

**Exploring the force-frequency relationship in people with
chronic heart failure**

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Chapters 6 and 7 contain work based on the following publication:

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*Dr Gierula and J. E. Lowry contributed equally.

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Dedication

To my Dad, Robert Redman. You have been there on my shoulder, all the way through. I just hope you can make it to my viva. x

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These are strange times. Throughout the last 12 months the world has been turned upside down by a global pandemic. Throughout the uncertainty, anxiety, and multiple lockdowns that this has resulted in, I have written up my thesis with the unfaltering support of many valued colleagues, friends, and my family. I acknowledge these people here.

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Abstract

A key feature of heart failure with reduced ejection fraction (HFrEF) is exercise intolerance. Correcting chronotropic incompetence using conventional age-guided rate-response pacemaker programming is not associated with improvements in exercise capacity in HFrEF. The force-frequency relationship (FFR), (increased left ventricular (LV) contractility as heart rate rises), is abnormal in HFrEF, and could explain this.

This thesis comprises a series of studies with the objectives of: describing the reproducibility of a non-invasive, echocardiographic measure of the FFR, exploring whether personalised programming of the rate-response algorithm using FFR data acutely affects treadmill walk time, and determining whether personalised programming of the rate-response algorithm using FFR data is associated with longer term benefits.

An observational study demonstrated that a reproducible, non-invasive assessment of the FFR, using echocardiography, is possible in patients with HFrEF and a pacemaker. I was able to show that critical heart rate, peak contractility, and the slope of the FFR were lower in patients with HFrEF compared to non-HFrEF controls.

In an interventional, double-blind, randomised, cross-over trial, I compared the effects of tailored pacemaker rate-response programming based on the FFR data with

conventional age-guided rate-response programming, on treadmill exercise time and oxygen consumption. This resulted in a greater improvement in exercise time and higher peak oxygen consumption with tailored rate-response programming.

A further interventional double-blind, randomised controlled, parallel-group study demonstrated that six months of rate-response programming based on the FFR data, was associated with improved exercise time, and that conventional age-guided rate-response programming might contribute to deteriorating left ventricular function.

Based on these novel findings, I can conclude that the FFR is abnormal in HFrEF. Optimising pacemaker settings based on the individual's FFR data is associated with improved exercise time and decreased decline in LV function in HFrEF.

'The interval between a contraction of the heart and the preceding beat is of such importance for the strength of contractility that the study of this effect is a prime necessity'

(Bowditch, 1871)

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Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
A-mode	Amplitude mode
ANOVA	Analysis of variance
ANP	A-type natriuretic peptide
ARB	Angiotensin II type I receptor blocker
ARNi	Angiotensin receptor neprilysin inhibitor
AV	Atrio-ventricular
β -blocker	Beta-adrenoceptor antagonist
BCE	Before the Common Era
B-mode	Brightness mode
BNP	B-type natriuretic peptide
bpm	Beats per minute
BSA	Body surface area
BSE	British Society of Echocardiography
Ca ²⁺	Calcium ion

CAD	Coronary artery disease
CE	Common Era
CHF	Chronic heart failure
CHR	Critical heart rate
CI	Confidence interval
CIED	Cardiac implantable electronic device
CMR	Cardiac magnetic resonance
CO ₂	Carbon dioxide
CONSORT	Consolidated standards of reporting trials
CPET	Cardiopulmonary exercise test
CRT	Cardiac resynchronisation therapy
CT	Computed tomography
CVCRF	Cardiovascular Clinical Research Facility
DICOM	Digital imaging and communications in medicine
ECG	Electrocardiogram
EF	Ejection fraction
EQ-5D	EuroQOL 5D-3L
ESC	European Society of Cardiology
ESP	End-systolic pressure
ESPVR	End-systolic pressure volume ratio

FFR	Force-frequency relationship
GP	General practitioner
HF	Heart failure
HFmEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICD	Implantable cardioverter-defibrillator
IHD	Ischaemic heart disease
IQR	Interquartile range
kg	Kilogram
kHz	Kilohertz
LA	Left atrium
LBbB	Left bundle branch block
LTHT	Leeds Teaching Hospitals NHS Trust
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESP	Left ventricular end-systolic pressure

LVESV	Left ventricular end-systolic volume
LVESVi	Left ventricular end-systolic volume index
LVSD	Left ventricular systolic dysfunction
m	Metre
mg	milligram
MHz	Megahertz
MI	Myocardial infarction
min	Minute
ml	Millilitre
ml/kg/min	Millilitres per kilogram per minute
MLWHF	Minnesota living with heart failure
M-mode	Motion mode
mmHg	Millimetres of mercury
mmol	Millimole
MRA	Mineralocorticoid/aldosterone receptor antagonist
MRI	Magnetic resonance imaging
m/s	Metres per second
msec	Millisecond
mSv	milliSievert
n/a	not applicable

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
O ₂	Oxygen
OMT	Optimal medical therapy
PPIE	Patient and public involvement and engagement
PPI-AG	Patient and public involvement and engagement advisory group
PPM	Permanent pacemaker
pVO ₂	Peak oxygen consumption
QOF	Quality and Outcomes Framework
QoL	Quality of life
QRS	Q, R and S waves
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
R&D	Research and development
RER	Respiratory exchange ratio

RV	Right ventricle
s	second
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical package for the social sciences
SR	Sinus rhythm
SV	Stroke volume
UK	United Kingdom
VAS	Visual analogue score
V_{CO_2}	Carbon dioxide production
VE/V_{CO_2} slope	Slope relating ventilation rate to carbon dioxide production
VO_2	Oxygen consumption
vs	Versus

Chapter 1 : A history of heart failure



Figure 1.1: Nebiri

Nebiri, an Egyptian dignitary, lived 3,500 years ago, under the reign of Thutmoses III (1479-1424 Before the Common Era (BCE); 18th Dynasty). In 1904 his tomb was discovered by Egyptologist Ernesto Schiaparelli (1856-1928), containing only the preserved head (Figure 1.1) and the four canopic jars holding the internal organs (lung, stomach, liver and intestines). The internal organs were removed from the body before mummification and embalmed separately. There was no jar for the heart because it was thought to be the centre of human intelligence and needed for judgement in the underworld; the heart was therefore left in the body. The jar inscribed for Hapi, the 'guardian of the lungs' was found to be broken, and this allowed direct access to organ sampling (Figure 1.2).



Figure 1.2: Canopic jar

This first chapter will illustrate the history behind the development of the diagnostic knowledge and skills gained during the previous 2,000 years, that allowed Bianucci et al. to conclude in 2015, that Nebiri presented as the earliest reported case of chronic heart failure (CHF) in ancient mummies (Bianucci et al., 2016).

1.1 Introduction

Heart failure is the end stage of all diseases of the heart, and is a major cause of morbidity and mortality (Davis et al., 2000). It is a common clinical syndrome, typically characterised by symptoms such as breathlessness, fatigue and ankle swelling. These symptoms may be generated by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (Ponikowski et al., 2016).

1.2 History of heart failure

1.2.1 Greek medicine

Prior to the advent of medicine as a science, it was religion that informed every aspect of medical culture, with remedies being provided by medical sorcerers and healers. Asclepius, son of Apollo, is said to be the creator of medical practice in Ancient

Greece, and his sign of a staff entwined with a snake is still the globally recognised symbol of medicine today (Hart, 1965), an example of which can be seen below (Figure 1.3).



Figure 1.3: Logo of the British Medical Association

For the Ancient Greeks, an understanding of how things worked was regarded as fundamental to the pursuit of scientific wisdom. Consequently, the sixth century BCE saw the Ancient Greeks moving away from the influence of religion on medical practice, towards a more rational and scientific outlook. As a result, Hippocrates (460-375 BCE) (Figure 1.4), often considered the father of Western medicine (Sallam, 2010), adopted an approach based on treating the patient as a whole, rather than dealing with specific illnesses.

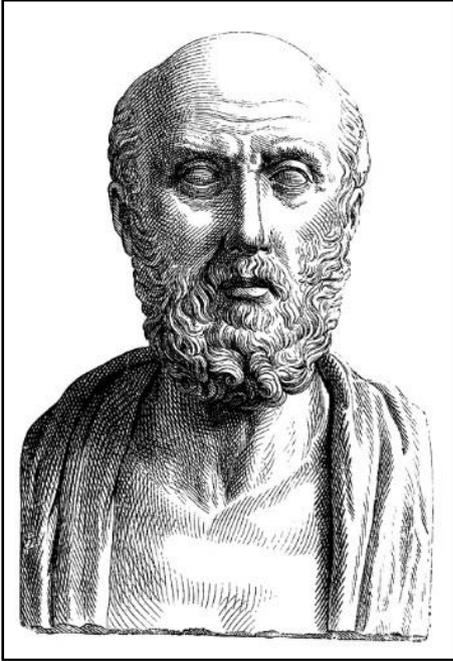


Figure 1.4: Hippocrates

Hippocrates was the first physician to systematically classify diseases based on the similarities and differences between them. Through his observations, Hippocrates concluded that the human body contained four 'humours' (blood, phlegm, black bile, and yellow bile), said to be bodily fluids essential to the physiological functioning of the body. An imbalance in the humours, or a shift in the pattern of flow within the body, resulted in disease (dis-ease). Since it was believed at the time that heat was distributed through the body by the blood, fevers were treated by drawing blood from the body, thus rebalancing the humours – hence the origin and justification for blood-letting (Thomas, 2014). Interestingly, into the 1940s venesection was regarded as 'very helpful' as a treatment in cases of heart failure with a clearly raised venous pressure (Bourne, 1949). However, current understanding is that bloodletting/venesection is ineffective, if not harmful, and is no longer used in modern medicine, except in the prevention or treatment of the effects of iron overload as in

hereditary haemochromatosis, or to decrease red blood cell excess as in polycythaemia vera (Jhang and Schwartz, 2012).

Whilst detailed descriptions of what may have been heart failure appear in the Hippocratic Corpus, there was little, if any, understanding of the connection between the clinical findings and heart disease (Katz, A.M., 1997). The belief that the primary function of the heart was to distribute heat by pumping air, also made it difficult to establish a link between cardiac function and dyspnoea (Ferrari et al., 2016). Although ancient writings suggest diagnoses of heart failure, the symptoms of dyspnoea and fatigue were also common in other diseases and so were not diagnostic. Furthermore, to an extent this remains in modern times, since the symptoms of heart failure are non-specific. However, without the ability at the time to relate clinical descriptions to anatomic pathology, it was not possible to attribute clinical findings to heart failure. Hence, prior to the 19th century, the role of the heart in causing an accumulation of fluid, or difficulty in breathing, was not understood.

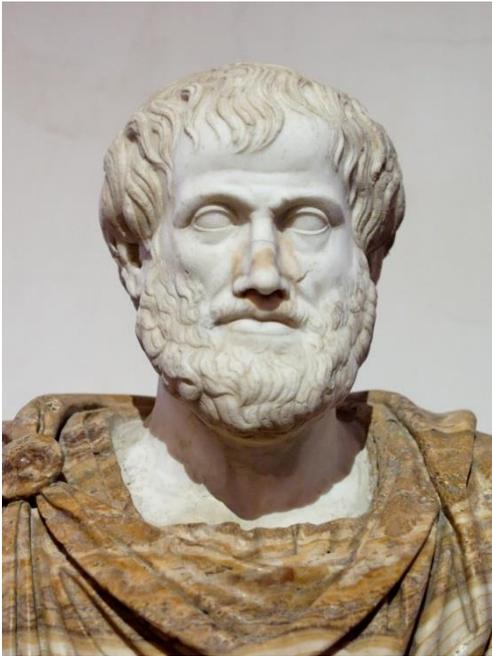


Figure 1.5: Aristotle

The Ancient Greeks had no preceding knowledge of the cardiovascular system (Aird, 2011), and there was a significant gap between clinical observation and pathophysiologic understanding. Aristotle (384-322 BCE) (Figure 1.5) described the heart as the most important organ. He considered the heart to be the seat of intelligence and the centre of vitality in the body; the first organ to come to life and the last to die. Whilst Aristotle is believed to be the first to understand that the arteries and veins both begin at the heart, it was not possible to clarify this until anatomy became a recognised discipline during the Renaissance (Ghosh, 2015). It was Leonardo da Vinci (1452-1519) who first produced accurate drawings of the heart (Figure 1.6); describing it as being 'made of thick muscle, vivified and nourished by artery and vein as are other muscles' (Aird, 2011).

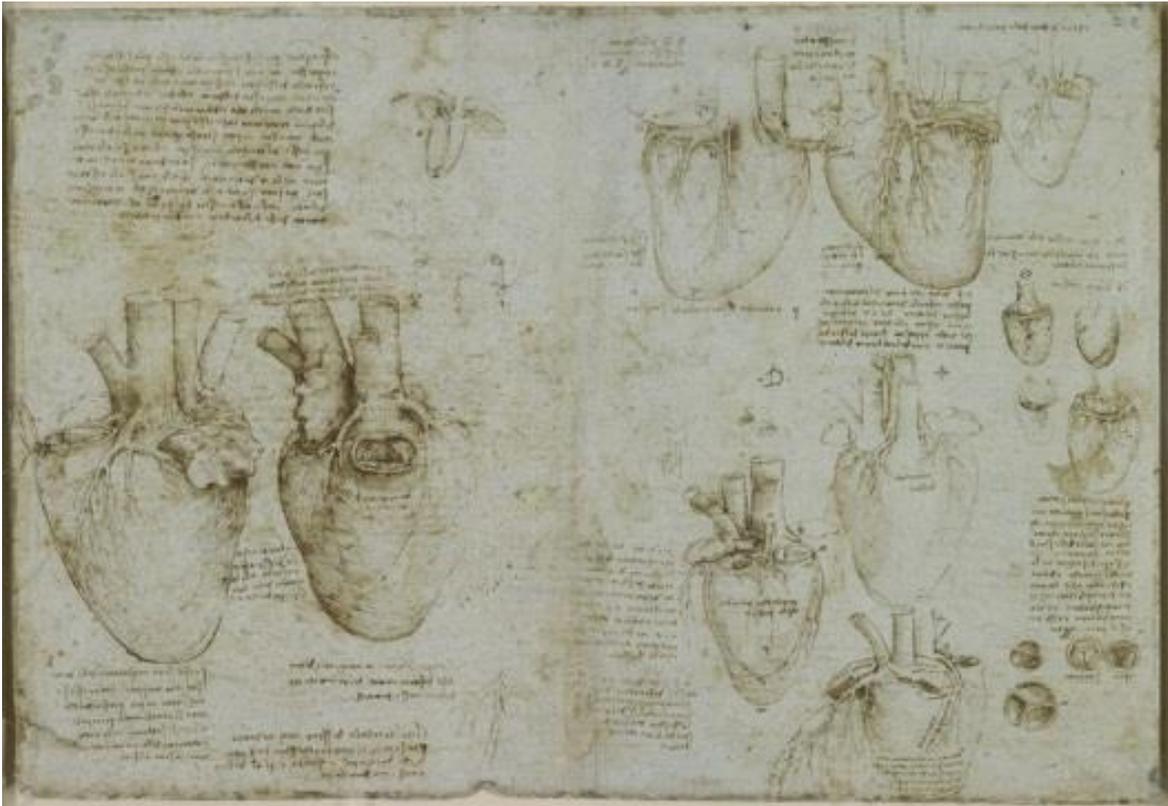


Figure 1.6: Leonardo da Vinci - The heart and coronary vessels c.1511-13.
 Royal Collection Trust / © Her Majesty Queen Elizabeth II 2020. (with
 permission) www.rct.uk/collection/919073

Claudius Galen (129 – circa 210 Common Era (CE)) (Figure 1.7) considered that a physician should be well-rounded, and familiar with other arts and scientific disciplines, including music, rhetoric, geometry and astronomy (Thorndike, 1922). His most significant contribution was to synthesise the existing knowledge, building on established models of physiology and disease (Aird, 2011). He also believed in Aristotle's teleology: that each part of the body was designed to perform a particular function (Strathern, 2005). The arterial pulse was used by Galen for prognostication, and whilst he identified the heart as being the source of arterial pulsations, he did not recognise it as a pump.

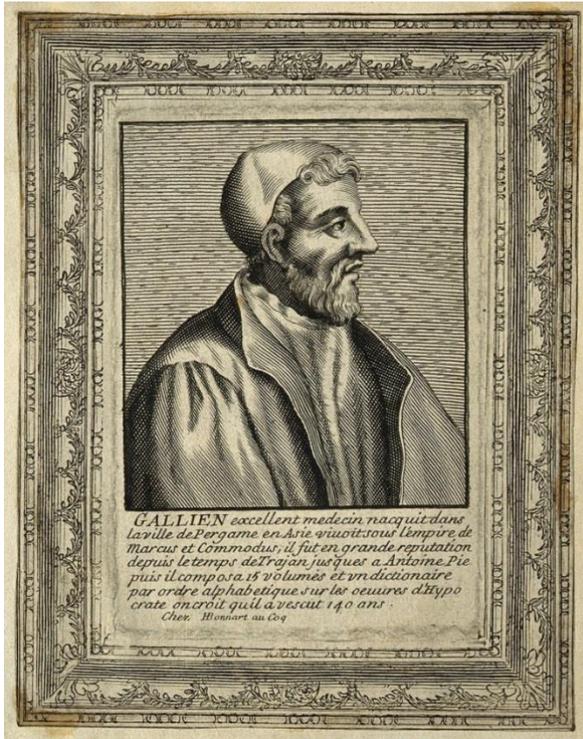


Figure 1.7: Galen Line engraving. Wellcome Collection

Although as a surgeon to the gladiators Galen would have frequently seen inside bodies, the dissection of humans was illegal in Rome during this time. Therefore, he gained experience through performing animal dissections. However, applying his findings from animal dissections to descriptions of human anatomy occasionally led to Galen forming inaccurate anatomical conclusions.

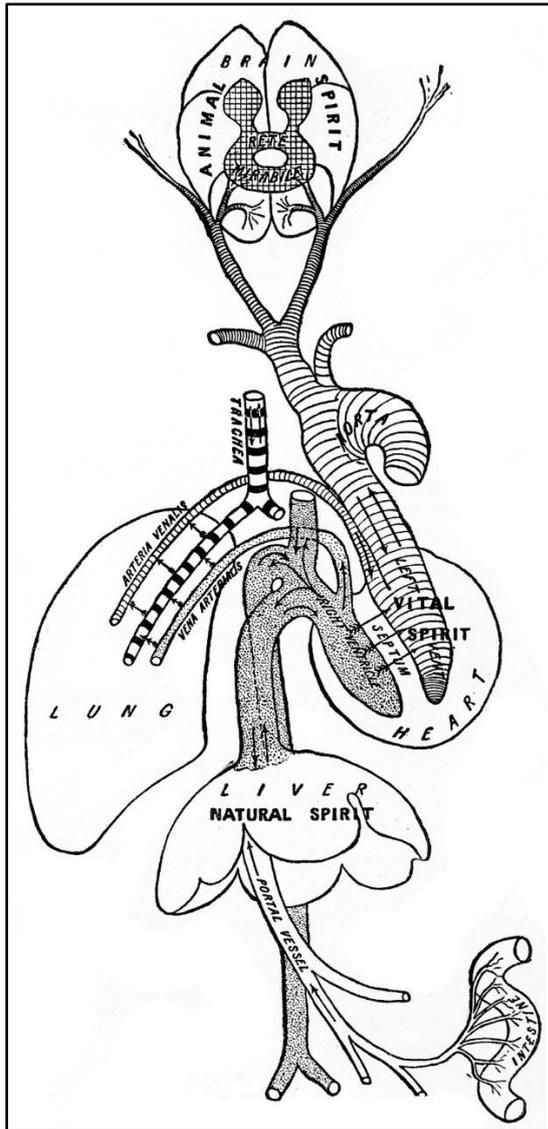


Figure 1.8: Galen's Physiological System. Wellcome Collection

According to the Ancient Greeks, the cardiovascular system comprised two distinct networks of arteries and veins. In this open-ended system, blood and air dissipated at the ends of the vessels, according to tissue demand (Figure 1.8). Whilst Galen demonstrated that arteries contain blood (rather than air as previously thought), he believed that the pulse was transmitted by the arterial walls rather than by the blood flowing through the lumen. Venous blood was thought to be produced in the liver from digested food, with its prime function being to nourish each part of the body through

the network of veins. Some of the venous blood reached the left ventricle, where it combined with the *pneuma* (spirits taken from the air in the lungs), to produce arterial blood. Arterial blood gave vitality to the body through the arterial system – which was independent of the venous system. Venous and arterial blood were ‘used up’ as it passed through the organs and tissue, and therefore had to be constantly replenished in the liver (venous blood) and the heart (arterial blood) (De Renzi, 2004). Nevertheless, the medical knowledge and ideas of Galen dominated medical thinking until the 17th century, when the physician William Harvey (1578-1657) began to challenge dogma and authority (Figure 1.9).



Figure 1.9: William Harvey demonstrating his theory of circulation of the blood before Charles I. Wellcome Collection

1.2.2 Renaissance

Harvey focussed his investigations on the heart, which, like Aristotle previously, he considered to be the body's chief organ. His experiments and deductive logic caused him to question three particular features of Galen's work (De Renzi, 2004):

- The theory that blood was 'used up' and had to be constantly replenished,
- The idea that arterial blood was produced in the heart through the mixing of the *pneuma* from the lungs with venous blood,
- The belief that when the heart dilates, the arteries also dilate and actively suck in and disperse the blood.

Subsequently, in 1628, Harvey was able to demonstrate that arteries and veins are functionally, if not structurally, connected in the lung and the peripheral tissues, and that blood circulates around the body (Aird, 2011). He fully described the circular blood flow in the body from the heart to the extremities via arteries, and from the extremities back to the heart via the venous system (McMullen, 1995). But of course, this could not be verified until it could be shown that the veins and arteries were interconnected. At the time, the magnifying lenses that Harvey had access to were not sufficiently powerful to enable the capillaries to be seen (De Renzi, 2004).

Holland and Italy were the principal countries involved in the construction and use of the microscope during the 16th and 17th centuries. Whilst there were many zoologists

and botanists who were using microscopy in the 17th century, there were few physicians. Marcello Malpighi (1628-1694) was the first person to see the anastomosis between venous and arterial capillaries (Hajdu, 2002), consequently providing visual evidence of the circulation of the blood.

Harvey's discovery of the circulation made it possible for the physicians of the time to use clinical and post-mortem data to explain the haemodynamic basis for the signs, symptoms, and consequences of heart failure. Subsequently, it became possible to recognise in patients who died with stenotic and regurgitant valves, that their dyspnoea and oedema were the clinical consequences of a failing cardiac pump. Valve abnormalities were commonly found in a large number of patients dying from heart failure at this time because, until the mid-20th century, rheumatic heart disease was the major cause of heart failure (Katz, A.M., 1998). Harvey's circulatory physiology, facilitated the use of anatomic pathology to draw correlations with clinical findings, heightening the advancement of medical discovery throughout the 17th and 18th centuries (Katz, A.M., 1997). However, until around 300 years later, when cardiac surgery made it possible to correct the structural abnormalities in these patients, there was little practical value in managing patients with heart failure (Katz, 2008).

1.2.3 18th and 19th centuries

Physicians began to relate various architectural changes in diseased hearts to specific clinical syndromes towards the end of the 18th century. The 19th century then saw efforts being made to understand the prognostic implications of different patterns of cardiac enlargement (Katz, A. and Konstam, 2009). Generally viewed as the first to

distinguish between dilatation and hypertrophy, Italian physician and anatomic pathologist Lancisi (1654-1720), noted that valvular regurgitation leads to ventricular dilatation because the cavities are 'easily distended by the force of the blood that is regurgitated', and suggested that dilatation weakens the heart (Wright, W.C., 1952). It was further noted that hypertrophy increased the energy of the heart's contraction, whilst dilatation of the heart weakened its ability to contract.

The various forms of cardiac enlargement, termed eccentric and concentric hypertrophy, acute and chronic heart failure, were subsequently described and evaluated at the bedside by palpation, percussion, and auscultation, with eventual confirmation by post-mortem.

Nicolas Corvisart (1755-1821), physician to Napoleon Bonaparte, recognised that the left ventricular dilatation seen in aortic and mitral regurgitation, represents a response to increased diastolic stress, whilst concentric hypertrophy, as seen with aortic stenosis, represents a response to increased systolic stress. Corvisart documented the signs and symptoms exhibited by patients with end-stage heart failure, observing that death, which 'always intervenes to terminate the painful scene which this combination of symptoms presents', may occur in two ways: progressive heart failure, which 'advances slowly, [until] life is insensibly extinguished,' and sudden death, which can occur at any time during the natural history of the syndrome (Katz, A. and Konstam, 2009).

In addition to the 19th century view that valvular disease was a cause of cardiac enlargement, it was observed that cardiac hypertrophy was common in renal disease (Bright, 1836). With his introduction, at the end of the 19th century, of the sphygmomanometer to measure brachial artery pressure, Scipione Riva-Rocci (1863-1937) made it possible to define the pathophysiological correlations between arterial hypertension, pressure overload, left ventricular hypertrophy, and heart failure (Mancia, 1997).

During the 19th century, attempts were made to establish the prognostic implications of different patterns of cardiac enlargement, and to determine whether hypertrophy was a compensatory and adaptive response to a haemodynamic overload, or whether the enlargement contributed to a clinical deterioration (Katz, A. and Konstam, 2009).

Amongst others, Austin Flint (1812-1886) described what is currently known as 'remodelling', with hypertrophy delaying the onset of dilatation:

'The increased growth for a certain period protects against the occurrence of dilatation. At length, the hypertrophy reaches a point beyond which it cannot advance; for the muscles of the heart, like other muscles, cannot increase indefinitely.'

(Flint, 1870) p33.

Osler also importantly noted that the hypertrophic response to overload, although initially beneficial, becomes maladaptive because the enlarged muscle slowly degenerates and weakens (Osler, 1892).

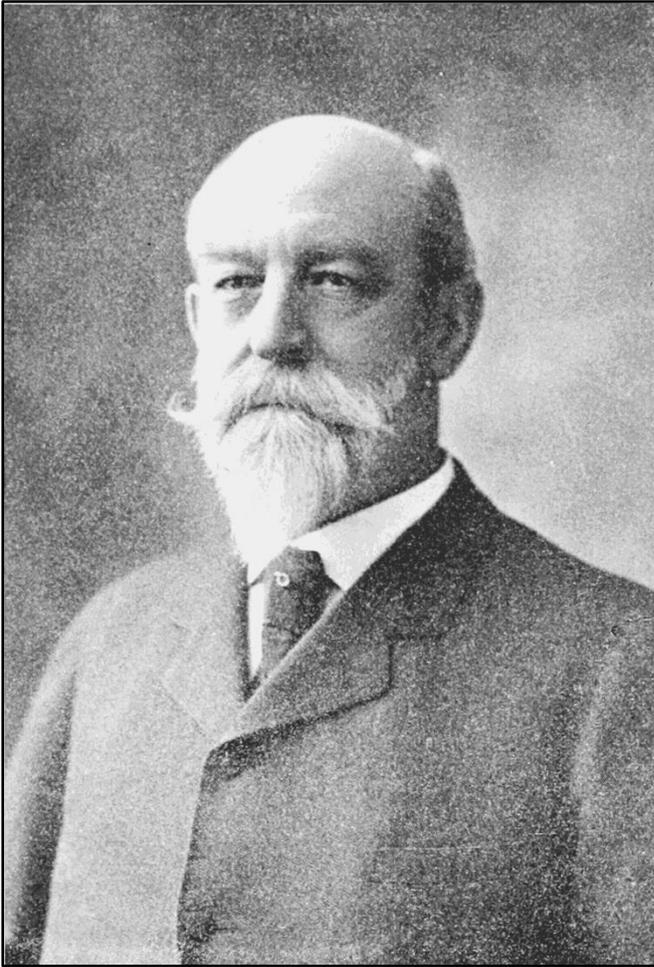


Figure 1.10: Henry Pickering Bowditch

In 1871, Henry Pickering Bowditch (1840-1911) (Figure 1.10) published the results of a series of animal experiments that he performed, looking at the conditions under which the excitation processes of the heart fatigue and recover (Bowditch, 1871). His work recognised that the force of contraction of cardiac muscle is dependent on the rate and rhythm of the heartbeat. The Bowditch effect showed cardiac contraction to be positively coupled to increments in heart rate.

1.2.4 20th century

James Mackenzie (1853-1925) attributed heart failure to myocardial abnormalities. He believed that since 'the heart muscle supplies the force which maintains the circulation', clinical manifestations of heart failure were not produced by valve abnormalities. Heart failure was due to the 'exhaustion of the reserve force of the heart muscle' – the reserve force being the ability to increase output in response to an increase in the circulatory demands (Mackenzie, 1908). As a result of Mackenzie's belief that heart failure was due largely to the exhaustion of overloaded, damaged, or energy-starved heart muscle, recommendations in textbooks, until the end of the 20th century, were for heart failure patients to be treated with rest.



Figure 1.11: Ernest Henry Starling. Photograph. Wellcome Collection

In 1915, Ernest Henry Starling's (1866-1927) (Figure 1.11) law of the heart refocused explanations of heart failure from pathophysiology and the architecture of failing hearts, back to haemodynamics. In the late 19th century, physicians based their views about the effects of increased cavity size on the pathological evidence that dilatation is associated with poor prognosis. Yet Starling's demonstration that increased end-diastolic volume increased the force of contraction, seemed to contradict the previous

concepts that dilatation weakens the failing heart (Mackenzie, 1908). However, Starling had noted that increasing diastolic volumes increased the work of the heart 'within physiological limits', concluding that dilatation is one of the principle means of adaptation to the needs of the organism (Cowan, 1922).

Katz and Konstam (2009) suggest that Starling's law of the heart is an acute functional response, on a beat-to-beat basis, which allows an increased end-diastolic volume to increase the work of the heart, whilst the more progressive and chronic dilatation, resulting from pathological hypertrophy, represents a long-term architectural response caused by abnormal transcriptional signalling.

Prior to 1785, treatment for the symptoms of heart failure was limited to bleeding, purgatives, blistering, garlic, 'medicinal' intake of wine or good ale, and the removal of ascitic fluid (Silverman, 1989).

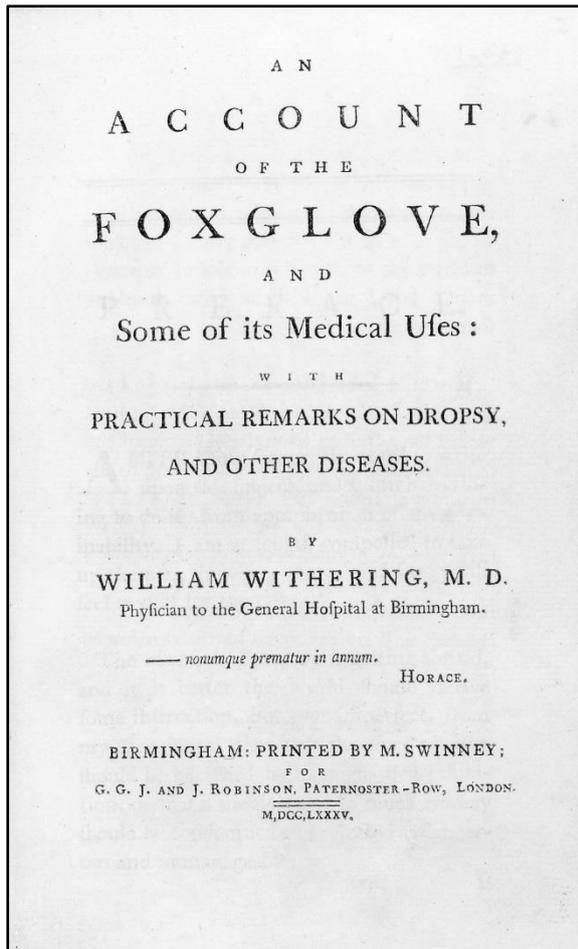


Figure 1.12: Withering, An account of the foxglove, 1785. Wellcome Collection

William Withering (1741-1799), a physician and botanist, described in his publication (Figure 1.12), how the use of herbal tea made from foxglove (*digitalis*), was effective in the treatment of dropsy (an old term for the swelling of soft tissues due to the accumulation of excess water) (Figure 1.13). After studying the effects of the foxglove on his patients he noted that:

'...it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends'

And *'...if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcaous*

limbs readily pitting under the pressure of the finger, we may expect the diuretic effect to follow in a kindly manner'

(Silverman, 1989).



Figure 1.13: Patient with dropsy

Although he recognised the therapeutic usefulness and the toxic effects of digitalis, Withering did not have the physiological knowledge to understand the mechanisms of

its action. It was John Ferriar (1761-1815) in 1799 who was the first to recognise that the primary site of action for digitalis was the heart; diuresis being a secondary effect (van Bronswijk and Cohen, 2008). Subsequently, in 1918 Arthur Cushny (1866-1926), a Scottish pharmacologist, improved knowledge regarding cardiac physiology and the causes of arrhythmias (Cushny, 1918). Cushny's work using animal models also led to a better understanding of the clinical effects of digitalis.

A degree of progress was made in the 19th and early 20th centuries with fluid retention being treated with Southey's tubes, which were inserted into oedematous peripheries, to facilitate drainage of fluid (Figure 1.14). Indeed in 1949, Geoffrey Bourne (1893-1970) stated that Southey's tubes could be used to drain fluid 'in quantity' and with 'great benefit' (Bourne, 1949)p.43. However, a significant impact was made on the treatment of heart failure when, in 1919, Alfred Vogl (1895-1973) discovered the dramatic diuretic effects produced by organic mercurials (Vogl, 1950). Whilst the effects of the parenterally administered organic mercurials were intense, they were also short-lived, with the inevitable fluctuations between copious diuresis and fluid retention, and were therefore of little benefit in end-stage heart failure (Vogl, 1960). This however, prompted research into the development of powerful diuretics that could be administered orally. Subsequently the 1950s and 1960s saw the discovery first of the thiazides and then of the loop diuretics (Katz, A. and Konstam, 2009).

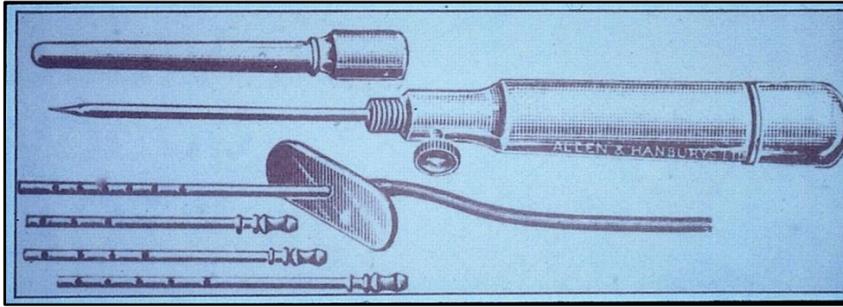


Figure 1.14: Southey's tubes (Davis et al., 2000)

The end of the 19th century saw the introduction of the use of technology, along with history taking and physical examination in the diagnosis of heart disease. The discovery of X-rays in 1895 by Wilhelm Röntgen (1845-1923), and the development of the electrocardiogram (ECG) in the 1890s, provided objective information about the structure and function of the heart, allowing important improvements in the investigation of heart failure (Davis et al., 2000). Whilst the first ECG from the intact human heart was recorded in 1887 with a mercury capillary electrometer by Augustus Waller, at St Mary's Hospital, London (Barold, 2003), it was Willem Einthoven (1860-1927), Professor of Physiology at the University of Leiden, who was the first to recognise the importance that the ECG would have in the diagnosis of heart disease (Davies, M.K. and Hollman, 1997). Einthoven advanced Waller's work by developing a string galvanometer with very high sensitivity, which he used in his electrocardiograph.

