The role of heart rate on functional capacity in chronic heart failure: association or contribution?

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

Dedication

This thesis is affectionately dedicated to my parents, Mohammed and Azra Jamil for their unremitting love and wisdom, and without whom none of my career would have been possible; to my brothers, Adeel and Nabeel for always providing a mixture of encouragement and welcome distractions; to my wife Sana for her selfless support and understanding throughout: and to my son Zackaria, for the joy he brings to all of our lives.

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This research has been carried out by a multi-disciplinary team, which included John Gierula, Roo Byrom-Goulthorpe, Maria Paton, Judith Lowry, Laura Allen, David Cairns and Caroline Bedford. My own contributions, fully and explicitly indicated in the thesis, have been to supervise, design, coordinate and carry out the research studies, as well as the subsequent analyses and discussions. The other members of the group and their contributions have been: exercise test supervision, echocardiography, randomisation, data collection and blinding.

I would also like to acknowledge the statistical advice provided by David Cairns (Senior Research Fellow in Biostatistics at University of Leeds), and the support of Caroline Bedford (Lead Pharmacist for Clinical Trials and Medicines Management Services at Leeds General Infirmary) for medication/placebo encapsulation and randomisation services.

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Abstract

A key feature of chronic heart failure (CHF) is an inability of the heart rate (HR) to increase in proportion to the level of physical exertion, known as chronotropic incompetence (CI). Increases in HR during exercise contribute to an increase in cardiac output and hence greater blood supply to exercising peripheral muscles. It is generally assumed therefore that a limitation to heart rate rise might contribute to exercise intolerance. Whether CI is a causal factor in CHF has been a long-standing topic of debate and conflicting opinions.

This thesis comprises a series of studies aiming to clarify the role of HR on exercise capacity in CHF.

The observational study demonstrated a relationship between exercise capacity and heart rate rise, both of which are reduced in the context of heart failure. I have identified an association between the degree of CI and the extent of exercise capacity reduction in CHF, however this relationship is weaker with more severe CHF.

I have also shown in two randomised controlled interventional double-blind crossover trials that increasing or decreasing the heart rate response in patients with CHF, does not result in any changes in exercise capacity.

Finally, in a double blind case-control study, I have demonstrated a marked difference in heart rate related contractility in CHF compared to controls. This suggests that correcting CI may improve exercise capacity in controls by increasing cardiac output via increases in contractility, and this might not be the case in CHF.

Based on these novel findings, I conclude that in patients with CHF, CI is a marker of reduced exercise tolerance in CHF, and cannot be considered to be a causal factor. Aggressively correcting CI should therefore not be pursued as part of the the symptomatic treatment of patients with moderate to severe heart failure in either sinus rhythm or atrial fibrillation. Instead the chronotropic adaptation seen with worsening heart failure should be optimised, with the aim to maintain the exertional heart rate rise between 50 to 110 beats per minute.

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Preface

The close relationship between heart rate and exercise capacity, and limited techniques to detach one from the other means that published data are inconclusive. The purpose of this series of investigations is to determine the role of the heart rate on exercise capacity in heart failure.

Chapter 1: Introduction to Heart Failure and Treatment

1.1 Introduction

The term heart failure (HF) refers to a common clinical syndrome that is the consequence of reduced cardiac pump function. This syndrome incorporates certain non-specific signs and symptoms, and can occur as a result of any mechanical, structural or electrical abnormality of the cardiac tissue. Impaired pump action also leads to myriad secondary consequences affecting various organs including kidneys, bone marrow and muscle.(1)

The pathophysiology of chronic heart failure (CHF) and the basis of treatment are incompletely understood. There is a complex interaction between the reduced perfusion of organs and systemic neuro-hormonal processes, which is believed to contribute to and exacerbate the systemic organ dysfunction that exists in established HF.

Thus ‘heart failure’ is a clinical syndrome in which the patient exhibits the typical HF signs and symptoms, along with objective evidence of impaired cardiac output at rest.

The term ‘heart failure’ encompasses any structural or functional impairment of either left ventricular filling in diastole or emptying during systole. Thus HF

can range from those with impaired ventricular filling but normal LV size and ejection fraction (EF), referred to as heart failure with preserved ejection fraction (HFpEF), to those with reduced EF and/or ventricular dilatation, known as heart failure with reduced ejection fraction (HFrEF). Most randomised controlled trials have enrolled patients with HFrEF, also known as systolic heart failure or left ventricular systolic dysfunction (LVSD).

At the time of writing, effective proven therapies are only available for the treatment of systolic heart failure. Furthermore, making the diagnosis of HFpEF is often challenging and relies on both the exclusion of non-cardiac causes for the HF symptoms, as well as multiple testing modalities to demonstrate LV wall stiffness and impaired diastolic LV function.

Chronic dysfunction of ventricular function results in abnormal remodelling which varies depending on the HF type, although often elements of both HFrEF and HFpEF co-exist. In pure HFpEF, LV cavity size is usually normal, however LV wall thickness and stiffness are both increased. In contrast, patients with predominant HFrEF usually develop LV dilatation.

Cellularly this represents a reduction in both cardiomyocyte density and diameter compared to HFpEF.(2) A difference in the extracellular matrix (ECM) has also been reported, with increased ECM synthesis due to enhanced inhibition of matrix metalloproteinases (MMPs) leading to increased LV wall stiffness and fibrosis, seen in HFpEF. Conversely, an increased in MMP function has been reported in the context of LV volume

overload and LV dilatation, seen in HFrEF.(3) All types of HF are associated with an increased myocardial cell death rate and abnormal cytoplasmic calcium cycling.(4)(5)

Using the current guidelines, it would have been difficult to accurately and confidently identity a group of patients with pure HFpEF. Thus this investigation in to the role of the heart rate will focus on those patients with symptoms that are predominantly due to HFrEF, defined as symptoms of HF, either at rest or on exertion, with objective evidence of LVSD.(6)

1.2 Epidemiology

HF affects 2% of the adult population in developed countries,(7)(8) and approximately 10% of over 65 year olds. The incidence has remained stable for the past 20 years,(9)(10) but the prevalence of the condition is increasing, partly as a result of decreasing mortality from ischaemic heart disease, advances in effective treatment regimens for CHF and an ageing population.(11)(12)

HF is the most common cause for hospital admission in those over 65 years old, and accounts for 5% of all hospital admissions.(12)(13) In addition to this, approximately 40% of patients die within one year of being newly diagnosed with heart failure.(14) Current overall mortality from CHF is 50%

in four years, worse than the long-term prognosis following myocardial infarction or for most cancers.(15)

Features suggestive of particularly poor prognosis include increased age, reduced functional capacity, male sex, coronary artery disease, low blood pressure, renal function impairment, hyponatraemia, and high plasma brain natriuretic peptide levels.

HF also results in more primary care consultations than angina, reflecting the impact of the syndrome on the overall quality of life of those affected.(16) It greatly impairs physical functioning as a result of persistent fatigue and dyspnoea.(17) This negative impact on exercise capacity exceeds that of other major chronic conditions such as chronic lung disease, diabetes or arthritis.

Better treatment of heart disease and an increase in cardiovascular risk factors such as diabetes and obesity, especially pertinent as healthy lifestyles continue to decline in countries with emerging economies, means that a new increase in global incidence of CHF is underway.

1.3 Aetiology

HF is a symptomatic syndrome resulting from any structural, electrical or mechanical cardiac abnormality that affects ventricular function occurring due to a multitude of causes. HF in developed countries is usually due to ischaemic heart disease,(18) with LVSD occurring as a result of myocardial infarction (MI) or severe coronary artery disease (CAD). Hypertension is the largest contributor to CAD, and together these two conditions form the most common causes of cardiac dysfunction.(19) The most important global risk factors for ventricular dysfunction are therefore hypertension, diabetes and obesity.(19)(20)(21)

Valvular disease can also lead to pump failure, due to cardiac pressure and volume overload. The most common causes for this are rheumatic valvular disease in developing countries, and degenerative valvular disease elsewhere.(22) Exposure to toxins, including chemotherapy agents, and excessive alcohol consumption can also result in a dilated cardiomyopathy.(23) Idiopathic cardiomyopathies account for a significant minority of cases.(24)

Arrhythmias such as atrial fibrillation (AF) are frequently associated with CHF, but these are more commonly due to cardiac structural changes, rather than the cause thereof.(25)

1.4 Systolic Heart failure and diastolic heart failure

The focus of this thesis is exploring the relationship between heart rate and exercise capacity in the context of chronic stable left ventricular systolic dysfunction (LVSD). Diastolic left ventricular dysfunction is often found to varying degrees in association with hypertension, valvular dysfunction, ischaemic heart disease, and as a normal part of the ageing process.(26) It is characterised by left ventricular hypertrophy and abnormal echocardiographic Doppler parameters, which frequently co-exist with systolic dysfunction.(27)(28)

Definitions for diastolic impairment vary, especially across research studies. There is also often an apparent mismatch between the degree of diastolic impairment and patient symptoms.(26*)* Nonetheless, this is in important condition, as the subgroup of patients with diastolic functional abnormalities has worse outcomes than those with normal cardiac function.(29) Whether this is purely a reflection of the underlying causal pathology remains unclear.

As a result, the clinical management of patients with diastolic HF continues to be both a diagnostic and a therapeutic challenge.(30) There is a lack of clarity and poor current understanding of diastolic heart failure, and how it impacts functional capacity. Thus, isolated diastolic heart failure is considered outside the scope of this discussion and the investigations that will follow. Henceforth, the term ‘heart failure’ will refer exclusively to chronic LVSD.

1.5 Pathophysiology

1.5.1 Acute compensatory changes

The pathophysiology of the cardiac response to an acute cardiac injury is well understood. In the face of a myocardial infarction for example, stroke volume is initially maintained through the Frank-Starling mechanism.(31)(32)

Stroke volume and ventricular function depend on a combination of preload, myocardial contractility and afterload. In the ischaemic model of HF, the sudden fall in stroke volume due to cardiac damage results in a rise in end diastolic volume, and hence, pressure. The abrupt rise in preload results in increased cardiac muscle fibre stretch. This results in increased contractile force due to augmented calcium ion sensitivity in response to the reduction in lateral interfilament spacing as a consequence of sarcomere stretch.(33) Similar maladaptive changes also occur as a result of valvular, hypertensive and idiopathic cardiomyopathies, however the onset is usually more insidious, with end-diastolic pressure usually being the first parameter to alter.

Thus, the preload and the end-diastolic pressures play a crucial role in maintaining adequate stroke volumes in the failing heart regardless of aetiology.(34) The degree of contractile force can also vary due to intrinsic factors such as the levels of intracellular ions, especially calcium and also as a consequence of pharmacological therapies.

1.5.2 Chronic structural remodelling

Cardiac output is also regulated by a complex interplay of humoral, autonomic and intracardiac regulatory mechanisms, which can become compromised as a consequence of the maladaptive changes in all types of CHF.(35) Afterload also plays a role, and increases in this due to arterial constriction and stiffening will result in greater impairment of ventricular function, and reduction in the stroke volume.

The rise in afterload and the increases in preload due to volume expansion and higher venous return are compensated for initially, through the development of concentric ventricular hypertrophy in order to maintain normal systolic wall stress.

Prolonged pressure overload will eventually cause this adaptation to be insufficient, and ventricular dilatation will occur. This may also cause functional mitral regurgitation due to changes in the shape of the mitral annulus, thus exacerbating the problem and causing further progression of the ventricular dysfunction.

1.5.3 Neurohormonal adaptation and adverse long term effects

The reduction in cardiac output over time triggers various neurohormonal pathways, such as the sympathetic nervous system and renin-angiotensin-aldosterone system, in order to maintain vital organ perfusion. These

compensatory mechanisms attempt to maintain systemic pressure and organ perfusion via vasoconstriction, and improve cardiac output by increasing myocardial contractility, heart rate and volume expansion through sodium retention and renin release.

Renin release leads to increased angiotensin II production, which in turn contributes to increased plasma aldosterone levels and vasopressin release, resulting in sodium and water retention, and enhanced myocardial remodelling.

Volume expansion is initially effective as the increase in end diastolic volume results in an increase in stroke volume via the Frank-Starling principle in response to the increased preload. However, the elevated diastolic pressure is transmitted into the venous circulation and can lead to pulmonary congestion or peripheral oedema.(36)

Although initially compensatory, the sarcomere stretch due to increased pressure can eventually reach a suboptimal stage such that contractile force is reduced. This becomes most pronounced with exertion, leading to exercise related decreases in ejection fraction and cardiac output. (37)

Sympathetic system activation initially results in maintained organ perfusion through increased heart rate and peripheral vasoconstriction. However, these changes result in increased afterload, which depresses cardiac

function, and increases myocyte ischaemia, resulting in damage. Apoptotic myocyte loss results in fibrosis, hypertrophy, cardiac chamber dilatation and remodelling, with associated electrical instability.(38)(39)

Thus sustained activation of neurohormonal mechanisms will result in a net worsening of the heart failure over time due to progressive loss of cardiac function and direct effects on myocardial remodelling, along with systemic maladaptive changes.(40)(41) These are a result of chronic oxidative stress, inflammation and loss of tissue, leading to muscle wasting, cachexia and osteoporosis.(42)

1.6 Diagnosis

The characteristic feature of heart failure is impaired cardiac pumping function. However, patients present with non-specific signs and symptoms, which have poor sensitivity and poor specificity, most commonly, fatigue and shortness of breath (table 1.1 and table 1.2).(43) Accurate diagnosis requires clinical evaluation, along with relevant investigations in order to demonstrate signs, symptoms and objective evidence of a cardiac abnormality that would be consistent with a diagnosis of heart failure. Further investigations are sometimes needed in order to determine the underlying aetiology.(44)

Symptom	Sensitivity (%)	Specificity (%)
dyspnoea	66	52
orthopnoea	21	81
paroxysmal nocturnal dyspnoea	33	76
history of oedema	23	80

Table 1.1 Sensitivity and specificity of symptoms in diagnosing chronic heart failure

1.6.1 Signs

Heart failure signs occur due to the reduction in cardiac output at rest, and impaired increase with exertion. Tissue perfusion is also reduced as a consequence of this, leading to a variety of signs such as resting sinus tachycardia, narrow pulse pressure, diaphoresis, peripheral constriction with cool, pale peripheries and reduced urine output.(45)

Reduced cardiac output also triggers the neurohormonal adaptations that lead to volume expansion and fluid retention. This manifests itself as pulmonary congestion, peripheral oedema and raised jugular venous pressure (table 1.2).(43) (46) Left ventricular dysfunction and enlargement can also result in a third heart sound on auscultation and a laterally displaced apex beat, which are both strong predictors of heart failure. One study has shown a combination of past history of myocardial infarction and displaced apex beat have the best combined specificity and sensitivity, with high positive and negative predictive value.(47)

Sign	Sensitivity (%)	Specificity (%)
raised JVP	10	97
third heart sound	31	95
peripheral oedema	10	93
tachycardia	7	99
crepitations	13	91

Table 1.2 Sensitivity and specificity of diagnostic signs in individuals with suspected heart failure

1.6.2 Symptoms

In advanced heart failure, patients often present with symptoms of fatigue, dyspnoea in a recumbent position (orthopnoea) and acute episodes of paroxysmal nocturnal dyspnoea.(48) The low cardiac output leads to lethargy and poor exercise tolerance. Once such symptoms are present (table 1.1), a physical examination (table 1.2) and further investigations are needed in order to confirm the diagnosis.

