and then every 3-6 monthly. All arrhythmia occurrence and appropriate device therapy for sustained tachyarrhythmias including anti-tachycardia pacing and cardioversion or defibrillation was recorded. Patients were followed up for 2 years post implant or until their first appropriate ICD shock (which was assumed to be a surrogate for sustained ventricular arrhythmia), whichever was sooner.

6.4.1 Analysis of HRV/QTVI and ECG restitution

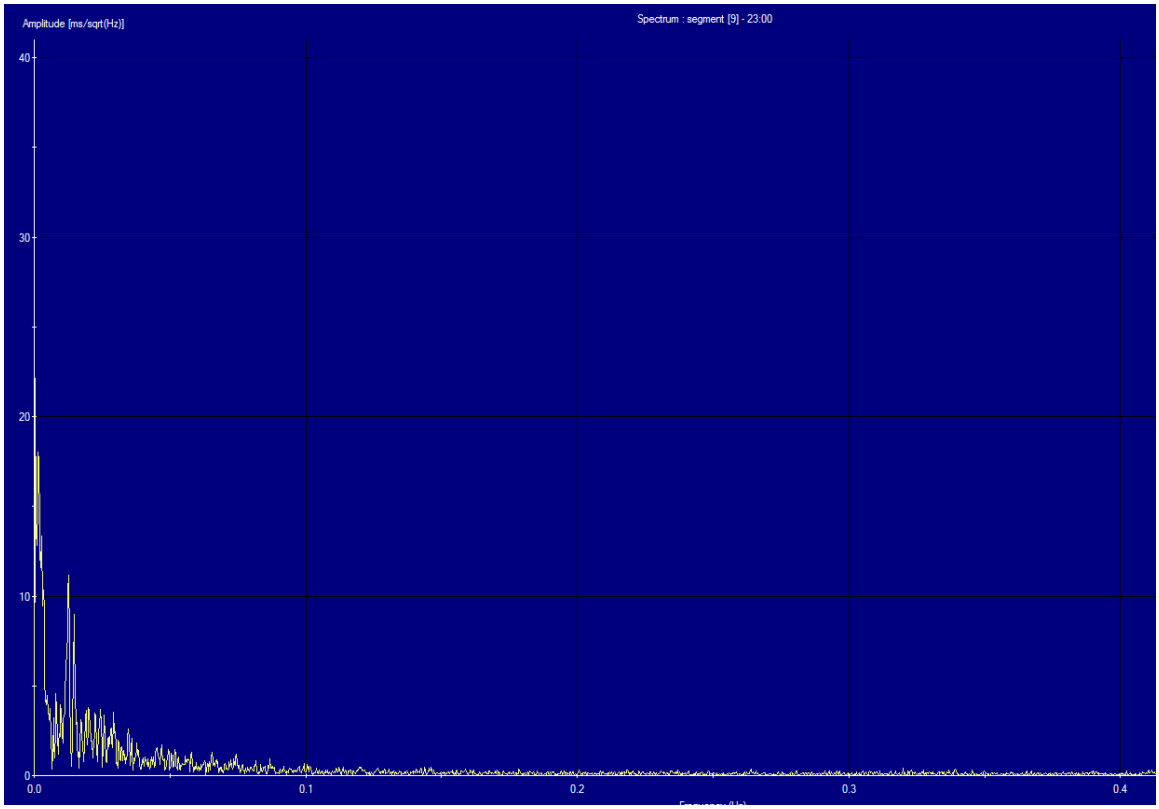
The tapes were analysed with Delmar Reynolds analysis software, which is used for normal clinical analysis at our centre. We used the analyser's built-in algorithms for recognition of appropriate types of beats. This was checked by manual overview. Patients who had less than 18 hours of data were not used in the full analysis, as were those in atrial fibrillation and those who had a high burden of ectopic activity which reduced the analysed proportion. Paced (atrial and ventricular) patients were also excluded. Once the data had been checked, it was saved as a '*.dat'* file. This could then be used by Delmar Reynolds HRV tools software to calculate the HRV data. The file was also used for the other parameters. The detailed methods for each individual parameter are outlined below.

6.4.1.1 HRV analysis

Time Domain and Frequency Domain measurements were calculated using Delmar Reynolds HRV Tools software. SDNN and RMSSD measures of time domain were used for analysis. These parameters were chosen as they had been evaluated in previous studies with SDNN reflecting total power and RMSSD reflecting predominantly vagal

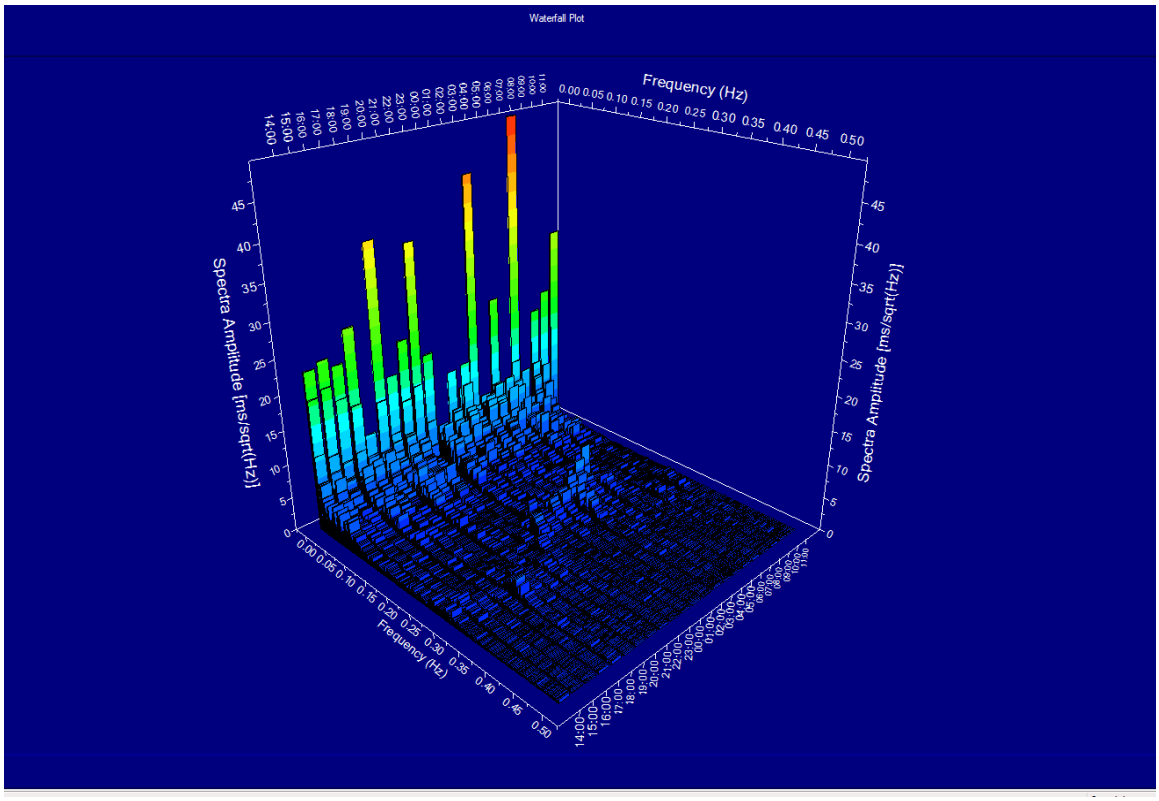
activity. The patients who had experienced appropriate ICD therapy were then compared with those who had remained arrhythmia free to look for differences in these HRV measures. For analyses in the frequency domain, the software utilised Fast Fourier Transform (FFT) to quantify the power spectra. Total power (ms^2) and the power in very low frequency (VLF below 0.04Hz), low frequency (LF, 0.04-0.15Hz) and the high frequency (HF 0.15-0.4Hz) bands were evaluated. Power in the LF and HF bands were also analysed in terms of normalised units. This represents the value of each power component in proportion to the total power, with the VLF component removed. The ratio of LF and HF power was also analysed. The data was analysed in hourly segments as per the software, and the mean values were used for analysis. Figure 6.1 shows a typical spectral analysis for a one hour segment on a study patient. Figure 6.2 shows a waterfall plot of the whole 24 hour spectral analysis for a study patient.

Figure 6.1 Typical one hour spectral analysis



This shows a typical spectral analysis for a patient (1 hour segment). The y axis refers to amplitude in ms^2, and the x axis the range of frequencies in Hz.

Figure 6.2 Waterfall plot of 24 hour spectral analysis



This shows the range of frequencies and power of each obtained from a Holter recording of a typical patient over a 24 hour period after FFT analysis.

6.4.1.2 QTVI analysis

The '.dat' file extracted from the raw data (after editing) was converted to an 'excel' file and this allowed beat to beat QT measurements to be tabulated. It was possible to ensure that each RR and QT reading was genuine by excluding outlier data in the RR column which occasionally gave higher measurements than physiologically possible due to the Delmar Reynolds' software method of inhibiting data (for example in areas of poor recording and ectopic data). This was done by comparing the measured interval between supposed consecutive QRS complexes and the true RR interval from the downloaded software. This then allowed the inclusion of true data and the exclusion of outlier data. This data was then used to calculate the components of the QTVI equation as explained earlier. The QTVI was calculated for the whole recording as well as for the hours between 1am and 5am for each individual patient.

6.4.1.3 ECG restitution analysis

After the data was downloaded from the analysis software as a '.dat' file it was converted to an Excel file. The sampling rate of the analyser was 128Hz or 61μs. Each 'q point', or each QRS complex / beat recorded was converted into milliseconds from the start of the tape. The difference between successive 'q points' were thus calculated. As the raw analyser download also gives RR intervals, it was possible to establish which beats were consecutive by comparing them with the difference between successive q points. The consecutive beats were retained and the QT intervals for these beats were then recorded in milliseconds from the raw recording. By subtracting the respective QT intervals from

the RR intervals, TQ intervals were generated. The TQ intervals preceding the subsequent QT intervals could then be analysed.

The restitution parameters using the beat to beat method that were described by Fossa et al[272] were analysed. The lowest 5% of TQ values were calculated with the assumption that as the TQ interval decreases arrhythmia is more likely to occur due to the re-entry phenomenon[265]. The percentage of beats in each recording with QT/TQ ratio >1 were also analysed. Fossa et al describes that if this ratio is >1, the heart is working more than it rests, thus increasing arrhythmia vulnerability[265,272]. To analyse the steepness of the ECG restitution relationship, the upper 98% quantile of the QT/TQ ratio was calculated. Slopes of the QT/TQ relationship were also analysed using a best fit linear method. This data was analysed using Origin 8 graphical software. Figure 6.3 shows typical scatterplots of QT and preceding TQ values for a typical 4 hour (1 to 5am) period for a study patient. Figure 6.4 shows a scatterplot for the whole recording of a study patient. Patients who experienced appropriate ventricular arrhythmia (as documented by appropriate ATP or shock therapy) were compared to those that did not, in the context of these parameters, to see if there were any identifiable differences. Patients who had appropriate shocks were then compared to those who were shock free. As well as analysing the whole recording, an analysis was also conducted looking at the period between 1 to 5 am to see if there were any discernable differences between groups. A nocturnal period was chosen to see if there could be any possible differences between patients as well as looking at the whole recordings.

Figure 6.3 Typical QT/TQ scatterplot for a study patient (1 to 5am) Each point represents a QT interval (y-axis) and preceding TQ interval (x-axis).

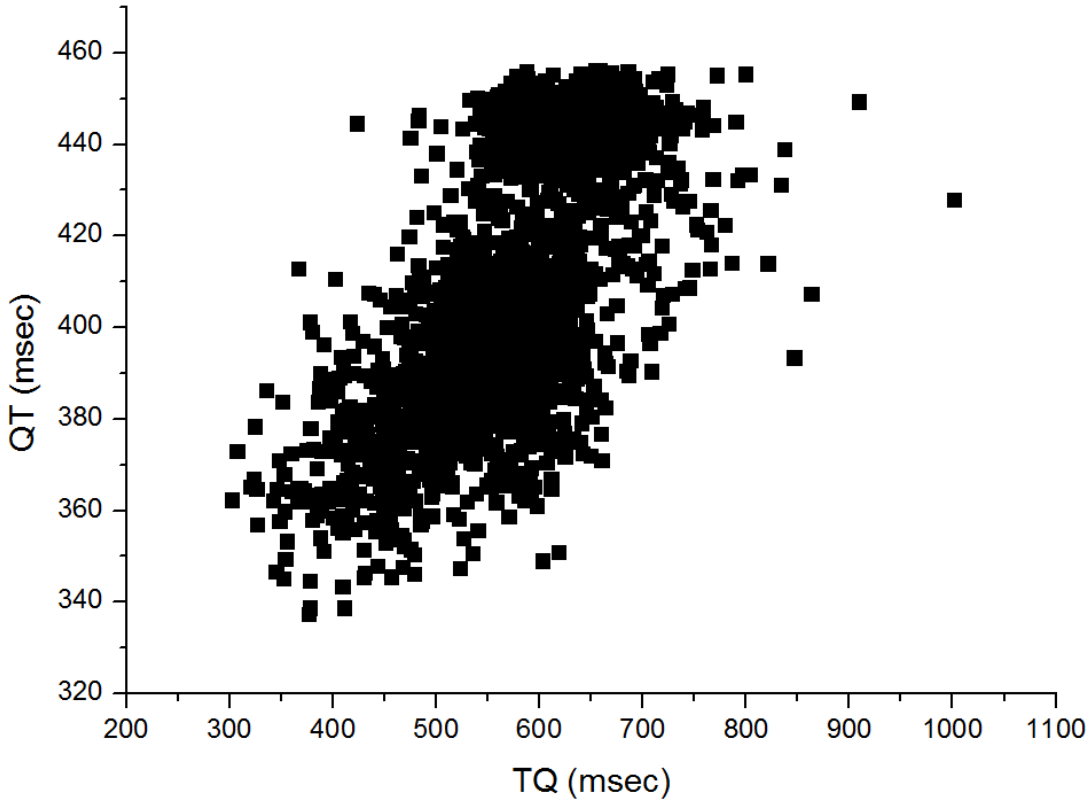
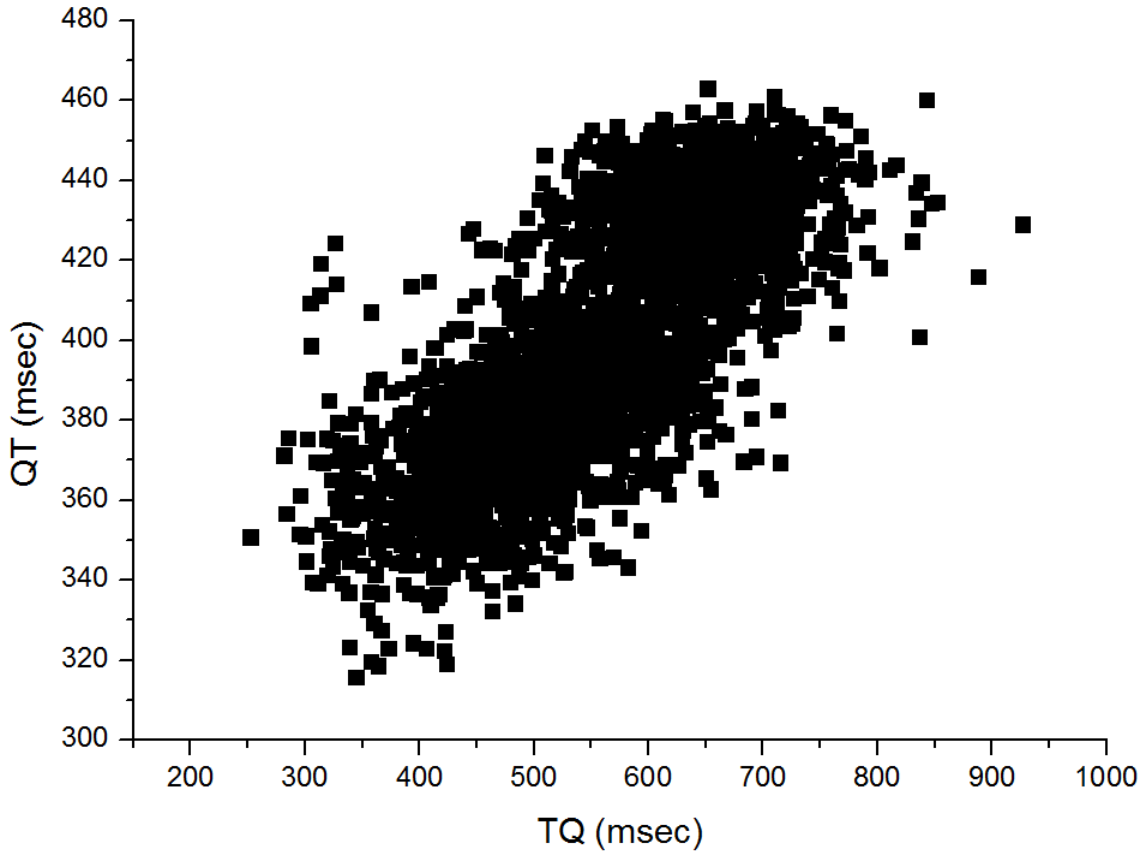


Figure 6.4 Typical QT/TQ scatterplot for a study patient (24hrs) Each point represents a QT interval (y-axis) and preceding TQ interval (x-axis).