The first ECG electrodes were cylinders of electrolyte solution in which the extremities were rinsed (Figure 1.15) (Burch and DePasquale, 1990; AlGhatrif and Lindsay, 2012).

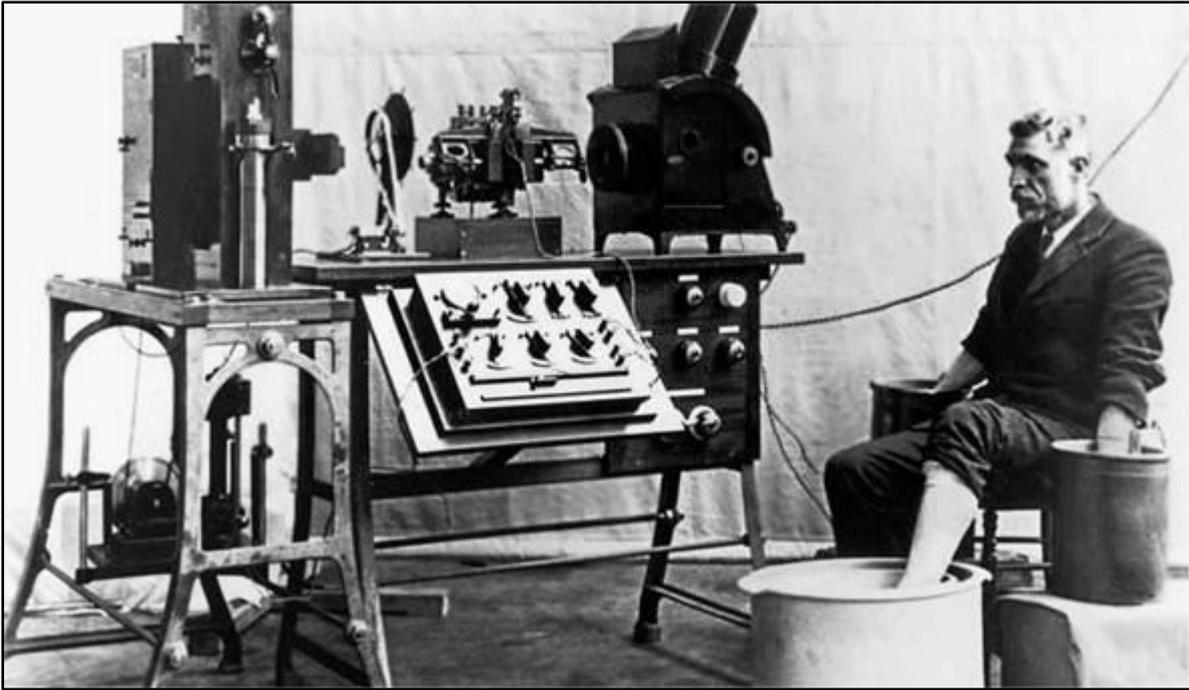


Figure 1.15: Early Electrocardiograph

In a similar way to Galen gaining his observational knowledge of human anatomy through seeing injuries sustained during gladiatorial combat, advances made in the treatment of cardiac injuries during World War II demonstrated the possibilities of cardiac surgery bringing ‘the heart within the province of safe surgery’ (Harken and Williams, 1946). This then allowed the development of open-heart surgery, and valve repair and replacement – a welcome advance, since the most common cause of heart failure up to this point had been rheumatic valve disease.

1.3 Conclusion

Despite the above significant advances having been made in cardiovascular medicine and surgery, an increasing number of patients are at risk of developing subsequent heart failure following the myocardial damage associated with acute coronary

syndromes, valvular and congenital heart disease, hypertension, and many arrhythmias (Braunwald, 2015). As will be discussed in the next chapter, heart failure is the most rapidly growing cardiovascular condition globally. Consequently, the determination to increase understanding of the syndrome of heart failure, and to develop new approaches to improve the care of patients remains important.

Whilst we should look to the future, we should also build on our past. Research surrounding heart failure is widespread, however progress in science is not an isolated occurrence. It builds on a foundation of knowledge. As William Harvey said 'there is no science which does not spring from pre-existing knowledge' (Harvey et al., 2020).

Chapter 2 : An introduction to heart failure and treatment

This chapter will discuss the complex clinical syndrome of chronic heart failure, its diagnosis, management, and treatment, whilst also introducing some of the gaps in our knowledge to frame the interventions described in future chapters.

2.1 Introduction

Chronic heart failure (CHF) is a clinical syndrome characterised by symptoms including breathlessness at rest and during exertion, fatigue, and ankle swelling, and has been defined as:

‘..the pathological state in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues during ordinary activity’ (Braunwald et al., 1967).

The key driver of the syndrome of CHF is reduced cardiac output on exertion, which can be the result of failure of the heart to contract effectively, or to fill effectively. In either setting, the primary effect is a reduction in stroke volume. The clinical syndrome, driven by reductions in stroke volume due to failure of cardiac contractility, is known as ‘heart failure with reduced ejection fraction’ (HFrEF) or ‘systolic heart failure’. On the other hand, CHF without a reduction in cardiac contractility is known as ‘heart failure with preserved ejection fraction’ (HFpEF). These two syndromes are usually determined by an echocardiographic assessment of ejection fraction, since the clinical features and symptoms are identical. A third category of CHF has also been suggested

of 'heart failure with mid-range ejection fraction' (HFmEF), where the left ventricular ejection fraction (LVEF) is 40-49% (Lam, C.S. and Solomon, 2014; Ponikowski et al., 2016).

The underlying pathophysiology of HFrEF on which this thesis will focus, can be the result of mechanical, structural, or electrical abnormalities of the myocardium. In developed countries, HFrEF is most often the consequence of myocardial injury due to ischaemia, although hypertension with chronic pressure overload or valvular disease remain the most common causes worldwide. Myocyte toxicity due, for example, to a chemotherapeutic agent, is also well recognised. The effects on the myocardium, be they acute or chronic insults, initiate a cycle of widespread neuro-hormonal adaptation. In the myocardium, these influences lead to a gradual change in the size, shape and function of the cells and the cardiac chambers, known as remodelling, which initially, through the lengthening and hypertrophy of cardiomyocytes, preserves stroke volume. However, this remodelling, and the influences that drive it, is associated with ongoing progressive myocyte hypertrophy, apoptosis, and necrosis, with accompanying fibroblast proliferation and interstitial fibrosis. Eventually, not only the muscle but also the fibrous structures of the heart are affected, leading to sphericity, and loss of competence of the atrio-ventricular valves which accelerates the process further due to volume overload (McMurray, J.J. and Pfeffer, 2005; Weber et al., 2009).

The neuro-hormonal activation, and the impaired haemodynamics, particularly impaired perfusion, has widespread effects, most notably on the kidneys, skeletal muscles, lung function, and immune system.

Overall, the syndrome of HFrEF is associated with shortened life expectancy, recurrent hospitalisations and significantly reduced quality of life (Dickstein et al., 2008) and despite great therapeutic advances, the mortality rate remains high at around 50% at 5 years (Hobbs, F.D.R. et al., 2007; Taylor et al., 2019).

2.2 Epidemiology

HFrEF is the most rapidly growing cardiovascular condition globally and is the common final end point for most forms of cardiovascular disease. Around 2% of the adult population in developed countries is affected by HFrEF, rising to approximately 10% of over 70-year-olds (Ponikowski et al., 2016). Whilst the incidence has remained stable over the last two decades, the prevalence of HFrEF is increasing due to: an ageing population, the improved survival from ischaemic heart disease (IHD), and also the development of modern treatments for HFrEF (Pazos-Lopez et al., 2011). The average age at diagnosis is 77 years, but is significantly lower in areas of economic deprivation (Sutherland, 2010). Since age is an important risk factor for HFrEF, the burden on healthcare systems in developed countries increases as these populations age (Bleumink et al., 2004). Societal burden is also increased by lifestyle choices, with more people than ever living alone. A high level of perceived societal isolation is associated with an increased risk of death, hospitalisations, and outpatient appointments (Manemann et al., 2018). Furthermore, improved treatment of heart

disease and an increase in such cardiovascular risk factors as type 2 diabetes mellitus and obesity, in the context of healthy lifestyles continuing to decline in countries with emerging economies, means that a new increase in global incidence of HFrEF is underway.

2.3 Economics

Whilst therapeutic advancements have improved the treatment of HFrEF, morbidity and mortality remain high. HFrEF is the most common cause for hospital admission in those over 65 years old (Roger, 2013), and causes or complicates 5% of all hospital admissions in the United Kingdom (UK) (NICE, 2014; NICOR, 2019).

Although heart failure accounts for approximately 2% of the entire National Health Service (NHS) budget, this does not include costs related to nursing home care and hospitalisations where heart failure is coded as a secondary diagnosis, which have been estimated to account for a further 2% of expenditure. Indeed, heart failure is thought to cost the NHS around £905 million per year (Stewart et al., 2002).

2.4 Aetiology and pathophysiology of heart failure

CHF, and particularly HFrEF, is the consequence of an acute or chronic insult to the cardiomyocytes from which the cardiac syncytium never fully recovers.

The leading cause of HFrEF in developed countries is IHD (Ziaieian and Fonarow, 2016). However, overall, hypertension is thought to be the greatest aetiological factor

(Vasan and Levy, 1996; Cleland et al., 2001; Lüscher, 2015). Not only does hypertension contribute to the development of chronic left ventricular (LV) dysfunction directly, it is also the most common driver of coronary artery disease (CAD) and thereby IHD. Moreover, the epidemic of the metabolic syndrome in the developed world where hypertension is a key player, but also compounds the atherosclerotic effects of type 2 diabetes mellitus (Drozd and Kearney, 2017), means that despite effective blood-pressure-lowering therapies, hypertension remains the most important global risk factor for LV dysfunction (Kuznetsova et al., 2010).

Given the high contribution of IHD to HFrEF, and the modest but key differences in treatment of HFrEF due to IHD, patients with HFrEF are often classified as having the syndrome due to IHD or not. 'Non-ischaemic cardiomyopathy' or 'non-ischaemic heart failure' can therefore be due to valvular heart disease, infiltration (amyloid, sarcoidosis), viral infection, idiopathic dilated cardiomyopathy, and can be induced by tachyarrhythmia. Indeed, a failure to adequately control ventricular rate in the long-term may also cause a progressive decline in LV function (Khand et al., 2000). Paradoxically, although a great contributor to HFrEF due to IHD, hypertension is also a common cause of non-ischaemic cardiomyopathy.

Chronic and acute IHD and particularly myocardial infarction (MI), lead to the death of cardiomyocytes which are then replaced by scar, leading to impaired cardiac contraction. Aneurysm formation can further worsen cardiac function, as can dyssynchronous motion within the infarcted region. Ventricular structure and geometry may be subsequently distorted by remodelling, further impairing cardiac function.

Indeed the progressive dilatation post MI plays an important role in the development of HFrEF (Gaudron et al., 1993). Whilst coronary occlusion may also lead to a persistent, but not permanent, loss of cardiac contraction without permanent cell death (hibernation), recurrent ischaemia can lead to a more short-term loss of cardiac contractility (stunning) (Cleland et al., 2001). However, less severe, or transient coronary occlusion with entirely reversible ischaemia, which may or may not provoke angina, does not usually lead to ventricular dysfunction.

Although the above conditions initiate myocardial dysfunction, the basic pathophysiological process is driven, accentuated and persists due to compensatory mechanisms that although initially successful, eventually fail to preserve cardiac output and ultimately contribute to the progression of the condition (Triposkiadis et al., 2009).

Many patients may have asymptomatic cardiac dysfunction for years before they experience symptoms. The compensatory mechanisms of increased stroke volume through LV remodelling, along with peripheral vasoconstriction because of increased renin-angiotensin-aldosterone system (RAAS) activation, increased heart rate and cardiac contractility via sympathetic nervous system activity, can maintain filling pressures and cardiac output.

Stroke volume and ventricular function depend on a combination of preload, myocardial contractility, and afterload. Hypertension contributes significantly to the development of HFrEF, both directly (through increased afterload) and indirectly

(through its role in IHD). The higher afterload, through elevated resistance of the peripheral vasculature results in a compensatory increase in myocardial mass in order to maintain normal cardiac output (Pazos-Lopez et al., 2011). Left ventricular hypertrophy is characterised by a higher myocardial stiffness and a decreased ability to relax and fill (Gaasch et al., 1982; Smith et al., 1985).

However, these compensatory mechanisms eventually fail, and rather than further dilatation of the LV causing an increase in stroke volume, it causes the end-diastolic pressure to increase, and contraction becomes mechanically inefficient. High levels of angiotensin II and adrenergic hormones stimulate continued peripheral vasoconstriction, increasing afterload further, and cause salt and water retention, leading to an increase in the circulating volume. These hormones also increase myocyte apoptosis leading to worsening LV function and an over-activation of compensatory mechanisms (Hilfiker-Kleiner et al., 2006). Furthermore, as the LV dilates, there is a concomitant widening of the mitral orifice, with resultant functional mitral regurgitation.

2.5 Signs and symptoms

Whilst the characteristic diagnostic feature of HFrEF is impaired cardiac pumping function, defining HFrEF from a clinical perspective is challenging because the signs and symptoms are non-specific (Table 2.1), and can be seen with normal ageing. For example, fatigue (Falk et al., 2009) and dyspnoea (Ekman et al., 2005) are often dismissed as a consequence of ageing and deconditioning, and therefore not

adequately explored as symptoms of HFrEF. Nevertheless, defining HFrEF into different types is critical due to the widely differing approaches to treatment.

The most common symptoms are breathlessness and fatigue, resulting in exercise intolerance (Watson et al., 2000).

Table 2.1: Signs and symptoms in heart failure

Signs	Symptoms
Cachexia and muscle wasting	Exertional breathlessness
Tachycardia	Ankle swelling
Pulsus alternans	Orthopnoea
Elevated jugular venous pressure	Paroxysmal nocturnal dyspnoea
Laterally displaced apex beat	Reduced exercise tolerance, lethargy, fatigue
Right ventricular heave	Nocturnal cough
Bi-basal fine crackles	Anorexia
Third heart sound	
Peripheral pitting oedema	
Hepatomegaly	
Ascites	
Wheeze	

Although these signs and symptoms have poor sensitivity and poor specificity, they can alert the healthcare practitioner to the possibility of underlying disease. On the other hand, the absence of symptoms does not exclude underlying disease. Consequently, accurate diagnosis of HFrEF requires thorough clinical assessment, in

combination with relevant investigations, to demonstrate signs, symptoms, underlying aetiology, and to provide objective measurements of severity (Figure 2.1). There are however limitations in a physical examination, since patients (particularly those with less severe HFrEF) may have few abnormal signs. Furthermore, many patients with significant cardiac disease and without apparent symptoms, may deteriorate slowly, assume this is a normal part of ageing and consequently do not seek help. Conversely, many patients presenting with the common and non-specific heart failure symptoms of shortness of breath on exertion, exercise intolerance, and ankle swelling, do not in fact have heart failure (Davie et al., 1997). Hence investigation must include people with seemingly mild symptoms and few signs, but who are at elevated risk of underlying HFrEF; such assessment must combine physical examination and clinical investigations.

The progressive nature of the syndrome contributes to a low quality of life score in the HFrEF patient population. Indeed, patients with HFrEF suffer a poor quality of life, worse than that of patients with other chronic conditions (chronic obstructive pulmonary disease and many cancers), not only due to the high probability of readmission (Stewart et al., 2001), but also due to frequent visits to their general practitioner (GP), and persistent reduced physical capacity because of the typical symptoms of breathlessness and fatigue (Hobbs, F.D. et al., 2002).

2.5.1 Assessing clinical severity

The functional classification developed by the New York Heart Association (NYHA) is most commonly used to provide a subjective assessment of symptoms and an

estimate of physical limitation (NYHA, 1994) (Table 2.2). Despite the somewhat lack of sensitivity to change and being subjective, the NYHA classification does give a guide to prognosis, is a criterion for additional medical management, and acts as an indication for implantation of a pacemaker device. Moreover, in an individual and a population, changing NYHA classification can provide a reflection of improvement or deterioration in clinical state, and aid in the evaluation of response to therapy.

Table 2.2: NYHA Classification

NYHA Classification	Level of symptoms
Class I	Symptoms of HFrEF only at levels that would limit normal individuals
Class II	Symptoms of HFrEF with ordinary exertion
Class III	Symptoms of HFrEF with less than ordinary exertion
Class IV	Symptoms of HFrEF at rest

2.5.2 Comorbidities

Multimorbidity is defined as the coexistence of two or more chronic conditions (Tinetti et al., 2012), and has been shown to be increasingly common in heart failure (Conrad et al., 2018). This is of particular concern in HFrEF since comorbidities may precipitate acute decompensation, increase hospitalisations and complications (Page and Lindenfeld, 2012), therefore impacting on the prognosis (Chamberlain et al., 2015). In an observational cohort study of 1,794 patients with HFrEF, comorbidity accounted for the majority of lost life expectancy in people with HFrEF (Drozd et al., 2020).

HFrEF may be exacerbated by anaemia, renal dysfunction, cachexia, and arrhythmias. Atrial fibrillation (AF) in particular, may contribute directly to an abrupt decline in function.

2.6 Diagnosis

Demonstration of underlying cardiac dysfunction is a fundamental component in the diagnosis of HFrEF, since precise pathology determines the specific treatment used (Ponikowski et al., 2016). Furthermore, accurate and early diagnosis is key in the reduction of mortality, morbidity, and cost of HFrEF. However, cardiac dysfunction results from many different disease processes, which may be related to causes other than HFrEF. Therefore, the clinical suspicion of HFrEF should be confirmed with objective investigations and the demonstration of cardiac dysfunction at rest (Watson et al., 2000) (Figure 2.1).

The routine use of an electrocardiogram (ECG) is mainly recommended to rule out heart failure, since a diagnosis of HFrEF is unlikely in the presence of a completely normal ECG (sensitivity 89%) (Ponikowski et al., 2016). An ECG may also identify the presence of any coexisting arrhythmias or evidence of IHD and may additionally provide indications for therapy.

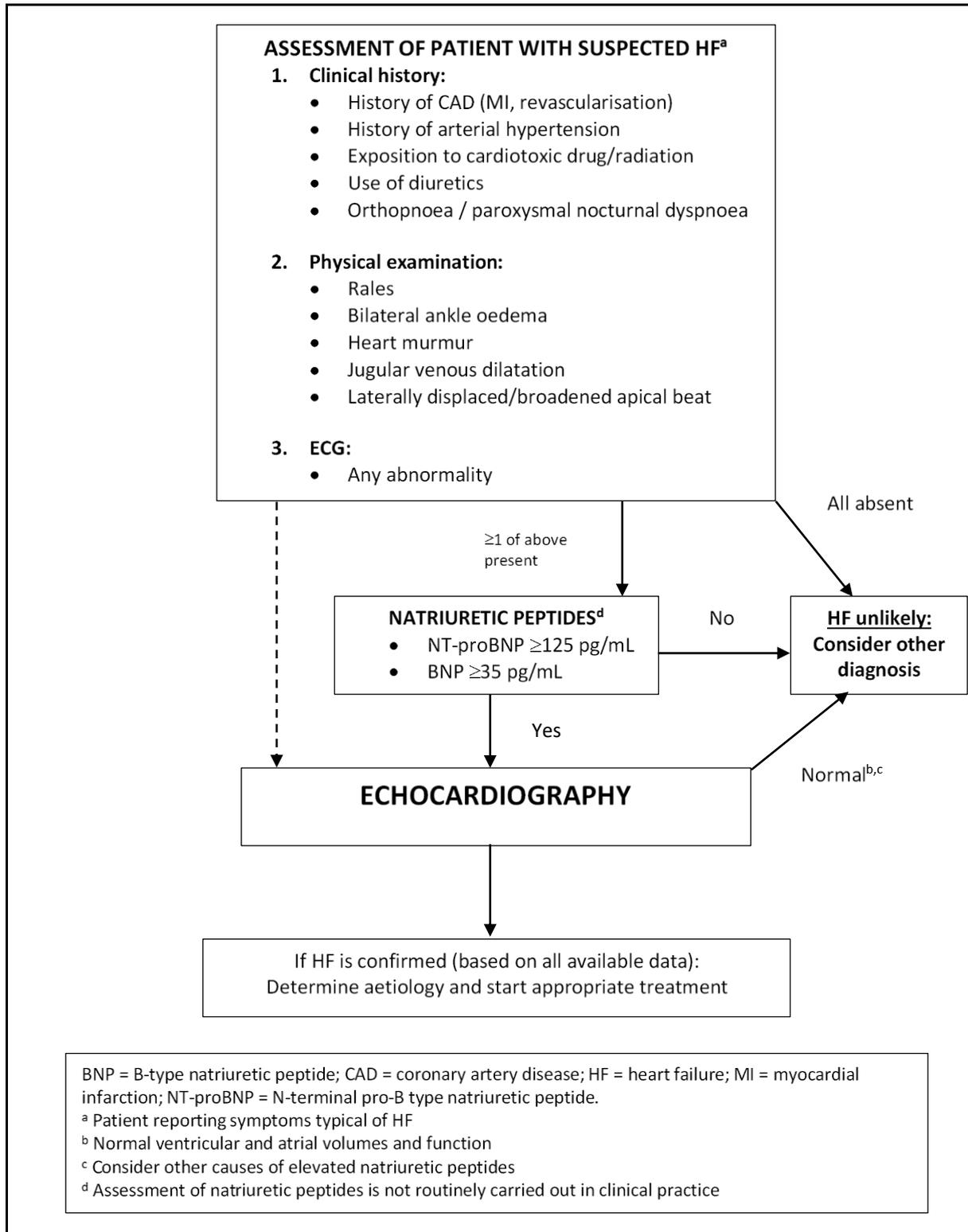


Figure 2.1: HFrEF diagnosis algorithm (adapted from Ponikowski et al., 2016)

UK and European guidance suggest that the plasma concentration of natriuretic peptides should be used as an initial diagnostic test and guide to further investigation

if HFrEF is suspected, particularly in the non-acute setting. Elevated natriuretic peptides can help identify those patients who require further cardiac investigations, whilst those with normal plasma natriuretic peptide concentrations are unlikely to have HFrEF (Ponikowski et al., 2016; NICE, 2018).

Natriuretic peptides may also be elevated because of several cardiovascular and non-cardiovascular reasons, which may reduce their effectiveness in diagnosing HFrEF. Most important amongst those reasons are AF, age and renal failure (Maisel et al., 2008). Natriuretic peptides have high negative predictive values (0.94-0.98) in acute and non-acute settings, and low positive predictive values in the acute (0.66-0.67) and non-acute (0.44-0.57) settings (Cowie et al., 1997; Yamamoto et al., 2000; Krishnaswamy et al., 2001; Zaphiriou et al., 2005; Fuat et al., 2006; Roberts et al., 2015). Therefore, the use of natriuretic peptides is recommended for ruling out, rather than confirming, a diagnosis of HFrEF (Ponikowski et al., 2016). As such, an elevated natriuretic peptide level can be an indicator as to which patients require an echocardiogram.

2.6.1 Echocardiography

Echocardiography (or cardiac ultrasound) is a well-established and recognised imaging modality, and as such performs a central role in not only the diagnosis of HFrEF, but also in determining appropriate treatment, assessment, and monitoring. It provides immediate, non-invasive diagnostic information about chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and pulmonary hypertension, reducing the necessity of invasive investigations in many

patients. Furthermore, echocardiography is a portable and relatively inexpensive imaging method. Since echocardiography forms a central outcome in the studies carried out for this thesis, a full review of the use of echocardiography in the context of HFrEF forms chapter 4.

2.6.2 Cardiopulmonary exercise testing

Over the past decade, acknowledgement of the importance and value of cardiopulmonary exercise testing (CPET) within healthcare settings has grown (Faghy et al., 2020). CPET is recommended in the assessment of patients with HFrEF to measure response to physical exertion, since impaired exercise tolerance is a key component in the diagnosis of HFrEF.

During a CPET, patients perform physical exertion whilst breathing room air. Workload is measured and controlled through an ergometer. This is usually a treadmill or a stationary cycle, or alternatively an arm-crank cycle or a rowing ergometer. Accurate assessment of workload is achieved through use of a standard protocol. The volume and concentration of inspired and expired oxygen (O_2) and carbon dioxide (CO_2), and respiratory rates and volumes, are collected via a mouthpiece or facemask. Metabolic gas exchange is analysed on a breath-by-breath basis by O_2 and CO_2 analysers.

Measurement of ventilatory and O_2 uptake patterns in HFrEF can quantify disease severity and prognosis (Malhotra et al., 2016). Exertional fatigue can be objectively measured as a reduction in peak oxygen consumption (VO_2) and an increase in ventilatory response to exercise (V_E/VCO_2 slope) during incremental exercise testing

with metabolic gas exchange analysis, suggesting that patients with HFrEF ventilate more for a given workload and given carbon dioxide output than controls (Buller and Poole-Wilson, 1990; Davies, S.W. et al., 1991).

2.7 Management

The objectives of treating patients with HFrEF are to improve symptoms, quality of life and functional capacity, to prevent hospitalisation, and extend longevity which is often described by a reduction in mortality over a finite time (Ponikowski et al., 2016). Multiple pharmacological therapies have been shown to improve mortality in prospective, randomised controlled trials (Hunt et al., 2009; Cubbon et al., 2011). Pacemaker devices have been shown to reduce mortality rates in selected patients (Bristow et al., 2004; Bardy et al., 2005; Cleland et al., 2005). However, the best way to integrate medical and device therapy, education and general approaches, is within a multidisciplinary team approach to delivery of care (Morton et al., 2018).

2.7.1 General management

Much of the advice provided to patients on lifestyle and general management, following a diagnosis of HFrEF is not evidence based. I have used the guidelines published by the European Society of Cardiology (ESC) working group on heart failure (Ponikowski et al., 2016).

Patient education on the aetiology, importance of adherence to treatment plans, benefits of medication dosage optimisation, and the prompt reporting of a deterioration in symptoms, can improve outcomes (Koelling et al., 2005), although this is not a

consistent finding (Jaarsma et al., 2008). Nevertheless, patient education may allow the patient to feel more in control and involved in management decisions.

Modification of risk factors may prevent or delay the development of HFrEF. Control of hypertension can delay the onset of heart failure development and may increase longevity.

2.7.1.1 Diet

Patients should eat a healthy, well-balanced diet. The most important element of diet management in patients with HFrEF is salt restriction. Fluid retention is the most prevalent cause for clinical worsening and hospitalisations in HFrEF. Since dietary salt intake directly contradicts the action of diuretics, reinforcement of the need to restrict salt intake is necessary (Katz, A. and Konstam, 2009). Alcohol consumption should not be excessive. Those taking warfarin should be warned that changes in their diet may result in loss of anti-coagulant control.

2.7.1.2 Exercise

Exercise-based cardiac rehabilitation can improve symptoms and reduce the risk of heart failure hospitalisations in patients with HFrEF, however access greatly varies (Sagar et al., 2015). The Quality and Outcomes Framework (QOF), under the guidance of the National Institute for Health and Care Excellence (NICE), developed 'indicators' for managing patients with HFrEF; these indicators are financially incentivised targets for GPs. Whilst the HFrEF guidelines of both the ESC and NICE recommend referral to an exercise-based cardiac rehabilitation programme, the 2019-

20 QOF indicators no longer reward GPs for referral (Ponikowski et al., 2016; NICE, 2018). Patients should nevertheless be encouraged to take regular exercise and be reassured that far from being something they should avoid, they should take exercise as their symptoms allow, rest and repeat.

2.7.1.3 Smoking

Cigarette smoking is a major contributor to all forms of cardiovascular disease. It increases risk factors for heart failure such as: raised blood pressure, increased heart rate, diabetes, and atherosclerosis. Gopal et al. found that current smokers exhibited a significantly increased risk of incident heart failure compared to non-smokers, after controlling for other clinical heart failure risk factors and incident coronary events (Gopal et al., 2012).

Although there has been a suggestion of a 'smoker's paradox', where smokers who were hospitalised with heart failure had lower risk adjusted in-hospital mortality and similar early post-discharge mortality compared with non-smokers, this was not fully explained by measured covariates (Fonarow et al., 2008).

A meta-analysis of nine articles (n=70,461) reported that 16% of smokers continued to smoke after a heart failure diagnosis (Son and Lee, 2020). Persistent smoking increased the hazard ratio (HR) of mortality by 38.4% (HR=1.384; 95% confidence interval (CI): 1.139-1.681) and readmission by 44.8% (HR=1.448; 95% CI: 1.086-1.930). Persistent smoking was found to be associated with poor health status, ventricular tachycardia, and arterial stiffness.

Since smoking continues to be a leading cause of preventable morbidity and mortality, continued attempts at smoking cessation aimed at both individual and population levels are appropriate.

2.7.2 Pharmacological treatment

The mainstay of HFrEF treatment is pharmacological therapy, with the key targets being symptomatic relief, slowing of disease progression and increasing survival. The treatment of HFrEF up until the 1980s focused primarily on symptom control using diuretics and digoxin. Contemporary pharmacological treatments are directed at the inhibition of the two major neuro-hormonal pathophysiological mechanisms that underlie the development and progression of HFrEF, namely the RAAS and the sympathetic nervous system. In the short-term, these systems are beneficial and adaptive, maintaining organ perfusion and cardiac output. But in the long-term, cardiomyocyte hypertrophy, apoptosis, and fibrotic proliferation result in adverse remodelling and pump dysfunction (Pazos-Lopez et al., 2011).

Neuro-hormonal antagonists (angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid/aldosterone receptor antagonists (MRAs) and beta-adrenoceptor antagonists (β -blockers)), have been shown to improve survival in heart failure, and are recommended for all patients with HFrEF, unless contra-indicated or not tolerated (Ponikowski et al., 2016).

2.7.2.1 Loop and thiazide diuretics

Diuretics are recommended to manage the symptoms of HFrEF that are associated with fluid and salt retention, such as shortness of breath, and peripheral and pulmonary oedema. Whilst no randomised controlled trials have demonstrated long term effects on mortality or morbidity (Ponikowski et al., 2016), they provide rapid and effective symptomatic relief (Faris et al., 2002) by blocking sodium reabsorption in the renal tubules, resulting in increased urinary sodium and water excretion. The aim is to use the lowest dose to achieve and maintain euvolaemia.

Diuretics are divided by mode and site of action. Spironolactone and eplerenone, both of which have a diuretic effect, are discussed below. The other two major groups are loop diuretics and thiazide diuretics. Loop diuretics (furosemide and bumetanide) are used most commonly in HFrEF, and work by inhibiting sodium and chlorine reabsorption from the ascending limb of the loop of Henle in the renal tubules. Loop diuretics are more potent and their effect is generally preserved in the presence of modest renal impairment (Pazos-Lopez et al., 2011). Thiazide diuretics inhibit sodium reabsorption at the beginning of the distal convoluted tubules and are often used in the later stages of the disease process when there is resistance to the effects of loop diuretics with persistent oedema. Loop and thiazide diuretics can be used in combination, but adverse effects such as dehydration and renal dysfunction are more likely (Ponikowski et al., 2016).

2.7.2.2 Angiotensin-converting enzyme inhibitors

With a reduction in cardiac output due to LV dysfunction, there is a fall in renal perfusion which leads to a compensatory rise in renin excretion. Renin converts angiotensinogen to angiotensin I, which through angiotensin converting enzyme is converted to angiotensin II. This agent has powerful vasoconstrictive, salt-retentive, and hypertrophic properties. ACE inhibitors impede the conversion of inactive angiotensin I to the active angiotensin II, and also inhibit the kininase enzyme which is involved in bradykinin degradation (Brown and Vaughan, 1998). Blockade of these systems has favourable effects on cardiac and vascular remodelling. As a result, there is arterial and venous dilatation, a slight drop in arterial blood pressure, and improved renal blood flow.

In patients with HFrEF, ACE inhibitors significantly improve survival, reduce hospitalisations, relieve symptoms and slow the progression of the disease (Swedberg and Kjeksus, 1988; Cohn et al., 1991; Yusuf et al., 1991). Additionally, randomised controlled trials have demonstrated increased survival with ACE inhibitors in patients who develop systolic dysfunction following an MI (Pfeffer et al., 1992; Julian et al., 1993; Kober et al., 1995).

The benefits of ACE inhibitors have been demonstrated in HFrEF and LV systolic dysfunction (LVSD) without symptoms. Consequently all patients with any grade of LVSD should be initiated on low dose ACE inhibitor therapy and up-titrated to the maximum tolerated dose to achieve inhibition of the RAAS (NICE, 2018). Possible side effects include cough, hypotension, and renal function impairment.

2.7.2.3 Adrenergic receptor antagonists (β -blockers)

The sympathetic nervous system is chronically overactive in HFrEF, which leads to increased heart rate and energy demands, adverse remodelling, interstitial fibrosis, arrhythmia provocation and stimulation of RAAS activation. Inhibition of adrenergic activity with the use of β -blockers is associated with reduction of all these effects. Chronic β -blocker therapy improves LV remodelling, reduces risk of hospitalisation, and improves survival (Triposkiadis et al., 2009; Bristow, 2011; Chatterjee, S. et al., 2013).

In patients with symptomatic HFrEF due to LVSD, β -blockers reduce mortality and morbidity, in addition to ACE inhibitors and diuretic therapy (Hjalmarson et al., 2000; Packer et al., 2002).

β -blockers should be introduced at a low dose and gradually up-titrated to the maximum tolerated dose, with regular monitoring of both heart rate and blood pressure for hypotension and bradycardia (NICE, 2018). Adverse effects of β -blocker use include symptomatic hypotension, bradycardia, and fatigue.

2.7.2.4 Mineralocorticoid/aldosterone receptor antagonists

Spirolactone and eplerenone are MRAs that block the receptors binding aldosterone and other steroid hormone receptors. Resulting in reduced salt and water retention, MRAs are recommended in all symptomatic patients with HFrEF and LVEF $\leq 35\%$. In conjunction with ACE inhibitors and β -blockers, MRAs reduce mortality and HFrEF

hospitalisation (Pitt et al., 1999; Pitt et al., 2003; Zannad et al., 2011). Treatment should be initiated at low doses with careful monitoring of serum potassium and renal function. The main side effects related to aldosterone antagonists are hyperkalaemia and gynaecomastia (Pazos-Lopez et al., 2011).