1.6.3 Investigations

An electrocardiogram (ECG) is useful in supporting the diagnosis of heart failure and also to investigate the presence of any co-existing arrhythmias or evidence of ischaemic heart disease. A normal ECG has a 98 percent negative predictive value for systolic dysfunction.(49) A chest radiograph can also be useful for confirming a diagnosis of heart failure, as the presence of cardiomegaly or pulmonary oedema have high specificity (>90%), however it is important to recognise that both findings have poor sensitivity.(50)(51)

Various further laboratory tests are recommended to aid diagnosis and guide treatment. These include full blood count, serum electrolytes (including calcium and magnesium), blood urea, serum creatinine, fasting blood glucose, lipid profile, liver function tests, serum thyroid-stimulating hormone and urinalysis.(1)(52)

The measurement of either brain natriuretic peptide (BNP) or the N-terminal fragment of its prohormone (NT-proBNP) is also currently recommended in various guidelines.(1)(52) Studies indicate that measuring BNP or NT-proBNP can assist in the diagnostic process, with BNP levels below 100pg/mL having a very high negative predictive value for heart failure.(44)(46)(53) Elevated levels need to be interpreted in context and cannot be used to diagnose heart failure in isolation, given their high sensitivity but low specificity.(1)(44) Intermediately raised BNP or NT-proBNP levels are neither specific nor sensitive for diagnosing heart failure, thus limiting BNP usefulness as a stand-alone test.(54)(55)

Echocardiography is a non-invasive diagnostic test around which the diagnosis of HF is usually based. It can be used to measure ventricular size, global function, regional wall motion abnormalities and the presence of any pericardial disease. This investigation is indicated when a patient presents with dyspnoea and the initial evaluation suggests that a cardiac cause is likely, or to assess for potential valvular abnormalities.(1)(52)(56)

The sensitivity of two-dimensional echocardiography is around 80 percent and the specificity is almost 100 percent for detecting left ventricular dysfunction.(57) The key measure of left ventricular systolic function is determination of the left ventricular ejection fraction (LVEF), with values below 55% considered to represent reduced function. Diastolic dysfunction is more subtle, and is identified when there is abnormal left ventricular relaxation or diastolic stiffness.(6)(27)

Heart failure and reduced cardiac output can occur as a result of either systolic or diastolic function. However symptomatic patients with normal left ventricular function and no echocardiographic abnormalities, including no evidence of restrictive or obstructive cardiomyopathies, often have an alternative diagnosis than diastolic dysfunction, such as coronary ischaemia, respiratory disease, intermittent arrhythmia, detraining or obesity.(58)

Investigations such as coronary angiography, cardiac magnetic resonance imaging and endomyocardial biopsy may be indicated once a diagnosis of dilated cardiomyopathy is made following an echocardiogram, in order to confirm the aetiology. Further investigations should also be considered if the underlying aetiology is not apparent from the history or if the disease progression and response to treatment are atypical (table 1.3).(1)

Class I - Evidence and/or general agreement that initial evaluation should include the following assessment:
• History and physical examination to identify disorders associated with development or progression of HF.
• Use of alcohol, illicit drugs, standard or "alternative" therapies, and chemotherapy drugs.
• Ability to perform routine and desired activities of daily living.
• Volume status, orthostatic blood pressure changes, height, weight and calculation of body mass index.
• Laboratory studies including full blood count, urinalysis, serum electrolytes (including calcium and magnesium), serum urea, serum creatinine, fasting blood glucose, lipid profile, liver function tests, and serum thyroid-stimulating hormone.
• A twelve-lead electrocardiogram and chest radiograph.
• Two-dimensional echocardiography with Doppler to assess left ventricular ejection fraction, left ventricular size, wall thickness, and valve function.
• Coronary arteriography if there is a history or angina or significant ischemia unless the patient is not eligible for revascularization of any kind.
Class IIa - Evidence or opinion in favour of performing the following studies:
• Coronary arteriography in patients who have chest pain that may or may not be of cardiac origin who have not had a prior evaluation of their coronary anatomy and are eligible for coronary revascularization.
• Coronary arteriography in patients with known or suspected coronary artery disease who do not have angina and are eligible for revascularization.
• Noninvasive imaging to detect myocardial ischemia and viability in patients with known or suspected coronary artery who do not have angina and are eligible for revascularization..
•, Maximal exercise testing with measurement of respiratory gas exchange: to identify candidates for cardiac transplantation or other advanced treatments, or when contribution of HF to exercise limitation is uncertain.
• Screening for hemochromatosis, sleep disturbed breathing, or human immunodeficiency virus infection, if indicated.
• Diagnostic tests for rheumatologic disease, amyloidosis, or pheochromocytoma, if suspected clinically.
• Endomyocardial biopsy when a specific diagnosis is suspected that would influence therapy.
• Measurement of serum B-type natriuretic peptide (BNP) in the urgent care setting if the clinical diagnosis of HF is uncertain. Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in risk stratification.
Class IIb - Evidence or opinion less well established for the following tests:
• Noninvasive imaging to define the likelihood of coronary artery disease in all patients with left ventricular dysfunction.
• Holter monitoring in patients who have a history of myocardial infarction and are being considered for electrophysiologic study to document the inducibility of ventricular tachycardia.
Class III - Evidence and/or general agreement that the following tests are not useful or may be harmful:
• Routine endomyocardial biopsy in the absence of suspicion of a specific diagnosis that would influence therapy.
• Routine signal-averaged electrocardiography.
• Routine measurement of serum neurohormones other than BNP (eg, norepinephrine or endothelin).

Table 1.3 Adapted from ACC/AHA guidelines: Initial evaluation for heart failure (HF)

1.7 Classification

The functional classification developed by the New York Heart Association (NYHA) is most commonly used to provide an estimate of physical limitation.(59) This is based on symptoms alone, and can thus reflect either an improvement or deterioration in clinical state.

1. Class I — symptoms of HF only at activity levels that would limit normal individuals.
2. Class II — symptoms of HF with ordinary exertion
3. Class III — symptoms of HF with less than ordinary exertion
4. Class IV — symptoms of HF at rest

The American College of Cardiology/American Heart Association (ACC/AHA) classification system is also used, but less commonly than the NYHA classification. It provides information on the status of disease progression.(60)

1. Stage A – Multiple risk factors for heart failure but no structural heart disease
2. Stage B – Asymptomatic with evidence of structural heart disease
3. Stage C – Structural heart disease and symptoms consistent with heart failure
4. Stage D – Refractory heart failure

1.8 General treatment

Ischaemic heart disease, particularly a history of myocardial infarction, and diabetes are the main risk factors for the development of systolic CHF. Others include hypertension, obesity, smoking, high resting heart rate and atrial fibrillation.(61)(62)(63) Thus, addressing these aspects through lifestyle changes, patient education and appropriate timely pharmacological interventions could reduce the incidence of CHF.(64)

The aim of treatment in a heart failure patient is to control symptoms, reduce hospital admissions and improve mortality. Patient education on the aetiology, importance of adherence to treatment, benefits of medication dosage optimisation, early detection and promptly reporting any symptoms of deterioration can improve outcomes.(65) Structured aerobic exercise may also improve functional capacity and quality of life.(66) Fluid and sodium restriction may be indicated during episodes of decompensation, however there is no supporting evidence for these interventions from clinical trials.(1) Smoking is considered to be detrimental in heart failure, primarily due to its peripheral vasoconstrictive effects.(1)

1.9 Pharmacological treatment

Pharmacological therapy is the mainstay of treatment, with the key goals being symptomatic relief, slowing progression of the disease process and increasing survival. Current pharmacological treatments are aimed at inhibition of the two major neurohormonal pathophysiological mechanisms that underlie the progression and development of CHF, namely the renin-angiotensin-aldosterone system and the sympathetic nervous system.

1.9.1 Diuretics

The mechanism of action of diuretics is to block sodium reabsorption in the renal tubules resulting in increased urinary sodium and water excretion. Diuretic therapy has minimal effect on mortality or morbidity, but provides rapid and effective symptomatic relief.(67) The aim is to use the lowest dosage possible in order to maintain a euvolaemic asymptomatic state.

Thiazide diuretics can be used when there is mild heart failure with normal renal function. These work by inhibiting sodium re-absorption at the beginning of the distal convoluted tubules. Loop diuretics, which inhibit sodium and chloride reabsorption from the ascending limb of the loop of Henle in the renal tubules, are more potent and their effect is preserved in the presence of renal impairment.

Thiazide and loop diuretics may be used in combination, but the resultant profound diuresis usually requires close monitoring of electrolyte levels. Effective diuresis can be measured with the use of daily patient weight assessment when performed in a standardised way.(1)(68)

1.9.2 Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors (ACEi) competitively inhibit the conversion of inactive angiotensin I to the active angiotensin II. ACEi also inhibit the kininase enzyme, which is involved in bradykinin degradation.(72) This inhibition results in kinin accumulation, which might be an important secondary action, since bradykinin is a potent endothelium-dependent vasodilator, and causes natriuresis. It is also responsible for a dry persistent cough in around 10%-20% of patients.(69)(70)

ACEi lead to lower levels of angiotensin II and aldosterone. Angiotensin II causes systemic and coronary vasoconstriction, increased sympathetic activity and catecholamine release, increased aldosterone and vasopressin release, inhibition of endothelial nitric oxide synthase and cardiac myocyte hypertrophy.(71) These effects are a potent stimulus for adverse cardiac remodelling.(72) Aldosterone causes sodium and water retention, sympathetic activation and also leads to cardiac fibrosis.

As a result, ACEi therapy reduces mortality and hospitalisation rates, as demonstrated in multiple large prospective randomised controlled trials (CONSENSUS, V-HeFT-II and SOLVD trials).(77)(73)(78) Randomised controlled trials have also demonstrated that ACEi usage increases survival in patients who develop systolic dysfunction following a myocardial infarction (SAVE, AIRE, TRACE trials).(74)(75)(76)

These benefits have been demonstrated regardless of the presence of symptoms, thus all patients with any grade of systolic dysfunction should be initiated on low dose ACEi therapy.(77)(78)(79)(80) This should be uptitrated to either the target doses used in relevant RCTs or the maximum tolerated dosage, whichever is lower, over several weeks in order to maximise efficacy (ATLAS trial).(81) Possible side effects are cough, hypotension and renal function impairment.

1.9.3 Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARB) block the binding of angiotensin II to the AT1-receptor (Angiotensin II receptor, type 1), which mediates the vasoconstrictor and left ventricular remodelling effects of angiotensin II, with no effect on kininase function.(82) Based upon the CHARM study series, current guidelines consider ARBs to be a suitable alternative to ACEi in those patients with heart failure who are intolerant of ACE inhibitors or have developed a persistent cough secondary to kinin accumulation.(52)(83)

1.9.3.1 Combining ACEi and ARB

ACEi and ARBs can be combined, but although this probably reduces hospitalisation rates, there is no benefit on mortality and an increased side effect rate.(84) In addition, a Cochrane review of outcomes comparing ACEi monotherapy to ACEi and ARB combination revealed no statistically significant difference in mortality.(85) Similar results were seen in the VALIANT post-infarction heart failure trial where there was an increase in the occurrence of adverse events with combined therapy and no additional benefit in comparison to monotherapy with either drug group.(86) Thus, ARB agents are only used in addition to ACEi in those patients who have not had a recent MI, remain symptomatic despite optimal treatment with ACEi and are intolerant of beta blockers and aldosterone antagonists.

1.9.4 Beta-blockers

Beta-receptor antagonists (known as beta-blockers) inhibit the effects of adrenaline and noradrenaline on beta-receptors, and as such are capable of reducing activation of the sympathetic nervous system. Since this is chronically overactive in patients with HF, these agents are a logical choice and indeed data from several large randomised placebo-controlled trials describe improved survival and hospitalisation rates.

There is often a dramatic slowing in the progression of the condition and a reversal of adverse remodelling especially when these agents are added to an ACE inhibitor, regardless of aetiology (CIBIS-II, MERIT-HF, COPERNICUS).(87)(88)(89)

Beta-blockers should be introduced early, starting at a low dose and then up-titrated to the target dosage over several weeks, with regular patient monitoring for hypotension and bradycardia. Symptomatic worsening due to transient fluid retention can be resolved by temporarily increasing diuretic therapy rather than stopping beta-blockers.

1.9.5 Aldosterone antagonists

Aldosterone is a steroid hormone with mineralocorticoid activity that is mostly released by the zona glomerulosa region of the adrenal cortex in adrenal glands, although some is also produced by myocardial tissue in proportion to the degree of heart failure severity. In health, aldosterone plays a crucial role in blood pressure regulation, by acting on the renal nephron distal tubule and collecting duct to promote sodium and water retention, in response to increases in Angiotensin II levels. It is also involved in vascular remodelling, inducing LV hypertrophy and renal mesangial cell proliferation.(90)

Aldosterone levels are often increased in heart failure, leading to cardiac hypertrophy, fibrosis and electrical remodelling.(91) Aldosterone antagonists act directly to block mineralocorticoid receptors including those of the heart, thereby reducing salt and water retention, along with reduced progression and sometimes regression of myocardial fibrosis.(92)(93)

Several randomised trials have shown a reduction in hospitalisation rates and mortality of patients with mild-moderate (EMPHASIS HF trial) or severe (RALES trial) HF symptoms, as well as those who develop HF following an MI (EPHESUS trial) with the use of aldosterone antagonists.(94)(95)(96)

Aldosterone antagonists have several important consequences in a heart failure population. They preserve serum potassium levels by reducing renal potassium excretion, thus counteracting the hypokalaemia associated with the use of loop diuretics. The use of aldosterone antagonists is also associated with a reduction in cardiac arrhythmias and sudden death.(97) A retrospective analysis of data from the SOLVD trial demonstrated increased arrhythmic mortality in HF patients who were treated with non-potassium sparing diuretics, while no such association has been demonstrated with potassium sparing agents.(98)

Aldosterone antagonists should be considered in those patients who remain symptomatic despite optimal treatment with diuretics, angiotensin converting enzyme inhibitors and beta-blockers.(99) Treatment should be initiated at low doses with careful monitoring of serum potassium and renal function.

Non-selective aldosterone antagonists (spironolactone) may also inhibit androgen receptors resulting in antiandrogenic effects such as painful gynaecomastia, decreased libido and menstrual irregularities.(100) Epleronone is more specific, and therefore avoids these side effects.

1.9.6 Digoxin

Digoxin is a formulation of digitalis glycoside, which increases intracellular calcium and myocardial contractility by inhibiting the cell membrane sodium–potassium adenosine triphosphatase (ATP) pump in myocardial cells.(101) Digoxin also has antiadrenergic effects, which result in augmentation of parasympathetic tone and sympathetic inhibition, leading to a decrease in the heart rate.

In patients with heart failure in sinus rhythm, digoxin has been shown to reduce hospital admissions, without any reduction in mortality.(102) A recent systemic review and meta-analysis of RCTs and observational data has also concluded that digoxin use in CHF has not been shown to reduce mortality risk.(103)

Thus, the addition of digoxin in a patient who is in sinus rhythm is only recommended if symptomatic heart failure remains despite therapy with ACE inhibitors, beta-blockers and either ARBs or aldosterone antagonists.(1) A loading dose of digoxin is not needed in stable patients in sinus rhythm, and a steady state is usually reached 7–10 days after starting treatment.(104)

In patients with atrial fibrillation, digoxin can also be initiated in order to control the ventricular rate, if beta-blockers are contra-indicated or side effects limit their dose. Given its effects on heart rate and cardiac

conduction, digoxin should be avoided in patients who have high degrees of atrio-ventricular block, sick sinus syndrome and pre-excitation syndromes.

Digoxin has a narrow therapeutic window so monitoring serum digoxin concentration is useful in guiding treatment. Hypokalaemia and renal dysfunction increase susceptibility to adverse effects, which include anorexia, nausea, arrhythmias, visual disturbances and confusion. Certain cardiac medications can also increase serum digoxin concentration, including amiodarone, verapamil and diltiazem.

1.9.7 Hydralazine and isosorbide dinitrate

One of the major pathophysiological features of heart failure is persistent vasoconstriction. Vasodilation, usually achieved with ACEi leads to improved outcomes. However, some patients cannot tolerate ACEi or ARB, and others have such severe renal dysfunction that optimal titration of these agents is difficult. Another way to achieve arterial and vasodilation is with a combination of hydralazine and isosorbide dinitrate. Combined therapy with these agents reduces both preload and afterload, and is associated with reduced adverse cardiac remodelling.(105)

These effects result in a mortality benefit that has shown to be more significant in the African-American population and has only been demonstrated with this combination of vasodilating agents (V-HeFT trials).(73)(106)(107)

Although ACE inhibitor therapy produces a greater reduction in mortality compared to the hydralazine plus isosorbide dinitrate combination in an unselected population, ACEi are less effective in the African-American population. Combining ACEi with hydralazine and isosorbide dinitrate in African-American patients seems to have additional benefits, with reduced mortality, less hospital admissions and improved quality of life (A-HeFT trial).(99)(108)

The addition of hydralazine plus isosorbide dinitrate may also be considered as an alternative in those patients with a left ventricular ejection fraction less than 40 and who are intolerant of ACE inhibitors and ARBs.(1)

1.9.8 Selective sinus node inhibitors (Ivabradine)

Ivabradine is a selective inhibitor of the sino-atrial 'funny' channels, that are responsible for generating the spontaneous I_f cardiac pacemaker current. The degree of activation is the key determinant of the rate of diastolic depolarisation.(109) At therapeutic doses, ivabradine specifically lowers the heart rate in sinus rhythm, and is not known to have any additional cardiac or vascular effects.(110) Furthermore, the magnitude of I_f current inhibition achieved with ivabradine is proportional to the resting heart rate (RHR), demonstrating a plateau-dose effect. Thus severe sinus bradycardia is uncommon, and there is no known torsadogenic potential.