6.5 Statistical analysis

Continuous variables were compared using the Student's t-test once normality was confirmed. The Mann Whitney U test was used for non-parametric data. Categorical data was analysed by the chi-squared test. Binary logistic regression was used for univariate and multivariate analyses in terms of the outcome data. A P value<0.05 was considered statistically significant.

6.6 Results

6.6.1 Demographics

6.6.1.1 Whole population

Of the 92 patients recruited into the whole study, 56 patients were included in these analyses. Five patients were withdrawn from the entire study. The supervising clinician decided not to implant an ICD in 3 patients, and 2 patients were lost to follow up as they had moved region. Other reasons for exclusion included AF (n=11), paced rhythm (n=3), removal of Holter by patient (n=2), and poor quality data or excessive ectopy (n=15). No inappropriate shocks were recorded.

The demographic characteristics of the patients included in this portion of the study are outlined in Table 6.1. The majority of the patients were male and had ischaemic heart disease. As expected there was evidence of significant left ventricular systolic dysfunction, and the proportion of patients on heart failure medications and anti-

arrhythmic therapy was high. There were more patients who fell into the secondary prevention category in addition.

Data was analysed in three ways. Firstly, people who experienced appropriate shocks were compared to those that did not (primary endpoint). Patients who experienced all appropriate therapy (ATP/shocks) were compared to those that did not. Finally, patients who experienced appropriate shocks were compared to those who did not experience any sustained arrhythmia requiring therapy (secondary endpoints).

Table 6.1. Clinical characteristics of study patients (n=56)

Age*	64±10
Gender (M/F)	44/12 (78.5/21.5)
NYHA class	
I	28 (50)
II	18 (32.1)
III	10 (17.9)
Aetiology	
Ischaemic	42 (75)
Non ischaemic	14 (25)
Ejection Fraction (%)*	29±11.9
Primary / Secondary prevention	24/32 (42.8/57.2)
QRS duration	0.10±0.02
Hypertension	21 (37.5)
Diabetes Mellitus	13 (23.2)
Smoking	43 (76.8)
Drugs pre implant	
Beta blockade	49 (87.5)
Amiodarone	11 (23.9)
ACE / Angiotensin II blockers	40 (71.4)
Digoxin	0 (0)
Serum creatinine*	123.6±96.9
VT stimulation study pre implant	17 (30.4)

*expressed as mean±SD; figures in brackets represent % of sample size

6.6.1.2 Appropriate Shock v. No shock Demographics

Of the 56 patients analysed here, 12 patients received appropriate ICD shocks for sustained VA. Four patients died (non-arrhythmic), of which 1 had received shocks following implant. Ten different patients received appropriate ATP therapy. The remainder were therapy and sustained VA free at 2 years.

Table 6.2 shows the differences between those patients who received appropriate ICD shocks, and those who remained shock free. As can be seen from the data, there was a significant difference in the proportion of patients with ischaemic aetiology who received shocks compared to those who were shock free. This relates to the sample size, the fact that there were small numbers of non ischaemic patients and the absence of appropriate shocks in this latter cohort. There were no shocks in those on amiodarone in this cohort. Older patients seemed to experience more shocks, although this did not reach a significant level. There were no other significant baseline differences between the groups.

Table 6.2 Characteristics in patients with appropriate shocks and no shocks

	Free of shock (n=44)	Shocks (n=12)	p value
Clinical Variables			
Age (years)	62.8±9.7	69.1±10.9	0.06
Gender (male / female)	34/10 (77.3/22.7)	10/2 (83.3/16.7)	0.65
Aetiology (Ischaemic / Non ischaemic)	30/14 (68.2/31.8)	12/0 (100/0)	0.02
NYHA I	23 (52.3)	5 (41.7)	0.72
II	13 (29.5)	5 (41.7)	
III	8 (18.2)	2 (16.6)	
EF (%)	29.5±12.5	28.5±10.5	0.83
Serum creatinine	128±108.4	107.6±24.3	0.25
Hypertension	18 (40.9)	4 (33.3)	0.63
Diabetes Mellitus	12 (27.3)	1 (8.3)	0.17
Smoking	33 (75)	10 (83.3)	0.54
Primary / Secondary	20/24 (45.5/54.1)	4/8 (33.3/66.7)	0.45
QRS durations (msec)	101.40±21.82	105.49±26.92	0.59
Drugs pre implant			
Beta blockade	39 (88.6)	10 (83.3)	0.62
Amiodarone	11 (25)	0 (0)	0.05
ACE / Angiotensin II blockers	39 (88.6)	10 (83.3)	0.63

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

6.6.1.3 Appropriate ATP/shock v no therapy demographics

Table 6.3 shows the patient characteristics between those who received appropriate therapy (ATP and appropriate shocks, used as a surrogate for arrhythmia) and those who were arrhythmia and hence event free. No significant differences are demonstrated between the 2 groups. LVEF is lower in the arrhythmia (therapy) group, but this does not reach statistical significance. Again, heart failure medication and anti-arrhythmic drug use was used in a large proportion of patients in both groups. In this part of the study, 22 patients experienced appropriate therapy for ventricular arrhythmia. No inappropriate therapy was recorded in this cohort. The majority of patients had an ischaemic aetiology, but this was not statistically significant.

Table 6.3 Characteristics in patients with shocks / ATP and those event free

	Free of shock/ATP (n=34)	Appropriate Shock/ATP (n=22)	p value
Clinical Variables			
Age (years)	62.9±9.9	66.0±10.8	0.29
Gender (male / female)	26/8 (76.5/23.5)	18/4 (81.8/18.2)	0.63
Aetiology (Ischaemic / Non ischaemic)	23/11 (67.6/32.4)	19/3 (86.4/13.6)	0.11
NYHA I	18 (52.9)	10 (45.5)	0.84
II	10 (29.4)	8 (36.4)	
III	6 (17.6)	4 (18.1)	
EF (%)	31.1±13.3	26.9±9.7	0.22
Serum creatinine	129.6±122.6	114.3±28.1	0.57
Hypertension	14 (41.2)	8 (36.4)	0.72
Diabetes Mellitus	9 (26.5)	4 (18.2)	0.47
Smoking	24 (70.6)	19 (86.4)	0.17
Primary / Secondary	13/21 (38.2/61.8)	11/11 (50/50)	0.39
QRS durations (msec)	107.56±28.44	98.86±17.94	0.17
Drugs pre implant			
Beta blockade	29 (85.3)	20 (90.9)	0.54
Amiodarone	7 (20.6)	4 (18.2)	0.83
ACE / Angiotensin II blockers	29 (85.3)	20 (90.9)	0.54

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

6.6.1.4 Appropriate Shock vs no therapy

There were 12 patients that experienced appropriate shocks. They were compared to patients who experienced no appropriate therapy at all (n=34). Table 6.4 shows the different baseline characteristics in this comparison. Again, the only parameter that appeared significant is ischaemic aetiology. However, this is probably related to the small sample size and may not represent a genuine observation. Patients who were older appeared to have more shocks but this was not statistically significant.

Table 6.4 Characteristics in patients with appropriate shocks and those arrhythmia free

	Free of shock/ATP (n=34)	Appropriate Shocks (n=12)	p value
Clinical Variables			
Age (years)	62.9±9.9	69.1±10.9	0.69
Gender (male / female)	26/8 (76.5/23.5)	10/2 (83.3/16.7)	0.62
Aetiology (Ischaemic / Non ischaemic)	23/11 (67.6/32.4)	12/0 (100/0)	0.02
NYHA I	18 (52.9)	5 (41.7)	0.73
II	10 (29.4)	5 (41.7)	
III	6 (17.6)	2 (16.6)	
EF (%)	31.1±13.3	28.5±10.5	0.65
Serum creatinine	129.6±122.6	107.6±24.3	0.21
Hypertension	14 (41.2)	4 (33.3)	0.63
Diabetes Mellitus	9 (26.5)	1 (8.3)	0.19
Smoking	24 (70.6)	10 (83.3)	0.39
Primary / Secondary	13/21 (38.2/61.8)	4/8 (33.3/66.7)	0.76
QRS durations (msec)	107.56±28.44	105.49±26.92	0.34
Drugs pre implant			
Beta blockade	29 (85.3)	10 (83.3)	0.87
Amiodarone	7 (20.6)	0 (0)	0.18
ACE / Angiotensin II blockers	29 (85.3)	10 (83.3)	0.65

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

6.6.2 HRV results

6.6.2.1 HRV measures; Appropriate Shocks v. No shocks

6.6.2.1.1 Time Domain

Table 6.5 demonstrates the time domain measures in those who experienced appropriate shocks and those who remained shock free over the 2 year follow period. As can be seen, there are no statistical differences and the values obtained are similar between the 2 groups. Figure 6.5 demonstrates this graphically. The ROC curve for SDNN is shown if Figure 6.6. The AUC was 0.55 in keeping with a low positive predictive value of SDNN in the prediction of ICD shocks in this population. The parameter RMSSD had low predictive accuracy in addition with an AUC of 0.56.

Table 6.5 Time Domain Measures of HRV in patients with appropriate shocks and no shocks

	Free of shock (n=44)	Appropriate shock (n=12)	p value
SDNN (ms)	97.5±29	105.3±38.7	0.44
RMSSD (ms)	24.3±11.9	28.4±17.3	0.34

Figure 6.5 Box and Whisker plot SDNN: shock v no shock

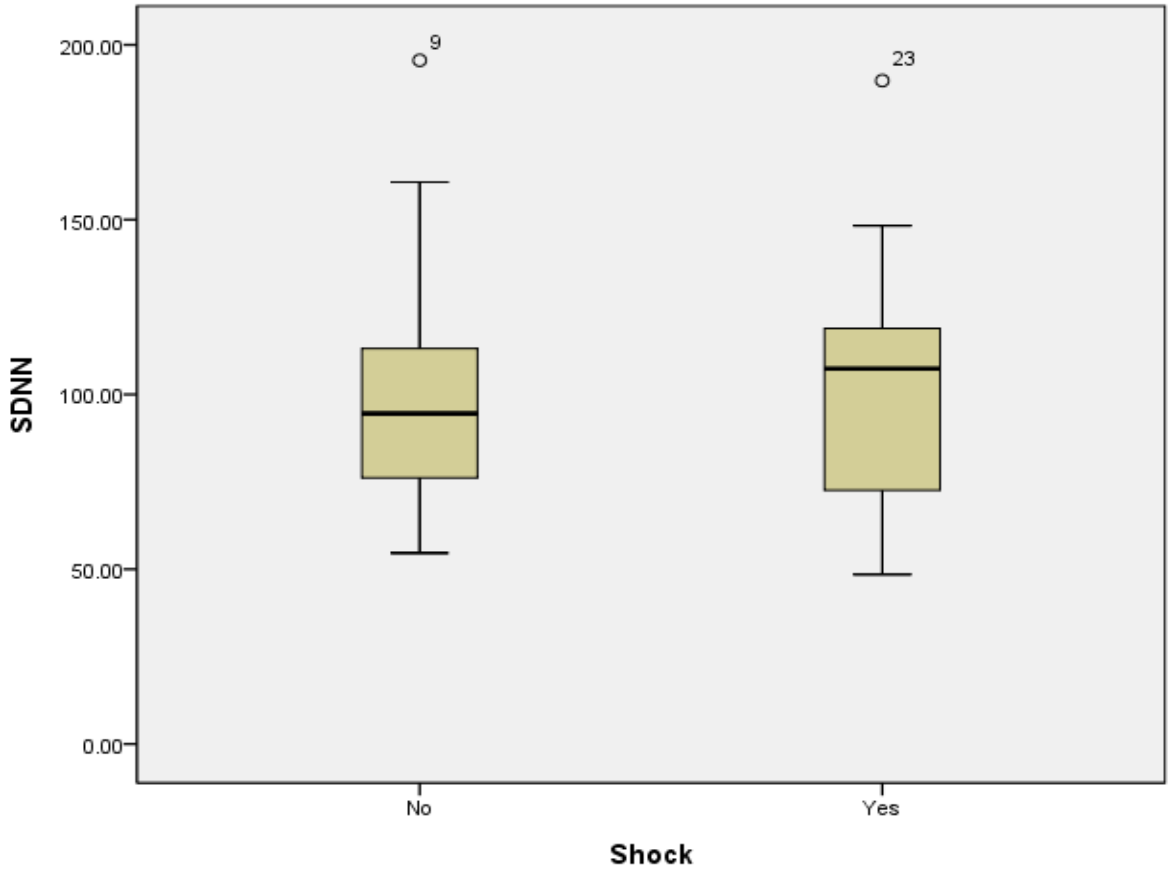
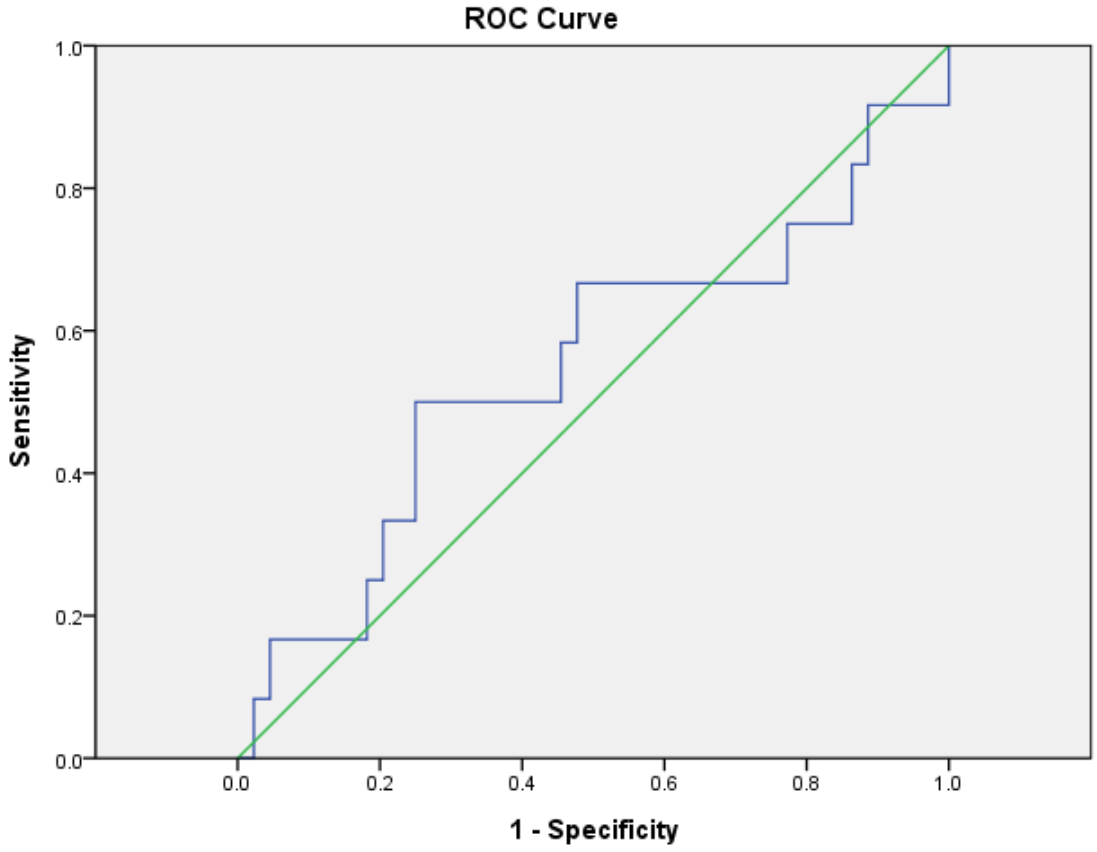


Figure 6.6 ROC curve analysis (SDNN, Shock vs no shock)