2.7.2.5 Angiotensin II type I receptor blockers

Despite treatment with currently recommended drugs, the actions of angiotensin II may contribute to the progression of HFrEF through increased impedance of LV emptying, adverse long term structural effects on the cardiovascular system, and the adverse effects of activation of other neuro-hormonal agonists (Cohn and Tognoni, 2001). Angiotensin II type I receptor blockers (ARBs) are recommended as an alternative therapy in those HFrEF patients who are intolerant of an ACE inhibitor, due, for example to cough or angio-neurotic oedema (Maggioni et al., 2002). Candesartan has been shown to reduce cardiovascular mortality in a randomised controlled trial (Granger et al., 2003), and valsartan showed a reduction in HFrEF hospitalisations in heart failure patients with LVSD and taking an ACE inhibitor (Cohn and Tognoni, 2001). However, combined ACE inhibitor/ARB therapy in HFrEF, which can lead to marked hyperkalaemia, is only recommended where other therapies are contraindicated or not tolerated. Combined ACE inhibitor/ARB should only be considered in patients with symptomatic HFrEF, receiving a β -blocker and intolerant of an MRA, and must be used under strict supervision because of the risk of serious side effects (Ponikowski et al., 2016)

2.7.2.6 Angiotensin receptor neprilysin inhibitor

Angiotensin receptor neprilysin inhibitors (ARNi) are a new class of therapeutic agents that have been developed to act on the RAAS and the neutral endopeptidase system. Sacubitril valsartan, a combination of valsartan (an angiotensin receptor blocker) and sacubitril (a neprilysin inhibitor), results in increasing levels of natriuretic peptides that counterbalance high circulating levels of neuro-hormones in HFrEF. Increased levels of A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) enhances diuresis, natriuresis, and myocardial relaxation, while reducing myocardial hypertrophy. Renin and aldosterone secretion are also inhibited by ANP and BNP. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention, and cardiac hypertrophy (King et al., 2015).

Sacubitril valsartan has been found to be superior to ACE inhibition alone in reducing the risks of death and of hospitalisation for HFrEF (McMurray, J. et al., 2014).

2.7.2.7 I_f -channel inhibitor

Ivabradine specifically inhibits the I_f current in the sinoatrial node and slows the heart rate without altering: myocardial contractility, the cardiac conduction system or coronary vascular resistance (Fox, 2006). Because of its specific action on the sinus node it is only effective in patients in sinus rhythm (Ponikowski et al., 2016). Ivabradine reduced the combined endpoint of mortality or hospitalisation for patients with symptomatic heart failure and LVEF $\leq 35\%$, with a heart rate of ≥ 70 beats per minute (bpm) in sinus rhythm, hospitalised for heart failure within the previous 12 months, and already on maximally tolerated doses of β -blocker, and ACE inhibitor (or ARB) and an

MRA (Swedberg et al., 2010). Ivabradine is approved for use in patients with HFrEF, LVEF $\leq 35\%$, in sinus rhythm with a resting heart rate ≥ 75 bpm, because of the survival benefit based on a subgroup analysis (Bohm et al., 2013; Ponikowski et al., 2016).

2.7.2.8 Digoxin

As noted in 1.2.4, digoxin (digitalis) has been used for over 200 years in the treatment of heart failure. With its mild inotropic and diuretic properties, digoxin moderates neuro-endocrine function and slows atrio-ventricular conduction (Pazos-Lopez et al., 2011). It is predominantly used in HFrEF to modulate ventricular rate in patients in AF, but only when other available treatments are not an option (Ponikowski et al., 2016). However, a recent meta-analysis confirmed that digoxin use is associated with an increased mortality risk in AF, and in heart failure patients treated according to contemporary guidelines, and suggests that until results of randomised placebo controlled trials become available, digoxin should be used with great caution (Vamos et al., 2019).

2.7.2.9 Anti-arrhythmic agents

Heart failure patients, particularly with an ischaemic aetiology, are at increased risk of ventricular tachyarrhythmia and sudden cardiac death (Cleland et al., 2002). However, anti-arrhythmic agents, other than β -blockers, do not improve survival in HFrEF (Ponikowski et al., 2016). This is probably because a ventricular arrhythmia most frequently represents a serious HFrEF problem that is not reversed by treatments targeting the arrhythmia.

2.7.3 Cardiac implantable electronic devices

Cardiac implantable electronic devices (CIEDs) have become a central feature of the management of HFrEF over the last 20 years. Beyond treatment of bradycardia, there are two main approaches to pacemaker therapy with considerable overlap of indications. Despite widespread acceptance of their benefits and excellent trials supporting their use, pacemaker devices remain underused in the HFrEF population (Lund et al., 2017).

2.7.3.1 Implantable cardioverter-defibrillator

Around 40% of patients with heart failure suffer sudden or unexplained death (Poole-Wilson et al., 2003b). This may be as a result of bradyarrhythmia or tachyarrhythmia, but may also be due to coronary, vascular or cerebrovascular episodes (Gatzoulis et al., 2017). Treatments to improve, or delay the progression of cardiovascular disease, can reduce the incidence of sudden cardiac death, but will not treat arrhythmic events as they occur. Anti-arrhythmic medications can reduce the frequency and burden of tachyarrhythmia, but as mentioned above, can worsen overall mortality (Ponikowski et al., 2016). However, implantable cardioverter-defibrillators (ICD) may reduce the risk of sudden cardiac death due to severe ventricular arrhythmias, either by anti-tachycardia pacing or delivering a shock to terminate ventricular tachycardia or ventricular fibrillation.

2.7.3.2 Cardiac resynchronisation therapy

Around one third of patients with HFrEF have some degree of intraventricular conduction delay, which may worsen LVSD (Cazeau et al., 2001). Cardiac

resynchronisation therapy (CRT) is a form of pacemaker therapy that aims to improve the coordination of cardiac contraction. A ventricular electrode is placed in the right ventricular (RV) apex, or on the RV septum, and a further electrode is positioned to stimulate the LV free wall (Kirk and Kass, 2013). By pacing through both electrodes simultaneously, it is possible to improve conduction timing, which can reduce dyssynchrony and improve cardiac output (Cleland et al., 2005). Current ESC guidelines (Table 2.3) recommend consideration of CRT in patients with LVEF <35% and QRS duration ≥ 150 milliseconds (msec) (Ponikowski et al., 2016).

CRT has been shown to improve symptoms and quality of life, and to reduce hospitalisation rates, morbidity and mortality in HFrEF (Cazeau et al., 2001; Abraham et al., 2002; Bristow et al., 2004; Cleland et al., 2005). However, implantation of CRT in patients who do not have LV dyssynchrony may be detrimental (Auger et al., 2012).

Table 2.3 Current ESC guidelines for CRT implantation

Recommendations	Class^a	Level^b
CRT is recommended for symptomatic HF _r EF patients in SR with a QRS duration ≥150 msec and LBBB QRS morphology with LVEF ≤35% despite OMT to improve symptoms and reduce morbidity and mortality.	I	A
CRT should be considered for symptomatic HF _r EF patients in SR with a QRS duration ≥150 msec and non-LBBB QRS morphology with LVEF ≤35% despite OMT to improve symptoms and reduce morbidity and mortality.	IIa	B
CRT is recommended for symptomatic HF _r EF patients in SR with a QRS duration of 130-149 msec and LBBB QRS morphology with LVEF ≤35% despite OMT to improve symptoms and reduce morbidity and mortality.	I	B
CRT may be considered for symptomatic HF _r EF patients in SR with a QRS duration of 130-149 msec and non-LBBB QRS morphology with LVEF ≤35% despite OMT to improve symptoms and reduce morbidity and mortality.	IIb	B
CRT rather than RV pacing is recommended for patients with HF _r EF regardless of NYHA Class, in SR or AF, with an indication for ventricular pacing and high degree AV block to reduce morbidity.	I	A
CRT should be considered for patients with LVEF ≤35% in NYHA Class III-IV despite OMT to improve symptoms and reduce morbidity and mortality if they are in AF and have a QRS duration ≥130 msec and good rate control to ensure bi-ventricular capture is in place or the patient is expected to return to SR.	IIa	B
Patients with HF _r EF who have received an RV pacemaker or ICD and develop worsening HF despite OMT with a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF _r EF.	IIb	B
CRT is contra-indicated in patients with a QRS duration <130 msec.	III	A
<p>AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronisation therapy; HF_rEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; msec = millisecond; NYHA = New York Heart Association; OMT = optimal medical therapy; RV = right ventricular; SR = sinus rhythm.</p> <p>^aClass of recommendation ^bLevel of evidence</p>		

2.7.3.3 Remote monitoring

Remote monitoring of pacemaker devices offers an opportunity to improve device follow-up efficiency. The ability to monitor technical function and disease-specific parameters allows the potential to modify disease progression in HF_rEF patients (Braunschweig et al., 2019), and the possibility of detecting decompensation earlier. Wireless, automated remote monitoring systems download patient data from the device using radio transmissions to communicate with a base station located in the

patient's home. The system can be programmed to transmit data at regular intervals, which has the advantage of reducing in-person device follow-up appointments. Additionally, the system can be set to transmit if specifically programmed triggers are activated.

Remote monitoring is standard in many cardiac centres for device function and safety reasons. The potential of remote monitoring, whilst thought to be significant (Brahmbhatt and Cowie, 2019), has not been shown to be consistent in large scale randomised controlled trials (Morgan et al., 2017). However, during the coronavirus disease 2019 pandemic, in-person follow-up of pacemaker devices was significantly affected. This has resulted in widespread increase in the use of remote monitoring for pacemaker devices (Varma et al., 2020).

2.7.4 Surgical treatment

Surgical treatment options for end-stage heart failure are limited. Heart transplantation is considered the gold standard treatment for eligible symptomatic patients with end-stage HFrEF (Patel et al., 2016). However, with a limited donor pool of hearts for the increasing number of patients requiring cardiac transplantation, other methods have been investigated.

Left ventricular assist devices can improve myocardial contractility and reverse remodelling. These devices are used for short term survival benefits, either as a bridge to transplant or as a destination therapy, where transplantation is contraindicated and prognosis is poor (Marinescu et al., 2017).

2.8 Acute heart failure

Acute heart failure refers to a rapid onset or a worsening of symptoms and/or signs of heart failure (Braunwald, 2013). It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospitalisation (Ponikowski et al., 2016). It may present as new onset of HFrEF, but most admissions with heart failure are acute decompensations of HFrEF. Whilst decompensation of HFrEF can occur without precipitant factors, it usually presents due to one or more factors, for example: infection, anaemia, uncontrolled hypertension, rhythm disturbances or non-adherence with medication or diet.

2.9 Right heart failure

Since the circulation is a closed system, the failure of one ventricle deleteriously affects the performance of the other. Right heart failure is a clinical syndrome with signs and symptoms of heart failure resulting from RV dysfunction, and is caused by the inability of the RV to support optimal circulation in the presence of adequate preload (Konstam et al., 2018).

Acute right heart failure can occur as a result of abruptly increased RV afterload, due to, for example, pulmonary embolus, hypoxia, or acidaemia, or to the decreased RV contractility that might occur with RV ischemia, myocarditis, or post-cardiotomy shock. On the other hand, chronic right heart failure most commonly occurs as a result of the gradual increases in RV afterload caused by pulmonary hypertension, which in turn, is most frequently a result of left heart failure (Ibrahim, 2016).

2.10 Conclusion

Since it is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality (Ponikowski et al., 2016), for pragmatic reasons my thesis will focus on those patients with symptoms that are predominantly due to HFrEF, and with objective evidence of LVSD.

Despite improvements in patient outcomes due to advances in the treatment and management of HFrEF, the prognosis of patients with HFrEF remains poor. The development of new therapeutic pathways for these patients remains a priority.

Chapter 3 : Heart rate in heart failure

Heart rate is the primary assessment in almost all interactions between healthcare providers and their patients, especially those patients with cardiovascular disease. Far from being simply a measure of the effect of diseases and drugs on the heart, it is appreciated that heart rate itself is a critical contributor to both symptoms and progression of cardiovascular disease.

In the 1870s, Henry Pickering Bowditch recognised that the force of contraction of cardiac muscle is dependent on the rate and rhythm of the heartbeat (Noble, 1992). Initially known as the Treppe (staircase) effect, and more recently described as the force-frequency relationship, chapter 3 will explore this critical mechanism, how it could be influenced by cardiovascular disease, and how it might be relevant in contemporary patients.

3.1 Introduction

Exercise requires an increase in delivery of oxygen and heightened removal of carbon dioxide and other waste products, therefore demanding greater cardiac output. In health, cardiac output increases during exercise through rises in both stroke volume (the amount of blood ejected with each heart beat) and heart rate (the number of times per minute that the heart beats) (Camm and Fei, 1996). The key feature of heart failure with reduced ejection fraction (HFrEF) is reduced exercise tolerance, one of the main

contributors to this is thought to be reduced cardiac output during activity (Camm and Fei, 1996; Stahlberg et al., 2011; MacIver and Dayer, 2012). However, resting left ventricular (LV) function is poorly related to exercise capacity (Clark et al., 1996). Since exercise intolerance experienced by patients with HFrEF leads to significant and persistent impairment of quality of life, this is an important area to address.

3.2 Cardiac output

Cardiac output is an important indicator of cardiac function, and is the product of heart rate and stroke volume according to the simple yet important equation:

$$\text{Heart Rate} \times \text{Stroke Volume} = \text{Cardiac Output}$$

Normally, during exercise, cardiac output increases to meet the requirements of metabolic demand. This increase is brought about through changes in both heart rate and stroke volume (Cooper and Storer, 2001).

Since cardiac output is a function of heart rate and stroke volume, it is possible that poor heart rate rise during exercise could contribute to reduced exercise capacity. However, the relationship between heart rate rise on exercise, cardiac output, and exercise capacity, in addition to how their interaction changes with age, sex, fitness and disease, is poorly understood. Furthermore, after over 80 years of research there is no clear 'target' heart rate in healthy adults (Tanaka et al., 2001).

3.3 Stroke volume

Stroke volume is the quantity of blood ejected from the LV into the aorta with each heartbeat, and is dependent on preload, contractile force, and afterload. Preload is determined by LV cavity pressure and volume at the end of diastole, such that increasing end-diastolic volume results in an increased stroke volume. Afterload is determined by the LV cavity pressure and volume during systole, and is the resistance to ejection during each ventricular contraction. Increased resistance results in a decreased stroke volume.

3.3.1 Stroke volume enhancement

As the heart rate rises during exercise, enhancement in the LV stroke volume results from increased LV filling, and from decreased LV systolic volume due to greater LV contractility. The increased LV contractility comes largely from three mechanisms. The most appreciated are the enhancement of contractility through adrenergic mechanisms and the cardiac contractility regulation known as the length-tension relationship, or Frank-Starling mechanism (Noble, 1992) through increased LV diastolic volume (representing stretch of the cardiomyocytes fibres) (Higginbotham et al., 1986; Vella and Robergs, 2005).

On the other hand, despite its crucial importance during exercise, the intrinsic capacity of the heart to increase the strength of contraction in response to an increase in contraction frequency (or heart rate), variably known as the force-frequency relationship, Bowditch effect, Treppe phenomenon or staircase phenomenon, has been paid little attention relative to the other fundamental physiological mechanisms.

3.4 Heart rate

3.4.1 Resting heart rate

As HFrEF progresses, the resting heart rate becomes increasingly elevated, which is associated with reduced cardiac efficiency, increased myocardial oxygen demands, and furthermore, represents a risk-marker (Nikolovska Vukadinović et al., 2017). In a sub-analysis of a randomised controlled trial, investigators tested the hypothesis that elevated resting heart rate at baseline, is a marker for subsequent cardiovascular death and morbidity. The investigators found a 34% increased risk of cardiovascular death in patients with impaired LV function following myocardial infarction, and a 53% increase in hospitalisation at a heart rate of >70 beats per minute (bpm) compared with those with a lower heart rate. Each 5 bpm increase in heart rate was associated with increased cardiovascular death by 8%, and increased HFrEF hospitalisation by 16% (Fox et al., 2008). Böhm et al. reported that in HFrEF, cardiovascular death is higher at rates >75 bpm, and HFrEF hospitalisation risk is elevated at rates >70 bpm (Böhm et al., 2010). DeVore et al. reported that despite broad use of beta-adrenoceptor antagonists (β -blocker), a heart rate ≥ 70 bpm was observed in 73% of HFrEF patients and was associated with worse 1-year outcomes, although the authors were not able to provide information about the actual dose of β -blocker (DeVore et al., 2016).

Large randomised trials have shown that β -blockers improve morbidity and mortality in patients with HFrEF (CIBIS-II, 1999; MERIT-HF, 1999; Poole-Wilson et al., 2003a). However, despite the burden of evidence showing that pharmacological treatment to lower the resting heart rate may improve both mortality and morbidity (Flannery et al.,

2008; Fiuzat et al., 2012), and that heart rate reduction should be a pivotal treatment target in HFrEF (Hori and Okamoto, 2012), there is a failure to achieve recommended doses in a large proportion of patients (Maggioni et al., 2010). This may be due to contraindications or intolerance, however, there is also a concern that lowering the resting heart rate could induce exercise intolerance and symptomatic bradycardia, thereby increasing symptoms of breathlessness and fatigue.

3.4.2 Heart rate during exercise

In adults with normal heart function, the heart rate rises steadily with increasing work, to a peak that is generally accepted to be inversely related to age. Key features of HFrEF thought to contribute to exercise intolerance are reductions in peak heart rate, LV contractility and cardiac output, during activity.

The relevance of peak heart rate on exercise has become particularly challenging since the advent of heart rate limitation as a key target of HFrEF therapy. The belief that limited heart rate rise during exercise, known as chronotropic incompetence, is a contributor to exercise intolerance in HFrEF (Al-Najjar et al., 2012; Brubaker and Kitzman, 2013) has been countered by observational and interventional data (Jamil et al., 2016; Chatterjee, N.A. and Heist, 2018).

3.4.3 Chronotropic incompetence

The 'Åstrand formula' of 220 bpm minus age, is the most frequently used benchmark to determine target peak heart rate (Robergs and Landwehr, 2002). The inability of the heart rate to increase in proportion to the level of physical exertion or metabolic

demand, known as chronotropic incompetence, is commonly found in HFrEF patients. Chronotropic incompetence is defined as either an inability of the peak heart rate to reach an arbitrary percentage (usually 80%) of the age-predicted maximum, or a reduction in the ratio of heart rate reserve to metabolic reserve, where a ratio <0.8 indicates chronotropic incompetence, irrespective of age, fitness, or functional capacity. However, these cut-offs are based upon small-scale observational studies of generally healthy people performing symptom-limited exercise tests.

The heart rate-response, or rate-adaptive, pacemaker function was developed in an attempt to optimise exercise tolerance in patients with chronotropic incompetence (Alt et al., 1995). Currently, no guidelines exist that offer advice on the programming of peak heart rate; generally, the formula of 220 bpm minus age is used. However, this does not consider the condition of the patient. Whilst heart rate-response pacing in people without HFrEF is associated with an increase in cardiac output during exercise (McMeekin et al., 1990), and better quality of life (Oto et al., 1991), using pacemakers to increase the peak heart rate in HFrEF has been shown to worsen both prognosis and cardiac function (Nägele, H. et al., 2008).

3.4.4 Heart rate and exercise capacity in HFrEF

Heart rate contributes to cardiac output, which plays a key role in determining exercise capacity (Clark et al., 1996). Although no conclusive evidence exists in the literature, of benefit to exercise time or quality of life in HFrEF through either increasing the mean and peak heart rate with rate-response pacing, or programming the rate-response function off (Jamil et al., 2016), the standard age-related rate-response algorithm of

220 bpm minus age is the only guidance currently available. How this guidance is used in clinical practice remains unknown.

Thus, the paradox, where medical therapy to reduce heart rate is proven and applied, but where pacemaker patients with HFrEF may be subjected to higher mean heart rates by the use of an unproven rate-response algorithm, suggests that a therapeutic opportunity is being missed, or perhaps even that harm is being done. Furthermore, this inconsistency potentially contributes to poorly defined heart rate targets in guidelines (Ponikowski et al., 2016), and low rates of achievement of optimal β -blocker doses in those with and without pacemaker devices (Fowler et al., 2007; Greene et al., 2019).

Moreover, there has been conflicting evidence as to whether chronotropic incompetence contributes to, or is the result of, the reduced exercise capacity that is characteristic of worsening HFrEF (Witte, K. K. and Clark, 2009).

In a study of 278 patients with stable HFrEF, on optimal medical therapy, a significant proportion of participants had chronotropic incompetence, which was associated with lower exercise capacity (Jorde et al., 2008). In a further study, looking at the relationship between the presence of chronotropic incompetence and mortality in an unselected cohort of 411 patients with HFrEF who underwent cardiopulmonary exercise testing, chronotropic incompetence was present in 42% of the study population. This was associated with significantly lower exercise time and peak oxygen consumption (millilitres per kilogram per minute (ml/kg/min)). There was

however no association between chronotropic incompetence and mortality (Al-Najjar et al., 2012).

Conversely, in a study looking at heart rate response to exercise in HFrEF, no significant difference in resting heart rate, age, maximal oxygen consumption achieved, or LV ejection fraction (LVEF) was demonstrated between those patients with and without chronotropic incompetence (Roche et al., 2001). Using a treadmill-based symptom-limited exercise protocol and gas exchange analysis, Clark et al. studied 57 participants with HFrEF (mean LVEF 30%) and 14 controls. In the HFrEF group, peak oxygen consumption was significantly reduced (19.6 (standard deviation (SD) \pm 7.6) versus (vs) 35.0 (\pm 9.9) ml/kg/min; $p < 0.001$), additionally there was a correlation between peak heart rate and heart rate rise with peak oxygen consumption ($r=0.47, 0.59$; $p < 0.001$). However no difference was seen in peak oxygen consumption or exercise time between those with chronotropic incompetence (defined as peak heart rate $< 80\%$ age predicted maximum; $n=16$) and those without chronotropic incompetence (Clark and Coats, 1995).

This was further investigated by Witte et al. in a study comprising controls ($n=9$) and patients with HFrEF ($n=11$) undertaking submaximal exercise testing at set proportions of maximal previously identified workloads (15%, 25%, 50%). The workload/heart rate ratio during the peak tests was found to be lower in patients than control subjects. In addition, although a relationship between heart rate and workload for control subjects was found ($r = 0.85$; $p < 0.0001$), no such relationship was found in patients with HFrEF ($r = 0.003$; $p = 0.98$). Despite a lower peak heart rate, patients with

HFrEF have a greater heart rate for a given workload during submaximal testing. The authors suggested that heart rate limitation is unlikely to be the cause of exercise intolerance in HFrEF patients (Witte, K. K. and Clark, 2009).

Heart rate response to exercise was investigated in 237 HFrEF patients and 118 controls, to establish the prevalence of chronotropic incompetence in patients with HFrEF and the effects of intrinsic or β -blocker induced chronotropic incompetence on exercise capacity (Witte, K. K. et al., 2006). The data demonstrated that patients taking β -blockers had significantly lower peak heart rates and more chronotropic incompetence than those not taking β -blockers, but that there was no overall difference in peak oxygen consumption despite a longer exercise time (498 vs 435 seconds; $p=0.02$). This higher exercise time despite lower heart rate is especially interesting, since it implies either an improvement in metabolic efficiency with β -blockers, or that the higher heart rate could be somehow detrimental to exercise capacity.

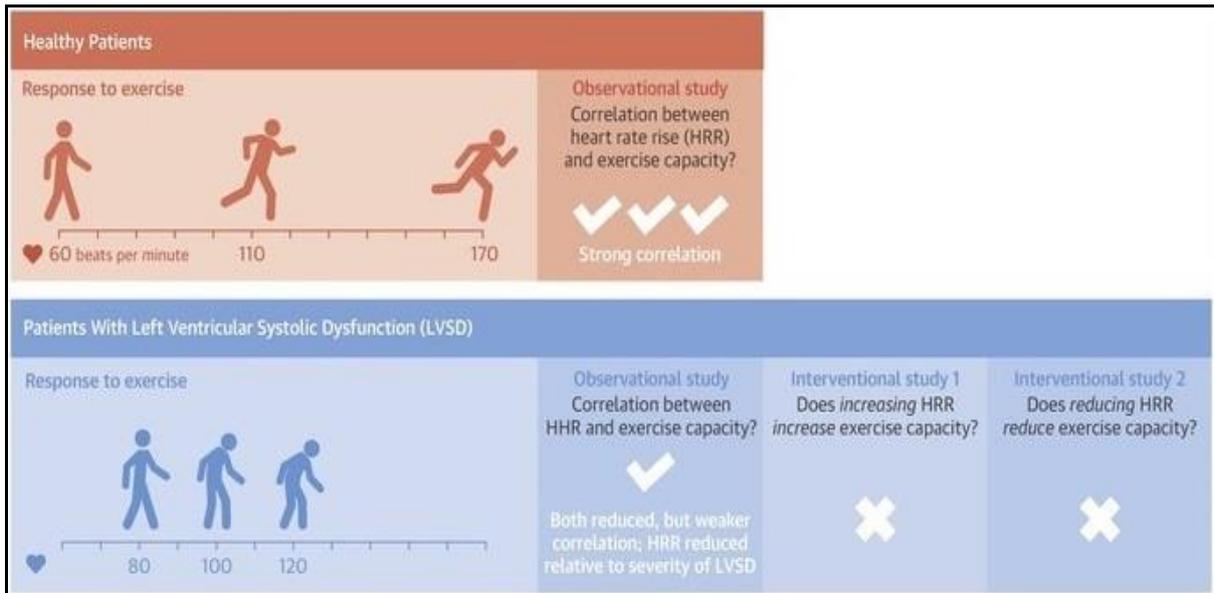


Figure 3.1: The relationship between heart rate rise and exercise capacity (Jamil et al., 2016)

In a series of randomised, placebo-controlled, double-blind studies, seeking to clarify the role of heart rate on exercise capacity in HFrEF, Jamil et al. reported a weaker association between exercise capacity and heart rate rise in severe HFrEF compared to controls; increasing heart rate rise using rate-response pacing (versus fixed-rate pacing) in unselected patients with HFrEF did not improve peak exercise capacity; furthermore, acutely lowering resting heart rate and peak heart rate using ivabradine did not result in worsening exercise capacity (Figure 3.1) (Jamil et al., 2016). These studies set the scene for an exploration of the mechanisms of a failure of patients with HFrEF to benefit from higher heart rates.

3.5 Force-frequency relationship

The depolarisation-rate dependent mechanism, where increases in heart rate lead to increases in the force of contraction, is variably known as the Bowditch effect, Treppe

phenomenon, or the force-frequency relationship (Bowditch, 1871). This frequency-dependent up-regulation of cardiac contractility is rapid and intrinsic to the myocardial cell, with no external involvement from neuronal or hormonal controls.

Cardiac contractility is the intrinsic capacity of cardiomyocytes to generate contractile force at a specific heart rate, independent of preload and afterload. Whilst the force-frequency relationship in the assessment of contractility has been used in studies of isolated strips of failing myocardium, and widely in animal models of heart failure, there has been no translation of the approach to clinical practice. To assess the cardiac contractility in vivo presents challenges that I shall outline, and although clinical research studies have to some extent overcome these technical issues (Bombardini, T et al., 2013), the lack of clinical utility has been a key limitation to moving the assessment to the clinical arena.

Formative work on the force-frequency relationship was descriptive. It was not until the latter decades of the 20th century that data on the cellular physiology of the force-frequency relationship arose to enhance our understanding of this important, intrinsic biological mechanism.

3.5.1 Discovery of the force-frequency relationship

The first account of the force-frequency relationship, was made in 1871 by Henry Pickering Bowditch (1840-1911), an American soldier, physician, physiologist, and dean of the Harvard Medical School (Bowditch, 1871; Bruce Fye, 1994). Known for his research on cardiac contractility and nerve conduction, Bowditch's work on the

force-frequency relationship and the 'all or nothing' principle of cardiac muscle contraction, are his most recognised within cardiovascular physiology.

Bowditch described that the contractile force of the frog heart increases as the heart rate rises (Janssen and Periasamy, 2007). Pioneering experiments were designed to study how the excitation process of the heart fatigues and recovers. By filling the isolated ventricle of an excised frog heart with fluids of variable composition, the strength of contraction could be determined by the degree of fluid movement in a manometer following ventricular contraction induced by external electrical stimulation.

Using this laboratory arrangement, Bowditch discovered that: a sufficient degree of stimulus strength is required to elicit a cardiac contraction, a prolonged period of stimulation and subsequent cardiac contraction reduces cardiac contractility (which Bowditch described as fatigue), and that pressure increased as the interval between stimuli decreased, but that at the shortest intervals pressure again declined. It was this last discovery that Bowditch named the 'staircase' or 'Treppe' phenomenon, writing:

'The interval between a contraction of the heart and the preceding beat is of such importance for the strength of contractility that the study of this effect is a prime necessity' (Bowditch, 1871).

In the early 1900s, Robert S. Woodworth (1869-1962), was able to identify that the Treppe phenomenon existed in mammalian as well as amphibian hearts. Woodworth also explored the force of cardiac contraction following different stimulation periods. He was able to demonstrate that the force of contraction diminished following a

shortened interval after the previous contraction (simulating an extra-systole), and that the force of the contraction following this was increased (post-extra-systolic potentiation). Subsequently, many investigations using isolated strips of myocardium have been published, but with no real understanding of the cellular physiology underpinning the force-frequency relationship (Cattell and Gold, 1938; Koch-Weser and Blinks, 1963).

The first half of the 20th century saw cardiovascular research being dominated by Starling's law of the heart. However, the realisation that cardiac rhythm and cardiac contraction influence each other through electro-mechanical coupling allowed Bowditch's findings to be re-discovered. Prompted, in part, by the development of cardiac pacemaker systems to alter heart rhythms in the treatment of cardiac arrhythmias, renewed interest was shown in the relationship between interval and developed force (Noble, 1992).

3.5.2 Development of the assessment of cardiac contractility

Efforts have been made to transfer the experimental methods of assessing contractility in isolated strips of myocardium, to the intact beating heart by measuring pressure/volume loops in animal models (Suga et al., 1973; Suga and Sagawa, 1974). The results of a study carried out in humans were found to be consistent with animal studies, and supported the potential usefulness of the end-systolic pressure/volume relationship as an index of myocardial contractile state in man (Grossman, W et al., 1977). This highlighted the need for further research, especially investigating non-

invasive methods to assess cardiac contractility using the force-frequency relationship.

In animal models, it has been shown that LV contractility could be indexed by end-systolic elastance (Kono et al., 1984; Chantler et al., 2008). End-systolic elastance is the slope of the end-systolic pressure volume relationship (ESPVR) and has also been measured in humans from pressure-volume loops acquired during cardiac catheterisation, as an index for assessing cardiac contractility at rest in the intact circulation (Shishido et al., 2000; Bombardini, T., 2005a). However, the invasive nature and the technical difficulties involved in measuring this index prevent its widespread clinical acceptance (Shishido et al., 2000) (Chantler et al., 2008).

A more practical non-invasive evaluation of the LV end-systolic pressure/volume ratio was first proposed by Sagawa and Suga, who reported that LV dimensions measured via ultrasound could be substituted for LV volume. They also suggested that peak carotid pressure could be substituted for end-systolic LV pressure (Sagawa et al., 1977). Further work has demonstrated that systolic blood pressure obtained using a manual sphygmomanometer and a standard stethoscope can be used as a surrogate for LV end-systolic pressure, due to their close approximation (Slutsky et al., 1980; Ginzton et al., 1984; Bombardini, T. et al., 2003)

Assessment of LV contractility requires: the measurement of left ventricular end-systolic pressure (LVESP), a measure of LV end-systolic volume (LVESV) indexed for body surface area (LVESVi), and a method by which to increase the heart rate in a

stepwise manner. Dividing LVESP by LVESVi gives a surrogate of LV contractility, which has been validated against invasive methods (Bombardini, T. et al., 2003; Bombardini, T., 2005a).

The force-frequency relationship is defined as: up-sloping (or positive) when peak end-systolic pressure volume ratio is higher than the baseline and intermediate values, biphasic when there is an initial up-sloping followed by a down-sloping and peak end-systolic pressure volume ratio is lower than the intermediate values, and flat or negative when peak end-systolic pressure volume ratio is equal to or lower than the baseline values (Figure 3.2).

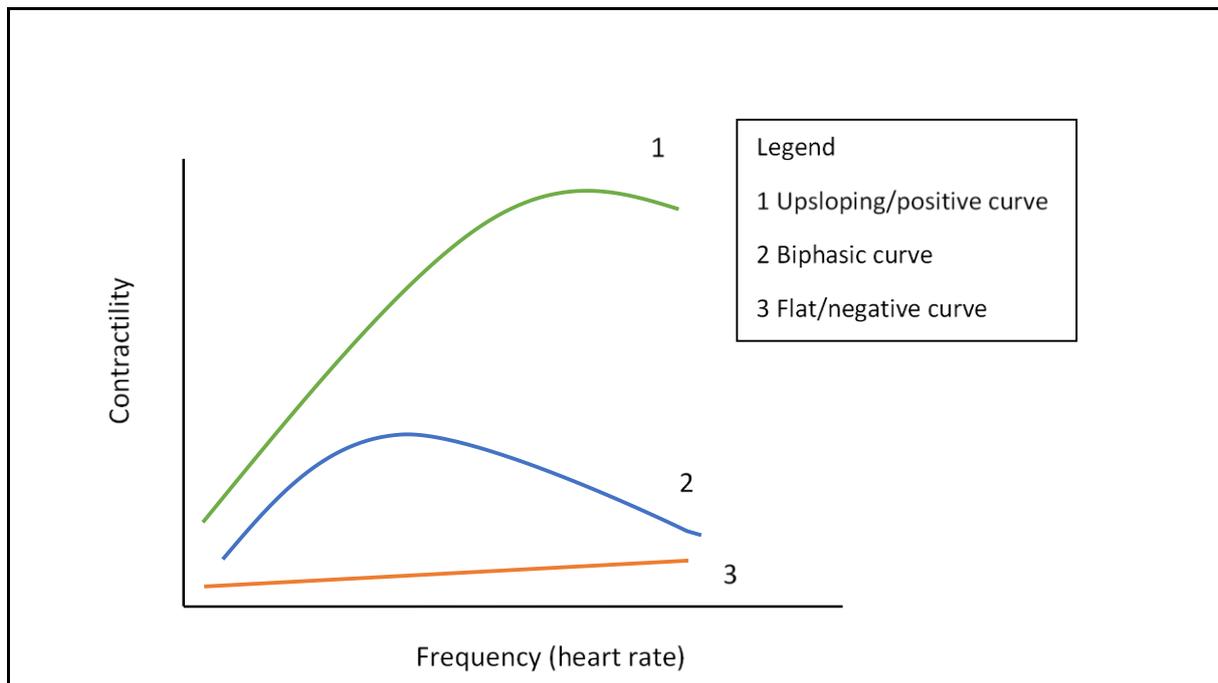


Figure 3.2: Force-frequency relationship curves

3.5.3 Mechanism

Whilst the molecular processes responsible for the regulation of cardiac force with an increase in heart rate are not completely understood, it is generally accepted that changes in calcium handling play a crucial role in the force-frequency relationship (Janssen and Periasamy, 2007; Balcazar et al., 2018).