Analysis of data from the BEAUTIFUL trial in which 10,917 patients patients with CAD and LVSD were randomised to placebo or ivabradine, suggested that even though HR reduction was not shown to improve outcomes in all patients with stable CAD and LVSD, there was a reduction in CAD outcomes in those with heart rates below 70 beats per minute.(111)

Ivabradine was subsequently investigated in the SHIFT trial,(112) which demonstrated a reduction in the primary end-point of hospitalisation or cardiovascular death when compared to placebo. Analysis of the placebo arm highlighted that a higher RHR is a continuous marker of disease, and the study results clarified once again that RHR is a target for treatment. Higher heart rates were shown to be associated with significantly higher mortality, with an sixteen percent increase in cardiovascular death or heart failure hospitalisation for every five beats per minute increase in heart rate.

1.9.9 Thromboprophylaxis: Antiplatelets and anticoagulation

Patients with HF, even those in sinus rhythm (SR), but especially those with atrial fibrillation (AF), are at increased risk of thromboembolic stroke. Those with HF and AF should be anticoagulated, but despite multiple studies comparing antiplatelet and anticoagulation therapy in CHF with sinus rhythm there are no convincing data that patients with HF and SR should receive formal anticoagulation.

The Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction study (WARCEF study(113): warfarin (INR aim 2.5), aspirin 325 mg, placebo), Warfarin/Aspirin Study in Heart failure study (WASH study(114): warfarin, aspirin 300 mg daily, placebo), Heart failurE Long-term Antithrombotic Study (HELAS Study(115): aspirin 325 mg daily or warfarin for patients with ischaemic heart disease and warfarin or placebo in the non-ischaemic group) and Warfarin and Antiplatelet Therapy in Chronic Heart failure study (WATCH study(116): warfarin, clopidogrel 75 mg daily, aspirin 162.5 mg daily) all failed to demonstrate any difference in all-cause mortality, myocardial infarction or stroke.

Thus, each of these studies suggested that anticoagulation was no better than aspirin therapy in patients with CHF and no other indications for anticoagulation.(117) The paradox is that there is of course also no evidence for the routine use of aspirin in heart failure patients whether they have a history of ischaemic heart disease or not, although it is recommended in guidelines.(118)(119)

1.9.10 Other antiarrhythmic medication

Despite the high incidence of fatal ventricular arrhythmias and sudden cardiac death in this patient group, there is no evidence that antiarrhythmic agents other than beta-blockers, improve survival in heart failure.(120) This is probably due to the fact that a ventricular arrhythmia most frequently represents a serious heart failure problem that is not reversed by treatments targeting the arrhythmia.

No systemic reviews or RCTs have looked specifically at class 1 antiarrythmics such as propafenone, flecanide and moricizine, however extrapolated evidence from post MI treatment studies suggests there may be increased mortality with antiarrythmic medications, other than amiodarone or beta-blockers, in the context of HF.(121) RCTs of amiodarone use in HF also do not provide strong evidence for mortality benefits, despite effective arrhythmia suppression.(122)(123)

The best treatments for ventricular arrhythmias would seem to be those that target the pathophysiology of the heart failure (beta-blockers, ACEi and spironolactone).(82)(88)(97)

1.10 Cardiac pacing in heart failure

Implantation of a standard cardiac pacemaker can be utilised as an adjunct to medical therapy in the treatment of CHF. However the impact is dependent on the initial indication, device type and pacemaker programming mode. Standard pacing also allows more aggressive heart rate reduction and beta-blocker therapy in CHF, as the risk of inducing significant bradycardia is minimised. This confidence often leads to better optimisation of therapy.

1.10.1 Right ventricular pacing

Right ventricular (RV) pacing is the simplest and earliest form of pacemaker therapy, most commonly utilised in the treatment of intermittent high level AV block. However, delivering a pacing stimulus from the RV apex results in an abnormal conduction pattern similar to that of left bundle branch block which results in dyssynchronous ventricular activation. This can lead to ventricular dysfunction due to a combination of atrio-ventricular (RV contraction not related to atrial contraction), inter-ventricular (RV contracts before LV) and intra-ventricular (septum contracts before lateral wall) dyssynchrony. The risk of developing left ventricular dysfunction is directly related to the degree of RV pacing exposure (percentage of RV pacing, %RVP).(124) High %RVP can also exacerbate symptoms associated with existing CHF, due to the reduction in cardiac pumping capability.(125)

1.10.2 Dual chamber pacing

Pacing in both the right atrium and right ventricle (dual chamber pacing) has several advantages over RV pacing that were thought to be relevant in the context of CHF.

In patients with underlying SR and intact atrioventricular (AV) conduction, atrial pacing can restore normal electrical synchrony. AV pacing has also been shown to be superior to ventricular pacing with regards to haemodynamics, improved cardiac output and optimising valve closure to minimise mitral regurgitation.(126)

Atrial systole as a consequence of an atrial based pacing system results in an increase in ventricular end-diastolic volume and cardiac fibre stretching. This results in an improvement in the end-systolic contraction, in keeping with the Frank-Starling principle.(127) Thus sequential AV pacing results in an increase in cardiac output when compared to single-chamber ventricular pacing (VVI) modes, ranging from 15% to 50%.(128)(129)

Several clinical trials have compared ventricular (VVI) and atrial/dual (AAI or DDD) pacemaker programming modes to investigate whether restoring atrioventricular synchrony is associated with any clinical benefits in terms of quality of life or outcomes.

In a large observation epidemiological study of >36,000 elderly Medicare patients with pacemaker implants (PASE study), DDD pacing was associated with lower mortality at 1 and 2 years compared to VVI pacing.(130) However observational studies such as this are limited due to the potential for confounding bias based on patient selection, and there were many differences present between the demographics of the two groups. However dual chamber pacing remained an independent predictor of survival even after adjustments were made for differences between the two patient groups. Several large scale randomised trials have also compared dual chamber with ventricular pacing, reporting the benefits of sequential pacing modes (AAI/DDD).

Anderson et al compared AAI and VVI in a randomised trial with a cohort of 225 patients with sinus node disease (SND), and demonstrated that atrial pacing was associated with more favourable long-term clinical end-points including improved mortality.(131)

Similarly, the PAC-A-TACH trial showed mortality benefit with DDDR pacing when compared to VVIR in a cohort of 200 subjects with SND.(132)

The Mattioli et al trial compared physiological (atrial based: AAI, DDD, VDD) pacing modes with VVI pacing in 210 patients. The results showed reduced incidence of stroke and atrial fibrillation in the physiological pacing group.(133)

The CTOPP study compared DDD(R)/AAI(R) modes with VVI(R) in 2568 patients. The results showed a reduction in the development of atrial fibrillation in the atrial based pacing modes (AAI/DDD).(134) Similarly, the MOST study in 2002, which looked at 2010 patients with SND, demonstrated a reduction in AF and HF in the DDDR paced patients compared to VVIR.(135)

Thus AV sequential pacing modes (AAI, DDD) are associated with lower mortality, reduction in risk of AF and HF, and improved quality of life, when utilised in a non-CHF population.

These theoretical benefits led to a randomised trial in order to assess whether dual-chamber pacing could improve CHF outcomes in the absence of any pacing indications (DAVID trial). A comparison was made between dual chamber pacing (with rate adaptive pacing and resting paced HR 70, DDDR-70) and sinus rhythm (with RV pacing backup if the HR dropped below 40, VVI-40) in the context of LVSD, and no benefit was seen.(136)

Similarly, post-hoc data analysis from the Mode Selection Trial (MOST), MADIT II, and Midas trials all revealed a proportionate increase in adverse HF outcomes with higher percentage of ventricular pacing therapy, regardless of the mode used (DDDR or VVIR).(137)(138)(139) Several studies have also assessed the impact of optimising atrio-ventricular delay

times (paced AV delay) in order to reduce MR severity and thus improve clinical outcomes in HF, with no differences seen between optimal medical therapy only and optimal medical therapy combined with dual chamber pacing.(140)

Additionally, the use of pacemaker programming modes and settings to minimise RVP, such as long AV delays and low base rates, result in improved LV function without any adverse effects on symptoms, exercise capacity or quality of life.(141) Thus dual chamber pacing with a short AV delay has no role to play in the routine treatment of CHF, in the absence of other primary arrhythmic indications.(142)

1.10.3 Rate adaptive pacing

There has also been a focus on developing sensor technology to facilitate heart rate variation in response to physical activity, in patients with presumed chronotropic incompetence, with the aim to improve quality of life by reducing exertional fatigue.

In the rate-adaptive pacing mode, motion sensors in the pacemaker device detect increasing levels of movement or activity akin to the swinging of a pendulum in response to increasing force. This is translated by various pacing algorithms to trigger a progressive increase in the rate at which the atria or ventricles are paced commensurate to the level of activity.

However, there is a paucity of research in this area with usage of rate adaptive pacing modes generally being based on general consensus or expert opinion, rather than any guidelines or class 1 evidence.

The ADEPT trial in 2003 compared DDD and DDDR in 870 patients.(143) The primary end point was quality of life, and no differences were seen in the two groups. Similarly, the UKPACE study compared DDD vs VVI vs VVIR in 2000 patients. There was no difference in mortality between the groups.(144) The RAMP study also compared DDD with DDDR pacing in 400 patients. The results of this study showed no difference in quality of life between the two groups.(145)

1.10.4 Implantable cardioverter defibrillator (ICD) as primary prevention

Ventricular arrhythmias are a major cause of mortality in HF, with almost fifty percent of patients dying suddenly. The relative risk of sudden death is greatest in patients with mild/moderate HF, and NYHA functional status of II/III.(146) Randomised, placebo controlled trials have demonstrated reductions in mortality with implantable defibrillators in patients with LVSD.(147)(148)

Thus all patients with NYHA status II/III, good quality of life, no significant co-morbidities and a left ventricular ejection fraction less than 35 should be

considered for an ICD, with the evidence for benefit being greatest in those patients with an ischaemic cause for heart failure (SCD-HeFT Trial).(1)(120)

1.10.5 Cardiac Resynchronisation Therapy (CRT)

Around 30% of patients with severe heart failure have some degree of intraventricular conduction delay (for example left bundle branch block). The electrical delay results in ventricular dyssynchrony, which can accelerate adverse remodelling. This results in wider QRS durations, which directly reflects the underlying electromechanical dysynchrony. Wide QRS durations are seen as a result of LVSD chronicity and severity, and may contribute to worse exercise capacity.(149)(150)

Cardiac resynchronisation therapy is a form of pacemaker therapy that aims to improve coordination of contraction of the heart. In order to achieve this a ventricular electrode is paced in the right ventricular apex as usual, and another is placed in a coronary vein on the lateral wall of the left ventricle. By pacing through both electrodes simultaneously, it is possible to improve conduction timing, which can reduce dyssynchrony and improve cardiac output (CARE-HF trial).(151)

CRT in LVSD improves symptoms, quality of life, hospitalisation rates, mortality and reverses abnormal myocardial remodelling (MIRACLE trial).(152) It is currently recommended in patients with severe left ventricular systolic impairment (LVEF<35%) and an intraventricular conduction delay

resulting in QRS durations greater than 120 ms on the 12 lead electrocardiogram.(1)(6)

1.10.6 Left Ventricular Assist Devices (LVAD) and Heart Transplant

Surgical treatment options for end-stage heart failure are limited. Left ventricular assist devices can improve myocardial contractility and reverse abnormal remodelling.(153)(154) These devices are used temporarily as bridging therapy prior to heart transplantation or permanently where transplantation is contraindicated and long-term prognosis is poor, for short-term survival benefits (REMATCH trial).(155)(156) Cardiac transplantation is considered to be definitive treatment, however the limited availability is usually restricted to younger patients, and those with no co-morbidities.(157)

Chapter 2: Cardiovascular physiology in health and disease

2.1 Cardiac physiological responses during exertion

Maximal exercise capacity refers to the maximum degree of physical exertion attainable. Normally during aerobic exercise, cardiac output increases in order to meet the upsurge in metabolic demand within skeletal muscles. This is achieved through rises in both stroke volume and heart rate, with the major contributions provided by the latter. In health there is a linear relationship between rise in heart rate and oxygen uptake (Vo_2) readings, and a hyperbolic relationship with stroke volume (figure 2.1).(158)(159)(160)

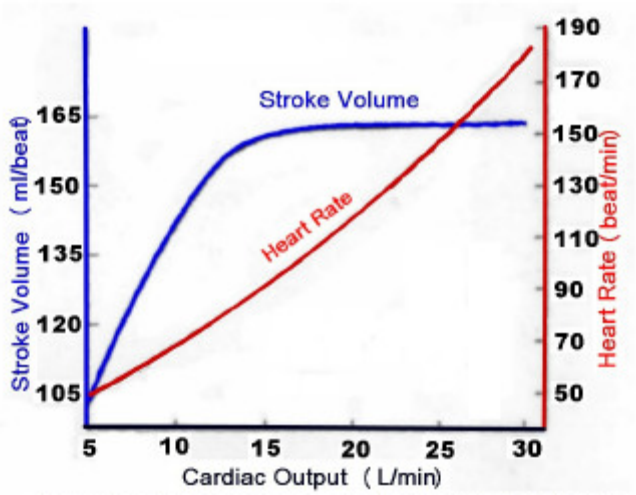


Figure 2.1 Increases in heart rate and stroke volume during exercise in non-competitive runners

2.1.1 Cardiac Output

During exercise, cardiac output increases via the stroke volume and heart rate (Cardiac output (CO) = stroke volume X heart rate). There can be a 50% increase in stroke volume through a reduction in the end-systolic volume, whilst maintaining the end-diastolic volume as a result of increases in cardiac contractility and the Frank-Starling mechanism. A four-fold increase in the heart rate can occur as exercise progresses, through a reduction in vagal tone and increase in sympathetic activation at the sino-atrial node.

Cardiac output is usually attributed as the most significant limiting factor during exercise, as demonstrated by the Fick principle, which states that the maximal skeletal oxygen consumption (peak V_{O_2}) is a product of cardiac output and arteriovenous oxygen difference. The latter is dependent on skeletal muscle vasculature and function. Thus, both peak cardiac output and oxygen delivery to muscles are responsible for the highest achievable skeletal muscle oxygen consumption, and determine aerobic exercise capacity.(161)

2.1.2 Stroke volume

The achieved stroke volume depends on preload, contractile force and afterload.(162)

2.1.2.1 Preload

A rise in end diastolic left ventricular volume (EDV), the preload, will result in an increase in cardiac myocyte sarcomere stretching. This raises myocardial calcium sensitivity leading to a greater number of force generating cross bridges, with a resultant increase in tension and force, as expected from the Frank Starling mechanism. Thus cardiac contraction is augmented in response to the increased EDV that occurs during physical activity, due to constriction of splanchnic and capacitance vessels and also as a result of improved venous return from vessels located within skeletal muscles.

2.1.2.2 Contractility

Stroke volume also depends of the contractility of myocardial cells. The degree of generated tension for any given sarcomere length is dependent on intracellular cyclic adenosine monophosphate (cAMP) levels and calcium concentrations. Increasing either of these results in an increase in the force generated with each contraction. Contractility is discussed in more detail later in this chapter.

2.1.2.3 Afterload

Afterload is the resistance to ejection during each ventricular contraction, and constitutes the wall stress in the aorta and conduit arteries during systole. A negative feedback mechanism is in place that alters the stroke volume in accordance to the afterload and aortic impedance. Moreover, the Anrep effect describes how the heart responds to any abrupt increase in

afterload, by increasing myofilament Ca^{2+} responsiveness, and thus increasing cardiac contractility and maintaining the end-diastolic volume.(163)

Episodic exercise leads to a reduction in systemic vascular resistance and systemic blood pressure, both acutely during exercise, and also for prolonged periods following a bout of exercise. Exercise training can also lead to beneficial adaptations in vascular beds resulting in persistent reductions in afterload. Although this is generally assumed to be a prognostically beneficial effect, this lower afterload requires an increase in stroke volume to maintain cardiac output.(164)

2.1.3 Heart rate

In health, there is a linear relationship between heart rate (HR) rise and the level of physical activity. HR increase during exercise is a major contributor to the rise in cardiac output. The maximum HR attainable is age-dependent.(165) Although physical training and conditioning can reduce the resting heart rate, they do not significantly affect the peak heart rate.(166)

The spontaneous rate of sino-atrial myocyte activity at rest and during exertion is governed chiefly by the autonomic nervous system. Cardiac parasympathetic outflow originates at the vagal nucleus in the medulla from the cardioinhibitory centre, and innervates the heart via the vagus nerve.

