Predicting Death in Chronic Heart Failure: Electrocardiographic, Autonomic and Neuroendocrine Risk Assessment

Dr. A. J. Morley-Davies

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University of Glasgow

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Department of Medical Cardiology

Glasgow Royal Infirmary

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University of Glasgow

Dr. A. J. Morley-Davies

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Prediction is difficult – especially of the future

Neils Bohr

Hofstadter's Law: It always takes longer than you expect, even when you take into account Hofstadter's Law

Douglas Hofstadter

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Summary

Chronic heart failure is a common condition with an adverse prognosis. Despite optimal treatment, ambulant patients with mild symptoms have an annual mortality of more than 15%. Clinical, exercise, echocardiographic and haemodynamic variables are known to carry prognostic information, but accurate identification of those most likely to die remains difficult. This work assessed abnormalities of ventricular activation and repolarisation respectively using the signal-averaged electrocardiogram and interlead QT interval variability of the standard 12-lead electrocardiogram. Disordered autonomic function is common in cardiac failure. This was assessed by 24 hour heart rate variability and baroreflex sensitivity. Plasma noradrenaline and plasma atrial and brain natriuretic peptide levels were used to assess neuroendocrine activation, a hallmark of chronic heart failure. These measures were determined prospectively and compared with known prognostic variables in a chronic heart failure population.

Original Hypotheses

1. Sudden cardiac death in patients with heart failure is caused predominantly by malignant ventricular arrhythmias. These may be predicted by non-invasive markers of the arrhythmogenic substrate i.e. signal-averaged ECG, QT dispersion; triggers i.e. non-sustained ventricular tacycardia, and autonomic modulators i.e. heart rate variability and baroreflex sensitivity. This assessment will provide additional independent prognostic information on mortality risk in patients with chronic heart failure.

2. Markers of neuroendocrine activation and autonomic dysfunction would predict progression of chronic heart failure, and all-cause and progressive heart failure death.

Patients

One hundred and ninety-five patients with stable chronic heart failure were recruited. Exclusion criteria included age >75 years; uncontrolled hypertension (BP >170/90 mmHg); recent (6 months) unstable angina or myocardial infarction; significant valvular heart disease; atrial fibrillation; insulin dependent diabetes mellitus; chronic renal failure (creatinine>200μmol/l); autonomic neuropathy or any non-cardiac condition likely to prove fatal over the study period.

Methods

ECG tracings were manually digitised at standard paper speeds of 25mm/sec and gain of 10mm/mV. A signal averaged ECG was acquired in accordance with published guidelines. Patients with bundle branch block were prospectively analysed using published criteria. Subjects able to exercise underwent symptom limited cardiopulmonary treadmill exercise testing using a standardised exponential workload protocol. Twenty-four hour ambulatory ECG's were obtained on all subjects during unrestricted out of hospital activity. Time domain measures of heart rate variability were calculated using accepted standards. Ejection fraction was determined echocardiographically by Simpson's biplane technique, or, in subjects with poor endocardial definition left ventricular ejection fraction was assessed semi-quantitatively, and by radionuclide ventriculography. Baroreflex sensitivity was measured using the bolus phenylephrine injection technique and non-invasive arterial pressure monitoring. Plasma BNP was measured by radioimmunoassay. Noradrenaline was measured by HPLC and electrochemical detection after prior extraction from plasma.

Follow-up and Classification of Endpoints

Follow-up information was extracted annually from review of their hospital and/or GP case records. Follow-up was closed on 1st Sept 1998. Vital status was determined in all cases from information from the Death section of the General Register Office of Scotland. Prospectively defined endpoints were cardiovascular death, progressive heart failure death and sudden death.

Statistical Analysis

Kaplan-Meier curves and the log-rank test were used to determine the statistical association of co-variates with mortality. A multivariate Cox proportional hazards analysis was performed to determine the incremental prognostic power of investigational variables. To simplify this model, NYHA status was grouped as class II or below, or III and above. Maximal oxygen consumption was dichotomised at 14ml/kg/min (as in previous studies), with patients unable to exercise (due to cardiac limitation) being assigned a value of <14ml/kg/min. Autonomic variables were dichotomised above and below the median values. Two types of Cox regression analyses were performed:

The incremental prognostic utility of each investigational variable was determined singly after adjustment by multivariate analysis of readily available parameters: age, aetiology of heart failure, NYHA class, left ventricular ejection fraction and presence of intra-ventricular conduction defect/bundle branch block on the 12 lead ECG.

In the second model, all investigational co-variates were analysed together using a forward conditional stepwise model after adjustment for baseline co-variates.

Results

Clinical characteristics of the study population are shown in **Table 1**. One hundred and ninety nine patients were recruited. Clinical details and follow-up were available in the complete cohort.

Table 1: Patient demographics and baseline variables

Patient Demographics			
Age, years*		61.6	54.2-67.5
NYHA class		2.7	0.8
Cause of CHF (n)	**Ischaemic**	163	
	Non-ischaemic	36	
Therapy (%)	**ACE Inhibitor**	89	
	Diuretics	66	
	Digoxin	27	
	Other vasodilators	41	
	β blockers	20	
	LVEF (%)	23	9
	Peak VO2 (ml/kg/min)	16.9	4.9
IVCD/BBB (n)	**Present**	64	
	Absent	135	

NYHA – New York Heart association functional class; IVCD – intraventricular conduction defect; BBB – bundle branch block. Values given as mean ± SD, except where indicated *, median ± IQR

Mortality

Follow up was complete on all patients. Median duration of follow-up was 1086 days IQR 734-1259 days. In those surviving, median follow-up was 1173 days, IQR 1031-1289 days. There were 54 (27%) deaths in total, and 47 (24%) cardiovascular deaths. There were 23 (12%) progressive heart failure deaths and 24 (12%) sudden deaths.

Univariate Analysis

Established clinical parameters (aetiology of heart failure, NYHA class, left ventricular ejection fraction and peak oxygen consumption) significantly predicted cardiovascular death (log rank test $p<0.01$). Age did not predict death, possibly because of the truncated upper limit. Intraventricular conduction defects/bundle branch block and a positive signal averaged ECG also predicted cardiovascular death (log rank test $p<0.01$). No electrocardiographic measure of QT dispersion (T wave end dispersion, T wave apex dispersion or the respective coefficients of variation) was prognostic. Plasma neurohormones, baroreflex sensitivity, and time domain measures of heart rate variability (Triangular Index, SDNN and SDNN-I) also predicted cardiovascular death (log rank test $p<0.01$).

Multivariate Analysis

After adjustment for baseline variables (age, NYHA status, presence/absence of IVCD, left ventricular ejection fraction and peak oxygen consumption), only a positive SAECG, the presence of non-sustained ventricular tachycardia, markers of autonomic dysfunction and plasma neurohormones retained prognostic power. When investigational variables were analysed concurrently, depressed heart rate variability and baroreflex sensitivity failed to predict cardiovascular mortality. However, plasma markers of neuroendocrine activation significantly predicted cardiovascular death: supramedian levels of plasma BNP or plasma Noradrenaline respectively conferred a 5 fold and 3 fold increase in risk. Perhaps surprisingly, a positive SAECG provided similar prognostic power, but the utility of this measure would be more limited, as only a minority of patients had a positive SAECG (31 of 124, 25%).

When subject to the scrutiny of multivariate analysis, a positive SAECG, the presence of non-sustained ventricular tachycardia on Holter monitoring and depressed baroreflex sensitivity

predicted sudden death significantly. Prognostic significance was retained even when the variables were analysed concurrently, rather than singly. All 3 variables were potent predictors of mortality, each conferring a 3 fold increased risk of sudden death.

Discussion

Chronic heart failure is a common, growing and major public health care burden. Identifying high-risk patients suitable for aggressive intervention, optimisation of treatment and prevention of death is of great importance. Despite extensive study by many investigators, identification of those patients who are most likely to deteriorate and die remains difficult.

In this well-characterised cohort of patients with chronic heart failure, neuroendocrine activation assessed by plasma BNP or plasma Noradrenaline predicted cardiovascular death. This information was additive to and independent of other powerful prognostic variables including NYHA class, age, left ventricular ejection fraction, peak VO_2 and presence/absence of bundle branch block. Howevr, plasma BNP may be measured from a simple venous blood sample, and has been proven to be stable at room temperature over 72 hours. It is inexpensive, and requires no specialised equipment at the bedside. Direct assay kits are now available which both simplify and lessen the cost of its measurement. This has implication for its more widespread use. Interestingly, a positive SAECG, the presence of non-sustained ventricular tachycardia and depressed baroreflex sensitivity all identified a patient cohort at high risk of sudden death. Linking this data with the prognostic importance of depressed baroreflex sensitivity in the study cohort with recent data on "electrical storms" in patients with implantable cardioverter-defibrillators, it suggests that these markers might be used to identify patients who would benefit from these devices.

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Dedication

To my wife, Ingrid

without whose support I could never and would never have finished this,

and to my children, Tom and Joe

without whom I would have finished it far sooner.

Declaration

I certify that this thesis has been designed, composed and written by myself. It has not been submitted previously for any degree.

Dr. A. J. Morley-Davies

Signed:

Date:

1 INTRODUCTION

1.1 A HISTORY OF HEART FAILURE

1.1.1 *Ancient Civilisations, Greeks and Romans*

The earliest civilisations first appeared more than 4000 years ago in the Middle East, China, South America and India. The first recorded medical text is a Sumerian tablet from around 4000 BC, commenting on various medicinal cures, and suggesting the addition of potassium nitrate to a number of them. The Ancient Greeks are often credited with first describing and counting the pulse. The following quotation from the Edwin Smith Surgical Papyrus (circa 3000 BC) suggests that the Egyptians antedated them by twelve centuries:

> *"Now if the priests of Sekhmet or any physician put his hands...upon the two hands, upon the pulse, upon the two feet he measures the heart, because its vessels are in the back of the head and in the pulse; and because its pulsation is in every vessel of every member"* [1]

The most important ancient text is the Ebers Papyrus, dating from around 1600 BC, over three hundred years before Moses was found in the bullrushes [2]. It may contain the first recorded description of angina, along with a recognition of its ominous prognosis:

> *"when you examine a man for illness in his cardia, he has pains in his arm, in his breast, on the side of the cardia...it is death which approaches him"*

Other passages state,

> *"The heart is tired; this means that the heart does not speak or the vessels of the heart are mute...When there is inundation of the heart, the saliva (sputum?) is in excess; therefore the body is weak."*

It is tempting to speculate that this may be the first recorded description of the clinical syndrome of heart failure [3]. These clinical descriptions of cardiac symptoms have

been confirmed by the pathological examination of Egyptian mummies revealing coronary disease with evidence of myocardial infarction. The Egyptians did believe that dyspnoea was due to a blockage in the flow of blood, and employed bleeding as a treatment. It has been suggested that this was the first use of preload reduction by venesection in the treatment of heart failure.

More recently, it has become apparent that other civilisations also had first hand knowledge of the anatomy of the heart, possibly because of human sacrifice. A statue dating from 1000 B.C. pictures the heart with both ventricles and pulmonary artery and aorta [4]. However, there are no medical texts surviving from the Olmec civilisation.

Greek civilisation flourished from 2000 BC to 100 BC, making lasting contributions to medical knowledge. Hippocrates (460-377 BC) believed that human temperaments and physiques depended on the humours, being phlegmatic, sanguine, melancholic or choleric. Even today, some 23 centuries later, we still use these descriptions. Hippocrates' commentaries are said to describe cardiac pain, along with recognition of its poor prognosis:

"frequent recurrence of cardialgia, in an elderly person, announces sudden death"

Erasistratus (330-250 BC) carried out many systematic human dissections, and indeed was said to have dissected criminals alive. He recognised that the heart provided the motive power for the circulation. Praxagoras of Cos (circa 340 BC) is first credited with using the pulse in diagnosis, and his pupil Herophilus (circa 300 BC) with recognising that it was synchronous with the heartbeat and was the first to count the rate using a water-clock [5]. Thus, although the ancient Greeks made great advances in

organising medicine and in the method of clinical observation, they did not advance knowledge of heart failure beyond that of the Egyptians.

From 100 BC to 476 AD Roman civilisation dominated the Western World. Celsus (53 BC -7 AD), a Roman author but not physician, wrote the first published textbook of general medicine. In it he describes a condition he terms "Kardiakon":

> *"...excessive weakness of the body...(which) wastes away through immoderate sweating...it may be recognised by the weak pulsation of the blood vessels, while sweat...breaks out...the feet and legs remaining more dry and cold..."* [1]

Some authorities have taken this to represent myocardial infarction, but it may describe the cardiac cachexia, sympathetic over-activity and peripheral vasoconstriction characteristic of heart failure. A large pharmacopeia from this time suggested scylla (which contains cardioactive glycosides) and opium for the treatment of breathlessness, being particularly useful "...when the patient has a bloody sputum." [3]. Galen, a Roman physician to the gladiators lived from 138-201 AD. He stated that blood ebbed and flowed throughout the body, and that it passed from the right to left ventricle through interventricular septal pores. This erroneous belief exerted a profoundly negative influence on medical thinking for the next 1500 years, during which time to even doubt Galen's beliefs was considered heretical.

1.1.2 *The Middle Ages and Renaissance*

During the Middle Ages the Arabic-speaking peoples of North Africa maintained and added to Greco-Roman medical knowledge. Avicenna (Ibn Sina, 980-1037 AD), a Persian called "the Prince of Physicians", wrote a five-volume influential "Canon of Medicine", which was reprinted over fifteen times and remained a standard medical text until the 17th century [6]. In the Third volume he describes dyspnoea and orthopnoea, although he ascribed this to imbalance of the humours. Another possible

description of heart failure dates from this time, along with realisation of its grim prognosis:

> *"dyscrasia (i.e. heart disease) stops the circulation inside the arteries, helping retention of fluids and leading to death"*

The first clear description of heart failure occurs in an account of the illness of Alexius I, ruler of the Byzantine Empire from 1081-1118 AD [7]. His daughter described his illness, along with the remedies proposed:

> *"the physicians...felt his pulse and found all sorts of irregularities...his heart, they said, was inflamed...every day it grew worse, attacking him no longer at intervals, but relentlessly, with no interruption. He was unable to lie on either side so weak that every breath involved great effort...his condition was serious, for never for one moment could he breath freely. He was forced to sit upright to breathe at all...but when his stomach was visibly enlarged to a great size and his feet also swelled up and fever laid him low, some of the doctors with scant regard for the fever, had recourse to cauterisation."*

Human dissection was finally authorised by Pope Sixtus IV in the late 15th century and gradually medical education passed from the Church to universities. This lead directly to the rise of the great anatomists, so ultimately refuting Galenic teachings. Andreus Vesalius (1514-1564), Professor of Anatomy at Padua, published the first great anatomical work, De Humani Corporis Fabrica in 1543. Leonardo da Vinci had produced similar illustrations decades earlier but these were in private collections (now in Windsor Castle) and would not have been known to him. Vesalius could not demonstrate Galen's interventricular pores, although he was careful not to deny their existence. The first discovery of the pulmonary circulation is attributed to the Arabic physician Ibn an-Nafis (1210-1288) although his work remained undiscovered for many centuries. The first European suggesting that blood flowed from the right to left ventricles through the lungs was Michael Servetus, who published "Christianismi restitutio" in 1553. Only three of the original five hundred copies survive. Following

the publication of this text Servetus was burnt at the stake for hereticism, although it seems more likely that this was due to his listing of sixty reasons why the pope was the AntiChrist, rather than his anatomical discoveries [8]. Vesalius' successor at Padua, Realdus Columbus wisely published his anatomical work "De Re Anatomica" posthumously in 1559. In it he argued for the existence of the pulmonary circulation, the function of the heart valves and described the timing of the pulse in relation to systole and diastole, refuting accepted Galenic wisdom.

Despite these significant advances in cardiovascular anatomy, the concept of heart failure remained poorly understood, as knowledge of the circulation of the blood awaited Harvey's great work.

1.1.3 *The 17th, 18th and 19th Centuries*

The death knell of traditionalism was supplied by William Harvey (1578-1657). His duties involved teaching anatomy by dissecting the bodies of felons. His lectures began the year that Shakespeare died. In 1628, aged fifty, Harvey published "Exercitatio anatomica de motu cordis et sanguinus in animalibus" or "The movement of the heart and blood in animals" [9]. This was based on extensive experimentation and dissection: indeed he dissected over one hundred species of animals, including his own pet parrot and monkey and even assisted at the dissections of his father, brother and sister. Harvey concluded that the heart, rather than the arteries, propelled the blood and, in agreement with Colombus, that the apex beat and pulse coincided with ventricular systole. In this he was aided by the remarkable case of the eldest son of the Viscount Montgomery who had suffered a fall as a child, and as the wound had failed to heal, the heart could be seen [10]. Harvey directly denied the existence of interventricular pores, and he reasoned that the blood passed through

"the invisible porosities of the lungs and the minute cavities of their vessels"

Capillaries were subsequently visualised and described by Malpighi (1628-1694) using the microscope in 1661. Later, Harvey clearly describes angina as a cause of "dropsy" or heart failure in a letter to colleague:

> *"Sir Robert Darcy...about the middle period of his life, made frequent complaint of a certain distressing pain in the chest. The disease going from bad to worse, he by-and-by became cachectic and dropsical..."* [11]

Boerhave (1668-1738), Professor at Leyden, is credited with first attributing "anasarca" to cardiac causes [3], but perhaps the first definition of heart failure was produced by Lower in his textbook of 1669 "Tractatus de Cordis" [12]

> *"...but when the parenchyma of the heart has been harmed by various diseases its motion is necessarily much altered; for if the parenchyma of the heart is burdened with too much fat, labours under inflammation, abcess or wound, so that it cannot vibrate or contract without great trouble or difficulty, it soon gives up its motion, whence the movement of the blood also to the same degree becomes weak and languid."*

Consequently, by the end of the 17th century, the concept of the hydropic state was related to heart disease, and the initial steps towards defining and understanding the syndrome of heart failure were made.

The pace of discovery increased: Albertini (1662-1738) described dyspnoea due to pulmonary oedema, stressing the importance of cardiac enlargement; Lancisi (1655-1720), a Papal physician who studied sudden death described its association with cardiac dilatation; whilst Senac (1693-1770) published the most comprehensive manual of heart disease in 1749, "Traite sur la structure du coeur, de son action et de ses maladies". In it he wrote that dilation of the cardiac chambers could lead to orthopnoea, oedema and cardiac asthma, and that medicine had few remedies for heart disease. Perhaps the most outstanding work of this century was Morgagni's (1682-1771) "The Seats and Causes of Diseases Investigated By Anatomy" [13], published in

1761 and translated into English in 1769. Amongst many other diseases he lucidly described anginal syndromes, cardiac rupture, pericardial tamponade and constriction and cardiac dilatation associated with "dropsy":

> *"serous fluid in the thorax..then hydrops; afterwards jaundice, dyspnoea, throbbing of the jugular vessels..."*

being credited with coining the term "cor bovinum".

The first breakthrough in the drug treatment of heart failure occurred in 1785, when Withering published the first work of clinical pharmacology [14]. Although glycosides had been used for many centuries [15], Withering discovered that the active ingredient of a herbal remedy for dropsy was the foxglove Digitalis purpurea. Unfortunately, much of Withering's advice was ignored, and digitalis was used rather indiscriminately- for example for tuberculosis and "nervous afflictions". It is thought that the latter may have played a role in Van Goch's vivid colourings, as a portrait of his physician Dr. Gachet reveals him holding a foxglove!

Bedside diagnosis was advanced by the popularisation of percussion by Corvisart (1755-1821), and the development of the stethoscope by Laennec (1781-1826). Further advances in the physiology of heart failure were provided by Potain (1825-1901), who correctly elucidated that gallop rhythms were due to reduced ventricular compliance or contractility. Cheyne (1777-1836) and Stokes (1804-1878) described periodic breathing and Traube (1818-1876) described pulsus paradoxus in patients with heart failure. Bright (1789-1858) was the first to differentiate congestion due to renal causes from those of cardiac cause. A unifying hypothesis for the patho-physiology of heart failure was propounded by Hope in 1832 [16]. This "back-pressure" theory considered the symptoms to be caused by increasing pressure behind the failing valve or ventricle. Later in the century, the concept of coronary disease as

a cause of heart failure was gradually accepted. As far back as 1776 Fothergill (1712-1780) had described the association of acute cardiac failure with death due to angina, but did not comprehend the link. In 1850 Quain (based at the Brompton Hospital) described eighty-three cases of "fatty degeneration", noting the close link with coronary "ossification". In 1874 Fagge (1838-1883) described heart failure associated with localised thinned, fibrotic areas of myocardium, and in 1884 von Leyden (1832-1910) described chronic diffuse coronary disease leading to "cardiac asthma and dropsy". Thus, by the end of this period, ischaemic heart disease was recognised as a cause of heart failure, even though angina and myocardial infarction had not, as yet, been differentiated.

Despite these advances, treatment options remained limited. Venesection, purgation and the misuse of digitalis were widespread. Pre-load reduction using tourniquets had been described by Parry in 1795, and fluid restriction by Hope in 1831. Direct drainage of the oedema by incision of the skin, or insertion of Southey's tubes, developed in 1877 by Southey (1835-1899), were popular measures. Brunton (1844-1916), who first described the therapeutic use of amyl nitrate for angina in 1867 [17], stated in 1888

> *"there are several diseases in which it is desirable to relax the blood vessels...in cases of the failing heart where the enfeebled ventricle is barely able to overcome the resistance of the arterial walls and force the blood onwards, we require a drug which will produce a prolonged dilatation of the vessels"* [18]

Unfortunately, this suggestion for after-load reduction was ignored for the next seventy years. Despite such advances, therapeutic nihilism remained common, as expressed by Oliver Wendell Holmes in 1860:

> *"with the exception of opium, anaesthetics and wine...if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, - and all the worse for the fishes."*

1.1.4 *The 20th Century: Technology and Therapeutics*

Roentgen discovered X-Rays in 1895, the X-Ray of his wife's hand being reproduced in publications across the world. Einthoven's string galvanometer revolutionised the development of electrocardiography, initially being used to facilitate the study of arrhythmias [19]. In 1912 Herrick proposed his theory of non-fatal coronary obstruction [20], and his student published the first ECG of myocardial infarction in the dog in 1918. Starling (1866-1927), determined the effects of different loading conditions on cardiac function in 1914, enabling the modern concepts of pre and after-load manipulation to emerge. With the advent of cardiac catheterisation haemodynamic measurements could be performed, leading to a greater understanding of cardiac function in health and disease [21]. Selective coronary angiography was introduced by Sones in 1962, finally allowing the definite ante-mortem diagnosis of heart failure secondary to coronary disease to be made.

The 20th century also saw great advances in therapeutics. Mercurial diuretics were discovered serendipitously in 1919 in Wenckebach's clinic, when mercury treatments for syphilis were noted to cause diuresis in a young girl [22]. Interestingly, over a century before, mercury had been used as a diuretic by Stokes (1804-1878). Subsequently, thiazides and loop diuretics (introduced in the 1950's and 1960's) dramatically changed the treatment of acute and chronic heart failure [23]. Despite this, the prognosis of patients with heart failure remained poor, with treatments suggested including thyroid ablation, inferior vena caval ligation [24] and even rib resection to allow the heart more space [25]. Direct acting vasodilators were introduced in the 1970's, large trials demonstrating their ability to produce prolonged symptomatic and haemodynamic benefit [26] by changing loading conditions. However, this concept of manipulating vascular tone was predated by the use of ganglion-blocking drugs,

nitrates and phentolamine [27]. Indeed, both Brunton and Osler had suggested the use of nitroglycerine for heart failure over a century before. During the 1980's, the angiotensin converting enzyme inhibitors were introduced, and have now been become a cornerstone of treatment [28]. Over two hundred years after its introduction, digoxin has finally been proven to be effective and safe [29].

1.1.5 *Conclusions*

For over 5000 years, continuing advances in anatomy, pathology and physiology have allowed identification of the heart as the cause of cardiac failure. The introduction of digitalis in the 18th century sparked the beginning of therapeutic optimism. Progress in clinical examination in the 19th century and the advance of technology, including radiology, electrocardiography, cardiac catheterisation and echocardiography in the 20th century have advanced our understanding of this highly lethal condition. The introduction of diuretics, direct acting vasodilators, angiotensin converting enzyme inhibitors and surgical techniques such as transplantation and cardiomyoplasty enable us to relieve symptoms and decrease mortality in patients with heart failure. Despite all these advances, the incidence and prevalence of heart failure are increasing in industrialised countries [30], and it continues to carry an ominous prognosis. Identification of those who are at greatest risk of death remains elusive, and it was the aim of this thesis to enhance risk stratification in chronic heart failure.

1.2 PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure is a complex clinical syndrome that continues to defy simple definition. This accounts, in part, for the variety of definitions that have been proposed (**Table 1-1**). These definitions encapsulate how understanding of the heart failure syndrome has changed from concentrating on an abnormality of cardiac function to a complex,

multi-system progressive disorder with adaptive and mal-adaptive compensatory responses. The presence of fluid retention or congestion classifies left-ventricular systolic dysfunction as decompensated.

Table 1-1: Definitions of chronic heart failure

a condition whereby the heart fails to discharge its contents properly – Lewis,1933
the heart fails to maintain an adequate output despite a satisfactory filling pressure – Wood, 1952
a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues [31]
a complex clinical syndrome characterised by abnormalities of ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity [32]
ventricular dysfunction with symptoms [33]

Subjective	Symptoms of heart failure
Objective	Evidence of important cardiac dysfunction
Retrospective	Response to appropriate treatment for heart failure [34]

1.2.1 *Symptoms*

The link between the severity of cardiac dysfunction and symptoms of breathlessness, exercise intolerance and fatigue in chronic heart failure is complex [35]. There is poor association between patients' perception of their symptoms and objective measures of the severity of left ventricular dysfunction.

Abnormalities of resting central haemodynamics correlate poorly with functional capacity on exercise testing, and acute improvements in haemodynamic indices do not result in acute improvements in exercise tolerance [36]. Studies with ambulatory

pulmonary flotation catheters fail to demonstrate any correlation between exercise capacity and peak-exercise left ventricular end-diastolic pressure [37], although there is a close correlation between peak cardiac output and peak VO_2 [38]. Thus, symptoms of breathlessness on exertion are not simply a reflection of resting or exercise induced changes in left ventricular filling pressure.

During exercise, ventilation increases more steeply in patients with chronic heart failure than in normal controls, and this altered pattern of breathing might lead to the sensation of dyspnoea. The slope of the plot of minute ventilation (V_E) Vs carbon dioxide production (VCO_2) is increased in chronic heart failure, representing an increased ventilatory drive, increasing gradients correlating with increasing severity of heart failure and decreasing exercise capacity [39]. Blood gases remain normal during such exercise [40]. It is thus unlikely that abnormalities of arterial (or venous) carbon dioxide content accounts for the increased ventilatory drive. Hypoxic chemosensitivity (measured by the ventilatory response to pure nitrogen inhalation) is increased in chronic heart failure [41]. Alterations in diffusing capacity have also been demonstrated [42], along with decreased pulmonary microvascular permeability [43], possibly related to increased pulmonary vascular resistance.

These alterations provide some, but not all of the reasons underlying the increased ventilatory drive and sensation of dyspnoea experienced by patients with chronic heart failure.

Patients with heart failure exhibit alterations in the regional distribution of blood flow [44]. Decreases in splanchnic and cutaneous flow on exercise precede decreased renal and skeletal muscle flow. Patients with heart failure fail to augment skeletal muscle blood flow during exercise [45] and the muscle wasting that occurs in mild/moderate

heart failure [46] may account for a proportion of the decreased flow. However, some patients with demonstrably normal muscle flow describe symptoms of fatigue [47]. Additionally, acute haemodynamic improvements in cardiac output which increase muscle flow do not improve exercise capacity or symptoms of fatigue [48], raising the possibility of metabolic abnormalities in exercising muscle. These data support the concept of "structural changes" in the microvasculature, rather than vasoconstriction alone, as a cause of diminished flow. Biopsy of skeletal muscle from patients with chronic heart failure reveals structural abnormalities, with decreased mitochondrial size, numbers, enzyme levels and fibre destruction [49]. Studies of muscle metabolism using ^{31}P-magnetic resonance spectroscopy have confirmed that muscle pH and phosphocreatine (a high-energy compound) fall more rapidly than in normal subjects and endurance in such muscles is decreased [50]. Exercise training can improve functional capacity whilst reversing metabolic abnormalities and mitochondrial oxidative enzyme deficiencies, without a change in mitochondrial density. Similar abnormalities seen in respiratory skeletal muscle may account for the respiratory muscle weakness present in chronic heart failure. Respiratory muscle training reverses the abnormalities seen on pulmonary function testing, improving symptoms of dyspnoea and effort tolerance.

However, it remains unproven whether these changes in skeletal muscle physiology provide the non-CO_2 ventilatory stimulus to respiration in chronic heart failure.

1.2.2 *Physical Signs*

The classical signs of heart failure may be masked by or become absent after treatment. Even when physicians agree on their presence, such signs are poorly discriminatory in defining underlying cardiac function [51]. Diastolic dysfunction with

normal systolic function occurs in up to 30% of chronic heart failure patients with classical congestive signs [52]. In chronic heart failure, high left ventricular filling pressures may cause little in the way of classical signs. Additionally, chest radiography may reveal no evidence of pulmonary venous congestion in the presence of significantly raised left ventricular filling pressures, leading to inappropriate care [53]. Thus, the bedside diagnosis of cardiac dysfunction is fraught with problems. Despite this, the presence of clinical and radiological features of congestion are strong predictors of mortality in populations, if not in the individual.

1.2.3 *Abnormal Cardiac Function and Structure*

Left ventricular injury causes a loss of effective contractile mass, leading to a complex and interrelated sequence of compensatory cardiac, haemodynamic and neuroendocrine responses. The end result of this sequence is: a) cardiac hypertrophy in non-damaged myocardium; b) neuroendocrine activation and c) salt and water retention.

These compensatory responses are beneficial in the short term, but have long term deleterious effects [54], accounting for the inexorable progression of cardiac dysfunction. Initially there may be no symptoms, but when these mechanisms fail or become unbalanced, the symptoms and signs of heart failure develop.

1.2.3.1 Global cardiac function in heart failure

Injury to the left ventricle causes an acute reduction in stroke volume and, if heart rate is constant, a decrease in cardiac output. Preload (left ventricular end diastolic volume) increases, returning cardiac output towards normal at the cost of increased left ventricular wall stress. Compensatory hypertrophy returns wall stress towards normal, and ventricular distensibility increases, so that the ventricle may pump from

an increased left ventricular end diastolic volume without increasing left ventricular end-diastolic pressure. Additionally, ventricular compliance increases, so that for any further increase in preload, left ventricular end-diastolic pressure increases less.

The ventricle thus operates on a flattened and depressed function curve, and "preload recruitment" allows the maintenance of a normal cardiac output. However, further increases in preload are not met by a corresponding increase in cardiac output, and preload reserve is eventually exhausted. In this situation, the ventricle becomes afterload dependent, increasing afterload decreasing cardiac output, and decreasing afterload increasing cardiac output. This forms the physiological basis for vasodilator therapy in chronic heart failure.

Global left ventricular systolic dysfunction may relate more to increased wall stress, distorted ventricular geometry, interstitial fibrosis and cell loss than myocyte contractile dysfunction [55].

1.2.3.2 Functional aspects of cardiac hypertrophy and remodelling

The pattern of compensatory hypertrophy is governed by the type of load placed on the heart. Increased afterload (systolic wall stress) leads to the addition of sarcomeres in parallel, increasing wall thickness and tending to decrease chamber size. This is termed "concentric hypertrophy" and is classically secondary to hypertension or aortic stenosis.. Increased preload (diastolic wall stress) leads to the addition of sarcomeres in series, increasing chamber size. This is termed "eccentric hypertrophy", usually secondary to valvular regurgitation [56].

Many stimuli may lead to hypertrophy. Cell stretching causes increases in myocardial protein synthesis in proportion to muscle tension. Stretch can modulate ion-channels

and enzyme levels, changing intracellular concentrations of second messengers. Increased expression of proto-oncogenes has also been reported, possibly regulating protein synthesis. There is evidence that activation of the sympathetic nervous system, in conjunction with the renin-angiotensin system and angiotensin-II, also plays a role, possibly explaining some of the beneficial effects of ACE inhibitors in regression of left ventricular hypertrophy [57].

Cytokines are another group of proteins secreted in response to number of different stimuli. There are two major classes that may play a role in heart failure: vasoconstrictor cytokines, such as endothelin; and vasodepressor pro inflammatory cytokines such as tumour necrosis alpha and interleukin 6. It is hypothesised that cytokines exert a deleterious progressive effect by necrosis, perhaps along with apoptopic myocyte cell death, progressive myocardial fibrosis and thus myocardial dysfunction [58].

1.2.3.3 Adverse functional consequences of left ventricular hypertrophy

The hypertrophic response to pathological stresses, including the mixed pattern seen in chronic heart failure, carries adverse consequences. The addition of sarcomeres in parallel or series decreases wall stress. However, the inter-capillary distance increases, collagen content increases, mitochondrial density decreases and coronary flow reserve falls. The failing hypertrophied heart is thus more likely to become ischaemic. Changes in the amount and activity of the sarcoplasmic reticulum Ca^{2+}–ATPase, increases in interstitial collagen content and the appearance of abnormal forms of collagen all contribute to impairment of relaxation and cardiac function. Angiotensin-II and aldosterone promote pathological hypertrophy, myocyte

necrosis and interstitial fibrosis, compounding the problem [59]. Animal models of heart failure demonstrate species specific alterations in gene expression causing isoform switching in myosin, thought to improve myocardial efficiency, at the expense of slowing the peak velocity of contraction. Downregulation of α-myosin heavy chain has recently been demonstrated in the failing human ventricle. The left ventricle enlarges, probably by elongation of myocytes, cell slippage and collagenase activity. Irrespective of the aetiology, an increase in left ventricular end systolic volume is an ominous sign [60].

1.2.3.4 Myocyte changes in hypertrophy and heart failure

There is consensus that cell elongation with defective transverse growth occurs, so that there is an increased myocyte length-to-diameter ratio. These changes could account for an increased cell volume, and correlate with left ventricular chamber size [55]. However, such changes are unable to account for all of the remodelling seen, and cell-cell slippage probably occurs [61].

There is debate over myocyte contractile function in left ventricular systolic dysfunction. Recent studies reveal normal contractile function in isolated myocytes taken from non-infarcted areas, despite evidence of significant structural remodelling [62]. Other groups have confirmed normal maximal contraction amplitude, albeit with delayed times to peak contraction and relaxation [63]. However, most studies have shown a flattened or reversed force-frequency relationship, confirming myocyte dysfunction.

Myocyte cell death may occur by apoptosis or necrosis. Apoptosis causes cell death in the absence of replacement fibrosis. In contrast, cell necrosis is characterised by an inflammatory reaction, macrophage infiltration and scar formation. Apoptosis or

programmed cell death has now been demonstrated in human ventricular myocardium [64]. Stretch can signal apoptosis, as would occur in left ventricular dilatation. Apoptosis would occur in the absence of interstitial collagen accumulation, and might be responsible for the inexorable left ventricular dilatation seen in progressive heart failure. Conclusive evidence regarding the role of apoptosis in the progression of heart failure is awaited.

Animal data suggest that although intracellular Ca^{2+} concentrations may be normal in the failing heart, time to peak Ca^{2+} concentration and rate of decline in Ca^{2+} concentration are slowed, because of a decrease in sarcoplasmic reticulum reuptake during diastole. Myofilament Ca^{2+} sensitivity is decreased and spontaneous oscillations in sarcoplasmic reticulum Ca^{2+} release augment diastolic tone, causing asynchronous systolic contraction with a possible role in arrhythmogenesis [65]. Similar changes have been found in the human heart [66]. These Ca^{2+} abnormalities may be secondary to changes in the sarcoplasmic reticulum Ca^{2+}-ATPase [67], compounded by diminished energy reserves and ATP levels. This reduction in sarcoplasmic reticulum Ca^{2+}-ATPase has been related to the extent of contractile dysfunction. It has been postulated that the inverse force-frequency relationship seen in human papillary muscle preparations from patients with severe heart failure may be consequent to these changes: decreased availability of sarcoplasmic reticulum Ca^{2+} consequent to shortened diastole with diminished reuptake. This could explain why interventions that increase heart rate reduce cardiac output in chronic heart failure, while lowering heart rate appears generally beneficial [68]. Excitation-contraction coupling is disturbed further by alterations in cross-bridging kinetics, possibly caused by actin/myosin isoform switches secondary to altered gene expression.

1.2.4 *Normal Cardiac Cell Electrophysiology*

Myocardial cells have a distinctive action potential profile (**see Figure 1-1**). From a threshold potential, there is rapid depolarisation (**phase 0**) followed by a rapid repolarisation (**phase 1**), a long plateau (**phase 2**) and subsequently a more rapid repolarisation (**phase 3**) to the resting membrane potential. Action potential duration correlates with the time course of repolarisation of cardiac tissue: lengthening of action potential duration correlates with prolongation of repolarisation. A transient outward current, $\mathbf{I_{to}}$ contributes to early repolarisation (**phase 1**) and helps "set" the plateau potential. The transient outward current demonstrates regional variation, being more marked sub-epicardially, giving rise to the so-called "spike and dome" action potential configurations. The situation is complicated by the fact that the normal ventricle demonstrates electrophysiological non-uniformity [69]. Action potential duration differs, being longer in the left than right ventricle, longer at the base than the apex and longer in the endocardium than epicardium. Recent work has demonstrated "M cells" in the mid-myocardial region of the canine ventricle, and there is evidence supporting their existence in the human heart. These cells have longer action potential durations than normal myocytes which prolong dramatically with slower heart rates [70], further adding to nonuniformity.