In the 1960s it became apparent that movement of calcium ions (Ca^{2+}) on a cellular level was related to the change in force of cardiac contraction produced by varying contraction intervals, and that it was possible that the amount of Ca^{2+} released to activate contraction may relate to the degree of contraction (Noble, 1992). Evidence for this hypothesis was made available through work on radioactive Ca^{2+} myocardial cellular entry and exit, which demonstrated a rise in Ca^{2+} entry and exit during episodes of increased inotropy, such as an increase in stimulus frequency (Winegrad and Shanes, 1962; Langer and Brady, 1963; Noble, 1992). The importance of Ca^{2+} in the force of cardiac contraction was confirmed by the work of Allen and Blinks in 1978 with the first measurements of intracellular Ca^{2+} concentration. Allen and Blinks were able to show that the main inotropic interventions of: increased stimulation frequency, cardiac glycosides, catecholamines, and raised extra-cellular calcium concentration, all lead to an increase in systolic Ca^{2+} (Allen and Blinks, 1978).

Hence increased cardiac contractility depends upon increased concentrations of Ca^{2+} in cardiomyocytes (Eisner et al., 2017). In HFrEF there are several abnormalities of Ca^{2+} handling which lead, especially at higher heart rates, to: decreased Ca^{2+}

sensitivity, depletion of Ca^{2+} stores, and delayed diastolic Ca^{2+} removal, which contribute to the attenuated force-frequency relationship (Mulieri et al., 1992; Mishra et al., 2002).

Consequently, cardiomyocytes from HFrEF patients display a flatter slope in response to more rapid stimulation, and the peak of the curve (optimal cardiac contractility) occurs at lower frequencies than in non-HFrEF patients. This may contribute to functional limitation, and moreover has the potential to lead to further progression of LV systolic dysfunction, and consequently further progression of HFrEF.

3.5.4 Clinical relevance in HFrEF

In the normal heart, cardiac output is positively coupled to the power of LV contractility by the force-frequency relationship (Bowditch, 1871), such that, as heart rate increases (and diastolic filling time shortens), cardiac output and LV contractility increase. Thus, a positive force-frequency relationship prevents a reduction in stroke volume due to reduced filling at higher heart rates, which would significantly impair cardiac efficiency. In health, the force-frequency relationship can contribute up to 40% of the increase in cardiac output experienced during exercise (Higginbotham et al., 1986).

However, in HFrEF, this critical physiological response is attenuated (Cotton et al., 2001). It has been suggested that the degree of abnormality of the force-frequency relationship may be a biomarker of progression or regression of HFrEF (Cotton et al., 2001; Palomeque et al., 2004; Bondke et al., 2010). Furthermore, there is a decrease

in LV contractility above a certain heart rate, known as the *critical heart rate*. Whilst the heart rate might increase beyond the critical heart rate, cardiac contractility beyond this point decreases (Figure 3.3).

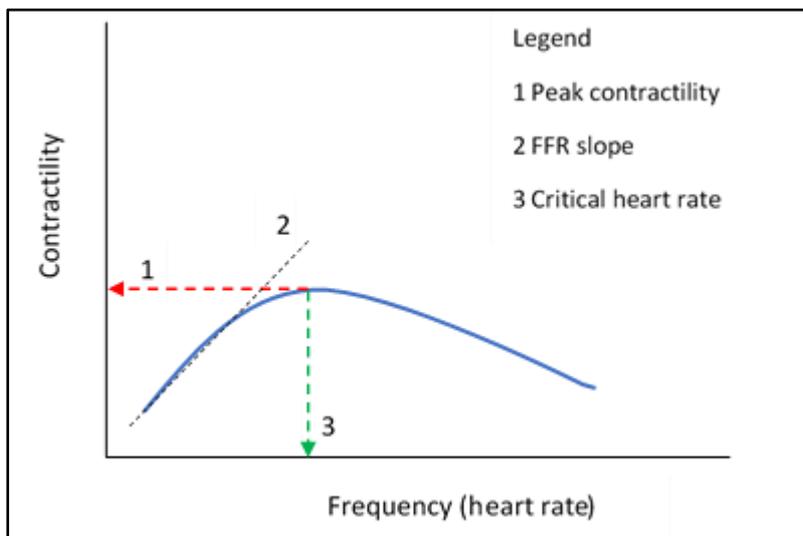


Figure 3.3: Force-frequency curve showing peak contractility, FFR slope, and critical heart rate

Therefore, the critical heart rate, as derived from the force-frequency relationship assessment, determines the heart rate at which cardiac contractility is optimal.

Subsequently, a fundamental feature in patients with HFrEF is an impaired force-frequency relationship, such that 'maximal' heart rate is not synonymous with 'optimal' heart rate. If the critical heart rate at which LV contractility begins to decline is at the level of resting heart rates, the response to increases in heart rate may be 'negative' not only during activity, but even over the entire range of heart rates.

Furthermore, any step over this 'critical heart rate' may contribute to functional limitation, and moreover has the potential to lead to further progression of the clinical syndrome of HFrEF.

3.6 Summary

Exercise intolerance is a key finding in patients with HFrEF. This is considered to be due to reduced cardiac output at rest, and impaired increase in cardiac output with exercise, resulting in lower oxygen consumption, exercise intolerance and fatigue. Cardiac output is dependent on heart rate and stroke volume. In patients with HFrEF, the heart rate rise during exercise is less than in controls doing the same proportion of peak exercise, known as chronotropic incompetence. Rate-response cardiac pacing was developed with the aim of improving exercise tolerance in patients with chronotropic incompetence. However, the use of rate-response pacing to increase peak heart rate in patients with HFrEF is associated with a worse prognosis and cardiac function (Nägele, H et al., 2008). Furthermore, heart rate limiting agents improve prognosis in HFrEF (Lechat et al., 2001; Poole-Wilson et al., 2003a).

The literature therefore highlights a critical conflict. A higher heart rate in HFrEF is associated with reduced cardiac efficiency and increased myocardial oxygen demand. Lowering the resting heart rate to improve mortality worsens heart rate rise and reduces the peak heart rate achieved. On the other hand, whilst using a pacemaker to treat chronotropic incompetence or reducing the dose of heart rate lowering medications will improve heart rate rise, this however, has a detrimental effect on overall survival and mortality. Moreover, although chronotropic incompetence in

HFrEF is associated with reduced functional capacity, correcting this in patients with HFrEF does not result in an improvement in oxygen consumption, symptoms, or exercise time.

Finally, the force-frequency relationship in HFrEF, linking heart rate, cardiac output, and cardiac contractility, is attenuated, such that cardiac contractility does not increase normally with increases in heart rate.

These observations lead to the conclusion that chronotropic incompetence does not cause the characteristic exercise intolerance seen in HFrEF, and the contrary concept that chronotropic incompetence could be a cardio-protective 'chronotropic adaptation'. Hence the question as to what the target heart rate should be, remains.

3.7 Conclusion

The focus of this thesis is to explore the relationship between heart rate and cardiac contractility, and the influence of HFrEF on this relationship. It will investigate the hypothesis that conventional rate-response, or rate-adaptive, algorithms do not take into account the altered force-frequency relationship in HFrEF, and that there may be a lower optimal heart rate range for cardiac contractility in HFrEF patients than in controls, and will present a personalised method of assessing this, and the clinical effects on exercise capacity of doing this.

Chapter 4 : Echocardiography

The heart, a dynamic cyclic pump, can respond to different loading conditions. Since it can respond and adapt to varying blood volumes and varying degrees of flow resistance, the ability to measure the changing characteristics and functional parameters of cardiac muscle is clinically relevant for assessing heart failure. Considered the most important advance in diagnostic cardiology since the discovery of X-rays by Röntgen (Roelandt, 2000), this chapter will explore the cardiovascular imaging modality of cardiac ultrasound.

4.1 Introduction

Transthoracic echocardiography, also known as cardiac ultrasound, has become an integral part of modern cardiology, providing information about the anatomy and physiology of the heart and great vessels, and is the most frequently used method for cardiac functional and structural assessment in patients with heart failure (Ponikowski et al., 2016; Omar et al., 2016). Echocardiography variables (for example, dimensions and ejection fraction) are incorporated into international guidelines as components of decision making in the management of heart failure, valve disease and arrhythmias. The critical benefits of echocardiography are that it is non-invasive, reproducible, inexpensive, portable, and easily repeatable.

4.2 History of echocardiography

The origin of ultrasound technology dates back to the discovery of the piezoelectric effect by Pierre and Jacques Curie in 1880. The use of ultrasound in medicine began in the 1940s, and specifically in cardiology, in the 1950s (Meyer, 2004).

In 1953, Hellmuth Hertz and Inge Edler modified a sonar device that they had borrowed from a local shipyard (Fraser, 2001) (Figure 4.1).



Figure 4.1: Hertz (left) and Edler and their modified sonar system
(Meyer, 2004)

They used their modified device to record images from Hertz's own heart, demonstrating the potential for ultrasound applications in cardiology. However, it was not until the early 1960s that this potential became more widely recognised (Houghton, 2013).

Work by Harvey Feigenbaum stimulated an interest in using ultrasound to examine the left ventricle (LV). This prompted the development of techniques for measuring LV wall thickness, LV internal dimension, and LV stroke volume (Edler and Lindström, 2004). Importantly, Feigenbaum recognised the relevance of training people (Feigenbaum, 2008), including non-physicians, in echocardiography (Figure 4.2). Indeed, the widespread use of echocardiography highlighted and reinforced the necessity for professional regulation, along with the use of published national and international guidelines to support evidence-based practice, and provide clear standards for performing echocardiograms (Wharton et al., 2015; Galderisi et al., 2017; Mitchell et al., 2019).



Figure 4.2: Harvey Feigenbaum (right) with an early M-Mode echocardiographic system, during his first training course

(Meyer, 2004)

Collaborations between engineers and physicians in the 1970s, resulted in the development of two-dimensional (2D) echocardiography (Feigenbaum, 1972), Doppler echocardiography (Goldberg, 1985), colour flow Doppler echocardiography (Kisslo, 1988) (although this was not widely used until the 1980s), and trans-oesophageal echocardiography (Meyer, 2004).

4.3 The cardiac cycle

The cardiac cycle describes the events that occur during each heartbeat, and echocardiography allows a visualisation of those events, allowing correlation of anatomic structures with their physiological functions (Brunner et al., 1995). A cardiac

cycle comprises four phases (Figure 4.3). Whilst the phases apply to both left and right heart, this brief review will concentrate on the left heart. Phases one and two correspond with LV systole; phases three and four correspond with LV diastole.

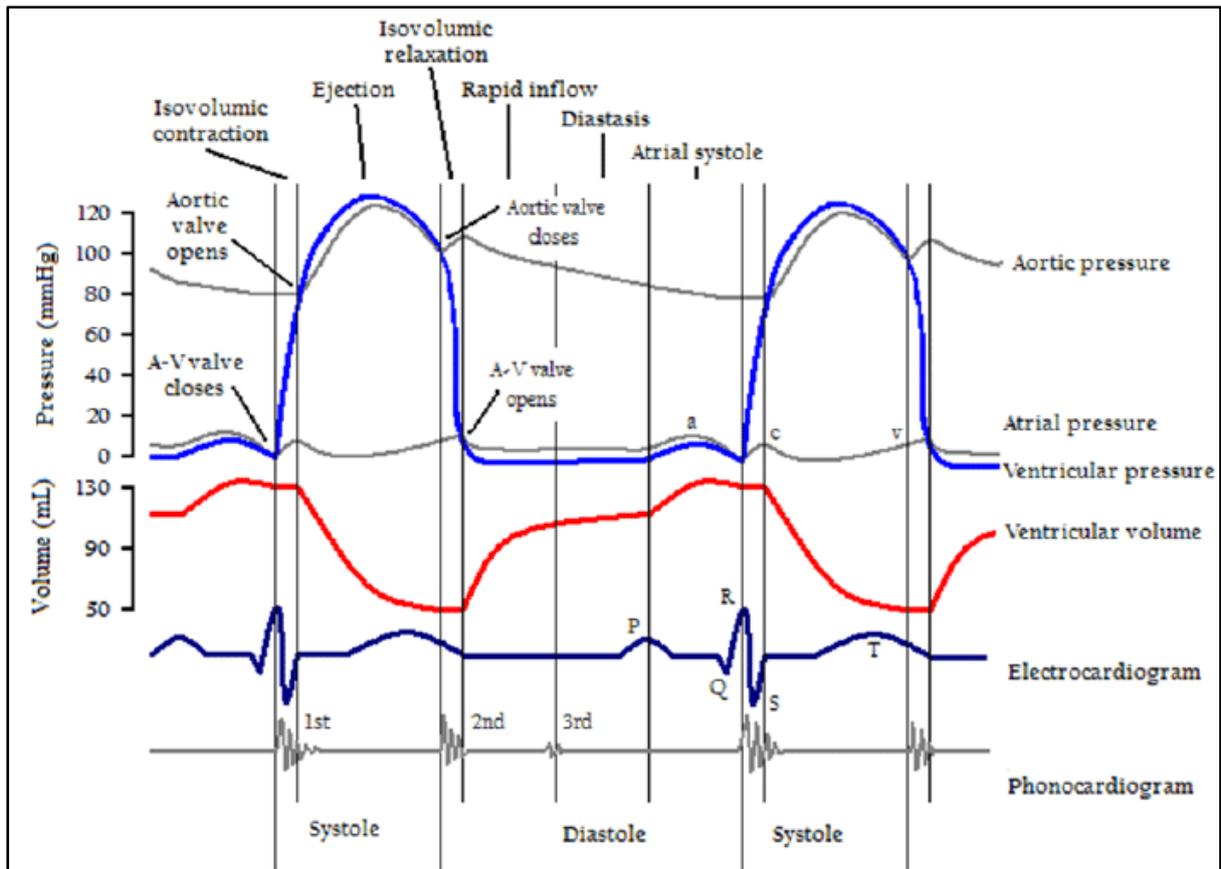


Figure 4.3: The Wiggers diagram

4.3.1 Isovolumic contraction

Isovolumic contraction begins with the closure of the mitral valve as the LV pressure rises at the start of ventricular systole. After mitral valve closure, the LV pressure continues to rise but the volume remains the same.

4.3.2 Ventricular ejection

The aortic valve opens when LV pressure exceeds aortic pressure, and blood is ejected through the aortic valve into the aorta. LV volume falls as the blood is ejected from the LV, but the pressure continues to increase until it peaks and then starts to decrease.

4.3.3 Isovolumic relaxation

The aortic valve closes due to falling LV pressure and initially the LV volume remains the same, until LV pressure falls below the left atrial (LA) pressure. Once pressure in the LV is lower than that in the LA, the mitral valve opens.

4.3.4 Ventricular filling

Ventricular filling occurs whilst the mitral valve is open and LA pressure remains higher than LV pressure, due to LA contraction and continuing LV relaxation. This phase ends when the mitral valve closes at the start of ventricular systole (when LV pressure rises above that of the LA).

4.4 Principles of echocardiography

Echocardiography provides tomographic moving images of cardiac structures and can also interrogate blood flow. Multiple imaging planes enable a comprehensive evaluation of cardiac chambers and valve function.

The term ultrasound describes a mechanical wave, similar in character to audible sound, but at frequencies greater than 20 kilohertz (kHz) (Duck, 2000). Ultrasound used for echocardiography is usually within the frequency range 1.5-7 megahertz (MHz). The velocity at which sound travels through a medium depends on the density and elastic properties of that medium. The average propagation velocity for the heart is 1,540 metres per second (m/s). Ultrasound pulses emitted from the transducer travel through body tissues and as the beam reaches a boundary between tissues with different acoustic impedances, a proportion of energy is reflected back towards the transducer. Complex analyses of the ultrasound waves that are reflected and backscattered from the patient's body, generate a display of cardiac images and flow data on the echocardiogram monitor.

4.4.1 Echocardiography imaging modalities

4.4.1.1 A-mode imaging

Early echocardiographic recordings were made using amplitude mode (A-mode), which recorded the amplitude of the reflected ultrasound (Figure 4.4). The amplitude of the spike is determined by the intensity of the reflected signal, the distance between the spikes represents the distance of the reflected signal from the transducer.

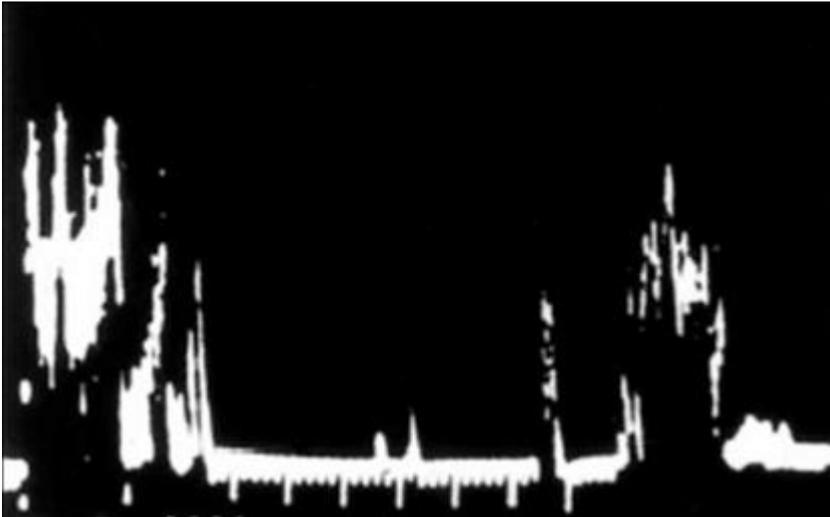


Figure 4.4: A-mode recording

(Meyer, 2004)

4.4.1.2 B-mode imaging

Brightness mode (B-mode) represents the amplitude of the reflected signal by the brightness of a dot, with the distance between dots corresponding with the distance of the reflected signal from the transducer.

4.4.1.3 M-mode imaging

The introduction of time as a second dimension to B-mode imaging, created motion mode (M-mode) imaging which records motion, transmitted and received along just one scan line, by positioning an on-screen cursor across the region of interest. This produces a highly sensitive display of movement along the vertical axis of the display screen, against time along the horizontal axis (Figure 4.5). Therefore this mode of scanning, with its high sampling rate, is very useful for assessing the rapid movement of valve leaflets, measuring cardiac dimensions, and allows accurate timing of events (Chambers, 1995).

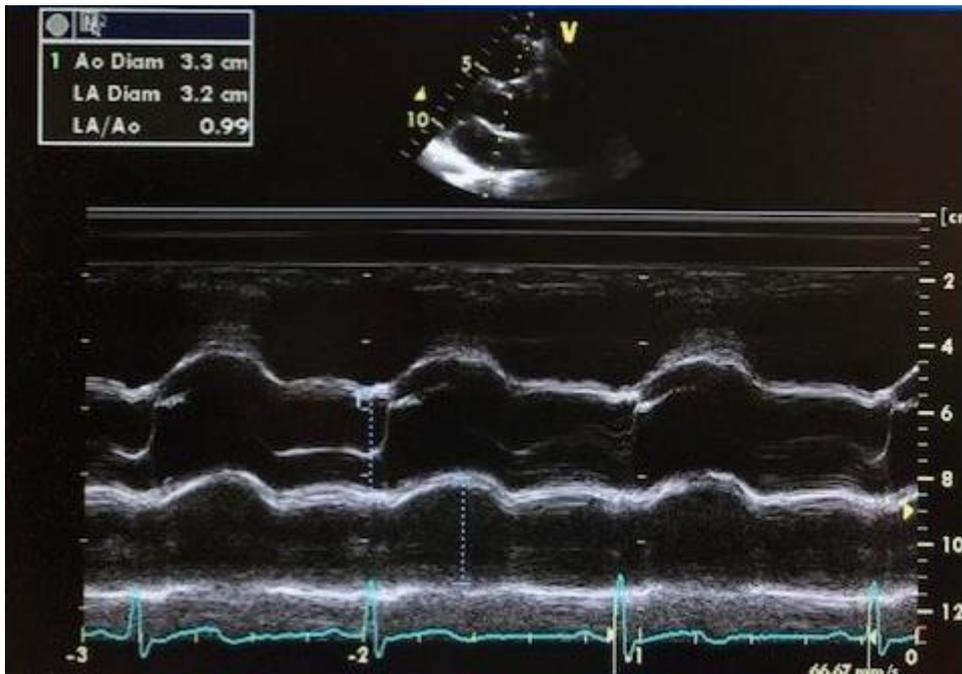


Figure 4.5: M-mode imaging, showing the aortic valve

4.4.1.4 Two-dimensional echocardiography

The data obtained from electronically scanning the ultrasound beam through an arc, generates a real-time 2D echocardiographic image (Figure 4.6). This allows more information than that produced by M-mode, about the geometry of the heart, and demonstrates the spatial relationships of its structures during the cardiac cycle.

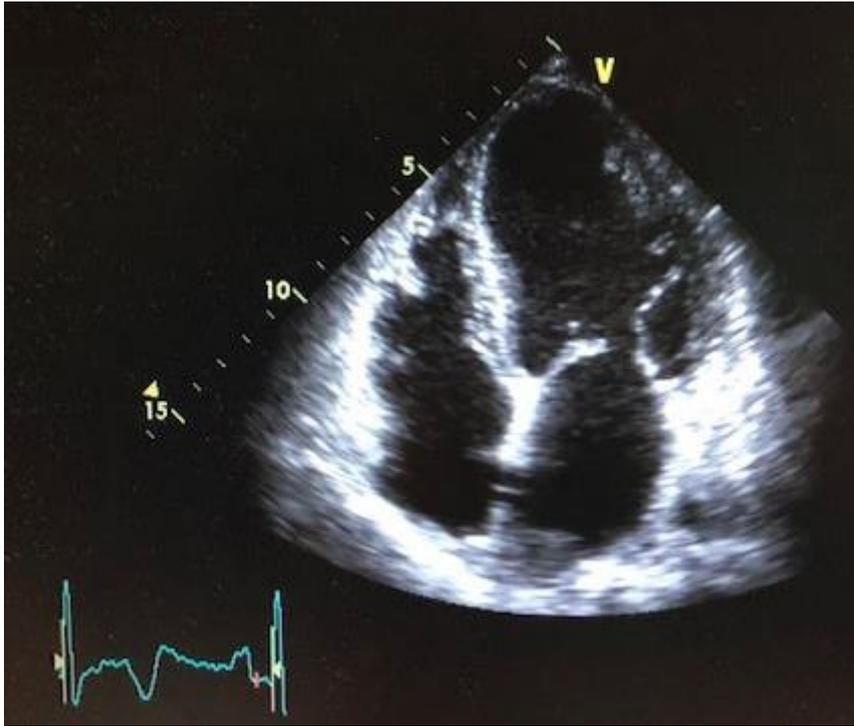


Figure 4.6: 2D imaging, showing apical 4-chamber view

Although standard ultrasound imaging is based on reflection of the fundamental transmitted frequency from tissue interfaces, tissue harmonic imaging is based on the harmonic frequency energy. The properties of harmonic frequencies (including increased signal strength with depth of propagation), result in improved LV endocardial definition, and thus more accurate endocardial border tracing for measurement of LV volumes (Otto, 2013). However, because lateral resolution is reduced through harmonic imaging, objects may appear thicker than with fundamental frequency imaging.

4.4.1.5 Doppler echocardiography

The Doppler effect was first described by the Austrian physicist Christian Döppler (1803-1853) in 1842 (Roguin, 2002) (Figure 4.7). It describes the apparent change in frequency of a wave when there is relative motion between the wave source and the

observer. The perceived frequency is higher, in comparison to the emitted frequency, when the wave source is moving towards the observer, and lower when moving away from the observer. The perceived change in frequency is referred to as a frequency shift. When applied to the heart, a frequency shift is induced when a sound wave strikes moving red blood cells. The transmitted frequency (transducer frequency) is compared with the frequencies within the returning signal to quantify the frequency shifts produced by the moving red blood cells. The velocity and direction of blood flow can be calculated by determining the frequency shifts.



Figure 4.7: Photographic portrait of Christian Döppler

Colour flow Doppler imaging is a method of estimating and displaying a 'map' of the mean velocity of blood flow. The velocities are assigned a colour (by convention blood flow towards the transducer = red; blood flow away from the transducer = blue), which is determined by the direction of blood flow in relation to the ultrasound transducer and

the relative velocity of flow. The colour map is superimposed on the 2D image, producing a real-time representation of the spatial extent of blood flow, generating a 2D image of intracardiac blood flow (Figure 4.8). The relative velocities of blood flow are displayed as differing hues.

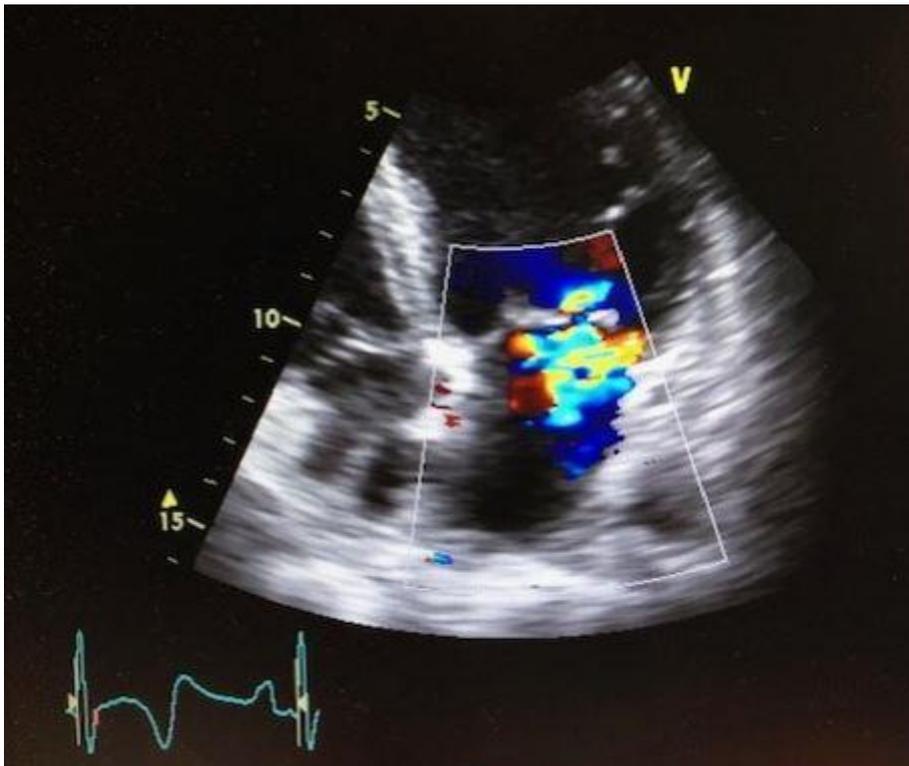


Figure 4.8: Colour Doppler imaging, showing mitral regurgitation

In addition to measuring the motion of blood cells, the Doppler principle can also be applied to myocardial tissue motion in the form of tissue Doppler, providing information on myocardial mechanics. It can be displayed as colour Doppler images to show myocardial tissue motion, or as spectral pulsed-wave Doppler traces when assessing motion in specific myocardial regions (Figure 4.9).

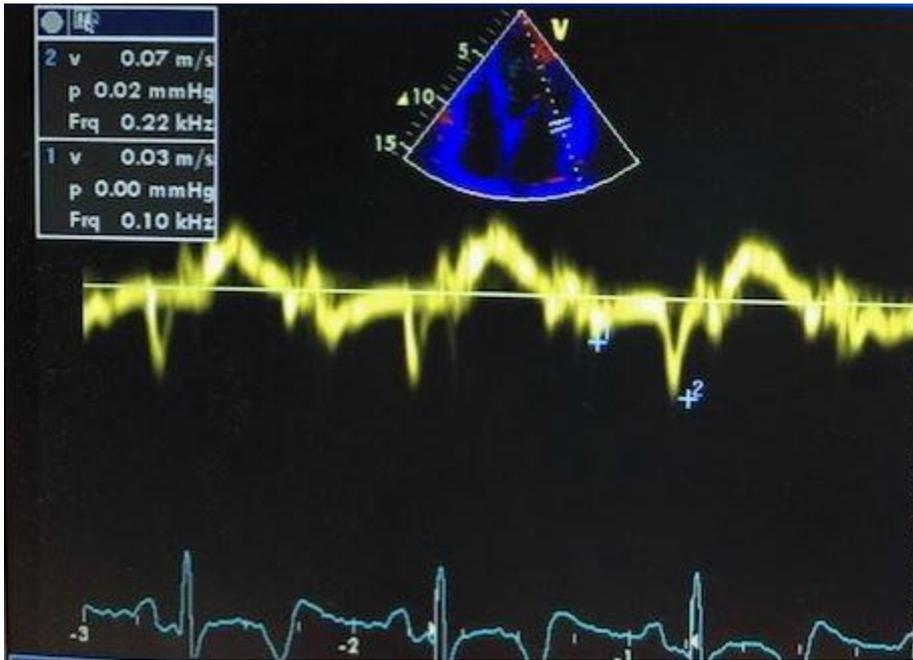


Figure 4.9: Pulsed-wave trace of lateral mitral annulus obtained with tissue Doppler imaging

4.4.1.6 Three-dimensional echocardiography

Three-dimensional (3D) echocardiographic imaging is based on the same principles as 2D imaging but uses a more complex full volume acquisition and display of data. Whilst a 2D transducer typically contains 128 elements arranged in a linear fashion and creates a tomographic slice of the heart, a 3D matrix array transducer contains almost 3,000 elements arranged in a rectangular grid which produces a pyramidal volume dataset (Houghton, 2013). Imaging in 3D offers several important advantages over 2D imaging. It measures in a third dimension, it does not rely on plane positioning, and does not require geometric modelling or assumptions about chamber shape. However, 3D echocardiography still depends on good image quality, and has lower spatial and temporal resolution than 2D images (Klaeboe and Edvardsen, 2019).

4.5 Measurement of the variables used in this thesis

The decrease in cardiac contractility associated with heart failure with reduced ejection fraction (HFrEF) results in a decrease in stroke volume and an increase in LV volumes. According to the law of Laplace, the increase in radius of the dilated, failing heart, reduces the pressure generated by a given contractile force. Thus, an important therapeutic aim in HFrEF management is to reduce cardiac distention and improve cardiac contractility. Therefore, measuring LV dimensions and volumes, using echocardiography, before and after interventions, such as those explored within this thesis, can be used in determining the efficacy of those interventions.

LV ejection fraction (LVEF) is a function of stroke volume (SV) and LV end-diastolic volume (LVEDV):

$$\text{LVEF} = \text{SV}/\text{LVEDV} \times 100$$

The role of stroke volume in the force-frequency relationship thus makes LVEF a relevant variable to measure in the studies presented within this thesis. LV volumes are also relevant parameters to measure since the end-systolic volume is required to calculate LV contractility, and end-diastolic volume is a measure of the size of the LV.

LVEF is the most validated and commonly used echocardiographic measure of systolic function. Playing a key role in the management of heart failure, LVEF helps to identify patients who are likely to respond to therapy for HFrEF, in addition to

identifying those who will benefit from cardiac implantable electronic device therapy (Marwick, 2015).

Although the terminology used to define HFrEF is centred on the measurements of LVEF, it should be remembered that the degree of cardiac dysfunction relates poorly to symptoms (Coats, 1996; Witte, K. K. et al., 2004).

Furthermore, the strict application of cut-offs in individual patients can potentially lead to misclassification (Lam, C.S.P. et al., 2020). However, since clinical trials forming the basis of evidence-based treatment recommendations are predicted on LVEF cut-offs, LVEF remains a key factor in guiding treatment decisions in clinical practice (Klaeboe and Edvardsen, 2019). Moreover, since other methods of definition currently lack clarity, and effective proven therapies are only available for the treatment of systolic heart failure, the classification of heart failure based upon LV function remains (Ponikowski et al., 2016).

Internal dimensions and volumes are the most frequently used variables to quantify LV cavity size (Ciampi and Villari, 2007). Measurements are taken at specific points during the cardiac cycle, usually end-diastole and end-systole, determined by the electrocardiogram (ECG). The measured dimensions can then be used in equations to derive parameters of LV function (Harkness et al., 2020).

LV internal cavity and wall thickness dimensions should be measured in the parasternal long-axis view, with measurements taken just distal to the mitral valve

leaflet tips (Wharton et al., 2015). This can be achieved using 2D guided M-mode (Figure 4.10), or using digital callipers in 2D imaging (Figure 4.11).



Figure 4.10: 2D guided M-mode image of LV cavity dimensions



Figure 4.11: LV end-diastolic dimension using digital callipers

Volumetric measurements require optimal endocardial definition, and are made by manually tracing the endocardial border of the LV, excluding the papillary muscles (Lang et al., 2006). The most common and robust method for assessing LV volumes is the modified Simpson's biplane method of discs, which combines two orthogonal views from the apical two chamber view and the apical four chamber view (Lang et al., 2006) (Figure 4.12). The LV cavity is divided into a number of slices, or discs, of known thickness. Volume is then calculated by adding together the volumes of the individual slices. This process makes fewer assumptions about LV geometry, allowing an accurate calculation of volume even when the chamber is distorted.