The vagus nerve regulates parasympathetic signals through acetylcholine release, which results in an increase in cell membrane potassium ion permeability and a reduction in the heart rate through inhibition of the hyperpolarisation dependent sino-atrial I_f (“funny current”). This controls the heart rate through its role in initiating diastolic depolarisation of sino-atrial myocytes at the end of every action potential.(167)

The reticular formation of the brain stem provides sympathetic cardiac innervation from the vasomotor centre, activation of which results in an increase in heart rate and cardiac contractility via the release of epinephrine and norepinephrine, both of which act on the cardiac beta-adrenergic receptors. This results in an increase in intracellular calcium ion concentrations and activation of the I_f current, leading to an increase in the heart rate.

Exertional heart rate changes are governed by multiple peripheral and central mechanisms. Initially there is a reduction in the parasympathetic tone, followed by an increase in sympathetic activation of the I_f, the degree of which depends on feedback from arterial baroreceptors and skeletal muscle mechanoreceptors, and is coordinated by the various brainstem centres.(168)

2.2 Cardiac myocyte contraction physiology

The normal physiological processes underlying each heart-beat, and the relationship between the heart rate and cardiac contractility are fundamental to understanding the basis of this thesis, and thus a detailed discussion of the cellular physiology follows.

2.2.1 Excitation-contraction coupling

Cardiac myocytes differ from skeletal muscle cells in that the activation of one cell results in mass depolarisation of adjacent cells. This is facilitated by the presence of tight junctions between myocytes, which ensure the existence of a cardiac muscle syncytium, with no role for spatial summation in the development of tension.(169)

The excitation-contraction coupling (ECC) of myocytes is modulated via receptors and channels located on the surface membrane, also known as the sarcolemma, and on membrane invaginations known as T-tubules.(170) These receptors allow compounds such as epinephrine, norepinephrine and acetylcholine to influence myocyte function.(171) An enclosed internal tubule network, known as the sarcoplasmic reticulum (SR), is also present which sequesters and releases calcium ions during diastole and systole, respectively. The cellular cytoplasm in myocytes, known as the sarcoplasm, contains large quantities of mitochondria and myoglobulins to ensure maximal aerobic metabolism.(172)

2.2.1.1 Excitation

The sino-atrial node generates each action potential, which initiates myocyte excitation. Depolarisation of the sarcolemma results in the opening of L-type calcium channels (LTCC), allowing a small influx of calcium ions.(173) The presence of a calcium ion current in the sarcoplasm induces further calcium ion release from the SR via ryanodine receptors (RyR2), in a process termed 'calcium-induced calcium-release'.(174) This binds to contractile proteins to produce physical shortening of the myocyte. RyR2 mediated calcium release is graded in response to the magnitude of the initial depolarisation induced calcium influx current (I_{Ca}).(175)

2.2.1.2 Contraction

These processes result in increased calcium ion concentration in the sarcoplasm surrounding the myofilaments.(170) The calcium ions are then free to bind to troponin C (TnC) on the thin filaments. This exposes the actin heads, allowing cross bridges to form between the actin and myosin components in an ATP dependent process, which results in sarcomere shortening and myocyte contraction.(172) This is discussed in further detail in the next section.

2.2.1.3 Termination

The process ends when the bound calcium ions are recycled in to the SR by the calcium activated MgATPase, SERCA2a. SERCA2a activity is modulated via phospholamban (PLB).(176) This proteolipid can inhibit

calcium ion transport. Phosphorylation of PLB via cAMP dependent protein kinase enhances calcium ion uptake.(177) The excess sarcoplasmic calcium ions which initially entered in response to the sino-atrial action potential are also returned to the extracellular space in exchange for sodium ions, via the sodium–calcium exchange protein, NCX, which is driven by the sodium ion gradient across the sarcolemma. This gradient is maintained by the sodium-potassium ATPase protein.(178) Some calcium ions also exit the sarcoplasm via sarcolemma calcium ion pumps, or in to the mitochondrial spaces.

2.2.1.4 Contractile reserve

Calcium ions do not saturate the TnC binding sites on the actin filaments at the basal resting heart rate. Thus a thin filament reserve exists, which allows the force of the contraction to be increased if more calcium ions are present.(179) Varying the sarcoplasmic calcium ion concentration allows control over the resultant number of force generating cross-bridges that can be formed between the actin and myosin components during each ECC.

2.2.2 Sarcomere physiology

Myocyte contraction is determined by sarcomere function. The sarcomere consists of thick filaments, which contain the power generating myosin molecules, and the thin filaments, which house the actin molecules.(172) Contraction and shortening is mediated by the formation of cross-bridges between the myosin heads and the actin molecules.

At the initiation of systole, actin becomes exposed to the myosin binding site when calcium ions bind to TnC and cause tropomysin (Tm) to move off the actin binding sites.(180) This allows the cross bridge to form, followed by movement of the myosin lever arm in order to drive the actin molecule and the attached thin filament towards the centre of the sarcomere.(181)

2.2.2.1 Sarcomere energy consumption

This process is energy dependent and requires the hydrolysis of one molecule of MgATP per cycle. During diastole MgATP is hydrolysed to ADP and Pi, and remains bound at the cross bridge.

In systole, movement of the Tm off the actin binding site allows the cross bridge to form, and resultant filament sliding and sarcomere shortening to occur.(182) ADP and Pi are release at the end of the myosin stroke, at which stage the actin and myosin components remain strongly bound until an MgATP molecule binds to the cross bridge, to allow actin release and further cross-bridge formation if required.(183)

In diastole, the passive tone of the myocytes is determined by the presence of the titin protein in the sarcomeres, which extend from the mid-line to the Z discs.(182) Titin has elastic properties that allow it to stretch in response to the increased venous return and ventricular filling in diastole, and allows the sarcomere to be restored to its diastolic parameters at the end of each myocyte contraction.(184)

2.2.3 Contractility

Cardiac contractility is determined by a complex interaction between the various sarcomere components. It relies on the number of myocardial fibres involved in cardiac contraction and the maximal velocity of the shortening of these fibres, which is determined by the concentration of calcium ions in myocardial cytosol.(185) The enhanced force development in response to greater calcium ion concentration is due to additional recruitment of cross bridges between the actin and myosin contractile proteins. This is further affected by adrenergic and cholinergic activation.(186)

2.2.3.1 Modulation

Contractile performance of the myocardium is modulated in three ways.(187)(188) Firstly, increases in sarcomere length due to increased preload decreases the actinomysin overlap, but increases calcium sensitivity and calcium release. Secondly, the presence of catecholamines leads to increased cyclic AMP phosphorylation and thereby increased calcium influx, increased calcium release from the SR and accelerated calcium removal.(189) Thirdly the contractile force is directly related to heart rate through augmentation of the amount of calcium that enters the cell per unit of time, increasing SR loading and hence the amount of calcium that can be released during contraction.(186) This is known as the Bowditch effect, and is discussed in greater depth later.

PLB phosphorylation via protein kinase A (PKA), under adrenergic stimulation, will cause increased calcium ion uptake into the SR, resulting in a shortening of the contraction-relaxation cycle. PKA also acts to phosphorylate LTCC and RyR2 receptors, resulting in increased calcium ion release from the SR.(176)

Cross bridge activity is also altered by PKA under adrenergic stimulation, due to phosphorylation of myosin binding protein C (MyBP-C) and phosphorylation of troponin I (TnI). This results in increased cross-bridge cycling and kinetics, and faster release of calcium ions from the TnC binding sites on the actin filaments.(190)

Thus the heart normally responds to the increased venous return associated with adrenergic stimulation and higher heart rates through improved contraction and relaxation dynamics, without any significant change in the EDV.

2.2.3.2 Mechanisms

Normal increases in contractility during exercise require both the depolarisation-rate dependent (heart rate dependent), and catecholamine-dependent mechanisms to be functioning normally.(191)

2.2.3.2.1 Catecholamine dependent mechanism

The catecholamine system is chronically overactive in CHF such that there is down-regulation of adrenergic receptors, making the sympathetic system less sensitive and responsive.

Adrenergic stimulation increases the heart rate and the force of contraction, with increased peak calcium ion concentration during an ECC. Adrenergic beta-receptors are linked to G-receptor proteins, which can inhibit and stimulate the formation of cAMP by altering activity of the enzyme adenylyl cyclase.(192)

Adenylyl cyclase activity is increased under adrenergic stimulation and is inhibited by cholinergic stimulation. Elevated cAMP levels result in increased PKA activation, which acts to modulate calcium ion levels in the sarcoplasm. Phosphorylation of PLB via cAMP dependent PKA enhances calcium ion uptake by the SR. Dephosphorylated PLB reduces calcium ion uptake by reducing SERCA2a activity.(193)

2.2.3.2.2 Depolarisation-rate dependent mechanism

The depolarisation-rate dependent mechanism (catecholamine independent) through which increases in heart rate lead to increases in the force of contraction is known as the Treppe phenomenon and was described by Bowditch in the late 19th century.(194) This frequency-dependent up-

regulation of contractility is both fast and intrinsic to the myocardial cell with no external involvement from neuronal or hormonal controls.(195)

2.2.3.2.2.1 Treppe phenomenon

Increases in heart rate result in an increase in the depolarisation induced I_{ca} amplitude, with an associated increase in calcium ion entry into the sarcoplasm. A stepwise increase ('staircase effect' – Treppe) in the myocardial contractile force occurs in response to increasing HR, known as the Treppe phenomenon (or force-frequency relationship (FFR)).(196).

Thus in controls, CO will increase by increasing the heart rate and reducing the end systolic volume (ESV), with little change in the EDV. Without such a compensatory increase in contractility, stroke volume would be reduced due to less filling time, significantly impairing efficiency and requiring greater increases in heart rate to achieve similar rises in cardiac output. The positive force-frequency relationship (FFR) exists to prevent a reduction in stroke volume at faster heart rates.(197)

In humans, the increase in contractility in response to increased heart rate seems to occur between heart rates of 60 -180 per minute, after which contractility declines.(198)(199)(200)

2.3 Pathophysiological cardiovascular responses to exercise in CHF

2.3.1 Introduction

The key feature of heart failure is exercise intolerance due to fatigue, which has a significant impact on quality of life. However, the severity of LVSD in CHF correlates poorly with functional capacity.(201) This is probably due to the fact that exercise intolerance is influenced by abnormalities in cardiovascular, respiratory or skeletal muscle response mechanisms and function, all of which are abnormal in patients with systolic heart failure.

2.3.2 Fatigue

The diagnosis of heart failure is inextricably linked to a reduction in functional capacity. As heart failure progresses, exercise capacity becomes progressively limited due to fatigue and dyspnoea, however this does not correlate with measures of left ventricular function at rest, such as the ejection fraction or fractional shortening.

Fatigue is a multifaceted symptom, which incorporates central and peripheral elements. Fatigue can represent either difficulty in initiating activity due to generalised weakness and poor concentration, or the inability to maintain prolonged activity.(202) The extent of the latter is dependent on the level and duration of physical activity, and the ability of the body to maintain effective oxygenation and acid-base homeostasis via adaptations in

the cardiovascular, respiratory and skeletal muscle systems. Thus multiple pathways may contribute to the increasing functional limitation that is pathognomonic of HF.

During exercise, energy substrate levels become depleted and metabolic by-products such as lactate accumulate. Both of these processes contribute to the fatigue associated with exercise and activity.(203) The lactate threshold (or anaerobic threshold) refers to the point at which the production of lactate in myocytes exceeds its metabolism via the Krebs cycle, and a sustained rise in serum lactate levels is detectable.(204) Thus, a steady metabolic state exists at V_{O_2} levels just below the lactate/anaerobic threshold (AT), and sustained activity is possible with less peripheral fatigue. Sustained exercise will cease due to fatigue once oxygen consumption exceeds AT.

The AT is a good marker for the ability to maintain prolonged activity, in comparison to peak V_{O_2} measurements.(205) AT is reduced in patients with heart failure compared to normal subjects, accounting for the reduced functional capacity, lower exercise tolerance and higher degree of fatigability.(206)

2.3.3 Cardiovascular adaptations

Exercise intolerance in systolic heart failure is likely to be the result of multiple physiological processes, but a key feature is impaired cardiac function due to abnormal cardiac remodelling. This results in reduced

cardiac output at rest because of myocyte contractile impairment, leading to diminished cardiac output rise with exercise.(207) There is a reduction in blood flow to skeletal muscle, which contributes to muscle wasting and dysfunction.(208)

2.3.3.1 Cardiac output

Adaptations to LVSD include an increase in sympathetic and neurohormonal system activity, through stimulation of the vasomotor regulatory centres in the medulla via aortic baroreceptors, as described previously. The role of increased sympathetic activity is to restore cardiac output through an improvement in contractility by increasing the amount of available intracellular cAMP and calcium, peripheral vasoconstriction and by increasing the heart rate, as a result of the increased plasma norepinephrine levels. This inotropic response may be sufficient to maintain a normal cardiac output in the early stages of the disease process, both at rest and during moderate activity.(209)

2.3.3.2 Stroke volume – Preload, contractility, afterload

2.3.3.2.1 Preload

The neurohormonal changes result in blood volume expansion via water and salt retention. This increases the preload, resulting in increased ventricular contraction as described by the Frank-Starling principle, and mal-adaptive changes in the ventricular structure including left ventricular hypertrophy, in an attempt to compensate for the preload changes and hence maintain cardiac output. (210)

In the long term, these adaptive changes are detrimental to cardiac function and result in a net worsening of ventricular systolic dysfunction. Thus further changes in the preload do not result in proportionate increases in contractile tension despite a maintained Frank-Starling mechanism.(211)

2.3.3.2.2 Afterload

The most common causes of heart failure are hypertension and ischaemic heart disease. A sustained chronic increase in afterload, which occurs in hypertension, can result in cardiac remodelling and hypertrophy.(212)

The increasing circulating volume that accompanies chronic renin-angiotensin and sympathetic nervous system activation causes a pressure overload in the left ventricle, resulting in further remodelling, dilatation, fibrosis and reduced compliance.

Over time, cardiac remodelling leads to an increase in EDV. This necessitates an increase in left atrial pressure to ensure LV filling in diastole, thereby raising pulmonary venous pressure. These maladaptive changes are responsible for the pulmonary oedema and reduced alveolar gas exchange, which are present in decompensated symptomatic heart failure.

2.3.3.3 Contractile dysfunction in heart failure

Another key feature of heart failure is reduced global cardiac contractility. Multiple mechanisms, including those described above lead to contractile

dysfunction, usually initiated by myocyte loss but exacerbated by efforts to compensate.(213)

These changes are an attempt to match the cardiac output to the venous return. While these adaptive mechanisms can restore near normal cardiac output at rest, a loss of contractility reserve results.(214) This is associated with a significant limitation in exercise tolerance and quality of life, as the cardiac output fails to increases sufficiently to meet the increased demands during exercise.

2.3.3.3.1 Impaired calcium handling

Myocyte structural change results in dysregulation of calcium ion control mechanisms and reduced phosphorylation activity. Similarly, myocardial ischaemia and myocardial infarction can result in cardiac remodelling due to reduced myocyte gas exchange and impaired local nutrient supply, which results in maladaptive changes affecting EC coupling and the response to increasing venous return. This depletes intracellular cAMP and calcium levels, and the abnormally remodelled cardiac tissue also has reduced contractility in response to sympathetic stimulation.(215)

Regardless of the cause of heart failure, a reduction in the delivery of calcium ions to the TnC binding sites on the actin filaments is commonly present. This contributes to the reduced contractility and impaired response to exercise that are key features of this disease process.

The molecular and cellular changes causing the abnormal contractile response to increases in heart rate seen in CHF are due to abnormalities of calcium (Ca^{2+}) handling.(216)(217) There is also a reduction in SERCA2a activity seen in CHF, which is partly due to reduced phosphorylation of phospholamban.(218) This leads to increased inhibition of SERCA2a and decreased Ca^{2+} sensitivity.(219)

These changes lead to depletion of SR calcium stores and delayed diastolic Ca^{2+} removal especially at higher heart rates.(220) Beyond a 'critical heart rate' calcium will be extruded from the cell rather than be taken up by the SR and oxygen consumption is doubled for each unit of force developed such that there is a marked decrease in efficiency of cardiac work.(221) Hence at high stimulation frequencies Ca^{2+}-lowering mechanisms play a crucial role in cardiac contractility and the altered functional balance between Ca^{2+} re-uptake and Ca^{2+} extrusion, are responsible for the blunted force-frequency relationship (impaired Treppe effect) that is present in the failing myocardium.(222)

2.3.3.3 Heart rate

Patients with heart failure have a significantly lower peak heart rate and reduced functional capacity compared to matched controls. It has been suggested that this is the major cause for the reduced exercise tolerance seen with chronic heart failure.(223)(224) It is as yet unclear whether this association indicates causality.