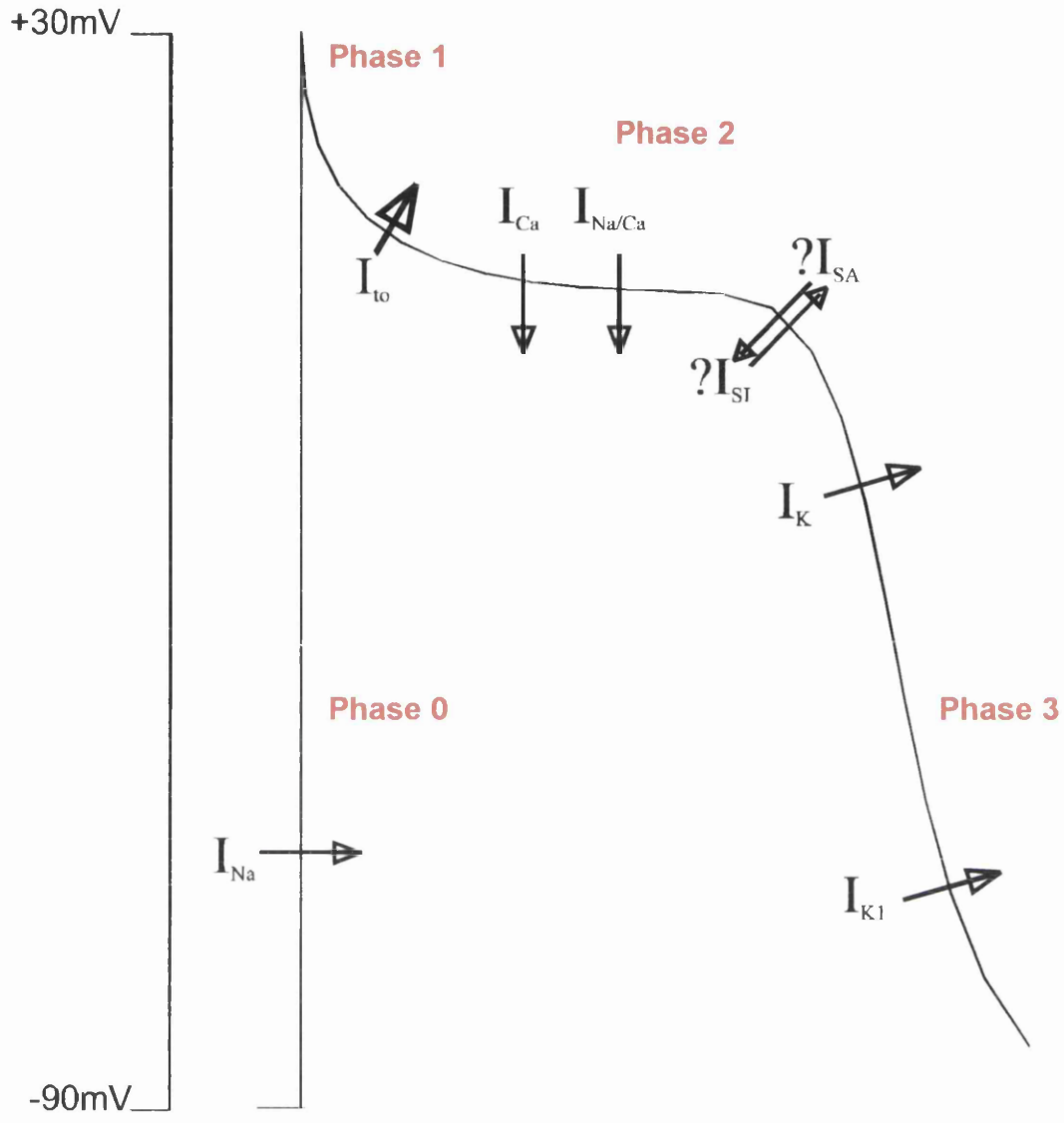


Figure 1-1: The ventricular action potential

1.2.5 *Electrophysiological Consequences of Failure and Hypertrophy*

Animal models of heart failure have produced inconsistent results. This inconsistency is attributable to both variation in experimental models and methods (e.g. coronary ligation, pressure or pacing induced heart failure) or within species. The nonuniformity of electrophysiological characteristics of the normal heart also complicates interpretation of the results. Data on electrophysiological properties of human tissue are even less complete.

The hallmark of hypertrophy is prolongation of the transmembrane action potential duration, generally in the absence of other electrophysiological abnormalities of the resting membrane potential, action potential amplitude or upstroke velocity [71]. This lengthening of action potential duration is caused by prolonged repolarisation.

1.2.5.1 Abnormalities of calcium current

The major Ca^{2+} current, $\mathbf{I_{Ca\text{-}L}}$, conveyed by L-Type ion channels, activates at potentials positive to –40 mV, and inactivates slowly (~100msec). Its inactivation kinetics are complex and dependent on voltage, time and the intracellular Ca^{2+} concentration, $\mathbf{[Ca^{2+}]_I}$. Increased channel density or decreased inactivation kinetics would prolong the plateau phase, and hence lengthen repolarisation. Animal models have yielded inconsistent results, but in human explanted transplant recipient hearts, no change in overall $\mathbf{I_{Ca}}$ was found. However, dihydropyidine binding receptor density was reduced, as was the mRNA encoding this protein. Activation kinetics seem to be unaltered, but the voltage dependence of inactivation has shown positive shifts, i.e. inactivation requires a more positive membrane potential, so that inactivation would be delayed at the normal plateau potential of approximately +10 mV.

Alterations in $[Ca^{2+}]_I$ and intracellular pH modify the voltage dependence of inactivation of L-Type Ca^{2+} channels, and both changes occur in the hypertrophied cell [72]. Catecholamines may regulate expression of L-Type Ca^{2+} channel mRNA, being decreased by α-agonists and increased by β-agonists [73]. Regional heterogeneities in sympathetic innervation and β-receptor downregulation could amplify spatial dispersion of repolarisation and refractoriness by this means.

1.2.5.2 Abnormalities of Na^+/Ca^{2+} exchange current

The Na^+/Ca^{2+} exchanger provides the principal mechanism of Ca^{2+} extrusion from the myocyte under normal conditions. It generates a small current because of the 3 Na^+ to 1 Ca^{2+} ratio, but the direction of current is dependent on the membrane potential, and the $[Ca^{2+}]_I$. At rest, inward current is generated as the combined equilibrium potential ($\mathbf{E_{Na\text{-}Ca}}$ = -30 to –40mV) is more positive than the resting membrane potential. At the action potential peak and during early repolarisation, when $\mathbf{E_{Na\text{-}Ca}}$ is negative to the membrane potential, a small outward current is produced. During the plateau, one would expect the same, but the increase in $[Ca^{2+}]_I$ makes $\mathbf{E_{Na\text{-}Ca}}$ more positive so that the exchanger produces a net inward current, i.e. it extrudes $1Ca^{2+}$ for 3 Na^+. As a result, higher levels of $[Ca^{2+}]_I$ increase the net inward current generated by the Na^+/Ca^{2+} exchanger, prolonging action potential duration.

Thus, intracellular Ca^{2+} concentrations may be normal in the failing heart, but time to peak Ca^{2+} concentration and rate of decline in Ca^{2+} concentration are slowed. There are also spontaneous oscillations in SR Ca^{2+} release. These Ca^{2+} abnormalities, which may be secondary to changes in the SR Ca^{2+}-ATPase, predispose to Ca^{2+} overload in the failing myocyte, promoting arrhythmogenesis [74].

1.2.5.3 Abnormalities of potassium currents

There are regional and interspecies variation in the transient outward current, I_{to}. This is thought to represent two separate currents; a K^+ current and a more rapidly deactivated intracellular Ca^{2+} dependent Cl^- current. Animal and human work documents a 30%-40% reduction in I_{to} density in myocytes from failing, hypertrophied hearts with no change in voltage dependence or kinetics of activation, inactivation or repriming. This current is of prime importance in "setting" the plateau potential, and consequently in determining action potential duration. The density of the inward rectifier, I_{Ki}, was also reduced by 40% in myocytes from humans with "end-stage" heart failure, with no change in the voltage dependence of gating.

The delayed rectifier K^+ current, I_K, provides the dominant repolarising current during the plateau of the action potential. The importance of this current in human ventricular myocytes is unknown.

1.2.5.4 Changes in cell to cell coupling

Interstitial fibrosis and changes in collagen seen in the hypertrophy of hypertrophic cardiomyopathy have been correlated with changes in latency and cell to cell coupling. Whether this is true of the hypertrophy present in heart failure is unknown, but electron microscopy freeze-fracture analysis has revealed reduced numbers of gap junctions, which would slow conduction velocity. Disruption of normal gap junction architecture (demonstrated by immunlocalisation of connexin 43, the principal gap-junctional protein) occurs early in hypertrophy and infarction [75]. These changes would be expected to influence myocardial conduction and have been correlated with inducibility of ventricular arrhythmias in a post myocardial infarction canine model [76].

1.2.5.5 Stretch

Myocardial stretch can change transmembrane potentials, which has been termed "Contraction-Excitation Feedback" [77]. Alterations in ventricular geometry, pressure, size and function are common to all types of chronic heart failure, irrespective of the underlying pathogenesis. These abnormalities magnify wall stress and stretch in a nonuniform manner, augmenting spatial dispersion of repolarisation and refractoriness.

Summarising animal and human data in the normal myocyte, stretch may

1. shorten action potential duration and repolarisation
2. increase dispersion of repolarisation
3. increase electrical instability
4. cause early afterdepolarisations

These changes are exaggerated in failing hearts. Ionic mechanisms proposed to account for these changes include stretch regulated activation of inward currents, or inactivation of outward currents. Increases in $[Ca^{2+}]_I$ secondary to reduced Ca^{2+}-troponin binding or altered sarcoplasmic reticulum Ca^{2+} release could activate an inward current by electrogenic Na^+/Ca^{2+} or Na^+/K^+ exchange, or may modify a non-specific "leak" channel. Both mechanisms would prolong action potential duration and repolarisation.

1.2.5.6 Ischaemia and acidosis

The failing hypertrophied heart is predisposed to ischaemia, particularly in the sub-endocardial region, even in the absence of coronary atherosclerosis [54].

Neurohormonal activation, autonomic dysfunction and alterations in endothelial function favour vasoconstriction, compounding ischaemia, which produces acidosis, secondary to lactate accumulation and CO_2 production. Acidosis depolarises the resting membrane potential, moving it closer to threshold. This is partly offset by a more positive threshold membrane potential. Conduction velocity is decreased, possibly due to the change in resting membrane potential, changes in voltage dependence of the Na^+ channel conductance variables, or increased gap junction resistance. Ionic changes implicated include

1. Inhibition of the electrogenic Na^+/K^+-ATPase
2. Increased $[Ca^{2+}]_I$. Acidosis increases $[Ca^{2+}]_i$. By two mechanisms a) displacement from mitochondria and sarcoplasmic buffering sites, and b) activation of Na^+/H^+ exchange, which extrudes H^+ for Na^+, causing an increase in intracellular Na^+. This decreases Ca^{2+} extrusion via the Na^+/Ca^{2+} exchanger, activating inward current via the Na^+/Ca^{2+} exchanger and a non-specific cation channel.
3. Decreases in K^+ currents
4. Accumulation of intercellular K^+, which would partially depolarise the membrane.
5. Direct effects of acidosis (via intracellular H+ concentration) on non-specific cation conductance and inhibition of the Na+/Ca2+ exchanger.

These changes augment the prolongation of action potential duration seen in hypertrophy, and predispose to afterdepolarisations.

1.2.5.7 Spatial and temporal heterogeneities

The most obvious structural and electrophysiological abnormality common to all types of chronic heart failure is the dispersion of change throughout the ventricle. Irrespective of aetiology, hypertrophy is nonuniform. Interstitial fibrosis, disruption of intercellular connections, regional disparity of sympathetic innervation and sensitivity, wall stresses, acidosis and intracellular Ca2+ overload produce variation in the density and time course of transmembrane currents. These compound spatial and temporal dispersion of action potential conduction, repolarisation, and refractoriness. This enhances the arrhythmogenic substrate provided by the isolated myocyte. Extrinsic factors such as diuretic induced electrolyte imbalance and antiaarrhythmic medication have important electrophysiological effects, which may promote arrhythmogenesis.

1.2.6 *Arrhythmias Present in Heart Failure*

Typical arrrhythmias include atrial and ventricular extrasystoles (in over 70% of patients), atrial fibrillation (arguably the most important, occurring in up to 20% of patients) and nonsustained polymorphic ventricular tachycardia [78]. Sustained monomorphic ventricular tachycardia is less common, but more likely in heart failure secondary to previous myocardial infarction [79]. This pattern of arrhythmia suggests complex functional re-entry and triggered automaticity as mechanisms rather than single circuit re-entry [80] (see **Table 1-2**).

Table 1-2: Mechanisms of arrhythmogenesis in chronic heart failure

Mechanism	Requirements
Reentry	
	Altered conduction velocity/ repolarisation
Enhanced Automaticity	
	Increased pacemaker current
	Increased T-type Ca2+ current
	Decreased outward K+ current
Afterdepolarisations	
Early	Reduced outward current
	Increased inward current
Delayed	Transient abnormal inward current

1.2.7 *Mechanisms of Arrhythmogenesis*

1.2.7.1 Re-entry in chronic heart failure

The essential requirements for re-entry are unidirectional conduction block and a specific pathway for impulse propagation. Areas of slow conduction facilitate re-entry, which is usually dependent on an initiating trigger, such as an extrasystole. These requirements may be met by anatomical or functional obstacles. It has been demonstrated that re-entry may occur in the absence of anatomical obstacles [81]. Functional slowing (or block) of conduction caused by abnormal cellular transmembrane properties (including the changes in the resting membrane potential, dispersion of repolarisation and heterogeneity of refractoriness discussed above) provide a substrate for re-entry. The abnormal prolonged repolarisation and heterogeneous recovery of excitation leads to dispersion of repolarisation. This

increases the susceptibility of the myocardium to ventricular arrhythmias. Cardiac muscle is anisotropic, such that conduction is faster in the direction of fibre orientation, and slower perpendicular to fibre orientation. It has been shown that anisotropic re-entry occurs in the epicardial border zone of infarction, and that in this region anisotropy is non-uniform and magnified. Disturbances in ventricular geometry and fibre orientation secondary to infarct scar, ventricular remodelling and dilatation, intercellular fibrosis and disrupted inter-cellular connections may all predispose to magnification of anisotropic conduction. Functional re-entry provided by anisotropy need not necessarily occur around an anatomical obstacle (although this may facilitate such re-entry), but the requirements for re-entry may be provided by the micro-anatomical structure, without abnormal transmembrane cellular current flow.

Thus, the distinction between functional and anatomical mechanisms is blurred in the failing, hypertrophied myocardium, and the requirements for re-entry may be provided by spatial and temporal dispersion of repolarisation and refractoriness rather than anatomical obstacles.

1.2.7.2 Afterdepolarisations

Afterdepolarisations are spontaneous oscillations of membrane potential that occur late in the action potential or immediately after repolarisation. They are caused by imbalance between outward repolarising currents and inward depolarising currents. There are two types

1. Early afterdepolarisations, which interrupt phase 2 or 3 repolarisation, and

2. Delayed afterdepolarisations, which occur after repolarisation is complete

When large enough, afterdepolarisations may induce a spontaneously propagating action potential. This is defined as "triggered activity". Even if the afterdepolarisations fail to reach threshold, they may still retard repolarisation and promote further dispersion of refractoriness.

Early afterdepolarisations are prominent at slow heart rates and low extracellular potassium concentrations. They have been demonstrated in hypertophied myocytes subject to acidosis and high concentrations of catecholamines. Membrane resistance is high during the plateau potential, such that even small changes in the net inward current may prolong repolarisation and produce early afterdepolarisations.

Delayed afterdepolarisations are prominent at faster heart rates. Increases in diastolic $[Ca^{2+}]_i$ induce a transient inward current, $\mathbf{I_{ti}}$, which can cause delayed afterdepolarisations. Intracellular diastolic myocyte Ca^{2+} overload, a feature of chronic heart failure, has been described above. In addition, prolonged repolarisation reduces Ca^{2+} extrusion during systole because the electrochemical Na^+ gradient is lowered at plateau potentials, compounding the problem. The mechanism of $\mathbf{I_{ti}}$ is unclear, but most evidence favours changes in Na^+/Ca^{2+} exchange induced by calcium release from the sarcoplasmic reticulum.

1.2.8 *Autonomic Nervous System Dysfunction in Chronic Heart Failure*

Following myocardial injury there is acute activation of the sympathetic nervous system. This is initially an adaptive response serving to maintain cardiac output and arterial pressure. Even when left ventricular dysfunction is asymptomatic [82], the sympathetic nervous system is activated. However, sustained sympathetic neuronal activation activates the renin angiotensin aldosterone system, with deleterious consequences.

Autonomic nervous system dysfunction may be assessed by a number of different methods: plasma markers of neuroendocrine activation; direct sympathetic nerve microneurography; noradrenaline spillover techniques; power spectral analysis of heart rate or measurement of baroreflex sensitivity.

Direct recordings of muscle sympathetic nerves in humans have demonstrated marked activation of the SNS in mild [83] and severe heart failure [84]. Noradrenaline spillover techniques have demonstrated that cardiac sympathetic nerve activity precedes changes in renal or muscle sympathetic nerve activity [85].

Atrial natriuretic peptide is activated early in heart failure. This has a direct renal natriuretic effect; inhibits renin and noradrenaline release; attenuates their vasoconstrictor actions and decreases sympathetic outflow by baroreceptor action [86]. In animal models of heart failure, ANP is elevated before plasma renin and aldosterone, i.e. before the RAAS is activated, and may in fact suppress it. However, in humans with severe heart failure, plasma renin and aldosterone are increased [82]. Initially, RAAS activation may be beneficial in increasing preload and afterload, but in the long-term it is deleterious. Angiotensin-II, a potent systemic vasoconstrictor, causes renal efferent arteriolar constriction, favouring proximal tubular sodium resorption; stimulates aldosterone release, further augmenting the sodium avid state; and increases thirst whilst decreasing water excretion [87]. Centrally, Angiotensin-II facilitates sympathetic nerve outflow, while peripherally it facilitates noradrenaline release from adrenergic nerves. As heart failure progresses, the effect of atrial natriuretic factor is blunted [88], and the beneficial vasodilatory effects of endothelium-derived relaxant factor are attenuated [89]. As sympathetic activity causes renin release, and angiotensin-II enhances the effects of noradrenaline [90], there is mutual neuroendocrine augmentation leading to unopposed vasoconstriction and salt and

water retention. Angiotensin-II and aldosterone are also implicated in promoting pathological hypertrophy, myocyte necrosis and interstitial fibrosis [91].

Chronic sympathetic overactivity leads to desensitisation of the myocardium to sympathetic stimulation [92]. In human heart failure, β_1 receptors are downregulated to a greater extent than β_2 receptors [93], and β_2 receptors are uncoupled from their effectors. The end result is decreased cardiac sensitivity to sympathetic stimulation, whilst vasoconstriction is unopposed.

Prior work has documented that parasympathetic function (assessed by bedside testing [94], heart rate variability techniques [95] or baroreflex sensitivity [96]) is depressed in chronic heart failure.

1.2.8.1 Aetiology of autonomic dysfunction

Sympathetic nervous system activity is modulated by

1. Baroreceptor inhibition
2. Excitatory afferents (muscle metaboreceptors, peripheral chemoreceptors and cardiac sympathetic afferents)
3. Centrally acting neurotransmitters, which can be inhibitory or excitatory.

1.2.8.1.A Baroreceptor abnormalities

Baroreceptors play a central role in autonomic cardiovascular control. Arterial and cardiopulmonary baroreceptor function is abnormal in heart failure [97]. The mechanism or mechanisms underlying this abnormality could involve any part of the reflex arc, including the afferent limb (generation and transmission of neural impulses), central processing (in the nucleus tractus solitarius), or the efferent limb. Studies using a canine model of low-output heart failure have demonstrated decreased

baroreceptor gain (change in baroreceptor firing rate per mmHg change in arterial pressure), but augmented central integration, allowing normal inhibition of renal efferent sympathetic nerve activity [98]. The same investigators subsequently demonstrated abnormalities in the afferent limb of the cardiopulmonary mechanoreceptor reflex [99]. In rat models, direct measurements of single-unit baroreceptor nerve activity demonstrate a higher threshold pressure for activation, diminished afferent baroreceptor gain, and a lower peak baroreceptor discharge rate [100]. These data confirm the presence of abnormalities in the afferent limb, but dysfunction of central integration and the efferent limb are as yet unproven.

There are 3 proposed models of baroreflex dysfunction:

1. Mechanical: changes in ventricular compliance may be linked to abnormalities of the pressure-discharge relationship
2. Humoral: although enalaprilat has been shown to improve baroreflex function in dogs with heart failure, most studies document that RAAS activation occurs after sympathetic excitation, and so it is difficult to implicate the RAAS in the induction of baroreflex dysfunction.
3. Ionic: dog models of heart failure demonstrate augmented carotid baroreceptor Na^+- K^+ adenosinetriphosphatase activity. This could be reversed with ouabain, which augmented baroreflex sensitivity.

Sympathetic nervous system hyperactivity in heart failure is limited to organs usually subject to baroreflex restraint. Thus skin sympathetic nerve activity is not increased in heart failure [101]. Baroreflex control of forearm blood flow is abnormal [102], as is baroreflex control of muscle sympathetic nerve activity [103]. There is also evidence that abnormal baroreflex control of sympathetic nerve activity precedes more

generalised neuroendocrine activation [83]. The fact that arterial as well as cardiopulmonary baroreceptors are important in the sympathetic overactivity is exemplified by normalisation of autonomic dysfunction following cardiac transplantation, even though cardiac baroreceptors would be denervated [104].

1.2.8.1.B Excitatory afferent abnormalities

Abnormalities of skeletal muscle metabolism and afferent nerve activity play a role in the symptoms of heart failure [105]. However, as sympathetic activity precedes demonstrable muscle abnormalities, being increased in asymptomatic heart failure, it seems unlikely that such abnormalities are the principal force behind the autonomic dysfunction seen in heart failure. Chemoreceptor sensitivity is increased in chronic heart failure. However, acute administration of oxygen to patients with heart failure does not reduce muscle sympathetic nerve activity [106]. Arterial hypoxaemia is uncommon in heart failure [40], so it is unlikely that chemoreceptor abnormalities initiate neuroendocrine activation.

1.2.8.1.C Central nervous system dysfunction

A number of potential central mechanisms exist for the sympathetic nervous system activation of heart failure:

1. Increased excitatory neurotransmission
2. Increased sympathoexcitatory endogenous brain oubain-like activity
3. Central activation of AT-II
4. Decreased nitric-oxide neuroinhibition
5. Abnormal insulin and/or opiate control of sympathetic outflow.

There is increased central nervous system turnover of noradrenaline and adrenaline in patients with heart failure [107], associated with increased cardiac noradrenaline spillover. Increases in brain ouabain like activity have been described in animal models of heart failure. The associated elevated resting noradrenaline levels were normalised by intracerebroventricular administration of digibind, implicating brain ouabain-like activity in the sympathoexcitation of heart failure [108]. The overall role played by central mechanisms in sympathoexcitation of heart failure remains unclear.

1.2.9 *Heart Rate Control*

The normal resting heart rate varies between individuals. It is dependent on physiological and pathological stresses, age and level of cardiovascular fitness. Heart rate is determined by the rate of depolarisation of phase IV of the cells in the sinoatrial node. There is a constant, autonomically mediated variation in the sinus node rate, which occurs on a beat-to-beat basis. The intrinsic heart rate, in the absence of neurohumoral influence (under full autonomic blockade) is approximately 100 bpm. At any one time, heart rate depends on the balance between the opposing effects of the sympathetic and parasympathetic nervous systems.

1.2.9.1 Parasympathetic (Vagal) control

The vagus nerve innervates the sinoatrial node, atrioventricular node and possibly the ventricles. Experimental stimulation of the vagus nerve slows the sinoatrial discharge rate and atrioventricular conduction. The latency of this effect is very short: maximal slowing may occur within 400 msec, i.e. within one beat. Paradoxically, at lower vagal firing frequencies close to the heart rate vagal activity may entrain the sinoatrial cells and cause small increases in heart rate. The physiological importance of this is unclear.

The slowing produced is dependent on the frequency of vagal firing, and the response curve best fits a hyperbola: although if the pulse-interval i.e. RR interval is plotted the relationship is linear. Thus the response to vagal stimulation is dependent on the initial heart rate: prolonging the RR interval by similar amounts will result in greater decreases in heart rate from higher initial heart rates.

1.2.9.2 Sympathetic control

Postganglionic sympathetic fibres innervate the whole heart, and sympathetic activation increases both rate and force of contraction. There is a latency of about 5 seconds with a progressive increase in heart rate that reaches a plateau after about 30 seconds. The effect is non-linear, and right sympathetic stimulation has a greater effect on heart rate than left stimulation, which is more concerned with inotropic regulation.

1.2.9.3 Baroreceptor control

Arterial baroreflexes were first discovered in 1900 by two Italian physiologists, Pagano and Siciliano. They demonstrated that the pressor effects of carotid occlusion depended on integrity of nervous structures located near the carotid vessels. Subsequent work by Hering and Koch in the 1920s identified the afferent part of the reflex as the glossopharyngeal nerve, and described the vasodepressor and cardioinhibitory results of carotid stimulation.

Baroreceptors consist of specialised nerve endings in the adventitia of the carotid sinus and aorta, which are capable of responding to fluctuations in arterial blood pressure. Increased blood pressure distends the walls of the arteries, causing increased frequency of baroreceptor afferent firing. After the initial rapid change, if the blood

pressure stabilises, baroreceptor firing readjusts to a moderately raised level. This resetting is both early and rapid, but if elevated blood pressure persists a chronic phase may take place over several months. Their discharge provides the central nervous system with beat by beat information on the state of the circulation: pressure changes as low as 1 mmHg alter baroreceptor discharge rate.

The relationship between distending pressure and heart rate is sigmoidal, and the cardiac response may operate at a different range to the vascular response. The net change is due to summation of carotid and cardiopulmonary baroreceptors.

The bradycardic response to baroreceptor stimulation is mediated by vagal cholinergic mechanisms: the response is abolished by atropine and unaffected by β-blockers [109]. Because the bradycardic response is vagally mediated, the latency of the reflex is short, from 200 to 475 milliseconds [110]. Thus, baroreceptors are able to modulate the sinus rate on a beat to beat basis. However, the tachycardic response to baroreceptor deactivation is not exclusively mediated by vagal/cholinergic mechanisms, as it requires combined autonomic blockade with atropine and propranolol to abolish it.

1.2.9.4 Assessment of autonomic dysfunction

Autonomic nervous system dysfunction may be assessed by a number of different methods: plasma markers of neuroendocrine activation; direct sympathetic nerve microneurography; noradrenaline spillover techniques; power spectral analysis of heart rate or measurement of baroreflex sensitivity. In large populations, direct sympathetic nerve microneurography and noradrenaline spillover techniques are impractical.

However, prior work has documented that parasympathetic function, assessed by bedside testing [94], heart rate variability techniques [95] or baroreflex sensitivity [96], is

depressed in chronic heart failure. In post-myocardial infarction populations these measures correlate poorly with each other, or with the extent of coronary disease or severity of left ventricular dysfunction. They provide independent prognostic information on cardiac mortality post-myocardial infarction [111]. At the time of the original grant proposal, their prognostic utility in patients with heart failure was not known.

1.3 EPIDEMIOLOGY OF CHRONIC HEART FAILURE

Epidemiological data on heart failure remain scarce, despite the condition being a growing and major health burden. There are a number of reasons for this.

1. There is no universally agreed definition of heart failure.
2. The diagnosis of heart failure on clinical grounds alone is often inaccurate [112], particularly in the elderly and obese.
3. Objectively documented cardiac dysfunction need not necessarily be accompanied by symptoms of heart failure, although there will often be biochemical evidence of neuroendocrine activation [113].

Thus epidemiological data on heart failure are heterogeneous, accounting for the widely disparate figures of incidence, prevalence and frequency of aetiology.

Heart failure in the Framingham community was defined on the basis of a scoring system [114]. It was found to be highly prevalent, affecting approximately 1% of people aged 50 or over, rising to 10% of those aged over 80. The mean incidence of 4 /1000 population/annum also rose rapidly with increasing age. At all ages, men were affected more frequently than women. Hypertension preceded 75% of cases, with 46% of men and 27% of women having co-existent coronary disease [115]. A large community study of

the North Glasgow population incorporated echocardiography [116] and biochemical markers of neuroendocrine activation [117]. The prevalence of definite left-ventricular systolic dysfunction (defined as a left-ventricular ejection fraction < or = 30%) was 2.9%. In contrast to the Framingham data, only 20% of cases were accompanied by hypertension (defined by WHO criteria as blood pressure >160/95 mmHg), and over 80% of cases had ischaemic heart disease. Hypertension was defined in the Framingham cohort as a blood pressure >140/90 mmHg. Reanalysis of the Glasgow data has shown that 50% of heart failure cases would have co-existant hypertension using this definition [118]. The consensus from this and other community data [119] is that the underlying aetiology in heart failure has changed, and that the majority of cases have an ischaemic aetiology.

It is also evident that heart failure is increasingly common. Analysis of hospital discharges from Scottish hospitals document a 60% increase in the heart failure discharge rate from 1980 to 1990, accounting for almost 4% of all general medical discharges [120]. The socio-economic burden of this is enormous: it has been estimated at 1-2% of the total health care budget, of which two thirds is accounted for by inpatient care. The more severe the heart failure, the greater the cost [121].

This increasing trend may represent an increasing community prevalence, presumably due to an ageing population and increasing survival from myocardial infarction. It is thus clear that heart failure represents a major public health burden in developed countries [122].

1.4 PROGNOSIS

It has long been recognised that heart failure carries an adverse prognosis:

> *"When left ventricular failure develops...the prognosis in untreated cases is poor, patients seldom living more than eighteen months." PD White: Diseases of the Heart, 1953*

Figures from the Framingham cohort estimated the median survival from the onset of heart failure as 1.7 years in men, and 3.2 years in women [123]. Mortality increased with increasing age, and there was no evidence of any appreciable improvement in prognosis over the four decades of study. Large trials of vasodilator therapy in chronic heart failure reveal a mortality of 50% at 6/12 months for severe heart failure [124], and 15% per annum for less symptomatic ambulant patients [125]. Patients with mild heart failure and ejection fraction >35% have a more favourable prognosis, but still manifest a 10% annual mortality despite treatment with vasodilators [126].

1.4.1 *Classification of Death in Heart Failure*

Early death occurs with alarming frequency after the onset of chronic heart failure. Death has been classified as that due to progressive pump dysfunction preceded by worsening symptoms, or as sudden death, occurring within one hour of the onset of symptoms and presumed to be secondary to ventricular arrhythmia [127]. Although total cardiac mortality increases with increasing severity of heart failure, the proportion of sudden death falls, such that the overall frequency is approximately 50% [128]. At the time of the original grant proposal for this study, published work suggested that sustained ventricular arrhythmias were the commonest cause of sudden death in chronic heart failure [129]. However, the limitations of the classification of cardiovascular death are now well recognised [130], and even given strict criteria for sudden death, the causes and mechanisms of death in chronic heart failure are diverse. The database provided by trials of implantable defibrillators [131] has confirmed earlier work that sudden death need not necessarily be caused by ventricular arrhythmias [132]. Even with electrocardiographic monitoring, precise definition of the mode of death is difficult [133]. Thus, mechanistic assumptions about sudden death are flawed, and the underlying assumption that sudden death is equivalent to death caused by ventricular

arrhythmias is untenable. However, irrespective of the definition used, sudden death constitutes the major mortality burden in patients with mild heart failure [134]. The causes of non-tachyarrhythmic sudden death that maybe prevalent in patients with severe heart failure eg pulmonary emboli [132], are unlikely in this population. As such, despite the above caveats, it is likely that a major proportion of sudden deaths in mild heart failure are secondary to ventricular arrhythmias.

The accurate elucidation of those patients at greatest risk of sudden death remains elusive. This is not entirely surprising, as the cellular mechanisms underlying arrhythmias in heart failure are complex (see **section 1.2.7**). The disorganised ventricular activation, abnormal Ca^{2+} handling, dispersion of repolarisation and/or refractoriness and disordered autonomic tone present in chronic heart failure all interact to promote arrhythmogenesis.

1.4.2 *Prognostic Clinical Variables*

1.4.2.1 Age and gender

The incidence and prevalence of chronic heart failure increase with age, and elderly patients have a worse prognosis. However, under the age of 75 years there is little age-specific difference in mortality in patients with chronic heart failure [135]. Figures from the Framingham cohort estimate the median survival from the onset of heart failure as 1.7 years in men, and 3.2 years in women [123]. One and five year survival rates were 57% and 25% in men, and 64% and 38% in women. The age adjusted mortality was also higher in men [136]. However, in the SOLVD registry female gender carried an adverse prognosis [137]. Generally, when subject to the scrutiny of multivariate analysis, gender carries little prognostic import.

1.4.2.2 Symptoms

Irrespective of whether symptoms are assessed crudely or using more objective measurements of quality of life scores and specific activity scales, increasing severity of symptoms correlate with a worse prognosis. The most widely used system of classification is that of the New York Heart Association, which divides patients into four classes based on their reporting of their level of daily activity [138]. Assessment of symptoms, particularly variation in grading of moderate heart failure, can be problematic [139]. In the present study, symptoms were also assessed objectively using a validated disease specific scale, the Minnesota living with heart failure questionnaire [140].

1.4.2.3 Signs

Despite the poor sensitivity, specificity and reproducibility of clinical signs in chronic heart failure, a number of features delineate a worse prognosis. Cardiac cachexia has recently been shown to carry independent prognostic information [141]. As in many other cardiac disease states, faster heart rates define a poorer outlook, and a group who may benefit most from specific therapies [142]. Although some studies have suggested that atrial fibrillation carries a worse prognosis [143], the V-HeFT studies revealed no difference in mortality or morbidity with this arrhythmia [144]. The reason for this difference is unclear, but may reflect increasing awareness of the dangers of using class Ia and Ic antiarrhythmic therapy for atrial arrhythmias in chronic heart failure [145]. As atrial fibrillation precludes assessment of heart rate variability or baroreflex sensitivity, and renders QT measurements difficult, patients with atrial fibrillation were excluded from the study. Low arterial pressure is an indicator of poor prognosis in chronic heart failure [146], but the increasing use of vasodilator therapy and the emerging role of β-blockade as a therapeutic option may confound this physical sign.

1.4.2.4 Concurrent disease

Hypertension increases morbidity but not mortality [137], possibly because of improved community treatment of hypertension. New ischaemic events worsen prognosis in chronic heart failure. Recurrent cardiac ischaemia, particularly myocardial infarction or unstable angina, is associated with an adverse prognosis [147]. The 1 year mortality rate of patients developing a myocardial infarction was 44.3%, compared to 7.3% of those without infarction. Indeed, 34% of all deaths in the SOLVD studies occurred in this combined patient group. Diabetes mellitus was a potent predictor of mortality in the SOLVD trials and the less stringently selected registry, remaining an independent prognostic factor despite treatment [148].

1.4.2.5 Aetiology of chronic heart failure

The question of whether an ischaemic aetiology carries a less favourable prognosis is vexed by the problem of the potential for misclassification of cardiomyopathy aetiology. In the SOLVD data set an ischaemic aetiology did not confer a statistically significant adverse prognosis, but over 11% of patients diagnosed as having a nonischaemic aetiology were admitted with a myocardial infarction or unstable angina. Although some of these events may have been embolic, it suggests a significant number of patients were misclassified despite quite stringent entry criteria. This data underscores the difficulty of making a clear-cut distinction between ischaemic and nonischaemic aetiologies.

1.4.3 *Plasma Biochemistry*

Serum sodium concentration is inversely related to plasma renin concentration and is a powerful predictor of cardiovascular mortality in chronic heart failure [149]. Most reports have studied patient populations with severe chronic heart failure referred for

cardiac transplantation. There are fewer data linking plasma sodium concentration with prognosis in milder chronic heart failure. However, the recent UK Heart study did confirm the prognostic power of serum sodium in an ambulant population with milder chronic heart failure [150]. Hypokalaemia and elevated urea and creatinine have also been linked to a poor prognosis [151]. Recent data support the view that hypokalaemia may be diuretic induced and linked to the development of ventricular arrhythmias and sudden death [152]. Generally, the prognostic power of these biochemical changes has been less when plasma natriuretic peptides or plasma noradrenaline are measured concurrently.

1.4.4 *Objective Assessment Of Left Ventricular Systolic Dysfunction*

Ejection fraction remains the most commonly used measure of left ventricular systolic dysfunction. Left ventricular ejection fraction measured by radionuclide ventriculography has predicted mortality in many studies of chronic heart failure. Although no randomised study has proven that echocardiographic assessment of left ventricular ejection fraction can predict prognosis, other echocardiographic variables such as left ventricular fractional shortening and internal dimensions carry prognostic weight [153]. However, echocardiography was used to measure ejection fraction in over 90% of ambulant subjects in a SOLVD registry, and did provide independent prognostic information [154]. European guidelines for the diagnosis of heart failure suggest that echocardiography should be used routinely to assess left ventricular function [34]. Echocardiography is simple, safe, and widely available. M-mode echocardiograms can be used to determine left ventricular end systolic and end diastolic dimensions. If the ventricle is assumed to be ellipsoid and to have a uniform contraction pattern left ventricular volumes and thus ejection fraction can be

calculated. However, regional wall motion abnormalities are common in heart failure, so that a biplane disc summation method is more valid. Recent data suggest that semi-quantitative assessment of overall left ventricular systolic function is a valid technique that correlates closely with formal echocardiographic or radionuclide measurement of left ventricular ejection fraction. This method also allows assessment of systolic function when there is insufficient definition of endocardial outline to allow formal calculation of ejection fraction [155].

1.4.5 *Cardiopulmonary Exercise Testing*

As oxidative metabolism consumes O_2 (VO_2) it produces carbon dioxide (VCO_2) - the metabolic source of CO_2. About 80 ml of CO_2 are produced for every 100 ml of O_2 consumed, so that the respiratory gas exchange ratio ($R=VCO_2/VO_2$) at rest is approximately 0.8. Cellular respiration is linked to cardiopulmonary respiration so that O2 delivery matches O_2 consumption. Normal arterial O_2 content is 19ml/100ml. Some is extracted by respiring tissues, and venous O_2 saturation is a function of O_2 delivery (i.e. systemic blood flow) and O_2 extraction. Both are linked to O_2 consumption, VO_2. At rest, VO_2 averages 245 ml/min, while O_2 delivery is 950 ml/min (i.e. 5L/min of blood $\times$ 19ml O_2/100ml of blood). Thus systemic O_2 extraction averages 25%.