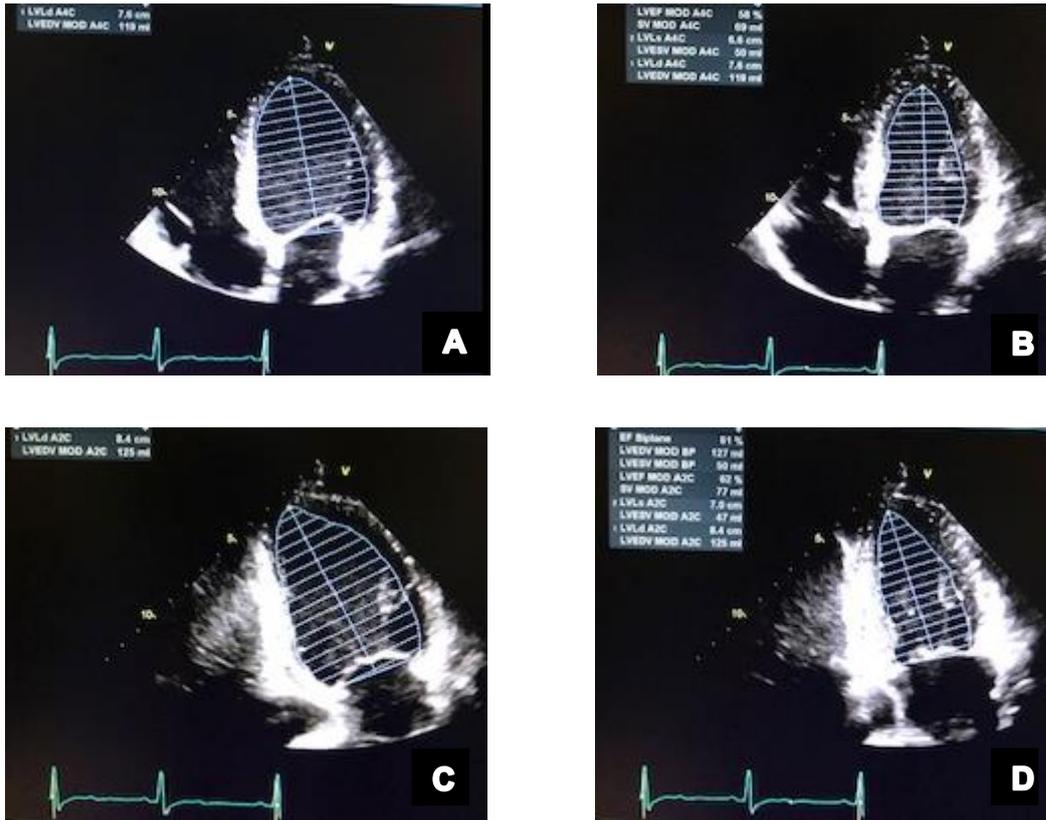


Figure 4.12: Simpson's biplane method of measuring LV volumes and LV ejection fraction

- (A) Apical four-chamber LV end-diastolic volume; (B) Apical four-chamber LV end-systolic volume; (C) Apical two-chamber LV end-diastolic volume; (D) Apical two-chamber LV end-systolic volume.

4.6 Other non-invasive cardiac imaging modalities

4.6.1 Cardiac magnetic resonance imaging

Magnetic resonance imaging (MRI) uses a powerful magnetic field, radio waves and computer technology to non-invasively produce high resolution images. An application of MRI is to image the structures within and around the heart (cardiac magnetic resonance imaging (CMR)). Like ultrasound, it does not use ionising radiation and is not known to have any long-term harmful effects.

CMR is considered as the gold standard for measuring LV volumes and ejection fraction (Hundley et al., 2010), because it is able to image the whole heart in multiple planes and provides good endocardial definition. The important differences in the accuracy of CMR when compared with 2D echocardiographic measurements of LV volume and ejection fraction, are based on the fact that CMR is a volumetric technique with high contrast and spatial resolution (Hudsmith et al., 2005).

Although it has been shown that CMR offers a complementary role to echocardiography in evaluating the underlying aetiology, and is considered the gold standard for assessment of LV volumes and ejection fraction (Peterzan et al., 2016), there are some restrictions. The strength of the magnet may affect devices or implants, for example pacemaker devices. Many devices are now MRI conditional, but there may be problems with older devices. Quickly changing magnetic fields may generate electrical currents in electrically conductive devices with the potential risk of inducing arrhythmia, or inhibiting therapy, in patients with pacemaker electrodes in place. Furthermore, metallic devices, such as pacemaker systems, may induce excessive local tissue heating, which in the case of cardiac devices could lead to temporary or permanent loss of capture (Levine et al., 2007).

Claustrophobia may also be a limiting factor in a patient undergoing a CMR, as may extreme obesity such that the patient cannot fit into the scanner. A limiting factor more pertinent to HFrEF is the inability to perform a CMR on a patient who is too breathless to be able to lie flat in the scanner.

Additionally, the gadolinium contrast medium used in some CMR investigations is contraindicated in people with estimated creatinine clearances <30 millilitres per minute (ml/min). Gadolinium contrast agent may cause nephrogenic systemic fibrosis, a rare but serious reaction, in patients with a history of kidney disease; renal dysfunction is relatively common in patients with heart failure (Peterzan et al., 2016). There is a very small risk of an allergic reaction in all patients who receive a contrast medium.

The cost, limited availability, and its incompatibility with metallic devices, for example pacemakers, make CMR impractical for widespread clinical use, and even as a research tool its application is limited due to cost, contraindications, generalisability, and patient acceptance of repeated scans.

4.6.2 Radionuclide imaging

The main clinical application for radionuclide imaging in heart failure is myocardial perfusion imaging for the assessment of ischaemia and viability for the diagnostic and prognostic workup of patients with coronary artery disease and heart failure (Boogers et al., 2011). A disadvantage of radionuclide imaging is the exposure to radiation. The radiation exposure varies between 10-18 milliSievert (mSv) depending on the radioactive tracer used. 10 mSvs is equivalent to 5 years of natural background radiation (Underwood et al., 2004). Furthermore, this method of imaging cannot perform real-time imaging at the rate required for the study protocols within this thesis, in the manner that echocardiography and CMR can.

4.6.3 Computed tomography

Whilst cardiac computed tomography (CT) is not considered a technique of choice for the evaluation of cardiac function, it is capable of measuring LV volumes and function for specific indications (Aziz et al., 2019). This is particularly so when for example, suboptimal echocardiographic windows or issues with CMR (claustrophobia, non-MRI conditional pacemaker device), mean that an alternative imaging modality is required to obtain the relevant information.

4.7 Study related echo strengths and limitations

Transthoracic echocardiography is widely accepted as being able to assess cardiac structure and function (Pastore et al., 2020), and furthermore is recognised as the first line imaging modality in heart failure (Aziz et al., 2019).

Although echocardiography can be used with a high degree of accuracy for clinical decision making, knowledge of the strengths and limitations of this modality is critical for correct clinical diagnosis and patient management (Otto, 2013).

4.7.1 Strengths

The strengths of echocardiography include that it is widely available, portable, allows a comprehensive and immediate non-invasive assessment of cardiac anatomy and function, is relatively inexpensive, and does not use ionising radiation (Modin et al., 2018). Furthermore, when carried out by appropriately trained and accredited staff, echocardiography is safe. Although echocardiography depends on interactions between ultrasonic energy and living tissues, with current ultrasound technology,

biological effects are unlikely to be caused directly by tissue heating (Duck, 2008). Moreover, there is no evidence of significant health risk from exposure to medical ultrasound for patients or clinical staff (Knuuti et al., 2014).

4.7.2 Limitations

Although it is generally accepted that echocardiography is able to assess cardiac structure and function (Pastore et al., 2020), there is evidence that it may be less accurate than other modalities (McGowan and Cleland, 2003), with the estimate of LVEF as a sequential test within individuals being constrained by limited test-retest (Marwick, 2003).

Limitations in the accuracy of the measurements made during echocardiographic imaging may include suboptimal images, with body habitus influencing the technical ability to acquire good quality images (thus affecting reproducibility), insufficient training, and lack of operator experience.

Bellenger et al., compared 2D echocardiography, radionuclide scanning and CMR, performed within four weeks, in patients with chronic stable heart failure. They reported mean LVEFs of $31 \pm 5\%$ with 2D echocardiography using modified Simpson's biplane method; $24 \pm 21\%$ with radionuclide scanning; and $30 \pm 9\%$ with CMR. All mean LVEFs were significantly different from all other techniques ($p < 0.001$), except for 2D echocardiography Simpson's biplane method and CMR ($p = 0.23$). Wide levels of agreement were revealed with end-diastolic volume and end-systolic volume assessed by 2D echocardiography Simpson's biplane method and CMR (52 ml to 216

and 11 ml to 188 respectively), despite good correlation (Bellenger et al., 2000). This suggests that, where available, CMR is the preferred option for volume and LVEF estimation in heart failure patients, because of its accuracy, reproducibility, and superior image quality.

4.7.2.1 Reproducibility

Good reproducibility, repeatability and reliability are essential in cardiac imaging. Reproducibility is defined as the variation in the same measurement made on the same subject in changing conditions, for example a different operator or time frame. Repeatability is the variation in repeat measurements made on the same subject in identical conditions, and reliability is the size of error between measurements (Bunting et al., 2019).

Whilst 3D echocardiography has been shown to be more reproducible than 2D echocardiography (Omar et al., 2016), this modality was not available during the series of investigations within this thesis. However, to reduce, as far as possible, any under or overestimations in volumetric measurements, all images were acquired and reported by an experienced, accredited clinical scientist. Furthermore, intra-, and inter-observer variability were assessed.

The intraclass correlation coefficient (ICC) is used to determine the reliability and reproducibility of numeric measurements, reflecting the degree of correlation and agreement between measurements. Values between 0.75 and 1.00 suggesting excellent correlation (Cicchetti, 1994). ICC was used in this series of investigations to

assess variability within a single operator (intra-observer) and between different operators (inter-observer), for LVEF and volume measurements.

4.7.2.2 Competency

The accurate acquisition of good quality images is dependent upon the operator's skill in firstly acquiring the images, and secondly making the correct measurements. This relies on good quality, on-axis imaging, with accurate endocardial border detection and tracing (Rösner et al., 2015). Appropriate training, accreditation and subsequent maintenance of skills and continuing professional development, play an essential role in the ability to accurately acquire and measure high quality echocardiographic images. Furthermore, the inter-observer variability of clinical echocardiographic measurements has been shown to improve with formalised training, (Donner et al., 2018).

Estimations of LVEF based on linear measurements of LV dimensions from M-mode and 2D imaging are not recommended, because of the likelihood of inaccurate geometric assumptions. It is recommended that assessment of LVEF and LV volumes should be made in 2D, by the modified Simpson's method of discs, or alternatively, when available and feasible, by 3D based full volume acquisition (Lang et al., 2006; Wharton et al., 2015). However, this method can also be subject to errors due to foreshortening, poor endocardial definition, and assumptions about LV geometry, leading to underestimations in LV volumes. In order to acquire high quality images, acquisition should use optimal gain settings and breath-hold techniques to clearly

delineate endocardial borders, and to avoid artefact related to excess noise, rib or lung movements and translational motion of the heart (Rösner et al., 2015).

4.8 Conclusion

2D echocardiography was the imaging modality of choice for the investigations reported in this thesis because it is safe, easily accessible, repeatable, patient-friendly, and cost-effective. Whilst it is acknowledged that CMR provides high resolution images and reproducible estimates of LV volumes and ejection fraction, the participants recruited to the studies necessarily had pacemaker devices. Although many pacemaker devices are now MRI conditional, some of the older pacemaker generators, or their pacing electrodes are not MRI conditional. I have described the steps I took to ensure that image quality and reproducibility of estimates of LV volume and ejection fraction remained high.

Chapter 5 : Methodology

My studies have all been designed in collaboration with patients; the primary outcomes of the interventional studies have therefore been patient-orientated, specifically walk distance, with secondary and exploratory outcomes of symptoms and quality of life. However, due to their mechanistic and prognostic relevance, I also included other more physiologically relevant endpoints from the cardiopulmonary exercise tests (CPET). Each study has included left ventricular (LV) function as a secondary outcome. The techniques employed for the echocardiographic outcomes of relevance have been outlined in chapter 4. This chapter will therefore focus on the exercise outcomes, their relevance to the syndrome of heart failure with reduced ejection fraction (HFrEF), and their assessment.

5.1 Measuring exercise capacity

The patient advisors in the Patient and Public Involvement and Engagement group at the Cardiovascular Clinical Research Facility (CVCRF) at Leeds Teaching Hospitals National Health Service (NHS) Trust (LTHT), have described that exercise capacity is the principle variable for patients. It is the primary reason for presentation, drives quality of life, and is a key marker of prognosis. Its value as an endpoint probably derives from the fact that it combines pulmonary gas exchange and cardiovascular performance in delivering oxygen (O_2) to exercising skeletal muscle, and the exercising muscle to extract O_2 from the blood (Krikler, 1992), and skeletal metabolism (Albouaini et al., 2007; Ferguson et al., 2016).

Exercise capacity is routinely assessed by measuring peak symptom-limited oxygen consumption during an incremental treadmill or cycle-based CPET. Considered as a gold standard, non-invasive, objective assessment of exercise capacity (Tran, 2018), CPET plays an important role in the diagnosis, quantification of symptoms, prognosis and assessment of therapeutic interventions in patients with HFrEF (Wright, D.J. and Tan, 1999). Beyond simply assessing maximal workload and exercise time, CPET allows the routine assessment of other variables, many of which are derived from the difference in O₂ and carbon dioxide (CO₂) concentration between inspired and expired air, ventilation, body weight and heart rate. The key derived variables include peak oxygen consumption, oxygen uptake at anaerobic threshold, and the slope relating ventilation rate to carbon dioxide production (VE/VCO₂ slope).

During a CPET, all gas exchange is measured breath-by-breath. During exercise, oxygen consumption (VO₂) and carbon dioxide production (VCO₂) at the mouth represent O₂ utilisation and CO₂ production at the musculoskeletal level.

5.1.1 Exercise protocols

Exercise is performed either on a powered treadmill or a stationary cycle. There are various incremental exercise protocols for both modes. Workload is increased on a treadmill by increasing the speed and slope, and on a cycle by increasing the resistance to wheel rotations. In both settings, the increases in workload can be gradual or stepwise, with the aim of a steady but consistent increase to allow adequate metabolic gas kinetic response, whilst maintaining an exercise time of between six

and twelve minutes, to maximize the accuracy of peak oxygen consumption measurements (Buchfuhrer et al., 1983).

5.1.1.1 Familiarity with the protocol

As many participants will be unfamiliar with the exercise modes and the equipment, a familiarisation test is recommended, especially when exploring the effect of an intervention in a longitudinal study. Although some have recommended several familiarisation tests to obtain reproducible results (Pinsky et al., 1990), performing multiple familiarisation tests is not practical. Furthermore, the greatest difference seems to occur between the first and second tests (ESC, 2001). Previous data have described that a familiarisation test or repeated CPET studies are not a training stimulus (Witte, K. K. et al., 2003; Bensimhon et al., 2008). Hence this provided reassurance that one familiarisation test was sufficient for the studies within this thesis, and also that following this, any changes would be a consequence of the intervention. Moreover, the intervention studies described are placebo-controlled and double-blind.

5.1.2 Measuring oxygen consumption

'Peak oxygen consumption', or more appropriately 'oxygen consumption at peak exercise', describes the highest oxygen consumption achieved in patients with HF_rEF (Albouaini et al., 2007). In this thesis I shall use the traditional term of peak oxygen consumption. Even this is a compromise to pragmatism of clinical practice. The true definition of 'maximal oxygen uptake' is represented as a plateauing of oxygen consumption measurements despite additional increases in workload. This

physiological maximum is rarely achieved in patients with HFrEF during a symptom-limited test, due to symptoms and motivation.

Peak oxygen consumption is a well-established measure of aerobic capacity and exercise tolerance, and is frequently used to assess HFrEF (Mancini et al., 1991; Bensimhon et al., 2008). The value is directly related to cardiac output and muscle blood flow at peak exercise based on the Fick equation (peak oxygen consumption = cardiac output x arteriovenous O₂ concentration difference at the respiring skeletal muscles during sustained maximal effort). Total oxygen consumption is usually normalised to weight, to allow a comparison between individuals of differing body mass, i.e. millilitres per kilogram per minute (ml/kg/min) (Wasserman et al., 2005).

Patients with HFrEF typically have lower than age-predicted peak oxygen consumption, and an increase in the ventilatory response to exercise (VE/VCO₂ slope), during incremental exercise testing with metabolic gas exchange analysis (Solal et al., 1990; Clark et al., 1996; Wasserman et al., 1997).

Importantly, peak oxygen consumption is poorly correlated with resting haemodynamic parameters such as left ventricular ejection fraction (LVEF), because haemodynamic parameters measured at rest do not accurately reflect cardiac pumping function during exercise (ESC, 2001). However, cardiac output is governed by heart rate and stroke volume, and during exertion, peak oxygen consumption correlates with maximal cardiac output (Miyamura and Honda, 1972). An insufficient cardiac output is the chief determinant of reduced aerobic capacity and reduced

exercise tolerance in asymptomatic and mildly symptomatic HFrEF patients (Harrington and Coats, 1997; ESC, 2001). On the other hand, those with moderate or severe HFrEF are limited by a combination of impaired cardiac output reserve, and abnormal peripheral mechanisms (ESC, 2001).

5.1.3 Respiratory exchange ratio

The respiratory exchange ratio (RER) is the ratio of V_{CO_2} production to VO_2 consumption. It relates to a similar ratio of cellular respiration known as 'RQ'. As exercise intensity increases, the ability of the skeletal muscles to respire predominantly aerobically is exceeded, and anaerobic metabolism becomes more dominant. The resultant increase in lactate production results in increasing V_{CO_2} production, in an attempt at buffering a reducing blood pH. Peak RER is used to determine adequate effort during a test, with ≥ 1.10 used as an indication of good volitional effort, and indicates that anaerobic threshold has been surpassed (Wasserman et al., 2005; Keteyian et al., 2016), rather than the test being terminated due to other limiting factors such as poor motivation or musculoskeletal pain.

5.1.4 VE/V_{CO_2} slope

A key prognostic measure in HFrEF is the relationship between minute ventilation and carbon dioxide production (VE/V_{CO_2} slope). HFrEF is associated with a greater amount of ventilation for a given carbon dioxide output, and therefore a degree of hyperventilation, for a given workload (Wasserman et al., 2005). The elevated VE/V_{CO_2} is inversely related to cardiac output at peak exercise (Reindl et al., 1998), and a steeper VE/V_{CO_2} slope being related to adverse prognosis (Sun et al., 2002; Ingle et

al., 2007). The origin of the increased ventilation is unknown, and although it has been proposed to be due to a mismatch of ventilation to perfusion (Mezzani, 2017), it is much more likely to be due to a combination of inputs including heightened signals from exercising muscle (Clark et al., 1996).

5.1.5 Anaerobic threshold

The anaerobic threshold is the point at which the body's capacity for exercise driven by aerobic metabolism is surpassed. Further increases in work are therefore largely facilitated by anaerobic metabolism, leading to a steeper increase in CO₂ output for a given O₂ consumption. The inflection point is frequently given the term 'anaerobic threshold'. From this point onwards, exercise can no longer continue in a steady state and, will eventually, have to cease.

From a clinical perspective, the anaerobic threshold is a recognised measure for submaximal exercise capacity and can be used to assess the functional benefits of a given therapy based on its correlation to activities of daily living (Wilmore et al., 1998). In HFrEF patients, anaerobic threshold tends to occur at around 70% of peak oxygen consumption, which is lower than in those without HFrEF (Shimizu et al., 1991; ESC, 2001). Increasing the anaerobic threshold to allow reasonable exercise to continue without accumulation of lactic acid or other products of anaerobic metabolism, is a key outcome of exercise interventions, since it determines symptoms, repeatability of exercise and thereby quality of life.

5.2 Measuring left ventricular contractility

Cardiac contractility is the intrinsic capacity of cardiomyocytes to generate contractile force at a specific heart rate, independent of preload and afterload. Therefore, assessment of the force-frequency relationship in vivo should ideally occur independently of loading.

5.2.1 Assessing the force-frequency relationship

To be of relevance to clinical care, the force-frequency relationship must be examined in a reproducible way in vivo, requiring a means to adjust heart rate without affecting other haemodynamic variables, and a method of measuring LV contractility.

Assessment of LV contractility requires: the measurement of LV end-systolic pressure (LVESP), a measure of LV end-systolic volume (LVESV) indexed for body surface area (LVESVi), and a method by which to increase the heart rate in a stepwise manner. Dividing LVESP by LVESVi gives a surrogate of LV contractility, which has been validated against invasive methods (Bombardini, T. et al., 2003; Bombardini, T., 2005a).

Most of the investigations into the force-frequency relationship have been carried out ex vivo in myocardial strips, either from explanted hearts during transplantation or from biopsy material. (Mulieri et al., 1992; Bondke et al., 2010). Moreover, many have been conducted at room temperature, such that the results do not necessarily reflect the force-frequency relationship as it occurs in vivo (Janssen and Periasamy, 2007).

5.2.2 Invasive assessment of the force-frequency relationship

Although used widely in animal studies, measuring end-systolic elastance for increasing heart rates is not practical in the clinical setting due to the complexities of using a temporary pacing electrode to increase the heart rate, alongside the catheters for measuring the pressure volume relationship. Conductance catheters have been used for *in vivo* measurements of pressure-volume loops to assess cardiac contractility. Whilst this approach may be accurate and robust, and can be useful to confirm the findings of non-invasive testing (Cotton et al., 2001), it is invasive, complex and technically demanding, and furthermore exposes the patient to contrast, radiation and infection (Bombardini, T. et al., 2003), and therefore rarely used in clinical practice.

5.2.3 Non-invasive assessment of force-frequency relationship

Scintigraphy has been proposed as a non-invasive method, offering a photographic (rest-peak stress) assessment of LV contractility. However, only assessing the rest and peak sections of the force-frequency relationship means that the dynamic variation at the intermediate frequencies is not measured, such that peak cardiac contractility and peak heart rate may not be correctly recorded. Furthermore, scintigraphy exposes the patient to ionising radiation.

Echocardiography is an appropriate and repeatable method of non-invasively measuring LV contractility *in vivo*. Via this modality, LV contractility can be estimated using either two-dimensional (2D) imaging or tissue Doppler velocities.

The LV systolic volume is measured using 2D images, with cuff systolic blood pressure (SBP) used as a surrogate for end-systolic pressure. This measure of LV contractility (SBP/LVESVi) has been validated against invasive methods (Bombardini, T. et al., 2003).

A limitation of this method is in the use of the systolic cuff pressure as a surrogate for end-systolic pressure in the LV contractility equation. Non-invasive measurement of pressure may lead to an overestimation of LV pressure since the brachial arterial pressure reflects an amplified LV pressure wave secondary to the rheological properties of the arterial tree (Bombardini, T. et al., 2007). However, it has been shown that there is a tight relationship between peak and end-systolic pressure, such that any error would be systematically distributed along the whole force-frequency relationship curve, as long as the heart rate rise is not due to an agent with vasoconstrictive properties (Slutsky et al., 1980). Furthermore, the peak systolic pressure / end-systolic volume ratio is a reproducible method of assessing LV performance during exercise (Mehmel et al., 1981).

Bombardini and colleagues have demonstrated the feasibility of a non-invasive estimation of the force-frequency relationship during stress echocardiography, using the patient's permanent pacemaker to increase the heart rate. Their work has allowed them to conclude that, theoretically, assessing global contractility in this way could be of use in the identification of limited contractile reserve and latent global LV dysfunction (Bombardini, T. et al., 2003; Bombardini, T., 2005a; Bombardini, T. et al., 2005b).

Cardiac contractility can also be estimated using tissue Doppler velocities to measure myocardial acceleration during isovolumic contraction (Vogel et al., 2003). This method also relates to invasive data and appears independent of preload and afterload (Dalsgaard et al., 2007).

Cardiac contractility has also been assessed using temporary pacing and tissue Doppler imaging, in a study comprising 11 children undergoing cardiac surgery. The aim was to investigate changes in the force-frequency relationship in the early post-operative period in selected groups of children undergoing cardio-pulmonary bypass and surgical repair of congenital heart defects. A marked variability in response was noted, ranging from no effect in patients undergoing atrial septal defect closure, to a significant reduction in cardiac contractility response following neonatal arterial switch. The authors concluded that this application of the force-frequency relationship might allow a refinement of myocardial protection and postoperative support (Cheung et al., 2006). However, the tissue Doppler approach to an assessment of the force-frequency relationship provides information that is limited to regional myocardial velocities and so, does not reflect the overall contractile performance of the LV (Dini et al., 2013).

Advantages of the echocardiography approach include that it is non-invasive, and does not present ionising radiation or biohazard risk to either the patient or the operator (Picano, 2003).

The force-frequency relationship has also been reliably assessed using a Doppler-derived method where LV ejection force was calculated according to the law of

conservation of momentum, at rest and during exercise (Dini et al., 2013). However, this method of assessment is limited to regional myocardial velocities and does not reflect the overall contractility of the LV. Further limitations to this method include transducer angulation, correct measurement of the LV outflow tract, and the assumption that the LV outflow tract diameter does not alter during exercise. However, this method could be useful in patients with poor endocardial definition.

A further non-invasive method of measuring LV contractility in vivo has been reported, demonstrating that it is feasible to record the force-frequency relationship using a non-invasive transcutaneous force sensor, attached to the mid-sternal precordial region by a solid gel electrocardiogram (ECG) electrode (Bombardini, T. et al., 2007). Using an accelerometer, the sensor measures the vibrations that result in the first heart sound, generated by isovolumic myocardium contractions (Sakamoto et al., 1965). Whilst it was found that the sensor-built force-frequency relationship was related to the standard stress echo-built force-frequency relationship, further studies are needed to compare the non-invasive sensor method with LV pressure-volume loops in humans.

Although cardiac contractility can also be estimated by intracardiac impedance around a permanently implanted pacing lead, only one company currently manufactures pacemakers capable of making these measurements (Bondke et al., 2010). However, the use of the right ventricle (RV) for pressure or impedance measurements, rather than the LV, limits the clinical use of this pacemaker in an NHS setting, since it is unclear in any one individual how the impedance measure in the RV relates to LV contractility. As a result, this method has not become standard practice.

5.2.4 Increasing the heart rate

Various methods of increasing the heart rate during force-frequency relationship assessment have been reported in the literature, including inotropes (Bombardini, T. et al., 2007), graded bicycle exercise (Bombardini, T. et al., 2003), and incremental pacing (Bombardini, T. et al., 2005b).

Whilst using an infusion of a cardiac stimulant is a convenient method to increase the heart rate in patients who do not have a pacemaker, these agents have an unpredictable effect on preload and afterload. For example, the most frequently used agent, dobutamine, leads to a decrease in LV end-diastolic pressure in HFrEF suggesting reduced LV filling pressures, which leads to a reduction in cardiac sympathetic activity (Azevedo et al., 2000; Al-Hesayen et al., 2002). This is unlikely to have a neutral effect upon LV contractility.

LV contractility measured during exercise is likely to be the most relevant method of increasing heart rate to patients. Stress echocardiography is an established clinical tool (Rodgers et al., 2000). Bicycle stress echocardiography, with blood pressure, electrocardiogram, and LV volumes obtained at each step of increased heart rate, has been used to build a force-frequency relationship over a wide range of frequencies. The advantage of this approach is that all the basic parameters are routinely acquired during exercise stress echocardiography (Bombardini, T. et al., 2003). A disadvantage is that echocardiography during exercise stress can be technically demanding for the sonographer. Furthermore, exercise stress evaluates the effect of heart rate increase

and the effect of inotropic stimulation, rather than pure heart rate effect (Bombardini, T. et al., 2005b).

Using a permanently implanted pacemaker, rather than exercise or inotropic stimulation, to increase the heart rate, has been shown to be feasible (Picano et al., 2002). Since this method does not involve peripheral muscle contraction, intrinsic catecholamine release, or intravenous inotropes, it has been suggested that pacing allows a 'pure' index of LV contractility (Bombardini, T. et al., 2005b). Patients with cardiac resynchronisation devices are the sickest HFrEF cohort in whom controlling heart rates might be most beneficial. Furthermore, optimisation of heart rate ranges can be carefully controlled and monitored in pacemaker patients, making this group a useful first step in developing an understanding of the force-frequency relationship in HFrEF.

5.3 Study protocols

5.3.1 Baseline visit

I collected information on comorbidities, past medical history, medication types and doses, pacemaker device settings, and New York Heart Association (NYHA) functional classification. Height and weight were measured at the start of each visit to enable oxygen consumption measures and echocardiographic parameters to be adjusted for body weight and body surface area, respectively.

All participants gave informed written consent, underwent a full echocardiographic assessment, and performed a peak, symptom-limited treadmill-based familiarisation

cardiopulmonary exercise test with breath-by-breath metabolic gas analysis. The results from the familiarisation tests were not included in the final analysis.

5.3.2 Blinding protocol

The interventional studies had a double-blind design, such that both the participant and I were blinded to the pacemaker settings and exercise time. An un-blinded clinical scientist programmed the pacemaker device according to the randomisation, including sham reprogramming where appropriate to avoid the risk of un-blinding (Hauptman and Gottlieb, 2014). The same un-blinded clinical scientist also monitored the ECG during the CPET. A screen prevented the participant and me from seeing the monitor. The resting, peak and recovery blood pressures were measured using a standard manual cuff sphygmomanometer.

5.3.3 Exercise testing protocol

CPETs were performed using the Ultima Cardio₂ CPET system (Medical Graphics UK Limited, Gloucester, UK). The equipment was calibrated using manufacturer-recommended volume and gas calibration techniques before each test.

5.3.3.1 Preparation of the participant

The procedure was explained in full to each participant, and it was made clear, before the test started, that since the aim was to assess peak exercise capacity, they would be encouraged to exercise to their limit. The participant was informed that their heart would be monitored using an ECG, and their blood pressure would be recorded every three minutes. The importance of not talking was impressed upon each individual.

Participants could try the mouthpiece or mask on before starting the test, and they were reassured that the treadmill would start very slowly. To stop the test, participants were instructed to raise their right hand.

Exercise-ECG electrodes were placed in standard positions, a blood pressure cuff was placed around the participant's left arm, and the participant was then asked to sit on a chair on the treadmill. The mouthpiece and nose-clip (or mask) were then fitted to the participant, and baseline ECG and blood pressure recordings were taken. Resting metabolic gas and ventilation readings were recorded for a period of six minutes to ensure steady-state conditions were achieved. Further reassurance was provided where necessary to ensure stable baseline readings.

5.3.3.2 Exercise protocol

Participants were exercised using the ramping treadmill protocol which is characterised by a gradual increase in work rate (Porszasz et al., 2003). An advantage of the ramping protocol is the lack of the abrupt increase in work rate typical of the step protocols. The participant was encouraged to use the treadmill handrails only as a guide and for balance, since dependence on handrails reduces the work being performed and the reliability of the oxygen uptake data (Berling et al., 2006). A 12-lead, real-time ECG was displayed throughout the rest, test, and recovery phases. My view of the ECG monitor was obscured by a screen, to maintain blinding. 12-lead ECGs were printed at baseline, end of every three-minutes during exercise, at peak exercise and during recovery. Inspired and expired air was collected using a mouthpiece, and metabolic gas exchange analysis was carried out breath-by-breath.

Participants were encouraged prior to the test, to perform a maximal test, and asked to exercise to exhaustion or to the onset of symptoms. No motivation or instructions were given during the exercise phase. Procedures were in place to ensure that the test would be terminated in the event of symptoms or ECG abnormalities. A recovery time of at least six minutes was observed, or until heart rate and any ECG changes returned to normal. All the study CPETs took place in the same exercise laboratory. The CPET and ECG data were all anonymised, recorded and stored securely for subsequent analysis. For safety reasons, participants were asked to remain in the department for 30 minutes following their CPET.

5.3.4 Echocardiography protocol

Full baseline transthoracic echocardiography was carried out by me in accordance with British Society of Echocardiography guidelines (Wharton et al., 2015). All echocardiographic images were acquired using a commercially available ultrasound system (GE Vivid E95, GE Healthcare, Milwaukee, Wisconsin). Subsequent images were recorded at each 15-beat frequency increase during the incremental pacing protocol.

Images were stored as a raw digital imaging and communications in medicine (DICOM) format and exported to an offline workstation (EchoPAC, GE Healthcare) for storage and subsequent analysis. All images for analysis were anonymised.

Echocardiogram analysis was performed by me in random order. I was blinded to patient and study visit. Analysis included calculation of LV end-diastolic volume, LV end-systolic volume and LVEF, using 2D imaging from the apical four and two chamber windows, using the modified Simpson's biplane summation of discs method by tracing the endocardial border in diastole and in systole, excluding the papillary muscles (Lang et al., 2006). Care was taken to ensure that the apical four and two chamber windows were separated by 60°, and that the LV was not foreshortened (Wharton et al., 2015; Harkness et al., 2020). The frame at the R-wave was taken as end-diastole, and the frame with the smallest LV cavity was taken to represent end-systole (Otto, 2013). Since chamber size can be influenced by body size, structural indices were indexed to body surface area (BSA). The LVESVi was calculated at each stage as LVESV divided by BSA, where BSA was calculated using the Mosteller equation (Mosteller, 1987). An average of three measurements in sinus rhythm or five measurements in atrial fibrillation, from representative cycles, was used in the final analysis.

5.3.4.1 Force-frequency relationship assessment protocol

Echocardiographic images were recorded at rest. Pacing was then initiated at the lowest multiple of 10 beats per minute (bpm) above baseline heart rate. After four minutes a further set of echocardiographic images was taken, along with a blood pressure measurement. Subsequently the pacing rate was increased in stepwise intervals of 15 bpm with echocardiographic images and blood pressure recorded after every four-minute stage, until the maximum predicted heart rate, as predicted by Åstrand (220 bpm minus age) was reached, or the onset of symptoms or other

contraindications to continuing. At this stage peak data were collected and the pacemaker settings were returned to their pre-test settings.

5.3.4.2 Reproducibility

I re-reported each echocardiographic image set for intra-operator reproducibility. For inter-operator reproducibility another clinical scientist also reported each image set. Calculating LV volumes using the modified Simpson's biplane method of discs is widely used and accepted (Marwick, 2003; Harkness et al., 2020). In addition, end-systolic volume evaluation from echocardiographic images has a higher reproducibility than end-diastolic volume, and only the former was used in the calculation (Bombardini, T. et al., 2005b).

5.3.5 Blood pressure protocol

Calculation of the end-systolic pressure-volume relationship requires a measurement of the LV pressure at end-systole (Grossman, W. et al., 1977; Mehmel et al., 1981). Manual SBP recordings made using a sphygmomanometer and a standard stethoscope, were used as a surrogate for end-systolic pressure. SBP was recorded at the point at which the first tapping sound (phase 1 Korotkoff) occurred for two consecutive beats (Nutter, 1978).

5.3.6 Left ventricular contractility calculation

LV contractility at each heart rate was calculated by dividing SBP by LVESVi. Contractility was plotted against heart rate to produce the force-frequency relationship

curve. From this it was possible to determine the peak LV contractility, the slope of the force-frequency relationship, and the optimal heart rate for LV contractility (the critical heart rate (CHR)).

The force-frequency relationship was defined as up-sloping (or positive) when peak exercise SBP/LVESVi (end-systolic pressure volume ratio (ESPVR)) is higher than the baseline and intermediate values; biphasic when there is an initial up-sloping followed by a down sloping and peak ESPVR is lower than the intermediate values; and flat or negative when peak ESPVR is equal to or lower than the baseline values (Figure 3.2).

5.4 Assessing quality of life in HFrEF

The term 'quality of life' tends to be used to characterise an individual patient's quality of life from his or her own perspective (Katschnig, 2006). Patients with HFrEF have lower quality of life compared to healthy individuals and other patients with chronic illnesses. Physical and mental complications, such as fatigue, depression, anxiety, oedema, shortness of breath, and therapeutic processes, have a serious and negative impact on the quality of life of HFrEF patients (Moradi et al., 2020). The aim of assessing quality of life in research is to have an appraisal of how the physical and emotional effects of a condition affect an individual's life (Guyatt, 1993; Katschnig, 2006), and also to assess the effect on quality of life of interventions that do not extend life or delay time to next hospitalisation. Moreover, quality of life scores are a surrogate for hospitalisation and mortality rates (Alla et al., 2002).