6.6.2.1.2 Frequency Domain

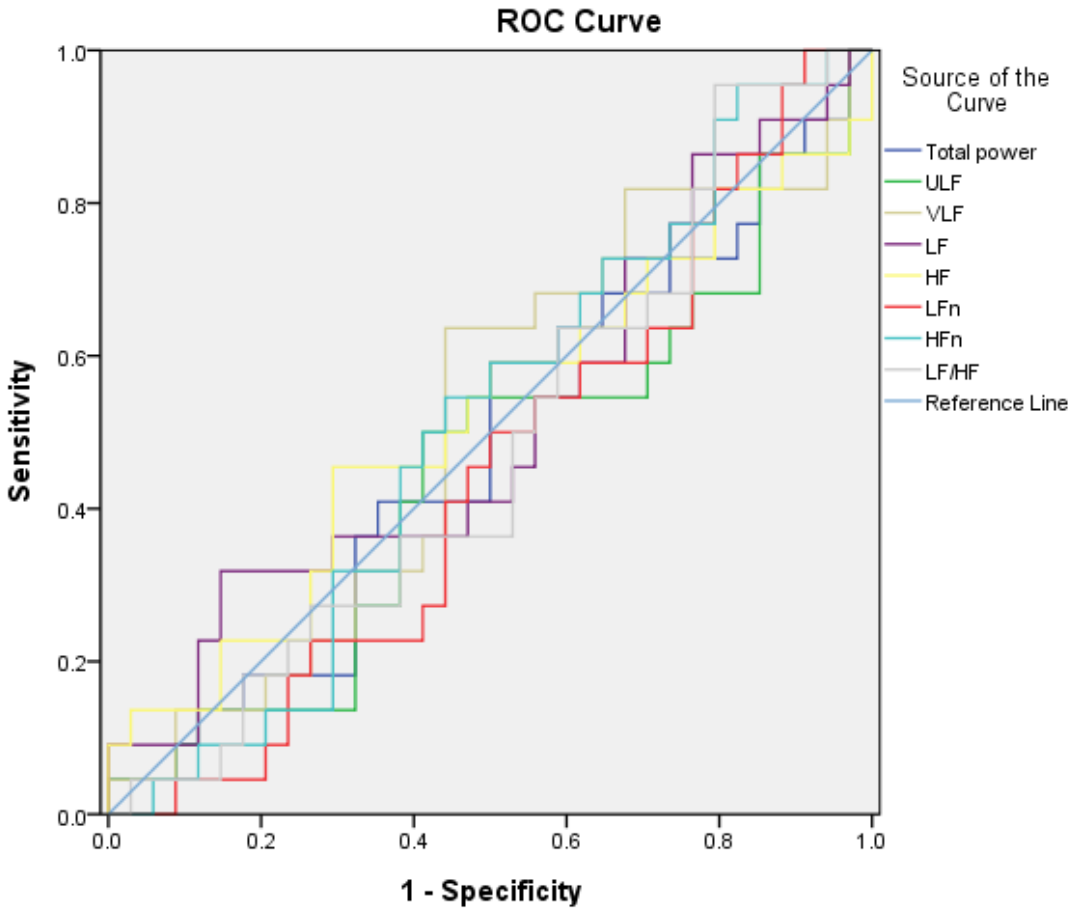
Table 6.6 shows the frequency domain parameters in patients who did and did not experience an appropriate shock during the follow up phase. The only parameter to achieve statistical significance is the HF band although this was not borne out when the data was normalised. The LF band approached a significant level, but again not after normalisation. The remainder of the parameters did not achieve a significant statistical difference between the groups. The ROC curves (figure 6.7) in these analyses did not demonstrate predictive accuracy of these parameters in terms of appropriate shocks with AUC values between 0.45 and 0.57.

Table 6.6 Frequency Domain Measures of HRV in patients with appropriate shocks and no shocks

	Free of shocks (n=44)	Appropriate shock (n=12)	p value	AUC
VLF (ms^2)	1237.44±975.67	1643.49±1726.10	0.28	0.57
LF (ms^2)	354.65±292.91	633.18±736.62	0.05	0.57
HF (ms^2)	203.04±186.09	396.37±519.43	0.04	0.55
LFn	60.89±14.92	57.01±12.91	0.41	0.40
HFn	33.67±12.7	33.37±9.45	0.94	0.52
LF:HF ratio	2.61±1.58	2.36±1.44	0.62	0.45
Total power (ms^2)	4007.17±2471.37	5222.82±50822.22	0.24	0.55

LFn/HFn normalized units; Data expressed as mean±SD

Figure 6.7 ROC curve analysis (Frequency Domain, Shock vs no shock)



6.6.2.2 HRV measures, Appropriate therapy v. No therapy

6.6.2.2.1 Time Domain

There were no significant differences in the HRV measures analysed between the 2 groups as can be seen in Table 6.7. The measured indices were fairly equal between the 2 groups. The ROC curves and AUC analysis showed low predictive accuracy in addition (AUC SDNN 0.46, AUC RMSSD 0.47).

Table 6.7 Time Domain Measures of HRV in patients with appropriate therapy and no therapy

	Free of therapy (n=34)	Appropriate therapy (n=22)	p value
SDNN (ms)	100.6±30.3	97.0±32.9	0.57
RMSSD (ms)	25.3±12.5	25.0±14.5	0.7

Data presented in mean ± SD or number of patients

6.6.2.2.2 Frequency Domain

Table 6.8 shows the data collected in the frequency domain. There were no significant differences between the 2 groups. In addition, no evident trends are seen. ROC curve analyses revealed low predictive accuracy.

Table 6.8 Frequency Domain data (appropriate therapy vs. therapy free)

	Free of therapy (n=34)	Appropriate therapy (n=22)	p value	AUC
VLF (ms^2)	1278.43±1048.2	1395.58±1359.63	0.71	0.51
LF (ms^2)	367.12±306.99	487.30±580.90	0.31	0.51
HF (ms^2)	208.33±198.52	300.32±402.13	0.25	0.52
LFn	60.76±16.08	58.97±11.9	0.65	0.45
HFn	33.82±13.31	33.27±9.92	0.87	0.51
LF:HF ratio	2.65±1.70	2.42±1.30	0.58	0.48
Total power (ms^2)	4174.88±2612.89	4411.06±3991.89	0.79	0.48

LFn/HFn normalized units; Data expressed as mean±SD

6.6.2.3 HRV Measures (appropriate shocks v no therapy)

6.6.2.3.1 Time Domain

Table 6.9 shows the time domain comparison in this section. There are no significant differences between the groups in either measure in univariate analysis. Predictive accuracy was low (AUC 0.52 for SDNN and 0.54 for RMSSD).

Table 6.9 Time Domain Measures of HRV in patients with appropriate shocks and no therapy

	Free of therapy (n=34)	Appropriate shock (n=12)	p value
SDNN (ms)	100.57±30.27	105.3±38.7	0.66
RMSSD (ms)	25.3±12.49	28.4±17.3	0.50

6.6.2.3.2 Frequency Domain

Table 6.10 shows the frequency domain parameters. The LF and HF measurements are higher in the appropriate shock group, but these results were not statistically significant. In addition, the normalised data was not suggestive of a statistically significant difference. Predictive accuracy was also low on ROC curve analysis.

Table 6.10 Frequency Domain Measures of HRV in patients with appropriate shocks and no therapy

	Free of therapy (n=34)	Appropriate shock (n=12)	p value	AUC
VLF (ms^2)	1278.43±1048.20	1643.49±1726.10	0.38	0.55
LF (ms^2)	367.12±306.99	633.18±736.62	0.09	0.56
HF (ms^2)	208.33±198.52	396.37±519.43	0.08	0.55
LFn	60.76±16.08	57.01±12.91	0.46	0.41
HFn	33.82±13.31	33.37±9.45	0.91	0.52
LF:HF ratio	2.65±1.70	2.36±1.44	0.60	0.46
Total power (ms^2)	4174.88±2612.89	5222.82±50822.22	0.35	0.53

LFn/HFn normalized units; Data expressed as mean±SD

6.6.2.4 NYHA class and HRV measures

There were no significant differences between any of the HRV measures across the NYHA classes in all of the sub-group analyses.

6.6.3 QTVI Results

6.6.3.1 Whole dataset

Table 6.11 shows the ECG variables in the 56 patients studied. These are the 24 hour period variables. Table 6.12 shows the same variables for the 4 hour nocturnal period. There were no significant differences between QTVI results across the NYHA groups in the study (P=0.43).

Table 6.11 Values of ECG variables in study subjects (24 hour period)

QTm (msec)	418.24±36.53
QTv ($msec^2$)	464.89±387.64
RRv ($msec^2$)	10206.44±6575.48
RRm (msec)	994.95±157.11
QTVI	-0.64±0.35

mean±SD

Table 6.12 Values of ECG variables in study subjects (1am to 5am)

QTm (msec)	433.90±41.00
QTv ($msec^2$)	210.60±293.27
RRv ($msec^2$)	6101.93±4534.55
RRm (msec)	1045.15±162.71
QTVI	-0.78±0.43

mean±SD

6.6.3.2 Appropriate Shock v. no shock (QTVI)

Table 6.13 shows the 24 hour derived ECG measures in patients who had experienced appropriate shocks, and those who had had no shocks. The latter group did include some patients who had appropriate ATP therapy alone. On ROC curve analysis (figure 6.8) these parameters had low predictive ability for ICD shocks in this population.

Table 6.13 Derived ECG values for patients with appropriate shocks and no shocks (24hrs)

	Appropriate shocks (n=12)	No shocks (n=44)	P value	AUC
QTm (msec)	421.22±37.26	417.42±36.72	0.75	0.53
RRv (msec^2)	11987.89 ± 8619.38	9720.59 ± 5930.47	0.29	0.57
QTv (msec^2)	466.50±288.05	464.45±413.49	0.99	0.52
QTVI	-0.64±0.34	-0.64±0.36	0.96	0.43
RRm (msec)	984.07±186.70	997.91±150.37	0.79	0.46

mean±SD

The 2 groups were very similar in terms of these measures. The QTVI was not different between patients who had appropriate shocks and those who did not. Table 6.14 shows the same parameters in the nocturnal analysis. Again, there are no significant differences in QTVI between the 2 groups with ROC curve analysis showing low predictive value.

Table 6.14 Derived ECG values for patients with appropriate shocks and no shocks (1 to 5am)

	Shocks (n=12)	No shocks (n=44)	p value	AUC
QTm (msec)	436.83±30.25	433.10±43.74	0.78	0.52
RRv (msec^2)	7571.12±6234.92	5701.24±3949.78	0.20	0.57
QTv (msec^2)	217.47±178.19	208.72±319.17	0.93	0.56
QTVI	-0.81±-0.60	-0.77±0.38	0.74	0.47
RRm (msec)	1038.98±182.55	1046.83±159.14	0.88	0.48

mean±SD

6.6.3.3 All appropriate therapy v. no therapy (QTVI)

Table 6.15 and 6.16 show the QTVI and the other derived ECG data for the whole 24 hour periods and the nocturnal analyses respectively.

Table 6.15 Derived ECG values for patients with appropriate therapy and no therapy (24hrs)

	Appropriate shock / ATP (n=22)	No shocks / ATP (n=34)	p value	AUC
QTm (msec)	414.74±37.55	420.50±36.24	0.56	0.45
RRv (msec^2)	10102.11±7010.86	10273.94±6385.21	0.92	0.48
QTv (msec^2)	461.16±503.18	467.30±298.84	0.95	0.39
QTVI	-0.73±0.49	-0.58±0.22	0.12	0.38
RRm (msec)	974.28±166.56	1008.32±151.71	0.42	0.44

mean±SD

Table 6.16 Derived ECG values for patients with appropriate therapy & no therapy (1 to 5am)

	Appropriate shock / ATP (n=22)	No shock / ATP (n=34)	p value	AUC
QTm (msec)	429.40±39.35	436.80±42.36	0.51	0.46
RRv (msec^2)	7082.24±5117.0	5467.60±4070.38	0.19	0.59
QTv (msec^2)	279.14±442.23	166.25±117.20	0.16	0.54
QTVI	-0.80±0.52	-0.76±0.37	0.73	0.44
RRm (msec)	429.40±39.35	436.80±42.36	0.43	0.44

mean±SD

The QTVI in the 24 hour analysis appears non-significantly greater in those with no therapy. There are no other significant differences between the groups including low predictive ability for all the parameters in both analyses.

6.6.3.4 Appropriate shocks vs. no therapy (QTVI)

Table 6.17 and 6.18 presents the QTVI and other derived ECG data for the whole 24 hour period and the nocturnal analyses respectively in this sub-group. There were no significant differences (and hence low predictive value) in these measurements including QTVI between patients who experienced an appropriate shock and those that were event free.

Table 6.17 Derived ECG values for patients with appropriate shocks and no therapy (24hrs)

	Appropriate shock (n=12)	No therapy (n=34)	p value	AUC
QTm (msec)	421.22±37.26	420.50±36.24	0.95	0.50
RRv (msec^2)	11987.89±8619.38	10273.94±6385.21	0.47	0.54
QTv (msec^2)	466.50±288.05	467.30±298.84	0.99	0.47
QTVI	-0.64±0.34	-0.58±0.22	0.45	0.40
RRm (msec)	984.07±186.70	1008.32±151.71	0.66	0.45

mean±SD

Table 6.18 Derived ECG values for patients with appropriate shocks & no therapy (1 to 5am)

	Appropriate shock (n=12)	No therapy (n=34)	p value	AUC
QTm (msec)	436.83±30.25	436.80±42.36	0.99	0.50
RRv (msec^2)	7571.11±6234.92	5467.60±4070.38	0.19	0.58
QTv (msec^2)	217.47±178.19	166.25±117.20	0.27	0.57
QTVI	-0.81±0.60	-0.76±0.37	0.72	0.45
RRm (msec)	1038.98±182.55	1058.97±161.98	0.72	0.46

mean±SD

6.6.3.5 QTVI in IHD

Given the possible myocardial inhomogeneity associated with ischaemic cardiomyopathy, the QTVI was also calculated for the patients with an ischaemic aetiology, excluding the others. This left 42 patients in the analysis. Of these, 19 patients experienced appropriate therapy, including 12 patients with appropriate shocks. In this sub-group analysis, there were no statistically significant differences in the baseline characteristics between those with and without appropriate therapy (Table 6.19). In addition, ECG derived measures including QTVI (p=0.27 (24 hour analysis) and p=0.7 (1 to 5am analysis) were non-significantly different (Table 6.20 & 6.21 respectively).

Table 6.19 Characteristics in ischaemic patients with appropriate therapy and those arrhythmia free

	Free of arrhythmia (n=23)	Appropriate Therapy (n=19)	p value
Clinical Variables			
Age (years)	64.5±8.5	66.7±10.6	0.47
Gender (male / female)	21/2(91.3/8.7)	16/3 (84.2/15.8)	0.48
NYHA I	11 (47.8)	8 (42.1)	0.90
II	7 (30.4)	7 (5.3)	
III	5 (21.7)	4 (21.1)	
EF (%)	26.2±8.5	26.3±10.0	0.96
Serum creatinine	149.0±146.6	115.1±26.1	0.32
Hypertension	9 (39.1)	7 (36.8)	0.88
Diabetes Mellitus	8 (34.8)	2 (10.5)	0.07
Smoking	20 (87.0)	16 (84.2)	0.80
Primary / Secondary	11/12 (47.8/52.2)	9/10 (47.4/52.6)	0.98
QRS durations (msec)	102.93±17.90	103.27±22.95	0.96
Drugs pre implant			
Beta blockade	21 (91.3)	17 (89.5)	0.84
Amiodarone	6 (26.1)	4 (21.1)	0.59
ACE / Angiotensin II blockers	22 (95.7)	18 (94.7)	0.70

Data presented in mean ± SD or number of patients; figures in () represent % of sample size

Table 6.20 Derived ECG values for ischaemic patients with appropriate therapy & no therapy (whole)

	Appropriate shock / ATP (n=19)	No shocks / ATP (n=23)	p value
QTm (msec)	417.40±34.05	416.20±32.73	0.91
RRv (msec^2)	10685.35±7233.61	8723.71±4636.50	0.29
QTv (msec^2)	484.81±531.72	392.61±171.04	0.44
QTVI	-0.70±0.46	-0.58±0.21	0.27
RRm (msec)	983.77±168.67	982.67±152.27	0.98

mean±SD

Table 6.21 Derived ECG values for ischaemic patients with appropriate therapy & no therapy (1 to 5am)

	Appropriate shock / ATP (n=19)	No shocks / ATP (n=23)	p value
QTm (msec)	432.09±35.59	429.26±34.28	0.80
RRv (msec^2)	7516.70±5366.28	5060.35±4605.60	0.12
QTv (msec^2)	295.88±470.60	159.70±113.14	0.19
QTVI	-0.79±0.55	-0.74±0.41	0.70
RRm (msec)	1033.48±164.83	1025.20±149.00	0.87

mean±SD

6.6.4 ECG restitution measures

6.6.4.1 Appropriate Shocks vs no shocks

Tables 6.22 and 6.23 describe the measured ECG restitution parameters for the whole recording and between the hours of 1 to 5am respectively. Figure 6.8 shows the ROC curve analyses for the 24 hour data. There is low predictive accuracy in this population in terms of ICD shock in both groups.