During strenuous exercise minute ventilation (V_E) increases as much as 8-fold. However, less than 50% of total possible ventilatory response (maximal minute ventilation $\times$ forced vital capacity) is needed for even heavy workloads. Cardiac output increases maximally by only 4-5 fold. Cardiac output increases by 2 mechanisms: a) vagal withdrawal and sympathetic drive increase heart rate, and b) increased venous return increases end diastolic volume, which along with increased

adrenergic drive augments cardiac contraction. Thus during exercise the stroke volume increases and end systolic volume decreases, i.e. heart size decreases. Tissue O_2 extraction increases to a maximum of 75%, but even with this mechanism the combined cardiac and tissue reserve poses a limitation to aerobic work, and determines maximal aerobic capacity, or maximal oxygen consumption, VO_2 max.

In the completely "average" subject

maximal cardiac output = 20L/min

maximal tissue extraction = 75%

arteriovenous O_2 difference =14ml/100ml=140ml/L

VO_2 max = CO × arteriovenous O_2 difference

VO_2 max = 2800ml/min (20× 140) = 40ml/min/kg

These compensations to exercise are abnormal in patients with chronic heart failure. Maximal cardiac output is decreased and correlates strongly with VO_2 max. In mild heart failure, stroke volume increases during light workloads, and then fails to rise further. As the severity of chronic heart failure increases, stroke volume becomes fixed earlier in exercise, such that cardiac reserve becomes solely dependent on increases in heart rate. Additionally, chronic changes in muscle and microvasculature described above further limit O_2 delivery to metabolising muscle cells.

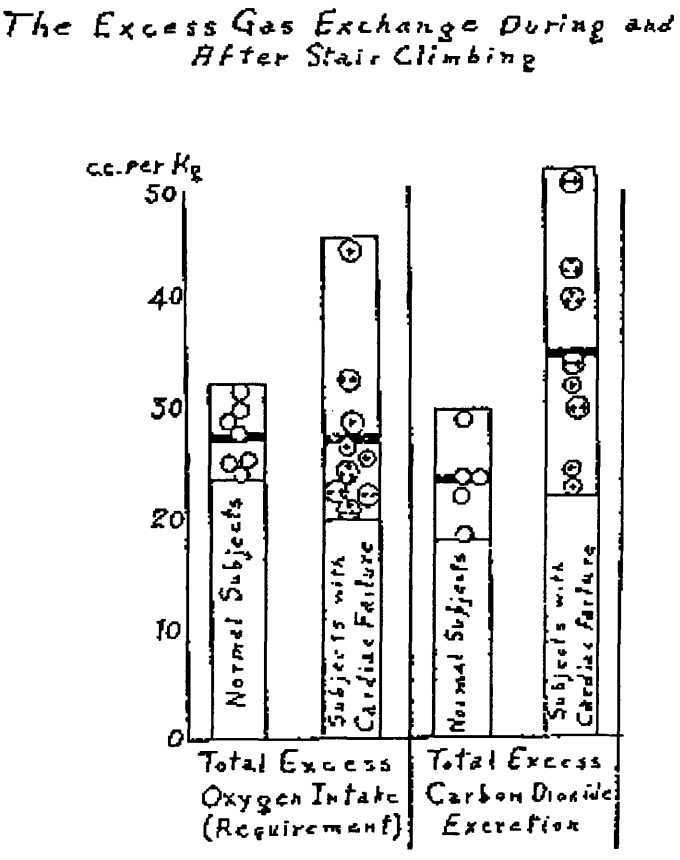


Figure 1-2: Early records of gas exchange measurements: stair climbing

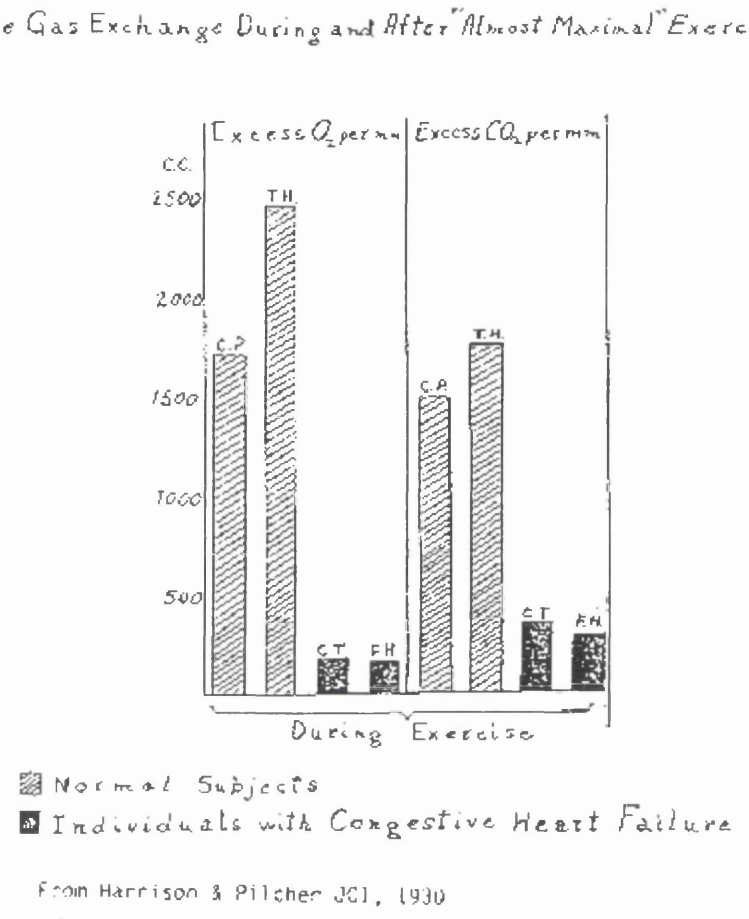


Figure 1-3: Early records of gas exchange measurements: maximal exercise

(Figure 1-2 & Figure 1-3 adapted from references 156 and 157)

The first work on gas exchange in patients with heart failure was undertaken seven decades ago by Harrison and colleagues in the 1920s [156] (see **Figure 1-2** & **Figure 1-3).** They demonstrated that the oxygen debt was increased and that VO_2 max was reduced in patients with heart failure. They also recognised that increased carbon dioxide production was derived from HCO_3^- because it buffered metabolic acid. It was subsequently recognised that lactate increased during exercise only at heavy work rates, thereby implying a lactate or anaerobic threshold.

Later work by Weber and colleagues [158] demonstrated that cardiopulmonary exercise testing provided objective measurement of cardiopulmonary impairment.

1.4.6 *Prognostic Power Of Exercise Variables*

Simple tests such as the 6-minute walk test carry independent prognostic information in patients with heart failure. Compared with patients walking at least 450m, subjects with the lowest level of performance have a 3.7 fold increased mortality [154]. Workload achieved on bicycle or treadmill or bicycle ergometer correlates closely with VO_2 . However both protocol and the patient can influence this association. Many studies during the 1970s and 1980s documented the relationship between exercise time and survival, but included a heterogeneous group of patients with disparate endpoints [159].

Numerous studies have reported the independent prognostic power of maximal or peak oxygen consumption. Two year event free survival rates for patients with peak $VO_2 \leq 14$ ml/kg/min was 48% compared with 84% of patients with a peak $VO_2 \geq 14$ ml/kg/min [160]. Because of this, peak VO_2 is the only cardiophysiological prognostic factor routinely used as a selection criteria in heart failure patients being evaluated for cardiac transplantation [161]. Which value should be used to as a cut-off

to dichotomise mortality outcome remains unclear [162], which ignores the fact that inability to exercise is in itself prognostic [163]. Indeed, the value of VO_2 used to dichotomise "good" or "bad" outlook appears unimportant. In one report, there was a 20% difference in three year mortality between the two groups, irrespective of the cut point chosen . However, the lower the value, the lower the survival in each group [159]. Whether VO_2 should be corrected for age and gender remains unclear. In one survival study of 500 patients, subjects whose peak VO_2 was $\leq$ 14ml/kg/min but > 50% of their age and gender predicted value had survival rates similar to patients achieving a VO_2 $\geq$ 14ml/kg/min. In this study the inability to raise systolic pressure to more than 120 mmHg identified a particularly poor prognostic group (three years survival 55%) [164].

In a recent prospective study, cardiopulmonary exercise testing was of more importance than resting haemodynamic data [165]. Resting data ignore the incremental prognostic power of the haemodynamic response to exercise [166] or improvements in haemodynamics with therapy, as even those patients with severe chronic heart failure who respond have a good prognosis [167].

Thus, cardiopulmonary exercise testing provides a non-invasive assessment of global cardiovascular function, and has a central role in the assessment of subjects with chronic heart failure.

1.4.7 *Holter Monitoring and Ventricular Ectopy*

Ventricular premature beats are common in patients with heart failure. Ambulatory electrocardiographic monitoring reveals single ventricular ectopic activity in over 70% of patients, and nonsustained ventricular tachycardia in 20% of patients. Many factors predispose to ventricular arrhythmias in heart failure: underlying structural disease, electrolyte abnormalities, neurohormonal changes and, possibly, therapeutic

interventions (see **section 1.2.5**). The frequency of ambulant ectopy is related to the severity of underlying cardiac function [168], although this is less clear in non-ischaemic cardiomyopathy [169]. There is considerable intra-individual day-to-day variation [170], which further confuses the situation. The most recent data are available from analysis of placebo controlled trials of amiodarone in heart failure. In the GESICA study [171], frequent ventricular ectopy and/or couplets did not predict death in the study cohort. However, the presence of nonsustained ventricular tachycardia (defined as 3 or more ventricular beats at a rate >100 bpm) identified a group at high risk of sudden death. This is at variance with previously published data. Most studies have found that frequent ventricular ectopy and nonsustained ventricular tachycardia indicate a worse prognosis [172], but are not strong independent predictors of sudden death.

1.4.8 *Signal-averaged Electrocardiography*

Late potentials on the body surface recorded by applying signal averaging techniques to the surface electrocardiogram are a manifestation of delayed, asynchronous ventricular activation [173].

Late potentials are predictive of arrhythmic events and SCD in a post myocardial infarction population. The first clinical application of the signal averaged ECG was in pre-discharge risk stratification after acute myocardial infarction [174]. The definition of a positive late potential was qualitative rather than quantitative, but patients with late potentials had a sudden death rate of 11% and ventricular tachycardia rate of 17% in short-term follow-up. Based on Simson's original work [175], subsequent investigators have used a quantitative approach. Comparison of the studies is made difficult by different standards for acquisition and identification of a positive late

potential. However, taken together, they demonstrated that ventricular arrhythmias and sudden death were more common in patients with a positive late potential. Combining the signal averaged ECG with other non-invasive indices of risk, particularly left ventricular ejection fraction, improves predictive accuracy [176]. The presence of a positive late potential is poorly related to left ventricular ejection fraction [177]. A combination of low heart rate variability and a positive signal averaged ECG increased the risk of any arrhythmic events 18 fold in one study [178]. However, the positive predictive value of an abnormal signal averaged ECG in this patient population remains low, at only 11 to 17% [179].

The prognostic utility of a positive late potential in patients with non-ischaemic dilated cardiomyopathy or advanced ischaemic heart failure is less clear. The frequency of bundle branch block and intraventricular conduction delay in this patient population makes analysis more difficult [180]. Late potentials are more common in ischaemic cardiomyopathy (40% vs 14%) [181], and in patients who have manifested ventricular arrhythmias [182]. Mancini et al [183] prospectively studied 114 patients referred for cardiac transplant assessment with a diagnosis of non-ischaemic cardiomyopathy. Sixty-six patients had a normal signal averaged ECG, 20 patients had an abnormal signal averaged ECG, and 28 patients had bundle branch block. There was no significant difference in clinical, haemodynamic or exercise variables between the three groups. One year event free survival (defined as absence of ventricular tachycardia or death) was 95% in patients with a normal signal averaged ECG, 88% in patients with bundle branch block but only 39% in those with a positive late potential. The signal averaged ECG retained prognostic power in multivariate analysis. However, a past history of sustained ventricular arrhythmia or aborted sudden death was significantly more common in patients with bundle branch block or

a positive late potential. In patients without a past history of ventricular arrhythmias an abnormal signal averaged ECG did not predict death in patients with non-ischaemic cardiomyopathy although patients with ischaemic cardiomyopathy and positive late potential had decreased survival (73% vs 81% one year mortality) [184]. In a recent report (utilising specific criteria for the diagnosis of an abnormal signal averaged electrocardiogram in the presence of bundle branch block), the incidence of spontaneous sustained ventricular tachycardia was significantly higher in the presence of late potentials. However, a positive signal averaged ECG did not predict cardiac mortality [185].

To date, no study has addressed the utility of combining the signal averaged ECG with markers of autonomic dysfunction in patients with chronic heart failure.

1.4.9 *Neuroendocrine activation*

The pathophysiology and time course of neuroendocrine activation in heart failure has been described above (see **section 1.2.8.1**). Neurohormonal activation has been recognised as a potential diagnostic, prognostic and therapeutic target.

1.4.9.1 Plasma noradrenaline

Plasma noradrenaline is elevated in heart failure. The predictive value of elevated noradrenaline in symptomatic heart failure [186] was confirmed in a multivariate analysis of V-HeFT II [187]. Plasma noradrenaline correlated poorly with left ventricular ejection fraction, peak oxygen consumption or cardio thoracic ratio, which were the most statistically significant prognostic variables in V-HeFT II. Mortality in patients with plasma noradrenaline > 900 pg/ml was 60% at 3 years, compared with 25% in patients with plasma noradrenaline <600 pg/ml. A sub study from the SOLVD investigators has extended these findings to patients with asymptomatic left ventricular

dysfunction [188]. Plasma noradrenaline levels above the median of 393 pg/ml were associated with a relative risk of 2.59 for all cause mortality, 2.55 for cardiovascular mortality, 2.55 for hospitalisations heart failure, 1.88 for development of heart failure, 1.90 for ischaemic events and 2.59 for myocardial infarction. These authors concluded that "even modest elevations in PNE levels had significant prognostic importance".

1.4.9.2 Natriuretic peptides

Atrial natriuretic peptide was first demonstrated in 1981, although the amino acid structure was identified three years later. In 1988 brain natriuretic peptide was discovered, although it was subsequently realised that its main source was the cardiac ventricles. The ANP pro hormone is cleaved into two fragments: N-terminal ANP and C-terminal ANP, which is the biologically active moiety but is less stable and more difficult to measure. Collectively, natriuretic peptides produce natriuresis, vasodilatation, antagonise the renin angiotensin aldosterone system and have growth suppressing actions [189]. Both peptides increase in response to volume expansion and pressure overload, cardinal features of cardiac failure. However, ANP may act as an acute response hormone while BNP is only activated after prolonged ventricular overload [190].

Natriuretic peptides correlate with the severity of heart failure but are elevated early in left ventricular systolic dysfunction, before the development of symptomatic heart failure [82]. Plasma BNP may track less closely with left ventricular ejection fraction than ANP [191]. In a random sample of the general population investigated by echocardiography, a BNP concentration of 17.9 pg/mL or more gave a sensitivity of 77% and specificity of 87% in the diagnosis of heart failure [117]. Similar results were found in patients referred with a primary care diagnosis of heart failure [192]. Recent

data did not confirm these findings [193]. Thus, there is a lack of consensus over the relation between plasma concentrations of natriuretic peptides and left ventricular function, possibly because of confounding factors such as blood sampling conditions and the presence of concomitant drug therapy and renal disease. However, elevated plasma ANP levels were associated with increased mortality in moderate [194] and severe [195] heart failure but failed to predict survival in patients with asymptomatic left ventricular dysfunction [188]. Circulating levels of brain natriuretic peptide are increased in patients with heart failure in proportion to the severity of heart disease [189]. Plasma brain natriuretic peptide provides additional independent prognostic information beyond left ventricular ejection fraction in the acute post myocardial infarction setting [196], and has been suggested to provide similar data in chronic heart failure [197].

None of these studies has addressed other measures of autonomic function in chronic heart failure, and the data on brain natriuretic peptide and prognosis remain limited. It was hoped that this study would help clarify these matters, so in a subset of patients natriuretic peptides were measured.

1.4.10 *Heart rate Variability*

The clinical relevance of heart rate fluctuations was first recognised in obstetric medicine when it was noted that foetal distress was preceded by alterations in beat to beat intervals not apparent from analysis of heart rate alone [198]. During the 1970's bedside tests of short term changes in RR intervals were used to detect autonomic neuropathy in diabetics. Subsequently Wolf et al demonstrated the association of reduced HRV (as reduced sinus arrhythmia) and post myocardial infarction

prognosis [199]. In 1981, power spectral analysis of RR intervals was introduced to quantify underlying periodicities in the data [200].

Normal QRS complexes are identified after filtering of artefact and ectopic beats. The QRS is used as a surrogate for the P wave (and hence sinoatrial node) because P wave identification is more problematic and prone to error. Heart rate variability analysis is performed on this sequence of normal to normal interbeat cycle lengths expressed as a function of the beat number. This is known as the NN or RR interval tachogram. There are two main approaches to the measurement of heart rate variability: analysis in the time domain or frequency domain. Time domain analysis addresses the amount of variability present, while frequency domain analysis elucidates the underlying rhythms.

1.4.10.1 Time domain analysis

Time domain measures may be based on the interbeat duration between normal intervals (NN intervals), or on differences between successive NN intervals.

SDNN is the standard deviation of all NN intervals in 24 hours. SDANN, the standard deviation of the 5-minute means, provides an estimate of changes in heart rate due to cycles longer than 5 minutes. SDNNI, the mean of the 5-minute standard deviations, estimates variability of cycle length shorter than 5 minutes. Variables based on differences between adjacent cycle lengths include rMSSD (the root mean square successive differences) and pNN50. rMSSD is calculated where each difference is squared, summed, the result averaged and the square root obtained. pNN50 may be expressed as counts, one count being when the difference between adjacent NN intervals exceeds an arbitrary limit (for example >50 msec), and when the number of counts is divided by the total number of analysed intervals pNN50 may

be expressed as a percentage. Both measurements record very short term heart rate variability and are thought to reflect alterations in autonomic tone that are predominantly vagally mediated. (see **Table 1-3**).

Table 1-3: Definitions of time domain indices of heart rate variability

Variable	Units	Definition
SDNN	msec	Standard deviation of all NN intervals in the 24 hour recording
SDANN	msec	Standard deviation of the mean of all NN intervals for each 5 minute period of the 24 hour recording (cycles >5 min)
SDNNI	msec	Mean of the standard deviations of all NN intervals for all 5 minute periods of the 24 hour recording (cycles <5 min)
pNN50	%	Percentage of all NN intervals where the differences between adjacent NN intervals > 50 msec
rMSSD	msec	The square root of the mean of the sums of the squares of the differences between adjacent NN intervals

SDNN reflects total 24-hour variation, SDANN reflects long term variability, pNN50 and rMSSD reflect very short term variability, and SDNNI may be thought of as an intermediate measure.

1.4.10.2 Frequency domain analysis

Frequency domain analysis is mathematically more complex, and more sensitive to artefact. Frequency domain analysis yields information about the variance in heart rate resulting from periodic oscillations of heart rate at various frequencies. Strictly speaking, to detect possible rhythmicity in the signal mandates absolute stationarity. Such conditions are unknown in biology, particularly over 24-hour time period. Shorter time sequences may be recorded under controlled conditions that approximate

stationarity. Across a remarkably wide range of species it appears that the tachogram signal contains well-defined rhythms.

There are three main components in short term recordings:

1. high frequency (centre frequency 0.25 Hz = 15 cycles per minute)
2. low frequency (centre frequency 0.1 Hz = 6 cycles per minute)
3. very low frequency (centre frequency 0.016 Hz = 1 cycles per minute)

Demonstration of very low frequency bands mandates at least 15 minutes of data. A further band may be demonstrated in data obtained from 24-hour recordings:

4. ultra low frequency (<0.0033 Hz = <0.1 cycles per minute). (See **Table 1-4**)

Table 1-4: Definitions of frequency domain indices of heart rate variability

Power Spectrum	Frequency range	Cycles/Time	Time/cycle
High frequency	0.15 – 0.40 Hz	9 – 24 cycles/min	2.5 sec/cycle – 6.6 sec/cycle
Low frequency	0.04 – 0.15 Hz	2.4 – 9 cycles/min	6.6 sec/cycle – 25 sec/cycle
Very low frequency	0.0033 – 0.04 Hz	0.2 – 2.4 cycles/min	25 sec/cycle – 5 min/cycle
Ultra low frequency	1.15×10^{-5} – 0.0033 Hz	0.2 cycles/min –1 cycle/24 hrs	5 min/cycle – 24 hrs/cycle
Total power	1.15×10^{-5} – 0.40 Hz	24 cycles/min –1 cycle/24 hrs	2.5 sec/cycle – 24 hrs/cycle

Abbreviation Hz: hertz

1.4.10.3 Physiological basis for frequency domain analysis bands

High frequency power (HF) reflects parasympathetic nervous system modulation, representing primarily respiratory variation. Low frequency power (LF) reflects both parasympathetic and sympathetic modulation, possibly representing baroreceptor oscillation [201]. The physiological basis of very low frequency (VLF, 0.0033 – 0.04 Hz) and ultra low frequency power (ULF, 1.15×10^{-5} – 0.0033 Hz) remains unclear, although it has been suggested that they represent the influence of the thermoregulatory, peripheral vasomotor and renin angiotensin systems [202,203].

However, it is incorrect to consider high and low frequency components of heart rate variability as direct measures of autonomic tone. The data supporting LF power as a measure of cardiac sympathetic activity is flawed. There is evidence to suggest that low frequency oscillations are strongly modulated by parasympathetic activity. Manoeuvres designed to block sympathetic nerve traffic have little effect on LF power, whereas low dose cholinergic blocking drugs paradoxically increase LF power. Surrogate measures of cardiac sympathetic activity such as muscle sympathetic nerve traffic or cardiac noradrenaline spillover have poor correlation with LF power. Evidence favouring HF power as a marker for cardiac parasympathetic activity is stronger. There is evidence that the high frequency component of muscle sympathetic nerve variability is positively and tightly correlated with the high frequency component of NN interval variability [204]. In an animal model efferent vagal activity correlated strongly with HF power. HF power can be abolished by high dose atropine in humans. Changes in HF power are strongly influenced by respiratory frequency [205], being 10 fold greater at slower breathing frequencies. This differing response to varying respiratory frequencies may simply reflect the kinetics of sinoatrial node response to

acetylcholine [206]. Therefore, there is little evidence that HF and LF power correspond to actual levels of nerve traffic. The ratio of low to high frequency power (LF/HF) has been suggested as a marker of sympathovagal balance. During graded upright tilt, muscle sympathetic nervous traffic and myocardial noradrenaline spillover increase, as does the LF/HF ratio. Most of this change is due to a progressive reduction in high frequency power rather than an increase in absolute low frequency power. Finally, it should be remembered that there is no physiological need that the level of sympathetic and parasympathetic nervous system activity be balanced, and certainly no physiological evidence that fluctuations of sympathetic nerve traffic and parasympathetic nerve traffic constantly interact [207].

1.4.10.4 Stability of heart rate variability measures

Heart rate variability measures increase with time after myocardial infarction [208]. There is continued debate whether heart rate variability is altered by chronic, uncomplicated coronary disease [209,210]. There is a paucity of data on the stability of heart rate variability over time. In one study of 17 patients with clinically stable NYHA II-III chronic heart failure [211], 24 hour-Holter measures were obtained at baseline and 2 weeks later. Group means and standard deviations were virtually identical, and intraclass correlation coefficients for nearly all time and frequency domain measures were > 0.8, better than repeat measures of noradrenaline. Thus, within group (i.e. NYHA class) and inter-individual measures were stable over this short time period. In a community based study of healthy individuals, short term measures of heart rate variability were found to be highly reproducible [212].

1.4.10.5 Prognostic value of heart rate variability measures

Despite the caveats regarding the underlying pathophysiological significance of various heart rate variability measures, there is growing evidence regarding their prognostic importance.

Early research on heart rate variability focused on post myocardial infarction patients. Using sinus arrhythmia as a marker of heart rate variability, Schneider and Costiloe [213] demonstrated that sinus arrhythmia was depressed in patients with acute myocardial infarction. Wolf et al reported that in patients with acute myocardial infarction who lacked sinus arrhythmia the in-hospital mortality rate was 15.5% compared with 4.1% in patients with retained sinus arrhythmia [199]. Later studies showed that decreased heart rate variability correlated with established post myocardial infarction risk factors such as Killip class, peak creatine kinase and left ventricular ejection fraction [214]. Subsequently, depressed heart rate variability has been shown to be a powerful multivariate prognostic indicator in patients with acute myocardial infarction. Analyses have included established prognostic indicators such as age, NYHA class, clinical evidence of pulmonary oedema in the CCU, left ventricular ejection fraction and ventricular arrhythmias on 24 hour Holter monitoring. Heart rate variability (measured as SDNN) less than 50 milliseconds carried a 5.3 fold increased mortality compared with a group with SDNN >100 milliseconds [215]. Although thrombolysis shifts "cut points" upward, the independent relative risk of depressed heart rate variability is maintained [216].

That heart rate variability is diminished in chronic failure was demonstrated decades ago [94]. Saul et al. [217] confirmed markedly reduced time and frequency domain measures of heart rate variability in patients with severe heart failure when

compared to controls. Heart rate variability measures correlate with left ventricular ejection fraction, although there remains debate regarding the tightness of correlation between heart rate variability and established clinical and haemodynamic indices of severity [218,219]. However, heart rate variability is closely and negatively linked to the degree of a sympathoexcitation measured by noradrenaline levels or muscle sympathetic nervous activity [218].

There is little correlation between depression of heart rate variability and surrogates for arrhythmic death such as the extent and severity of ventricular arrhythmias [220]. Small retrospective studies have addressed the prognostic utility of heart rate variability in dilated cardiomyopathy [221,222] or chronic heart failure [223-226] due to both ischaemic and non-ischaemic aetiologies. Despite different analysis techniques and patient characteristics, most have documented that heart rate variability measures independently identify patients at greatest risk of cardiovascular death. When both time and frequency domain analyses have been performed, spectral measures appear to add little prognostic information to that provided by simple time domain measurements. In a manner analogous to the acute myocardial infarction studies, overall variance (SDNN or total power) provides the greatest prognostic information. Most data suggest that depressed heart rate variability is correlated with clinical and haemodynamic indices of heart failure severity, but that it can still provide independent prognostic information. The total number of deaths in these studies is small, and some investigators found that none of the conventional time and frequency domain measures were related to survival [224]. However, a recent large study has confirmed that patients with low values of SDNN constitute a particularly high-risk group [150].

1.4.11 *Baroreflex Sensitivity*

1.4.11.1 Techniques of assessing baroreflex function

Various techniques have been used to study arterial baroreflexes. Carotid sinus massage has been used for centuries, and was used in primitive medicine to induce unconscious. It is still used as a means of terminating supraventricular tachycardia and for diagnosis of carotid sinus hypersensitivity. Although the baroreceptor stimulation produced by massage is very strong, it is neither precise nor reproducible enough for research studies of baroreflex impairment. Electrical stimulation of carotid nerves was first performed in 1958, and was subsequently used for the treatment of supraventricular tachycardia, hypertension, and angina. Electrical nerve stimulation using an implantable device is now an accepted procedure for refractory angina. Although reproducible, it is invasive, recruits all baroreceptor and chemoreceptor fibres simultaneously and augments ventilation so that the cardiovascular effects are non-physiological and represent the sum of opposing influences. Surgical denervation of the carotid nerves is obviously non-ethical although some earlier workers produced similar results by anaesthetising the carotid sinus with local anaesthetic agents. Apart from the possibility of major complications, the technique also affects chemoreceptor fibres, and it is difficult to assess the completeness of baroreceptor blockade. Occlusion of the common carotid arteries inhibits carotid baroreceptors, and has been used in anaesthetised and conscious animals. Almost unbelievably, it has been reported in humans! Roddie and Shepherd trained subjects to compress their own carotid arteries against the cervical column. As has been pointed out, "there are obvious limitations to the occlusion method".

The two ways of assessing baroreflex impairment in current practice are the variable pressure neck chamber or the use of vasoactive drugs. The bradycardia caused by pressure induced baroreceptor activation may be used to quantify baroreflex function. Two methods have been proposed: incremental bolus injections of phenylephrine until a satisfactory hypertensive response is seen [227], or a ramp method of increasing infusions until a steady state is achieved [228]. Baroreflex sensitivity may also be assessed by off loading the baroreceptors using arterial or venous vasodilators. Generally, values obtained by ramp infusions of phenylephrine or vasodilators are less than those obtained by bolus injection phenylephrine. The advantages of using vasoactive drugs are that the stimulus is physiological, the technique is safe and easy to use, and subjects are unaware of the stimulus. That the heart rate responses are neural is confirmed by the fact that they are absent in denervated hearts and reduced or abolished when the pressure changes are prevented. Limitations of the technique include limited reproducibility (which may reflect unavoidable spontaneous central modulation of baroreflex control) and simultaneous stimulation of cardiopulmonary baroreceptors, although carotid stimulation predominates. However, this latter may be seen as an advantage, acting as a global asssessment of baroreflex function.

A number of investigators have attempted to analyse baroreflex sensitivity from spontaneous fluctuations in heart rate and systolic arterial pressure [229]. Local baroreflex sensitivity is calculated by performing multiple linear regression slopes on sequences of intervals that demonstrate 3 successive increases (or decreases) in systolic pressure and NN interval. Baroreflex gain is defined as the cross-spectral gain of the NN and SAP power spectra where coherence is >0.5. Spectral [230] and linear sequence [231] methods correlate highly with baroreflex sensitivity calculated from phenylephrine slopes in control subjects without evidence of cardiovascular

disease. However, in post myocardial infarction patients the phenylephrine technique allows assessment of baroreflex sensitivity where the non-invasive methods cannot, particularly in patients whose baroreflex sensitivity is depressed [232].

1.4.11.2 Factors modifying baroreflex control

Baroreflex sensitivity is inversely related to age, and declines more rapidly over the age of 65 [233]. Mental stress and exercise diminish the effects of baroreflex stimulation on heart rate, a phenomenon that may be postulated as a link with sudden death in these situations. Baroreflex sensitivity increases during sleep, and there is evidence to suggest a circadian variation in baroreflex sensitivity. Baroreflex sensitivity is decreased in hypertension and a number of cardiac disease states [94].

The location of the defect altering baroreflex sensitivity in patients with cardiac disease is unclear. The abnormality may be localised to the afferent limb, involve abnormal central integration, or involve defects in the efferent limb. All three areas may be involved. Single-unit baroreceptor activity measured from vascularly isolated carotid sinus from dogs with pacing induced heart failure provides insight into the potential abnormalities. The threshold pressure for baroreceptor activation was higher; there was a decreased baroreceptor gain (i.e. change in baroreceptor discharge rate to change in arterial pressure); and the peak baroreceptor discharge rate was decreased compared to controls. Digoxin partly normalised these abnormalities, suggesting that augmented Na^+K^+ATPase could be implicated in baroreceptor dysfunction [234]. However, in a different study, central integration of the afferent impulses appeared to be preserved. Central gain (defined as the ratio of efferent renal sympathetic nerve activity to afferent aortic depressor nerve activity) appeared unimpaired or even increased. However, it should be noted that baroreceptor

modulation of efferent sympathetic nerve activity may be normal when baroreceptor control of heart rate is abnormal [235].

1.4.11.3 Prognostic role of baroreceptor function

Baroreflex sensitivity provides prognostic information in cardiac disease. Interest was first stimulated by a seminal paper using a myocardial infarction model in dogs [236]. Myocardial infarction depressed vagal reflexes, and those dogs demonstrating the greatest depression of baroreflex sensitivity were most likely to develop ventricular fibrillation during a further episode of myocardial ischaemia. Conversely, those animals with preserved baroreflex sensitivity were less likely to develop ventricular fibrillation under similar circumstances.

Clinical studies of baroreflex sensitivity in myocardial infarction have addressed 2 major issues: the time course of recovery and its prognostic value. There is an acute depression of baroreflex sensitivity following myocardial infarction, and in most studies values returned towards normal within one to three months [237].

In an pilot study of 78 post infarct patients, depressed baroreflex sensitivity provided independent prognostic information: annual mortality was 3% in patients with baroreflex sensitivity > 3 msec/mm Hg, but rose to 50% in those with baroreflex sensitivity <3 msec/mmHg [238]. In this small study baroreflex sensitivity did not correlate with left ventricular ejection fraction, and in those patients with depressed left ventricular ejection fraction mortality was increased if there was co-existent depression of baroreflex sensitivity. Subsequently, depressed baroreflex sensitivity post myocardial infarction was also associated with inducibility of sustained ventricular tachycardia at electrophysiological study [239], and the development of future arrhythmic events [240]. A recent large multicentre study has confirmed these

findings [241]. Depressed heart rate variability or baroreflex sensitivity carried a significant multivariate risk of cardiac mortality (hazard ratios 3.2 and 2.8 respectively).

At the time of the grant proposal for this study, evidence linking baroreflex sensitivity with prognosis in patients remote from myocardial infarction was scarce. In a case-control study of patients remote from myocardial infarction with and without ventricular arrhythmias no difference was found in any frequency domain measure of heart rate variability. However patients with ventricular arrhythmias had a significantly lower baroreflex sensitivity (4.2 ± 0.5 vs 8.0 ± 1.1 msec/mm Hg) [242]. A small study (n=35) of patients with mild moderate heart failure demonstrated that a low baroreflex sensitivity (assessed by neck suction) correlated with a poor prognosis. However, in a multivariate model including haemodynamic indices and plasma noradrenaline baroreflex sensitivity did not provide independent prognostic information [243]. More recent data is discussed in Chapter 4 (see section **4.3.2.6 Baroreflex sensitivity**)

1.4.12 *QT Dispersion*

1.4.12.1 Genesis of the T wave

The history of the QT interval began in 1856 went two German physiologists ingeniously attached a frog sciatic nerve to the surface of the ventricle and observed contraction of the gastrocnemius muscle immediately preceding systole. Occasionally they observed a second twitch at the beginning of diastole, and thus were the first to demonstrate that there were two major voltage deflections during each ventricular beat. Subsequently, Burden-Sanderson and Page used a capillary electrometer to obtain continuous records of potential changes in the frog heart, demonstrating a

biphasic deflection. They elegantly obtained monophasic action potentials using heated electrodes, and demonstrated that the duration of electrical excitation in the tissue did indeed last 1.5 seconds, and that spatial variation in action potential duration was responsible for the negativity of the T wave (see **Figure 1-4**). Other investigators confirmed these findings and it was felt that the shape of T wave reflected action potential duration differences between the base and apex of the ventricle [244]. Recent data suggests that the T wave is secondary to electrophysiological heterogeneity across the ventricular wall, with major distinctions in action potential characteristics between epicardium and endocardium [245].

1.4.12.2 QT dispersion: clinical and methodological aspects

There was little clinical interest in the QT interval until 3 reports linking prolongation of the QT interval with sudden death [246-248]. Subsequent investigators correlated a prolonged QT interval with risk of cardiovascular death in a normal healthy population, ischaemic heart disease, post myocardial infarction, diabetic neuropathy and patients presenting with ventricular arrhythmias despite structurally normal hearts [249]. Two major limitations in the use the QT interval heart are determining the end of the T wave and correcting the QT interval for heart rate.

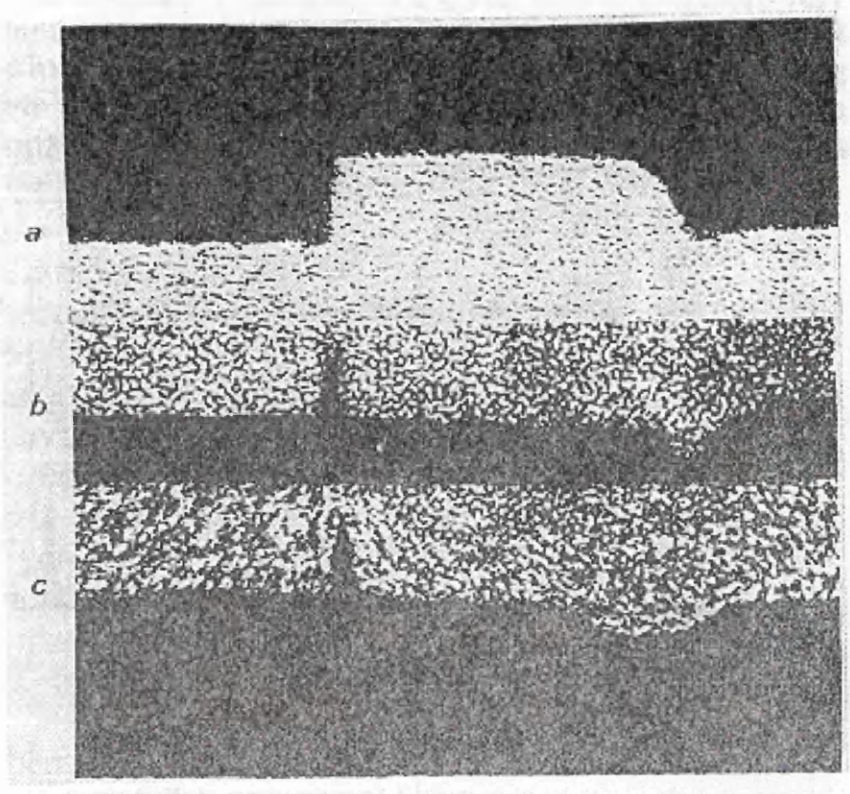


Figure 1-4: The first recorded monophasic action potential (after ref 239)

a) monophasic action potential

b) } surface electrocardiograms

c)

This record demonstrated that the duration of the cardiac action potential was long, about 1.5 seconds in the frog, and could thus acount for the negative voltage deflection of the T wave. See section **1.4.12.1** for details.

That spatial variation in the QT interval of the 12 lead electrocardiogram could provide important information regarding arrhythmia risk was first suggested in 1990 in a seminal report by Day et al [250]. This variation had been commented on previously, although its significance was unrecognised [251]. The surface electrocardiographic QT interval reflects complex and interrelated aspects of cellular electrophysiology, cardiac geometry, torso shape, thoracic impedance and signal processing [252]. There are 2 assumptions: the end of the surface electrocardiographic QT interval is a surrogate for the end of ventricular repolarisation, and that spatial variation in surface electrocardiographic QT intervals measure the known underlying heterogeneity of ventricular repolarisation [253]. This latter assumption is supported by little evidence. In an isolated heart study, total T wave area and T peak to T end interval correlated more significantly with monophasic action potential duration than did QT interval [254]. However, monophasic action potentials measured during cardiac surgery correlated strongly with surface QT dispersion for both sinus and paced beats [255].