Improving health-related quality of life is acknowledged as a key goal in the management of patients with HFrEF (Ponikowski et al., 2016), although individual patients may differ in their priorities with some regarding quality of life, and others longevity and a compromise to their quality of life, as their main objectives (Lewis et al., 2001).

Numerous quality of life assessment tools have been presented, although not all have been validated or are in routine use in heart failure (Koshy et al., 2020). The most frequently used are the Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire (Coelho et al., 2005). In general, these quality of life tools have not been assessed in relation to each other and are usually used independently.

The quality of life measures used for the studies in this thesis are the Minnesota Living with Heart Failure Questionnaire, and the generic EuroQOL 5D-3L (EQ-5D) questionnaire and visual analogue score.

The Minnesota Living with Heart Failure Questionnaire (Figure 5.1) is a 21-item patient self-assessment that measures patients' perceptions regarding the effect of HFrEF on their daily lives, and evaluates the response to heart failure treatment (Rector, 1987). Questions are answered using a Likert scale of 0-5, where 0 = the question has no impact on the patient's quality of life or is not applicable, and 5 = the greatest adverse effect. The overall quality of life score ranges from 0-105, with a higher score representing a poorer quality of life.

MINNESOTA LIVING WITH HEART FAILURE³ QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little			Very Much	
1. causing swelling in your ankles or legs?	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 yard difficult?	0	1	2	3	4	5
5. making your going places 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 your 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 recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods 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 a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your 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

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Figure 5.1: Minnesota Living with Heart Failure Questionnaire

The EQ-5D is a generic health questionnaire comprising two parts. The first part (Figure 5.2) assesses the patient's ability to mobilise, self-care and perform their usual activities, and also scores their pain/discomfort and anxiety/depression levels. The second part (Figure 5.3), a visual analogue score, allows the patient to rate their current overall health state on a scale of 0-100, with 0 being the lowest and 100 being the best possible health. The scores can then be converted into a country-specific index, where the maximum health value index of 1 indicates perfect health.



Health Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

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Figure 5.2: EQ-5D health questionnaire

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

Figure 5.3: EQ-5D visual analogue score

Chapter 6 : Can the force-frequency relationship be reliably described in patients with chronic heart failure and a pacemaker device?

Hypothesis: The force-frequency relationship can be reliably described in patients with chronic heart failure and a pacemaker.

6.1 Introduction

Chronic heart failure secondary to left ventricular systolic dysfunction, also known as heart failure with reduced ejection fraction (HFrEF), is a common syndrome characterised by symptoms of breathlessness and fatigue in the presence of left ventricular systolic dysfunction (LVSD). This limits the ability to perform even minor levels of exercise and activities of normal daily life, and may also contribute to long term deterioration in cardiac function.

In the normal heart, heart rate increases with increasing work to a peak that reduces with ageing. Patients with HFrEF have a lower peak heart rate than matched controls, and this has been considered as one reason for the reduced exercise tolerance in HFrEF (Colucci et al., 1989; White et al., 1995).

Cardiac output, heart rate and stroke volume are interdependent; continuously increasing the heart rate will affect stroke volume by reducing left ventricular (LV) filling

time and hence the LV end-diastolic volume (LVEDV) (Mattera et al., 2011). Increasing the force of contraction during exercise ensures that cardiac output matches venous return.

Increases in cardiac contractility during exercise are under two major influences: depolarisation-rate dependent (heart rate dependent; force-frequency relationship), and catecholamine-dependent. Increasing LV contractility through the force-frequency relationship compensates for reductions in diastolic filling time and avoids a paradoxical fall in cardiac output. It is therefore reasonable to assume that each heart has its own individual force-frequency relationship with a unique LV contractility rise with increasing heart rate, a unique heart rate at which LV contractility peaks, and its own unique downward slope following this peak, where LV contractility worsens with increasing heart rate. It is also recognised that the force-frequency relationship is abnormal in patients with HFrEF, with a lower contractile rise in response to an increase in heart rate, a lower peak LV contractility and a lower heart rate at which this occurs (Cotton et al., 2001; Kayhan et al., 2002). Whether the slope of deterioration is greater following this critical heart rate is unknown. This therefore leads to the hypothesis that patients with HFrEF might benefit from a lower heart rate to remain on the upward part of the force-frequency relationship slope.

Consequently, the aim of this observational study was to describe, using echocardiography, the contractile response to an increase in heart rate, in patients with HFrEF and controls, using their pacemaker device to increase the heart rate.

6.2 Methods

6.2.1 Study design

This investigation was an observational cohort study, designed to examine LV contractility in response to increases in heart rate, in patients with HFrEF and a pacemaker. All participants were approached at routine outpatient clinic appointments (either the heart failure clinic or pacemaker follow-up clinic) and given patient information sheets.

Ethical approval¹ was granted by the Health Research Authority (National Research Ethics Service Centre: Yorkshire and the Humber Research Ethics Committee reference: 12/YH/0097). National Health Service (NHS) permission² for this research was granted at Leeds Teaching Hospitals NHS Trust (LTHT) Research and Development Department (R&D) (LTHT R&D reference: CD12/10115).

6.2.2 Study population

Patients with HFrEF, persistent symptoms on exertion, and a pacemaker device, were recruited from the heart failure clinic. Each patient was invited to the Cardiovascular Clinical Research Facility (CVCRF) at LTHT. An unselected consecutive group of patients with a standard pacemaker, normal atrioventricular conduction, and no evidence of HFrEF, was also recruited from the pacemaker follow-up clinic, as a control group. Within this cohort of 105 participants, 90 had HFrEF (HFrEF group),

¹ See Appendix A

² See Appendix B

and 15 had pacing devices, with no symptomatic or structural evidence of heart failure (control group). All participants had a pacemaker device in situ for a clinical indication, with stable pacemaker device and lead variables for at least the previous three months.

6.2.3 Inclusion and exclusion criteria

Inclusion criteria for the test patients were: HFrEF with a left ventricular ejection fraction (LVEF) $\leq 50\%$ and symptoms of breathlessness or fatigue on exertion, on optimally tolerated medical therapy, with no change in medication over the previous three months, and stable symptoms. The pacemaker must have been implanted for at least three months and have stable lead variables. No other invasive cardiac procedures should have been undergone for at least the previous three months. All participants were capable of performing a peak cardiopulmonary exercise test on a treadmill and provided informed written consent.

Participants who were pacing dependent in the atrium, such that no heart rate rise during activity would be exhibited, were excluded. Other exclusion criteria consisted of the inability to provide informed written consent, and the presence of comorbidities that would limit exercise capacity, such as: uncontrolled angina, peripheral vascular disease, severe valvular dysfunction, severe obstructive or restrictive respiratory conditions, oxygen dependence, and any musculoskeletal abnormalities or disorders that could restrict walking on a treadmill. People with poor echocardiographic imaging quality were also excluded.

6.2.4 Study procedures

Each participant attended the CVCRF for a single visit. I collected information on comorbidities, past medical history, medication, pacemaker settings, and New York Heart Association (NYHA) functional class.

Echocardiographic images were collected at baseline, as described in chapter 5. Atrial pacing was then initiated in DDD mode³ (or VVI in patients with atrial fibrillation (AF)) for patients with a cardiac resynchronisation therapy (CRT) pacing device, or in AAI mode (or DDD with long atrioventricular delays to avoid right ventricular pacing, or VVI for patients in AF) for subjects without CRT, at the lowest multiple of 10 beats per minute (bpm) above baseline heart rate. The heart rate was then increased in stepwise 15 bpm intervals every four minutes, with echocardiographic images recorded at each stage. This was repeated until: the maximum predicted heart rate of 220 bpm minus age was reached, the patient complained of any discomfort, or significant electrocardiogram (ECG) changes were detected. LV contractility was calculated non-invasively using the systolic blood pressure and the LV end-systolic volume index, as described previously in chapter 5, to enable the force-frequency relationship curve to be plotted. The patient was not made aware of the heart rate, blood pressure or echocardiographic measures at any stage of the testing process. All pacemaker settings were returned to pre-test settings following the test.

³ Pacing codes, see Appendix E

6.2.4.1 Sample size calculation

Previous studies investigating LV contractility in patients with heart failure were able to demonstrate significance using heart failure cohorts of 11 ± 4 patients and control cohorts of 8 ± 3 subjects (Bombardini, T., 2005a). Therefore, the aim was to recruit at least 12 control participants. We expanded the HF_rEF cohort to allow for a greater standard deviation and lower reproducibility of non-invasive assessment of LV contractility to 90 subjects.

6.2.4.2 Reproducibility

I re-reported each image set, for intra-observer variability. Each anonymised set of echocardiographic images was also reported by my colleague for inter-operator variability. The three features of the force-frequency relationship were documented for each dataset: the heart rate at which peak LV contractility occurred (the critical heart rate), peak LV contractility, and the slope of the force-frequency relationship. Reproducibility of echocardiographic measures between myself and a clinical scientist colleague were described by intraclass correlation coefficient (ICC).

6.2.5 Statistical analysis

Data analysis was undertaken using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, New York), *R*: A Language and Environment for Statistical Computing version 3.2.3 (R Development Core Team, Vienna, Austria), and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as the mean and standard deviation, and non-normally distributed continuous variables were reported as the median and interquartile range.

Groups were compared using either the analysis of variance test (ANOVA) and unpaired Student *t* test for normally distributed values, or the Kruskal-Wallis *H* test (one-way analysis of variance of ranks) for non-normally distributed data. Categorical variables were analysed using the chi-squared test for contingency tables. All statistical tests were two-sided, and any *p* value less than 0.05 was considered to be statistically significant.

Reproducibility of echocardiographic measures were described by intraclass correlation coefficient (ICC) for both intra- and inter-observer variability.

6.3 Results

In total, 90 patients (mean age 73.5 ± 8.9 years) with chronic heart failure (mean LVEF $33.3 \pm 10.8\%$); and 15 control subjects (mean age 71.1 ± 16.0 years) with normal left ventricular function (mean LVEF, $55.6 \pm 5.3\%$) were recruited. The baseline clinical, echocardiographic, and pacemaker variables are shown in the baseline characteristics table (Table 6.1).

Table 6.1: Baseline characteristics

Demographic	Control (n = 15)	HFrEF patients (n = 90)	P Value ^a
Male	14 (93)	79 (88)	0.53
Age, years	71.1 ± 16.0	73.5 ± 8.9	0.39
Ischaemic heart disease	2 (13)	54 (60)	0.0008
Diabetes mellitus	4 (27)	28 (31)	0.73
BSA, m ²	1.9 ± 0.1	2.0 ± 0.2	0.07
NYHA functional class			0.0001
I	15 (100)	1 (1)	
II	n/a	70 (78)	
III	n/a	19 (21)	
Beta-blockers	3 (20)	82 (91)	0.0001
ACE inhibitor/ARB	3 (20)	77 (86)	0.0001
Furosemide dose, mg/day	0	47 (26)	
Digoxin	0 (0)	15 (17)	0.084
Aldosterone antagonist	0 (0)	38 (42)	0.001
Device (PPM/ICD/CRT)	n/a	14/9/67 (16/10/74)	
Atrial fibrillation	3 (20)	25 (28)	0.51
LV ejection fraction, %	55.6 ± 5.3	33.3 ± 10.8	0.0001
Critical heart rate, beats/min	126 ± 15	103 ± 22	0.0002
Peak contractility, SBP/LVESVi	9.8 ± 4.1	3.8 ± 3.7	0.0001
Force-frequency relationship ^b	0.054 ± 0.042	0.011 ± 0.028	<0.0001

Key: Values are n (%) or mean ± SD. ^ap values are from unpaired Student *t* tests or chi-squared tests as appropriate. ^bfrom likelihood ratio test in linear mixed model.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; CRT = cardiac resynchronisation therapy; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVESVi = left ventricular end-systolic volume index; m = metre; mg = milligram; min = minute; n/a = not applicable; NYHA = New York Heart Association functional class; PPM = permanent pacemaker; SBP = systolic blood pressure; SD = standard deviation.

The three key variables of peak LV contractility, critical heart rate, and the slope of the relationship between heart rate and LV contractility were established in all participants. This demonstrated that patients with HFrEF had lower peak LV contractility (3.8 ± 3.7 systolic blood pressure (SBP) divided by left ventricular end-systolic volume index (LVESVi) versus (vs) 9.8 ± 4.1 SBP/LVESVi; $p = 0.0001$), lower mean critical heart rate (103 ± 22 bpm vs 126 ± 15 bpm; $p = 0.0002$), and a lower slope of the relationship between heart rate and LV contractility below the critical heart rate (0.011 ± 0.028 vs 0.054 ± 0.042 ; $p = <0.0001$) than controls (Table 6.1, Figure 6.1).

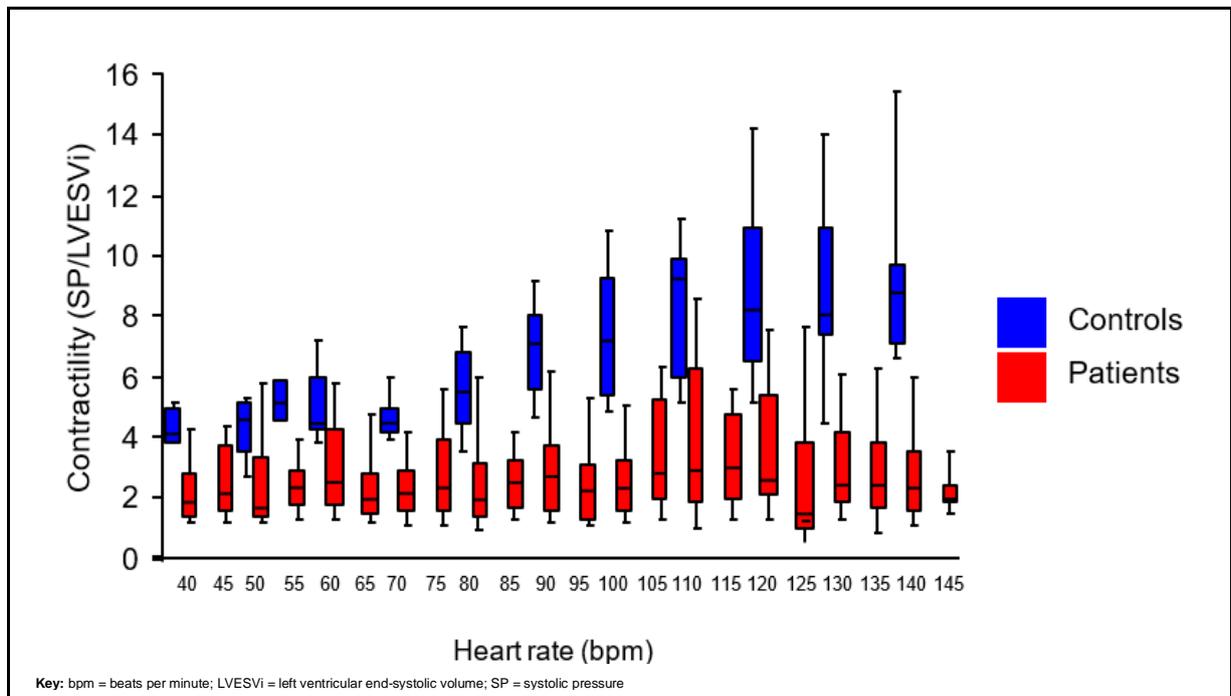


Figure 6.1: Force-frequency relationship in patients and controls

Separate models were required for each group, as compared with considering the data overall. We confirmed this by a likelihood ratio test for a saturated model compared with a simple additive model for heart rate, heart rate², and patient group (chi-square test = 214.63; $p < 10^{-15}$). We further examined the relationship in linear mixed effects

models and showed that there was little evidence of a quadratic relationship in each group of patients:

$$\text{Controls: } 0.2915604 + 0.0844503 \times \text{heart rate} - 0.00017 \times \text{heart rate}^2$$

$$\text{HFrEF: } 1.971 + 7.170e^{-03} + 2.510e^{-05} \times \text{heart rate}^2$$

In the controls, the linear term was significant ($p < 0.05$), and the quadratic term showed weak evidence of being required ($p = 0.15$). However, for HFrEF the linear term was not significant ($p = 0.334$), and the quadratic term was not significant ($p = 0.525$). Thus, in controls, for every 10-bpm increase in heart rate there was a 0.8-unit increase in LV contractility; in HFrEF the relationship was significantly less, at < 0.02 .

Using the Åstrand formula a higher peak heart rate was calculated than the measured critical heart rate for all except one HFrEF patient (mean heart rate 146 ± 9.0 bpm vs 103 ± 22 bpm; $p < 0.0001$), and all except three control participants (149 ± 16 bpm vs 126 ± 15 bpm; $p = 0.002$).

No relationship was found between age and any of the measures of cardiac function, including LV contractility. Critical heart rate and resting LV function were also unrelated in both groups. However, there was a strong correlation between peak LV contractility and baseline LVEF (0.50; 95% confidence interval (CI), 0.33 to 0.64; $p < 0.0001$) in patients with HFrEF (Figure 6.2).

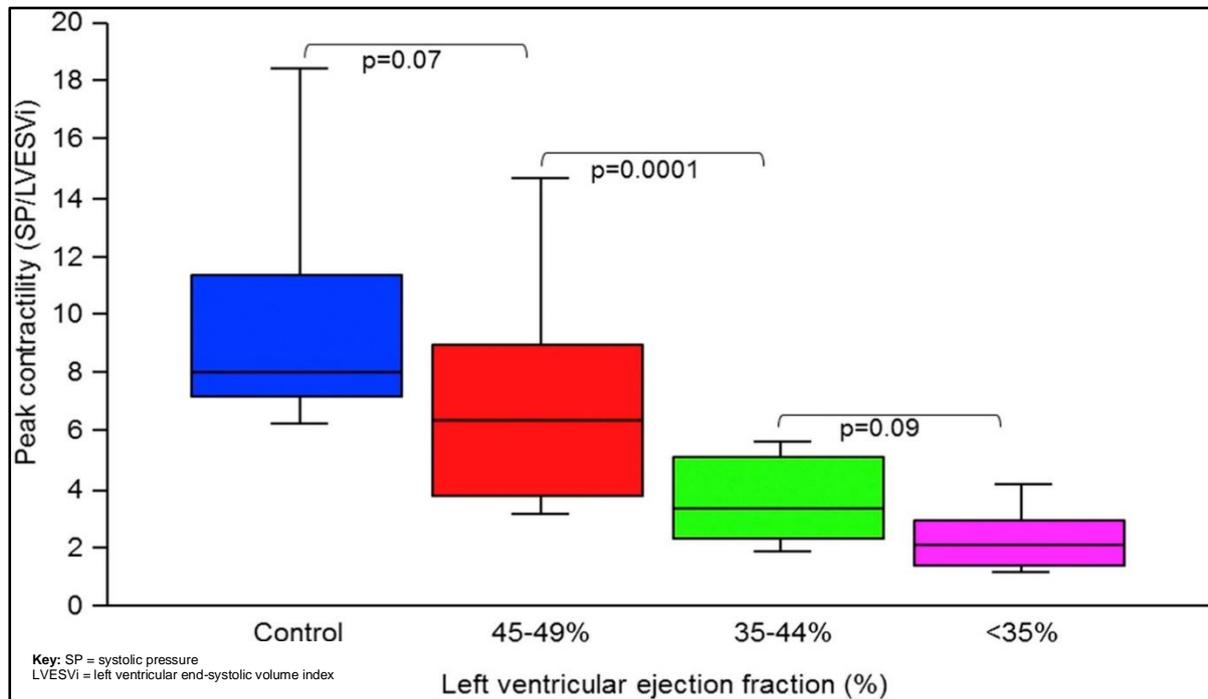


Figure 6.2: Peak contractility by levels of left ventricular dysfunction

Echocardiographic outcome measures demonstrated strong intra-observer agreement for LVEF [ICC 0.980 (95%CI, 0.794 to 0.998)]; LV end-diastolic volume (LVEDV) [ICC 0.996 (95%CI, 0.977 to 0.999)]; and LV end-systolic volume (LVESV) [ICC 0.991 (95%CI, 0.935 to 0.999)]. Strong inter-observer agreement was also demonstrated for LVEF [ICC 0.971 (95%CI, 0.776 to 0.997)]; LVEDV [ICC 0.993 (95%CI, 0.954 to 0.999)]; and LVESV [ICC 0.974 (95%CI, 0.754 to 0.997)].

6.4 Discussion

This study demonstrates that patients with HFrEF have an impaired force-frequency relationship curve, compared to the controls, which can be assessed using a non-

invasive, reproducible echocardiographic method. Furthermore, peak LV contractility is related to the baseline cardiac function. This impairment of the force-frequency relationship is likely to contribute to the lower cardiac output during activity that is a recognised feature of HFrEF.

Whilst LV contractility is seen to increase in both groups, the rate of change is very different. In the control group, LV contractility continues to increase until high heart rates are achieved, up to 140 bpm. However, in the patient group, the LV contractility response is slow, the peak LV contractility is lower, and the LV contractility declines at a lower heart rate, i.e. the critical heart rate is lower. Furthermore, increasing the heart rate beyond the critical heart rate in the patient group did not result in an increase in LV contractility.

Many datasets exist that describe maximal heart rate changes with ageing (Robinson, 1938; Cotes et al., 1973; Bassey, 1978; Robergs and Landwehr, 2002). However, the Åstrand formula (220 bpm minus age), an extrapolation of data from various sources, is the most frequently used dataset to describe maximal heart rate changes and age. All these datasets are based on experiments on healthy individuals exercising to physiological maximum.

Consequently, it is possible that conventional pacemaker heart rate-response algorithms applied to HFrEF patients, increase the heart rate beyond the critical heart rate and onto the downward portion of the LV contractility curve, such that the cardiac output *decreases* as the heart rate *increases*.

6.5 Limitations

This observational study contains biases that are common in studies of this type. A degree of patient selection bias is present since those patients with advanced heart failure or comorbidities may be less enthusiastic to participate in clinical research.

The study necessarily restricts recruitment to those patients with a pacemaker device, although it is possible that they may have a different contractile response to increased heart rates from those without a pacemaker device.

Image quality can be a limiting factor in obtaining accurate measurements using echocardiography. In this study, LV end-diastolic and end-systolic volumes were measured using the modified Simpson's biplane method. This method, using echocardiography, is widely used, and accepted. The evaluation of end-systolic volume has a higher reproducibility than end-diastolic volume, using echocardiography, and only the former is used to build the force-frequency relationship (Bombardini, T. et al., 2005b). Furthermore, strong intra-observer and inter-observer agreement were found.

6.6 Conclusion

The force-frequency relationship can be reliably and non-invasively assessed in patients with HFrEF, and non-HFrEF participants, with a pacemaker device providing the heart rate increments. In control participants, higher heart rates resulted in greater

LV contractility, and greater potential for increased cardiac output in response to activity. However, the key findings from this observational study of a lower slope in response to heart rate increases, a lower peak LV contractility, and a lower critical heart rate in patients with HFrEF, confirm, non-invasively, the marked impairment of the force-frequency relationship in HFrEF, independent of cardiac loading or physical activity levels. Moreover, the data provide solid evidence that pacemaker heart rate programming should consider the underlying cardiac disease and not simply the age of the patient.

Chapter 7 : Does pacemaker programming tailored to the force-frequency relationship improve exercise tolerance in patients with chronic heart failure?

Hypothesis: Tailoring pacemaker settings based on a non-invasive assessment of the force-frequency relationship in patients with chronic heart failure can improve exercise capacity.

7.1 Introduction

Heart failure with reduced ejection fraction (HFrEF) is characterised by exercise intolerance and symptoms of breathlessness and fatigue. This limits patients' ability to perform even minor levels of exercise, impacting on their daily activities of life, for example walking to the local amenities. Key features of HFrEF thought to contribute to exercise intolerance include impaired cardiac contractility and therefore cardiac output during activity. It is commonly perceived that these are compounded by reduced heart rate rise, and that this in turn is worsened by high dose beta-adrenoceptor antagonists (β -blocker).

Optimal treatment for around one third of patients with HFrEF includes a resynchronisation pacemaker (cardiac resynchronisation therapy (CRT)). In addition to retuning the timing of cardiac contraction to increase cardiac efficiency, the device can also increase the heart rate during activity (rate-response pacing). The Åstrand formula of 220 beats per minute (bpm) minus age, is the only available guidance for

programming the rate-response setting. However, this formula, along with many published datasets describing heart rate changes with age, is based on data from experiments in healthy individuals exercising to physiological maximum.

My data shown in chapter 6 demonstrated, using a non-invasive, reproducible method, that patients with HFrEF have a lower slope in response to heart rate increases, lower peak left ventricular (LV) contractility and a lower critical heart rate than controls. I also showed that by using this method, an ideal range for heart rate during activity could be determined in all patients. The optimal heart rate for most patients was between 90 and 110 bpm. It is therefore possible that using conventional heart rate-response algorithms in HFrEF will increase the heart rate beyond the critical heart rate, so that LV contractility and cardiac output are decreasing whilst the heart rate is continuing to increase.

The aim of this study, therefore, was to determine, whether maintaining heart rate during exercise on the upward slope of the force-frequency relationship curve, and below the critical heart rate, has a beneficial effect on exercise time in patients with HFrEF.

7.2 Methods

7.2.1 Study design

The design was a randomised, double-blind, placebo-controlled, cross-over study, to compare treadmill exercise time using conventional heart rate-response settings with

heart rate-response settings based on the data from a force-frequency relationship assessment.

Ethical approval⁴ was granted by the Health Research Authority (National Research Ethics Service Committee: Yorkshire and the Humber Research Ethics Committee reference: 12/YH/0097). National Health Service (NHS) permission⁵ for this research was granted at Leeds Teaching Hospitals NHS Trust (LTHT) Research and Development Department (R&D) (LTHT R&D reference: CD12/10115). All participants provided informed written consent.

7.2.2 Study population

Patients with HF_rEF, who had taken part in the observational study and who did not have peripheral vascular disease or non-cardiac conditions that could restrict walking on a treadmill, were invited to return for two additional visits, one week apart, at the Cardiovascular Clinical Research Facility (CVCRF) at LTHT. An unselected subgroup was invited to return for a third (blinded) exercise test, with the pacemaker device programmed to fixed rate pacing during exercise.

7.2.3 Study procedures

Before each test the pacemaker was interrogated. Patients were then randomly assigned to: conventional settings (heart rate-response on exercise to achieve age-

⁴ Ethical approval, see Appendix A

⁵ NHS permission, see Appendix B

determined maximum), optimised heart rate-response on exercise, based on the individual's force-frequency relationship assessment from the observational study (chapter 6) (limiting heart rate rise to below the critical heart rate), or, for patients consenting to perform a third test, fixed-rate pacing with rate-response settings programmed to 'off'. Randomisation was achieved through a computer-generated random number method.

The cardiopulmonary exercise test equipment was recalibrated prior to each test, using the manufacturer-recommended volume and gas calibration techniques. Participants performed a peak, symptom-limited exercise test, using the ramping treadmill protocol (Porszasz et al., 2003) at each visit, to measure exercise time. Expired air was collected, and metabolic gas exchange analysis was performed throughout the test (Ultima CardO₂, Medical Graphics, St. Paul, Minnesota). Heart rate (bpm), oxygen consumption (VO₂) (millilitres per kilogram per minute (ml/kg/min)), and carbon dioxide output (VCO₂) (ml/kg/min), were recorded as 15-second averages. The V-slope method was used to calculate anaerobic threshold. Participants were asked to exercise to exhaustion, and no further motivation or instructions were given.

To maintain blinding, neither I nor the participants were made aware of the pacemaker programming mode or the randomisation. Furthermore, the electrocardiogram (ECG) monitor was obscured throughout the test (baseline, exercise, and recovery) from the participants and me. An un-blinded clinical scientist monitored the ECG throughout, communicated with the other team members only if there were safety concerns, and reprogrammed the pacemaker to its pre-test settings after the cardiopulmonary

exercise test was completed. Participants' pacing files were labelled to indicate that the patient was taking part in a research study, and that pacemaker settings should remain unchanged for the intervening week between research visits, unless symptomatic. For safety reasons, participants remained in the CVCRF for 30 minutes after completion of their test. All data were stored in a secure anonymised electronic database.

7.2.3.1 Sample size calculation

The primary endpoint of the study was change in exercise time. A key secondary endpoint was peak oxygen consumption. Using the guidelines for pilot studies (Lancaster et al., 2004; Julious, 2005), and a dropout rate of 20%, the aim was to recruit 28 patients to achieve 20 participants with complete data.

7.3 Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, New York), *R*: A Language and Environment for Statistical Computing version 3.2.3 (R Development Core Team, Vienna, Austria), and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

The Shapiro-Wilk test was used to determine whether the participant demographics, cardiopulmonary exercise test and echocardiogram variables were normally distributed. Normally distributed variables were reported as mean and mean \pm standard deviation (SD), and non-normally distributed continuous variables were

reported as median (interquartile range). Associations between groups or interventions and baseline characteristics were assessed using either analysis of variance and the 2-sample Student t test for normally distributed values, or the Kruskal-Wallis H test (one-way analysis of variance on ranks) for non-normally distributed data. Similar associations with categorical variables were analysed using the chi-squared test for contingency tables.

Once a familiarisation test has been performed, a peak exercise test is not a training stimulus (Witte, K. K. et al., 2003). However, to account for any carryover effects, we analysed the interventional crossover study using a linear mixed model with a random effect for subject. For each endpoint Y_{ak} (e.g., exercise time) under consideration in the study:

$$Y_{ak} = \mu + d_i + \pi_j + i_n + \alpha_k + i_{nk}$$

where, $i_{nk} \sim N(0, \sigma_{\varepsilon}^2)$, $\alpha_k \sim N(0, \sigma_{\alpha}^2)$ and μ is the overall mean, τ is the treatment effect, π is the period effect, and λ is the carryover effect (which is mathematically identical to an interaction term between treatment and period). This model was estimated using PROC MIXED in SAS, and least squares means were estimated for each of these terms and their differences.

All statistical tests were 2-sided, and any p-value <0.05 was considered to be statistically significant.

7.4 Results

In total, 52 patients (mean age 73.8 ± 9.6 years; mean left ventricular ejection fraction (LVEF) $\pm 11\%$) who had taken part in the observational cohort study (Chapter 6) were recruited to this subsequent interventional study.

Table 7.1: Baseline characteristics

Variable	(n = 52)
Male	44 (85)
Age, years	73.8 ± 9.6
Aetiology	
Ischaemic heart disease	33 (63)
Diabetes mellitus	15 (29)
BSA, m ²	2.0 ± 0.2
NYHA functional class	
I	0 (0)
II	43 (83)
III	9 (17)
Beta-blockers	47 (90)
ACE inhibitor/ARB	47 (90)
Furosemide dose, mg/day	43 ± 24
Digoxin	6 (12)
Aldosterone antagonist	21 (40)
Device (CRT/ICD)	50/2 (96/4)
Atrial fibrillation	15 (29)
LV ejection fraction, %	32 ± 11
Critical heart rate, beats/min	101 ± 19
Peak contractility, SBP/LVESVi	3.4 ± 2.0
Key: Values are n (%) or mean \pm SD.	
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; CRT = cardiac resynchronisation therapy; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVESVi = left ventricular end-systolic volume index; m = metre; mg = milligram; min = minute; NYHA = New York Heart Association functional class; SBP = systolic blood pressure; SD = standard deviation.	

The baseline clinical and echocardiographic variables (Table 7.1) were not different from those of patients in the observational cohort study. A sub-group of 12 patients underwent a third test with their device programmed to fixed-rate pacing. Exercise variables for conventional and heart rate-response tailored for LV contractility are shown in Table 7.2.

Table 7.2: Exercise variables during conventional and optimised heart rate-response programming

Variable	Programming	Mean	95% Confidence interval	Mean difference	95% Confidence interval	p value
Exercise time, s	Tailored	474.74	(420.69 to 528.79)	49.85	(18.41 to 81.29)	0.0025
	Not tailored	424.89	(370.84 to 478.94)			
Peak Vo₂, ml/kg/min	Tailored	17.31	(16.00 to 18.62)	0.75	(0.16 to 1.34)	0.0134
	Not tailored	16.56	(15.25 to 17.87)			
O₂ pulse	Tailored	13.39	(12.33 to 14.45)	3.21	(2.33 to 4.08)	<0.0001
	Not tailored	10.19	(9.13 to 11.25)			
VE/Vco₂ slope	Tailored	31.80	(29.81 to 33.78)	-1.89	(-3.38 to -0.40)	0.0139
	Not tailored	33.69	(31.70 to 35.67)			
Peak RER	Tailored	1.01	(0.99 to 1.04)	-0.00	(-0.03 to 0.02)	0.7456
	Not tailored	1.02	(0.99 to 1.05)			
Peak heart rate, beats/min	Tailored	109.11	(106.01 to 112.21)	-28.88	(-32.83 to 24.93)	<0.0001
	Not tailored	137.99	(108.87 to 167.12)			

Key: min = minute; ml/kg/min = millilitre/kilogram/minute; O₂ = oxygen; RER = respiratory exchange ratio; s = second; VE/Vco₂ slope = relationship between ventilation and carbon dioxide output; Vo₂ = oxygen consumption.

Optimised settings (heart rate-response tailored to the force-frequency relationship) were associated with improved exercise time (475 ± 189 seconds (s) versus (vs) 425 ± 198 s; p = 0.003) (Figure 7.1A), peak oxygen consumption (17.3 ± 4.6 ml/kg/min vs 16.6 ± 4.7 ml/kg/min; p = 0.01) (Figure 7.1B), oxygen pulse (13.39 (95% confidence interval (CI), 12.33 to 14.45) vs 10.19 (95%CI, 9.13 to 11.25); p <0.0001) (Figure 7.1C), and lower slope of the relationship between ventilation and carbon dioxide

(VE/VCO_2 slope) (31.80 (95%CI, 29.81 to 33.78) vs 33.69 (95%CI, 31.70 to 35.67); $p = 0.014$). Peak heart rate was also lower with optimised settings (109.11 (95%CI, 106.01 to 112.21) vs 137.99 (95%CI, 108.87 to 167.12); $p < 0.0001$) (Figure 7.1D).