It is generally assumed that a limitation to heart rate rise might contribute to exercise intolerance. However, heart rate is closely related to workload and subjects with impaired exercise capacity have a lower peak heart rate. Whether impaired HR rise in heart failure actually induces a reduction in exercise capacity remains controversial. This close relationship, and limited techniques to detach one from the other means that published data are inconclusive. A detailed discussion of this follows.

2.4 Chronotropic incompetence

Chronotropic incompetence (CI) refers to an inability of HR to increase in proportion to the level of physical exertion or metabolic demand. This is commonly seen to be present in the context of heart failure, and is also known to be present in patients with coronary artery disease or sick sinus syndrome.(225)

2.4.1 Definition

The most widely used definition for CI is a failure of HR to reach an arbitrary percentage (usually 80%) of the age-predicted maximum based on the '220−age' equation, obtained during an incremental exercise test.(226) The chronotropic index is a more objective measurement for CI, consisting of the ratio of HR reserve to metabolic reserve.(227) A ratio of less than 0.8 is indicative of CI, irrespective of age, level of fitness or functional capacity. Reports of the prevalence of CI in moderate to severe chronic heart failure

vary between 28% and 70%, depending on the definition and testing strategy used.(228)(229)(230)(231)

2.4.2 Potential pathophysiology of CI

The presence of CI has also been related to increased cardiovascular mortality.(232) In subjects with LVSD, CI has been associated with down-regulation and de-sensitisation of myocardial beta-receptors due to heightened catecholamine levels as a result of neuro-hormonal activation.(224)(233) Structural remodelling of the sino-atrial node with associated impairment of electrical conduction of the sinus impulse in heart failure patients has also been demonstrated, which may play an additional role in CI.(234)

2.5 Literature review of HR and exercise capacity in CHF

The degree of CI relates to both the severity of LVSD and the level of exercise limitation, although it is unclear as to whether this is merely an association or a causative link.(235) Over the years, numerous studies have looked into this area with conflicting results.

2.5.1 Evidence supporting causal relationship

Jorde et al reported a significant relationship between exercise capacity in a cardio-pulmonary exercise test and the presence of CI in their sample of 278 stable CHF patients (ejection fraction <=40%) on optimal medical therapy. Almost half of the cohort (n=128) had CI as defined by a peak heart rate less than 80% of the age-predicted maximum. By stratifying their sample based on peak oxygen consumption measurements (pVO_2; ml/kg/min), they were able to show that the prevalence of CI increased significantly, from 24% in the 'pVO2 >20ml/kg/min' group to 48% in the 'pVO_2 between 14.0-20.0 ml/kg/min' group and was the highest in those with the worst exercise capacity, 72% in the 'pVO_2 <14ml/kg/min' group. This study demonstrated that CI was present in a significant proportion of CHF patients, and was associated with reduced exercise capacity.(230)

Al-Najjar et al looked at the relationship between the presence of CI in CHF and mortality in an unselected cohort of 411 patients with CHF who underwent cardio-pulmonary exercise testing. They found that CI was

present in 42% of the study population, and was associated with significantly lower exercise time and pVO_2. Peak VO_2 was an independent prognostic marker, but there was no association between CI and mortality.(228)

Lele et al also demonstrated some correlation between pVO_2 and HR ($r=0.45$; $p=0.04$) using erect cycle ergometry in 20 patients with mild-moderate CHF (mean ejection fraction 47%).(236)

2.5.2 Evidence opposing causal relationship

However, such a relationship between HR and exercise capacity was not seen in all studies. Roche et al performed a study to evaluate HR response to exercise in CHF. They performed symptom limited exercise testing with metabolic gas exchange measurements to determine pVO_2 in 21 subjects, and reported no significant difference in resting heart rate, age, maximal VO_2 achieved or left ventricular ejection fraction between the subjects with and without CI.(231) Similarly Clark et al tested 57 CHF subjects (mean LVEF 30%) and 14 controls using a treadmill based symptom limited exercise protocol and gas exchange analysis. Peak VO_2 was significantly reduced in the CHF group (19.6 (S.D. ±7.6) vs. 35.0 (±9.9) ml/kg/min; $P < 0.001$), and there was a correlation between peak heart rate and heart rate rise with pVO_2 ($r=0.47$, 0.59; $P <0.001$). However, there was no difference in peak VO_2 or exercise time between those CHF subjects with CI (defined as peak heart rate less than 80% age predicted maximum; n=16) and those without CI.(229)

Witte et al explored this association further, in the context of submaximal exercise. Controls (n=9) and CHF subjects (n=11) performed steady state exercise tests with gas exchange analysis at 15%, 25%, 50% and 100% of peak workload. They found that the CHF cohort had lower oxygen consumption at each steady state sub maximal stage compared to the controls, with the same heart rate. However, peak heart rate was reduced in CHF, such that there was no correlation between peak heart rate and exercise capacity ($r=0.003$; $p=0.98$), whereas the control cohort showed a strong correlation ($r=0.85$, $p<0.001$). This would suggest that a lower peak heart rate during exercise is a consequence of the reduced functional capacity in CHF rather than the cause.(235)

In most heart failure patients, there is an iatrogenic component to the impaired heart rate rise due to beta-blocker therapy. This was also investigated by Witte et al who demonstrated higher exercise time despite worse heart rate rise (exercise time: 498 vs 435 seconds; $p=0.02$) in a study of 237 patients with severe CHF (mean LVEF 30%) of whom 74 were not taking a beta-blocker. There was no difference in resting LVEF or baseline symptom class between the beta-blocked and non-beta-blocked cohorts.(237) However, in those with a low HRR in the presence of beta-blocker usage, CI did not predict a poorer outcome. Similarly, acute alpha and/or beta-blockade reduces sub-maximal ventilation during exercise, with no difference in pVO_2, exertion time or perceived exertion scores.(238)

Hirsh et al also showed in a study on 19 CHF subjects on beta-blocker therapy, that acute withdrawal of beta-blockers did not result in any change in exercise time, pVO_2 or 'normalisation' of the chronotropic response during a cardio-pulmonary exercise test.(239)

2.5.3 Heart rate control in AF

Studies of whether strict AF resting heart rate control (resting heart rate below 80) improves mortality and reduces hospitalisation have shown that lenient HR control (HR<110 at rest) is non-inferior.(240)(241) Thus stringent HF control does not seem to improve quality of life, symptoms, hospitalisation or outcomes, even in the presence of HF (EF<40%).(242)(243) The role of heart rate rise during exercise in AF and HF has hitherto not been explored in the context of any RCTs.

2.5.4 Evidence for rate adaptive pacing

The objective of rate adaptive pacing modes is to simulate the physiological heart rate rise that occurs in response to increasing levels of physical activity. Multiple studies have been carried out to assess the optimal slope for the relationship between heart rate and work rate.

Lewalter et al looked at the heart rate response to a ramping incremental treadmill exercise protocol in 41 middle aged subjects. They showed significant heterogeneity in heart rate response of men compared to women,

and suggested an average heart rate increase of 5 beats per minute for each 10 Watt increase in workload.(244)

In a further study, Lewalter et al also demonstrated a curvilinear HR response to minute ventilation, with a reduction in HRR at higher workloads.(245) Limitations for these studies include a small cohort size, no randomisation or blinding, and being carried out entirely using healthy middle aged volunteers.

Early rate adaptive pacing systems were based on single sensor systems, which used either pendulum based acceleration sensors to detect body acceleration (accelerometer), minute ventilation rate detection, intrathoracic impedance measurements or pacing electrode sensors. Each differed with respect to sensitivity, specificity, effectiveness and response speed.(246)(247) Thus modern pacemakers utilise a multisensor pacing system and algorithms to alter efficacy and responsiveness, with the aim to match paced heart rate response to metabolic demands.(248)(249)

Rate adaptive pacing with multi-sensor technology is also available in bi-ventricular pacing systems for heart failure, however these systems aim to mimic the physiological heart rate response derived from previous studies that recruited subjects with dual chamber pacemakers, and excluded those with severe LVSD.(250)

Thus the efficacy of rate adaptive pacing to match physiological heart rate rise, and alter the chronotropic adaptation seen in the context of severe LVSD, is unknown. Tse et al assessed the potential benefit of rate adaptive pacing in conjunction with cardiac resynchronisation therapy on metabolic exercise testing parameters in a small study of 20 patients with CI and LVSD. The increased heart rate achieved was not associated with any increase in peak oxygen consumption.(251)

2.6 Limitations of current research

Limited HRR is accepted as a contributor to exercise intolerance and the correction of CI as a potential target that could improve exercise capacity in health. This is usually achieved through the use of an implanted pacemaker. Pacemakers can be programmed to deliver either fixed rate pacing or utilise a rate-adaptive pacing algorithm, where the heart rate is altered in proportion to the level of activity as detected by internal device sensors. Rate-adaptive pacing in people without CHF is associated with an increase in cardiac output during exercise,(252) better quality of life(253)(254)(255) but with inconsistent(256)(257) improvements in peak exercise capacity, when compared to fixed rate pacing.

On the other hand, in patients with CHF, there is clear evidence that a high resting HR is a strong predictor of poor outcome.(258) Using a pacemaker to increase the heart rate in CHF patients worsens both the outcomes and cardiac function.(259)(260) Outcomes in CHF are clearly improved by inducing a bradycardia at rest; with the prognostic benefit increasing as the degree of resting heart rate reduction is increased.(111) This does lead to a limitation of HRR during exercise, and worsening of any CI that may be present.

It is currently unknown whether CI, intrinsic or iatrogenic, either contributes to (261)(262) or is the consequence of reduced exercise capacity in

CHF.(229) Thus, heart rate reducing agents, for which there are clear prognostic indications, are used at sub-optimal doses for fear of inducing exercise intolerance, fatigue or lowering blood pressure. In addition to this there is no conclusive evidence of benefit on exercise time or quality of life in CHF from rate-responsive atrial pacing.(263) Despite this, rate-adaptive pacing remains the standard of care for most CHF patients with pacemakers, creating a paradox that medical therapy to reduce mean heart rate is aggressively applied and proven, yet those with a pacemaker are programmed to rate-adaptive pacing and thus may be subjected to higher mean heart rates.

2.7 Discussion

CO is dependent on HR, contractility of the cardiac myocytes and end diastolic left ventricular volume. These three factors are interdependent, and continuously increasing the heart rate will affect the stroke volume by reducing the filling time and hence the end diastolic volume. There is a reduction in cardiac function and cardiac contractility in CHF. The purpose of the initial adaptive changes is to match CO to venous return. While these mechanisms can restore near normal CO at rest, a loss of contractile and heart rate reserve results.

Limitations to either heart rate rise or cardiac contractility, or a combination of both might contribute to lower CO during exercise. This is associated with a significant limitation in exercise tolerance and quality of life, as the CO fails to increase sufficiently to meet the increased demands during exercise. Because contractility is impaired, increasing the heart rate in an attempt to improve the CO becomes an energy intensive response, which may result in increased ischaemic insult due to the reduced diastolic time, and impaired ventricular filling.

These processes cause the CO to decrease over time, as the compensatory mechanisms are overwhelmed. Initially CO fails to increases appropriately on exertion, resulting in lower peak V_{O_2}, exercise intolerance and fatigue, but later in the course of the disease CO becomes limiting even at rest.

2.8 Clinical implications

In health, HR directly influences cardiac output and is thus an important aspect of the biological response to increasing levels of activity and exercise.(63) HR is also a determinant of total body and myocardial oxygen consumption, and increased heart rates at rest lead to higher myocardial oxygen consumption at rest, with the potential to cause ischaemia.(264)

The role of the heart rate rise achieved during exercise in the context of heart failure is less clearly understood. Myocardial tissue in chronic heart failure may exhibit a negative force-frequency association with inefficient energy expenditure to maintain or increase cardiac output during exercise. (35)(218)(265) In such a situation, achieving a higher heart rate during activity could lead to higher than expected myocardial oxygen consumption and thus limit exercise tolerance.

In systolic dysfunction, there is a reduction in cardiac output, so the therapies used for treatment aim to alter the preload and afterload, in order to maintain or improve the stroke volume. These therapies also have a role in reversing the abnormal cardiac remodelling, and hence improving the function and contractility of the heart over time.

The traditional view is that chronic changes in the myocardial electrical conduction pathways, adrenergic sensitivity and the sino-atrial node may be the reason for the reduced heart rate rise seen in chronic heart failure, in which case CI could be a potential therapeutic target to improve exercise capacity.

However, in a dilated heart, more ventricular filling time is necessary in order to allow sufficient wall tension to develop to achieve a given pressure, so necessitating a lower heart rate to produce the same cardiac output in the presence of heart failure, in accordance with the law of LaPlace ($\Delta P = 2\lambda h/r$; P: Internal pressure, λ: Wall tension, h: Wall thickness, r: Radius).(266)

In the presence of a higher EDV, cardiac contractility and the resulting stroke volume may be increased if the heart rate is lowered and the ventricular filling time is maximised. The greater radius of the dilated left ventricle in heart failure requires greater sarcomere shortening, and thus more ATP hydrolysis, in order to generate the same cardiac ejection pressure in order to maintain cardiac output. The lower heart rate would also favour these cardiac cellular energy kinetics, allowing greater delivery of oxygen and nutrients to the myocytes.(267)

Thus, patients with heart failure who demonstrate CI may be able to maintain near normal cardiac output and peak V_{O_2} during exercise with greater energetic efficiency via increases in the stroke volume in accordance

with the Frank-Starling principle.(268) So CI may be an adaptive response to limit myocardial damage.

Meta-analysis of trials involving beta-blockers in chronic heart failure has demonstrated that the reduction in baseline heart rate is of great prognostic significance irrespective of the beta-blocker type or dose.(269) The prognostic benefit of heart rate lowering is borne out by the results of trials involving other heart rate lowering agents, such as the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study and SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial). In these studies the sinus node inhibitor ivabradine was used to reduce the resting heart rate of patients in sinus rhythm with severe chronic heart failure, resulting in prognostic and symptomatic improvement.(258)

However, there is conflicting evidence as to whether CI contributes to, or is the result of, the reduced exercise capacity that is pathognomonic of worsening heart failure. Chronic multi-system abnormalities in the respiratory, skeletal and cardiovascular systems as a direct result of CHF, may all be contributing to the limited exercise capacity, such that simply increasing the heart rate rise and achieving ‘chronotropic competence’ may not result in any improvement in exercise capacity (Figure 2.2).(270)

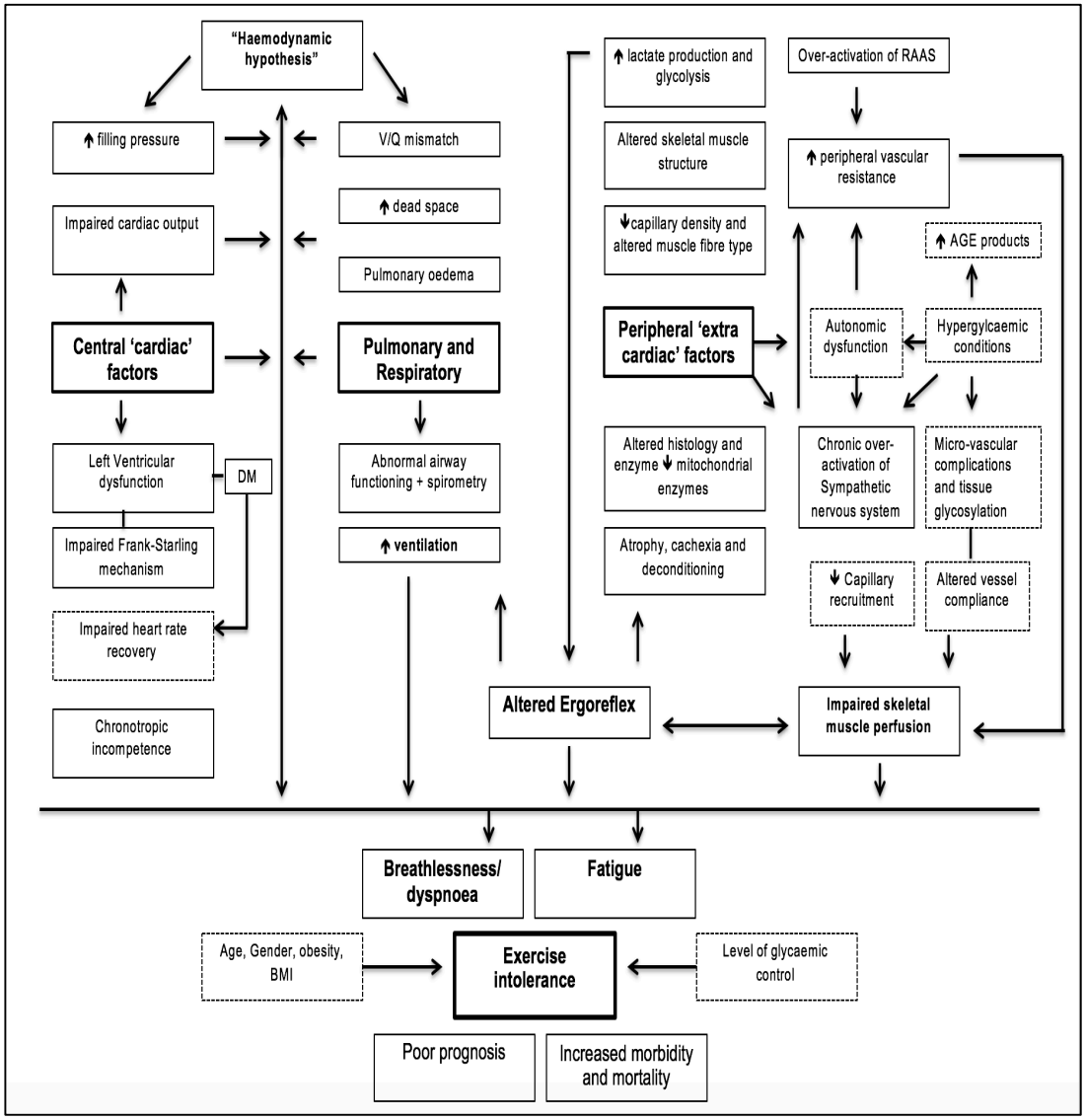


Figure 2.2 Various physiological mechanisms that may contribute to limited exercise capacity and fatigue in systolic heart failure

2.9 Conclusion

The aim of this thesis is to explore and unravel the connection between heart rate and the reduced functional capacity that is pathognomonic for heart failure. It is unclear whether the lower heart rate response to exercise that manifests as the heart failure syndrome progressively worsens, is a cardio-protective mechanism or whether exercise capacity in heart failure could be improved by increasing the heart rate response during activity.