There is still no accepted standard for QT dispersion measurement. QT dispersion has been measured by photocopy magnification, using digitising pads, and by automated or computer interactive techniques. The problem of the definition of the end of the T wave remains more important than the method used [252]. Manual measurements of QT intervals are affected by paper speed and amplifier gain [256], but automated measurements fair no better [257]. Intra-observer variability has been documented at about 8 milliseconds [258], but inter-observer reproducibility is worse [259]. Fundamental electrocardiographic theories should also be taken into account: information contained in limb leads is redundant in that if any of 2 of the 6 of recorded, the other 4 may be calculated. Additionally complete information regarding electrical activity is contained only in the vectorcardiogram. If the last 40

milliseconds of ventricular repolarisation is negative in lead I, and equally positive in lead II, then there would be no electrical activity in lead III creating a spurious QT dispersion of 40 milliseconds [260]. Therefore, QT dispersion measured in the frontal plane derived from only 2 leads is unlikely to provide information on local electrical repolarisation.

There is now a growing literature devoted to the prognostic utility of QT dispersion. It is a marker of arrhythmia risk post myocardial infarction [261], in congenital long QT syndromes [250], in patients with documented ventricular arrhythmias [262], and in hypertrophic cardiomyopathy [263] (see **Table 1-5**). Subsequent reports suggested that QT dispersion could be used for prognostic assessment in patient populations at high risk of cardiovascular death such as peripheral vascular disease [264] and non-insulin-dependent diabetes mellitus [265]. However, a recent large study using the best available methodology (previously validated against monophasic action potential duration [254]) failed to demonstrate prognostic significance of any measured QT variable post myocardial infarction [266].

1.4.12.3 QT dispersion in chronic heart failure

The prognostic utility of QT dispersion in chronic heart failure remains unclear. There are data supporting [267-269] and refuting its use [270,271] (see **Table 1-6**).

In the first reported study, Barr et al. characterised 44 patients suffering from severe chronic heart failure. Left ventricular ejection fraction was lower, and plasma neurohormones higher in patients who died of progressive heart failure (n = 12), but only QT dispersion was significantly different between survivors and those who died suddenly (n = 7). Exclusion criteria were not stated, although no patient was on antiarrhythmic drug therapy. The small number of events and flawed statistical

methodology dilutes the significance of these findings.. Subsequently, in 163 patients with left ventricular dysfunction (126 ischaemic) prolonged QTc had a 94% sensitivity and 92% specificity in identifying subsequent sudden death, and was the most important multivariate predictor of survival [269]. Exclusion criteria included atrial fibrillation and antiarrhythmic drug treatment, but not bundle branch block. There were 24 sudden deaths, 10 patients experienced ventricular tachycardia, and 19 died from pump failure. The cut-off value for JTc dispersion was 85 milliseconds, giving a 74% positive and 98% negative predictive accuracy in identifying patients at risk of sudden death or ventricular tachyarrhythmia. Over a quarter of patients at study entrance had JTc dispersion > 85 msec, and 76% of these died suddenly or experienced a ventricular tachyarrhythmia. In comparison, a study of 80 more severely ill patients awaiting transplantation (including ischaemic and non-ischaemic aetiologies) reported that a QT dispersion > 140 milliseconds carried a 4.1 relative risk increase in all cause mortality, but did not predict sudden death. There were 14 cardiovascular deaths in total. However, 17% of patients were in atrial fibrillation, 31% were receiving antiarrhythmic therapy and 50% had bundle branch block. Data from patients with idiopathic dilated cardiomyopathy have been even less rewarding [270,271]. These 2 reports documented that QT dispersion was increased in DCM, and that there was a greater increase in patients with bundle branch block and those who had subsequent arrhythmias. However, the large overlap between values precluded clinically or statistically significant differences.

These data would suggest that the pathophysiological significance, confounding effect of bundle branch block and prognostic role of QT dispersion in patients with chronic heart failure remain unclear.

Table 1-5: Associative studies of QT dispersion

Author	Year	Type	Disease	Subjects (n)	Exclusion	Method	Control QTd	Disease QTd	
Day	1990	Case-control	Long QT vs Sotalol	10	unclear	Manual (50)	60	170	p<0.0001
Linker	1992	Case-control	Long QT vs control	9	unclear	Manual (*4)	45	110	p<0.04
Buja	1993	Case-control	HCM +/- VF	26	unclear	Manual (25/50)	43	115	p<0.001
Pye	1994	Case-control	VT	57	BBB/AF	Manual (*4)	32	77	p<0.01
Higham	1995	Case-control	MI vs UA	55	unclear	Manual (50)	38	66	p<0.01
Glancy	1995	Case-control	MI deaths	163	none	Interactive (25)	94	94	ns
Sporton	1997	Case-control	IHD	18	BBB/AF	Manual (50)	44	82	p<0.001
Oikarinen	1998	Case-control	VF survivors	50	BBB/AF	Manual (50)	44	53	p<0.01

Abbreviations: HCM - hypertrophic cardiomyopathy; VF – ventricular fibrillation; VT – ventricular tachycardia;

MI – myocardial infarction; UA – unstable angina; IHD – ischaemic heart disease; BBB – bundle branch block; AF – atrial fibrillation.

Table 1-6: Prognostic studies of QT dispersion

Author	Year	Type	Disease	Subjects (n)	Events (n)	Exclusion	Method	Alive QTd	Cardiovascular death QTd	
Barr	1994	Prognostic	CHF-both	44	19	none	Manual (25)	53	98*	p<0.0001
Fei	1996	Prognostic	CHF-DCM	135	17	BBB/AF	Manual (25)	62	67	ns
Darbar	1996	Prognostic	PVD	49	12	CAD	Manual (25)	56	86	p<0.002
Grimm	1996	Prognostic	CHF-DCM	107	12	AF/Drugs	Manual (50)	60	76	ns
Fu	1997	Prognostic	CHF-both	163	59	none	Manual (50)	54	95*	p<0.001
Pinsky	1997	Prognostic	CHF-both	80	14	none	Manual (25)	85	112	p<0.005
Naas	1998	Prognostic	NIDDM	182	not given	Not stated	Manual (25)	78 (cut pt)		not given
Zabel	1998	Prognostic	MI	280	30	Not stated	Interactive (50)	61	65	ns

Abbreviations: CHF – chronic heart failure; DCM – dilated cardomyopathy; PVD – peripheral vascular disease; NIDDM – non-insulin dependent diabetes mellitus.
MI – myocardial infarction.

1.4.13 *Summary*

For over 5000 years, continuing advances in anatomy, pathology and physiology have allowed identification of the heart as the cause of cardiac failure. It is now recognised that heart failure is a common clinical disorder characterised by abnormal ventricular function associated with neuroendocrine dysregulation, autonomic dysfunction and symptoms of breathlessness, fatigue and effort intolerance. It is highly prevalent, affecting 1% of the population over age 50, rising to 10% of those aged over 80. Over the last decade it has become increasingly common, and in conjunction with the ageing population is a major public health burden in developed countries. Symptoms are related more to ventilatory and skeletal muscle abnormalities than to central haemodynamics, and clinical signs may be masked by treatment. Thus the clinical history and examination are poorly discriminatory in defining the severity of underlying cardiac dysfunction. Cardiac injury leads to a loss of effective myocyte mass, with compensatory salt and water retention, neuroendocrine activation and cardiac hypertrophy. These processes cause "remodelling", and if unopposed, progressive left ventricular dilatation. Abnormalities of calcium handling and ventricular repolarisation associated with hypertrophy combine with autonomic dysfunction to predispose the failing heart to ventricular arrhythmias, an important cause of death in heart failure.

The socio-economic burden of chronic heart failure is enormous: it has been estimated at 1-2% of the total health care budget, of which two thirds is accounted for by inpatient care. The more severe the heart failure, the greater the cost. Thus, chronic heart failure is a common, growing and major public health care burden [121]. Identifying high-risk patients suitable for aggressive intervention, optimisation of

treatment and prevention of death is of great importance. Despite extensive study by many investigators, identification of those patients who are most likely to deteriorate and die remains difficult. Whilst many features are predictive of prognosis in populations, their clinical utility in an individual setting is less clear. Clinical, exercise, echocardiographic and haemodynamic variables are known to carry prognostic information, but accurate identification of those most likely to die remains difficult.

The aim of this work was to determine the prognostic significance of abnormalities of ventricular repolarisation, autonomic dysfunction and neuroendocrine activation in chronic heart failure.

2 METHODOLOGY

2.1 RECRUITMENT AND SCREENING

Patients were recruited from medical/cardiology wards, outpatient departments and echo clinics of Glasgow Royal Infirmary and the Western Infirnary.

Patients were screened:

if they had been admitted with undiagnosed breathlessness or with a diagnosis of heart failure,

if they had a previously documented admission with a diagnosis of heart failure,

if they had been referred for assessment of breathlessness/heart failure or

if they were found to have documented left ventricular systolic dysfunction at angiography, radionuclide ventriculography or echocardiography.

One experienced observer screened all patients. Because of the limited reliability of physical signs in the diagnosis of heart failure [272-275], the following features were used as a guideline for the diagnosis of heart failure [34]

Symptoms of heart failure: breathlessness, fatigue or exercise intolerance

Clinical signs of heart failure: a third heart sound, basal crepitations, elevated jugular venous pressure, peripheral oedema and alteration of signs induced by diuretic therapy

Radiological: cardiomegaly, pulmonary venous congestion/pulmonary oedema

Objective evidence of left ventricular systolic dysfunction determined by echocardiography or radionuclide ventriculography (LVEF <40%).

The major inclusion criteria were currently or previously documented objective evidence of left ventricular systolic dysfunction with stable chronic heart failure. Stable chronic heart failure was defined as heart failure outside the context of recent myocardial infarction with no change in symptoms, signs or diuretic dosage for four weeks before the study protocol.

The following exclusion criteria were applied:

age greater than 75 years

uncontrolled hypertension (defined as >170/100 mmHg)

atrial fibrillation

permanent pacemaker

recent myocardial infarction or unstable angina (< 6 months)

previously documented ventricular tachycardia or ventricular fibrillation outside the context of acute myocardial infarction

chronic renal failure (defined as serum creatinine >200 μmol/l)

longstanding diabetes mellitus

any co-morbid disease likely to lead to significant mortality within two years.

Age over 75 years, hypertension, longstanding diabetes, chronic renal failure and autonomic impairment are associated with blunted cardiovascular reflexes, disturbing the assessment of baroreflex sensitivity and heart rate variability. Chronic atrial fibrillation precludes measurement of heart rate variability or baroreflex sensitivity.

2.2 ETHICAL CONSIDERATIONS

The study received ethical approval from the Ethics Committees of Glasgow Royal Infirmary and the Western Infirmary.

The same physician (A M-D) recruited all patients. After initial contact and a verbal explanation, patients were invited to attend for study. If they agreed, contact information was obtained, and an appointment arranged by telephone or letter. This was then confirmed in writing, and on attendance for the study protocol informed consent was obtained (see **Appendix A**). Patients could decline or withdraw from any part of the study protocol at any point. Informed consent included provision to review hospital and community medical records in the future.

2.3 CLINICAL ASSESSMENT

Following screening, a full explanation of the study was given to all eligible patients. In those who offered to take part, the same observer obtained informed consent. If subjects were outpatients with stable heart failure (see above) they were studied as soon as practicable. Patients recruited from wards were studied at earliest 4 weeks from the index admission. All patients continued their normal medication before the and during the study period.

2.3.1 *Symptoms*

Patients were stratified by New York Heart Association functional class based on responses to standardised questionairres. All subjects completed a questionnaire giving demographic details, current medication, a history of physician diagnosed myocardial infarction, angina, or diabetes mellitus and their smoking status (current, never or ex). They also completed 2 general health questionnaires: the Nottingham Health Profile and the SF36, in addition to a disease specific questionnaire: the Minnesota "Living with Heart Failure" questionnaire [276] (see **Appendix B**) which has previously been validated as an accurate and reproducible tool. This consists of 21 questions, each of which assesses the patient's perception of how his or her emotional

or physical state is impaired by heart failure. The answer to each question ranges from 0 (no impairment) to 5 (severe impairment). Questions 2 (needing to rest during the day), 3 (walking and climbing stairs), 4 (housework), 5 (going away from home), 6 (disturbance in sleep pattern), 7 (doing things with others), 12 (dyspnoea) and 13 (fatigue) focus primarily on physical limitation. These were combined to give a score for physical limitation. Other questions focus primarily on emotional limitation.

2.4 ELECTROCARDIOGRAPHY

2.4.1 *Resting 12 Lead ECG*

Patients were studied in the resting, supine, post-absorptive state. A 12 lead ECG was recorded on a Siemens Megacart R (Siemens Elema), computer analysed and the analysis confirmed by one experienced observer. Rate, rhythm and evidence of previous myocardial infarction, left ventricular hypertrophy, conduction defects or ST/T wave changes were documented. Left atrial strain was determined by computer algorithm and manually checked (P wave > 0.12 seconds, bifid P wave in lead I/II, ± negative terminal P wave in lead V1).

2.4.2 *QT Measurements*

The Siemens Megacart R records all 12 leads simultaneously, so removing temporal variation errors in QT dispersion measurement. There is no accepted standard methodology for QT dispersion measurement, although some authors have examined the intra and inter-observer errors associated with various paper speeds and gain settings [256]. For these reasons, a pragmatic decision was taken to analyse all ECG tracings at standard paper speeds of 25mm/sec and gain of 10mm/mV – a technique which had been reported to provide prognostic information in patients with heart failure [267].

The hard-copy ECG format chosen for analysis allowed 3 successive complexes to be analysed in each lead. The following points were digitised on each lead:

P wave onset

QRS onset

QRS end

T wave peak

T wave end

In leads where the T wave was not clearly visualised, no measurement was made. No ECG was analysed if less than 8 leads were analysable.

The following T wave morphologies were recognised [277]:

Inverted T waves

Biphasic T waves

Humped T waves

U waves

In the presence of these T wave morphologies, the nadir of the T-U wave or the return of the T wave to the isoelectric line was chosen to represent the end of the T wave. Measurements were performed on all 12 leads, and QT dispersion calculated from all available leads, and then on a separate analysis on only the chest leads. This has been suggested to be less dependent on intra/inter-observer variability whilst providing similar information.

The data were manually analysed using a high resolution digitising pad (Drawing Board 3, Calcomp Corporation) and a software package made available by the Department of Academic Cardiology, Freeman Hospital, Newcastle upon Tyne. This

software had been extensively validated in prior studies [278]. Subsequent data manipulation and analysis was performed in Microsoft Excel.

Table 2-1: QT measurement definitions

QT measure	Definition
QTend	QT measured to end of T wave
QTpeak	QT measured to peak of T wave
QT_{end} max	maximum QT measured to end of T wave
QT_{end} min	minimum QT measured to end of T wave
QT_{peak} max	maximum QT measured to peak of T wave
QT_{peak} min	minimum QT measured to peak of T wave
QT_{end} dispersion	maximum QT_{end} minus minimum QT_{end}
QT_{peak} dispersion	maximum QT_{peak} minus minimum QT_{peak}
Coefficient variation	standard deviation of QT variable/mean of QT variable

2.4.3 *Signal-Averaged Electrocardiography*

A signal averaged ECG was acquired according to the Joint Task Force Committee standards [279]. The patient's skin was cleaned thoroughly with alcohol and abraded to provide excellent contact. A Frank orthogonal 3 lead XYZ lead set was used for acquisition. Two to three hundred successive QRS complexes were recorded. The signals were amplified, band pass filtered (low band pass 40 Hz, high band pass 250 Hz), and AD converted. A QRS template was chosen, each successive beat compared and aligned with this template, and sequential beats averaged. As noise is random, signals that repeat on a beat to beat basis will remain, while noise averages to zero. Acquisition was terminated when a predetermined noise level was reached. Each lead

was further amplified and filtered, and the vector magnitude calculated from the filtered XYZ leads using the formula $(X^2 + Y^2 + Z^2)^{1/2}$. The QRS onset and offset were then identified, allowing determination of QRS duration (QRSd). Two further measurements are obtained by analysis of the last 40 milliseconds of the QRS complex. These were the root mean square voltage of the terminal 40 milliseconds (RMS 40), and the duration of low amplitude signal under 40 μV (LAS40). A late potential appears as low-level "tail": a low RMS 40 and long LAS40 describe a low-level "tail". The abnormalities described in the above section on basic electrophysiology all contribute to delayed ventricular conduction which may manifest as a late potential and positive signal averaged ECG. Thus the signal averaged ECG noninvasively assesses conduction delay in sinus rhythm.

Criteria for the definition of a late potential are outlined below (**Table 2-2**). Bundle branch block and intraventricular conduction delay are common in the ECG's of patients with heart failure, and alter the predictive value of a late potential defined by normal criteria. Patients with bundle branch block were prospectively analysed using the criteria below [180].

Table 2-2: Definition of a positive Signal-Averaged ECG

	Filtered QRS_d (msec)	RMS_{40} (μV)	LAS_{40} (msec)
Normal conduction	>114	<20	>38
Bundle branch block	>145	<17	>55

RMS_{40} : root mean square voltage of the terminal 40 msec of the filtered QRS; LAS40 : the duration of low amplitude signal under 40 μV.

2.5 CARDIOPULMONARY EXERCISE TESTING

2.5.1 *Test Protocol*

All exercise test were performed using the same equipment and were supervised by the same physician and one of two technicians. Testing was carried out in an air conditioned exercise laboratory under standardised conditions.

Patients able to exercise underwent symptom limited, maximal cardiopulmonary treadmill exercise testing using a standardised exponential workload protocol [280]. This is suitable for heart failure patients, and has a validated normal range from 2000 randomly chosen age and sex stratified subjects from the North Glasgow population. Most subjects were familiar with treadmill exercise testing, but a short demonstration was given before the test. Patients were allowed to familiarise themselves with treadmill walking and breathing through the mouthpiece of the gas analysis system. Before commencing the test, they were instructed in the use of standardised hand signs to allow communication once the mouthpiece of the gas-exchange analyser was in place.

Patients were allowed one minute to acclimatise. Heart rate and 12 lead electrocardiograms were monitored continuously using a Siemens Megacart R with a dedicated exercise ECG module, and hard-copy 12 lead ECG's recorded during the last 10 seconds of each stage, and at 1 minute and 3 minutes of the recovery stage. Blood pressure was measured manually every 3 minutes, and immediately after cessation of exercise. Gas exchange data were collected continuously at rest and during exercise using an automated breath by breath system (Medical Graphics Corporation, St Paul, Minnesota). A clamp was placed on the nose, and the patient breathed through a mouthpiece connected to a

non rebreathing valve. Expired airflow, O_2 and CO_2 were respectively measured using a pneumotach, a zirconia cell O_2 analyser and an infrared CO_2 analyser, all connected to a dedicated PC. The gas exchange analyser was calibrated before every session with precise reference gases corrected for barometric pressure, ambient temperature and humidity. Rapidly responding O_2 and CO_2 analysers linked to a portable computer allowed O_2 and CO_2 to be monitored on a breath by breath basis. By also measuring respiratory air flow, VO_2, VCO_2, V_E, were estimated noninvasively. Electrocardiographic and gas exchange data were acquired for three minutes post exercise.

Patients were encouraged to exercise for as long as possible. The attending physician could also stop the test. The reason for the termination of the test was recorded in a standardised fashion (fatigue, dyspnoea and/or pain).

2.5.2 *Test Analysis*

Resting and end exercise heart rate, systolic and diastolic blood pressures, and ST segment changes (at 80 milliseconds post J point) were collected for subsequent analysis. Gas exchange data were stored on a dedicated computer.

Maximal oxygen consumption (VO_2 max) was defined as the mean of the last 30 seconds of exercise data. The anaerobic threshold was determined by "V slope analysis" [281]. Both values were calculated automatically using the Cardiokinetics software package.

Further analyses were performed "off-line". The breath by breath gas exchange data file was exported as 10 second averages, and subsequent data manipulation performed in Microsoft Excel. The slope of the regression line (V_E/VCO_2 slope) of minute ventilation (V_E) vs carbon dioxide production (VCO_2) was also

determined [39], as discussed in the introduction (see **Chapter 1 section 1.4.6 Prognostic Power Of Exercise Variables**). This value is proven to be less effort dependent than peak VO_2.

2.6 AMBULATORY ECG MONITORING

2.6.1 *Acquisition*

Twenty-four hour ambulatory ECG's were obtained on all patients during normal, unrestricted out of hospital activity using new Oxford MR 45 recorders (Oxford Medical, UK), whose use was confined to this study cohort. The sampling rate was 125 per second, giving a temporal resolution of 8 milliseconds. Channel 1 and 2 recorded the ECG, channel 3 provided beat classification from real-time analysis, and channel 4 was a quartz generated timing track, reducing tape speed errors to <0.5%. These recorders were suitable for heart rate variability analysis. A separate, new, demagnetised tape was used for each patient. The patients' skin was appropriately prepared to ensure electrode stability, to minimise impedance, and to decrease noise and artefact. A standard 2 channel lead set up was used, and an automatic ECG check performed before commencing each tape. If either channel was unsatisfactory, then the appropriate electrodes were removed, the skin recleaned, and new electrodes applied. If, despite these measures, unsatisfactory ECG signals were obtained, new electrodes were applied at different positions. These measures ensured high-quality, low noise recordings.

2.6.2 *Arrhythmia Analysis*

Twenty-four hour ambulatory ECG's were replayed through the Oxford Xcel arrhythmia analyser. Initial automated computer analysis classified beats by QRS template morphology, and the trigger section of the analysis detects individual QRS complexes. Manual editing was then performed by two technicians experienced in 24-hour arrhythmia analysis to further refine data accuracy. Ectopic beats, arrhythmic events, missing data and artefact were appropriately classified.

Arrhythmia analysis provided the following parameters:

mean, maximum, and minimum heart rate

bradycardic arrhythmia events

supraventricular ectopic and supraventricular arrhythmia counts

ventricular ectopic counts: these were subdivided into single VE's, couplets, and nonsustained ventricular tachycardia defined as > 3 consecutive ventricular beats at a rate > 100 beats per minute

2.6.3 *Heart Rate Variability Analysis*

Ambulatory ECG's <22 hours duration and/or with < 90% of the recording suitable for analysis were excluded from heart rate the ability analysis. From the edited ambulatory electrocardiograms, the remaining normal-normal RR intervals were stored as a tachogram for heart rate variability measurement. Time and frequency domain measures of heart rate variability (see **Table 2-3** and **Table 2-4**) were calculated in accordance with accepted standards [282], using the Oxford Xcel analysis package.

Table 2-3: Definitions of time domain measures of heart rate variability

Variable	Units	Definition
SDNN	msec	Standard deviation of all NN intervals in the 24 hour recording
SDANN	msec	Standard deviation of the mean of all NN intervals for each 5 minute period of the 24 hour recording (cycles>5 min)
SDNNI	msec	Mean of the standard deviations of all NN intervals for all 5 minute periods of the 24 hour recording (cycles<5 min)
pNN50	%	Percentage of all NN intervals where the differences between adjacent NN intervals > 50 ms
rMSSD	msec	The square root of the mean of the sums of the squares of the differences between adjacent NN intervals

Abbreviation: mssec– milliseconds

Table 2-4: Definitions of frequency domain indices of heart rate variability

Power Spectrum	Frequency range	Cycles/Time	Time/cycle
High frequency	0.15 – 0.40 Hz	9 – 24 cycles/min	2.5 sec/cycle – 6.6 sec/cycle
Low frequency	0.04 – 0.15 Hz	2.4 – 9 cycles/min	6.6 sec/cycle – 25 sec/cycle
Very low frequency	0.0033 – 0.04 Hz	0.2 – 2.4 cycles/min	25 sec/cycle – 5 min/cycle
Ultra low frequency	1.15×10^{-5} – 0.0033 Hz	0.2 cycles/min –1 cycle/24 hrs	5 min/cycle – 24 hrs/cycle
Total power	1.15×10^{-5} – 0.40 Hz	24 cycles/min –1 cycle/24 hrs	2.5 sec/cycle – 24 hrs/cycle

Abbreviation Hz = hertz

2.7 ECHOCARDIOGRAPHY

Standard two-dimensional, colour and doppler echocardiography (Accuson 128) was performed with subjects recumbent at 40 degrees, in the left lateral position. Images were stored on videotape and analysed on line using the pre-installed Accuson software package.

2.7.1 *Left Ventricular Ejection Fraction*

Left ventricular volumes were obtained using a disc summation method (Simpson's rule) from the apical 4-chamber and 2-chamber views. The endocardium was traced in systole (smallest left ventricular dimension) and diastole (ECG R wave onset), in triplicate, avoiding post-extrasystolic beats [283]. Left ventricular volumes were calculated using the mean of the 3 values by the internal software of the Accuson 128. Left ventricular ejection fraction was automatically calculated from these volumes as

$$\frac{[\text{LV end diastolic volume} - \text{LV end systolic volume}]}{\text{LV end systolic volume}} \times 100$$

In subjects with poor endocardial definition (defined as less than less than 80% of the endocardium being visible), a semi-quantitative assessment of left ventricular ejection fraction was made [155]. If echo quality precluded analysis of ejection fraction, the results of recent radionuclide ventriculography were used.

2.7.2 *Structural Abnormalities*

Echocardiograms were also analysed for significant structural heart disease: atrial or ventricular septal defect, valvular disease, ventricular hypertrophy and/or pericardial disease.

2.7.3 *Colour-Doppler Echocardiography*

Patients with documented valvular heart disease were excluded from the study. Standard Doppler assessment of valvular flow was performed. Pulsed wave-Doppler waveform through the mitral valve and continuous wave Doppler waveform through the aortic valve were determined, and semi-quantitative assessment of valvular regurgitation performed by visual inspection of regurgitant jet width and length.

2.8 BAROREFLEX SENSITIVITY TESTING

An indwelling cannula was placed in an antecubital fossa vein. Continuous electrocardiographic monitoring was performed with a single channel V lead. To avoid the hazards of intra-arterial pressure monitoring, beat to beat arterial pressure was measured non-invasively using a Finapres 2300 (Ohmeda, Englewood, USA). The Finapres method is based on dynamic unloading of the finger arterial walls using an inflatable finger cuff with built-in photo-electric plethysmograph. By keeping finger volume constant, the arteries will not change in size. Thus, at constant volume (i.e. determined by the photoplethysmogram) instantaneous cuff pressure equals instantaneous arterial pressure. A rapid pneumatic servo system and a dynamic servo set point adjuster ensure accuracy. From the finger pressure waveform, systolic, diastolic and mean arterial pressures were output on a beat by beat basis. This methodology had been extensively validated in published studies [284,285]. After an initial start-up period for calibration, a representative pressure waveform was obtained. If no satisfactory arterial pressure waveform was obtained, a different sized cuff was used or, if necessary, the patient's hand was warmed. Patients were instructed to keep the hand and arm immobile during the testing procedure. The servo set point adjuster was switched off immediately before each test. The analogue

outputs of the ECG and Finapres were AD converted (sampling rate 200 Hz) and the digitised signals monitored real-time using a PC and commercially available software package (CAFTS, Medikro Oy, Finland). At the end of each study, files were analysed and stored.

After 20 minutes of rest in a semi-recumbent position, a "trial run" was performed after explanation of the testing procedure and equipment. If this was satisfactory, 15 minutes of simultaneous ECG and BP data were recorded during controlled respiration. Tidal volume was not fixed, but patients were instructed to breathe in time with an electronic metronome at 12 breaths per minute. Data from this rest period were analysed to determine baroreflex gain and short term measures of heart rate variability. After this rest study, baroreflex challenges were performed.

Baroreflex gain was measured by means of the spectral analysis of simultaneous RR and systolic blood pressure variabilities [230]. Cross spectral analysis was performed on both high and low frequency bands and values analysed only if the weighted coherence between systolic pressure and RR interval was greater than 0.5 [286].

Baroreflex challenges were performed using a bolus phenylephrine injection [227]. An intravenous bolus of 25 to 400μg of phenylephrine hydrochloride was followed by 10 mls saline flush, to induce a 20 to 30 mmHg increase in systolic arterial pressure. The software allowed online analysis of baroreflex slopes where systolic pressure was plotted against the succeeding RR interval. The slope of the linear regression line of this plot was taken as baroreflex sensitivity if there was a significant correlation coefficient. Three tests were averaged to provide mean baroreflex sensitivity.

2.9 VENOUS BLOOD SAMPLING

2.9.1 *Natriuretic Peptides*

Venesection was performed in a standardised fashion after 20 minutes of supine rest. Venous blood was withdrawn by syringe and needle into pre-prepared chilled tubes containing EDTA and trasylol (50IU/ml). Care was taken to prevent painful or prolonged venepuncture that might artefactually raise plasma noradrenaline. Samples were centrifuged at 3,000 rpm for 10 minutes at 4 °C, and the supernatant plasma stored at –70 °C. Subsequent analyses were performed at a laboratory experienced in neurohumoral measurement. The plasma was acidified with trifluoroacetic acid, and natriuretic peptides extracted by gel chromatography. Recoveries were 87% and 82% for N-ANP and BNP respectively.

N-ANP was measured, after dilution (1:100), by radioimmunoassay using an antibody from Peninsula Laboratories (RAS 9129) raised against the 1 to 30 N-terminal fragment. This antiserum has no detectable cross reaction with either C terminal ANP or BNP and has an IC50 of 18pg/tube in the assay. The within-assay and between-assay coefficients of variation for this assay were 15% (n=16) and 16% (n=48) respectively [287].

BNP was measured in the extract (1:4) using a radioimmunoassay kit for human BNP obtained from Peninsula Laboratories (RIK 9086). This has an IC_{50} of 20pg/tube. The within-assay and between-assay coefficients of variation were 18% (n=16) and (n=46) 15% respectively.

The range of a sample of controls for plasma ANP was less than 50 ng/ml, and the mean for plasma BNP was 12 ± 9 pg/ml (unpublished internal reference ranges).

2.9.2 *Plasma Noradrenaline*

Noradrenaline was measured by HPLC and electrochemical detection after prior extraction from plasma [288]. The coefficient of variation for the method is <10% and recovery is corrected by including an internal standard. The range of a sample of controls for this laboratory is less than 5 nmol/l (unpublished internal reference range).

2.10 CLASSIFICATION OF ENDPOINTS

Specified mortality endpoints were:

Cardiovascular death: defined as death due to myocardial infarction, progressive heart failure, stroke, attempted resuscitation from ventricular arrhythmia or urgent cardiac transplantation.

Progressive heart failure death: defined as death occurring in the context of increasing symptoms/signs of heart failure, with no recent (>4 weeks) antecedent ischaemic event.

Sudden death: a pragmatic classification of sudden death was chosen. Patients who died of a documented ventricular arrhythmia, or who did not survive a community resuscitation attempt were classed as sudden death. Patients who died at home with no recent (>4 weeks) documented change in cardiac status were also classed as sudden death, unless an obvious alternative aetiology was documented. If patients died of an arrhythmia while in a decompensated state, this was classed as a progressive heart failure death. If they had been treated and had become stable, death was classified as sudden.

The limitations of classification of death are well documented and are discussed in **Chapter 1.4.1 Classification of Death in Heart Failure.**

2.11 FOLLOW-UP

Patients did not undergo routine follow-up. However, appropriate information was extracted annually from review of their hospital and/or GP case records. Follow-up was closed on the first of September 1998. Vital status was determined in all cases from information from the death section of the General Register Office of Scotland.

2.12 STATISTICAL ANALYSIS

A power calculation was performed at the time of the original proposal. It was estimated that a cohort of 300 patients followed up for 2 years with an annual mortality of 15% would provide 55 cardiovascular deaths. Patient recruitment was truncated early (as the principal investigator took up another appointment). However, follow-up was extended, and subsequent analysis demonstrated that the original power of the study was retained.

Statistical analyses were performed using SPSS for Windows Version 8. Results are given as mean ± SD, except where indicated as median and inter-quartile range. Spearman's rank correlation procedure was used to compare non-normally distributed variables, and Pearson's correlation coefficient if variables were normally distributed or could be transformed to a normal distribution. The statistical association of co-variates with mortality was determined by Kaplan-Meier curves and the log-rank test. A multivariate Cox proportional hazards analysis was performed to determine the incremental prognostic power of investigational variables. To simplify this model, NYHA status was grouped as class II or below, or III and above. Maximal oxygen consumption was dichotomised at 14ml/kg/min (as in previous studies), with patients unable to exercise being assigned a value of <14ml/kg/min. Autonomic variables

were dichotomised above and below the median values. Two types of Cox analyses were performed:

1. The incremental prognostic utility of each investigational variable was determined singly after adjustment by multivariate analysis of readily available parameters: age, aetiology of heart failure, NYHA class, peakVO_2, left ventricular ejection fraction and presence of intraventricular conduction defect/bundle branch block on the 12 lead ECG.

2. In the second model, all investigational co-variates were analysed together using a forward conditional stepwise model after adjustment for baseline co-variates.

Analyses of cause specific mortality should be interpreted with caution. There are potential confounding problems with definitions of and smaller numbers of events. Additionally, there is the conceptual difficulty that one event may interact with or alter the probability of another occurring. For example, it might be assumed that patients who succumb to sudden death have died before they can develop progressive heart failure, and so their data cannot contribute to analyses of progressive heart failure death.

Cox proportional hazards analysis uses the hazard function to estimate the risk of death cocurring. This is an estimate of the potential for death per unit time at any given instant. "Proportional hazards" implies that the hazard ratio for a co-variate (eg previous myocardial infarction) remains constant over time, and is not altered by censored data. Log minus log plots were analysed for each co-variate to ensure that assumptions of constant proportionality were not violated.

3 RESULTS

3.1 CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

Table 3-1: Clinical and demographic characteristics

Patient Demographics			
Age, years*		61.6	54.2-67.5
NYHA class		2.7	0.8
Cause of CHF (n)	**Ischaemic**	163	
	Non-ischaemic	36	
Therapy (%)	**ACE Inhibitor**	89	
	Diuretics	66	
	Digoxin	27	
	Other vasodilators	41	
	β blockers	20	
	LVEF (%)	23	9
	Peak VO2 (ml/kg/min)	16.9	4.9
IVCD/BBB (n)	**Present**	64	
	Absent	135	

NYHA – New York Heart association functional class; IVCD – intraventricular conduction defect; BBB – bundle branch block.
Values given as mean ± SD, except where indicated *, median ± IQR

3.1.1 *Clinical Demographics*

The mean age of the study population was 60.0 years (SD 10.3 years). There were 148 (74.4%) men and 51 (25.6%) women. Age did not differ significantly between sexes (men, mean 59.3 SD 10.3 vs women 61.9 SD 10.1). Median duration of heart failure was 16 months, IQR 8–48 months. Ischaemic heart disease was the commonest cause of chronic heart failure: 163 patients had an ischaemic aetiology (81.9%), and 153 (76.8 %)

had documented prior myocardial infarction. One hundred and four patiens had undergone previous coronary angiography, and 58 had been revascularised with coronary bypass grafting. Risk factors for coronary disease were common: 94 (47.2%) patients had hypercholesterolaemia (defined as random cholesterol >5.5 mmol/l), 68 (34.2%) had a past history of hypertension but only 21 (10.0%) were diabetic. This latter finding reflects selection criteria as longstanding diabetics were excluded. Only 38 (19.1%) patients were current smokers, but 109 (55%) were ex-smokers.

3.1.2 *Symptoms and Questionnaire Data*

Mean NYHA status was 2.7 (SD 0.8). Twelve (6%) patients were in NYHA class I, 68 (34%) in NYHA class II, 89 (45%) in NYHA class III and 30 (15%) in NYHA class IV. For the purposes of multivariate analysis, patients were grouped as being in functional class 1 (NYHA classes I and II, 80 patients) or functional class 2 (NYHA classes III and IV, 119 patients).

Mean Minnesota Living with Heart Failure Questionnaire (MLHFQ) Physical Score was 19.1 (SD 11.0) of a possible score value of 40. The score differed significantly between all NYHA classes and functional status ($p<0.001$ ANOVA): see **Table 3-2).** Substituting MHFQ physical score in place of NYHA class produced almost identical survival analysis results.

Table 3-2: Minnesota heart failure questionnaire score by NYHA Status

NYHA Class	Mean MHFQ Score	SD
I	2	2.5
II	11	6.8
III	23	7.7
IV	33	5.5

3.2 LEFT VENTRICULAR EJECTION FRACTION

An objective assessment of left ventricular function was available in all patients. Left ventricular ejection fraction was determined by radionuclide ventriculography in 57 patients whose echocardiograms demonstrated poor or moderate definition of endocardial outline. Mean left ventricular ejection fraction was 23.4% (SD 8.7%). Mean left ventricular ejection fraction was statistically different between groups classified as having mild, moderate, severe or very severe left ventricular impairment at "eyeball" assessment ($p<0.001$ ANOVA, see **Table 3-3** and **Figure 3-1**).

Left ventricular ejection fraction correlated poorly with age (Pearson correlation coefficient $r = -0.16$, $p = 0.90$). There was no significant difference in left ventricular ejection fraction between ischaemic/non-ischaemic aetiologies (mean 22.9%, SD 8.1% vs 25.2%, SD 10.2%); or between male and female gender (mean 22.9%, SD 8.4% vs 24.6%, SD 9.3%). There was a trend toward lower left ventricular ejection fraction in higher NYHA class. Left ventricular ejection fraction was significantly lower in patients with prolonged compared with normal QRS duration (mean 20.4%, SD 8.3% vs 24.7%, SD 8.5%, $p<0.001$ unpaired T test).