Table 6.22 ECG restitution in those with appropriate shocks vs. no shocks (whole)

Variables	Free of shocks (n=44)	Appropriate Shocks (n=12)	p value	AUC
RR interval (ms)	997.91±150.37	984.07±186.70	0.79	na
QT interval (ms)	417.42±36.72	421.22±37.26	0.75	na
TQ interval	579.38±124.75	562.80±163.37	0.71	na
TQ min (5^{th} quantile)	439.05±104.25	414.97±115.98	0.49	0.42
%(QT/TQ ratio)>1	8.77±16.19	19.45±27.47	0.09	0.64
(QT/TQ ratio)max 98% quantile	1.10±0.21	1.00±0.24	0.22	0.60
Means of slopes	0.11±0.07	0.10±0.10	0.61	0.46

Data presented in mean ± SD or number of patients

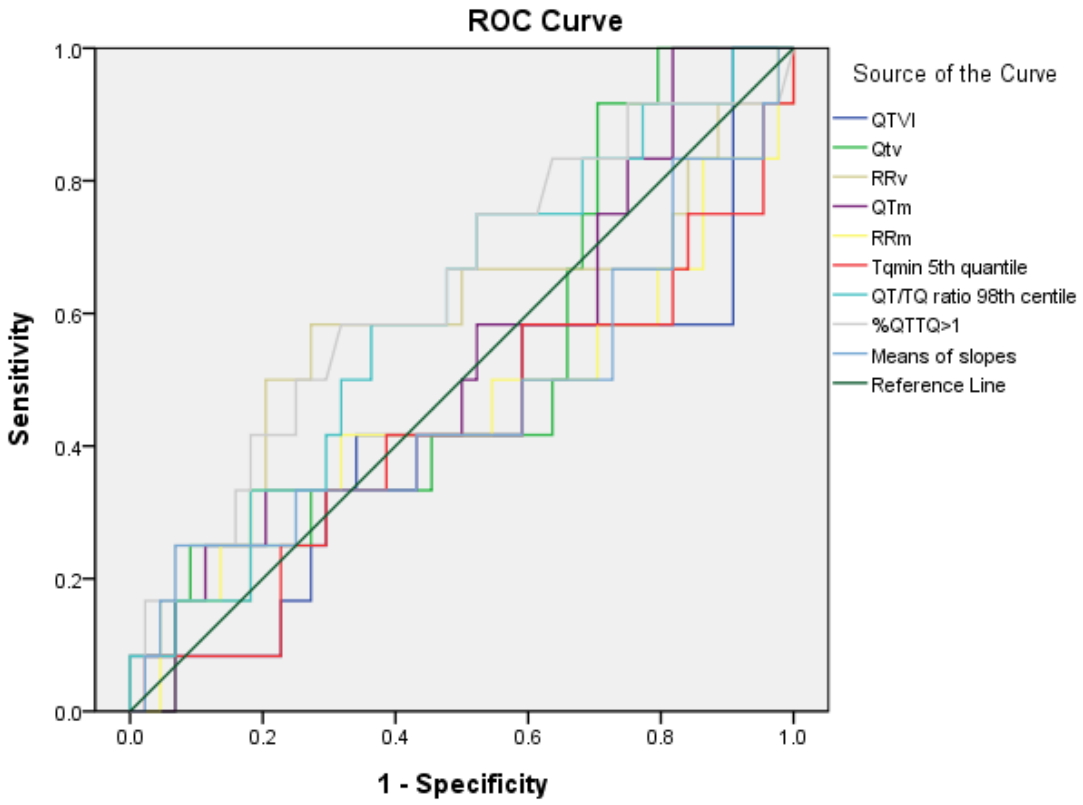
Table 6.23 ECG restitution in those with appropriate shocks vs. no shocks (1 to 5am)

Variables	Free of shocks (n=44)	Appropriate shocks (n=12)	p value	AUC
RR interval (ms)	1046.83±159.14	1038.98±182.55	0.88	na
QT interval (ms)	433.1±43.74	436.83±30.25	0.78	na
TQ interval	613.73±128.61	602.11±170.45	0.80	na
TQ min (5th quantile)	503.28±112.93	473.91±123.97	0.44	0.42
%(QT/TQ ratio)>1	5.43±14.13	17.74±30.97	0.05	0.68
(QT/TQ ratio)max 98% quantile	0.94±0.17	1.03±0.22	0.11	0.63
Means of slopes	0.11±0.07	0.10±0.10	0.61	0.46

Data presented in mean ± SD or number of patients

The percentage of QT/TQ beats >1 approaches significance in both of these analyses. In patients with appropriate shocks, there is a higher percentage of beats where this ratio is >1. This could represent the time on the restitution slope where rhythm stability is not as certain, and hence explain the findings seen here. The other ECG restitution parameters are not significantly different between the groups.

Figure 6.8 ROC curves for ECG restitution and QTVI (shocks vs. no shocks)



6.6.4.2 Appropriate therapy vs. no appropriate therapy

Tables 6.24 and 6.25 show the measured ECG restitution parameters in this section. In this group, 22 patients experienced appropriate therapy.

Table 6.24 ECG restitution in those with appropriate therapy vs. no therapy (whole)

Variables	Free of therapy (n=34)	Appropriate therapy (n=22)	p value	AUC
RR interval (ms)	1008.32±151.71	974.28±166.56	0.42	na
QT interval (ms)	420.50±36.24	414.74±37.55	0.56	na
TQ interval	586.39±125.83	559.51±143.63	0.45	na
TQ min (5^{th} quantile)	441.21±107.07	422.59±106.41	0.52	0.47
%(QT/TQ ratio)>1	7.21±12.02	17.00±26.38	0.06	0.58
(QT/TQ ratio)max 98% quantile	0.99±0.25	1.06±0.22	0.33	0.54
Means of slopes	0.11±0.10	0.11±0.07	0.69	0.44

Data presented in mean ± SD or number of patients

Table 6.25 ECG restitution in those with appropriate therapy vs. no therapy (1 to 5am)

Variables	Free of therapy (n=34)	Appropriate therapy (n=22)	p value	AUC
RR interval (ms)	1058.97±161.98	1023.80±165.28	0.43	na
QT interval (ms)	436.80±42.36	429.40±39.35	0.51	na
TQ interval	622.15±130.71	594.38±147.68	0.46	na
TQ min (5^{th} quantile)	513.62±114.27	471.26±113.53	0.17	0.40
%(QT/TQ ratio)>1	4.16±9.52	14.11±27.82	0.06	0.65
(QT/TQ ratio)max 98% quantile	0.94±0.17	0.99±0.19	0.29	0.60
Means of slopes	0.11±0.10	0.11±0.07	0.69	0.44

Data presented in mean ± SD or number of patients

As can be seen from the data, there are no significant differences between the groups except for the percentage of time the QT:TQ ratio is greater than 1, which approaches significance, with a higher percentage seen in the therapy groups of both the whole and nocturnal recordings. However, predictive ability of these parameters is low.

6.6.4.3 Appropriate shock vs. no therapy

Tables 6.26 and 6.27 show the ECG restitution measurements for this cohort (patients with shocks versus patients with no therapy at all including ATP). The percentage of the QT/TQ ratio>1 is statistically significant in with a higher percentage in patients with shocks compared to those with ICDs who are completely therapy and hence arrhythmia free at the 2 year follow up point. This is seen in the whole recording as well as when the data is analysed for the nocturnal time period. The other measurements were not significantly different between the 2 groups. However, the predictive accuracy of this parameter is relatively low (AUC 0.65 in whole, and 0.69 in nocturnal analyses).

Table 6.26 ECG restitution in those with appropriate shocks vs. no therapy (whole)

Variables	Free of therapy (n=34)	Appropriate shocks (n=12)	p value	AUC
RR interval (ms)	1008.32±151.71	984.07±186.70	0.65	na
QT interval (ms)	420.50±36.24	421.22±37.26	0.95	na
TQ interval	586.38±125.83	562.80±163.37	0.60	na
TQ min (5th quantile)	441.21±107.07	414.97±115.98	0.47	0.43
%(QT/TQ ratio)>1	7.21±12.02	19.45±27.48	0.04	0.65
(QT/TQ ratio)max 98% quantile	0.99±0.25	1.10±0.21	0.22	0.60
Means of slopes	0.11±0.07	0.10±0.10	0.59	0.45

Data presented in mean ± SD or number of patients

Table 6.27 ECG restitution in those with appropriate shocks vs. no therapy (1 to 5am)

Variables	Free of therapy (n=34)	Appropriate shocks (n=12)	p value	AUC
RR interval (ms)	1058.97±161.98	1038.98±182.55	0.72	na
QT interval (ms)	436.80±42.36	436.83±30.25	0.99	na
TQ interval	622.15±130.71	602.11±170.45	0.67	na
TQ min (5^{th} quantile)	513.63±114.27	473.91±123.97	0.31	0.40
%(QT/TQ ratio)>1	4.16±9.52	17.74±30.97	0.03	0.69
(QT/TQ ratio)max 98% quantile	0.94±0.17	1.03±0.22	0.13	0.65
Means of slopes	0.11±0.07	0.10±0.10	0.59	0.45

Data presented in mean ± SD or number of patients

6.7 Discussions

6.7.1 Heart Rate Variability

This analysis has not revealed any association between 24 hour time and frequency domain HRV measures and appropriate ICD therapy in a population of patients who have LVSD as well as primary and secondary indications for ICD implantation. This is the case even when a composite endpoint of shocks and ATP is evaluated, which led to an overall event rate of over 30% in 2 years, similar to previous data[147].

In heart failure states, autonomic function has been shown to be abnormal, as discussed earlier. Heart Rate Variability is a relatively straightforward method of analysis of autonomic activity. Data collection is non invasive. However, analysis can be time consuming, although validated automated analyses such as that used in this study are available. Manual editing is still required and the quality of the data is limited by the constraints of measurement and analysis[287].

Previous studies have demonstrated possible associations with depressed SDNN and increased all cause mortality in heart failure patients. However, different groups have presented conflicting data[196,209]. There does not appear to be a strong association between 24 hour HRV time domain measures and SCD. Bilchick and colleagues showed an association between low values of SDNN and SCD in heart failure patients in univariate but not multivariate analysis[207]. The present study would again point away from a significant association between SDNN and SCD (using appropriate ICD therapy as a surrogate). Similarly, the vagally mediated measure RMSSD was not significantly

different between the groups, supporting previous observations that the vagally mediated measures are not useful measures of outcome in these populations[199].

The latter assertion is also supported looking at the data in the frequency domain. Vagal activity has been shown to be the major contributor to HF power[173]. In this study, although HF power seemed higher in the shock group (which would be opposite to what is expected) compared to the no shock group, normalization of the data did not confirm this. This would support previous studies' findings[199]. In this analysis VLF and LF bands were not significantly associated with arrhythmia. Previous studies have suggested an association with LF and sudden death[209,288], but this has not been borne out here.

The population studied had a mean ejection fraction comparable with previous reported heart failure studies but the NYHA class seemed higher in our patients. This functional difference may have had a bearing on the HRV values despite the ejection fraction, possibly representing a less severe heart failure class. Heart Rate Variability has been shown to be depressed in heart failure settings. In the UK Heart study, SDNN was significantly different between survivors and non survivors (116.6±39.3 v. 93.4±48.1; p=0.005)[198]. This was a large study powered to look at mortality, but the markedly depressed SDNN may in part be related to decompensated cardiac failure and the resultant autonomic state. None of the patients seen in the current study had decompensated features at the time of recruitment. This is in part due to the nature of patient selection for ICD treatment as per NICE guidance[155].

HRV is also influenced by other factors, such as age, gender and heart failure medication such as ACE inhibitors and β blockers[287]. The patients studied here were well treated with the latter medications which may have had a bearing on HRV parameters. In earlier studies where the HRV parameters were appreciably lower than those in this study, β blocker use was an exclusion criterion. In addition ACE use was not documented in some of these studies[198,200,201,203,209,288]. Aranson and colleagues showed a markedly depressed SDNN in a study of decompensated heart failure patients. In this population, β blocker use was less than 30% although ACE use was high[204]. The current study has a high percentage of β blocker and ACE use which may have affected the HRV parameters. Nessler and colleagues showed a decrease in the number of heart failure patients with SDNN<100ms treated with carvedilol. They concluded that β blocker use reduced the risk of SCD by improvement in HRV[289]. However, Sanderson and colleagues did not show any improvement in SDNN after treatment with metoprolol or carvedilol in heart failure[290].

In this study patients not in stable sinus rhythm and those with a high ectopic burden were excluded. This led to a relatively small sample size and may have affected the outcomes seen. This is reflected in the relatively small number of patients who experienced outcomes. This analysis would not support the routine use of 24 hour time domain analyses of HRV for ventricular arrhythmia risk stratification in patients with LVSD.

6.7.2 QT Variability Index

This study has not demonstrated an association between QTVI and ventricular arrhythmia susceptibility in a population of patients with LVSD and clinical indication for ICD implantation. In a paper by Piccirillo and colleagues, the mean QTVI for healthy controls at rest was -1.4±0.71 and for patients with NYHA class III and IV heart failure was -0.16±0.61[273]. The mean QTVI in the present study was -0.64±0.35. This is larger than the QTVI seen in controls, suggesting that patients with LVSD who fulfill the criteria for ICD implantation have a higher temporal dispersion of cardiac repolarisation[273]. However, the QTVI results seen here are smaller than the QTVI values seen in patients with worse heart failure[273]. This difference seen in this current study reflects a different population who were on average in a better NYHA class, and hence who had less severe heart failure.

The patients with arrhythmia were similar to those with no arrhythmia in terms of baseline characteristics. The ejection fractions and heart failure classes were similar. Drug therapies were not significantly different especially when all arrhythmia was compared to patients with no arrhythmia at all. The non significant difference in QTVI may therefore not be that surprising. There is an increased temporal dispersion of QT intervals in this population compared to published healthy controls[273]. However, between the study population groups, the fact that there is no difference may merely reflect the fact that this parameter is not suitable as a risk stratification tool. However, a sub group analysis of the MADIT II population has produced different results. This study showed that increased QTVI was an independent risk factor for defibrillator therapy with a hazard

ratio of 1.8[277]. However, the authors of this study showed that there was a low negative predictive value.

The current study is limited by its small size and this may have had a bearing on the results. In addition, the QTVI data was collected over a longer period of time compared to the MADIT II data[277]. The use of heart failure and anti-arrhythmic medication also seems higher in the current study. It is possible that these factors influenced the results, culminating in a negative study. Certainly, larger studies of QTVI and ICD therapy may be beneficial, although confounding variables such as use of heart failure medication will remain. The size of the study also makes it difficult to comment on potential associations between aetiology and QTVI.

6.7.3 ECG restitution measures

There were no significant differences seen between patients with LVSD who had ICDs fitted as per current recommendations in terms of the majority of the measured ECG restitution parameters. This was the case for both the whole time and nocturnal readings. However, the QT:TQ >1 percentage was significantly higher in patients with appropriate shocks when compared to those who were therapy free at the 2 year follow up point. In addition in the other analyses this parameter approached a significant level. However, the predictive accuracy of this appeared to be relatively low. In addition, given the fact that the other parameters do not show statistically significant association with the end points, multivariate analysis was not possible. The TQ 5th quantile was not different between the groups. The rationale for this measure is that as the TQ interval approaches zero, there is a higher risk of arrhythmia[265]. However, this study did not seem to suggest that this

would be useful. The means of the slopes (by linear regression) were very similar across all the groups. This most probably reflects the fact that given the in-patient nature of these patients, and hence their relative sedentary status, there was not much heart rate variation. The relative homogeneity of anti arrhythmic drugs used will also have influenced this. Hence, the data seen is not a true classical restitution curve, which is generated by programmed ventricular stimulation, but merely a portion of the true curve. This may explain the lack of differences between the slopes between those with and without arrhythmia. Although the data is presented in this way, it seems that simple 24 hour tape analyses will not provide the classical restitution data quoted by animal studies. It is likely that more invasive methods of analysis will be required to give a measure of true restitution and to generate a 'full' restitution curve. Alternatively, methods to change heart rate such as exercise, or pacing may provide this data. The latter would have to employ atrial pacing, with patients with intact AV conduction, or ventricular pacing with the inherent risk of inducing ventricular arrhythmia. These methods are not always feasible. As with the patients examined in this study, patients with LVSD deemed to need an ICD, often have symptoms of heart failure limiting their exercise capacity and generally are older with potentially other functionally limiting co-morbid conditions. In addition, atrio-ventricular (AV) nodal conduction is often impaired in these patients with a lower Wenkebach point. Therefore, with more rapid atrial pacing, 1:1 AV conduction may not occur. These factors will make the generation of a restitution curve more difficult in a non-invasive manner. However, if a more complete restitution curve is generated, there may be a role for further refinement in terms of patient selection.