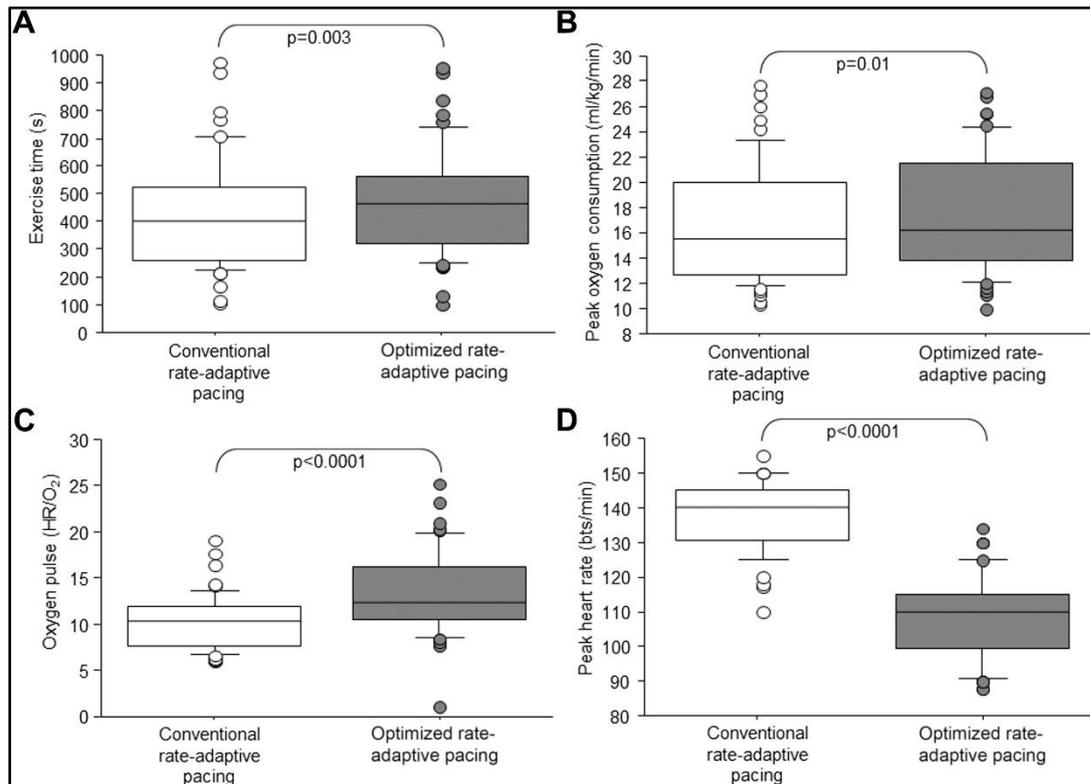


Figure 7.1: Results of the randomised, placebo-controlled double-blind crossover study of conventional versus optimised rate-adaptive pacing settings

The sub-group of 12 unselected patients programmed to fixed-rate pacing (rate-response function programmed 'off'), for the duration of the cardiopulmonary exercise test, had similar exercise times to conventional age-related rate-response pacing (Figure 7.2B).

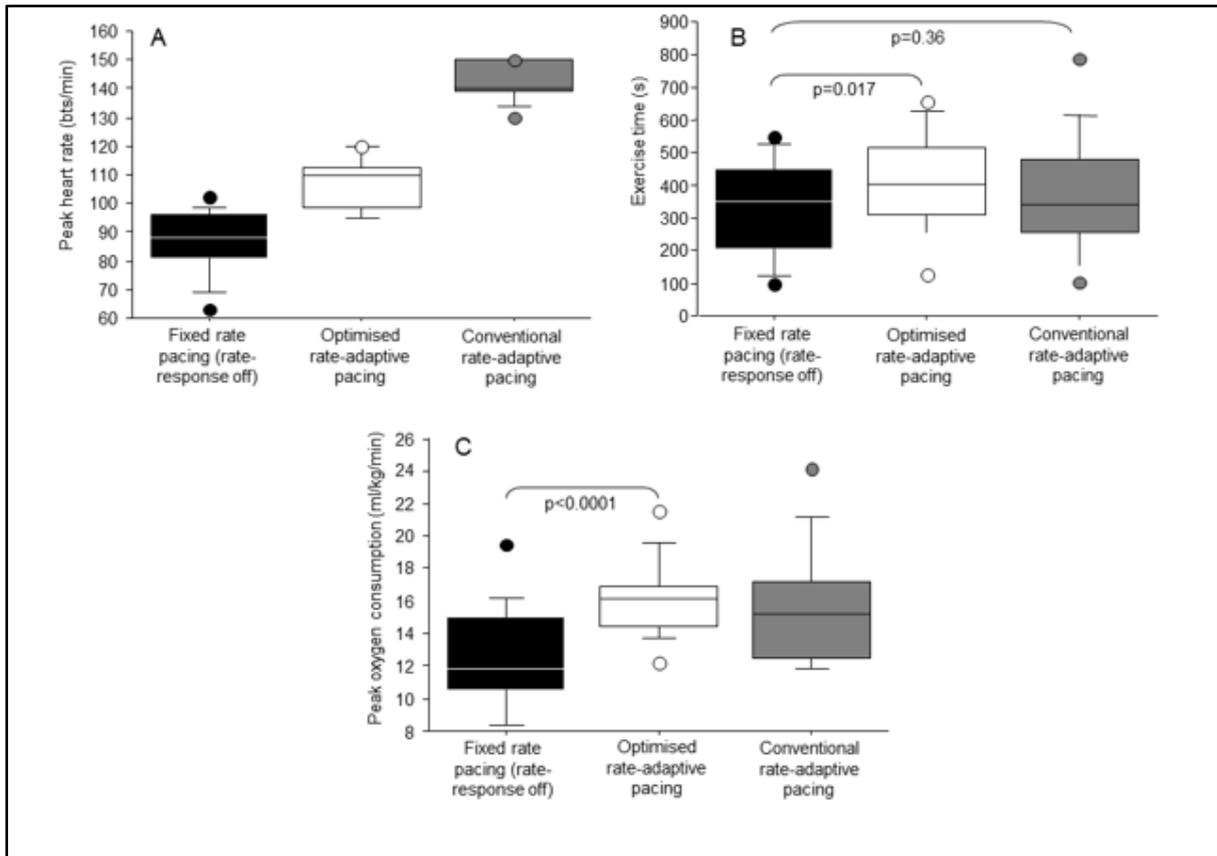


Figure 7.2: Results comparing fixed-rate, tailored and conventional rate-response programming

Table 7.3: Exercise variables in patients with diabetes mellitus during conventional and optimised heart rate programming

Variable	Programming	Mean	95% Confidence Interval	Mean difference	95% Confidence Interval	p-value
Exercise time, s	Tailored	433.00	(332.87 to 533.13)	74.78	(14.07 to 134.49)	0.0196
	Not tailored	358.22	(258.09 to 458.36)			
Peak VO₂ (ml/kg/min)	Tailored	15.99	(13.89 to 18.08)	0.63	(-0.37 to 1.63)	0.1956
	Not tailored	15.36	(13.86 to 17.45)			
O₂ pulse	Tailored	13.53	(11.70 to 15.36)	3.43	(1.94 to 4.92)	0.0003
	Not tailored	10.10	(8.27 to 11.93)			
VE/CO₂ slope	Tailored	32.05	(27.96 to 36.13)	-2.14	(-4.70 to 0.42)	0.0940
	Not tailored	34.19	(30.10 to 38.27)			
Peak RER	Tailored	1.00	(0.95 to 1.06)	0.00	(0.07 to 0.06)	0.9562
	Not tailored	1.00	(0.95 to 1.06)			
Peak heart rate (beats/min)	Tailored	108.39	(102.21 to 114.57)	-29.56	(-37.60 to -21.51)	<0.0001
	Not tailored	137.94	(131.77 to 144.12)			

Values are means (SD)

Key: min = minute; ml/kg/min = millilitre/kilogram/minute; O₂ = oxygen; Peak VO₂ = peak oxygen consumption; RER = respiratory exchange ratio; s = second; SD = standard deviation; VE/CO₂ slope = relationship between ventilation and carbon dioxide output.

Table 7.4: Exercise variables in patients with atrial fibrillation during conventional and optimised heart rate programming

Variable	Programming	Mean	95% Confidence Interval	Mean difference	95% Confidence Interval	p-value
Exercise time, s	Tailored	447.60	(336.01 to 559.19)	63.45	(-4.68 to 131.58)	0.0654
	Not tailored	384.15	(272.56 to 495.74)			
Peak VO₂ (ml/kg/min)	Tailored	15.13	(12.79 to 17.47)	0.49	(-0.67 to 1.64)	0.3788
	Not tailored	14.65	(12.30 to 16.99)			
O₂ pulse	Tailored	11.51	(9.78 to 13.25)	3.00	(1.58 to 4.42)	0.0005
	Not tailored	8.51	(6.78 to 10.25)			
VE/VCO₂ slope	Tailored	33.53	(29.70 to 37.35)	-0.81	(-5.08 to 3.47)	0.6906
	Not tailored	34.33	(30.51 to 38.51)			
Peak RER	Tailored	1.04	(0.97 to 1.10)	0.03	(-0.05 to 0.10)	0.4734
	Not tailored	1.01	(0.94 to 1.08)			
Peak heart rate (beats/min)	Tailored	106.05	(100.39 to 111.71)	-31.50	(-40.11 to -22.89)	<0.0001
	Not tailored	137.55	(131.89 to 143.21)			

Values are means (SD)

Key: min = minute; ml/kg/min = millilitre/kilogram/minute; O₂ = oxygen; Peak VO₂ = peak oxygen consumption; RER = respiratory exchange ratio; s = second; SD = standard deviation; VE/VCO₂ slope = relationship between ventilation and carbon dioxide output.

There was no significant difference in the benefits of tailored programming between those with and without diabetes mellitus (Table 7.3), those with and without atrial fibrillation (Table 7.4), and those with and without ischaemic heart disease (Table 7.5).

Table 7.5: Exercise variables in patients with ischaemic heart disease during conventional and optimised heart rate programming

Variable	Programming	Mean	95% Confidence Interval	Mean difference	95% Confidence Interval	p-value
Exercise time, s	Tailored	451.79	(392.22 to 511.35)	57.30	(16.93 to 97.67)	0.0069
	Not tailored	394.49	(334.92 to 454.06)			
Peak VO₂ (ml/kg/min)	Tailored	16.59	(14.91 to 18.27)	0.94	(0.20 to 1.69)	0.0150
	Not tailored	15.65	(13.97 to 17.33)			
O₂ pulse	Tailored	13.19	(11.85 to 14.54)	3.74	(2.76 to 4.71)	<0.0001
	Not tailored	9.46	(8.12 to 10.80)			
VE/CO₂ slope	Tailored	32.10	(29.78 to 34.42)	-1.99	(-3.99 to 0.00)	0.0505
	Not tailored	34.09	(31.77 to 36.42)			
Peak RER	Tailored	1.02	(0.99 to 1.06)	0.00	(-0.04 to 0.03)	0.8828
	Not tailored	1.03	(0.99 to 1.06)			
Peak heart rate (beats/min)	Tailored	106.26	(102.67 to 109.85)	-31.56	(-36.16 to -26.95)	<0.0001
	Not tailored	137.82	(134.22 to 141.41)			

Values are means (SD)

Key: min = minute; ml/kg/min = millilitre/kilogram/minute; O₂ = oxygen; Peak VO₂ = peak oxygen consumption; RER = respiratory exchange ratio; s = second; SD = standard deviation; VE/CO₂ slope = relationship between ventilation and carbon dioxide output.

7.5 Discussion

This study has demonstrated that by programming the heart rate-response algorithm in patients with HFrEF, so that heart rate during exercise remains below the critical heart rate and on the upward slope of the LV contractility curve, exercise capacity can be improved.

A characteristic of HFrEF is exercise intolerance. This is thought to be as a result of reduced cardiac output at rest because of myocardial contractile impairment, and impaired increase in cardiac output during exercise, leading to lower VO_2 , exercise intolerance, and fatigue. Cardiac output is dependent on both heart rate and stroke volume, which are interdependent because of the force-frequency relationship. The attenuation of the force-frequency relationship seen in HFrEF, such that LV contractility does not increase to the same degree or in the same manner as in the normal heart, raises the possibility that there may be a lower optimum heart rate range for cardiac contractility in patients with HFrEF than in non-HFrEF patients.

Heart rate-response cardiac pacing was developed with the intention of optimising exercise tolerance in patients with chronotropic incompetence (Alt et al., 1995; McElroy et al., 1988). Pacemakers can be programmed to deliver either fixed-rate pacing or use a rate-response pacing algorithm, where the heart rate is altered in proportion to the level of activity as detected by internal device sensors. Rate-response pacing in patients without HFrEF is associated with an increase in cardiac output during exercise (McMeekin et al., 1990), but inconsistent improvements in exercise capacity (Osswald et al., 1996; Galtes and Lamas, 2004), when compared to fixed rate pacing. However, it has been demonstrated that conventional rate-response pacing in patients with HFrEF does not improve exercise capacity compared with fixed-rate pacing (Ginzton et al., 1984), and that rate-response pacing may worsen prognosis and cardiac function (Thackray et al., 2006; Nägele, H et al., 2008). This might be because in HFrEF, conventional rate-response pacing algorithms do not consider the altered cardiac contractile function.

Using the critical heart rate (calculated from the force-frequency assessment in chapter 6), the current randomised, double-blind, placebo-controlled, cross-over study of optimised rate-response programming versus conventional rate-response programming, aimed to optimise rate-response pacemaker programming in patients with HFrEF. The results have demonstrated that personalised, precise-approach rate-response pacemaker programming can acutely improve treadmill exercise time and peak oxygen consumption.

7.6 Limitations

The study included only patients with a pacemaker device, who may present a different contractile response to increased heart rates from patients without a pacemaker device.

Although the treadmill exercise modality and the ramping protocol may not have been ideal for all patients, it was used to allow comparison of exercise times, in addition to metabolic gas analysis data, and because treadmill-based activity is associated with greater upper body movement required for activation of the rate-response algorithms in pacemaker devices. Furthermore, the early, low workload at the beginning of the protocol, allowed those patients with the greatest limitation in exercise capacity to complete some exercise, reducing the bias towards less limited patients.

7.7 Conclusion

Optimising heart rate-response programming of the pacemaker device to maintain the heart rate below the critical heart rate during exercise, as determined by the individual's force-frequency curve, is associated with an increase in exercise time.

This raises the possibility that one might want to remove the term chronotropic incompetence and perhaps replace it with 'chronotropic adaptation' which in worsening HFrEF could be a cardio-protective mechanism to maximise contractile response and cardiac output during exercise.

Chapter 8 : Can optimised heart rate settings lead to longer term benefits in exercise capacity?

Hypothesis: Six months of tailored pacemaker heart rate settings based on a non-invasive assessment of the force-frequency relationship in patients with HFrEF improves exercise capacity.

8.1 Introduction

Although a limitation in heart rate rise is a potential contributor to a lower cardiac output, heart rate lowering medication is not associated with impaired submaximal or peak exercise tolerance. Furthermore, increasing heart rate during exercise in patients with heart failure with reduced ejection fraction (HFrEF) and a pacemaker device, does not increase exercise capacity (Jamil et al., 2016). In health, higher heart rates lead to greater left ventricular (LV) contractility, and therefore greater potential for cardiac output to increase in response to increasing activity. However, in HFrEF the normally close relationship between heart rate, LV contractility, and stroke volume, known as the force-frequency relationship, is attenuated, such that LV contractility does not increase normally as the heart rate rises during activity. Indeed, in HFrEF, this physiological response is attenuated and is characterised by a decline in LV contractility above the critical heart rate (Cotton et al., 2001; Kayhan et al., 2002).

In chapter 6, I described that the force-frequency relationship can be reliably assessed in patients with HFrEF who have a pacemaker device, in a non-invasive manner, using

echocardiography. I have also demonstrated that optimising heart rate-response pacing to keep heart rate below the critical heart rate during exercise, is associated with an acute increase in exercise time (chapter 7). The aim of the current study was to determine whether tailoring the rate-response pacing algorithm, using the physiology of the individual patient's force-frequency relationship, leads to longer term improvements in exercise capacity and quality of life, compared with conventional age-guided rate-response pacing, in patients with HFrEF and a pacemaker device, without compromising cardiac function.

8.2 Methods

8.2.1 Study design

The study design was a randomised, controlled, double-blind, parallel-group trial comparing optimised rate-response programming with conventional rate-response settings, to determine whether the short-term improvements demonstrated in chapter 7, translate into longer term benefits.

Ethical approval⁶ was granted by the Health Research Authority of the United Kingdom (National Research Ethics Service Committee: East Midlands-Derby REC reference: 17/EM/0004). National Health Service (NHS) permission⁷ for this research was granted at Leeds Teaching Hospitals NHS Trust (LTHT) Research and Development Department (R&D) (LTHT R&D reference: CD16/88879).

⁶ Ethical approval, see Appendix C

⁷ NHS permission, see Appendix D

8.2.1.1 Patient and public involvement and engagement

The research question was prompted by patients with HFrEF and pacemakers attending outpatient clinics, with symptoms suggestive of HFrEF. The study was initially discussed with a well-established local patient and public involvement and engagement advisory group (PPIE-AG) consisting of people with cardiovascular disease and their families. The PPIE-AG advised on suitable follow-up periods, study procedures, information sheets and dissemination plans. Since reduced exercise capacity is a fundamental feature of HFrEF, members of the PPIE-AG were particularly interested in the potential for increased exercise capacity.

8.2.2 Study population

Patients attending the heart failure outpatient clinic, the pacemaker follow-up clinic, and previous participants in the acute crossover study (chapter 7) from 22 June 2017, were approached and given the participant information sheet. This was followed up with a telephone call to ensure that any remaining questions were answered. Those patients who agreed to take part were invited to the Cardiovascular Clinical Research Facility (CVCRF) at LTHT.

8.2.3 Inclusion and exclusion criteria

Patients with stable (for at least three months) symptomatic HFrEF, a cardiac pacemaker (for at least three months), taking optimal guideline-directed medical therapy, able to perform a symptom limited peak exercise test, willing and able to give written informed consent, were invited to take part. Those patients who had angina pectoris symptoms limiting exercise tolerance, unstable heart failure symptoms

(medical therapy alterations within the previous three months), poor echocardiographic image quality, or taking calcium channel blockers, were excluded from taking part in the study.

8.2.4 Baseline study procedures

A standard pacemaker device check was performed, along with a full baseline echocardiogram. Information was collected on comorbidities, past medical history, medication, pacemaker settings, and New York Heart Association (NYHA) functional class. The force-frequency relationship was assessed, to allow the critical heart rate and the optimal range of heart rate to be determined. This was achieved using echocardiography to non-invasively estimate cardiac contractility, and the pacemaker to increase the heart rate.

8.2.4.1 Echocardiography

Images were recorded in two- and four-chamber views (GE Vivid E95, GE Healthcare, Milwaukee, Wisconsin) at resting heart rate and at each 15 beats per minute (bpm) increase during an incremental pacing protocol. Images were stored anonymously in the EchoPAC digital imaging system (GE Healthcare) and analysed offline. Analysis included a calculation of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LV ejection fraction (LVEF), using the modified Simpson's biplane method of discs, by tracing the endocardial border, excluding the papillary muscles (Wharton et al., 2015). The frame at the R-wave was taken as end-diastole, and the frame with the smallest LV cavity was taken as end-systole. A mean of three measurements (or five measurements if in atrial fibrillation (AF)) was used in the final

analysis. The LV end-systolic volume index (LVESVi) was calculated by dividing end-systolic volume by body surface area, where body surface area was calculated using the Mosteller equation (Mosteller, 1987). To minimise observer bias, the analysis of the follow-up echocardiographic images was performed blinded to the images taken at baseline.

8.2.4.2 Blood pressure measurement

Dividing systolic blood pressure (measured manually) by LV end-systolic volume index gives a surrogate of LV contractility, which has been validated against invasive methods (Bombardini, T. et al., 2003; Bombardini, T. et al., 2005b). Blood pressure recordings, using a sphygmomanometer and a standard stethoscope, were taken at the same time as the echocardiographic images at each heart rate stage.

8.2.4.3 Pacemaker programming protocol

The first set of echocardiographic images was recorded at rest, with intrinsic atrial rhythm or a base rate of 40 bpm. Atrial pacing was then initiated at the lowest multiple of 10 bpm above baseline heart rate in the DDD mode⁸ (or VVI in patients with AF) for patients with a cardiac resynchronisation therapy (CRT) device, and AAI mode (or DDD with long atrioventricular delays to avoid right ventricular pacing, or VVI for those in AF) for patients without CRT. After four minutes of these programmed settings, another set of echocardiographic images was recorded. The pacing rate was subsequently increased in stepwise intervals of 15 bpm, along with echocardiographic

⁸ Pacing modes, see Appendix E

images being recorded after every four-minute stage, until the maximum heart rate as predicted by the Åstrand equation (220 bpm minus age) was reached or patients became symptomatic of angina or breathlessness. Peak data were then collected before reprogramming the pacemaker device back to its pre-test settings. Patients then rested within the CVCRF for 30 minutes after this testing procedure.

8.2.4.4 Force-frequency calculation

Systolic blood pressure was divided by the end-systolic volume index to give a surrogate of LV contractility. Plotting LV contractility against each programmed heart rate allowed the critical heart rate, peak LV contractility, and the slope of the force-frequency relationship, to be calculated for each patient.

8.2.4.5 Exercise protocol

The cardiopulmonary exercise test (CPET) equipment was recalibrated prior to each test, using the manufacturer-recommended volume and gas calibration techniques. Participants then performed a peak symptom-limited, CPET, using the ramping treadmill protocol (Porszasz et al., 2003), to measure exercise time. Expired air was collected, and metabolic gas exchange analysis was performed throughout the test (Ultima CardO₂, Medical Graphics, St. Paul, Minnesota). Heart rate (bpm), oxygen uptake (VO₂) (millilitres per kilogram per minute) (ml/kg/min), and carbon dioxide output (VCO₂) (ml/kg/min), were recorded as 15-second averages. The V-slope method was used to calculate anaerobic threshold. Participants were asked to exercise to exhaustion, and no further motivation or instructions were given.

The effective delivery of biventricular stimulation in those patients with CRT, was confirmed from electrocardiographic (ECG) traces at peak exercise, at both time points (baseline and follow-up), by the absence of fusion or other QRS morphology changes.

8.2.4.6 Quality of life

Participants were also asked to complete three questionnaires: (Minnesota Living with Heart Failure (Figure 5.1), EuroQOL 5D-3L (EQ-5D) (Figure 5.2), and visual analogue score (Figure 5.3)), to assess their quality of life.

8.2.5 Randomisation

After the baseline data had been collected, participants were randomised on a 1:1 basis to either optimised programming as predicted by their individual force-frequency curve assessment (to maintain heart rate during exercise below the critical heart rate), or to conventional settings whereby peak heart rate was determined by the Åstrand calculation of 220 bpm minus age. Randomisation was determined by a random number generator. Pacemaker programming was undertaken by an un-blinded clinical scientist, to maintain blinding. Atrioventricular delay programming was optimised to avoid fusion and to maintain consistent biventricular stimulation at higher heart rates in patients with CRT devices. Device-specific pacing avoidance algorithms were activated in patients in sinus rhythm without CRT devices. VVIR programming was used for patients in AF. Patients were blinded to their allocation. However, details were provided so that participants could contact the CVCRF if they were not tolerating any changes.

8.2.6 Follow-up

Each participant was telephoned one week after baseline testing and randomisation to check that they were tolerating any changes, and then invited back for follow-up testing after six months. Participants' pacing files were labelled to indicate that the patient was taking part in a research study, and that unless the patient became symptomatic, the pacing settings should be left unchanged.

A resting echocardiogram was performed to allow assessment of LV size and function. The cardiopulmonary exercise test was repeated to allow change in exercise time to be calculated. To maintain blinding, the ECG monitor was positioned so that I could not see it. Only the un-blinded clinical scientist was aware of the pacemaker settings and the study arm. The effective delivery of biventricular stimulation in patients with CRT devices was confirmed from ECG traces at peak exercise by the absence of fusion or other QRS morphology changes. Participants were also asked to complete the quality of life assessments again.

8.2.7 Sample size calculation

The study was designed as a single-centre phase II trial, since there was an absence of data describing variability in outcomes to be able to robustly design a definitive trial. The aim was to make initial unbiased comparisons of groups and inform variability in outcomes in the target population of patients. Therefore, the target sample size was based on achieving a sample size appropriate to estimate the variability in the six-month primary outcome measure. It is recommended that a pilot study such as the current one, has 70 measured subjects (35 per group) (Teare et al., 2014). The aim

for the current study was to have outcome data at six months for a minimum of 70 patients. The recruitment target was inflated to 85 patients to account for anticipated dropout.

8.2.8 Reproducibility

Each echocardiographic image set was anonymised and re-reported by me, as the initial reporter, to check for intra-operator reproducibility. The anonymised image sets were also reported by a second clinical scientist, for inter-operator reproducibility. For each dataset, the critical heart rate, the peak LV contractility, and the force-frequency relationship slope were all documented.

8.2.9 Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) (version 23; IBM Corporation, Armonk, New York, USA). As a pilot trial, the aim was to describe outcomes, and variability in outcomes, descriptively. Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean and standard deviation (mean \pm (SD)), and non-normally distributed continuous variables were reported as median and interquartile range (median \pm IQR). Categorical variables were presented as count and percentages. Analysis of covariance (ANCOVA) was used to assess inter-group differences in outcome variables. All statistical tests were two-sided and presented as mean \pm SD and 95% confidence interval (CI).

Reproducibility of echocardiographic measures were described by intraclass correlation coefficient (ICC) for both intra- and inter-observer variability.

8.3 Results

In total, 83 patients were recruited between 2 November 2017 and 16 January 2019. Of these, 38 were randomised to force-frequency relationship-guided rate-response programming, and 45 were randomised to conventional age-guided programming (Figure 8.1).

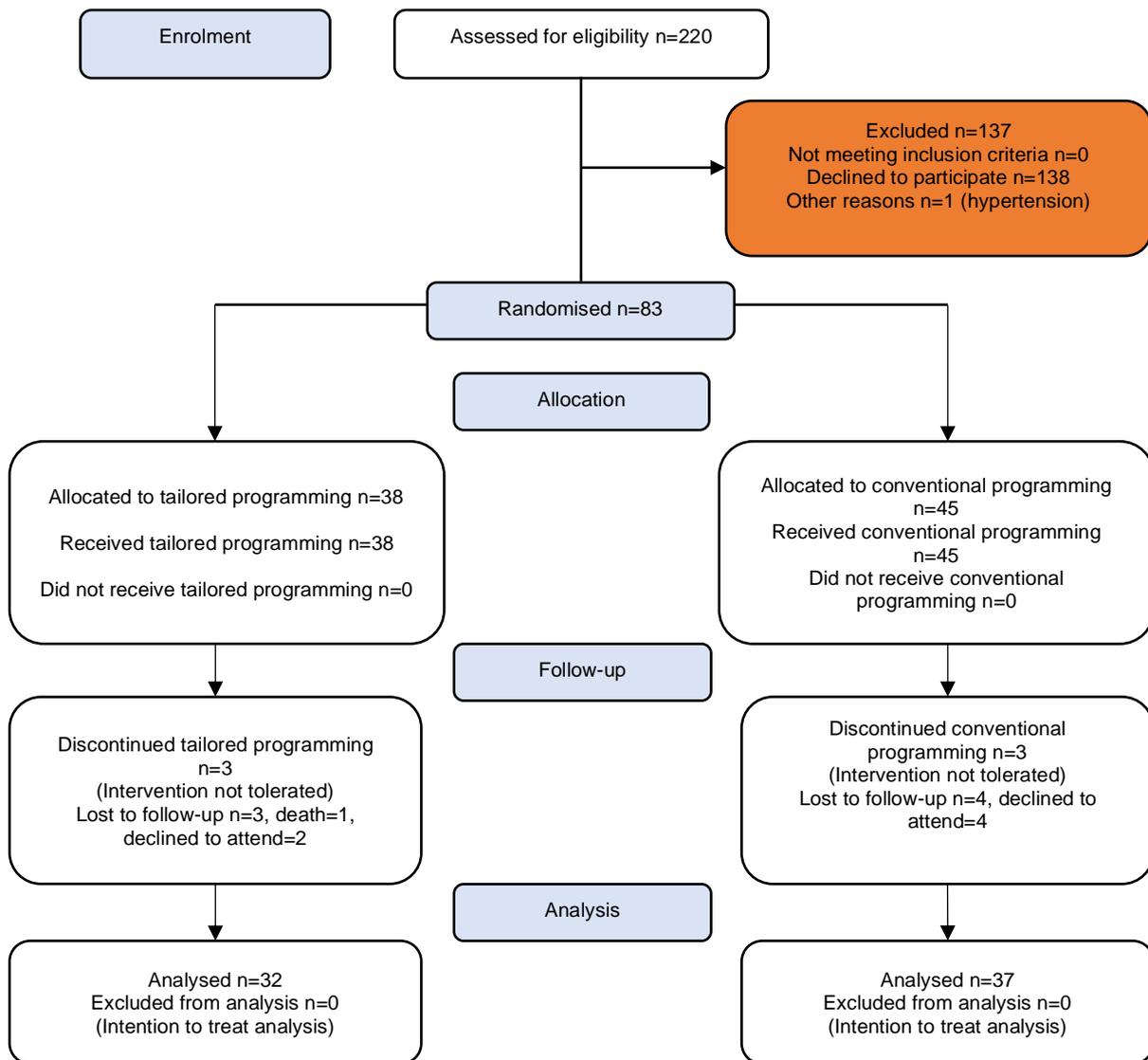


Figure 8.1: Consolidated Standards of Reporting Trials (CONSORT) diagram of patient enrolment, randomisation, and disposition during the study

The six-month follow-up assessment was completed by 76 out of the 83 patients. Of the 76 patients, 35 were allocated to the force-frequency relationship-guided rate-response programming group, and 45 were allocated to the conventional age-guided programming group. In total, 7 patients were lost to follow-up; there was one death and six patients declined to attend their six-month follow-up assessment. There were three patients in each group who did not tolerate the intervention; their pacemakers

were reprogrammed to their pre-study settings and the patients remained in the intention to treat analysis (Figure 8.1).

The baseline characteristics of the two groups (force-frequency relationship-guided rate-response programming and conventional age-guided programming) were balanced, in particular including for force-frequency relationship variables of critical heart rate (106.7 ± 18.0 bpm versus (vs) 102.8 ± 17.7 bpm; $p = 0.320$) and peak LV contractility (4.6 ± 3.1 vs 4.2 ± 2.5 ; $p = 0.574$), and for exercise testing variables of resting heart rate (65.9 ± 9.4 bpm vs 66.4 ± 9.1 bpm; $p = 0.787$) and peak exercise heart rate (116.2 ± 21.8 bpm vs 120.4 ± 19.5 bpm; $p = 0.375$) (Table 8.1).

Table 8.1: Patient demographic and baseline characteristics at randomisation: intention-to-treat population

Characteristic	Total (n=83)	Tailored (n=38)	Conventional (n=45)
Male sex	58 (71)	27 (73)	31 (69)
Age, years	74.6±8.7	73.7±10.6	75.4±6.8
IHD	52 (63)	26 (68)	26 (58)
AF	30 (36)	13 (34)	17 (38)
Hypertension	39 (47)	16 (42)	23 (51)
Creatinine, µmol/L	108.3±37.2	107.7±27.5	108.9±45.5
NYHA			
II	58 (70)	27 (71)	31 (69)
III	25 (30)	11 (29)	14 (31)
Medication			
β-blocker	80 (96)	38 (100)	42 (93)
Bisoprolol equivalent dose, mg/d*	7.4 (3.8)	7.7 (3.2)	7.0 (4.2)
ACE inhibitor/ARB	78 (94)	34 (90)	37 (82)
Ramipril equivalent dose, mg/d*	6.2 (3.5)	6.3 (3.3)	6.2 (3.6)
Loop diuretic	50 (60)	24 (63)	26 (58)
Statin	69 (83)	30 (79)	39 (87)
Device allocation			
CRT with defibrillator	35 (42)	13 (34)	22 (49)
CRT with pacemaker	23 (28)	9 (24)	14 (31)
Dual-chamber ICD	25 (30)	16 (42)	9 (20)
Resting haemodynamics			
Resting heart rate, bpm	66.1±9.2	65.9±9.4	66.4±9.1
Systolic blood pressure, mmHg	123.8±20.5	122.0±21.4	125.2±19.9
Echocardiography and FFR data			
LV ejection fraction, %	35.2±10.5	35.3±10.6	35.1±10.6
LV end-diastolic volume, ml	142.7±62.5	141.2±73.0	144.0±52.8
LV end-systolic volume, ml	95.9±62.5	95.7±60.7	96.1±45.1
Peak LV contractility	4.4±2.8	4.6±3.1	4.2±2.5
Critical heart rate, bpm	104.6±17.8	106.7±18.0	102.8±17.7
Exercise test results			
Treadmill walk time, s	397.1±185.9	376.4±172.1	414.9±197.2
Peak VO₂, ml/kg/min	15.5±5.6	15.1±6.4	15.9±4.9
VE/VCO₂ slope	32.7±9.6	32.3±9.4	33.2±9.8
Peak exercise heart rate, bpm	118.5±20.6	116.2±21.8	120.4±19.5
O₂ pulse, ml/beat	10.89±3.69	10.46±3.67	11.28±3.71
Quality of life scores at baseline			
EQ-5D-5L	0.72±0.17	0.71±0.14	0.72±0.19
Visual analogue scale	66.4±16.2	64.7±17.2	67.8±15.1
MLWHF Questionnaire	31.1±19.7	32.8±18.7	29.7±20.5

Continuous variables expressed as mean±SD; categorical variables as n (%). * mean doses

Key: ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; β-blocker = beta-adrenoceptor antagonist; bpm = beats per minute; CRT = cardiac resynchronisation therapy; EQ-5D-5L = 5-level EQ-5D; FFR = force-frequency relationship; ICD = implantable cardioverter-defibrillator; IHD = ischaemic heart disease; kg = kilogram; LV = left ventricular; mg = milligram; min = minute; ml = millilitres; MLWHF = Minnesota living with heart failure; mmHg = millimetres of mercury; µmol/l = micromole per litre; NYHA = New York Heart Association functional class; s = second; VE/VCO₂ slope = slope relating ventilation and carbon dioxide output; VO₂ = oxygen consumption.

8.3.1 Primary outcome measure

Treadmill walk time was the primary outcome measure. At the six-month visit, patients in the force-frequency relationship-guided rate-response programming group demonstrated a greater improvement in treadmill walk time, compared to the patients who were randomised to conventional age-guided programming. From baseline to six-month follow-up, changes in treadmill walk time in the force-frequency relationship-guided group versus (vs) the conventional age-guided group were respectively: 376 to 483 seconds vs 402 to 415 seconds, with a mean difference between the groups of 72 seconds (95% CI: 2 to 143; $p = 0.044$) in favour of force-frequency relationship-guided programming (Figure 8.2).