For description of box & whisker plot see section **3.8 Correlative Statistics**

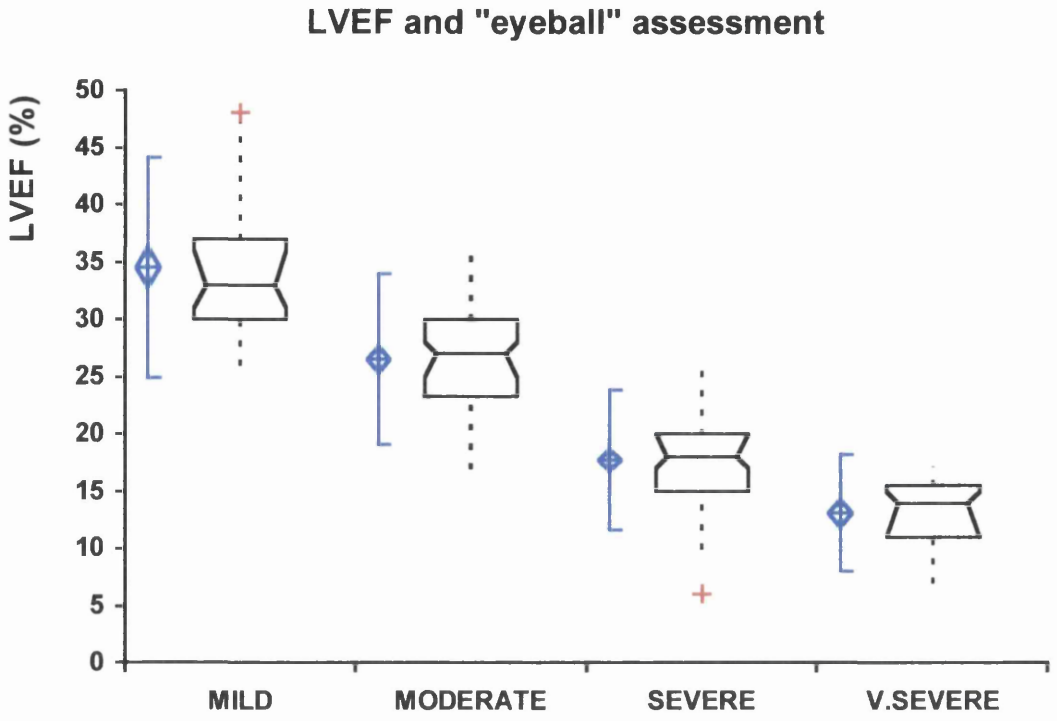


Figure 3-1: Left ventricular ejection fraction by "eyeball" assessment

Table 3-3: Left ventricular ejection fraction and subjective assessment

Subjective LV impairment	Mean LVEF (%)	SD
Mild	34.5	5.8
Moderate	26.6	4.5
Severe	17.9	3.8
Very Severe	12.9	3.1

3.3 ELECTROCARDIOGRAPHY

3.3.1 *Resting 12 Lead Electrocardiography and Measures of Ventricular Repolarisation*

One hundred and ninety five subjects were in sinus rhythm. Four subjects were found to be in atrial fibrillation at the time of study. Their data are not included in heart rate variability, baroreflex sensitivity, QT dispersion or signal averaged ECG analysis. The following data are expressed as mean ± SD in msec: PR interval 169 ± 30.1, QRS duration 114 ± 27.9, QT interval 407 ± 43.3, corrected QT interval 428 ± 30.6. Normal atrial activity was present in 164 and 30 had electrocardiographic features of left atrial strain. First degree heart block was present in 28 patients, left axis deviation in 56, right axis deviation in 6 and a normal frontal plane axis in 137. The QRS duration was normal in 135 subjects, and prolonged in 64 subjects (non-specific intraventricular conduction delay in 30, LBBB in 22 and RBBB in 12). One hundred and nineteen subjects had ECG evidence of prior Q wave myocardial infarction (76 anterior, 43 inferior). ST/T wave changes were common. Of 119 patients without IVCD or LVH, 40 patients had anterior or anterolateral ST/T changes, 30 lateral changes and 37 inferior or inferolateral changes. The remaining 12 patients had ECG evidence of Q wave infarction. Only one patient had a completely normal ECG.

Measures of QT interval and QT dispersion are reported by presence or absence of IVCD (Table 3-4). One hundred and fifty ECG's were suitable for QT dispersion analysis: no QT dispersion measures were analysed for the 4 subjects in atrial fibrillation, or if more than 3 leads were unsuitable for T wave analysis. QT interval and corrected QT interval were significantly longer in the IVCD group ($p<0.001$). In contrast, QTE Dispersion, corrected QTE dispersion and QTE CV were significantly longer in the normal conduction group ($p<0.05$, unpaired T test). The normal conduction group contained 19 records with electrocardiographic LVH.

Table 3-4: Measures of ventricular repolarisation and presence/absence IVCD

	Normal		IVCD		p
	Mean (msec)	SD (msec)	Mean (msec)	SD (msec)	
QT_{end}	396	38	430	46	<0.05
Corrected QT_{end}	419	24	447	34	<0.05
QT_{end} Dispersion	111	44	91	30	<0.05
QT_{end} CV	8.6	3.3	6.9	2.3	<0.05
QT_{peak} Dispersion	66	29	59	28	NS
QT_{peak} CV	6.8	2.8	6.5	2.7	NS
Corrected QT_{end} Dispersion	118	45	95	29	<0.05
Corrected QT_{end} CV	9.2	3.5	7.2	2.5	<0.05
Corrected QT_{peak} Dispersion	69	30	70	27	NS
Corrected QT_{peak} CV	7.2	3.0	6.8	2.7	NS

QT_{end} = QT measured to end of T wave; QT_{peak}= QT measured to peak of T wave; QT_{end} CV = standard deviation of QT_{end} /mean of QT_{end}; QT_{peak} CV = standard deviation of QT_{peak} /mean of QT_{peak}

3.3.2 *Signal Averaged Electrocardiography*

Signal averaged electrocardiography was performed in all patients. The noise level was too high for reliable analysis in 2 subjects and these subjects were excluded from further analysis. Prospectively defined abnormal ranges were used in the presence of IVCD (see section **1.4.8 Signal-averaged Electrocardiography** and **Table 2-2**). Results are presented by presence or absence of conduction defect. The presence of a late potential was defined in 3 ways: all 3 criteria abnormal, any 2 criteria abnormal or QRS duration prolongation and any one other criteria abnormal (see **Table 3-5**). A representative positive Signal-Averaged ECG is presented in **Figure 3-2**.

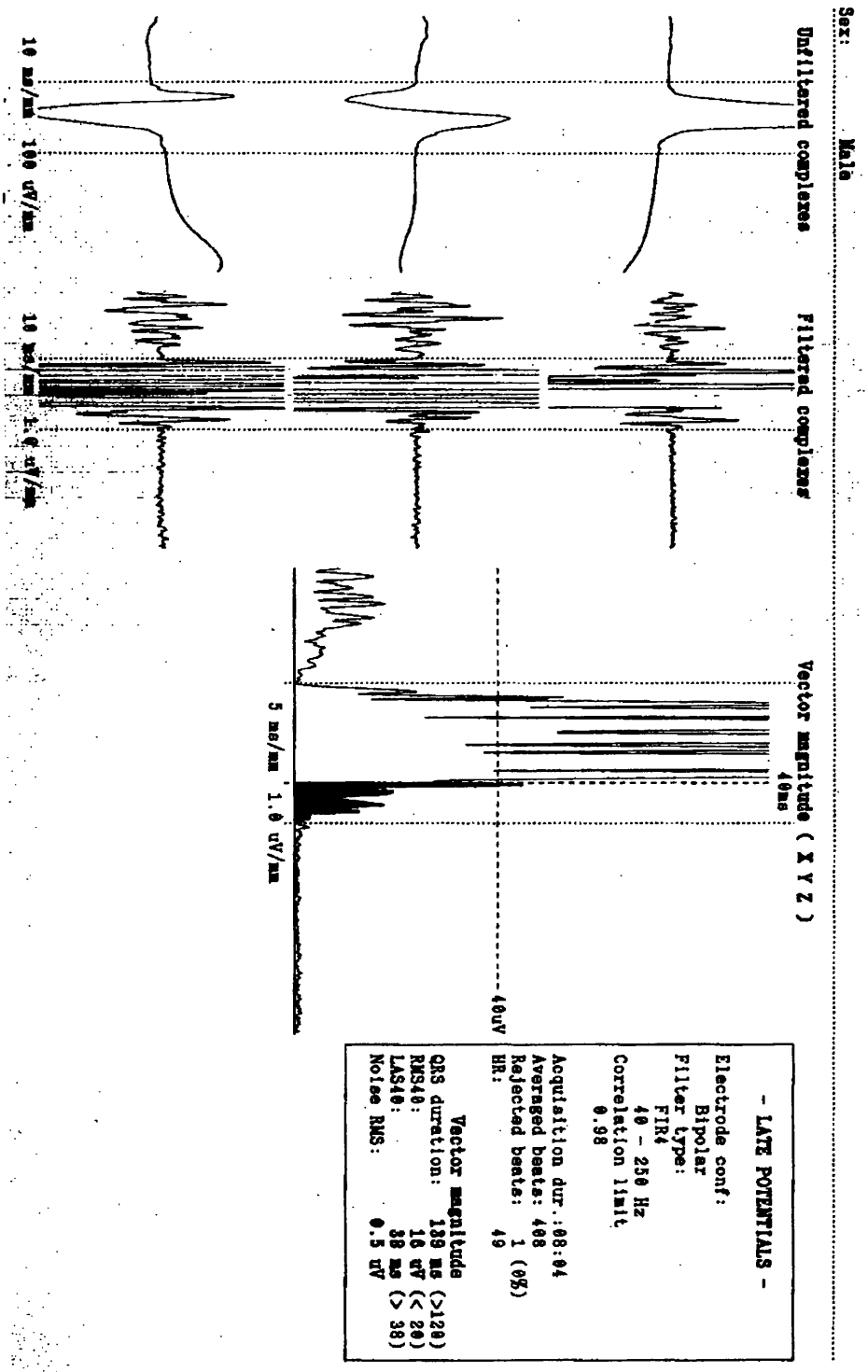


Figure 3-2: A positive Signal-Averaged ECG

Table 3-5: Signal averaged ECG and conduction defect

	Normal conduction (n = 133)	IVCD) (n = 64	Combined (n = 197)
QRS_d prolonged and any 1 other criteria abnormal	28	23	51
Any 2 criteria abnormal	44	25	69
All 3 criteria abnormal	21	16	37

QRS_d – QRS duration

No measure of QT dispersion differed significantly between groups with positive or negative signal averaged ECG.

3.4 EXERCISE VARIABLES

Twenty six patients did not undergo exercise testing, 20 because of patient preference or inability to exercise and 6 because of limiting osteoarthritis. Five patients could not tolerate the noseclip and mouthpiece necessary for gas exchange analysis. Thus, 173 patients underwent exercise testing, and expired gas analysis was available on 168 of these. Breathlessness and/or fatigue were the commonest limiting symptoms (163/173, 94.2%). Eight subjects experienced chest pain as a limiting symptom, but none demonstrated significant ST change on exercise. Exercise variables are shown below (see **Table 3-6**).

All patients demonstrated significant impairment of functional capacity compared with age matched normal values.

Table 3-6: Cardiopulmonary exercise test variables

Variable	Mean (SD)
Exercise time (seconds)	436 (218)
Δ Heart rate (bpm)	48 (20)
Δ Systolic arterial pressure (mmHg)	27 (17)
Peak VO_2 (mls/kg/min)	16.8 (4.9)
Peak RER	1.03 (0.11)

3.5 HOLTER ANALYSES:

CARDIAC RHYTHM AND HEART RATE VARIABILITY

One tape was damaged and was not analysable. Median tape duration was 23 hours and 30 minutes: only 4 tapes had less than 20 hours of data. Four patients were found to be in chronic atrial fibrillation, and 2 patients had evidence of sustained (>30seconds) paroxysmal atrial arrhythmias. Ventricular and supraventricular arrhythmia analysis for the entire study cohort is presented in **Table 3-7**. Ventricular arrhythmias were common, and over 25% of the study cohort demonstrated nonsustained ventricular tachycardia.

Heart rate variability was analysed only if more than 80% of the 24 hour recording was artefact and arrhythmia free. One hundred and seventy-three tapes were included in analysis (1 tape was damaged, 4 patients were in atrial fibrillation, and the remainder had frequent ectopy). Time and frequency domain measures of heart rate variability are presented respectively in **Table 3-8** and **Table 3-9**. Short term time domain measures of heart rate variability and all frequency domain measures of heart

rate variability were significantly skewed and required log transformation for normality. Time and frequency domain measures of heart rate variability were highly correlated (see **Table 3-10**). Time and frequency domain measures of heart rate variability were depressed compared to published normal controls of similar age [95].

Correlations between measures of heart rate variability, age, left ventricular ejection fraction, NYHA status and other autonomic variables are shown in **Table 3-12**.

Table 3-7: Ventricular and supraventricular arrhythmia analysis

VENTRICULAR ARRHYTHMIA Variable	Variable present	Median (IQR)
Tape duration (hrs)	198	24 (23.5-24.0)
Total VE/24 hours	197	264 (53-1512)
VE/hour	197	11 (2-63)
VE/1000 beats	197	3 (1-13)
Ventricular couplets	127	8 (2-60)
NSVT	57	2 (1-5)
VT	9	1 (1-5)
SUPRAVENTRICULAR ARRHYTHMIA **Variable**	**Variable present**	**Median (IQR)**
Total SVE/24 hours	192	68 (27-225)
NSSVT/24 hours	68	4 (2-15)
SVT/24 hours	2	12 (6-23)

VE = ventricular ectopic beat;

NSVT = nonsustained ventricular tachycardia (>3 beats<10 beats, rate>120 bpm);

VT = ventricular tachycardia (>10 beats, rate>120 bpm);

SVE = supraventricular ectopic beat;

NSSVT = nonsustained supraventricular tachycardia (>3 beats<10 beats, rate>120 bpm);

SVT = supraventricular tachycardia (>10 beats, rate>120 bpm).

Table 3-8: Heart Rate Variability: time domain analysis

	Units	Mean (SD)	Median	IQR
SDNN	msec	120 (41)	119	89-144
Triangular Index	msec	30 (10)	30	23-38
SDANN	msec	108 (38)	106	80-131
SDNN Index	msec	45 (18)	43	31-54
r-MSSD	msec	30 (19)	26	19-36
pNN50	%	6.4 (7.2)	4	1.4-8.9
Ln rMSSD		1.4 (0.2)	1	1.3-1.6
Ln pNN50		0.5 (0.6)	1	0.2-1.0

Ln: natural logarithm transform

Table 3-9: Heart Rate Variability: frequency domain analysis

	Units	Mean (SD)	Median	IQR
Total power	$msec^2$	2607 (2051)	2122	1105-3269
ULF power	$msec^2$	383 (502)	244	131-447
VLF power	$msec^2$	1592 (1230)	1342	685-1998
LF power	$msec^2$	431 (469)	290	127-532
HF power	$msec^2$	199 (224)	133	68-248
Ln Total Power		7.6 (0.8)	7.7	7.0-8.1
Ln ULF Power		5.5 (1.0)	5.5	4.9-6.1
Ln VLF Power		7.1 (0.9)	7.2	6.5-7.6
Ln LF Power		5.6 (1.1)	5.7	4.8-6.3
Ln HF Power		4.9 (1.0)	4.9	4.2-5.5

Ln: natural logarithm transform

Table 3-10: Correlation between time and frequency domain heart rate variability

	Triangular Index	SDNN	Ln All Power	Ln ULF Power	SDANN	Ln VLF Power	SDNN -I	Ln LF Power	LnpNN50	LnrMSSD	Ln HF Power
Triangular Index	1.00										
SDNN	0.88	1.00									
Ln All Power	0.73	0.73	1.00								
Ln ULF Power	0.66	0.66	0.90	1.00							
SDANN	0.86	0.97	0.64	0.58	1.00						
Ln VLF Power	0.72	0.73	0.96	0.84	0.65	1.00					
SDNN I	0.66	0.70	0.91	0.75	0.57	0.87	1.00				
Ln LF Power	0.67	0.66	0.89	0.68	0.57	0.84	0.89	1.00			
Ln pNN50	0.38	0.39	0.48	0.39	0.31	0.37	0.61	0.51	1.00		
Ln rMSSD	0.37	0.43	0.57	0.51	0.30	0.44	0.70	0.56	0.85	1.00	
Ln HF Power	0.54	0.53	0.71	0.57	0.43	0.58	0.77	0.73	0.88	0.86	1.00

pearson correlaton coefficient, all values $p<0.05$

3.6 PLASMA NEUROHORMONES

Due to a freezer breakdown, 29 noradrenaline samples, 47 natriuretic peptide and the 47 corresponding spare samples were thawed and unsuitable for analysis. Comparison of cases available for analysis against those where samples were missing revealed no significant difference in age, left ventricular ejection fraction, baroreflex sensitivity, or heart rate variability indices. The frequency distributions of plasma adrenaline, BNP and ANP were markedly skewed and are presented along with their natural logarithmic transforms:

Table 3-11: Plasma noradrenaline and natriuretic peptides

Variable	Mean (SD)	Median	IQR
Atrial natriuretic peptide (ng/ml)	5.4 (4.2)	4.2	2.2-7.1
Brain natriuretic peptide (pg/ml)	87.3 (48.3)	48.3	24.1-93.1
Plasma noradrenaline (nmol/l)	4.79 (3.9)	3.9	2.9-5.7
Ln atrial natriuretic peptide	1.38 (1.43)	1.4	0.79-1.96
Ln brain natriuretic peptide	3.89 (3.88)	3.9	3.18-4.53
Ln plasma noradrenaline	1.42 (1.37)	1.4	1.06-1.74

Correlations between plasma neurohormones, age, left ventricular ejection fraction, NYHA status and other autonomic variables are shown in **Table 3-12**.

3.7 BAROREFLEX MEASUREMENTS

Phenylephrine baroreflex challenges were available on all patients in sinus rhythm. Subjects demonstrated 2 types of heart rate response to the phenylephrine challenge: a normal response with heart rate slowing (n=151) or a delayed, absent or paradoxical heart rate response (n=44). Mean baroreflex sensitivity for the entire cohort was 6.7 (SD 6.1)

milliseconds/mmHg. This high mean is because absent or paradoxical responses were dichotomised as below the median for survival analysis, but not quantitatively determined.

Correlations between plasma baroreflex sensitivity measurements, age, left ventricular ejection fraction, NYHA status and other autonomic variables are given and discussed in the section below.

3.8 CORRELATIVE STATISTICS

Plasma neurohormones, baroreflex sensitivity and short term time domain and all frequency domain measures of heart rate variability were log transformed, because of their skewed distribution. Correlations between age, left ventricular ejection fraction, peak VO_2 and autonomic variables are shown in **Table 3-12**. For simplicity, only time domain measures of heart rate variability are shown, as frequency domain measures duplicated the time domain results.

Age was weakly, but significantly and negatively correlated with peak VO_2, plasma neurohormones, baroreflex sensitivity and SDNN-I (**Table 3-12**). There were weak but significant correlations between all autonomic variables, but the correlation coefficients would suggest that they could still provide independent prognostic information. Baroreflex sensitivity was most strongly correlated with log transforms of plasma BNP and ANP ($r = -0.47$ and -0.52) and with peak VO_2 ($r = 0.48$). Perhaps surprisingly, baroreflex sensitivity correlated only weakly (albeit significantly) with short term "parasympathetic" measures of heart rate variability (log transform rMSSD and pNN50 $r = 0.20$ and 0.24 respectively). This was also true for the respective frequency domain measure (log transform HF power $r = 0.30$, $p < 0.01$).

Table 3-12: Correlations between clinical, exercise and autonomic variables

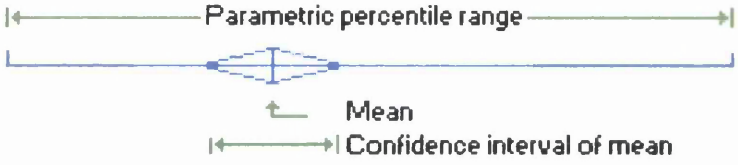
	Age	LVEF	Peak VO2	Ln ANP	Ln BNP	Ln NOR	BRS Mean	SDNN	TRI Index	SDANN-I	SDNN-I	Ln RMSSD	Ln pNN50
Age	1.00												
LVEF	-0.02	1.00											
Peak VO2	**-0.37 ****	**0.22 ****	1.00										
Ln ANP	**0.36 ****	**-0.29 ****	**-0.38 ****	1.00									
Ln BNP	**0.28 ****	**-0.32 ****	**-0.41 ****	**0.85 ****	1.00								
Ln NOR	**0.16 ***	**-0.25 ****	**-0.26 ****	**0.27 ****	**0.35 ****	1.00							
BRS Mean	**-0.53 ****	**0.17 ***	**0.48 ****	**-0.52 ****	**-0.47 ****	**-0.25 ****	1.00						
SDNN	-0.09	**0.18 ***	**0.29 ****	**-0.25 ****	**-0.38 ****	**-0.31 ****	**0.34 ****	1.00					
Triangular Index	-0.06	**0.24 ****	**0.37 ****	**-0.31 ****	**-0.43 ****	**-0.35 ****	**0.36 ****	**0.88 ****	1.00				
SDANN-I	-0.06	**0.19 ***	**0.25 ****	**-0.23 ****	**-0.38 ****	**-0.32 ****	**0.29 ****	**0.97 ****	**0.86 ****	1.00			
SDNN-I	**-0.29 ****	**0.22 ****	**0.39 ****	**-0.30 ****	**-0.32 ****	**-0.25 ****	**0.51 ****	**0.70 ****	**0.66 ****	**0.57 ****	1.00		
Ln RMSSD	-0.10	0.12	**0.19 ***	-0.05	-0.05	-0.07	**0.20 ****	**0.43 ****	**0.37 ****	**0.30 ****	**0.70 ****	1.00	
Ln pNN50	-0.10	0.13	**0.20 ***	-0.02	-0.04	-0.08	**0.24 ****	**0.39 ****	**0.38 ****	**0.31 ****	**0.61 ****	**0.85 ****	1.00

**: pearson correlation significant at $p<0.01$; * pearson correlation significant at $p<0.05$ Ln: natural log transform

Peak VO_2 was strongly and inversely related to NYHA class ($p<0.0001$ by ANOVA). Long term indices of heart rate variability (triangular index, SDNN and SDANN) were also strongly and inversely related to NYHA class ($p<0.05$ by ANOVA). Short term indices of heart rate variability were not significantly related to NYHA Class. Plasma BNP and baroreflex sensitivity were significantly different between NYHA Class I and IV ($p<0.05$ by ANOVA) (see **Figure 3-3** to **Figure 3-6**).

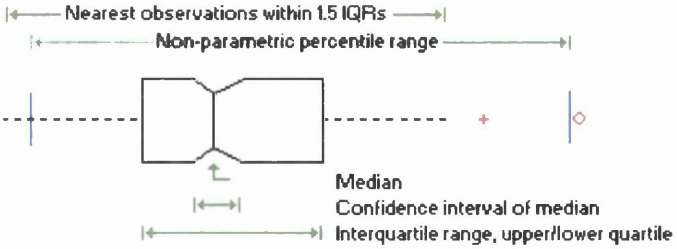
Explanation of Box & Whisker Plots

The blue line series shows parametric statistics:



The blue diamond shows the mean and the 95% confidence interval around the mean. The blue notched lines show the 95% parametric percentile range.

The notched box and whiskers show non-parametric statistics:



The notched box shows the median, lower and upper quartiles, and confidence interval around the median. The dotted-line connects the nearest observations within 1.5 inter-quartile ranges (IQRs) of the lower and upper quartiles.

Red crosses (+) and circles (o) indicate possible outliers - observations more than 1.5 IQRs (near outliers) and 3.0 IQRs (far outliers) from the quartiles. The blue vertical lines show the 95% non-parametric percentile range.

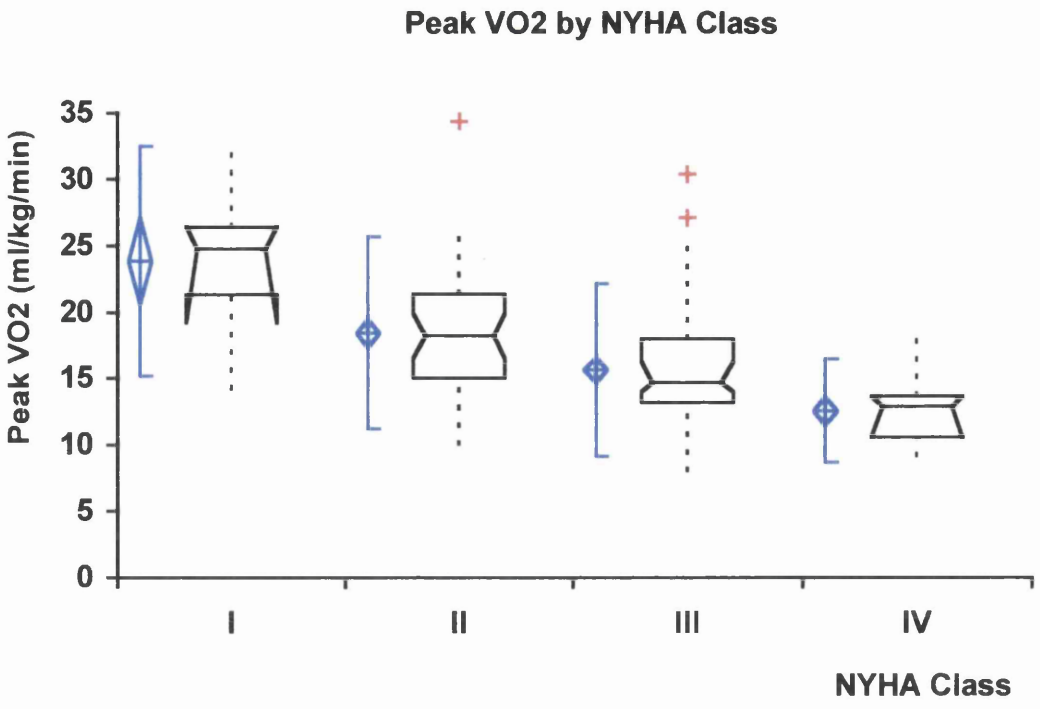


Figure 3-3: Peak VO2 and NYHA Class

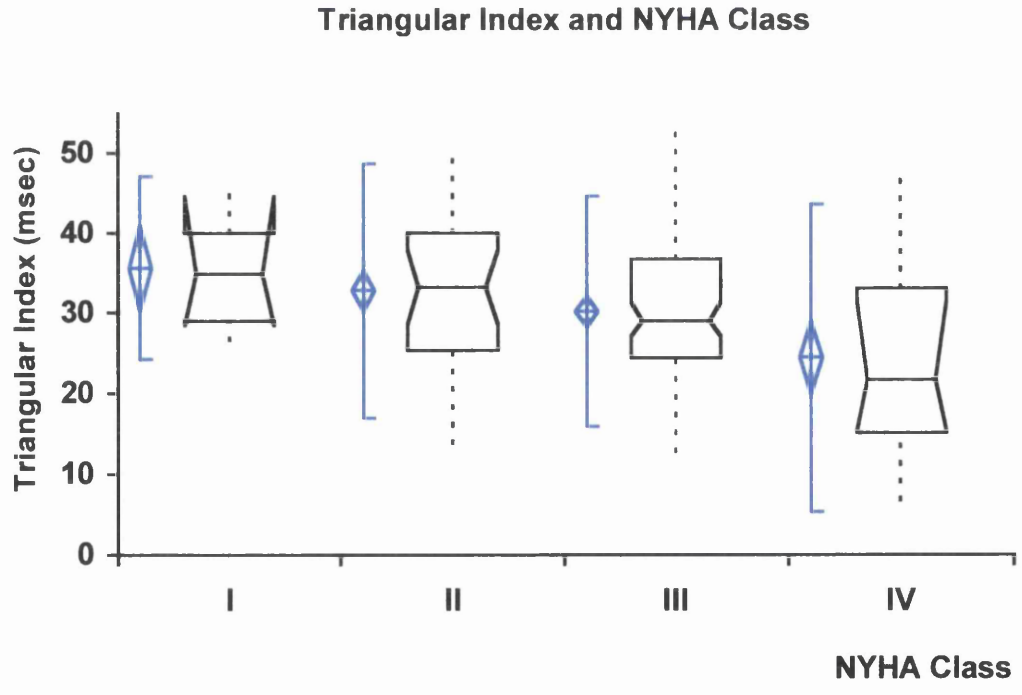


Figure 3-4: Triangular Index and NYHA Class

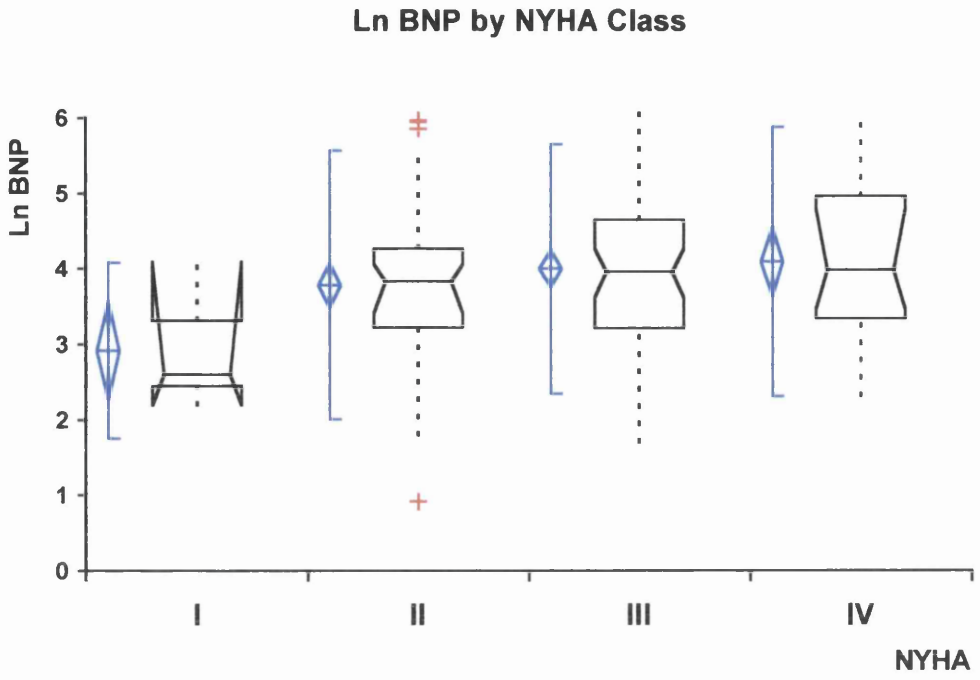


Figure 3-5: Ln BNP by NYHA Class

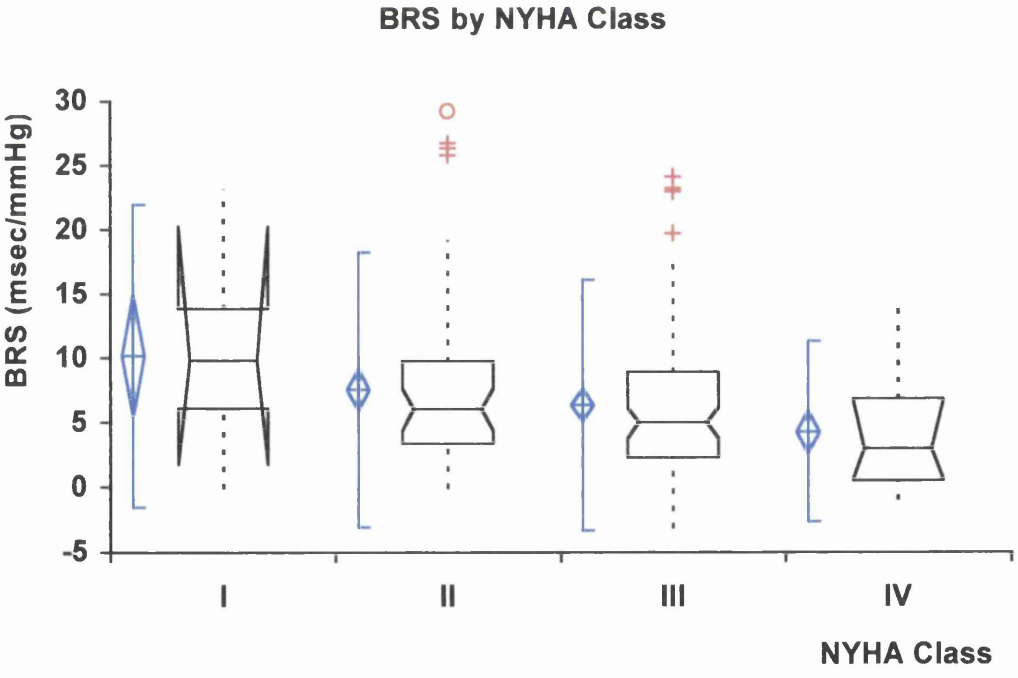


Figure 3-6: BRS by NYHA Class

3.9 SURVIVAL ANALYSIS

All data are expressed as mean ± SD, except where indicated as median and IQR. Follow up was complete on all patients. Median duration of follow-up was 1086 days, IQR 734–1259 days. In survivors, median follow–up was 1173 days, IQR 1031–1289 days. There were 54 (27%) deaths in total, and 47 (24%) cardiovascular deaths. Six patients died of cancer, and one of multi-organ failure following an appendicectomy. For statistical purposes, follow-up of these patients was censored at the time of death, and the data included in the survival analyses. There were 23 (12%) progressive heart failure deaths and 24 (12%) sudden deaths. Median time to cardiovascular death was 376 days, IQR 203–734 days. Median time to progressive heart failure death was 342 days, IQR 200–583 days and to sudden death was 483 days, IQR 247–877 days (Mann whitney p = 0.2, NS). The proportion of sudden death (6 of 8 total) in NYHA class I/II patients was not statistically different to that in NYHA class III/IV patients (18 of 29, p= 0.27, Fisher exact test).

To simplify univariate and multivariate analysis, continuous variables were categorised by prospectively defined cut-points. Continuous variables were dichotomised above and below median values. NYHA status was grouped as Class I/II vs III/IV. Because of concerns over the use of 2 different methodologies to determine LVEF, ejection fraction was dichotomised at the cohort median value (22), and with the RNVG and Echo determined LVEF groups dichotomised at their respective group medians. In only 6 patients did the dichotomisations conflict (of the 43 patients where data was available from both methods). Whether LVEF was dichotomised at the total cohort median value, the RNVG group median, Echo group median or by eyeball assessment made no difference to the results of survival analysis.

To ensure further statistical validity, analyses were repeated with the continuous variables entered as continuous co-variates, dichotomised at the median value, categorised into tertiles and categorised into quartiles. All analyses produced similar results, and, in particular, made no difference to the multivariate analysis of cardiovascular death, progressive heart failure or sudden death. The absence of data (eg because of freezer breakdown for plasma BNP, non-analysable QT dispersion, non-analysable echocardiogram) was not statistically associated with survival.

3.9.1 *Univariate Analysis*

Kaplan-Meier survival curves were constructed for all variables according to the level of categorisation described above, and comparison between groups was assessed using the Log Rank test.

Survival of the entire cohort is presented in **Figure 3-7**. Cumulative mortality at follow-up of 1, 2 and 3 years was respectively 12, 18 and 24%. Established clinical parameters (aetiology of heart failure, NYHA class, left ventricular ejection fraction and peak oxygen consumption) predicted cardiovascular death significantly (log rank test $p<0.01$ in all). Therapy was associated with survival: β-blocker use was favourable, whereas digoxin, diuretic and amiodarone therapy was associated with an increased mortality. However, duration of chronic heart failure and prior revascularisation did not affect survival. Plasma neurohormones, baroreflex sensitivity, and time and frequency domain measures of heart rate variability (Triangular Index, SDNN, SDNN-I) predicted cardiovascular death (log rank test $p<0.01$). Intraventricular conduction defects/bundle branch block and a positive signal averaged ECG also predicted death (log rank test $p<0.01$). However, none of the electrocardiographic measure of ventricular repolarisation was statitically

associated with prognosis. This was true if analyses were repeated excluding patients with intraventricular conduction defect, or if different dichotomisation values were chosen. These results are summarised in **Figure 3-8** to **Figure 3-29**.

The association of established and investigational variables with prognosis was studied by Cox regression analysis. Total cardiovascular mortality, death due to progressive heart failure and sudden death was analysed and hazards ratios were calculated for each investigational co-variate (see **Table 3-13**). Recognised prognostic clinical, echocardiographic and exercise variables predicted cardiovascular death significantly in the study cohort. Aetiology was "synonymous" with cardiovascular mortality: 45 of 47 deaths occurred in the ischaemic group. Because there were so few patients with non-ischaemic aetiology, and even fewer events in this group, further statistical analysis would not provide discriminant information. As such, following statistical advice, aetiology of heart failure was excluded from further statistical analyses.

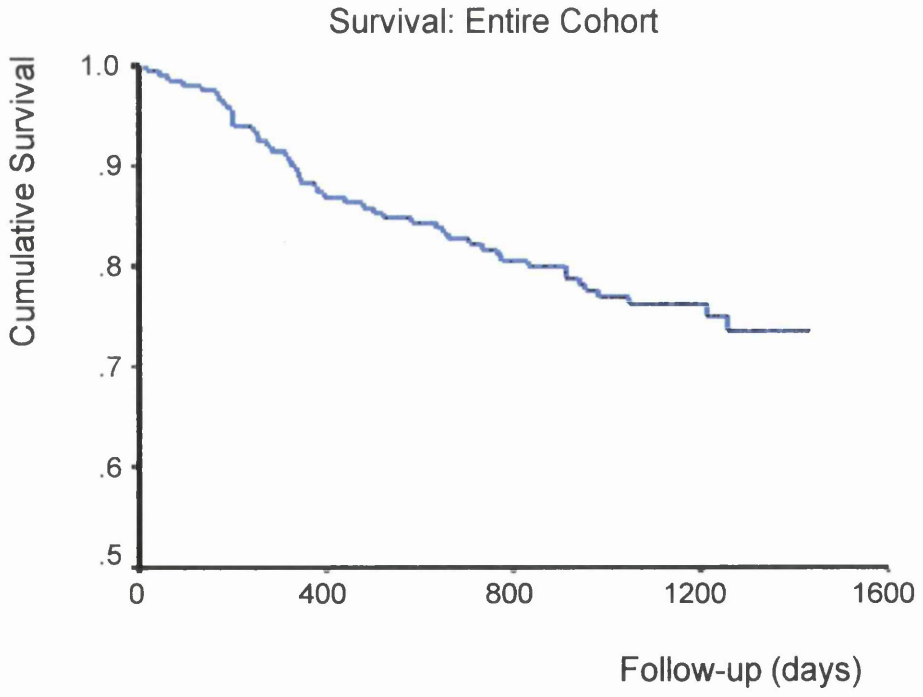


Figure 3-7: Survival for entire study cohort.