Fossa and colleagues demonstrated that the percentage of beats with a QT/TQ ratio>1 was increased in a coronary heart disease patient prior to the onset of Torsades[265]. In the present study, patients with therapy did have a higher percentage of beats with a QT/TQ ratio>1, and this was significant when appropriate shocks were compared with no therapy. The theory here is that as the ventricle spends less time at rest (shorter TQ), there may be greater ventricular instability[265]. This reflects time spent on a steeper restitution slope, which from animal studies has been shown to be pro-arrhythmic[262,264,268]. The results here suggest that patients more at risk of ventricular arrhythmia may be identified in this manner. However, the wide standard deviation should be noted. In patients with LV dysfunction there is a heightened sympathetic state[76]. Basic science work has shown that sympathetic activation steepens the restitution curve[291] and VF is prevented by flattening the curve[262]. Thus, restitution parameters may hold promise for risk stratification purposes.

The data presented here reflects QT and TQ intervals collected over time, as opposed to data collected in animal studies which allow analyses of the whole restitution curve of a specific heart. The method of data collection and analysis does not permit the latter. Similarly, there is no group where these parameters are measured off anti-arrhythmic medication. The data from this study seems to show promise not only in terms of potential risk stratification, but also identification of ICD patients who are more susceptible to arrhythmia. The absence of baseline differences between the groups would seem to suggest a true difference in the derived parameter. Larger studies are required to check the validity of this parameter. In addition normal ranges in healthy individuals need

to be accurately defined. If these are shown to be helpful, they will show that this parameter may be a potential easy non-invasive tool. Similarly, studies assessing dynamic restitution are needed in patients similar to those assessed here, as well as normal controls.

6.7.4 Limitations

Standard 24 hour Holter analysis has some inherent limitations. Data quality can be variable, and over a 24 hour period requires stable electrode contact and can be adversely affected by patient posture and activity. Furthermore, the analysis thereafter is labour intensive to ensure accurate data quality. The measurements here also require the patient to be in stable sinus rhythm. Patients in AF were excluded, as were patients with poor quality recordings and a high ectopic burden. This reduced the patient population in this study affecting the results. This is in addition to the exclusion criteria and other factors mentioned earlier, which reduced patient recruitment further. This feature about the Holter analysis also has real world implication in that many patients with LVSD being considered for ICD therapy are susceptible to arrhythmia which can hamper this form of assessment.

7 Conclusions and Limitations

This study was designed to assess a variety of non invasive measures and their ability to predict ventricular arrhythmia occurrence in a selected population of patients (with LVSD) already deemed to be at high risk of sudden cardiac death as deemed by current NICE guidance[155].

There is a large burden of SCD in the general population, especially amongst those with LVSD[4]. Implantable Cardioverter Defibrillator therapy has been shown to be effective at reducing mortality and morbidity and has been shown to be superior to best medical therapy[142,155,165]. However, it remains an expensive and largely crude palliative treatment. Implantation can be associated with complications and there are physical and psychological issues in patients fitted with these devices[145]. Accurate identification of patients at risk of SCD is thus crucial to ensure patients at high risk of arrhythmia receive ICD therapy to prevent SCD. To date, guideline producing trials have only identified ejection fraction as a prognostic marker[292]. However, it has been established that currently only about 30% of ICD patients receive appropriate therapy for ventricular arrhythmia and a similar number experience often painful inappropriate therapy[147]. Thus, further risk stratification is needed to refine patient selection.

None of the measures analysed were significantly predictive of early arrhythmia occurrence as determined by the use of appropriate ICD therapy as a surrogate in univariate analysis. As a result a multivariate model was not constructed. However, there were some measures that tended towards statistical significance when comparing patients with therapy and no therapy. Median NTproBNP was higher in patients with shocks

compared to those without, but this was not statistically significant with wide interquartile ranges. There was less of a difference when looking at any therapy against no therapy. The results of this study would not support the use of NTproBNP in risk stratification, but there may be a role using it to identify patients at higher risk of appropriate shocks and thus targeting more intensive anti-arrhythmic therapy at this group. As discussed earlier, previous studies have yielded mixed results with some negative and positive results[211].

The ECG restitution parameter QT/TQ ratio>1 was also approaching significance when therapy v no therapy groups were compared and was significant when patients with appropriate shocks were compared to those with no therapy at 2 years. However, predictive accuracy of this seems limited on the basis of this data. As discussed, this represents the time on the restitution slope when stability is less certain[265]. It is possible that patients with ECG restitution characteristics where the QT/TQ ratio>1 for a higher proportion of time have a greater tendency towards arrhythmia. The technique discussed here looks at the overall 24 hour tendency. However, as discussed, this is not the whole restitution slope as generated by programmed stimulation, and only represents a small part of this. This is especially in light of the fact that the patients studied here were in-patients who were sedentary with little heart rate change. In addition there was a high percentage of medication such as β blockers. These drugs are anti-adrenergic and have been shown to reduce sudden death[103,104,293]. Adrenergic stimulation in animal models has shown that the restitution slope steepens with a subsequent lower VF threshold[263]. Similarly, drugs which block the sympathetic system flatten it and convert more unstable

arrhythmia such as VF to more stable VT[263]. Hence, the use of such drugs in patients in this study may have introduced some bias, although as the groups were well matched, this was taken into consideration. Therefore, the technique described here has its limitations and more dynamic protocols may show different results. Even if this is the case, the nature of Holter recording is limited in terms of data quality. Patients had to be excluded in this study for this reason. Furthermore, with a more dynamic protocol, the data may be less reliable. Invasive assessments of restitution may offer more promise in this area, but evidently there are disadvantages with more inherent risk, for example.

Heart rate variability assessment in this study was not shown to be predictive of arrhythmia in the time or frequency domains. Other studies have revealed mixed results, with some positive and some negative studies[289,290]. Overall, the literature and the results from this study, would suggest that HRV is not a good marker in isolation. It is also inherently limited in terms of technique. Firstly, the data produced is very dependent on the quality of the Holter data. A number of patients in this study had to be excluded due to poor quality data or a high ectopic burden. The latter is commonly seen in heart failure populations. Furthermore, patients in AF were excluded, which again removes a significant number of patients. In this study, removal of these patients made the study group smaller. It is possible that a larger study may have yielded different outcomes, not only in terms of HRV, but also with the other measures. Furthermore, given the higher incidence of atrial arrhythmia and ventricular ectopy in heart failure patients, the use of Holter measures is limited. The manual checking of Holter data is also time consuming and not practical in a clinical setting.

The problems with Holter data also affected the QTVI data. Again, a negative result was seen in this study. The much larger MADIT II data did produce different results, but despite this, this parameter is not used in routine clinical practice[277]. Certainly, it is not validated as a prognostic tool, and the data in the current study would not support its use.

Given that there were no statistically significant parameters found in this study, a multivariate analysis was not conducted as was originally planned.

As mentioned earlier, more refinement and examination of cardiac restitution in terms of ECG restitution and 'true' restitution could be helpful. Another marker not examined here is T wave alternans, which has been investigated previously[294]. Microvolt T wave alternans describes the beat to beat variation of the T wave, and can be measured using the Spectral or Modified Moving Average method during exercise testing[295]. Recent meta-analysis and international guidance has concluded that there is insufficient evidence to support this modality in the decision making to implant or withhold ICD therapy[294,295]. Furthermore, a recent study by Jackson and colleagues concluded that a large proportion of heart failure patients were not suitable for exercise testing, limiting the technique and in those who performed the test, the result is often indeterminate[296]. There has also been promise with cardiac MRI looking at the burden of myocardial fibrosis[297,298].

There are numerous mechanisms which influence the possibility of SCD in the failing heart. These include structural, autonomic and neurohormonal factors which have been

discussed earlier. As a result of this, it is unlikely that any one single marker will firstly identify anyone, and secondly have a good negative predictive value as well. This fact is well borne out by the situation with LVEF. Furthermore, changes in heart failure class, LVEF, coronary status, ischaemia and scar will change over time and influence risk, causing the latter to change[292]. Although there is some promise with ECG restitution and NTproBNP, the other measurements in this study do not appear to be helpful in the refinement of patient selection when considering ICD implantation in patients with LVSD. Certainly, further studies here may add to our knowledge and understanding. The size of this study is a clear limitation and has meant that even with some promise with the markers, further subgroup analysis would be impossible. This study was a single site study performed by one researcher. Recruitment took place over two years, but despite this the recruitment was relatively low due to the exclusion of patients with recent acute coronary events and revascularisation as well as the exclusion of patients listed for biventricular implants. The use of appropriate ICD therapy as an endpoint itself may be a limitation as not all arrhythmia which triggers ICD therapy may not have resulted in SCD without intervention. However, a mortality study without the ICD therapy in this high risk population would not be ethical. It is likely, that whatever markers show promise, EF will still be used as part of the decision making process. The fact that ICD evolution has occurred for some time now, and that risk stratification still remains challenging, highlights the difficulties in this important area of cardiology. The EUTrigTreat Clinical Study is a risk stratification study in ICD patients looking at a variety of markers that includes restitution parameters. This is a multi-centre trial that is currently recruiting

patients and may answer some of the questions[299]. Certainly, further studies of restitution measured directly or indirectly, as here, would be valuable.

After completing the study, I feel that there may be promise in further analyses of restitution in terms of arrhythmia risk stratification in this kind of population. In any form of clinical test, a non-invasive approach is preferable. However, in the initial instance, an invasive assessment of human restitution would be interesting. This would take the form of data collection during programmed electrical stimulation during VT stimulation studies. This would allow researchers to investigate the restitution properties in patients deemed to be at high risk of arrhythmia. In addition, those with a negative VT stimulation study could be compared to those with a positive one, and their restitution properties could be compared. This kind of study would also allow comparison of patients in terms of their restitution characteristics who have positive VT stimulation studies and undergo ICD implantation. This would be beneficial as patients who experience arrhythmia (those who experience ICD therapy), could be compared to those that do not. Thus, the restitution properties between these groups could be compared to see if these markers could be used as a predictor of ICD therapy. This form of study could be used to chart restitution curves in individual patients. Non-invasive assessments of restitution could also be done simultaneously. This could be in the form of Holter assessment, and in the form of exercise testing to obtain more of a restitution curve. In terms if the other markers that have been examined in this study, the evidence from this study and other studies show that there may be limited value in further analysis. With regards to the current study, if I were performing it again, I would use a larger population as there are a

number of different parameters within each analysis that diluted the population in each. This could be done with a multi-centre approach. Furthermore, I would have designed the study to ensure that there was reproducibility of the various measures. For example, the Holter recording could be made on 2 separate occasions which would then allow comparison of all the analyses in the same patient to ensure accuracy of analysis and reproducibility. In addition the NTproBNP measurements and ECGs for QTd measurement could be done on 2 separate occasions. Evidently, these repeated assessments would be time consuming and carry logistical consideration, especially if a muti-centre approach is chosen. Finally, it would be preferable that the analyses are conducted by independent blinded persons. Although much of the analyses are automated, thus reducing observer variability, some of the measurements, especially QTd could be repeated by different observers and the findings compared, thus improving accuracy.

8 References

1. Cowie MR, Wood D a, Coats a J, et al. Incidence and aetiology of heart failure; a population-based study. *European heart journal*. 1999;20(6):421–8.

2. Lopshire J ZD. Sudden Cardiac Death. 2006:1124–1136.

3. Kokolis S, Clark LT, Kokolis R, Kassotis J. Ventricular arrhythmias and sudden cardiac death. *Progress in cardiovascular diseases*. 2006;48(6):426–44.

4. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? *Circulation research*. 2004;95(8):754–63.

5. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993-2001. *Heart (British Cardiac Society)*. 2003;89(6):615–20.

6. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. *Circulation*. 1997;96(10):3308–13.

7. Zipes, Douglas P, Heger James J PEN. Sudden Cardiac Death. *Circulation*. 1981:1151–1154.

8. Zipes Douglas P WHJ. Sudden Cardiac Death. *Circulation*. 1998;98:2334–2351.

9. Virmani R, Burke AP, Farb A. Sudden cardiac death. *Cardiovascular Pathology*. 2001;10(5):211–218.

10. Huikuri H, Castellanos A MR. Sudden Death due to Cardiac Arrhythmia. *The New England Journal of Medicine*. 2001;345(20):1473–1482.

11. Myerburg RJ, Mitrani R, Interian A, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. *Circulation*. 1998;97(15):1514–1521.

12. Estes M, Houmoud M, Link M WP. Assessment of risk of Sudden Cardiac Death. *Current Problems in Cardiology*. 2002;27(6):246–266.

13. Kannel WB, Schatzkin A. Sudden death: Lessons from subsets in population studies. *Journal of the American College of Cardiology*. 1985;5(6):141B–149B.

14. Hallstrom AP, Cobb LA, Ray R. Smoking as a Risk Factor for Recurrence of Sudden Cardiac Arrest. *New England Journal of Medicine*. 1986;314(5):271–275.

15. Milan David J MCA. Animal models for arrhythmias. *Cardiovascular Research*. 2005;67:426–437.

16. Saffitz JE. The pathology of sudden cardiac death in patients with ischemic heart disease--arrhythmology for anatomic pathologists. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*. 2005;14(4):195–203.

17. Shah M, Akar FG, Tomaselli GF. Molecular basis of arrhythmias. *Circulation*. 2005;112(16):2517–29.

18. Nass Robert D, Takeshi Aiba, Tomaelli Gordon F AFG. Mechanisms of disease: ion channel remodeling in the failing ventricle. *Nature Clinical Practice Cardiovascular Medicine*. 2007;5(4):196–207.

19. CLARK RB, BOUCHARD RA, GILES WR. Action Potential Duration Modulates Calcium Influx, Na+-Ca2+ Exchange, and Intracellular Calcium Release in Rat Ventricular Myocytesa. *Annals of the New York Academy of Sciences*. 1996;779(1):417–429.

20. Lehnart SE, Ackerman MJ, Benson DW, et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affe. *Circulation*. 2007;116(20):2325–45.

21. Basso C, Carturan E, Pilichou K, et al. Sudden cardiac death with normal heart: molecular autopsy. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*. 2010;19(6):321–5.

22. Bastiaenen R, Behr ER. Sudden death and ion channel disease: pathophysiology and implications for management. *Heart (British Cardiac Society)*. 2011;97(17):1365–72.

23. Kapa S, Tester DJ, Salisbury B a, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. *Circulation*. 2009;120(18):1752–60.

24. Hedley PL, Jørgensen P, Schlamowitz S, et al. The genetic basis of long QT and short QT syndromes: a mutation update. *Human Mutation*. 2009;30(11):1486–1511.

25. Antzelevitch C. Heterogeneity and cardiac arrhythmias: an overview. *Heart rhythm the official journal of the Heart Rhythm Society*. 2007;4(7):964–972.

26. Cross B, Homoud M, Link M, et al. The short QT syndrome. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2011;31(1):25–31.

27. Triedman JK. Brugada and short QT syndromes. *Pacing and clinical electrophysiology : PACE*. 2009;32 Suppl 2(July):S58–62.

28. Antzelevitch C. Cardiac repolarization. The long and short of it. *Europace European pacing arrhythmias and cardiac electrophysiology journal of the working groups on cardiac pacing arrhythmias and cardiac cellular electrophysiology of the European Society of Cardiology*. 2005;7 Suppl 2(s2):3–9.

29. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada Syndrome: Report of the Second Consensus Conference . *Circulation* . 2005;111 (5):659–670.

30. Benito B, Brugada R, Brugada J, Brugada P. Brugada syndrome. *Progress in cardiovascular diseases*. 2008;51(1):1–22.

31. Priori SG, Napolitano C, Memmi M, et al. Clinical and Molecular Characterization of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia . *Circulation* . 2002;106 (1):69–74.

32. Cerrone M, Noujaim SF, Tolkacheva EG, et al. Arrhythmogenic Mechanisms in a Mouse Model of Catecholaminergic Polymorphic Ventricular Tachycardia . *Circulation Research* . 2007;101 (10):1039–1048.

33. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2011;13(8):1077–109.