The close relationship between the heart rate and any measure of exercise capacity makes determining the causality difficult, and requires placebo controlled double blind studies during which the heart rate response is either corrected or worsened during exercise to determine whether CI is adaptive or maladaptive, and is either a cause or consequence of exercise intolerance in heart failure.

Chapter 3: Methodology

The pathophysiological changes in CHF that lead to a reduction in exercise performance relate to a complex interplay between peripheral and central defects in the oxygen transport chain during exertion. Complete functional assessment requires some form of standardised exercise testing to objectively measure the degree and nature of the symptoms, in addition to appropriate cardiac imaging to assess structural changes and confirm aetiology.

3.1 Measuring exercise capacity

There are several different ways to measure exercise capacity, which can range from history taking to laboratory testing. While history taking and patient interview using activities of daily living questionnaires, NYHA status or six-minute walk tests, can give a valuable insight in to the extent and impact of any exercise limitation, they cannot accurately be used as a comparative marker between small populations of people, time-points or treatments.(271)

Exertional performance is crucially reliant on the ability of the cardiovascular system to transport oxygen to and remove carbon dioxide from respiring skeletal muscles, thus increasing the level of oxygen uptake. The upper limit

of the cardiovascular system and an overall estimate of the exercise capacity can be defined by measuring peak symptom-limited oxygen consumption (pVO_2) during an incremental cardio-pulmonary exercise test.

3.1.1 Cardio-pulmonary exercise testing

3.1.1.1 Introduction

Cardio-pulmonary exercise testing (CPX) is the gold-standard for simultaneously measuring the cardiovascular and respiratory physiological responses involved in providing the skeletal muscles with an adequate oxygen supply to maintain and allow any increases in the intensity of the exercise stimulus. CPX testing also plays a vital role in prognostic and functional assessment, and understanding the causes for exercise intolerance, dyspnoea and fatigue.(272)

Exertional fatigue can be objectively assessed as a reduction in pVO_2 and an increase in the ventilatory response to exercise (V_E/VCO_2 slope) during incremental exercise testing with metabolic gas exchange analysis.(273) Once a familiarisation test has been performed, a peak exercise test is not a training stimulus, and produces reliable, reproducible results.(238)

3.1.1.2 Test overview

During a CPX test, subjects breathe room-air via a face mask or mouth piece and nose clips, and all gaseous exchange is measured breath-by-breath by real time high speed O_2 and CO_2 analysers, which adjust for environmental factors such as the ambient room temperature and humidity, while performing an incremental exercise test. Various exercise modalities are available such as treadmill, cycle ergometer, supine bicycle or arm ergometer, using a variety of different exercise protocols such as continuous ramp, multi-stage or constant workload. Sensors can also measure the minute ventilation (V_E), which incorporates both the breathing rate (respiratory rate, RR) and the tidal volume (Vt).

During higher levels of exercise, O_2 and CO_2 uptake and production at the mouth represent utilisation and production at the skeletal muscle level. Hence calculations derived from measuring the difference between inhaled and exhaled O_2 and CO_2 concentrations and ventilation parameters, provide an accurate assessment of cellular metabolic homeostasis. In this way, CPX can be used to identify which part of the cardiovascular-respiratory-skeletal triangle in responsible for causing the restriction in exercise capacity.

3.1.1.3 Peak V_{O_2}

Peak V_{O_2} (normalised for body weight; mL/kg/min) is a well-established measure of aerobic capacity.(274) Oxygen uptake V_{O_2} readings show a

linear relationship to work load.(275) This can be increased with physical training and is decreased in cardiovascular, pulmonary or neuromuscular system dysfunction.(276)

Maximal exercise capacity can be reliably expressed by measuring the peak oxygen consumption in an incremental exercise regime, referred to as the peak V_{O_2}.(277) It is based on the Fick equation (Peak V_{O_2} = Cardiac Output X arteriovenous O_2 concentration difference at the respiring skeletal muscles during sustained maximal effort). Cardiac output response to exercise is dependent on increases in both heart rate and stroke volume.(278)

Thus V_{O_2} is calculated as the product of V_E and the oxygen fraction that can be utilised by the actively respiring skeletal muscles during sub-maximal (anaerobic threshold; AT) or maximal exercise (peak V_{O_2}).(279) Oxygen delivery to the respiring skeletal muscles during exercise is dependent on the cardiovascular system, and measuring the peak V_{O_2} provides an accurate and reproducible measure of cardiovascular performance.

Attaining maximal oxygen uptake is also evidenced by a plateauing of V_{O_2} measurements despite increasing the workload at the maximum level of perceived exertion. The rate at which steady state is reached is represented by the exponential time constant of V_{O_2} rise, known as the mean response time (MRT).(280)

The normal value for an individual's maximum V_{O_2} will depend upon the age, sex, body size and normal level of physical ability. Conditions that reduce cardiac function and exertional response, or are associated with a reduction in pulmonary gas exchange, will lead to a reduction in V_{O_2} measurements.(271)

3.1.1.4 Respiratory exchange ratio

Whether a measured V_{O_2} is truly reflective of a high degree of exertional effort can be determined by calculating the respiratory exchange ratio (ratio of V_{CO_2} to V_{O_2}; RER). As the aerobic metabolic capacity of the respiring muscles is exceeded, there is an increase in lactate production that results in an increase in exhaled V_{CO_2}, so an RER greater than 1.1 is taken to reflect peak workload and effort, and can thus identify those subjects who terminate the exercise test prior to achieving peak workload due to other factors such as poor motivation.(281)

3.1.1.5 V_E/V_{CO_2} slope

Skeletal oxygen consumption results in a concomitant increase in CO_2 release, the homeostasis of which is dependent on respiratory system efficiency during exertion. Ventilation (V_E) is normally closely matched to CO_2 production (V_{CO_2}) but in heart failure, there is a hyperventilation

response to carbon dioxide production that is seen as a steeper V_E/V_{CO_2} slope.

Although a steeper V_E/V_{CO_2} slope is a strong marker of adverse prognosis, (282)(283) the pathophysiological stimulus is incompletely understood. It is likely that the increased V_E/V_{CO_2} slope is a consequence of complex feedback mechanisms that link skeletal muscle activity or metabolism to ventilatory centres.(284)(285)

3.1.1.6 End tidal carbon dioxide

The partial pressure of end tidal CO_2 (Pet_{CO_2}, mmHg) is also measured by the CPX equipment. Low Pet_{CO_2} measurements at rest and at peak exercise reflect a mismatch in lung ventilation and perfusion, and can be used as an additional marker of prognosis and disease severity.(286)(287)

3.1.1.7 Sub-maximal exercise

CPX testing can also provide information at sub-maximal effort levels, which is a better indicator for the level of exertional intensity during a person's usual activities of daily living (ADL). Minute ventilation increases linearly at the onset of exercise, however an abrupt transition occurs at the point where aerobic metabolism reaches the maximum sustainable level and skeletal mitochondria have to increasingly rely on increases in the anaerobic metabolism in order to continue cellular respiration and ATP production.

The increase in anaerobic glycolysis leads to a rapid increase in blood lactate levels, which results in excess CO_2 production via bicarbonate in order to buffer the sudden excess in H+ ions. At this point, there is an abrupt non-linear rise in the V_E measurements and a sudden increase in the ratio of measured V_{CO_2} to V_{O_2}. This point is known as the ventilatory or anaerobic threshold (VT or AT; mL/kg/min).(288)

AT is a recognised measure for sub-maximal exercise capacity and can be used to assess the functional benefits gained from a given therapy in terms of increasing the person's ability to perform ADLs.(289) AT also tends to occur earlier relative to the peak V_{O_2} in CHF (<30%) and is usually normal in pulmonary disease (40-60% of peak V_{O_2}).(290)

3.1.1.8 Oxygen pulse

The 'oxygen pulse' (O_2 pulse; mL/beat) can also be calculated using CPX testing, by dividing the peak V_{O_2} by the peak HR (or similarly for submaximal exercise using the AT and the HR reached at the point of AT). This provides an index of stroke volume with oxygen extraction, and is reduced in conditions associated with cardiac output reduction.(291)(292)

3.1.1.9 Oxygen uptake efficiency slope

Analysis of the rate of increase of the V_{O_2} in relation to the VE can be used to determine the effectiveness of O_2 extraction and utilisation. This measure is known as the oxygen uptake efficiency slope (OUES). It is considered to

be independent of the level of effort achieved, and improves with physical training.(293)(294)

Although the relation between ventilation and oxygen uptake is not linear, the OUES is derived by plotting V_{O_2} as a function of $\log_{10}V_E$, which is an approximately linear relationship.(294) This represents the effectiveness of oxygen extraction, demonstrated by the rate of V_{O_2} increase during incremental exercise in response to a given V_E. The steeper the slope, the more oxygen is taken up for a given unit of ventilation.(295)

OUES is reduced in CHF in proportion to disease severity, and is lower in those with AF compared to normal sinus rhythm.(296)(297) It can be increased with physical training and improvements in exercise tolerance.(298) One advantage of the OUES as a measure is that it can be measured from submaximal data and does not depend upon effort levels or reaching peak exertion. The OUES is predictive of prognosis even from submaximal tests.(296)(299)

3.1.1.10 Critical power

The term ‘critical power’ refers to the highest sustainable power where both the V_{O_2} and lactate are at a steady state.(300) Several studies have shown this to occur at around 70% peak power in young healthy individuals,(300)(301) with higher values in the context of aerobic training.(302) Critical power is a marker of the sustainable upper limit of

aerobic intensity levels, however it requires at least four constant-power exercise tests of varying intensities above the level of the AT for accurate determination.(300) A close correlation has been demonstrated between the critical power and the power at respiratory compensation point, which is obtainable from a single metabolic exercise test.(303) No conclusive data are currently available on changes in critical power in the context of CHF, and as such this measurement considered to be outside the scope of this investigation.(304)(305)(306)

3.1.1.11 Exercise protocols

Various incremental exercise protocols are available for both stationary cycle and treadmill exercise. The aim is to provide a gradual workload increase to allow adequate metabolic gas kinetic response, while keeping exercise time between six and twelve minutes, to maximise the accuracy of pVO_2 measurements.(307)

3.1.1.11.1 Stationary cycle

Stationary cycle is utilised in such circumstances where better haemodynamic monitoring is required, with gradual and constant workload increments until exhaustion is reached. A ramp protocol is most commonly used, whereby the resistance (watts) continuously increases, aiming for ten minutes of exercise time.

3.1.1.11.2 Treadmill

Treadmill based protocols provide a better reflection of peak exertional capability, and lead to a higher peak VO_2. The Bruce protocol modified by the addition of a 'stage 0' at onset, consisting of 3 minutes of exercise at 1.61km/hr (1mile/hour) with a 5% gradient, is often used in the CHF setting (figure 3.1).(308) Other protocols exist with smaller speed and incline increments, such as the Balke protocol or the Naughton protocol, however these can lead to excessive exercise times.(309)(310) Faster protocols do not allow steady state gas exchange to occur.(311)

Stage	Speed (mph)	Grade (%)	Duration (min)
0	1.7	0	3
0.5	1.7	5	3
1	1.7	10	3
2	2.5	12	3
3	3.4	14	3
4	4.2	16	3
5	5.0	18	3
6	5.5	20	3
7	6.0	22	3

Figure 3.1 Modified Bruce protocol

3.2 Measuring force-frequency relationship

3.2.1 Literature review

Cardiac contractility refers to the intrinsic capacity of cardiac myocytes to generate contractile force at a specific heart rate, independent of the preload and afterload. Thus assessment of this force-frequency relationship (FFR) in vivo should ideally take place independently of loading. This requires end-systolic pressure (ESP) and end systolic LV volume (LVESV) measurements, which can be done either invasively or non-invasively. These are divided by each other (ESP/LVESV) to give an end-systolic pressure volume ratio (ESPVR), which has been shown to be a reliable representative measure of the FFR.(30)(312)(313)

FFR is usually measured invasively, however this is generally complex, technically demanding, time consuming and exposes the patient to increased risk. Invasive methods include the use of exercise cineangiography, which requires a significant volume of nephrotoxic contrast agents and high radiation doses, using a high fidelity left ventricular catheter to measure pressure-volume loops, which is costly, or nuclear scintigraphy, which results in prolonged exposure to ionising radiation with limited temporal resolution.(314)(315)(316)

FFR can also be measured noninvasively using echocardiography. This has been shown to be accurate, reproducible and safe.(313)(317) Contractility can be estimated either from 2-dimensional images or by the new technique

of tissue Doppler imaging. There are two main issues: accurately measuring subtle changes in contractility, and increasing the heart rate in predefined stages. Using 2D images, the ratio of systolic pressure and end-systolic volume can be obtained. The systolic pressure divided by the end-systolic volume index (LVESVi = biplane ESV/BSA) gives a surrogate of contractility (SP/LVESVi) that has been tested and validated against invasive methods.(288)(313)(318)

3.2.2 Limitations

A limitation of this method is using the systolic cuff pressure as a surrogate for end-systolic pressure in calculating the end-systolic pressure–volume relationship. This does introduce an approximation, however, there is a tight relationship between peak and end-systolic pressure (314)(316)(319) so any error will be systematically distributed along the whole FFR, provided the heart rate rise is not pharmacologically mediated. Thus this would not affect the comparative analysis between CHF and controls, and also within each cohort.

3.3 Thesis interventional study protocols

3.3.1 Baseline visit

Height and weight were measured at the start of each visit to allow oxygen consumption measures to be adjusted for body-weight and calculation of the body mass index (BMI, body weight (kg) divided by height squared (metres)). Information regarding co-morbidities, past medical history, medication types and dosages, pacemaker settings, NYHA symptom class and activities of daily living were collected during the baseline consent appointment, and stored in a secure anonymised electronic database.

At baseline, each participant was consented for the study, underwent a full echocardiographic assessment, and performed a peak, symptom-limited treadmill-based familiarisation cardiopulmonary exercise test with breath-by-breath metabolic gas analysis. Once a familiarisation test has been performed, a peak exercise test is not a training stimulus. The results from these familiarisation tests were not included in the final analysis.

The echocardiogram images were stored on a commercially available database, (Echopac PC, Vingmed, Norway) and analysed offline to assess LV systolic and diastolic function variables, mitral regurgitation and pulmonary artery pressure.

3.3.2 Blinding protocol

All interventional studies had a double-blind design and both the supervising physician and the patient were blinded to the pacemaker settings and to the heart rates throughout the visit. An un-blinded technician, who also monitored the electrocardiogram throughout the study, performed the pacemaker programming.

The metabolic cart was separated from the electrocardiogram and heart rate monitors by a screen, and observed by the blinded physician. The blinded physician also measured the resting, peak and recovery blood pressures using a standard manual cuff sphygmomanometer.