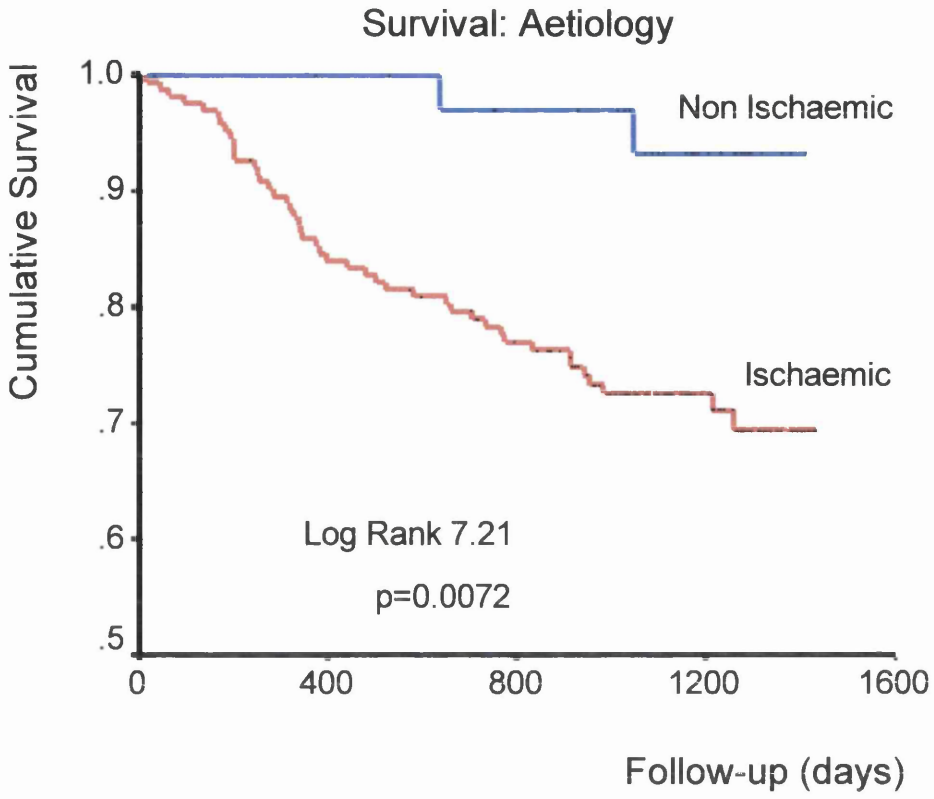


Figure 3-8: Survival and aetiology of heart failure

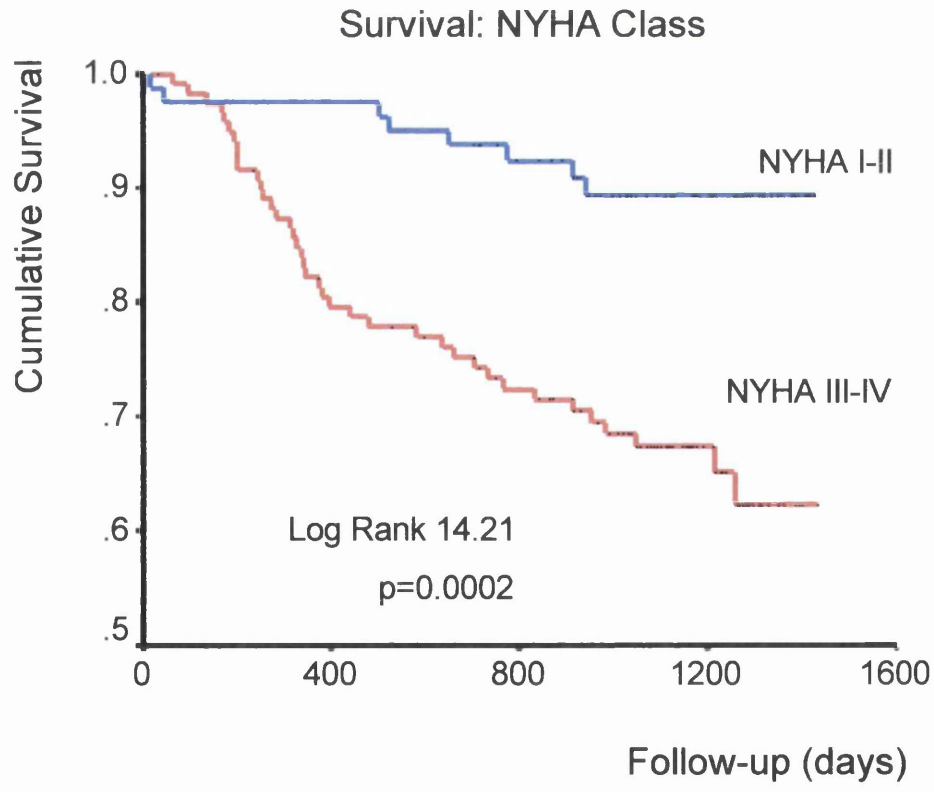


Figure 3-9: Survival and severity of heart failure: NYHA Class

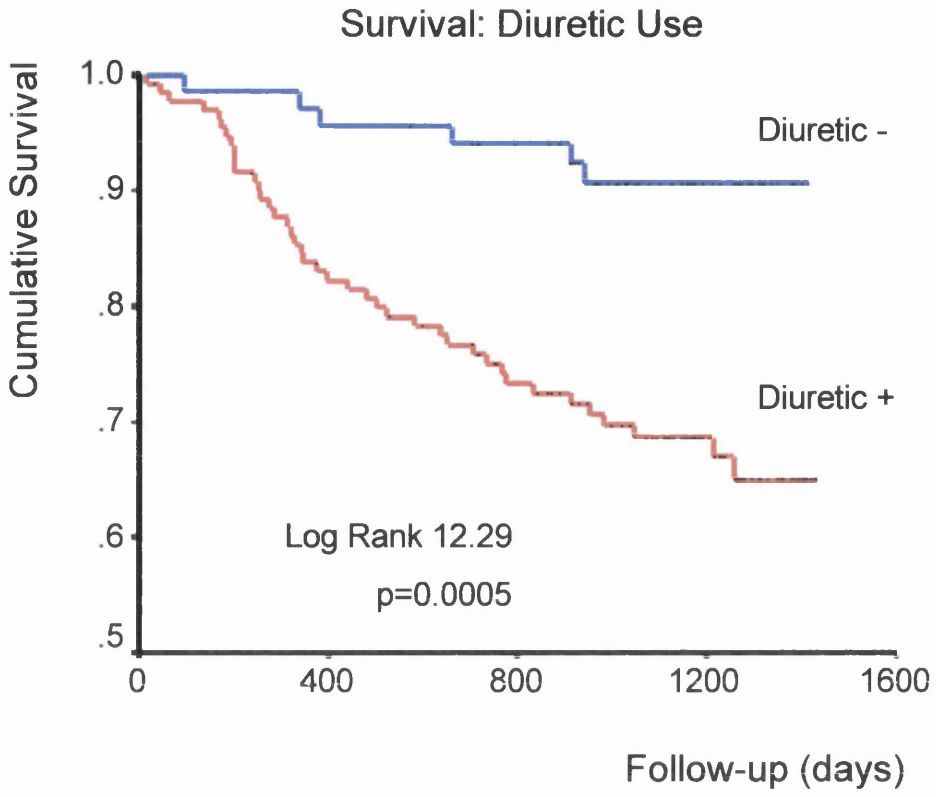


Figure 3-10: Survival and drug therapy: Diuretic use

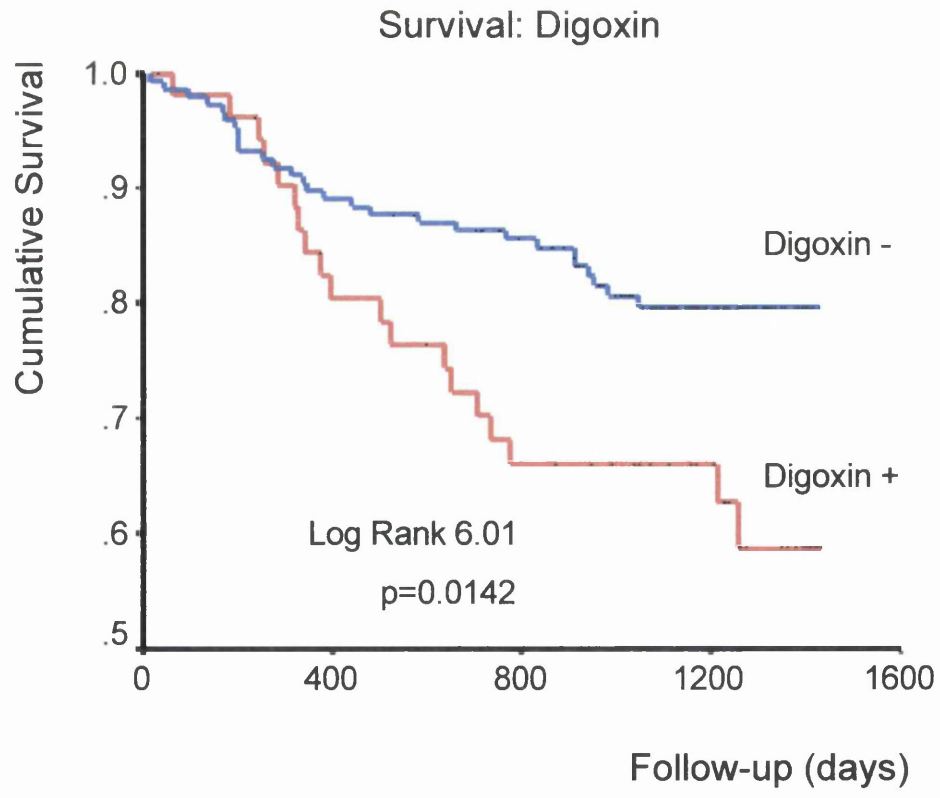


Figure 3-11: Survival and drug therapy: Digoxin use

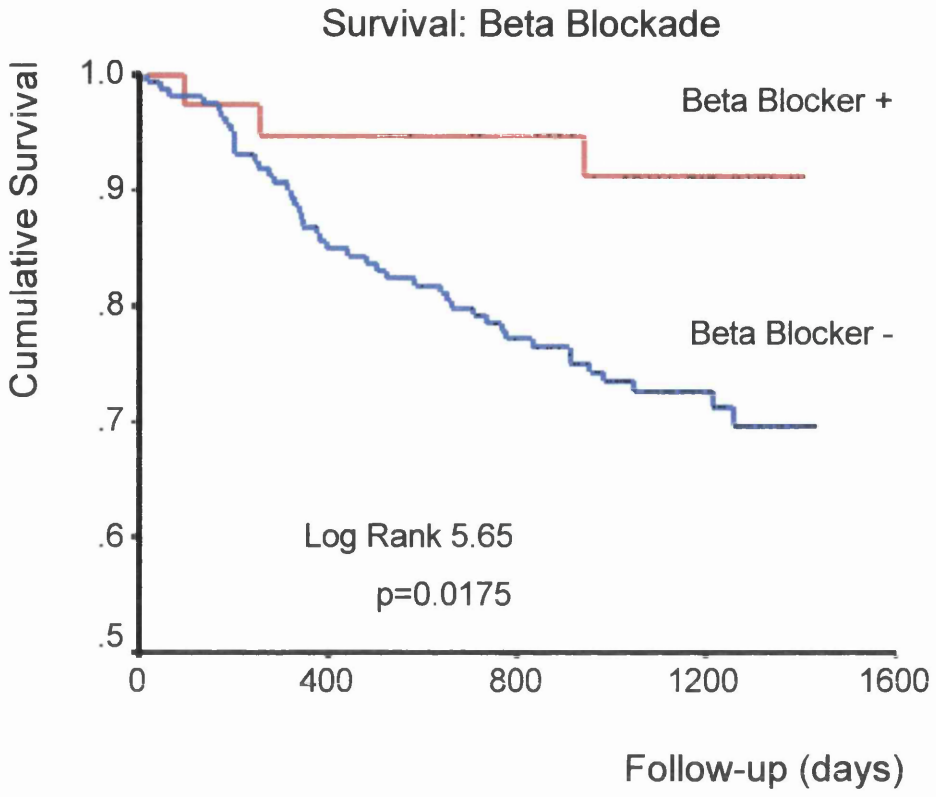


Figure 3-12: Survival and drug therapy: β-blockade

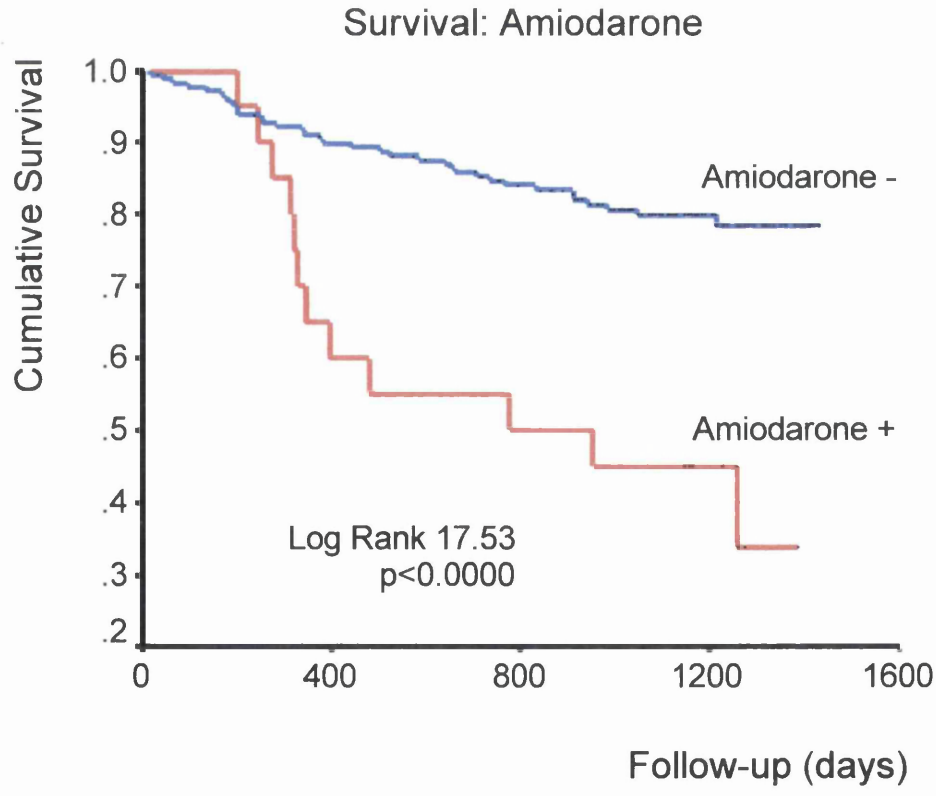


Figure 3-13: Survival and drug therapy: Amiodarone use

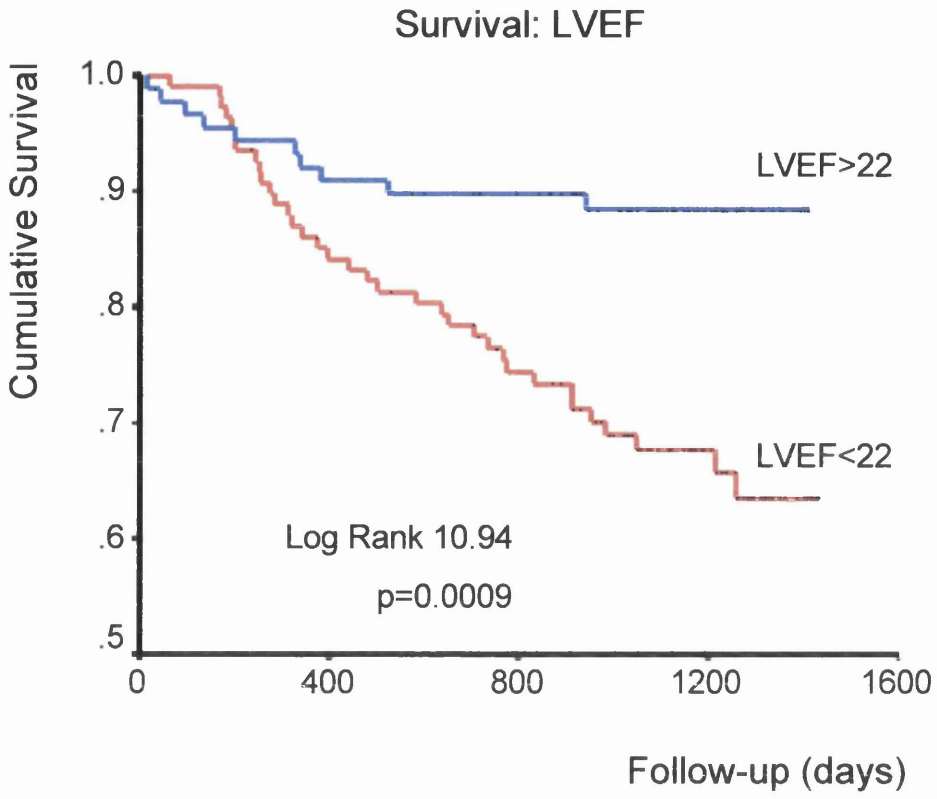


Figure 3-14: Survival and severity of pump dysfunction: LV ejection fraction

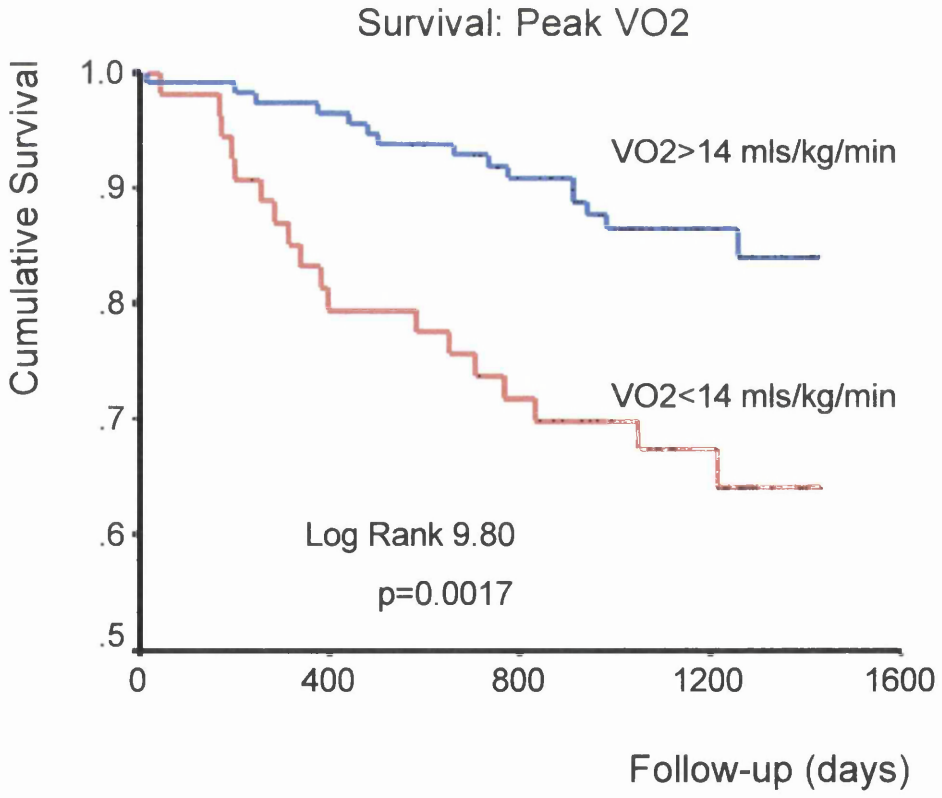


Figure 3-15: Survival and severity of exercise intolerance: Peak VO_2

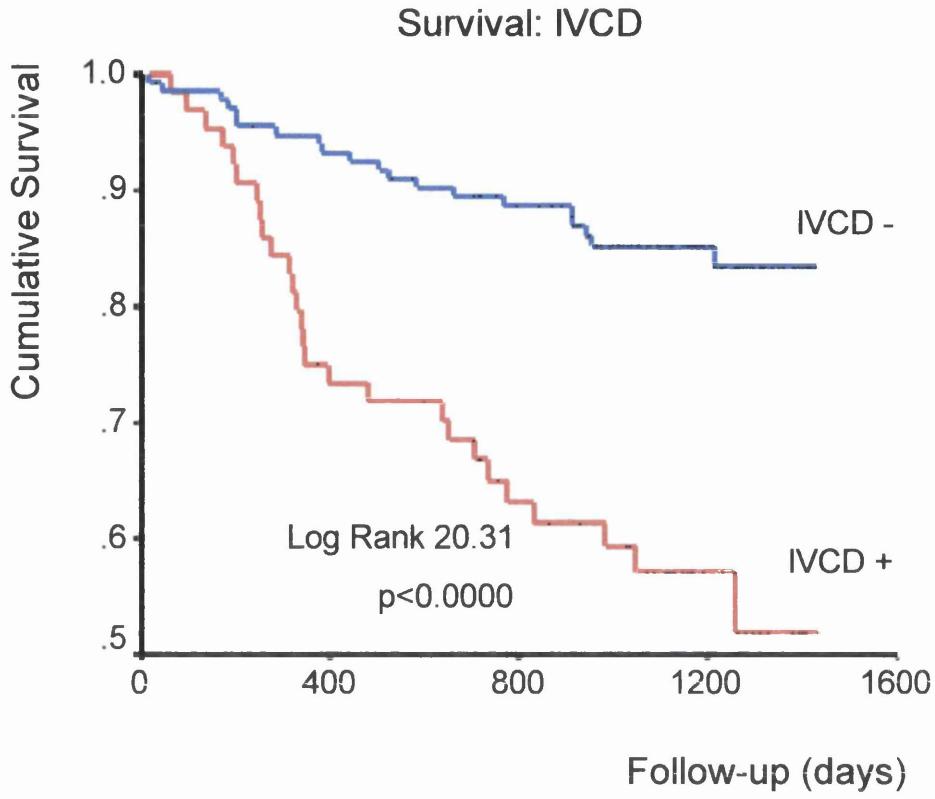


Figure 3-16: Survival and presence/absence of conduction defects: IVCD

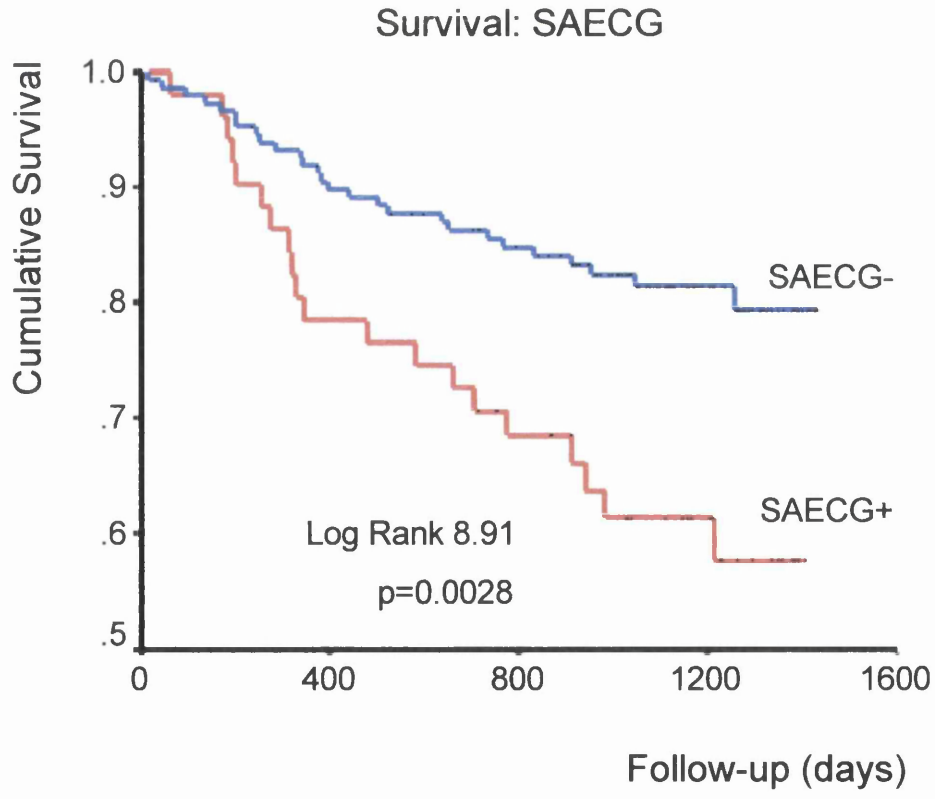


Figure 3-17: Survival and presence/absence of late potentials: SAECG

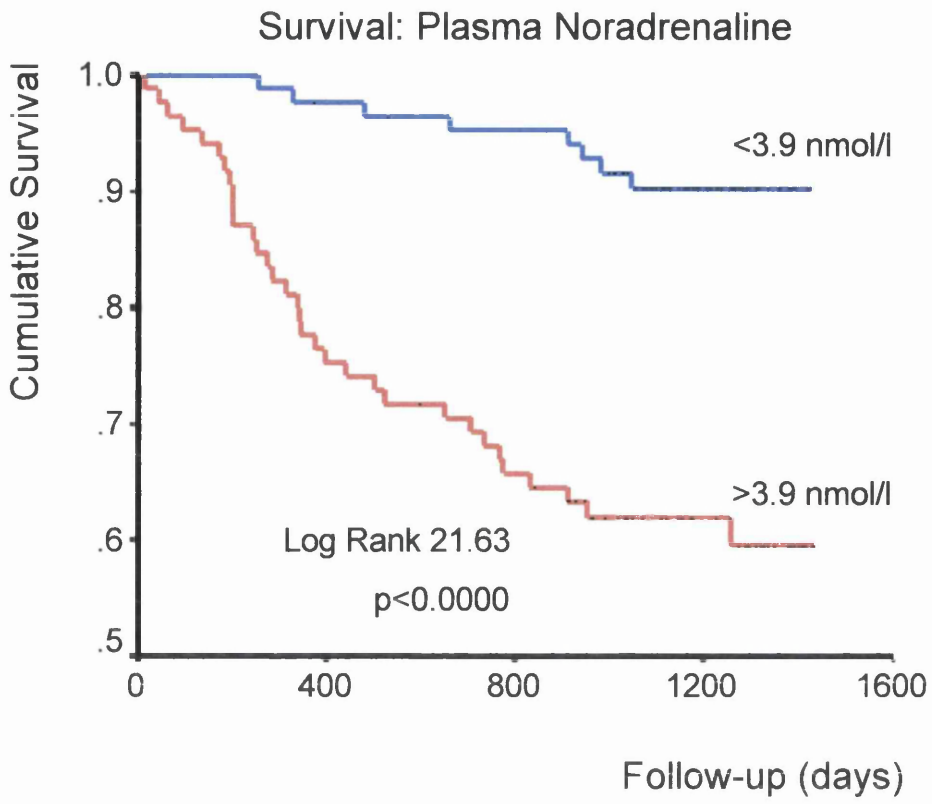


Figure 3-18: Survival and neurohormones: Plasma Noradrenaline

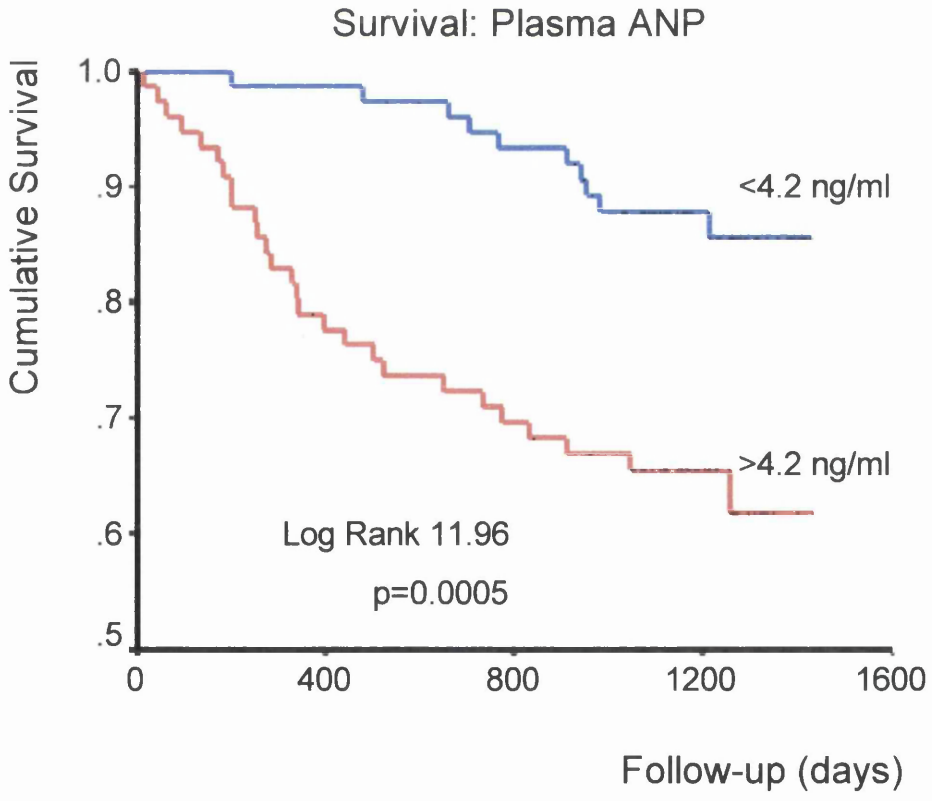


Figure 3-19: Survival and neurohormones: Plasma Atrial Natriuretic Peptide

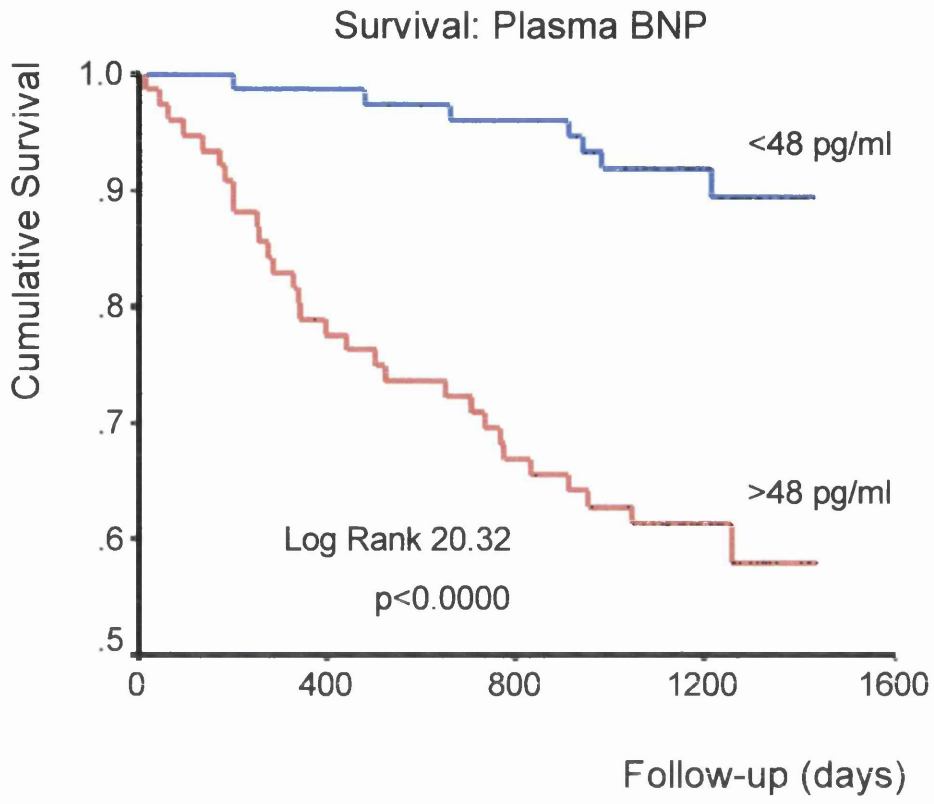


Figure 3-20: Survival and neurohormones: Plasma Brain Natriuretic Peptide

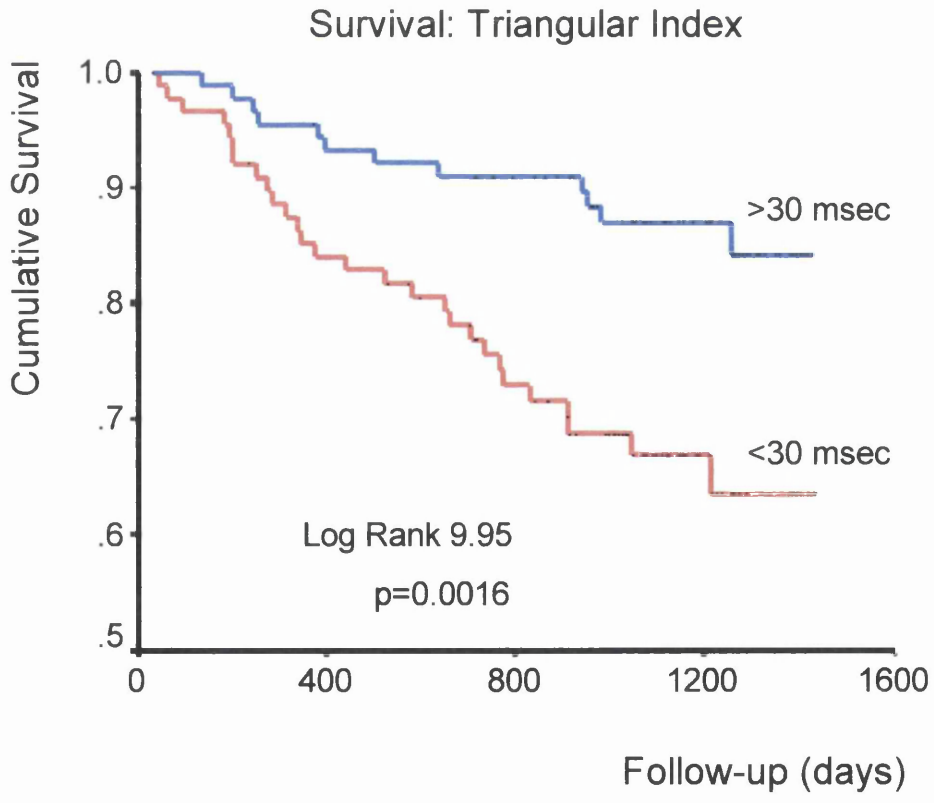


Figure 3-21: Survival and time domain heart rate variability :Triangular Index

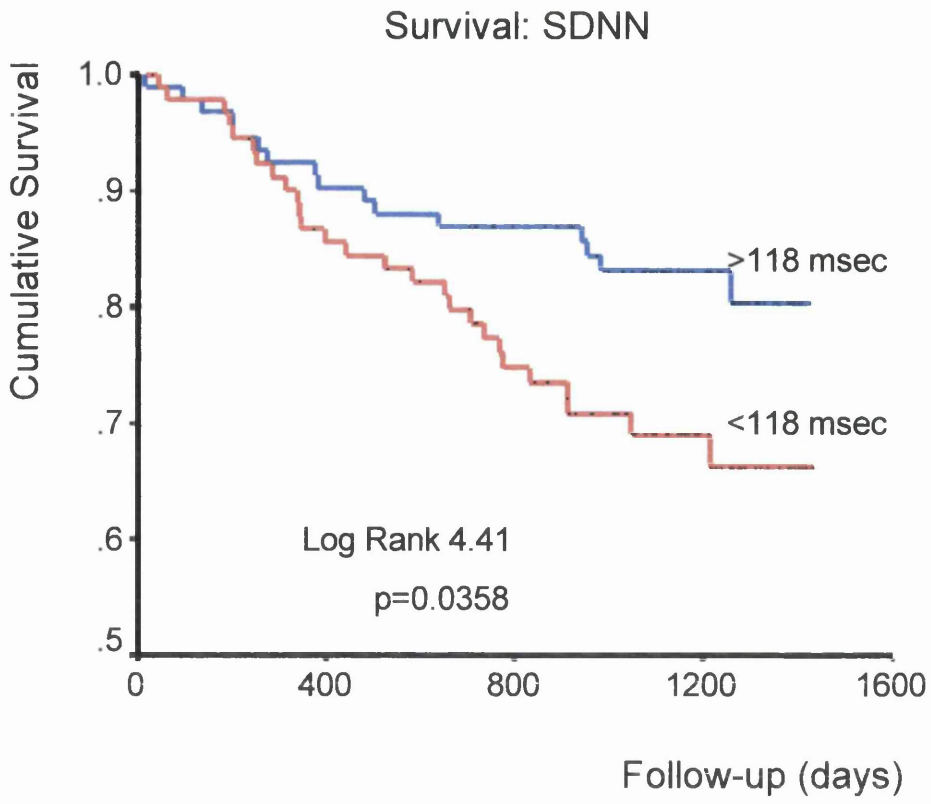


Figure 3-22: Survival and time domain heart rate variability: SDNN

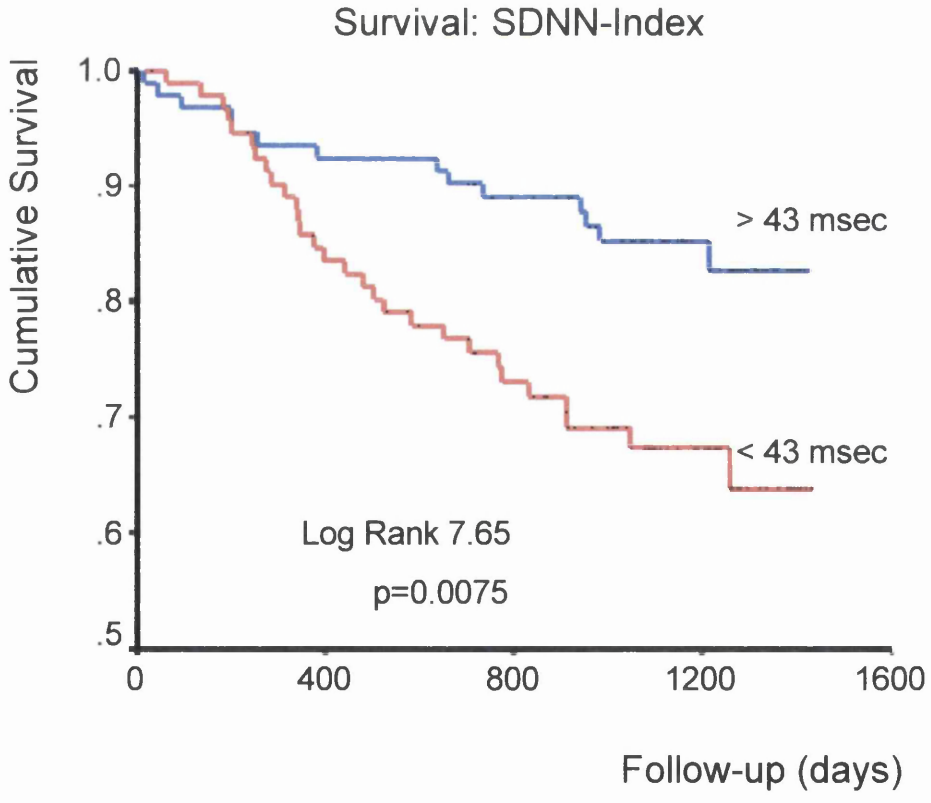


Figure 3-23: Survival and time domain heart rate variability: SDNN-Index

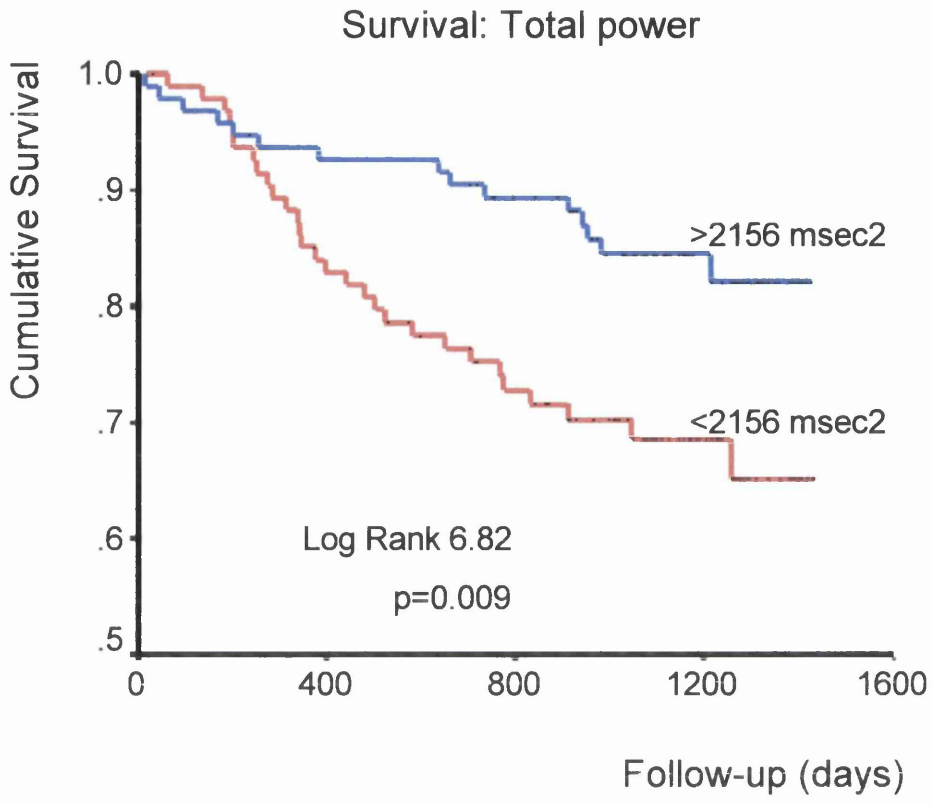


Figure 3-24: Survival and frequency domain heart rate variability: Total power

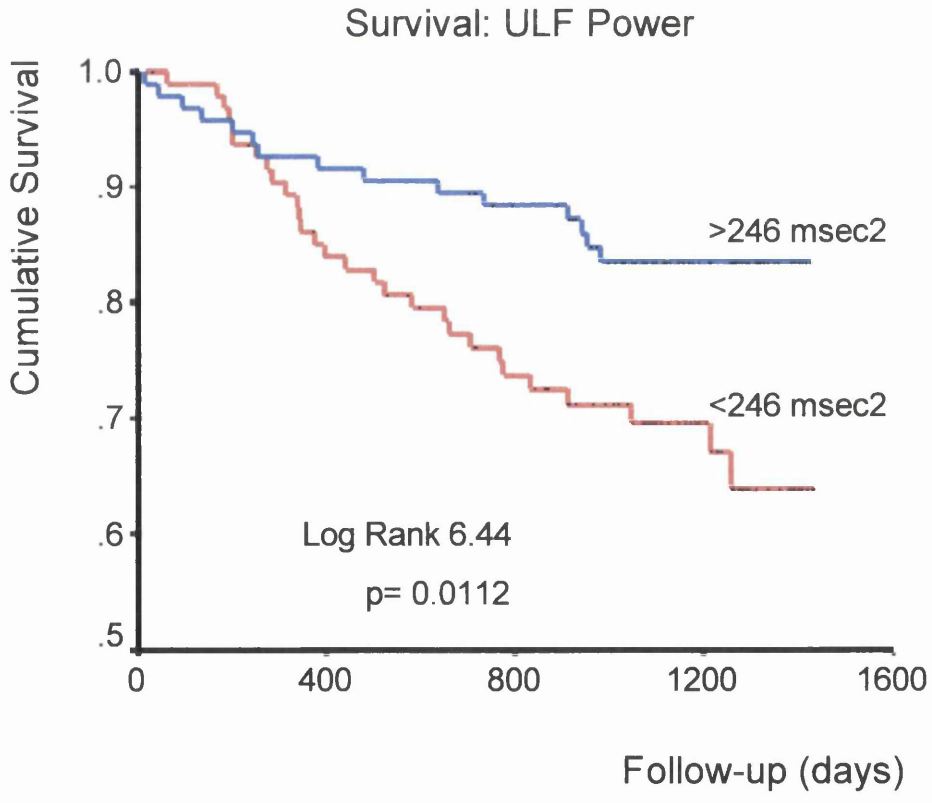


Figure 3-25: Survival and frequency domain heart rate variability: ULF power

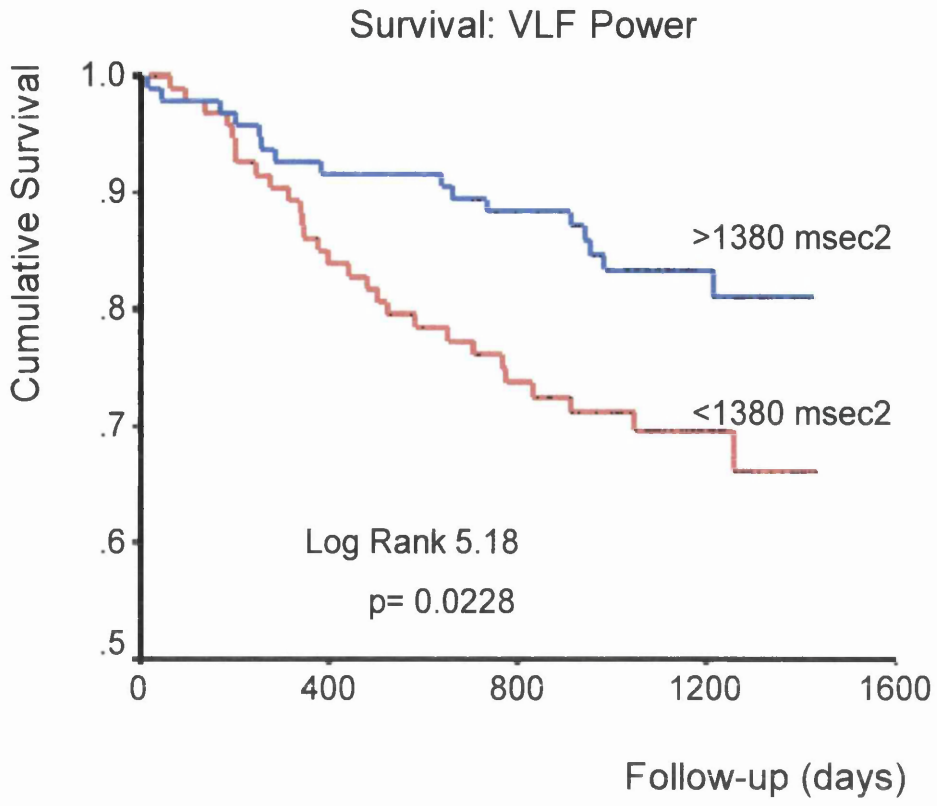


Figure 3-26: Survival and frequency domain heart rate variability: VLF power

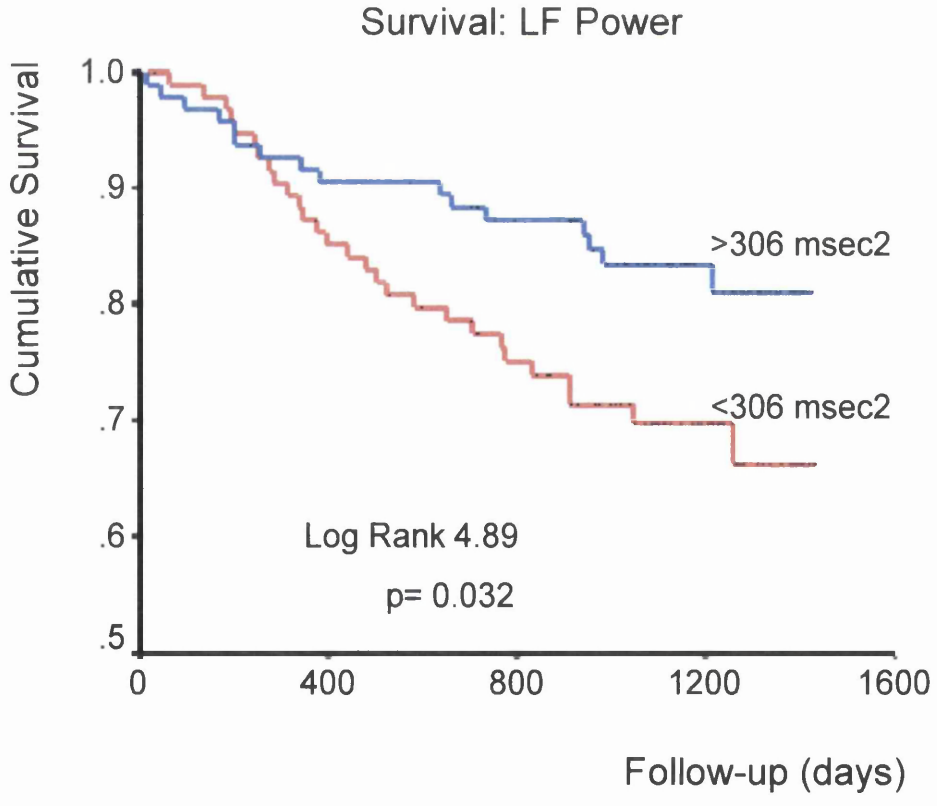


Figure 3-27: Survival and frequency domain heart rate variability : LF power

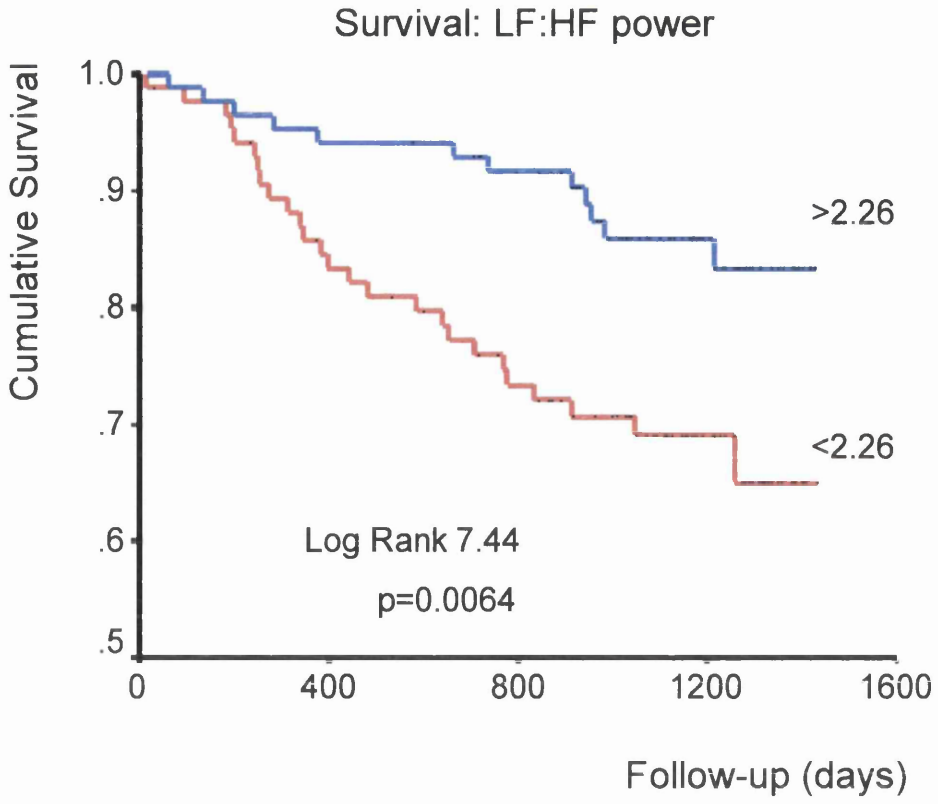


Figure 3-28: Survival and frequency domain heart rate variability: LF:HF power

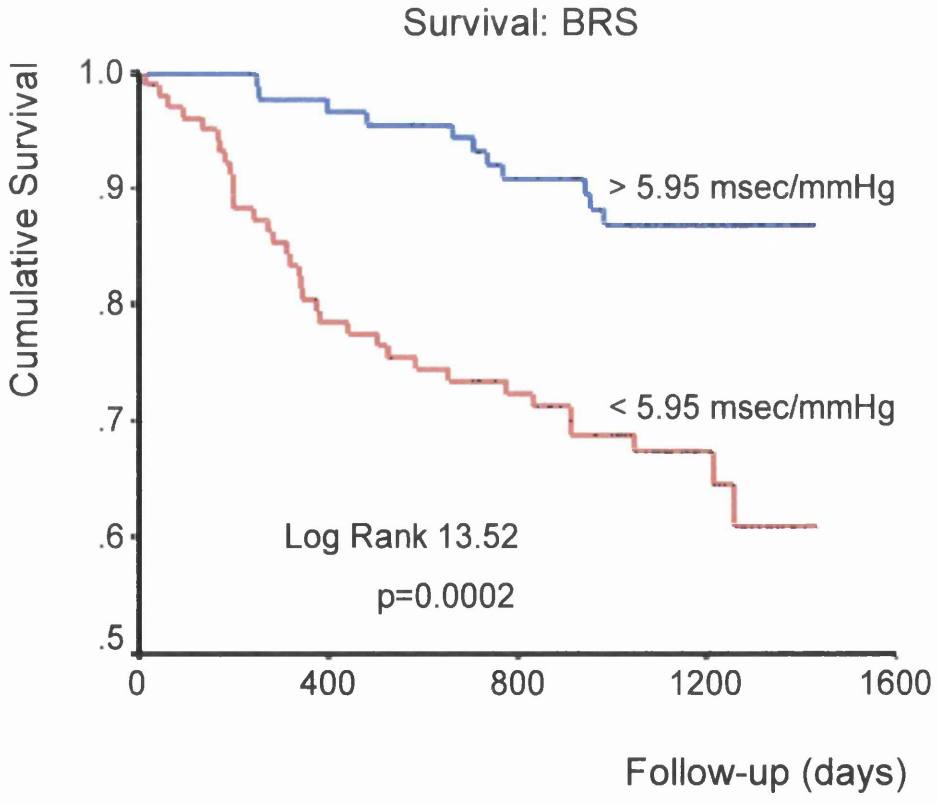


Figure 3-29: Survival and baroreflex sensitivity

3.9.1.1 Univariate Analysis: Cardiovascular death

Established clinical, echocardiographic and electrocardiographic variables predicted cardiovascular death in this patient cohort (see **Table 3-13**). Functional class significantly predicted cardiovascular death (hazards ratio for class III/IV 3.9 compared with class I/II). A similar hazards ratio was seen for patients unable to exercise due to cardiac limitation or with peak VO_2 <14 mls/kg/min. Interestingly, the presence of intraventricular conduction delay carried important prognostic information and was more powerful than the signal averaged ECG (hazards ratio 3.5 vs 2.4).

Treatment with diuretics, digoxin or amiodarone significantly worsened prognosis. β-blockade was associated with a better prognosis.

Holter variables predicted cardiovascular death significantly: higher average heart rates and the presence of non-sustained ventricular tachycardia carried respective hazards ratios of 2.0 and 2.5.

Autonomic dysfunction identified patients with a poorer prognosis. Higher levels of plasma neurohormones, and lower values of baroreflex sensitivity or heart rate variability conferred increased risk. In particular, patients with supramedian levels of plasma noradrenaline or plasma BNP had a five-fold increase in risk of death. These variables were the strongest univariate predictors of mortality: depressed baroreflex sensitivity or heart rate variability (triangular index) carried a lower, but still statistically and clinically significant risk (3.3 and 2.8 respectively).

These results were replicated when analysis was repeated with variables dichotomised at the median, the tertile or at the quartile values.

3.9.1.2 Univariate Analysis: Progressive heart failure death

Functional status significantly predicted death due to progressive heart failure: patients with higher NYHA status had an 8 fold increased risk of death. Inability to exercise or a peak VO2 <14 mls/kg/min conferred a similar hazard (see **Table 3-13**).

The presence of intraventricular conduction delay identified patients at high risk of death, reflecting both lower left ventricular ejection fraction and ventricular dyssynchrony.

Signal averaged electrocardiography and/or the presence of non-sustained ventricular tahycardia did not predict progressive heart failure death.

Elevated plasma neurohormones were very strong predictors of death due to progressive heart failure (hazards ratios categorised at median values: plasma noradrenaline 23.1, plasma BNP 10.0). With the exception of SDNN-Index, depressed spectral domain measures of heart rate variability performed better than the respective time domain measures in predicting progressive heart failure death.

3.9.1.3 Univariate Analysis: Sudden death

Generally, variables predictive of progressive heart failure death either did not identify patients at risk of sudden death (NYHA status/peak VO2), or, in the case of plasma neurohormones, demonstrated reduced prognostic power (see **Table 3-13**).

Current smoking carried a 4 fold increased risk of sudden death.

A positive signal averaged ECG, the presence of non-sustained ventricular tachycardia and depressed baroreflex sensitivity conferred more than threefold increased risk of sudden death.

Table 3-13: Univariate association of variables with cardiovascular death, progressive heart failure death and sudden death

VARIABLE		CARDIOVASCULAR DEATH			PROGRESSIVE HEART FAILURE DEATH			SUDDEN DEATH		
		HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
Clinical										
Aetiology		5.6	1.3 – 23.7	0.0173			NS			NS
Age by decile		1.4	1.0 – 2.0	0.0238	2.1	1.2 – 3.6	0.0050			NS
NYHA Status	I/II vs III/IV	3.9	1.8 – 8.5	0.0005	8.4	1.9 – 36.8	0.0041			NS
MHFQ		2.2	1.1 – 4.1	0.0175			NS			NS
Hypertension	Yes/no			NS	2.3	1.0 – 5.3	0.0448			NS
Smoker	Yes/no			NS			NS	4.0	1.8 – 9.1	0.0007
Drug Therapy										
Diuretic		4.1	1.7 – 9.6	0.0012			NS	13.1	1.8 – 97.2	0.0119
Digoxin		2.1	1.1 – 3.7	0.0162			NS	2.6	1.2 – 5.7	0.0214
β–blockade		0.27	0.1 – 0.9	0.0270			NS			NS
Amiodarone		3.7	1.9 – 7.2	0.0001			NS			NS

NYHA – New York Heart Association; MHFQ – Minnesota living with heart failure questionnaire

Table 3:12 continued: Univariate association of variables with cardiovascular death, progressive heart failure death and sudden death

VARIABLE		CARDIOVASCULAR DEATH			PROGRESSIVE HEART FAILURE DEATH			SUDDEN DEATH		
		HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
Echocardiographic/CPETT										
LVEF	<> 22%	3.1	1.5 – 6.3	0.0017	3.9	1.3 – 11.8	0.0138			NS
Peak VO2	<> 14 mls/kg/min	2.9	1.4 – 5.7	0.0028	7.9	2.6 – 24.1	0.0002			NS
Electrocardiographic										
Conduction defect	IVCD/normal	3.5	1.9 – 6.3	0.0000	4.0	1.7 – 9.3	0.0013	3.1	1.4 – 7.1	0.0056
QT dispersion*	<>98 ms			NS	0.3	0.1 – 0.8	0.0135			NS
SAECG	+ve/–ve	2.4	1.3 – 4.2	0.0038				3.2	1.4 – 7.2	0.0044
Holter										
Mean NN	<> 800 msec	2.0	1.1 – 3.9	0.0262						NS
NSVT	present/absent	2.5	1.4 – 3.9	0.0024				2.8	1.2 – 6.3	0.0151

LVEF – left ventricular ejection fraction; Peak VO_2 – peak oxygen consumption; SAECG – signal averaged ECG; NSVT – non-sustained ventricular tachycardia.

Lower values of LVEF and peak VO_2 are associated with increased risk. *Higher values of QT dispersion are associated with lower risk

Table 3:12 continued: Univariate association of variables with cardiovascular death, progressive heart failure death and sudden death

VARIABLE		CARDIOVASCULAR DEATH			PROGRESSIVE HEART FAILURE DEATH			SUDDEN DEATH		
		HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
Plasma Neurohormones										
Noradrenaline	<> 3.9 nmol/l	5.2	2.4 – 11.4	0.0000	23.1	3.2 – 172.0	0.0022	2.6	1.0 – 6.6	0.0402
Plasma ANP	<> 4.2 ng/ml	3.4	1.6 – 7.0	0.0011	4.3	1.4 – 13.4	0.0102	2.7	1.0 – 7.3	0.0437
Plasma BNP	<> 48.2 pg/ml	5.4	2.3 – 12.6	0.0001	10.0	2.2 – 44.7	0.0022	3.6	1.3 – 10.2	0.0143
Baroreflex Sensitivity*										
BRS	<> 5.9 msec/mmHg	3.3	1.7 – 6.7	0.0005	3.0	1.2 – 7.8	0.0203	3.7	1.3 – 10.3	0.0099
Heart Rate Variability*										
SDNN	<> 118 msec	1.9	1.0 – 3.6	0.0392			NS			NS
Triangular Index	<> 30 msec	2.8	1.4 – 5.7	0.0026			NS	3.3	1.3 – 8.6	0.0129
SDNN–Index	<> 48 msec	2.4	1.2 – 4.6	0.0074	6.4	1.8 – 22.5	0.0030			NS
Total power	<> 2156 msec2	2.3	1.2 – 4.3	0.0110	6.8	2.0 – 23.8	0.0021			NS
ULF power	<> 246 msec2	2.2	1.2 – 4.2	0.0134	4.7	1.6 – 14.4	0.0051			NS
VLF power	<> 1380 msec2	2.0	1.1 – 3.8	0.0257	4.8	1.6 – 14.6	0.0048			NS
LF power	<> 306 msec2	1.9	1.0 – 3.6	0.0354	3.5	1.2 – 9.7	0.0150			NS

Higher values of plasma neurohormones conferred increased risk. *Lower values of BRS and HRV measures imply increased risk

3.9.2 *Multivariate Analysis*

The association of variables with prognosis was studied by Cox regression analysis. To establish the incremental prognostic utility of investigational variables over parameters easily obtained in clinical practice, a 2 block Cox regression was performed. Age, NYHA status (grouped as I/II or III/IV), presence or absence of intraventricular conduction defect, left ventricular ejection fraction (dichotomised above and below median), and peak VO_2 (dichotomised at 14 ml/kg/min) were classed as baseline variables. The first block of the Cox regression was the forced entry of baseline co-variates. Each of the investigational co-variates was then added singly to this base model to form the second block of the Cox analysis. Those investigational variables demonstrating statistical significance in this model were then added concurrently in the second block, and these co-variates were analysed using a forward stepwise model. These analyses were repeated for cardiovascular death, progressive heart failure death and sudden death.

Because not all variables were available in all patients (particularly plasma markers of neuroendocrine activation), the numbers given as deaths out of total at risk in each table varies slightly and are therefore not additive.

3.9.2.1 Multivariate Analysis: Cardiovascular death

After adjustment for baseline variables (age, NYHA status, presence/absence of IVCD, left ventricular ejection fraction and peak oxygen consumption), only a positive SAECG, markers of autonomic dysfunction and plasma markers of neuroendocrine activation retained prognostic power (see **Table 3-14**). When investigational variables were analysed concurrently, depressed heart rate variability and baroreflex sensitivity failed to predict all cause cardiovascular mortality.

However, plasma markers of neuroendocrine activation significantly predicted cardiovascular death: only 4 of 64 subjects with a plasma BNP <48 pg/ml died, compared with 23 of 60 with a plasma BNP > 48 pg/ml, a 5 fold increase in risk. Elevated plasma noradrenaline also predicted cardiovascular death significantly, supramedian values were associated with a hazards ratio of 2.9. Perhaps surprisingly, a positive SAECG provided similar prognostic power, but the utility of this measure would be more limited, as a smaller proportion of patients had a positive SAECG (31 of 124, 25%).

3.9.2.2 Multivariate Analysis: Progressive heart failure death

Examining investigational co-variates singly after adjustment for baseline variables, plasma noradrenaline and plasma BNP strongly and significantly predicted death from progressive heart failure (see **Table 3-15**). Patients with supramedian levels of plasma noradrenaline or plasma BNP had respective increases of 17 fold and 10 fold in their risk of progressive heart failure death. The only other investigational co-variate retaining prognostic power was total power obtained by frequency domain analysis of heart rate variability, with depressed values conferring a 5 fold increased risk of death. However, no other measure of heart rate variability predicted progressive heart failure death, and this isolated finding must be accepted with caution.

Adjusting for all these investigational variables concurrently in addition to the baseline model, only plasma noradrenaline predicted death from progressive heart failure. Only 1 of 66 patients with a plasma noradrenaline below the median value of 3.9 nmol/l died of progressive heart failure during the study period, while 13 of 66 patients with elevated plasma noradrenaline succumbed (hazards ratio 12.4). This was highly statistically significant.

3.9.2.3 Multivariate Analysis: Sudden death

When subject to the scrutiny of multivariate analysis, a positive SAECG, the presence of non-sustained ventricular tachycardia during Holter monitoring and depressed baroreflex sensitivity predicted sudden death significantly (see **Table 3-16**). Prognostic significance was retained even when the variables were analysed concurrently, rather than singly. A positive SAECG carried a 3.4 fold increased risk of sudden death. The presence of non-sustained ventricular tachycardia was also a potent predictor of sudden death: of 54 patients with non-sustained ventricular tachycardia, 10 succumbed to sudden death. Only 5 of 87 (6%) patients with preserved baroreflex sensitivity died, while 15 of 95 (16%) patients with depressed baroreflex sensitivity succumbed, a 4.1 fold increased risk of sudden death.