34. Watkins H, Ashrafian H, Redwood C. Inherited Cardiomyopathies. *New England Journal of Medicine*. 2011;364(17):1643–1656.

35. Ommen SR. Hypertrophic cardiomyopathy. *Current problems in cardiology*. 2011;36(11):409–53.

36. Azaouagh A, Churzidse S, Konorza T, Erbel R. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2011;100(5):383–94.

37. Francés RJ. Arrhythmogenic right ventricular dysplasia/cardiomyopathy. A review and update. *International journal of cardiology*. 2006;110(3):279–287.

38. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. *Progress in cardiovascular diseases*. 2008;51(3):213–28.

39. Excellence NI for H and C. Chronic heart failure. *National Institute for Health and Clinical Excellence*. 2010;(August).

40. Marrouche NF, Verma A, Wazni O, et al. Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. *Journal of the American College of Cardiology*. 2004;43(9):1715–20.

41. Janse MJ. Electrophysiological changes in heart failure and their relationship to arrhythmogenesis . *Cardiovascular Research* . 2004;61 (2):208–217.

42. Saffitz J, Hames K, Kanno S. Remodeling of Gap Junctions in Ischemic and Nonischemic Forms of Heart Disease. *Journal of Membrane Biology*. 2007;218(1):65–71.

43. Minicucci MF, Azevedo PS, Polegato BF, Paiva SAR, Zornoff LAM. Heart Failure After Myocardial Infarction: Clinical Implications and Treatment. *Clinical Cardiology*. 2011;34(7):410–414.

44. Lim H, Fallavollita JA, Hard R, Kerr CW, Canty JM. Profound Apoptosis-Mediated Regional Myocyte Loss and Compensatory Hypertrophy in Pigs With Hibernating Myocardium . *Circulation* . 1999;100 (23):2380–2386.

45. Luk A, Ahn E, Soor GS, Butany J. Dilated cardiomyopathy: a review . *Journal of Clinical Pathology* . 2009;62 (3):219–225.

46. Akar FG, Tomaselli GF. Conduction abnormalities in nonischemic dilated cardiomyopathy: basic mechanisms and arrhythmic consequences. *Trends in cardiovascular medicine*. 2005;15(7):259–64.

47. LOPERA G, STEVENSON WG, SOEJIMA K, et al. Identification and Ablation of Three Types of Ventricular Tachycardia Involving the His-Purkinje System in Patients with Heart Disease. *Journal of Cardiovascular Electrophysiology*. 2004;15(1):52–58.

48. Richard S, Leclercq F, Lemaire S, Piot C, Nargeot J. Ca2+ currents in compensated hypertrophy and heart failure . *Cardiovascular Research* . 1998;37 (2):300–311.

49. Winslow RL, Rice J, Jafri S, Marbán E, O'Rourke B. Mechanisms of Altered Excitation-Contraction Coupling in Canine Tachycardia-Induced Heart Failure, II : Model Studies . *Circulation Research* . 1999;84 (5):571–586.

50. Marx SO, Reiken S, Hisamatsu Y, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*. 2000;101(4):365–76.

51. Pogwizd S. Intracellular Na in animal models of hypertrophy and heart failure: contractile function and arrhythmogenesis. *Cardiovascular Research*. 2003;57(4):887–896.

52. Poelzing S, Rosenbaum DS. Nature, significance, and mechanisms of electrical heterogeneities in ventricle. *The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology*. 2004;280A(2):1010–1017.

53. Michael G, Xiao L, Qi X-Y, Dobrev D, Nattel S. Remodelling of cardiac repolarization: how homeostatic responses can lead to arrhythmogenesis . *Cardiovascular Research* . 2009;81 (3):491–499.

54. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation*. 1983;67(6):1356–1367.

55. Shimizu W, Antzelevitch C. Sodium Channel Block With Mexiletine Is Effective in Reducing Dispersion of Repolarization and Preventing Torsade de Pointes in LQT2 and LQT3 Models of the Long-QT Syndrome . *Circulation* . 1997;96 (6):2038–2047.

56. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *The Journal of Clinical Investigation*. 2005;115(9):2305–2315.

57. Vaseghi M SS. The role on the autonomic nervous system in sudden cardiac death. *Progress in Cardiovascular Diseases*. 2008;50(6):404–419.

58. Zipes DP. Heart-brain interactions in cardiac arrhythmias: role of the autonomic nervous system. . *Cleveland Clinic Journal of Medicine* . 2008;75 (Suppl 2):S94.

59. Bylund DB, Eikenberg DC, Hieble JP, et al. International Union of Pharmacology nomenclature of adrenoceptors. . *Pharmacological Reviews* . 1994;46 (2):121–136.

60. Rozec B, Gauthier C. Beta3-Adrenoceptors in the Cardiovascular System: Putative Roles in Human Pathologies. *Pharmacology & therapeutics*. 2006;111(3):652–73.

61. Triposkiadis F, Karayannis G, Giamouzis G, et al. The Sympathetic Nervous System in Heart Failure: Physiology, Pathophysiology, and Clinical Implications. *Journal of the American College of Cardiology*. 2009;54(19):1747–1762.

62. Dorian P. Antiarrhythmic Action of -Blockers: Potential Mechanisms. *Journal of Cardiovascular Pharmacology and Therapeutics*. 2005;10(4 suppl):S15–S22.

63. Schwartz PJ. Vagal Stimulation for Heart Diseases: From Animals to Men. *Circulation Journal*. 2011;75(1):20–27.

64. Bibevski S, Dunlap ME. Evidence for impaired vagus nerve activity in heart failure. *Heart failure reviews*. 2011;16(2):129–35.

65. Barber MJ, Mueller TM, Davies BG, Gill RM, Zipes DP. Interruption of sympathetic and vagal-mediated afferent responses by transmural myocardial infarction. *Circulation*. 1985;72(3):623–631.

66. Lamba S, Abraham WT. Alterations in Adrenergic Receptor Signaling in Heart Failure. *Heart Failure Reviews*. 2000;5(1):7–16.

67. Kaye DM, Lefkovits J, Jennings GL, et al. Adverse consequences of high sympathetic nervous activity in the failing human heart. *Journal of the American College of Cardiology*. 1995;26(5):1257–1263.

68. Cohn JN, Levine TB, Olivari MT, et al. Plasma Norepinephrine as a Guide to Prognosis in Patients with Chronic Congestive Heart Failure. *New England Journal of Medicine*. 1984;311(13):819–823.

69. Rundqvist B, Elam M, Bergmann-Sverrisdottir Y, Eisenhofer G, Friberg P. Increased Cardiac Adrenergic Drive Precedes Generalized Sympathetic Activation in Human Heart Failure . *Circulation* . 1997;95 (1):169–175.

70. Hasking GJ, Esler MD, Jennings GL, et al. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. . *Circulation* . 1986;73 (4):615–621.

71. Kaye DM, Lambert GW, Lefkovits J, et al. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *Journal of the American College of Cardiology*. 1994;23(3):570–578.

72. Esler M, Kaye D. Sympathetic Nervous System Activation in Essential Hypertension, Cardiac Failure and Psychosomatic Heart Disease. *Journal of Cardiovascular Pharmacology*. 2000;35.

73. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *Journal of the American College of Cardiology*. 1992;20(1):248–254.

74. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *Journal of the American College of Cardiology*. 2009;54(5):375–85.

75. Han J, Garcia de Jalon P, Moe GK. Adrenergic Effects on Ventricular Vulnerability. *Circulation research*. 1964;14:516–24.

76. P AK. Sympathetic Nervous System Activity and Ventricular Tachyarrhythmias: Recent Advances - Anderson - 2. *A.N.E.* 2003;8(1):75–89.

77. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. *Circulation*. 1983;67(4):787–796.

78. Cao J, Fishbein MC, Han JB, et al. Relationship between Regional Cardiac Hyperinnervation and Ventricular Arrhythmia. *Circulation*. 2000;101:1960–1969.

79. Dillon SM, Allessie M a, Ursell PC, Wit AL. Influences of anisotropic tissue structure on reentrant circuits in the epicardial border zone of subacute canine infarcts. *Circulation Research*. 1988;63(1):182–206.

80. Cao J, Chen LS, Kenknight BH, et al. Nerve Sprouting and Sudden Cardiac Death. *Circulation Research*. 2000;86:816–821.

81. Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure . *European Heart Journal* . 2001;22 (13):1136–1143.

82. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure . *European Heart Journal* . 2012;33 (9):1058–1066.

83. Bibevski S, Dunlap ME. Prevention of diminished parasympathetic control of the heart in experimental heart failure . *American Journal of Physiology - Heart and Circulatory Physiology* . 2004;287 (4):H1780–H1785.

84. Eckberg DL, Drabinsky M, Braunwald E. Defective Cardiac Parasympathetic Control in Patients with Heart Disease. *New England Journal of Medicine*. 1971;285(16):877–883.

85. Mortara A, La Rovere MT, Pinna GD, et al. Arterial Baroreflex Modulation of Heart Rate in Chronic Heart Failure : Clinical and Hemodynamic Correlates and Prognostic Implications . *Circulation* . 1997;96 (10):3450–3458.

86. Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. . *Circulation* . 1982;66 (4):874–880.

87. Billman GE. Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training . *American Journal of Physiology - Heart and Circulatory Physiology* . 2009;297 (4):H1171–H1193.

88. Schwartz PJ, La Rovere MT. ATRAMI: a mark in the quest for the prognostic value of autonomic markers . *European Heart Journal* . 1998;19 (11):1593–1595.

89. Nishime E Blackstone EH, Pashkow FJ, Lauer MS CCR. HEart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ecg. *JAMA: The Journal of the American Medical Association*. 2000;284(11):1392–1398.

90. Li M, Zheng C, Sato T, et al. Vagal Nerve Stimulation Markedly Improves Long-Term Survival After Chronic Heart Failure in Rats . *Circulation* . 109 (1):120–124.

91. De Ferrari GM, Crijns HJGM, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure . *European Heart Journal* . 2011;32 (7):847–855.

92. Sobotka P a, Krum H, Böhm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. *Current cardiology reports*. 2012;14(3):285–92.

93. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. . *Circulation* . 1981;63 (3):645–651.

94. Hillege HL, Girbes ARJ, de Kam PJ, et al. Renal Function, Neurohormonal Activation, and Survival in Patients With Chronic Heart Failure . *Circulation* . 2000;102 (2):203–210.

95. Carey RM, Siragy HM. Newly Recognized Components of the Renin-Angiotensin System: Potential Roles in Cardiovascular and Renal Regulation . *Endocrine Reviews* . 2003;24 (3):261–271.

96. Benavente D, Chue CD, Ferro CJ. THE IMPORTANCE OF RENIN-ANGIOTENSIN BLOCKADE IN PATIENTS WITH CARDIO-RENAL DISEASE. *Journal of Renal Care*. 2010;36:97–105.

97. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure . *European Heart Journal* . 26 (9):906–913.

98. Solal AC, Jondeau G, Beauvais F, Berdeaux A. Beneficial effects of carvedilol on angiotensin-converting enzyme activity and renin plasma levels in patients with chronic heart failure . *European Journal of Heart Failure* . 2004;6 (4):463–466.

99. Fung JWH, Yu CM, Yip G, et al. Effect of beta blockade (carvedilol or metoprolol) on activation of the renin-angiotensin-aldosterone system and natriuretic peptides in chronic heart failure. *The American Journal of Cardiology*. 2003;92(4):406–410.

100. Holmer SR, Hense H-W, Danser AHJ, et al. β Adrenergic blockers lower renin in patients treated with ACE inhibitors and diuretics . *Heart* . 1998;80 (1):45–48.

101. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *The American journal of cardiology*. 1983;51(7):1196–202.

102. Lechat P, Investigators C. A Randomized Trial of / -Blockade in Heart Failure The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;90:1765–1773.

103. Investigators C. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9–13.

104. Group MS. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001–7.

105. Packer et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. *The New England Journal of Medicine*. 2001;344(22):1651–1658.

106. Arshad A, Mandava A, Kamath G, Musat D. Sudden cardiac death and the role of medical therapy. *Progress in cardiovascular diseases*. 2008;50(6):420–38.

.

107. Rouleau JL, Roecker EB, Tendera M, et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Journal of the American College of Cardiology*. 2004;43(8):1423–9.

108. Anon. A Trial of the Beta-Blocker Bucindolol in Patients with Advanced Chronic Heart Failure. *New England Journal of Medicine*. 2001;344(22):1659–1667.

109. Anon. Timolol-Induced Reduction in Mortality and Reinfarction in Patients Surviving Acute Myocardial Infarction. *New England Journal of Medicine*. 1981;304(14):801–807.

110. McMurray J, Køber L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: Results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *Journal of the American College of Cardiology*. 2005;45(4):525–530.

111. Furberg CD, Yusuf S. Effect of drug therapy on survival in chronic congestive heart failure. *The American Journal of Cardiology*. 1988;62(2):41A–45A.

112. Anon. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *Journal of the American College of Cardiology*. 1983;2(4):755–763.

113. Group TC trial study. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. *New England Journal of Medicine*. 1987;316(23):1429–1435.

114. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation*. 1990;82(5):1730–1736.

115. Investigators TS. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. *The New England Journal of Medicine*. 1991;325(5):293–302.

116. Garg Rekha YS. Overview of Randomized Trials of Angiotensin-Converting Enzyme Inhibitors on Mortality and Morbidity in Patients with Heart Failure. *JAMA*. 1995;273(15):1450–1456.

117. ALBERTE C, ZIPES DP. Use of Nonantiarrhythmic Drugs for Prevention of Sudden Cardiac Death. *Journal of Cardiovascular Electrophysiology*. 2003;14:S87–S95.

118. Domanski MJ, Exner DV, Borkowf CB, et al. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarctionA meta-analysis of randomized clinical trials. *Journal of the American College of Cardiology*. 1999;33(3):598–604.

119. Lee VC, Rhew DC, Dylan M, et al. Meta-Analysis: Angiotensin-Receptor Blockers in Chronic Heart Failure and High-Risk Acute Myocardial Infarction. *Annals of Internal Medicine*. 2004;141(9):693–704.

120. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *The Lancet*. 1997;349(9054):747–752.

121. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *The Lancet*. 2000;355(9215):1582–1587.

122. Cohn NJ et al. A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure. *The New England Journal of Medicine*. 2001;345(23):1667–1675.

123. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and Morbidity Reduction With Candesartan in Patients With Chronic Heart Failure and Left Ventricular Systolic Dysfunction . *Circulation* . 2004;110 (17):2618–2626.

124. Pitt B, Zannad F, Remme W, Cody R. THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE. *The New England Journal of Medicine*. 1999;341(10):709–717.

125. Pitt B, Williams G, Remme W, et al. The EPHESUS Trial : Eplerenone in Patients with Heart Failure Due to Systolic Dysfunction Complicating Acute Myocardial Infarction. *Cardiovascular Drugs and Therapy*. 2001:79–87.

126. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Journal of the American College of Cardiology*. 2005;46(3):425–31.

127. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. *New England Journal of Medicine*. 2010;364(1):11–21.

128. Grassi G, Cattaneo BM, Seravalle G, et al. Effects of Chronic ACE Inhibition on Sympathetic Nerve Traffic and Baroreflex Control of Circulation in Heart Failure . *Circulation* . 1997;96 (4):1173–1179.

129. Ramchandra R, Hood SG, Watson AMD, Allen AM, May CN. Central Angiotensin Type 1 Receptor Blockade Decreases Cardiac But Not Renal Sympathetic Nerve Activity in Heart Failure . *Hypertension* . 2012;59 (3):634–641.

130. Binkley PF, Haas GJ, Starling RC, et al. Sustained augmentation of parasympathetic tone with angiotensin-converting enzyme inhibition in patients with congestive heart failure. *Journal of the American College of Cardiology*. 1993;21(3):655–661.

131. Osterziel KJ, Dietz R. Improvement of Vagal Tone by ACE Inhibition: A Mechanism of Cardioprotection in Patients with Mild-to-Moderate Heart Failure. *Journal of Cardiovascular Pharmacology*. 1996;27.

132. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients . *Cardiovascular Research* . 1997;35 (1):30–34.

133. Barr CS, Lang CC, Hanson J, et al. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *The American Journal of Cardiology*. 1995;76(17):1259–1265.

134. Sim Ida, McDonald Kathryn, Lavori Phiip, Norbutas Catherine HM. Quantitative Overview of Randomized Trials of Amiodarone to Prevent Sudden Cardiac Death. *Circulation*. 1997;96:2823–2829.