3.3.3 Research exercise testing protocol

After randomisation and prior to starting the test, a rest period of six minutes was implemented to ensure that steady-state conditions were achieved. Both the blinded physician and the unblinded technician constantly monitored the test data. A continuous 12 lead ECG was displayed on the screens in real-time through the rest, test and recovery phases. Standard 12 lead ECGs were also printed out at baseline, end of each stage, at peak exercise and during recovery, and stored for analysis.

All participants performed a symptom limited maximal CPX test on a motorised treadmill using the Bruce protocol, modified by the addition of a 'stage 0' at onset consisting of 3 minutes of exercise at 1.61km/hr (1mile/hour) with a 5% gradient (figure 3.1). During each test, expired air was collected continuously and metabolic gas exchange analysis performed breath-by-breath with the MedGraphics Ultima CardioO_2 equipment (Medical Graphics UK Limited, Gloucester, UK).

The equipment was re-calibrated using manufacturer recommended volume and gas calibration techniques before every exercise test, and each patient was familiarised with the equipment prior to starting the protocol. The height and weight for each patient are measured at the start of the visit and entered into the analyser software so that the breath-by-breath V_{O_2} values were calculated in mL/min/kg.

All test subjects were encouraged to exercise to exhaustion prior to starting the protocol, and no motivation or instructions were given during the exercise test. Procedures were in place to ensure that the test would be stopped if the subject developed chest pain or ECG abnormalities.

At the end of each stage and at peak exercise, subjects were asked to indicate their score for dyspnoea or fatigue on a chart that showed a scale from 0 (no symptoms) to 10 (maximal symptoms) using the standardised Borg scoring system.(320) All subjects were rested for six minutes following the test, and recovery CPX and ECG data were monitored.

All tests were carried out in the same exercise laboratory by trained cardiac physiologists who were unaware of the echocardiographic data. The following week the other mode was activated. At the end of each test the pacemaker was re-programmed back to the original settings by the un-blinded technician. All CPX and ECG data were recorded and stored in a secure server for post hoc analyses.

3.3.4 CPX data analysis

Heart rate (HR, bpm), oxygen consumption (V_{O_2}, ml/kg/min) and carbon dioxide release (V_{CO_2}, ml/kg.min) were recorded as 15-second averages taken at the start of each stage and at peak. A respiratory exchange ratio ($V_{CO_2}/V_{O_2;}$ RER) of greater than 1.1 was taken to indicate maximal effort.

Peak oxygen consumption was defined as the maximal fifteen-second average of V_{O_2} achieved during the last 60 seconds of exercise. The AT was manually determined using the V_{O_2}/V_{CO_2} slope method. Ventilatory variables such as tidal volume (V_T), frequency (*f*) of ventilation, OUES, O_2 pulse, mean response time (MRT), mean response time recovery (MRT recovery) and V_E/V_{CO_2} slope (at peak and AT) were determined using average values from 15-second intervals. The V_E/V_{CO_2} slope was measured from start to peak (V_E/V_{CO_2} peak) and from start to AT (V_E/V_{CO_2} AT).

3.3.5 Echocardiography protocol

All echocardiographic assessments were carried out by a highly specialised certified echocardiographer, who collected datasets in line with the European Society of Cardiology (ESC) Echocardiography guidelines.(321) All participants underwent a full 2-dimensional transthoracic echocardiographic study with with grey-scale and tissue Doppler images recorded in the two and four chamber views using harmonics to improve border definition if necessary.

Images were obtained using a Philips ultrasound machine (3.5 MHz transducer; Model 7500, Philips Medical Systems, Andover, Massachusetts, USA) and stored offline to allow post-hoc analysis and measurements. Left ventricular systolic function assessment was done both visually and using the modified Simpson's bi-plane method, whereby the 2 dimensional end systolic and end diastolic left ventricular areas were measured in orthogonal planes using the apical 4-chamber and 2-chamber views. The echocardiographer was blinded to the study arm and protocol. All echocardiographic data was analysed by two independent echo-sonographers, independently of the exercise data analysis.

3.3.6 FFR measurement protocol

Following the baseline echocardiogram, further images were recorded at each 10 beat frequency increase during the interventional FFR protocol for

study 3 (OPT-Rate 3 – Chapter 7). All echocardiogram images were stored on a commercially available database, (Echopac PC, Vingmed, Norway) and analysed offline to assess LV systolic and diastolic function variables, contractility, cardiac output, mitral regurgitation and pulmonary artery pressure.

This analysis included a calculation of LV end diastolic and end systolic volumes using the biplane discs (modified Simpson's) method by tracing the endocardial border excluding the papillary muscles. An average of three measurements was used in the final analysis. The frame at the R-wave was taken as end diastole, and the frame with the smallest LV cavity, as end systole. This was carried out by two independent fully qualified senior echo-sonographers, and an average was taken for each measurement or calculation.

3.3.7 Statistical analysis protocol

All statistical analyses were performed using the IBM SPSS Statistics program, version 22, for Windows. The Shapiro-Wilk test was used to determine whether the subject demographics, CPX and echocardiogram parameters were normally distributed (parametric).

Continuous variables within and between groups were reported as either the mean and standard deviation (SD) if normally distributed, or as the median and interquartile range (IQR) if non-normally distributed (non-parametric).

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 ANOVA on ranks) for non-parametric data, adjusting baseline values where appropriate.

The Levene statistic was used as a test of homogeneity of variances, and the Welch and Brown-Forsythe statistical tests for ‘equality of means’ to confirm the results obtained from the one way ANOVA test if variances differed.

Where the ANOVA test was significant, post hoc analysis was performed using either the Gabriel test, if variances were homogeneous, or the Games-Howell test, if variances were not homogenous.

Categorical variables were analysed using the Chi-squared test. The relationship between heart rate changes and CPX parameters was assessed by calculating the paired correlation coefficients and using linear regression techniques.

Any p-value less than 0.05 was considered to be statistically significant. All numerical and graphical data was also visually analysed prior to statistical testing to ensure validity.

Chapter 4: Retrospective CPX data analysis study

4.1 Abstract

Chronic heart failure (CHF) is associated with both impaired exercise capacity, measured as lower peak oxygen consumption (pVO_2), and a reduction in heart rate rise during exertion, known as chronotropic incompetence (CI).

The aim of this study was to assess whether there is a relationship between the severity of resting left ventricular systolic dysfunction (LVSD) assessed on echocardiography ejection fraction (EF) and exercise capacity assessed on cardiopulmonary exercise (CPX) testing, and whether this relationship is influenced by the heart rate response during exercise.

A retrospective analysis of clinical, echocardiographic and CPX data from 147 CHF patients and 48 hospital based control subjects was performed. The CHF cohort was split in to two groups based on LVSD severity on echocardiography.

Hospital based controls delivered the best exercise performance, and this group also exhibited the best heart rate rise during exercise. Both CHF

groups showed a similar blunting in the heart rate response. However, whilst the control group had a strong correlation between peak VO_2 and heart rate rise, this correlation was much weaker in the mild/moderate LVSD group and non-existent in the severe LVSD group. The total CHF cohort was then re-stratified by the presence and the degree of CI present. Those with CI had lower pVO_2, despite similar EF, co-morbidities and medications.

Thus, this study demonstrates the principle underlying the thesis. There is a definite association between HRR and exercise capacity in LVSD, but it is unknown whether the reduced HRR in CHF is an adaptive or maladaptive physiological response.

4.2 Introduction

Heart failure is associated with a sustained reduction in cardiac output and limited ability for the cardiac output to increase appropriately during exercise.(322)(323) Cardiac output is a composite of the stroke volume and heart rate. In health both increase during activity in order to match the supply of oxygenated blood to the demands of respiring metabolically active skeletal muscles.(324)

A limited adaptation to the demands of physical exercise is characteristic of CHF and reduced stroke volume is typical.(325) However it is unclear what role heart rate plays in determining exercise capacity in CHF. The aim of this study was to determine whether there is a reduction in heart rate rise in the context of heart failure, and if there is any relationship between an impaired heart rate response and the degree of exercise intolerance in patients with CHF.

4.3 Methods

All out-patients attending the Leeds General Infirmary Cardiology Investigations Unit for a cardiopulmonary exercise test as part of their clinical assessment, between August 2011 and August 2012, were included in this retrospective cohort analysis. The population was a convenience cohort of consecutive patients referred for assessment of their heart failure syndrome. Control subjects were people without heart failure referred for pre-operative assessment.

All subjects also underwent a transthoracic echocardiogram (TTE) with acquisition of the full minimum dataset in accordance with the ESC, and a 12 lead ECG as part of their outpatient assessment. All subjects were instructed to omit heart rate limiting medications for 24 hours prior to, and on the day of, the CPX test, as part of routine practice with CPX testing in this Cardiology Investigations Unit. All the raw data from these tests were analysed retrospectively.

Patients with primary valvular disease were excluded from the heart failure cohort, and subjects in the non-heart failure group were excluded if echocardiography revealed structural cardiac disease including left ventricular dysfunction or if they had musculoskeletal conditions limiting exercise capacity.

All patients underwent a cardiopulmonary exercise test as described in chapter 3 according to the standard protocol. Data were stored for offline analysis. Subsequent statistical analysis was undertaken as described in chapter 3 using SPSS for windows.

4.4 Results

During the 12 month period from August 2011 to August 2012, 214 patients underwent outpatient clinical assessment, 12 lead ECG, CPX testing and echocardiography. Of these, 19 were found to have primary valvular disease with severe dysfunction, and were thus excluded. No patients were limited by extertional symptoms relating to cardiac ischaemia, evidenced by the presence of chest pain or ischaemic ECG changes during the exercise test.

4.4.1 Groups

The remaining 195 subjects formed the study cohort and were sub-divided into three groups based on their resting echocardiographic left ventricular ejection fraction (LVEF) and clinical diagnosis. The echocardiographic data showed that the left ventricular internal dimensions at both systole (LVIDs) and diastole (LVIDd) were significantly increased with worse LVEF (figure 4.1 and table 4.1).

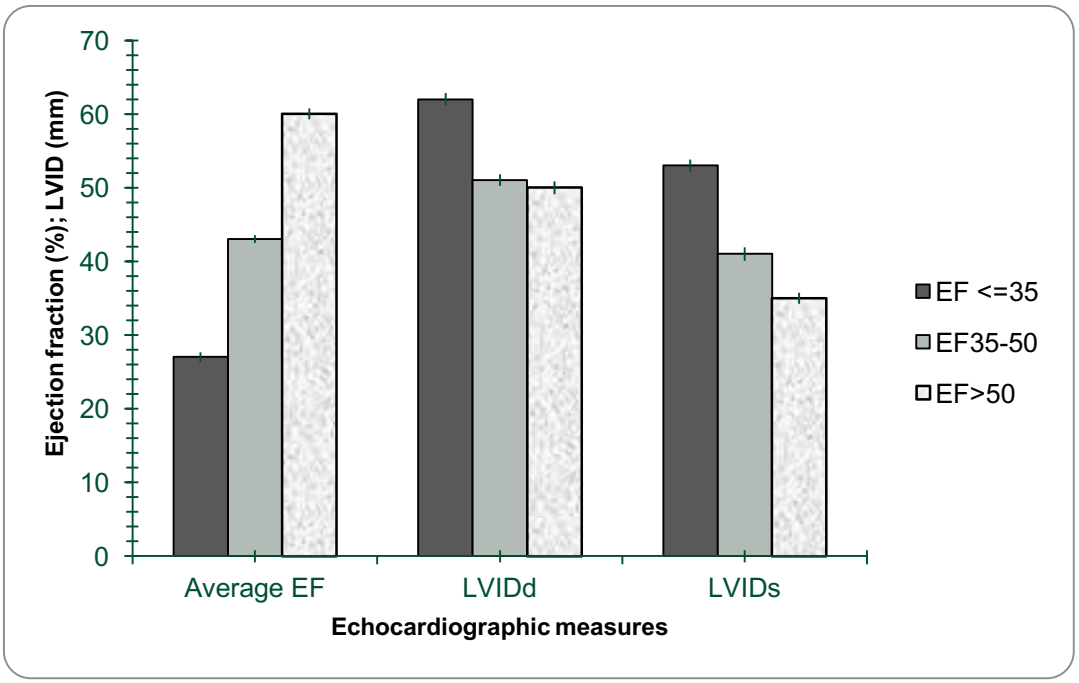


Figure 4.1 Cardiac function and measurements

Parameters (mean (SD))	**Control**	**Mild-Mod LVSD**	**Severe LVSD**
Ejection Fraction (%)	60 (5)	43 (5)	27 (6)
Left ventricular end diastolic diameter (mm)	50 (6)	51 (6)	62 (8)
Left ventricular end systolic diameter (mm)	35 (5)	41 (7)	53 (8)

Table 4.1 Echocardiographic parameters

The hospital based control group of convenience consisted of 48 patients with a normal resting echocardiogram (no echocardiographic evidence of systolic or diastolic dysfunction, as defined by the BSE criteria; EF>55%), who primarily had CPX tests and echocardiograms as part of their non-cardiac pre-operative assessment. The remainder were divided into two

groups based on resting EF: mild-moderate LVSD (n=57, EF between 35 and 55 %) and severe LVSD (n=90, EF less than 35%).

4.4.2 Demographics

The characteristics of the three groups are shown in Table 4.2. The Levene statistical test revealed that the variances in ejection fraction, height, QRS duration, VO_2 peak and beta-blocker dose were not homogenous ($p<0.05$).

There were differences in the groups with regards to age ($F=0.819$; $p<0.05$), and QRS duration ($F=23.279$; $p<0.05$). The control group were younger (63 ± 13 years; $p<0.05$), had shorter QRS duration (median 90 ± 0 ms; $p<0.05$) and were not taking any heart failure medication (beta-blocker or ACEi). Doses of these agents were not different between the two groups with LVSD.

The 1 year all-cause mortality was higher in the presence of heart failure (severe LVSD 14%, mild-moderate LVSD 12%, controls 2%), although the numbers were too small to be significant (n=21; $\chi^2 = 5.169$, $p = 0.075$).

4.4.3 Aetiological factors

Table 4.3 shows the aetiologies of the 147 heart failure subjects. The ‘other causes’ included chemotherapy related cardiomyopathy, postpartum cardiomyopathy, alcoholic cardiomyopathy, right ventricular pacing

cardiomyopathy and idiopathic cardiomyopathy. Cardiomyopathy due to IHD was found to be the most frequent cause (48% in the ‘Severe LVSD’ group and 56% in the ‘Mild-moderate LVSD’ group).

A comparison was made of the frequency of risk factors. Ischaemic heart disease was present in 47%, diabetes mellitus in 15%, atrial fibrillation in 23%, left bundle branch block in 37% and the presence of a pacemaker in 42%. The two groups with LVSD had a higher incidence of coronary artery disease, diabetes mellitus and abnormal ECG changes such as atrial fibrillation and a left bundle branch block. The ECG abnormalities were also increased in the severe LVSD group compared to the mild/moderate LVSD group, as was the likelihood of having a pacemaker device in-situ (table 4.3).