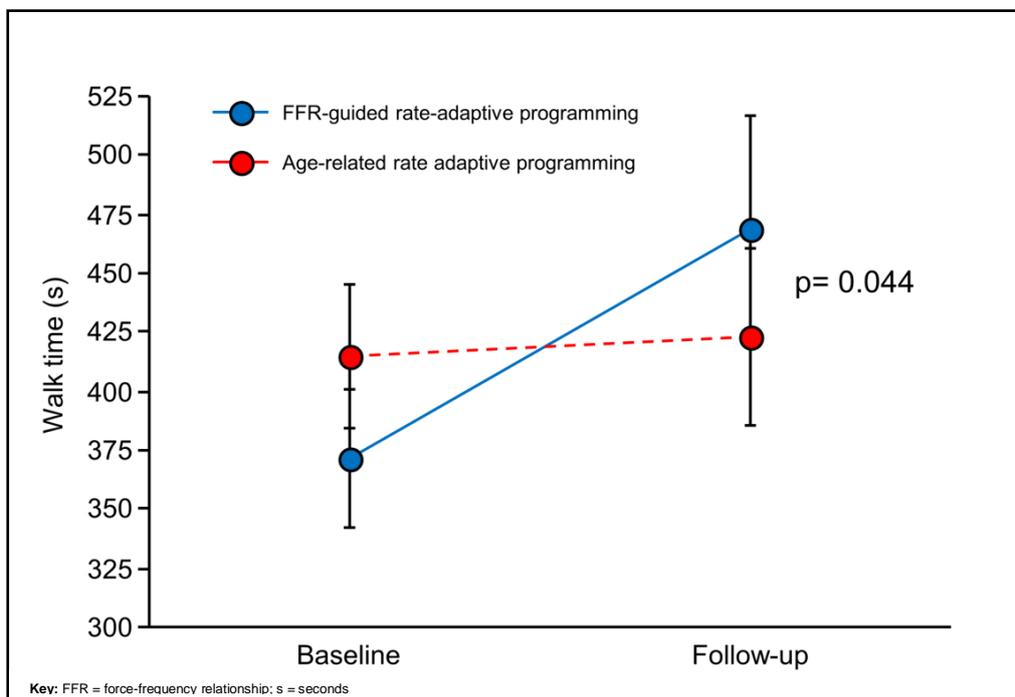


Figure 8.2: Change in treadmill walk time after six months of conventional versus force-frequency relationship-guided rate-adaptive pacing programming

Table 8.2: Change in primary and secondary outcome variables after six months of tailored versus conventional pacemaker heart rate-response programming: intention-to-treat population

End point	Final value, mean (95% CI)	Change after 6/12, mean (95%)	ANCOVA, mean change (95%)	p-value
Primary outcome				
Treadmill walk time, s				
Tailored	483.15 (431.10 to 535.20)	75.40 (23.35 to 127.45)	72.31 (1.94 to 142.67)	0.044
Conventional	401.84 (363.62 to 458.07)	3.09 (-44.14 to 50.31)		
Secondary outcomes				
Left ventricular ejection fraction, %				
Tailored	35.79 (33.80 to 37.78)	-0.23 (-2.31 to 1.84)	3.66 (0.94 to 6.38)	0.009
Conventional	32.13 (30.28 to 33.00)	-3.69 (-5.62 to -1.76)		
Left ventricular end-diastolic volume, ml				
Tailored	146.63 (135.87 to 157.39)	3.24 (7.52 to 14.00)	-2.29 (-16.99 to 12.42)	0.757
Conventional	148.92 (138.91 to 158.92)	5.52 (-4.48 to 15.53)		
Left ventricular end-systolic volume, ml				
Tailored	97.36 (89.36 to 105.35)	1.78 (-6.22 to 9.77)	-8.26 (-19.18 to 2.67)	0.136
Conventional	105.61 (98.18 to 113.05)	10.03 (2.60 to 17.47)		
Peak oxygen consumption, ml/kg/min				
Tailored	16.72 (15.81 to 17.64)	0.84 (-0.07 to 1.75)	1.14 (-0.10 to 2.38)	0.071
Conventional	15.59 (14.75 to 16.43)	-0.30 (-1.14 to 0.54)		
Peak O₂ pulse, ml/beat				
Tailored	13.84 (12.75 to 14.94)	2.74 (1.64 to 3.83)	2.02 (0.53 to 3.51)	0.009
Conventional	11.82 (10.82 to 12.83)	0.72 (-0.29 to 1.73)		
VE/VCO₂ slope				
Tailored	32.81 (30.30 to 35.32)	-0.73 (-3.24 to 1.78)	0.50 (-2.91 to 3.91)	0.770
Conventional	32.31 (30.00 to 34.62)	-1.23 (-3.54 to 1.08)		
EQ-5D-5L				
Tailored	0.73 (0.68 to 0.78)	-0.02 (-0.07 to 0.04)	0.06 (-0.01 to 0.14)	0.078
Conventional	0.66 (0.62 to 0.71)	-0.06 (-1.11 to -0.01)		
EQ-VAS				
Tailored	67.13 (62.18 to 72.07)	-1.16 (-6.72 to 4.40)	4.28 (-2.46 to 11.02)	0.210
Conventional	62.84 (58.28 to 67.41)	-3.35 (-8.56 to 1.86)		
Minnesota Living With Heart Failure Questionnaire				
Tailored	31.68 (27.45 to 35.91)	-0.04 (-4.33 to 4.26)	1.43 (-4.34 to 7.21)	0.622
Conventional	30.25 (26.34 to 34.15)	-0.63 (-4.65 to 3.40)		
Key:				
Values are mean change (95% confidence intervals)				
EQ-5D-5L = Euro-quality of life score – 5 questions; kg = kilogram; min = minute; ml = millilitre; O ₂ = oxygen; pVO ₂ ; s = second; VAS = visual analogue score; VE/VCO ₂ slope = slope relating ventilation and carbon dioxide output.				

8.3.2 Secondary outcome measures

There was no change to LVEF from baseline (35.3%) to six-month follow-up (35.9%) after six months of force-frequency relationship guided-guided rate-response pacing. However, in the conventional age-guided group, there was a reduction in LVEF from

baseline (35.1%) to six-month follow-up (32.1%), with a mean difference between groups of 3.7% (95% CI: 0.9 to 6.4; $p = 0.009$) in favour of force-frequency relationship-guided programming (Table 8.2 and Figure 8.3).

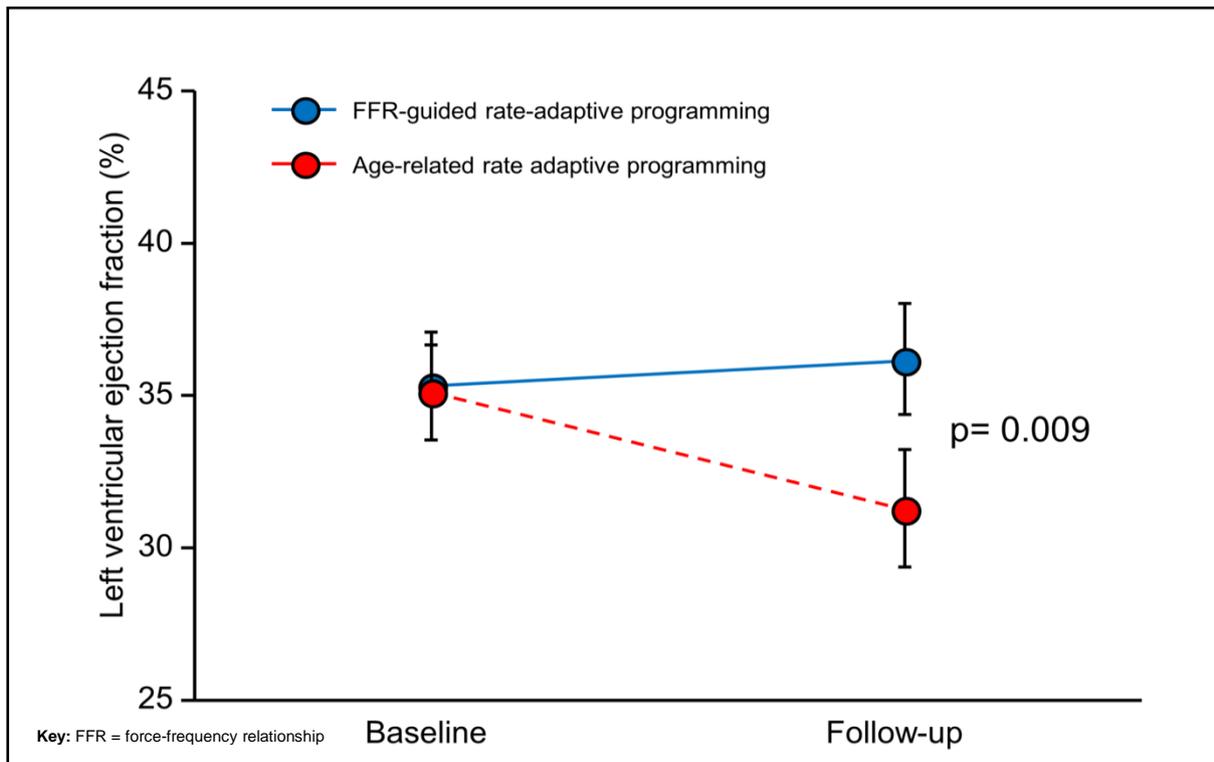


Figure 8.3: Change in LV ejection fraction after six months of conventional versus force-frequency relationship-guided rate-adaptive pacing programming

No significant change in LVEDV was seen in either group. LVEDV in the force-frequency relationship-guided group changed from 141 to 147 ml, and from 144 to 149 ml in the conventional age-guided group, with a mean difference between groups of -2.3 ml (95% CI: -17.0 to 12.4; $p = 0.757$). Change in LVESV in the force-frequency relationship-guided group from baseline to six-month follow-up was 96 to 97 ml. A larger change was seen in the conventional age-guided group of 96 to 106 ml. The mean difference between the groups was 8.26 ml (95% CI: -19.18 to 2.67; $p = 0.136$),

trending towards favouring force-frequency relationship-guided programming Table 8.2 and Figure 8.4A and B).

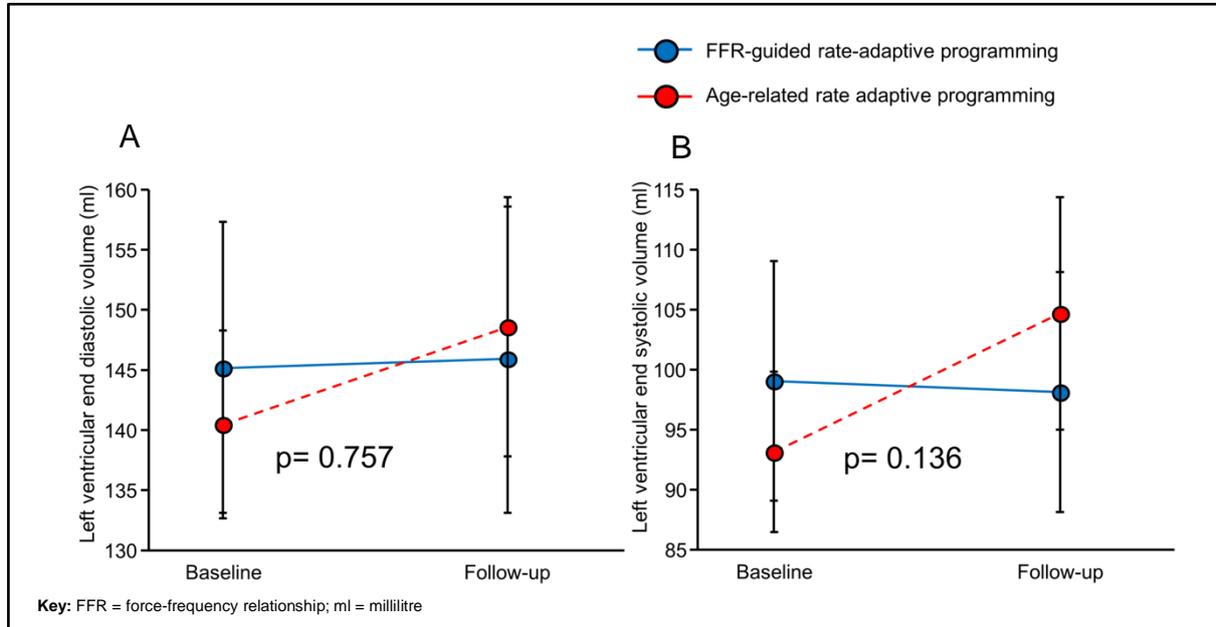


Figure 8.4: Change in LV end-diastolic and end-systolic volumes

Change in LV end-diastolic volume (A) and LV end-systolic volume (B) after six months of conventional versus force-frequency relationship-guided rate-adaptive pacing programming

In terms of the cardiopulmonary exercise testing variables, there was a trend towards favourable changes in peak oxygen consumption in the force-frequency relationship-guided group (15.1 to 16.7 ml/kg/min) compared to the conventional age-guided group (15.9 to 15.6 ml/kg/min), with a mean difference between groups of 1.14 ml/kg/min (95% CI: -0.1 to 2.4 ml/kg/min). Peak oxygen pulse increased in the force-frequency relationship-guided group from 10.46 to 13.84 ml/beat, and from 11.28 to 11.82 ml/beat in the conventional age-guided group, with a mean difference between the groups of 2.02 ml/beat (95% CI: 0.5 to 3.5 ml/beat) in favour of force-frequency relationship-guided programming (Table 8.2).

There was no difference in change in quality of life assessments from baseline to six-month follow-up between the two groups. Mean change in the EQ-5D score from baseline to six-month follow-up in the force-frequency relationship-guided group was -0.02 (95% CI: -0.07 to 0.04) vs -0.06 (95% CI: -1.11 to -0.01) in the conventional age-guided group. Mean change in the visual analogue scale score was -1.16 (95% CI: -6.72 to 4.40) in the force-frequency relationship-guided group vs -3.35 (95% CI: -8.56 to 1.86) for the conventional age-guided group. Mean change from baseline to six-month follow-up for the Minnesota Living with Heart Failure questionnaire score was -0.04 (95% CI: -4.33 to 4.26) for the force-frequency relationship-guided group vs 0.63 (95% CI: -4.65 to 3.40) for the conventional age-guided group (Table 8.2).

Echocardiographic outcome measures demonstrated strong intra-observer agreement for LVEF [ICC 0.988 (95%CI, 0.858 to 0.998)]; LVEDV [ICC 0.987 (95% CI, 0.824 to 0.998)]; and LVESV [ICC 0.985 (95%CI, 0.903 to 0.998)]. Strong inter-observer agreement was also demonstrated for LVEF [ICC 0.970 (95%CI 0.778 to 0.996)]; LVEDV [ICC 0.988 (95%CI, 0.927 to 0.998)]; and LVESV [ICC 0.993 (95%CI, 0.956 to 0.999)].

8.4 Discussion

The key findings in the current study are that in patients with HFrEF and a pacemaker, receiving optimal guideline-directed medical therapy, six months of tailored force-frequency relationship-guided heart rate-response pacemaker programming leads to

improved exercise time, and furthermore prevents the decline in LVEF experienced by patients who were randomised to conventional age-guided programming.

These findings are particularly relevant because although disease modifying treatments have significantly improved life expectancy for patients with HFrEF, they have had much less impact on exercise capacity.

In the normal heart, cardiac output is positively coupled to the power of LV contractility by the force-frequency relationship, such that as heart rate rises, cardiac output and LV contractility increase. In adults with normal heart function, the heart rate rises steadily with increasing work, to a peak that is generally accepted to be inversely related to age. However, heart rate rise and peak heart rate during exercise are reduced in HFrEF (Colucci et al., 1989). Since cardiac output is a function of heart rate and stroke volume, it is possible that poor heart rate rise during exercise could contribute to the impaired exercise tolerance associated with HFrEF through adversely affecting cardiac output. However, the relationship between heart rate rise, cardiac output, and exercise capacity, and how their interaction changes with age, sex, fitness, and disease, is poorly understood.

The relevance of heart rate rise has become particularly challenging in the context of heart rate limitation being a key target of HFrEF therapy. Observational and interventional data (Jamil et al., 2016; Chatterjee, N.A. and Heist, 2018) have challenged the belief that limited heart rate rise during exercise, known as chronotropic incompetence, is a contributor to exercise intolerance commonly seen in HFrEF.

In around 30% of patients with HFrEF, optimal medical therapy includes implantation of a pacemaker device. One of the programmable functions is heart rate-response, or rate-adaptive, pacing, which was developed with the aim of optimising exercise tolerance in patients with chronotropic incompetence. The objective of heart rate-response pacing is to simulate the physiological heart rate rise that occurs, in health, in response to increasing levels of activity. In people without HFrEF, rate-response pacing is associated with an increase in cardiac output during exercise (McMeekin et al., 1990) when compared with fixed rate programming (heart rate-response function programmed to 'off'), but shows inconsistent improvements in exercise capacity (Osswald et al., 1996; Galtes and Lamas, 2004).

However, heart rate-response pacing using an age-guided algorithm during exercise in patients with HFrEF, unreliably improves exercise capacity (Tse et al., 2005; Witte, K. K. and Clark, 2006), and furthermore, worsens outcomes and cardiac function (Thackray et al., 2006; Nägele, H et al., 2008).

A key therapeutic aim in HFrEF is to limit the heart rate. Bradycardia at rest improves outcomes in HFrEF (Fox et al., 2008), but leads to a limitation of heart rate rise during exercise. Even without beta-adrenoceptor antagonists (β -blockers), patients with HFrEF often do not achieve their age-predicted maximal heart rate during exercise (Witte, K. K. and Clark, 2005; Witte, K. K. and Clark, 2009; Al-Najjar et al., 2012), which is commonly believed to contribute to reduced exercise tolerance in HFrEF (Colucci et al., 1989; White et al., 1995). This paradox, whereby heart rate limitation

using β -blockers is known to reduce hospitalisation and mortality (Maurer et al., 2009; McAlister et al., 2009) yet is proposed to worsen exercise intolerance, may contribute to poorly defined heart rate targets in guidelines (Ponikowski et al., 2016).

During exercise the force-frequency relationship ensures that LV contractility, and thus stroke volume, increase with heart rate to compensate for the reduced filling time. In chapter 6, I demonstrated, using echocardiography, that this relationship is abnormal across the entire heart rate range in HFrEF, with a lower slope in response to heart rate increases, lower peak LV contractility, and a lower heart rate for peak LV contractility (the critical heart rate). Therefore, in HFrEF, maximal heart rate is not synonymous with optimal heart rate.

Programming a pacemaker device to increase the heart rate during activity, up to the conventional age-guided maximal heart rate, does not improve exercise time. Furthermore, medications that limit the heart rate range response to exercise do not compromise exercise capacity (Jamil et al., 2016). This could be because conventional age-guided heart rate-response pacing algorithms do not consider the altered force-frequency relationship in HFrEF.

Using echocardiography, I have been able to determine an optimum heart rate range, tailored using the individual's force-frequency relationship curve, throughout which LV contractility increased in patients with HFrEF. This current randomised, double-blind, controlled study, comparing six-months of tailored heart rate-response programming with six-months of conventional age-guided heart rate-response programming, found

that force-frequency relationship-guided programming is associated with improved exercise time and reduced progressive deterioration in LV function.

An improvement in quality of life was not seen in this study. A longer follow-up period might be necessary to determine whether the intervention produces an improvement in quality of life. However, in a condition such as HFrEF, which is associated with a gradual decline in quality of life, the result of no deterioration might be a result of the intervention preventing further decline.

8.5 Limitations

The study was performed within a single centre in the United Kingdom, limiting generalisability. However, baseline demographic data indicate that the study population was representative of a pacemaker population with HFrEF. The study necessarily included only patients with a pacemaker device, who may present a different contractile response to increased heart rates from patients without a pacemaker device.

It is possible that so-called 'responders' to CRT might have less to gain from tailored rate-response programming. However, the selection criteria were deliberately inclusive, and participants were approached consecutively, with no selection bias in terms of CRT response.

The trial was randomised and undertaken in a double-blind fashion, to reduce bias.

Although the treadmill exercise modality and the ramping protocol may not have been ideal for all patients, it was used to allow comparison of exercise times, in addition to metabolic gas analysis data, also because treadmill-based activity is associated with greater upper body movement required for activation of the rate-response algorithms in pacemaker devices. Furthermore, the early, low workload, allowed those patients with the greatest limitation in exercise capacity to complete some exercise, reducing the bias towards less limited patients.

8.6 Conclusion

This novel, single-centre, randomised, double-blind, controlled trial, has demonstrated that after six-months of the heart rate-response pacing settings being programmed in accordance with the optimal heart rate range, defined by the individual's non-invasive force-frequency relationship data, is associated with improved exercise time and reduced progressive deterioration in LV function in patients with HF_rEF. Furthermore, conventional age-guided rate-response programming might be a suboptimal choice in HF_rEF and could contribute to deteriorating LV function in HF_rEF.

Chapter 9 : Discussion

Aristotle considered the heart to be the seat of intelligence and the centre of vitality in the body; the first organ to come to life, and the last to die. In almost all interactions between healthcare providers and their patients, heart rate is the primary assessment. Indeed, heart rate is a significant contributor to both the symptoms and progression of cardiovascular disease. When the heart starts to fail, the heart rate will adapt to compensate.

9.1 Introduction

Heart failure has become epidemic in the developed world (Katz, A. and Konstam, 2009). It is the end stage of all diseases of the heart and is a major cause of morbidity and mortality (Davis et al., 2000). Heart failure with reduced ejection fraction (HFrEF) is a common syndrome characterised by symptoms of breathlessness and fatigue in the presence of left ventricular systolic dysfunction (LVSD). A key feature of HFrEF is reduced exercise tolerance, which can have a significant impact on the daily activities of patients with HFrEF.

The exercise intolerance associated with HFrEF is thought to be because of reduced cardiac output which leads to lower oxygen delivery to exercising skeletal muscle, exercise intolerance, and fatigue. Cardiac output is a function of heart rate and stroke volume, both of which are impaired in HFrEF. With normal cardiac function, during

activity the heart rate increases, leading to an increase in the force of contraction and cardiac output. This relationship, linking heart rate, left ventricular (LV) contractility and cardiac output, the force-frequency relationship, is impaired in patients with HFrEF, with a decrease in LV contractility over a certain heart rate (the critical heart rate). Increasing the heart rate beyond the critical heart rate may contribute to functional limitation and could potentially contribute to further progression of LVSD.

Although improvements are reported in patient outcomes, due to advances in the treatment and management of HFrEF (Cleland et al., 2005; Hunt et al., 2009; Bristow, 2011; Cubbon et al., 2011), the prognosis of this cohort of patients remains poor. The development of new therapeutic pathways for these patients, therefore, remains a priority.

The literature highlights a conflict within the optimal therapies used for patients with HFrEF. Although chronotropic incompetence in HFrEF is associated with reduced functional capacity, correcting this with rate-response pacing in HFrEF patients does not lead to an improvement in oxygen consumption, symptoms, or exercise time. Moreover, the force-frequency relationship in HFrEF is attenuated, such that LV contractility does not increase normally with increases in heart rate.

I have investigated the hypothesis that conventional rate-response algorithms do not consider the altered force-frequency relationship seen in HFrEF, and that there may be a lower optimal heart rate range for LV contractility in HFrEF. Rather than a one-size fits all approach, I have presented a personalised method of assessing this.

9.2 Observational study

In an observational cohort study of 105 participants (90 with HFrEF; 15 non-HFrEF), I demonstrated that the force-frequency relationship can be reliably assessed non-invasively, using transthoracic echocardiography, and a pacemaker device.

I was able to show that patients with HFrEF had lower peak LV contractility, lower mean critical heart rate, and a lower slope of the relationship between heart rate and LV contractility below the critical heart rate, than controls. This confirms that in HFrEF, the force-frequency relationship is impaired, independent of cardiac loading or physical activity levels. Furthermore, in terms of optimal LV contractility, maximal heart rate is not synonymous with optimum heart rate. Therefore, pacemaker heart rate programming should consider the underlying cardiac disease of the individual patient.

9.3 Interventional studies

9.3.1 Tailoring rate-response programming to the force-frequency relationship (acute response)

Conventional age-related heart response algorithms applied to patients with HFrEF could increase the heart rate beyond the critical heart rate, onto the downward portion of their LV contractility curve, such that, as heart rate increases, cardiac output decreases. This could be a contributing factor as to why HFrEF patients have reduced exercise capacity. Therefore, this investigation was designed to test whether programming the heart rate-response function to consider the patient's force-frequency relationship, would affect exercise tolerance.

I applied the technique used in the observational study and performed a randomised, double-blind, placebo-controlled, cross-over study of 52 HFrEF patients who had participated in the observational study. This demonstrated that maintaining the rate-response programmed heart rate below the critical heart rate (as calculated in the observational study) during exercise, was associated with improved treadmill exercise time. Therefore, personalised programming of the heart rate-response function, using the patient's individual force-frequency relationship data, can improve exercise time.

9.3.2 Tailoring rate-response programming to the force-frequency relationship (longer term response)

A further randomised controlled trial was conducted in order to demonstrate whether the acute benefits described in the first interventional study could be translated into longer term benefits in terms of exercise time, cardiac function, and quality of life, in patients with HFrEF and a pacemaker device.

A total of 83 patients were recruited into this interventional, double-blind, randomised, parallel-group trial. Patients were randomised on a 1:1 basis to either, tailored rate-response programming based on individual force-frequency data, or to conventional age-guided rate-response programming, for a period of six months. I was able to demonstrate a greater improvement in treadmill exercise time in the tailored rate-response group, than those randomised to conventional age-guided rate-response programming. Furthermore, there was reduced progressive LV dysfunction in the tailored rate-response group.

9.4 Clinical implications

The novel findings reported here have clinical implications for the management of pacemaker devices in the context of HFrEF. I have demonstrated that a reproducible, non-invasive assessment of patients' physiological response to increased heart rates, can be translated into clinical benefits by facilitating personalised heart rate-response pacemaker programming. Furthermore, this approach may provide a mechanism for the lack of benefit of conventional rate-response pacemaker programming in patients with HFrEF.

The association of conventional settings, for a period of six months, with reduced progressive deterioration in LV function, could imply that the only available 'age-guided' guidance for programming heart rate-response pacing might be a suboptimal choice in patients with HFrEF.

The reduced heart rate increase associated with HFrEF corresponds to the heart rate range on the upslope of the LV contractility curve, raising the possibility that the 'chronotropic adaptation' seen in HFrEF may be a cardio-protective measure, with the aim of maximising contractile response and exertional cardiac output. Furthermore, exercise capacity is not worsened by reducing the resting heart rate in patients with HFrEF. Consequently, pharmacological goals and pacemaker programming in patients with HFrEF should be different from that in those patients with normal LV function. A tailored, patient specific approach is necessary in interventions that may alter the heart rate, in the context of HFrEF.

9.5 Future research

Future work is now needed to explore the mechanisms of the findings within this thesis, to determine whether the greater increase in exercise time than peak oxygen consumption represents greater cardiac efficiency, and to determine whether the critical heart rate can be predicted from clinical variables. The findings should also be confirmed in a multicentre setting, and on longer-term clinical outcomes, including hospitalisation.

Additionally, an investigation into whether patients with less severe LV systolic dysfunction and those with persistent symptoms but no existing indication for a pacemaker device might also benefit from this approach, would be valuable.

9.6 Conclusion

This work has shown that using a non-invasive assessment of the force-frequency relationship to determine a tailored optimal heart range to guide the personalisation of heart rate-response pacemaker programming in patients with HFrEF, can improve exercise capacity, by emulating the natural chronotropic adaptation evident in HFrEF, rather than attempting to exceed it.

Appendix A - HRA ethical approval for studies in chapters 6 and 7



Health Research Authority

NRES Committee Yorkshire & The Humber - Bradford

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13 March 2012

Dr Klaus Witte
Senior Lecturer in Cardiology
University of Leeds
The LIGHT Laboratories
Leeds
LS2 9JT

Dear Dr Witte

Study title: Bowditch revisited: defining the optimum heart rate range in chronic heart failure
REC reference: 12/YH/0097

Thank you for your letter of 28 February 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0097

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely


 Dr Ian Woollands (Bradford REC)
 Chair

Email: sinead.audsley@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Clare Skinner, University of Leeds*
Dr Derek Norfolk, Leeds Teaching Hospitals NHS Trust

Appendix B – LTHT R&D approval for studies in chapters 6 and 7

The Leeds Teaching Hospitals 
NHS Trust

Ref: Ananda Burd

18/04/2012

Dr Klaus Witte
Consultant Cardiologist
University of Leeds
LIGHT building
University of Leeds
LS2 9JT

Research & Development

Leeds Teaching Hospitals NHS Trust

34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dear Dr Klaus Witte

**Re: NHS Permission at LTHT for: Bowditch revisited: defining the optimum heart rate range in chronic heart failure
LTHT R&D Number: CD12/10115
REC: 12/YH/0097**

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/sites/research_and_development/.

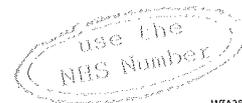
This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

Chairman Mike Collier CBE Chief Executive Maggie Boyle

The Leeds Teaching Hospitals incorporating:
Chapel Allerton Hospital Leeds Dental Institute Seacroft Hospital
St James's University Hospital The General Infirmary at Leeds Wharfedale Hospital

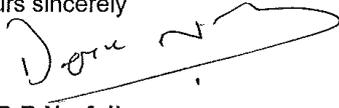


WTA260

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The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely



Dr D R Norfolk
Associate Director of R&D

Approved documents

The documents reviewed and approved are listed as follows

<i>Document</i>	<i>Version</i>	<i>Date of document</i>
NHS R&D Form	3.4	23/12/2011
SSI Form	3.4	23/12/2011
Directorate Approval		13/03/2012
REC Letter confirming favourable opinion		29/03/2012
Insurance/Indemnity		28/09/2011
Protocol	1.0	05/09/2011
Patient information sheet (REC approved) - Controls	1.3	03/03/2012
Patient information sheet (REC approved) - CHF	1.3	03/03/2012
Consent form (REC approved)	1.3	03/03/2012
GP/Consultant information sheets (REC approved)	1.0	05/09/2011

Appendix C – HRA ethical approval for study in chapter 8



Health Research Authority

Dr Klaus Witte
LICAMM,
LIGHT building,
Clarendon Way
LS2 9JT

Email: hra.approval@nhs.net

28 February 2017

Dear Dr Witte

Letter of HRA Approval

Study title:	The safety and efficacy of optimising pacemaker heart rate for contractility: effects on walk time, cardiac remodelling and quality of life.
IRAS project ID:	218963
REC reference:	17/EM/0004
Sponsor	University of Leeds

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	216963
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It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *‘After Ethical Review – guidance for sponsors and investigators’*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](http://www.hra.nhs.uk), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](http://www.hra.nhs.uk).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rc-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	218963
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procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

Your IRAS project ID is 218963. Please quote this on all correspondence.

Yours sincerely

Miss Helen Penistone
Assessor

Email: hra.approval@nhs.net

Copy to: governance-ethics@leeds.ac.uk, University of Leeds

Mrs Amanda Burd, LTHT R+I

IRAS project ID	218963
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Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters [GP letter]	1.0	04 November 2016
IRAS Application Form [IRAS_Form_05122016]		05 December 2016
Letter from funder [The Leeds Teaching Hospital Charitable Foundation]		24 January 2017
Letter from funder [Confirmation of Clinical Research Fellowship]		17 January 2017
Letters of invitation to participant	1	05 December 2016
Other [Clarification email from KW]		05 December 2016
Other [Response Letter]		17 January 2017
Other [Statement of Activities]	2	28 February 2017
Other [Schedule of Events]	1	28 February 2017
Participant consent form	1.1	17 January 2017
Participant information sheet (PIS)	1.2	17 January 2017
Research protocol or project proposal [Protocol]	1.0	04 November 2016
Summary CV for Chief Investigator (CI) [KWCV]		08 November 2016
Summary CV for student		04 December 2016
Validated questionnaire [mlhfq_questionnaire]		11 October 2004
Validated questionnaire [EQ-5D]		

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) sections in this appendix.*

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Dr Klaus Witte
Email: k.k.witte@leeds.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor intends that the statement of activities will act as agreement of an NHS organisation to participate. No separate agreement is expected.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

IRAS project ID	218963
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Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	Funding has been granted by the Leeds Teaching Hospitals Charitable Trust. According to the Statement of Activities, the sponsor will provide funding to site to cover the cost of the exercise tests.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

This is a single site study where all study activities will be undertaken as per protocol.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local

LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research.**

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capability will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The *Assessing, Arranging, and Confirming* document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

It is expected that there will be a Principal Investigator at site to oversee the conduct of research activities.

No details of training provision or training expectations have been stipulated by the sponsor in the Statement of Activities.

GCP training is not a generic training expectation, in line with the [HRA statement on training expectations](#).

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

According to A18 and A19 all research activities will be undertaken by an individual with an existing contractual arrangement with site. Therefore, no additional HR Good Practice arrangements are expected.

IRAS project ID	218963
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Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix D – LTHT R&D approval for study in chapter 8

R&I No: CD16/88879 | Optimising Pacemaker Therapy for Contractility | LTHT Confirmation of Capacity and Capability

Dear Dr Witte,

Re. Optimising Pacemaker Therapy for Contractility, R&I No: CD16/88879

This email confirms that the Leeds Teaching Hospitals NHS Trust has the capacity and capability to deliver the above research study, based upon Protocol version 1.0 (04 November 2016). You may now begin the study at this organisation.

Please find attached:

- agreed statement of activities

It is the responsibility of the principal investigator to ensure that the study is conducted in accordance with the terms of the Health Research Authority approval and Leeds Teaching Hospitals NHS Trust policies and procedures including the requirements for research governance and clinical trials performance management. These are available at <http://www.leedsth.nhs.uk/assets/Uploads/PI-responsibilities-v1.3-210716.docx>

Please note: If your study will involve the testing or use of an interventional procedure which is new to LTHT you must obtain the approval of the New Interventional Procedures Group (NIPG). Details and application form are available from Jason Dunne, secretary to NIPG, telephone 0113 - 206 6951 or email jason.dunne@nhs.net. If your study will involve an interventional procedure which is new to you as an individual (but not to LTHT) you must ensure you have agreement from your clinical director, clinical lead and general manager

Important

As an NHS Provider, for clinical trials we must submit information regarding performance in initiating clinical research to the Department of Health. One of the data points we require is the date this study is ready to start i.e., recruit study participants, provide data or tissue. Therefore please either copy us into any "green light" emails you receive or send us a separate email with this date when it is confirmed with the sponsor.

If you have any queries please do not hesitate to contact the R&I team at leedsth-tr.lthtresearch@nhs.net.

Best wishes,

Anne Gowing
Research Governance Manager, Research & Innovation Department

Appendix E – Pacemaker codes table

Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programmability / rate-response	Multisite pacing
0 = none	0 = none	0 = none	0 = none	0 = none
A = Atrium	A = Atrium	I = Inhibit	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	T = Triggered		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)		D = Dual (A+V)

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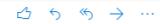
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Agata Rutkowska <agata.rutkowska@rct.uk>

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If you have any further questions or requests, please do not hesitate to contact me.

Kind regards,

Agata

Agata Rutkowska, Picture Library Assistant



St James's Palace, London SW1A 1JR

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Expected presentation date	Mar 2021
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