135. Singh S, Fletcher R, Fisher S, Singh B, Lewis H, Deedwania P, Massie B, Colling C LD. Amiodarone in Patients with Congestive Heart Failure and Asymptomatic Ventricular Arrhythmia. *The New England Journal of Medicine*. 1995;333(2):77–82.

136. Cairns JA, Connolly SJ, Roberts R, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations : CAMIAT. *The Lancet*. 1997;349:675–682.

137. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction : EMIAT. *The Lancet*. 1997;349:667–674.

138. Investigators TCASTI. Effect of the Antiarrhythmic agent Moricizine on Survival after Myocardial Infarction. *The New England Journal of Medicine*. 1992;327:227–233.

139. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in Patients with Congestive Heart Failure and Left Ventricular Dysfunction. *New England Journal of Medicine*. 1999;341(12):857–865.

140. Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? *Journal of the American College of Cardiology*. 1997;30(7):1589–97.

141. Janse MJ. A brief history of sudden cardiac death and its therapy. *Pharmacology & Therapeutics*. 2003;100(1):89–99.

142. Siddiqui A KP. Sudden Death secondary to Cardiac Arrhythmias: mechanisms and treatment strategies. *Curr Opinion Cardiol*. 1006;21:517–525.

143. Albouaini K, Mudawi T, Pyatt JR, Wright DJ. Implantable cardioverter defibrillator: what a hospital practitioner needs to know. *European journal of internal medicine*. 2009;20(6):591–7.

144. Freeman JV, Wang Y, Curtis JP, Heidenreich P a, Hlatky M a. The relation between hospital procedure volume and complications of cardioverter-defibrillator implantation from the implantable cardioverter-defibrillator registry. *Journal of the American College of Cardiology*. 2010;56(14):1133–9.

145. Borek PP, Wilkoff BL. Pacemaker and ICD leads: strategies for long-term management. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2008;23(1):59–72.

146. Freedenberg V, Thomas SA, Friedmann E. Anxiety and Depression in Implanted Cardioverter-Defibrillator Recipients and Heart Failure: A Review. *Heart Failure Clinics*. 2011;7(1):59–68.

147. van Welsenes GH, van Rees JB, Borleffs CJW, et al. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2011;13(3):389–94.

148. Groarke JD, Buckley U, Collison D, et al. Cost implications of defibrillator lead failures . *Europace* . 2012.

149. Bhatia A, Cooley R, Berger M, et al. The implantable cardioverter defibrillator: technology, indications, and impact on cardiovascular survival. *Current problems in cardiology*. 2004;29(6):303–56.

150. Wathen M. Implantable cardioverter defibrillator shock reduction using new antitachycardia pacing therapies. *American heart journal*. 2007;153(4 Suppl):44–52.

151. Banna M, Indik JH. Risk stratification and prevention of sudden death in patients with heart failure. *Current treatment options in cardiovascular medicine*. 2011;13(6):517–27.

152. Wyse DG, Friedman PL, Epstein AE. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *The New England Journal of Medicine*. 1997;337(22):1576–1583.

153. Sheldon R, Connolly S, Krahn A, et al. Identification of Patients Most Likely to Benefit From Implantable Cardioverter-Defibrillator Therapy. The Canadian Implantable Defibrillator Study. *Circulation*. 2000;101:1660–1664.

154. Kuck K, Cappato R, Siebels J, Rüppel R. Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest. The Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000;102:748–754.

155. National Institute for Health and Clinical Excellence. Implantable cardioverter defibrillators for arrhythmias. *NICE*. 2007.

156. Moss AJ, Hall WJ, Cannom DS, et al. Improved Survival with an Implanted Defibrillator in Patients with Coronary Disease at High Risk for Ventricular Arrhythmia. *New England Journal of Medicine*. 1996;335(26):1933–1940.

157. Buxton AE, Lee KL, Fisher JD, et al. A Randomized Study of the Prevention of Sudden Death in Patients with Coronary Artery Disease. *New England Journal of Medicine*. 1999;341(25):1882–1890.

158. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *New England Journal of Medicine*. 2002;346(12):877–883.

159. Bigger JT. Prophylactic Use of Implanted Cardiac Defibrillators in Patients at High Risk for Ventricular Arrhythmias after Coronary-Artery Bypass Graft Surgery. *New England Journal of Medicine*. 1997;337(22):1569–1575.

160. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic Use of an Implantable Cardioverter–Defibrillator after Acute Myocardial Infarction. *New England Journal of Medicine*. 2004;351(24):2481–2488.

161. Bänsch D, Antz M, Boczor S, et al. Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy . *Circulation* . 2002;105 (12):1453–1458.

162. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. *New England Journal of Medicine*. 2005;352(3):225–237.

163. Kadish A, Dyer A, Daubert JP, et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy. *New England Journal of Medicine*. 2004;350(21):2151–2158.

164. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone Versus Implantable Cardioverter-Defibrillator : Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia — AMIOVIRT. *Journal of the American College of Cardiology*. 2003;41(10):1707–1712.

165. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. *Journal of the American College of Cardiology*. 2004;44(11):2166–72.

166. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. *Circulation*. 2008;117(21):e350–e408.

167. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary . *European Heart Journal* . 2006;27 (17):2099–2140.

168. John Camm A, Nisam S. European utilization of the implantable defibrillator: has 10 years changed the “enigma”? . *Europace* . 2010;12 (8):1063–1069.

169. Plummer CJ, Irving RJ, McComb JM. The incidence of implantable cardioverter defibrillator indications in patients admitted to all coronary care units in a single district . *Europace* . 2005;7 (3):266–272.

170. Freeman R. Assessment of cardiovascular autonomic function. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2006;117(4):716–30.

171. Stein PK, Bosner MS, Kleiger RE, Conger BM, Louis BSS. Heart rate variability : autonomic tone A measure of cardiac. *American Heart Journal*. 1994;127:1376–1381.

172. BILCHICK KC, BERGER RD. Heart Rate Variability. *Journal of Cardiovascular Electrophysiology*. 2006;17(6):691–694.

173. Malik M et al. Heart Rate Variability : Standards of Measurement, Physiological Interpretation, and Clinical Use. *Circulation*. 1996;127(5):1043–1065.

174. Reed MJ, Robertson CE, Addison PS. Heart rate variability measurements and the prediction of ventricular arrhythmias . *QJM* . 2005;98 (2):87–95.

175. Eckberg DL. Sympathovagal Balance . *Circulation* . 1997;96 (9):3224–3232.

176. Furlan R, Guzzetti S, Crivellaro W, et al. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects . *Circulation* . 1990;81 (2):537–547.

177. Malliani A. The Pattern of Sympathovagal Balance Explored in the Frequency Domain . *Physiology* . 1999;14 (3):111–117.

178. Huikuri HV, Mäkikallio T, Airaksinen KE, et al. Measurement of heart rate variability: a clinical tool or a research toy? *Journal of the American College of Cardiology*. 1999;34(7):1878–83.

179. Bigger JT, Fleiss JL, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction . *Circulation* . 1992;85 (1):164–171.

180. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain . *Circulation* . 1991;84 (2):482–492.

181. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog . *Circulation Research* . 1986;59 (2):178–193.

182. Akselrod S, Gordon D, Ubel F, Shannon D, Berger A CR. Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of beat-to-beat cardiovascular control. *Science*. 1981;213(July):220–222.

183. Malliani A, Lombardi F PM. Power Spectrum analysis of heart rate variability:a tool to explore neural regulatory mechanisms. *British Heart Journal*. 1994;71:1–2.

184. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis . *American Journal of Physiology - Heart and Circulatory Physiology* . 1985;248 (1):H151–H153.

185. Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope . *Circulation* . 1990;81 (6):1803–1810.

186. Malpas SC, Purdie GL. Circadian variation of heart rate variability . *Cardiovascular Research* . 1990;24 (3):210–213.

187. Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death . *Circulation* . 1987;75 (1):131–138.

188. Willich SN, Levy D, Tofler GH, Stone PH. Circadian Variation in the Incidence o Death in the Framingham Heart Study Population. *Cardiology*. 1987;60:801–806.

189. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease . *Circulation* . 1989;79 (4):733–743.

190. Stein PK. Assessing Heart Rate Variability from Real-World Holter Reports. *Cardiac Electrophysiology Review*. 2002;6(3):239–244.

191. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients . *Heart* . 2004;90 (11):1248–1255.

192. Kleiger RE, Miller JP, Bigger JT, Moss a J. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *The American journal of cardiology*. 1987;59(4):256–62.

193. Teresa M, Rovere L, Jr JTB, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *The Lancet*. 1998;351:478–484.

194. La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex Sensitivity and Heart Rate Variability in the Identification of Patients at Risk for Life-Threatening Arrhythmias : Implications for Clinical Trials . *Circulation* . 2001;103 (16):2072–2077.

195. Boveda S, Galinier M, Pathak A, et al. Prognostic Value of Heart Rate Variability in Time Domain Analysis in Congestive Heart Failure. *Journal of Interventional Cardiac Electrophysiology*. 2001;5(2):181–187.

196. Bonaduce D, Petretta M, Marciano F, et al. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. *American Heart Journal*. 1999;138(2 Pt 1):273–284.

197. Nolan J, Flapan AD, Capewell S, et al. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. *British Heart Journal*. 1992;67(6):482–485.

198. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998;98(15):1510–1516.

199. Sandercock GRH, Brodie DA. The role of heart rate variability in prognosis for different modes of death in chronic heart failure. *Pacing and clinical electrophysiology PACE*. 2006;29(8):892–904.

200. Mäkikallio TH, Huikuri HV, Hintze U, et al. Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *The American journal of cardiology*. 2001;87(2):178–82.

201. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *The American Journal of Cardiology*. 1997;79:1645–1650.

202. Fauchier L, Babuty D, Cosnay P, Autret ML, Fauchier JP. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *Journal of the American College of Cardiology*. 1997;30(4):1009–14.

203. Jiang W, Hathaway WR, McNulty S, et al. Ability of heart rate variability to predict prognosis in patients with advanced congestive heart failure. *The American journal of cardiology*. 1997;80(6):808–11.

204. Aronson D, Mittleman M BA. Measures of Heart Period Variability as Predictors of Mortality in Hospitalized Patients with Decompensated Congestive Heart Failure. *American Journal of Cardiology*. 2004;93:59–63.

205. Hadase M, Azuma A, Zen K, et al. Very low frequency power of heart rate variability is a powerful predictor of clinical prognosis in patients with congestive heart failure. *Circulation journal : official journal of the Japanese Circulation Society*. 2004;68(4):343–7.

206. Guzzetti S, Rovere MTL, Pinna GD, et al. Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure . *European Heart Journal* . 26 (4):357–362.

207. Bilchick KC, Fetics B, Djoukeng R, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). *The American journal of cardiology*. 2002;90(1):24–8.

208. Fauchier L, Babuty D, Cosnay P, Fauchier JP. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *Journal of the American College of Cardiology*. 1999;33(5):1203–7.

209. Galinier M, Pathak A, Fourcade J, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure . *European Heart Journal* . 2000;21 (6):475–482.

210. Daniels LB, Maisel AS. Natriuretic peptides. *Journal of the American College of Cardiology*. 2007;50(25):2357–68.

211. Scott PA, Barry J, Roberts PR, Morgan JM. Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: a meta-analysis . *European Journal of Heart Failure* . 2009;11 (10):958–966.

212. Hall C. Essential biochemistry and physiology of (NT-pro)BNP . *European Journal of Heart Failure* . 2004;6 (3):257–260.

213. Cheung BMY, Kumana CR. Natriuretic Peptides—Relevance in Cardiovascular Disease . *JAMA: The Journal of the American Medical Association* . 1998;280 (23):1983–1984.

214. McDonagh TA, Cunningham AD, Morrison CE, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population . *Heart* . 2001;86 (1):21–26.

215. Groenning BA, Raymond I, Hildebrandt PR, et al. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population . *Heart* . 2004;90 (3):297–303.

216. O'Donoghue M BE. Natriuretic peptides in heart failure: should therapy be guided by BNP levels? *Nature Reviews Cardiology*. 2010;7:13–20.

217. Ng LL, Loke I, Davies JE, et al. Identification of previously undiagnosed left ventricular systolic dysfunction: community screening using natriuretic peptides and electrocardiography . *European Journal of Heart Failure* . 2003;5 (6):775–782.

218. Doust JA, Pietrzak E, Dobson A, Glasziou PP. How well does B-type natriuretic peptide predice death and cardiac events in patients with heart failure : systematic review. *BMJ*. 2005;330(March):625–634.

219. Masson S, Latini R, Anand IS, et al. Prognostic Value of Changes in N-Terminal Pro-Brain Natriuretic Peptide in Val-HeFT (Valsartan Heart Failure Trial). *Journal of the American College of Cardiology*. 2008;52(12):997–1003.

220. Anand IS, Fisher LD, Chiang Y-T, et al. Changes in Brain Natriuretic Peptide and Norepinephrine Over Time and Mortality and Morbidity in the Valsartan Heart Failure Trial (Val-HeFT) . *Circulation* . 2003;107 (9):1278–1283.

221. van Veldhuisen DJ, Genth-Zotz S, Brouwer J, et al. High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. *Journal of the American College of Cardiology*. 1998;32(7):1811–8.

222. Palazzuoli A, Gallotta M, Quatrini I, Nuti R. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. *Vascular health and risk management*. 2010;6:411–8.

223. Rosenberg J, Gustafsson F, Remme W, Riegger G, Hildebrandt P. Effect of Beta-blockade and ACE Inhibition on B-type Natriuretic Peptides in Stable Patients with Systolic Heart Failure. *Cardiovascular Drugs and Therapy*. 2008;22(4):305–311.

224. Tsutamoto T, Wada a, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *Journal of the American College of Cardiology*. 2001;37(5):1228–33.

225. Gundogdu F, Bozkurt E, Kiziltunc A, et al. The Effect of Beta-Blocker (Carvedilol) Therapy on N-Terminal Pro-Brain Natriuretic Peptide Levels and Echocardiographic Findings in Patients with Congestive Heart Failure. *Echocardiography*. 2007;24(2):113–117.

226. Shiga T, Hosaka F, Wakaumi M, et al. Amiodarone decreases plasma brain natriuretic peptide level in patients with heart failure and ventricular tachyarrhythmia. *Cardiovascular drugs and therapy*. 2003;17(4):325–33.

227. Bayes-Genis A, Vazquez R, Puig T, et al. Left atrial enlargement and NT-proBNP as predictors of sudden cardiac death in patients with heart failure . *European Journal of Heart Failure* . 2007;9 (8):802–807.

228. Tapanainen JM, Lindgren KS, Mäkikallio TH, et al. Natriuretic peptides as predictors of non-sudden and sudden cardiac death after acute myocardial infarction in the beta-blocking era. *Journal of the American College of Cardiology*. 2004;43(5):757–63.

229. Berger R, Huelsman M, Strecker K, et al. B-Type Natriuretic Peptide Predicts Sudden Death in Patients With Chronic Heart Failure . *Circulation* . 2002;105 (20):2392–2397.

230. Tigen K, Karaahmet T, Kahveci G, et al. N-terminal pro brain natriuretic peptide to predict prognosis in dilated cardiomyopathy with sinus rhythm. *Heart, lung & circulation*. 2007;16(4):290–4.

231. Verma A, Kilicaslan F, Martin DO, et al. Preimplantation B-type natriuretic peptide concentration is an independent predictor of future appropriate implantable defibrillator therapies . *Heart* . 2006;92 (2):190–195..

232. Blangy H, Sadoul N, Dousset B, et al. Serum BNP, hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction . *Europace* . 2007;9 (9):724–729.

233. Klingenberg R, Zugck C, Becker R, et al. Raised B-type natriuretic peptide predicts implantable cardioverter-defibrillator therapy in patients with ischaemic cardiomyopathy . *Heart* . 2006;92 (9):1323–1324.

234. Klein G, Lissel C, Fuchs A-C, et al. Predictors of VT/VF-occurrence in ICD patients: results from the PROFIT-Study . *Europace* . 2006;8 (8):618–624.

235. Battipaglia I, Barone L, Mariani L, et al. Relationship between cardiac autonomic function and sustained ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillators . *Europace* . 2010;12 (12):1725–1731.

236. Budeus M, Reinsch N, Wieneke H, Sack S, Erbel R. The prediction of ICD therapy in multicenter automatic defibrillator implantation trial (MADIT) II like patients : a retrospective analysis. *Indian Pacing And Electrophysiology Journal*. 2008;8(2):80–93.

237. Manios EG, Kallergis EM, Kanoupakis EM, et al. Amino-terminal pro-brain natriuretic peptide predicts ventricular arrhythmogenesis in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillators. *Chest*. 2005;128(4):2604–10.