3.10 SUMMARY

Measures of abnormal ventricular depolarisation (expressed as a positive SAECG), the presence of non-sustained ventricular tachycardia during Holter monitoring, increased plasma markers of neuroendocrine activation, depressed baroreflex sensitivity and depressed heart rate variability all identified a cohort of patients with chronic heart failure who have a particularly poor prognosis. However, after adjustment for baseline variables of age, NYHA status, the presence of intraventricular conduction defects, left ventricular ejection fraction and exercise tolerance (peak oxygen consumption), plasma markers of neuroendocrine activation remained strongly significant predictors of all cause cardiovascular mortality and death due to progressive heart failure. These co-variates failed to predict sudden death, whereas a positive SAECG, the presence of non-sustained ventricular tachycardia and depressed baroreflex sensitivity were all associated with a high risk of sudden death.

Table 3-14: Multivariate association of investigational variables with cardiovascular mortality.

MORTALITY: CARDIOVASCULAR DEATH					
Adjusted model (age, NYHA, IVCD, LVEF, peak VO_2): Single additional variable					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
SAECG					
Negative	**21/138**	**1**			
Positive	**20/49**	**2.2**	**1.1 – 4.2**	**5.8**	**0.0162**
Noradrenaline (nmol/l)					
<3.92	**8/79**	**1**			
≥3.92	**28/80**	**3.4**	**1.4 – 8.2**	**8.0**	**0.0045**
Plasma BNP (pg/ml)					
<48.2	**6/72**	**1**			
≥48.2	**26/70**	**4.1**	**1.5 – 11.4**	**7.9**	**0.0050**
BRS (msec/mmHg)					
<5.95	**10/87**	**1**			
≥5.95	**30/95**	**2.4**	**1.1 – 5.3**	**4.6**	**0.0318**
NSVT					
Absent	**23/130**	**1**			
Present	**18/57**	**2.9**	**1.5 – 5.5**	**9.9**	**0.0017**
Triangular index (msec)					
>30	**9/88**				
<30	**26/84**	**2.3**	**1.0 – 5.1**	**4.0**	**0.0460**
Adjusted model (age, NYHA, IVCD, LVEF, peak VO2): Stepwise additional variables					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
SAECG					
Negative	**16/93**	**1**			
Positive	**11/31**	**2.6**	**1.1 – 6.0**	**5.4**	**0.0206**
Noradrenaline (nmol/l)					
<3.92	**6/62**	**1**			
≥3.92	**21/62**	**2.9**	**1.0 – 8.3**	**4.0**	**0.0449**
Plasma BNP (pg/ml)					
<48.2	**4/64**	**1**			
≥48.2	**23/60**	**5.0**	**1.3 – 18.6**	**6.1**	**0.0137**

Table 3-15: Multivariate association of investigational variables with progressive heart failure death.

MORTALITY: PROGRESSIVE HEART FAILURE DEATH					
Adjusted model (age, NYHA, IVCD, LVEF, peak VO_2): Single additional variable					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
Noradrenaline (nmol/l)					
< 3.92	**0/79**	**1**			
≥ 3.92	**16/80**	**17.0**	**2.1 – 138.4**	**7.3**	**0.0068**
Plasma BNP (pg/ml)					
< 48.2	**1/72**	**1**			
≥ 48.2	**14/70**	**10.1**	**1.2 – 83.4**	**4.8**	**0.0281**
Total power ($msec^2$)					
≥ 2156	**2/88**	**1**			
< 2156	**16/88**	**4.7**	**1.0 – 22.1**	**4.0**	**0.0446**
Adjusted model (age, NYHA, IVCD, LVEF, peak VO_2): Stepwise additional variables					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
Noradrenaline (nmol/l)					
<3.92	**1/66**	**1**			
≥3.92	**13/66**	**12.4**	**12.0 – 104.3**	**5.6**	**0.0183**

Table 3-16: Multivariate association of investigational variables with sudden death.

MORTALITY: SUDDEN DEATH					
Adjusted model (age, NYHA, IVCD, LVEF, peak VO2): Single additional variable					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
SAECG					
Negative	**9/138**	**1**			
Positive	**12/49**	**2.9**	**1.2 – 7.2**	**5.4**	**0.0205**
BRS (ms/mmHg)					
<5.95	**5/87**	**1**			
≥5.95	**15/95**	**4.3**	**1.2 – 15.8**	**5.3**	**0.0210**
NSVT					
Absent	**11/130**	**1**			
Present	**10/57**	**3.3**	**1.3 – 8.3**	**6.5**	**0.0106**
Adjusted model (age, NYHA, IVCD, LVEF, peak VO2): Stepwise additional variables					
VARIABLE	**DEATHS/TOTAL**	**HAZARDS RATIO (95% CI)**		**WALD**	**P VALUE**
SAECG					
Negative	**9/135**	**1**			
Positive	**11/47**	**3.4**	**1.3 – 9.5**	**6.1**	**0.0136**
BRS (ms/mmHg)					
<5.95	**5/87**	**1**			
≥5.95	**15/95**	**4.1**	**1.1 – 14.9**	**4.6**	**0.0328**
NSVT					
Absent	**10/128**	**1**			
Present	**10/54**	**2.9**	**1.1 – 7.4**	**4.7**	**0.0310**

4 DISCUSSION

4.1 STATEMENT OF PRINCIPAL FINDINGS

In a prospective cohort study of chronic heart failure, I have demonstrated that the presence of intraventricular conduction delay, a positive signal averaged ECG, the presence of non-sustained ventricular tachycardia and abnormal autonomic function can identify patients at high risk of death. These variables carry prognostic information that is additive to and independent of established risk indicators.

1. Abnormal ventricular depolarisation manifest as intraventricular conduction delay on a resting ECG, or the presence of late potentials on the signal averaged ECG both identify a high risk group.

2. Autonomic dysfunction, evaluated by plasma markers of neuroendocrine activation or baroreflex sensitivity and/or heart rate variability, is also associated with a poor prognosis.

3. Abnormalities of ventricular depolarisation, ventricular arrhythmias and abnormal cardiovascular reflexes, delineated by late potentials on the signal averaged ECG, non-sustained ventricular tachycardia during Holter monitoring and low baroreflex sensitivity identify a cohort likely to die a sudden death.

4. No electrocardiographic parameter of ventricular repolarisation predicted death significantly.

I conclude that non-invasive testing aids risk stratification in this common and highly lethal condition.

4.2 STRENGTHS AND LIMITATIONS OF THE STUDY

4.2.1 *General Limitations*

The exclusion of those patients with atrial fibrillation, longstanding diabetes and aged over 75 precludes extrapolation of these results to such patient cohorts. Invasive haemodynamic measurements were not performed. However, recent data suggest that invasive risk models (utilising measurement of pulmonary capillary wedge pressure) do not add discriminant information above comprehensive non-invasive risk assessment [165]. Additionally, such measurements are logistically complex, and difficult to justify in patients with milder chronic heart failure. For pragmatic reasons, tests were performed only once in each patient. Whether repeated analyses at regular time intervals would allow earlier identification of patients at risk is conjectural. As discussed previously (see **1.4.2.2 Symptoms**) new ischaemic events and recurrent admissions with heart failure worsen prognosis. There are no follow-up data on such events. The problems of defining cause of death in chronic heart failure (outlined in section **1.4.1 Classification of Death in Heart Failure**) are recognised and discussed below.

4.2.2 *Patient Cohort*

This was a prospective study of a well-characterised patient cohort. Recruitment, methodology and endpoints were all pre-defined. Categorisation of variables for survival analysis was performed using median values, or pre-specified cut points based on published literature. The study design was simple and deliberately inclusive: subjects maintained normal medication, no invasive haemodynamic measurements were made, and follow-up was maintained through normal hospital after-care, as opposed to specialist clinics.

There are a number of questions that may be asked of any study regarding its more widespread application:

Was the cohort too selected for results to be more widely applicable? Patients with more severe heart failure have symptoms and signs at rest that are easy to identify, have an annual mortality of 40% despite optimal therapy, but constitute a minority of chronic heart failure patients [172]. Although the current study was hospital based, all patients were clinically stable ambulant outpatients with mild to moderate heart failure – an important proportion of the chronic heart failure population. Despite optimal treatment, this group has an annual mortality of 10% [126]. Determining which of these patients is most at risk of early death is difficult, but important. It is a strength of this study that it was not an analysis of a highly selected group referred for cardiac transplantation. In keeping with criticisms of other studies, patients were younger than those seen in epidemiological studies and clinical practice, but comparable to those recruited into recent large trials of vasodilator therapy [289]. Most patients had chronic heart failure caused by ischaemic heart disease, the commonest aetiology in most recent epidemiological studies [116]. Patients with longstanding diabetes mellitus, pre-existant chronic renal failure or atrial fibrillation were excluded. Diabetes mellitus and chronic renal failure are themselves associated with autonomic dysfunction, and are potent predictors of mortality [148]. Thus, the current results cannot be extrapolated to such a patient population. Small studies have suggested that atrial fibrillation confers a worse prognosis [143], but the presence of atrial fibrillation did not influence morbidity or mortality in the V-HeFT studies [144]. Atrial fibrillation precludes baroreflex sensitivity or heart rate variability analysis, and patients with chronic atrial fibrillation were therefore excluded from this study. It is not possible to state whether the prognostic importance of plasma neurohormones would be affected by the presence of atrial fibrillation.

Could drug effects be implicated in survival, or have affected investigational variables? Although drug therapy was associated with differing prognosis at univariate analysis, after adjustment for baseline variables drug treatments were not significantly related to survival. Long term treatment with angiotensin converting enzyme inhibitors [290], digoxin [291] or β-blockers [292] is associated with restoration of autonomic balance, assessed by augmentation of "parasympathetic" measures of heart rate variability, and diminished levels of plasma noradrenaline. Angiotensin converting enzyme inhibitors have also been demonstrated to augment cardiopulmonary and arterial baroreflex control of sympathetic nerve activity in chronic heart failure [293], leading to a persistent reduction in central sympathetic outflow. This may have affected some of the investigational variables. However, in keeping with previously published similar studies, a pragmatic decision was made to continue medication during the study investigations. The principal study aim was risk assessment of patients with optimally treated chronic heart failure, rather than the patho-physiological assessment of autonomic dysfunction in chronic heart failure.

Why should the mortality in the current study be relatively low? All subjects were outpatients, and patients with recent myocardial infarction or acute coronary ischaemic events were excluded. Although the majority of the study cohort had an ischaemic aetiology, none had limiting angina, and only 8 patients experienced limiting angina on cardiopulmonary exercise testing. Patients were studied only if clinically stable for 4 weeks: frequent heart failure admissions were an exclusion criterion. Thus, the cohort studied was a non-transplant population of clinically stable ambulant outpatients with chronic heart failure free from limiting angina. It is in such a group that prognostication using conventional techniques is most difficult, emphasising the need for novel risk indicators.

4.2.3 *Methodology*

NYHA status was assessed by standard questionnaires: a reproducible and valid tool, which is less subject to observer bias than normal clinical assessment. Echocardiographic assessment of left ventricular function may be problematic: standard M mode fractional shortening and cube root left ventricular ejection fraction ignore the complex regional wall motion abnormalities which characterise ischaemic heart failure. The Simpson's biplane disc summation method overcomes these flaws, but necessitates clear endocardial outline. The advent of new technologies such as tissue harmonic imaging can only add to the applicability of this technique. An overall "semi-quantitative" estimation of left ventricular function was available on all patients. This assessment by an experienced echocardiographer collated wall motion abnormalities, left ventricular size, and global left ventricular function. It does not require clear endocardial definition or complex technology, and would be widely applicable in clinical practice. It has been demonstrated to be valid and robust means of estimating left ventricular ejection fraction [155]. This assessment provided similar statistical power to measurement of ejection fraction. Where echocardiographic image quality precluded biplane Simpson's methodology, left ventricular ejection fraction was determined by radionuclide ventriculography. These two methods are not directly comparable, but caveats regarding their combined use are addressed in section **3.9 Survival Analysis.** That the survival analyses were unaffected whether formal measurement of left ventricular ejection fraction or "eyeball" assessment were used in the Cox model makes it unlikely that differences between the techniques would have confounded the results.