238. Nagahara D, Nakata T, Hashimoto A, et al. Predicting the Need for an Implantable Cardioverter Defibrillator Using Cardiac Metaiodobenzylguanidine Activity Together with Plasma Natriuretic Peptide Concentration or Left Ventricular Function . *Journal of Nuclear Medicine* . 49 (2):225–233.

239. Yu H, Oswald H, Gardiwal A, Lissel C, Klein G. Comparison of N-terminal pro-brain natriuretic peptide versus electrophysiologic study for predicting future outcomes in patients with an implantable cardioverter defibrillator after myocardial infarction. *The American journal of cardiology*. 2007;100(4):635–9.

240. Konstantino Y, Kusniec J, Reshef T, et al. Inflammatory Biomarkers are not Predictive of Intermediate-term Risk of Ventricular Tachyarrhythmias in Stable CHF Patients. *Clinical Cardiology*. 2007;30(8):408–413.

241. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *Journal of the American College of Cardiology*. 2000;36(6):1749–66.

242. Bluzaite I, Brazdzionyte J, Zaliūnas R, Rickli H, Ammann P. QT dispersion and heart rate variability in sudden death risk stratification in patients with ischemic heart disease. *Medicina (Kaunas, Lithuania)*. 2006;42(6):450–4.

243. Day P, McComb J CR. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *British Heart Journal*. 1990;63(6):342–4.

244. Sahu P, Lim PO, Rana BS, Struthers AD. QT dispersion in medicine: electrophysiological Holy Grail or fool's gold? . *QJM* . 2000;93 (7):425–431.

245. Zabel M, Lichtlen PR, Haverich A, Franz MR. Comparison of ECG variables of dispersion of ventricular repolarization with direct myocardial repolarization measurements in the human heart. *Journal of Cardiovascular Electrophysiology*. 1998;9(12):1279–1284.

246. Batchvarov V, Malik M. Measurement and interpretation of QT dispersion. *Progress in cardiovascular diseases*. 2000;42(5):325–44.

247. Glancy JM, Weston PJ, Bhullar HK, et al. Reproducibility and automatic measurement of QT dispersion . *European Heart Journal* . 1996;17 (7):1035–1039.

248. Campbell RWF, Gardiner P, Amos PA, Chadwick D, Jordan RS. Measurement of the QT Interval . *European Heart Journal* . 1985;6 (suppl D):81–83.

249. Turrini P, Corrado D, Basso C, Nava A, Thiene G. Noninvasive Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy. *Annals of Noninvasive Electrocardiology*. 2003;8(2):161–169.

250. Galinier M, Vialette J-C, Fourcade J, et al. QT interval dispersion as a predictor of arrhythmic events in congestive heart failure . *European Heart Journal* . 1998;19 (7):1054–1062.

251. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lance*. 1994;343(8893):327–329.

252. Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? *British Heart Journal*. 1994;71(6):511–514.

253. Grimm W, Steder U, Menz V, Hoffmann J, Maisch B. QT Dispersion and Arrhythmic Events in Idiopathic Dilated Cardiomyopathy. *American Journal of Cardiology*. 1996;78:458–461.

254. Fu G-S, Meissner A, Simon R. Repolarization dispersion and sudden cardiac death in patients with impaired left ventricular function . *European Heart Journal* . 1997;18 (2):281–289.

255. Fei L, Goldman JH, Prasad K, et al. QT dispersion and RR variations on 12-lead ECGs in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy . *European Heart Journal* . 1996;17 (2):258–263.

256. Pedretti RF, Catalano O, Ballardini L, et al. Prognosis in myocardial infarction survivors with left ventricular dysfunction is predicted by electrocardiographic RR interval but not QT dispersion. *International journal of cardiology*. 1999;68(1):83–93.

257. Davey PP, Bateman J, Mulligan IP, et al. QT interval dispersion in chronic heart failure and left ventricular hypertrophy: relation to autonomic nervous system and Holter tape abnormalities. *British Heart Journal*. 1994;71(3):268–273.

258. Perkiömäki JS, Koistinen MJ, Yli-Mäyry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *Journal of the American College of Cardiology*. 1995;26(1):174–9.

259. Perkiömäki JS, Huikuri HV, Koistinen JM, et al. Heart rate variability and dispersion of QT interval in patients with vulnerability to ventricular tachycardia and ventricular fibrillation after previous myocardial infarction. *Journal of the American College of Cardiology*. 1997;30(5):1331–8.

260. Fauchier L, Douglas J, Babuty D, Cosnay P, Fauchier JP. QT dispersion in nonischemic dilated cardiomyopathy. A long-term evaluation . *European Journal of Heart Failure* . 2005;7 (2):277–282.

261. Bass BG. Restitution of the action potential in cat papillary muscle . *American Journal of Physiology -- Legacy Content* . 1975;228 (6):1717–1724.

262. Garfinkel a, Kim YH, Voroshilovsky O, et al. Preventing ventricular fibrillation by flattening cardiac restitution. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;97(11):6061–6.

263. Ng GA, Brack KE, Patel VH, Coote JH. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart . *Cardiovascular Research* . 2007;73 (4):750–760.

264. Taggart P, Sutton P, Chalabi Z, et al. Effect of Adrenergic Stimulation on Action Potential Duration Restitution in Humans . *Circulation* . 2003;107 (2):285–289.

265. Fossa AA, Wisialowski T, Crimin K, et al. Analyses of Dynamic Beat-to-Beat QT–TQ Interval (ECG Restitution) Changes in Humans under Normal Sinus Rhythm and Prior to an Event of Torsades de Pointes during QT Prolongation Caused by Sotalol. *Annals of Noninvasive Electrocardiology*. 2007;12(4):338–348.

266. Weiss JN, Chen P-S, Qu Z, Karagueuzian HS, Garfinkel A. Ventricular Fibrillation . *Circulation Research* . 2000;87 (12):1103–1107.

267. Riccio ML, Koller ML, Gilmour RF. Electrical Restitution and Spatiotemporal Organization During Ventricular Fibrillation . *Circulation Research* . 1999;84 (8):955–963.

268. Ng GA, Mantravadi R, Walker WH, et al. Sympathetic nerve stimulation produces spatial heterogeneities of action potential restitution. *Heart rhythm the official journal of the Heart Rhythm Society*. 2009;6(5):696–706.

269. Weiss JN, Qu Z, Chen P-S, et al. The Dynamics of Cardiac Fibrillation . *Circulation* . 2005;112 (8):1232–1240.

270. Fossa AA, Wisialowski T, Crimin K. QT Prolongation Modifies Dynamic Restitution and Hysteresis of the Beat-to-Beat QT-TQ Interval Relationship during Normal Sinus Rhythm under Varying States of Repolarization . *Journal of Pharmacology and Experimental Therapeutics* . 2006;316 (2):498–506.

271. Fossa AA, Wisialowski T, Magnano A, et al. Dynamic Beat-to-Beat Modeling of the QT-RR Interval Relationship: Analysis of QT Prolongation during Alterations of Autonomic State versus Human Ether a-go-go-Related Gene Inhibition . *Journal of Pharmacology and Experimental Therapeutics* . 2005;312 (1):1–11.

272. Fossa AA, Zhou M. Assessing QT prolongation and electrocardiography restitution using a beat-to-beat method. *Cardiology journal*. 2010;17(3):230–43.

273. Piccirillo G, Magnanti M, Matera S, et al. Age and QT variability index during free breathing, controlled breathing and tilt in patients with chronic heart failure and healthy control subjects. *Translational research : the journal of laboratory and clinical medicine*. 2006;148(2):72–8.

274. Berger RD. QT interval variability is it a measure of autonomic activity? *Journal of the American College of Cardiology*. 2009;54(9):851–2.

275. Berger RD, Kasper EK, Baughman KL, et al. Beat-to-Beat QT Interval Variability : Novel Evidence for Repolarization Lability in Ischemic and Nonischemic Dilated Cardiomyopathy . *Circulation* . 1997;96 (5):1557–1565.

276. Murabayashi T, Fetics B, Kass D, et al. Beat-to-beat QT interval variability associated with acute myocardial ischemia. *Journal of Electrocardiology*. 2002;35(1):19–25.

277. Haigney MC, Zareba W, Gentlesk PJ, et al. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *Journal of the American College of Cardiology*. 2004;44(7):1481–7.

278. Piccirillo G, Magrì D, Matera S, et al. QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular systolic dysfunction: a prospective study . *European Heart Journal* . 2007;28 (11):1344–1350.

279. Talwar S, Squire IB, Downie PF, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction. Correlation with left ventricular systolic dysfunction . *European Heart Journal* . 2000;21 (18):1514–1521.

280. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *Journal of the American College of Cardiology*. 2006;47(1):91–7.

281. Tang WHW, Francis GS, Morrow D a, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical utilization of cardiac biomarker testing in heart failure. *Clinical biochemistry*. 2008;41(4-5):210–21.

282. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure. *New England Journal of Medicine*. 2002;347(3):161–167.

283. Januzzi JL, Camargo C a, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *The American journal of cardiology*. 2005;95(8):948–54.

284. Yusoff R, Clayton N, Keevil B, Morris J, Ray S. Utility of Plasma N-Terminal Brain Natriuretic Peptide as a Marker of Functional Capacity in Patients With Chronic Severe Mitral Regurgitation. *The American Journal of Cardiology*. 2006;97(10):1498–1501.

285. Galante O, Amit G, Zahger D, et al. B-type Natruiretic Peptide Levels Stratify the Risk for Arrhythmia Among Implantable Cardioverter Defibrillator Patients. *Clinical Cardiology*. 2008;31(12):586–589.

286. Barron HV LM. Autonomic Nervous System and Sudden Cardiac Death. *JACC*. 1996;27, No 5(April 1996):1053–60.

287. Liew R. Prediction of sudden arrhythmic death following acute myocardial infarction . *Heart* . 2010;96 (14):1086–1094.

288. La Rovere MT, Pinna GD, Maestri R, et al. Short-Term Heart Rate Variability Strongly Predicts Sudden Cardiac Death in Chronic Heart Failure Patients . *Circulation* . 2003;107 (4):565–570.

289. Nessler J, Nessler B, Kitliński M, et al. Sudden cardiac death risk factors in patients with heart failure treated with carvedilol. *Kardiologia polska*. 2007;65(12):1417–22; discussion 1423–4.

290. Sanderson JE, Chan SK, Yip G, et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. *Journal of the American College of Cardiology*. 1999;34(5):1522–8.

291. Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart--a novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation . *Experimental Physiology* . 2001;86 (3):319–329.

292. Santangeli P, Dello Russo A, Casella M, et al. Left ventricular ejection fraction for the risk stratification of sudden cardiac death: friend or foe? *Internal Medicine Journal*. 2011;41(1a):55–60.

293. Domanski M. A comparative analysis of the results from 4 trials of β-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *Journal of Cardiac Failure*. 2003;9(5):354–363.

294. Cutler MJ, Rosenbaum DS. Risk stratification for sudden cardiac death: Is there a clinical role for T wave alternans? *Heart Rhythm*. 2009;6(8, Supplement):S56–S61.

295. Verrier RL, Klingenheben T, Malik M, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility--consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *Journal of the American College of Cardiology*. 2011;58(13):1309–24.

296. Jackson CE, Myles RC, Tsorlalis IK, et al. Profile of microvolt T-wave alternans testing in 1003 patients hospitalized with heart failure . *European Journal of Heart Failure* . 2012;14 (4):377–386.

297. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *Journal of the American College of Cardiology*. 2006;48(10):1977–85.

298. Iles L, Pfluger H, Lefkovits L, et al. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. *Journal of the American College of Cardiology*. 2011;57(7):821–8.

299. Seegers J, Vos MA, Flevari P, et al. Rationale, objectives, and design of the EUTrigTreat clinical study: a prospective observational study for arrhythmia risk stratification and assessment of interrelationships among repolarization markers and genotype . *Europace* . 2012;14 (3):416–422.

9 Appendix

ECG RESTITUTION CHARACTERISTICS IN PATIENTS WITH LVSD & ICD

S Kundu, J Tuan, M Jeilan, F Osman, R Mantravadi, GA Ng - University of Leicester, Leicester, United Kingdom

Introduction

Restitution kinetics have been shown to impact on arrhythmia vulnerability. Studies have shown that ECG restitution can be quantified by Holter recording using analysis of sequential QT and TQ interval measures. These include QT/ preceding TQ ratio, and percentage of beats with a QT/TQ ratio >1, which relates to time on the restitution curve with greatest predisposition to arrhythmia. We compared patients with LV systolic dysfunction undergoing ICD implantation for primary prevention (PP, n=12) to those for secondary prevention (SP, n=13) of sudden death to examine potential differences in these parameters.

Methods

24 hour, 3 channel Holter monitoring was performed in all patients prior to ICD implantation. QT, R-R and TQ intervals were subsequently analysed (Delmar Reynolds Pathfinder systems). The recordings were analysed according to 4 time periods: (A) 0000-06 00, (B) 0600-1200, (C) 1200-1800 & (D) 1800-0000.

Results

Beta-blocker & amiodarone use did not differ between the 2 groups. Median RR was higher ($p<0.05$) nocturnally in SP and PP. RR was lower in B for both PP & SP arms. Median QT (QT) was significantly longer nocturnally in both groups. There were no significant differences in the regression slopes of QT-RR or QT-TQ clouds either within or between PP & SP groups. Maximum QT/TQ ratio was significantly higher in PP ((mean±SEM) 2.186±0.2344) in C compared to SP (1.467±0.1117, $p=0.0155$). No other significant differences between or within groups in terms of maximum QT/TQ ratio were seen. There were no significant differences between PP and SP when the percentage of beats with QT/TQ ratio >1 were analysed.

Conclusions

Subtle differences exist in ECG restitution characteristics measured from Holter recordings in ICD patients implanted for PP and SP. Although significance was not achieved in a number of the studied parameters, further work is required to allow comparison with normal controls and to correlate with arrhythmia occurrence. This non-invasive tool may hold promise in refining risk stratification.

Clinical implications of adopting revised NICE guidelines on Implantable Cardioverter Defibrillators for primary prevention of sudden cardiac death

Authors:
S. Kundu[1], M. Farooq[1], M. Zaman[1], A. Ali[1], P.J. Stafford[1], R.K. Pathmanathan[1], G.A. Ng[1], [1]Glenfield Hospital - Leicester - United Kingdom,

Topic(s):
Automatic implantable cardioverter/defibrillator

Citation:
European Heart Journal (2007) 28 (Abstract Supplement), 285

Introduction: Implantable Cardioverter Defibrillators (ICDs) reduce mortality in patients at risk of Sudden Cardiac Death (SCD) with underlying coronary disease (CAD) and left ventricular systolic dysfunction (LVSD). The UK National Institute for Clinical Excellence (NICE) and ESC guidelines for ICD implantation for primary prevention were updated in 2006. NICE recommends ICDs in CAD patients with an ejection fraction (EF)< 30% and ECG QRS duration>120ms. This is in addition to previous guidelines where primary prevention was advised if EF<35% (CAD patients) was combined with non sustained VT on 24 hour tape and a positive VT stimulation study (VTS). This study investigates the potential impact of these changes on the practice at a UK tertiary cardiology centre. **Methods:** Patients who had VTS for risk stratification in 2005 were included. Data collected from case notes and EP database were analysed. **Results** (Table 1): Out of a total of 135 procedures, 95 patients had CAD. From this CAD cohort, 47 patients had a positive VTS (who were fitted with ICDs) and 48 had a negative VTS (no ICDs). Patient characteristics (EF and QRS) were similar in both groups. Based on the new guidelines 26 patients would be eligible for an ICD without VTS assessment. By previous guidelines 53.8% of these patients underwent ICD implantation. With the new guidelines, 27.4% fewer VTS would be required but patients with severe LVSD and QRS<120ms would still require VTS. 28 such patients required an ICD previously (59.5% of positive VTS). All 95 of these CAD patients would be eligible for an ICD according to the new ESC guidelines. **Conclusions:** Adherence to the new NICE guidelines necessitate 50% more ICD implants in primary prevention in CAD. Fewer VTS are required. EF does not appear to predict VTS outcome. This increase in implant rates will have implications for health provision. If the ESC guidelines are adopted, the number of implants would increase again (by 250%) placing an immense strain on the UK national health system.

Sub-analyses of VTS in the CAD cohort}

	Positive VTS			Negative VTS	
	QRS>120ms	**QRS <120ms**		**QRS>120ms**	**QRS<120ms**
EF 30-40% n=5	0	5	EF 30-40% n=9	1	8
EF<30% n=42	14	28	EF<30% n=39	12	27
Total n=47	14	33	Total n=48	13	35