Signal averaged electrocardiography was performed in accordance with published guidelines [279]. However, in the presence of intraventricular conduction delay pre-determined abnormal criteria were applied from published literature [180]. There is no

standard accepted methodology for QT dispersion measurement, so QT dispersion was determined using a method previously validated in chronic heart failure [267]. Heart rate variability analysis was performed as per accepted guidelines [282]. New Holter monitors used solely for this study ensured that tape errors were minimised. Time domain measures of heart rate variability were determined using two separate ectopic filtering algorithms and software programs. The results for all time domain measures produced by these two algorithms were strongly correlated ($r>0.9$, $p<0.001$), and survival analyses identified no differences between the methodologies. This demonstrates the robustness of the results. Frequency domain analysis was performed with commercial software. As expected [294], there were strong correlations between time and frequency domain measures, supporting the validity of these results. However, from theoretical considerations underlying the mathematics of spectral analysis, total spectral power should be equal to the time domain variance. Therefore, a plot of total power vs the square of SDNN should be a straight line with a regression slope of 1. In this data set the regression coefficient was 0.72. The potential reasons include analysis of the raw rather than resampled tachogram, problems with interpolation algorithms used to reconstruct sequence defects caused by ectopy, and the inherent non-stationarity of the 24-hour RR interval time series. Whether reanalysis using resampled tachograms and different spectral windowing would change these data has not been addressed, but remains an area for future attention. However, frequency domain analyses added little to time domain measures, supporting the routine use of time rather than frequency domain data.

At the time of planning of this work, little prospective data were available as to the best technique for assessing baroreflex sensitivity. Of the available methodologies there is general agreement that the bolus phenylephrine technique is superior (see

section **1.4.11.1 Techniques of assessing baroreflex function**). It is the technique most widely applied for risk stratification [241,295]. Calculation of linear sequence, spectral and complex demodulation measures did not form part of the main body of this thesis, but at preliminary analysis they fail to add to the prognostic model.

4.2.4 *Follow-up and Endpoint Analysis*

The logistics of the study precluded follow-up in a dedicated clinic. Consequently, I have not included data on time to first hospital admission or frequency of readmission with heart failure. As discussed (see section **1.4.1 Classification of Death in Heart Failure**), the classification of cardiovascular death is fraught with problems and mechanistic assumptions regarding the aetiology of sudden death are flawed. To overcome this problem, a pragmatic definition of sudden death was used i.e. death occurring without evidence of a recent change in symptoms. This definition does not allow differentiation between primary arrhythmic death, or death secondary to arrhythmia in the setting of acute myocardial infarction. From the potential victim's standpoint, this is of academic interest. The data suggesting a high incidence of bradyarrhythmic death in chronic heart failure is based on a highly selected subset of patients [132]. The applicability of these data to the wider population of ambulant patients with milder heart failure has not been demonstrated. The three variables that predicted sudden death viz. a positive SAECG, non-sustained ventricular tachycardia and depressed baroreflex sensitivity may model the substrate, trigger [296] and abnormal cardioprotective reflexes [297] necessary for the development of sustained ventricular tachyarrhythmias . One may postulate that these variables identify a group most likely to die during a primary ventricular tachyarrhythmia or most likely to develop a life-threatening ventricular tachyarrhythmia during myocardial

ischaemia or infarction. This assumption is supported by published data. Recent reports suggest that baroreflexes are important in maintaining systolic arterial pressure during episodes of ventricular tachycardia. Depressed baroreflexes correlate with lower systolic arterial pressures during episodes of induced or simulated ventricular tachycardia [298,299]. A positive signal averaged ECG has been correlated with inducibility of ventricular tachycardia during programmed electrical stimulation [300], and with recurrence of ventricular arrhythmias following myocardial infarction [178]. Animal models have demonstrated the development of ventricular tachyarrhythmias during acute myocardial ischaemia in dogs with depressed baroreflexes but not in dogs with preserved baroreflexes [236]. Depressed baroreflexes predict recurrent ventricular tachyarrhythmias post myocardial infarction [240], and predict "electrical storms" in patients with implantable defibrillators [301]. Variables predicting sudden death also predicted all cause cardiovascular mortality, making it unlikely that these were spurious results.

4.3 RELATION TO OTHER STUDIES

4.3.1 *Established Prognostic variables*

Elderly patients have a worse prognosis, but under the age of 75 years there may be little difference in mortality [135]. Age was a univariate but not multivariate predictor of mortality in the study cohort. However, because the data on the effect of age are mixed, it was decided to include age in the multivariate Cox regression. Gender was not found to predict prognosis in the study cohort, concurring with previous studies using multivariate analysis.

In contrast to the findings of the SOLVD trial and registry [148], diabetes mellitus did not predict death in this study cohort. However, the small numbers of patients with

diabetes preclude further comment. In large studies, whether an ischaemic aetiology confers a poorer prognosis is vexed by the problem of the potential for misclassification of cardiomyopathy aetiology. In the study cohort, cause was synonymous with outcome. However, patients with non-ischaemic cardiomyopathy were significantly younger and less "sick". The statistical relevance of aetiology as a prognostic predictor must be interpreted with caution because of these caveats and because the number of patients with a non-ischaemic aetiology was small.

A number of clinical signs may delineate a worse prognosis. In agreement with previously published data [165], more rapid heart rates defined a poorer outlook – but only with univariate analysis (hazards ratio 2.0 p=0.03). A low, resting systolic arterial pressure dichotomised at 100 mmHg was a univariate (log rank 9.1, $p<0.002$), but not multivariate predictor of mortality, as indicated by previous data [146,165]. However, resting SAP dichotomised at the median value of 115 mmHg did not predict death. It is possible that frequent use of vasodilator therapy and emerging role of β-blockade as a therapeutic option [302] may confound this physical sign.

In agreement with a large body of work reporting the independent prognostic power of peak oxygen consumption [159], peak VO_2 was found to be a strong prognostic indicator – irrespective of which value was used for dichotomisation.

Many factors predispose to ventricular arrhythmia in heart failure (see section **1.2.6 Arrhythmias Present in Heart Failure**): underlying structural disease, electrolyte abnormalities, neurohormonal changes and, possibly, therapeutic interventions [151]. The frequency of ambulant ectopy is related to the severity of underlying cardiac function [168], although this is less clear in non-ischaemic cardiomyopathy [169]. Most studies have found that frequent ventricular ectopy and nonsustained ventricular

tachycardia indicate a worse prognosis [172]. In the GESICA study of amiodarone in chronic heart failure, 300 of 516 patients with chronic heart failure had 24-hour Holter tapes available for study [303]. At multivariate analysis nonsustained ventricular tachycardia and couplets retained independent significance (RR 1.75 and 1.81 respectively). For sudden death, relative risks were higher (nonsustained ventricular tachycardia 2.43, couplets 3.37) [171]. Frequent ventricular ectopy and/or couplets did not predict death in the current study cohort. However, nonsustained ventricular tachycardia (defined by the criteria used in the Gesica trial i.e. >3 ventricular premature beats at > 100bpm occurring at least once on the 24 hour tape) was a univariate and multivariate risk predictor. Nonsustained ventricular tachycardia was seen in 52 patients. The hazards ratio for all cause mortality was 2.5 (1.9-3.1) and 2.8 (2.0 -3.6) for sudden death. Combining couplets and/or nonsustained ventricular tachycardia did not add prognostic power. However, in keeping with results from the Gesica study, nonsustained ventricular tachycardia was seen in only 26.1% of the study group, limiting its usefulness as a prognostic indicator.

4.3.2 *Investigational Variables*

4.3.2.1 Assessment of autonomic dysfunction

Autonomic nervous system dysfunction may be assessed by a number of different methods (see section **1.2.9.4 Assessment of autonomic dysfunction**). A number of different authors have investigated the prognostic utility of various markers of autonomic dysfunction in heart failure, but no study yet published has simultaneously compared the prognostic utility of plasma markers of neuroendocrine activation, heart rate variability, baroreflex abnormalities and the signal averaged ECG in patients with heart failure.

4.3.2.2 Signal-averaged Electrocardiography

As discussed previously (see section **1.4.8 Signal-averaged Electrocardiography**) late potentials are predictive of arrhythmic events and sudden death in a post myocardial infarction population but are poorly correlated with the severity of left ventricular dysfunction [177]. However, the positive predictive value of late potentials is low in this patient population [179].

The prognostic utility of late potentials in patients with non-ischaemic dilated cardiomyopathy or ischaemic heart failure remote from myocardial infarction is less clear. The frequency and prognostic importance of bundle branch block and intraventricular conduction delay in the chronic heart failure population makes analysis even more difficult [180]. Only one other published study other than the current analysis has prospectively utilised specific criteria for the diagnosis of an abnormal signal averaged electrocardiogram in the presence of bundle branch block [185]. The investigators followed 151 patients with chronic heart failure for a mean of 27 months. Late potentials were present in 49 patients. The incidence of late potentials was not different in patients with or without bundle branch block. A past history of ventricular arrhythmias was significantly more common in patients with a positive signal averaged ECG (8.2% vs 1.9%). A positive signal averaged ECG did not predict total, cardiac or sudden mortality. However, during follow up the incidence of spontaneous sustained ventricular tachycardia was significantly higher in the presence of late potentials. Why should this study of a similar patient cohort reveal different results? Age, mean NYHA and left ventricular ejection fraction were similar to the present study. However, in the study by Galinier et.al atrial fibrillation was present in 13% of patients, 45% were receiving chronic amiodarone therapy, and there were only 13 sudden deaths. In the current cohort, only 4 patients were in sustained atrial

fibrillation, only 10% of patients were taking amiodarone, and there were a greater number of sudden deaths. These reasons may account for the disparate results between these 2 studies.

4.3.2.3 QT Dispersion

The surface electrocardiographic QT interval reflects complex and interrelated aspects of cellular electrophysiology, cardiac geometry, torso shape, thoracic impedance and signal processing [252]. There are two assumptions on which QT dispersion is based: that the end of the surface electrocardiographic QT interval is a surrogate for the end of ventricular repolarisation, and that spatial variation in surface electrocardiographic QT intervals measures the known underlying heterogeneity of ventricular repolarisation. As discussed previously (see section **1.4.12.2 QT dispersion: clinical and methodological aspects**) both assumptions are supported by debatable evidence. Monophasic action potentials measured during cardiac surgery correlated strongly with surface QT dispersion for both sinus and paced beats [255]. However, in an isolated heart study, total T wave area and T peak to T end interval correlated more significantly with monophasic action potential duration than did QT interval [254]. There are many methodological problems. There is still no accepted standard methodology for QT dispersion measurement. The problem of the definition of the end of the T wave seems more important than the method used [252]. Inter-observer reproducibility is poor, with low voltage and morphologically abnormal T waves contributing significantly to inter-observer variability [259]. Fundamental electrocardiographic theories should also be taken into account: information contained in limb leads is redundant in that if any of 2 of the 6 of recorded, the other 4 may be calculated. Additionally complete information regarding electrical activity is

contained only in the vectorcardiogram. If the last 40 milliseconds of ventricular repolarisation is negative in lead I, and equally positive in lead II, then there would be no electrical activity in lead III creating a spurious QT dispersion of 40 milliseconds [260]. Therefore, QT dispersion measured in the frontal plane derived from only 2 leads is unlikely to provide information on local electrical repolarisation.

Continuing the uncertainty regarding underlying pathophysiology and methodology, the prognostic utility of QTd in heart failure remains unclear, with studies supporting [267-269] or refuting its importance [270,271] (see section **1.4.12.3 QT dispersion in chronic heart failure**). Previous investigators have retrospectively studied small numbers of widely differing populations, using different methodologies, excluding or including (or not mentioning) patients with atrial fibrillation and bundle branch block.

There is thus a plethora of literature on the prognostic utility of QT dispersion, much of the data being retrospective, case-controlled studies of limited statistical power. Recent work using the best available methodology (previously validated against monophasic action potential duration [254]) failed to demonstrate prognostic significance of any measured QT variable post myocardial infarction [266]. Data from the UK-HEART study also confirms that QT dispersion offers no prognostic information in chronic heart failure in a prospective well designed study [304]. These data corroborate the present findings that QT dispersion is not associated with mortality in chronic heart failure.

4.3.2.4 Plasma markers of neuroendocrine activation

Elevated plasma noradrenaline carries prognostic information in symptomatic [187] and asymptomatic [188] chronic heart failure. These data are confirmed in the current study cohort. There is less data on the prognostic importance of natriuretic peptides in

chronic heart failure. Natriuretic peptides correlate with the severity of heart failure and are elevated early in left ventricular systolic dysfunction, before the development of symptomatic heart failure [82]. However, plasma BNP tracks less closely with left ventricular ejection fraction than ANP [191]. Elevated plasma ANP levels have been associated with increased mortality in moderate [194] and severe [195] heart failure. Plasma ANP was a significant univariate, but not multivariate predictor of mortality in the study cohort. Plasma BNP provides additional independent prognostic information beyond left ventricular ejection fraction in the acute post myocardial infarction setting [196], and it has been suggested to provide similar information in chronic heart failure [197]. A recent substudy from the Australia-New Zealand heart failure group investigated the role of plasma neurohormones, including plasma BNP [305]. Supramedian levels of plasma BNP were associated with a mortality rate 3 fold greater than that of inframedian levels. There are few other prospective data on the prognostic utility of plasma BNP in chronic heart failure. The available data on plasma BNP and prognosis in chronic heart failure supports the current finding of its prognostic importance. However, no other study has investigated the role of heart rate variability, baroreflex sensitivity and plasma markers of neuroendocrine activation in patients with chronic heart failure. Despite being subject to this multivariate scrutiny, plasma BNP remained highly predictive of total cardiovascular and progressive heart failure mortality.

4.3.2.5 Heart rate variability

A body of work has established that depressed heart rate variability is a powerful multivariate prognostic indicator in patients after acute myocardial infarction. Heart rate variability (measured as SDNN) less than 50 milliseconds carried a 5.3 fold

increased mortality compared with a group with SDNN >100 milliseconds [215]. Longer term frequency domain measures derived from 24 hour data or from recordings 2 to 15 minutes long have similar prognostic utility but do not add to the simple time domain measures [306]. Although thrombolysis shifts "cut points" upward, the independent relative risk of depressed heart rate variability is maintained [216].

It has been known for decades that heart rate variability is diminished in chronic heart failure [94]. Small studies have addressed the prognostic utility of heart rate variability in dilated cardiomyopathy [221,222] or chronic heart failure [223,225,226] due to both ischaemic and non-ischaemic aetiologies. Despite different analysis techniques and patient characteristics, most reports have documented that heart rate variability independently identifies patients at greatest risk of cardiovascular death. When both time and frequency domain analyses have been performed, spectral measures appear to add little prognostic information to that provided by simple time domain measurements. The total number of deaths in these studies is small, and some investigators found that none of the conventional time and frequency domain measures were related to survival [224].

A recent large study (UK–Heart [150]) has demonstrated that patients with low values of SDNN constitute a particularly high-risk group. Values of SDNN<100 msec carried a hazard ratio of 1.8 for cardiovascular death after adjusting for baseline variables. There are caveats to this study: the characterisation of patients was limited, left ventricular ejection fraction was calculated from M-mode measurements and no other autonomic variables were determined. M-mode echo techniques can artefactually overestimate ejection fraction in patients with previous anterior myocardial infarction, who would otherwise be expected to have the lowest value of SDNN and a poor prognosis. This could have overestimated the prognostic power of

depressed SDNN. However, my data confirm that reduced heart rate variability is an independent predictor of all cause cardiac and progressive heart failure death, but fails to predict sudden death.

4.3.2.6 Baroreflex sensitivity

There is an acute depression of baroreflex sensitivity following myocardial infarction, but values return towards normal within one to three months [208]. The largest prospective post myocardial infarct study (ATRAMI), compared the prognostic power of baroreflex sensitivity with heart rate variability [241]. Low values of either heart rate variability (SDNN <70 msec) or baroreflex sensitivity (<3 msec/mm Hg) carried a significant multivariate risk of cardiovascular mortality (3.2 and 2.8 respectively). The one year mortality was 15% when both variables were low compared to 1% if both were preserved. Baroreflex sensitivity but not heart rate variability maintained its multivariate prognostic power even when left ventricular ejection fraction was <35%: the relative risk of dying in young patients (<65 years) with low LVEF (<35%) and low baroreflex sensitivity (<3.0 msec/mm Hg) was 11.5. These figures are even more impressive when one considers that the study population was relatively low risk.

There are fewer data linking baroreflex sensitivity with prognosis in patients with chronic heart failure remote from myocardial infarction. The largest study investigated the prognostic role of baroreflex sensitivity in 282 patients with chronic stable heart failure [295] but did not include plasma markers of neuroendocrine activation. Baroreflex sensitivity was found to be significantly associated with symptoms of heart failure, but only weakly related to left ventricular ejection fraction, cardiac index, and pulmonary capillary wedge pressure. At multivariate analysis, baroreflex sensitivity was an independent predictor of death, and was more

informative in patients with ischaemic rather than idiopathic cardiomyopathy. When haemodynamic indices were added to the multivariate model, baroreflex sensitivity did not provide independent prognostic information. However, haemodynamic indices require instrumentation and are time-consuming to measure. Additionally, the patients studied by Mortara et al were a pre-transplant population with severe heart failure. Thus, these data relate to a more selected cohort, and are less widely applicable.

4.4 IMPLICATIONS OF THE STUDY

The socio-economic impact of chronic heart failure is enormous: it has been estimated at 1-2% of the total health care budget, of which two thirds is accounted for by inpatient care [121]. The more severe the heart failure, the greater the cost. Thus, chronic heart failure is a common, growing and major public health care burden.

Identifying high-risk patients suitable for aggressive intervention, optimisation of treatment and prevention of death is of great importance. Despite extensive study by many investigators, identification of individuals who are most likely to deteriorate and die remains difficult. Identification of those most likely to die unexpectedly is even more problematic. Answers to these questions were the principal aim of this thesis.

I have demonstrated that autonomic dysfunction, neuroendocrine activation and/or abnormal ventricular depolarisation identify patients with chronic heart failure at high risk of death. Plasma BNP may be measured from a single venous blood sample, and has been proven to be stable at room temperature over 72 hours. It is inexpensive, and requires no specialised equipment at the bedside. Direct assay kits are now available which both simplify and lessen the cost of its measurement. This finding is particularly important, because of the possibility for its widespread application. Obviously, identification of those at greatest risk is only the initial step towards

preventing death in this condition. However, optimising therapy in those with severe heart failure has been shown to improve symptoms and outcome. The present study suggests that plasma BNP may be a simple, inexpensive, and widely applicable means of selecting such patients. Linking the prognostic importance of depressed baroreflex sensitivity in the study cohort with recent data on "electrical storms" in patients with implantable cardioverter-defibrillators [301], it is attractive to speculate that these markers might be used to identify patients who would derive greatest benefit from such devices.

4.5 FUTURE RESEARCH

The opportunities for future research relate to larger scale studies of the prognostic value of BNP. These in due course may lead to the use of BNP as a means of targeting or monitoring therapy in high-risk patients with heart failure.

Invasive electrophysiological testing has proved disappointing for risk stratification in chronic heart failure. Although certain patients who have inducible ventricular arrhythmias benefit from implantable cardioverter-defibrillator therapy [307], these data have been criticised and the technical demands of the technique limit its widespread application. Perhaps as a result, the role of non-invasive assessment of arrhythmia risk has expanded. The utility of non-sustained ventricular tachycardia, baroreflex sensitivity and the signal averaged ECG in prediction of sudden death could be clarified by examination of subjects who already have implantable cardioverter-defibrillators. Validated prognostic models based on nonsustained ventricular tachycardia, the signal averaged ECG and markers of autonomic dysfunction could then be applied to identify high risk patients without manifest ventricular arrhythmias who would benefit from these devices. At least one such trial (SCD–Heft, a randomised comparison of implantable

cardioverter-defibrillator use in patients with chronic heart failure at high risk of sudden death) is already recruiting. SCD–Heft is using depressed heart rate variability as a risk marker for appropriate patient selection. The results from this thesis are now being incorporated into the protocol of a similar study.

4.6 SUMMARY

In this well-characterised cohort of patients with chronic heart failure, the presence of intraventricular conduction delay, a positive signal averaged ECG or autonomic dysfunction carried a poorer prognosis. The most powerful variable predicting cardiovascular mortality was neuroendocrine activation assessed by plasma BNP. The presence of nonsustained ventricular tachycardia on Holter monitoring, an abnormal signal averaged ECG or depressed baroreflex sensitivity identified patients at risk of sudden death – a unique finding which requires further investigation and clarification. This information was additive to and independent of other powerful prognostic variables including NYHA class, age, left ventricular ejection fraction and presence/absence of intraventricular conduction delay on the surface ECG.

Appendix A

Consent Form

Patient Summary: Predicting Problems in Heart Failure

We would like to ask you to participate in this study.

Heart failure is a common condition caused by damage to the pump of the heart, leading to symptoms of breathlessness, fatigue and limitation of exercise capacity. We are interested in predicting which patients will benefit from which particular treatments.

To do this, we shall first ask you to come to **Glasgow Royal Infirmary** where you will have a special heart tracing, or ECG, which takes about 15 minutes. This is entirely painless. Following this, we will measure your heart rate response to an increase in blood pressure that requires a small injection into a vein in the arm. The drug injected is called "Phenylephrine", a standard medical preparation. The injection is painless, but some people may experience a mild feeling of flushing, headache or palpitation which passes quickly. The whole procedure would be performed by an experienced doctor, and would take about one hour. Lastly, you will be asked to wear a 24-hour heart rhythm recorder, very much like a personal stereo cassette.

The following afternoon you would be asked to attend the **Clinical Research Initiative** (the **CRI**) based at the **Western Infirmary** in Glasgow. Here you would have an ultrasound scan of your heart. This is a completely painless procedure that builds up moving pictures of your heart from sound waves (the same type of scan that is used to show the baby in a pregnant woman's abdomen). The next examination we would ask you to undertake is a treadmill walking test. A treadmill is like a moving walkway, which slowly increases in speed in stages. You would be asked to exercise until you felt you needed to stop. We would not ask you to go on exercising longer than you felt able, and although different people are able to exercise for different durations the average time is about 5 minutes. This test would allow us to measure your fitness. Finally, we hope that you would allow us to take a sample of blood from a vein in your arm to measure a substance made by the heart. Giving the blood is in no

way dangerous. An experienced doctor will oversee the whole series of tests, but your treatment will continue to be supervised by your own hospital doctors and GP.

In order to decide whether the tests are useful in predicting your progress, we request your permission to review your hospital and GP case records which are relevant to the project. This access will be restricted to the doctors who are involved in the study.

It should be noted that your participation in this study may not be of direct benefit to you, but could help in the development of treatments for the benefit of future patients.

If you do not wish to participate in this study, or wish to withdraw at any time after commencing the study, your care will in no way be affected.

If you wish to take part in this study, your General Practitioner will be advised of your participation and the clinical management that you will undergo.

If you are, or are likely to become, pregnant, you should not participate in the study.

CONSENT

I, _____ **of** _____

give my consent to the research procedures described above, the nature, purpose and possible consequences of which have been explained to me by

_____

Sign _____ **Date** _____

Witness _____

Appendix B

Minnesota Living With Heart Failure Questionnaire

We would be grateful if you would complete and return the following questionnaire. These questions concern how your heart problem has prevented you from living as you wanted in the last month. If the item does not apply to you or is not due to your heart problem, **circle 0 (No)**, and go to the next item. If an item does apply to you, **then circle the number rating how much it prevented you living as you wanted.**

Did your heart problem prevent you from living as you wanted during the last month	***No***					***Very much***
		Very little				
1. Causing swelling in your ankles, legs, etc	0	1	2	3	4	5
2. Making you sit or lie down to rest during the day	0	1	2	3	4	5
3. Making your walking about or climbing stairs difficult	0	1	2	3	4	5
4. Making your working around the house or garden difficult	0	1	2	3	4	5
5. Making your going away from home difficult	0	1	2	3	4	5
6. Making your sleeping well at night difficult	0	1	2	3	4	5
7. Making your relating to or doing things with friends or family difficult	0	1	2	3	4	5
8. Making your working to earn a living difficult	0	1	2	3	4	5
9. Making your recreation, hobbies, sports etc difficult	0	1	2	3	4	5

Did your heart problem prevent you from living as you wanted during the last month	***No***					***Very much***
		Very little				

10. Making your sexual activities difficult	0	1	2	3	4	5
11. Making you eat less of the foods that you like	0	1	2	3	4	5
12. Making you short of breath	0	1	2	3	4	5
13. Making you tired, fatigued or low on energy	0	1	2	3	4	5
14. Making you stay in hospital	0	1	2	3	4	5
15. Costing you money for medicines	0	1	2	3	4	5
16. Giving you side effects from medicines	0	1	2	3	4	5
17. Making you feel a burden to family or friends	0	1	2	3	4	5
18. Making you feel a loss of self-control in your life	0	1	2	3	4	5
19. Making you worry	0	1	2	3	4	5
20.Making it difficult for you to concentrate or remember things	0	1	2	3	4	5
21. Making you feel depressed	0	1	2	3	4	5

PATIENT DETAILS

SURNAME: _____ **DOB:** __/__/__

STUDY NO: __ - _ - _ _ _ _ _ _

Appendix C

HEALTH QUESTIONNAIRE

We would be grateful if you could complete this questionnaire and bring it with you when you attend the examination. if you have any questions, please ask when you come to the examination. We are there to help you, and will check through the record with you.

Listed below are some problems people might have in their daily lives. Read the list carefully

Circle YES for any problem that applies to you at the moment

Circle NO for any problem that does not apply to you.

PLEASE ANSWER EVERY QUESTION.

Remember, if you are not sure whether to answer YES or NO to a problem, circle whichever answer you think is more true at the moment.

1.	I'm tired all the time.	Yes	No
2.	I have pain at night.	Yes	No
3.	Things are getting me down.	Yes	No
4.	I have unbearable pain.	Yes	No
5.	I take tablets to help me sleep	Yes	No
6.	I've forgotten what it's like to enjoy myself.	Yes	No
7.	I'm feeling on edge.	Yes	No
8.	I find it painful to change position.	Yes	No
9.	I feel lonely.	Yes	No
10.	I can only walk about indoors.	Yes	No
11.	I find it hard to bend.	Yes	No

Remember, if you are not sure whether to answer YES or NO to a problem, circle whichever answer you think is more true at the moment.

12.	Everything is an effort.	Yes	No
13.	I'm waking up in the early hours of the morning.	Yes	No
14.	I'm unable to walk at all.	Yes	No
15.	I'm finding it hard to make contact with people.	Yes	No
16.	The days seem to drag.	Yes	No
17.	I have trouble getting up and down stairs or steps.	Yes	No
18.	I find it hard to reach for things.	Yes	No
19.	I'm in pain when I walk.	Yes	No
20.	I lose my temper easily these days.	Yes	No
21.	I feel there is nobody I am close to.	Yes	No
22.	I lie awake for most of the night.	Yes	No
23.	I feel as if I'm losing control.	Yes	No
24.	I'm in pain when I'm standing.	Yes	No
25.	I find it hard to dress myself.	Yes	No
26.	I soon run out of energy.	Yes	No
27.	I find it hard to stand for long (e.g. at the kitchen sink, waiting for a bus).	Yes	No

Remember, if you are not sure whether to answer YES or NO to a problem, circle whichever answer you think is more true at the moment.

28.	I'm in constant pain.	Yes	No
29.	It takes me a long time to get to sleep.	Yes	No
30.	I feel I am a burden to people.	Yes	No
31.	Worry is keeping me awake at night.	Yes	No
32.	I feel that life is not worth living.	Yes	No
33.	I sleep badly at night.	Yes	No
34.	I'm finding it hard to get on with people	Yes	No
35.	I need help to walk about outside (e.g. a walking aid or some one to support me)	Yes	No
36.	I'm in pain when going up and down stairs or steps.	Yes	No
37.	I wake up feeling depressed.	Yes	No
38.	I'm in pain when I'm sitting.	Yes	No

Now please go back to page 1 and make sure that you have answered YES or NO to every question, on all three pages of the questionnaire.

THANK YOU FOR YOUR HELP

Please bring this questionnaire with you to your next appointment.

Appendix D

PERSONAL HEALTH RECORD

(All information is confidential)

Please answer the questions in this record as far as you are able and bring it with you when you attend the examination. Please answer every question, as far as you can, (except those you are told to skip) and circle the answer which applies to you. We cannot use those questions that you leave completely blank. If the answer in your case is 'No' or 'I don't know' you still need to show this on the paper. If you need any help, or have any questions, please ask when you come to the examination. We will check through the record with you.

Personal history

1. (a) Please circle the appropriate box Male Female

   (b) Date of birth: day month year

   (c) How many years have you lived in this town or within 10 miles of this town? _____ years

   (d) Where were you born?

   Town/place

   County

   Country

2. Please circle the number showing your present marital status

1	married	2	widowed
3	cohabiting	4	divorced
5	single	6	separated

3. (a) What is the highest level of education you have completed?

1 university degree

2 other professional or technical qualification/diploma after leaving school

3 secondary school

4 primary school

(b) How many years altogether have you gone to school or studied full-time from the age of 5 years? _____ years

4. (a) Please circle the appropriate number about your employment situation.

1 in a full-time job

2 in a part-time job

3 unemployed, seeking work

if **unemployed and seeking work,** for how long have you been unemployed?

Years _____ Months _____

4 unemployed because sick or disabled

5 housewife/homemaker

6 wholly retired from employment

7 full-time student

4. (b) Please give full and precise details of your occupation (if unemployed now, give details of last job).

Your occupation

Description of your work

Husband/wife's occupation

Description of his/her work

4. (c) What is your employment status? (if unemployed now, give details of last job.)

1 employee not supervising other employees

2 employee supervising other employees

3 self-employed not employing others

4 self-employed employing others

5. (a) How do you and your household occupy your accommodation?

1 as an owner-occupier (including purchase by mortgage)

2 by renting, or rent-free, or by lease from a local authority (council or New Town) or from a housing association

3 by renting or rent-free, from a private landlord or in some other way

5. (b) If you are **owner-occupier,** is your house one which **you** previously rented from a local authority Yes No

Family history

6. Did your mother or father have heart disease before they were 60 years old?

   Yes No Don't know

7. How many brothers and sisters did you have in your family (not counting yourself)? _____ brothers and sisters

8. Did any of your brothers and sisters have heart disease before they were 60 years old?

   Yes No

9. How many children have you had (including any who died at birth or in childhood)?

   _____ children

Medical history

10. Have you ever been told by a doctor that you have, or have had any of the following? Circle **Yes** or **No** for each condition.

Angina	Yes	No
Heart attack (coronary thrombosis, myocardial infarction)	Yes	No
High blood pressure	Yes	No
Stroke	Yes	No
Diabetes	Yes	No
High cholesterol	Yes	No

11. Are you now taking any medication for high blood pressure?

Yes No

If yes, please write the names of the medicines you are taking:

_____

_____

_____

12. Are you now taking any medication for high cholesterol?

Yes No

If yes, please write the name of the medicine you are taking:

_____

13. Are you now taking aspirin regularly?

Yes No

If **no,** go to question 14.

If **yes,** is it for your heart? Yes No

Don't know

If it is for your heart, why did you start taking it?

the doctor told you to take it

you decided for yourself other reason

please give details

14. (a) Are you regularly taking any other medication at present?

Yes No

If **yes,** write the name of the medicine(s) and what you are taking them for (if you know). Please include all pills, bottles, tablets, inhalers (puffers), injections, etc.

_____

_____

_____

_____

14. (b) Are you regularly taking any vitamins, minerals or food supplements at present?

Yes No

If **yes,** give the type of supplement, brand name and how often you take each one.

Type Brand (and strength) Frequency

_____

_____

_____

_____

Men miss out the next page and go to question 18

WOMEN ONLY

14. (a) Are you pregnant now?

Yes No

If no, have you ever been pregnant?

Yes No

(b) How old were you when you had your first pregnancy? ____ years old

16. (a) Have you ever been on the contraceptive pill?

Yes If **yes,** for how many years? _____years.

No **If no, go to question 17.**

(b) Are you on the contraceptive pill now?

Yes No

If **no,** how long ago did you stop? _____ years _____ months ago

17. (a) Are you still having periods (menstruating)?

Yes, as usual

Yes, but irregularly

No If **no,** how old were you when you stopped.? _____ years old

Was this because of a hysterectomy (surgical removal of the womb)?

Yes No

(b) Have you ever taken hormone replacement therapy (HRT)?

Yes No

If **yes,** for how many years? years

If **no,** go to question 18.

(c) Are you on hormone replacement therapy (HRT) now?

Yes No If **no,** how long ago did you stop taking it?

_____ years _____months

Chest Pain

18. (a) Have you ever had any pain or discomfort in your chest?

Yes No If **no**, go to question 20

(b) Do you get this pain or discomfort when you walk uphill or hurry?

Yes No

(c) Do you get it when you walk at an ordinary pace on the level?

Yes No

(d) When you get any pain or discomfort in your chest, what do you do?

Stop

Slow down

Continue at the same pace

(e) Does it go away when you stand still?

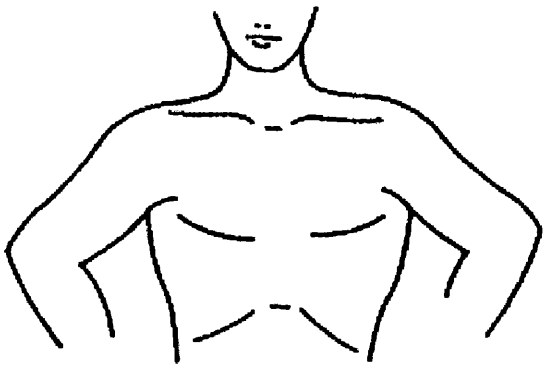
Yes No If **no**, go to question 18(g)

(f) How soon?

10 minutes or less

more than 10 minutes

(g) Where do you get this pain or discomfort? Mark the place(s) with **X** on the diagram.



19. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

Yes No

Leg problems

20. (a) Do you get a pain or discomfort in your leg(s) when you walk?

Yes No If **no,** go to question 22

I am unable to walk If **unable to walk,** go to question 22.

21. (a) Does this pain ever begin when you are standing still or sitting?

Yes No

(b) Do you get it if you walk uphill or hurry?

Yes No

(c) Do you get it when you walk at an ordinary pace on the level?

Yes No

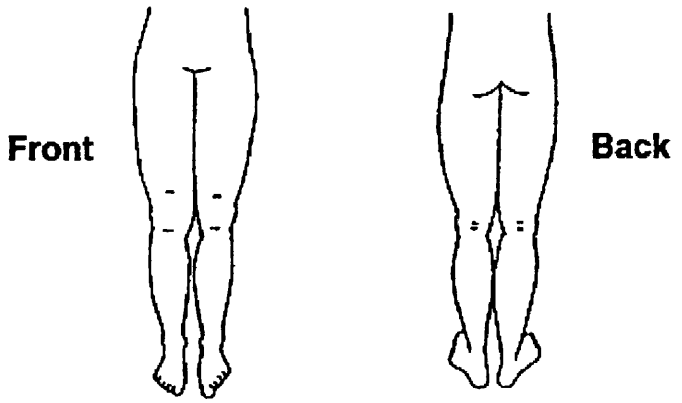
(d) What happens to it if you stand still?

Usually continues more than 1 0 minutes

Usually disappears in 10 minutes or less

(e) Where do you get this pain or discomfort?

Mark the place(s) with X on the diagram below.



Cough

22. (a) Do you usually cough first thing in the morning in the winter?

Yes No

(b) Do you usually cough during the day, or at night, in the winter?

Yes No

(c) Do you cough like this on most days for as much as three months each year?

Yes No does not apply

Phlegm

23. (a) Do you usually bring up any phlegm from your chest first thing in the morning in the winter?

Yes No

(b) Do you usually bring up any phlegm from your chest during the day, or at night, in the winter?

Yes No

(c) Do you bring up phlegm like this on most days for as much as three months each year?

Yes No does not apply

Breathlessness

24. (a) Do you get short of breath when hurrying on level ground or walking up a slight hill?

Yes No

b) Do you get short of breath walking with other people of your own age on level ground?

Yes No

(c) Do you have to stop for breath when walking at your own pace on level ground?

Yes No

(d) Do you get short of breath when washing or dressing?

Yes No

(e) Are you ever wakened from sleep by breathlessness?

Yes No

Cigarette smoking

25. (a) Do you smoke cigarettes now?

Yes, regularly

No If **no,** go to question 26.

Occasionally (usually less than one a day)

(b) On average, about how many cigarettes do you smoke a day?

_____ cigarettes a day

(c) On average, on how many days a week do you smoke cigarettes?

_____ days a week

(d) How old were you when you began to smoke cigarettes?

_____ years old

26. Did you ever smoke cigarettes?

Yes, regularly

No, never

Occasionally (usually less than one a day)

Cigar smoking

27. (a) Have you ever smoked cigars?

No If **no,** go to question 28.

Used to, but not now If **used to,** go to question 28.

Yes, now smoke occasionally (usually less than one a day)

Yes, now smoke regularly

(b) About how many cigars do you smoke a week? _____ cigars a week

Pipe smoking

28. (a) Have you ever smoked a pipe?

No — If **no,** go to question 29.

Used to, but not now — If **used to,** go to question 29.

Yes, now smoke a pipe occasionally (usually less than one a day)

Yes, now smoke a pipe regularly

(b) About how many ounces of tobacco do you smoke a week?

_____ ozs a week

Physical activity

29. Which of the following four activity classes best describes your present activity outside of your job? Please consider going to and from work, sporting activity and other physical effort during your leisure time, like gardening or dancing. (please circle one box only.)

1 No physical activity weekly

2 Only light physical activity in most weeks

3 Vigorous physical activity at least 20 minutes once or twice a week (Vigorous activity causes breathlessness, a rapid heart rate and sweating)

4 Vigorous physical activity for at least 20 minutes three or more times a week.

Thankyou for completing this questionnaire.

Please bring it with you to your next appointment.

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