Demographics (mean (SD)/median (IQR)*)	**Control (EF >50) n=48**	**Mild-Mod LVSD (EF 35-50) n=57**	**Severe LVSD (EF <=35) n=90**	**F statistic/ Chi-squared**	**Significance**	**Control vs LVSD (any) P value**	**Mild-Mod vs Severe LVSD P value**
Ejection Fraction, %	60 (5)	43 (5)	27 (6)	555.993	0.000	<0.05	<0.05
Height (cm)	171 (12)	168 (10)	171 (8)	2.478	0.087	0.453	0.116
Weight (kg)	83 (21)	81 (18)	87(18)	1.537	0.218	0.676	0.641
BMI (median (IQR))	28 (25-29)	29 (26-31)	30 (26-31)		0.311		
BSA	1.99 (0.3)	1.94 (0.2)	2.03 (0.2)				
Age (median (IQR), years)	68 (55-74)	74 (66-78)	72 (63-80)	4.819	0.009	<0.05	0.688
Male (tally)	34 (71%)	43 (75%)	72 (80%)		0.472		
Peak predicted heart rate	156 (14)	150 (12)	150 (12)	4.819	0.009	<0.05	0.967
Heart Rate Rise	67 (28)	46 (23)	48 (26)	11.518	0.000	<0.05	0.948
Resting Heart Rate	78 (17)	76 (15)	77 (18)	0.289	0.750	0.850	0.909
Peak Heart Rate*	157 (39)	121 (26)	130 (53)	18.486	0.000	<0.05	0.840
QRS duration (ms)	90 (81-94)	101 (83-129)	113 (86-137)	23.279	0.000	<0.05	0.06
BB (bisoprolol equivalent, mg)*	0 (2.5)	5 (7.5)	5 (7.5)	28.104	0.000	<0.05	0.868
ACEi/ARB (ramipril equivalent, mg)*	0 (3)	10 (8)	10 (7)	25.315	0.000	<0.05	0.978
pVo_2 (ml/kg/min)*	23.2 (8)	16.5 (6)	15.9 (6)	26.000	0.000	<0.05	0.481
Chronotropic Index	0.9 (0.4)	0.7 (0.5)	0.7 (0.5)	3.891	0.022	<0.05	0.860
Exercise Time	595 (268)	427 (212)	399 (216)	11.882	0.000	<0.05	0.840
Anaerobic Threshold	16 (7)	13 (4)	12 (3)	8.716	0.000	<0.05	0.957
RER	1.13 (0.1)	1.08 (0.1)	1.07 (0.1)	3.428	0.035	<0.05	<0.05
V_E/Vco_2 slope (AT)	27 (6)	32 (6)	30 (7)	5.687	0.004	<0.05	0.394
V_E/Vco_2 slope (Peak)	30 (6)	36 (9)	37 (12)	7.057	0.001	<0.05	0.993
LVIDd	50 (6)	51 (6)	62 (8)	46.293	0.000	<0.05	<0.05
LVIDs	35 (5)	41 (7)	53 (8)	45.165	0.000	<0.05	<0.05
Resting SBP	135 (19)	130 (24)	122 (21)	6.391	0.002	0.514	<0.05
Resting DBP	90 (99)	71 (11)	70 (12)	2.623	0.075	0.082	0.998
Peak SBP	169 (28)	151 (28)	137 (24)	23.414	0.000	<0.05	<0.05
Peak DBP	78 (12)	72 (11)	73 (12)	4.867	0.009	<0.05	0.996

Non-parametric variables reported as median (interquartile range). Normally distributed variables as mean (SD).

KEY: NYHA: New York Heart Association functional classification, HR: heart rate, LVIDd: left ventricular internal diameter in diastole, LVIDs: left ventricular internal diameter in systole, DT: deceleration time, PMH: past medical history, IHD: ischaemic heart disease, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker.

Table 4.2 Group demographics

	Control		Mild-Mod LVSD		Severe LVSD	
	Tally	***%***	**Tally**	***%***	**Tally**	***%***
IHD	7	***15***	37	***65***	47	***52***
DCM	2	***4***	12	***21***	39	***43***
Diabetes mellitus	4	***8***	11	***19***	15	***17***
Any pacing device	5	***10***	22	***39***	55	***61***
Bi-ventricular CRT	0	***0***	16	***28***	52	***58***
Atrial fibrillation	5	***10***	13	***23***	27	***30***
LBBB (QRS >120ms)	2	***4***	21	***37***	50	***56***
KEY: IHD: ischaemic heart disease, DCM: dilated cardiomyopathy, CRT: cardiac resynchronisation therapy, LBBB: left bundle branch block						

Table 4.3 Group co-morbidities

4.4.4 Differences in exercise test findings and HR

Peak V_{O_2} and peak heart rate followed a non-parametric distribution (Shapiro-Wilk test, $p<0.05$). These are therefore reported as median and interquartile range. The median peak heart rate was 127 ± 38 beats/min, and the mean heart rate rise achieved was 52 ± 27 beats/min. The median pV_{O_2} was 17.1 ± 9.2 ml/kg/min.

Peak V_{O_2} differed between controls (23.2 ± 18 ml/kg/min; $p<0.05$) and the LVSD groups (Mild-mod LVSD 16.5 ± 6 ml/kg/min; Severe LVSD 15.9 ± 6 ml/kg/min, $p=0.481$).

The Kruskal-Wallis H test on pV_{O_2} showed $\chi^2(2) = 26$, $p = 0.000$, with a mean rank of 133.25 for ‘controls’, 92.78 for ‘mild-moderate LVSD’ and 82.51 for ‘severe LVSD’, and in peak heart rate $\chi^2(2) = 18.486$, $p = 0.000$, with a mean rank of 128.23 for ‘controls’, 85.43 for ‘mild-moderate LVSD’ and 89.84 for ‘severe LVSD’.

Oxygen consumption at AT during cardiopulmonary exercise testing was also significantly different between all groups, as were the calculated slopes of the ratio of minute ventilation to CO_2 volume exhaled (V_E/V_{CO_2} slope) at peak exercise and at the anaerobic threshold (table 4.2, figure 4.2). Heart rate responses were equally limited in both LVSD groups (figure 4.3).

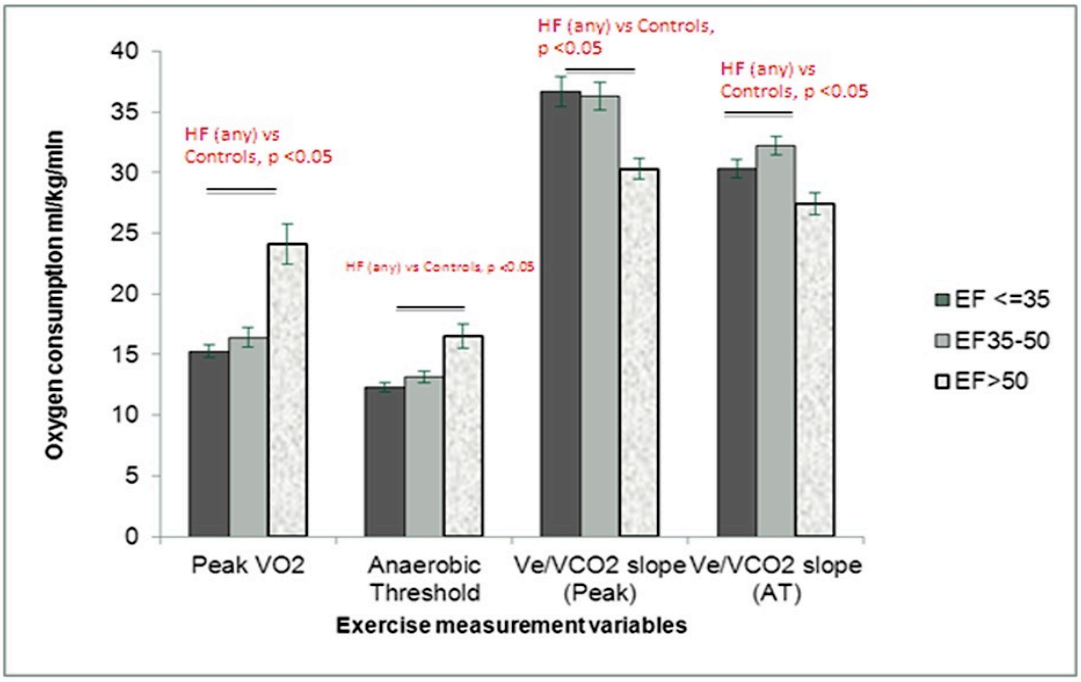


Figure 4.2 Cardio-pulmonary exercise testing results

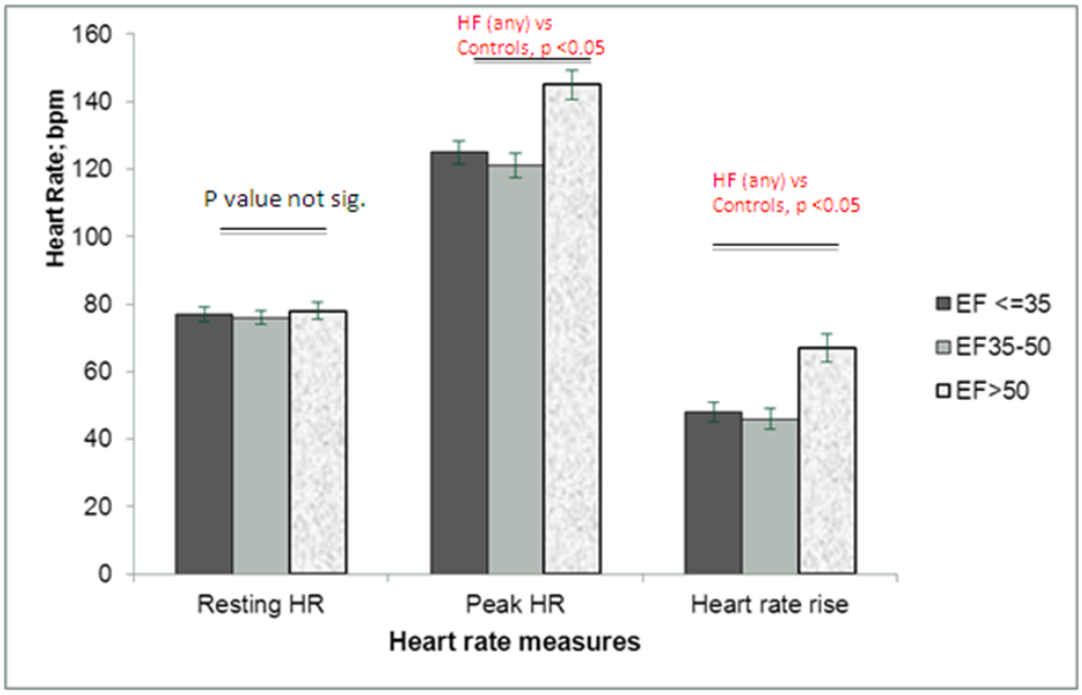


Figure 4.3 Heart rate comparisons

4.4.5 Relationship between exercise capacity and HR

Whilst the control group had a strong correlation between peak oxygen consumption and heart rate rise (peak HR – resting HR), this correlation was much weaker in the mild/moderate LVSD group and non-existent in the severe LVSD group (Figure 4.4).

In the entire cohort, there was a significant linear relationship between heart rate rise and peak V_{O_2} where a heart rate rise of 10 bpm resulted in an increase in peak V_{O_2} of 1.8 ml/kg/min ($p<0.05$, fitted lines represented by dashed lines). However, in control patients the rate of increase in peak V_{O_2} relative to a 10 bpm increase in HRR was 2.6 ml/kg/min ($p<0.05$), whereas this was less in patients with mild-moderate LVSD (1.6 ml/kg/min per increase of 10 bpm, $p<0.05$) and no clinically significant in those with severe LVSD (0.085 ml/kg/min per increase of 10 bpm, $p<0.05$).

This relationship was further investigated using linear regression of the HRR as a predictor of peak V_{O_2} in the three groups: controls $R^2=0.420$ (ANOVA F value <0.01), mild-moderate LVSD $R^2=0.366$ (ANOVA F value <0.01) and severe LVSD $R^2=0.179$ (ANOVA F value <0.01).

A likelihood ratio test comparing these regression lines against a single line for all points confirmed that there were significant differences in the HR relationship in control subjects and patients with mild-moderate and severe heart failure ($\chi^2_1=4.01$, $p=0.035$). Furthermore, comparing the regression

lines pair-wise suggested that there are also significant differences in the slopes between control and mild-moderate patients and mild-moderate patients and severe patients ($p<0.05$).

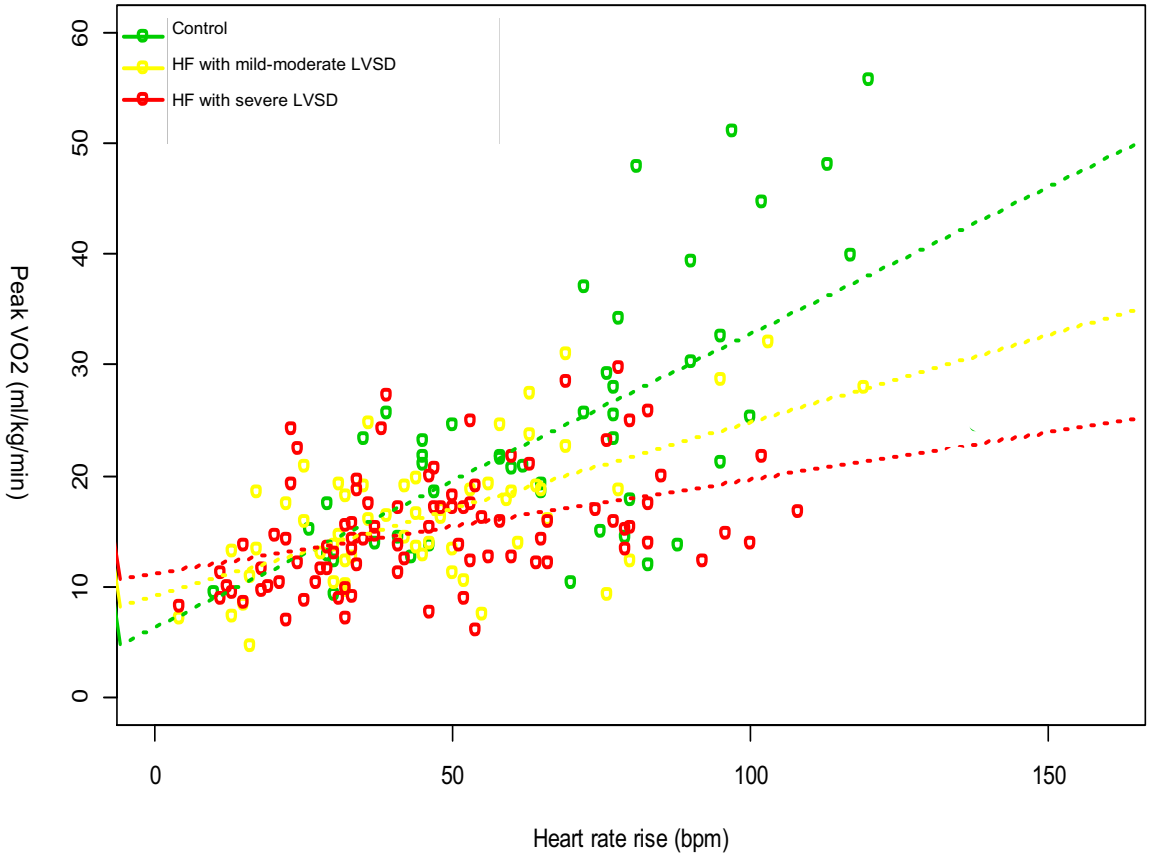


Figure 4.4 Correlation of heart rate rise to peak oxygen consumption

4.4.6 Association with CI

Patients with LVSD were then divided by the presence or absence of CI, defined as a chronotropic index of less than/equal to 0.8 (discussed in Chapter 3; (Peak HR –Resting HR)/(Peak Predicted HR – Resting HR)). The demographics and results from the two groups (No CI [n=43] and CI [n= 104]) are shown in Table 4.4.

Variables in both groups were tested for normality using the Shapiro-Wilk test. In the 'no CI' group, chronotropic index, peak predicted heat rate, height, pVO_2, RER, peak diastolic blood pressure, QRS duration, bisoprolol dose and ACE/ARB dose were not normally distributed. In the 'CI' group, chronotropic index, pVO_2, resting heart rate, resting diastolic blood pressure, QRS duration, bisoprolol dose and ACE/ARB dose were not normally distributed. All non-parametric data were therefore reported as median and interquartile range (Table 4.4).

The Levine statistic revealed that variance differed in age, peak predicted heart rate, heart rate rise, resting heart rate and peak heart rate, thus appropriate statistical tests were used to ensure accuracy of 'equality of means' in the ANOVA test results (discussed in chapter 3).

The two groups were similar with respect to age, sex, height, weight, BMI, EF, LVIDd, LVIDs, beta-blocker dose, ACEi dose and resting blood pressures. There was a higher occurrence of diabetes, coronary artery

disease, LBBB and pacing devices in the ‘CI’ group, and increased AF and DCM in the ‘no CI’ group.

The ‘no CI’ group with higher HRR (73 (23) v 36 (16) beats/min), had better exercise time (477 (217) vs 382 (209) seconds, $F(1,145) = 6.2$, $p<0.05$) and AT (13.7 (3) v 12.1 (3) ml/kg/min, $F(1, 81) = 4.28$, $p<0.05$), but similar V_E/V_{CO_2} slope (peak), V_E/V_{CO_2} slope (AT) and RER (figure 4.5).

Non-parametric variables were compared using the Kruskall Wallis test. This showed higher peak V_{O_2} (16.3 (6) v 15.9 (6) ml/kg/min, $\chi^2=6.4$, $p<0.05$), CI index (1.07 (0.7) v 0.6 (0.3), $\chi^2=90.6$, $p<0.05$) and QRS duration ($\chi^2=5.96$, $p<0.05$). There were no differences in bisoprolol ($\chi^2=0.293$, $p=0.588$) and ACEi/ARB ($\chi^2=0.130$, $p=0.719$) dosages (table 4.4).

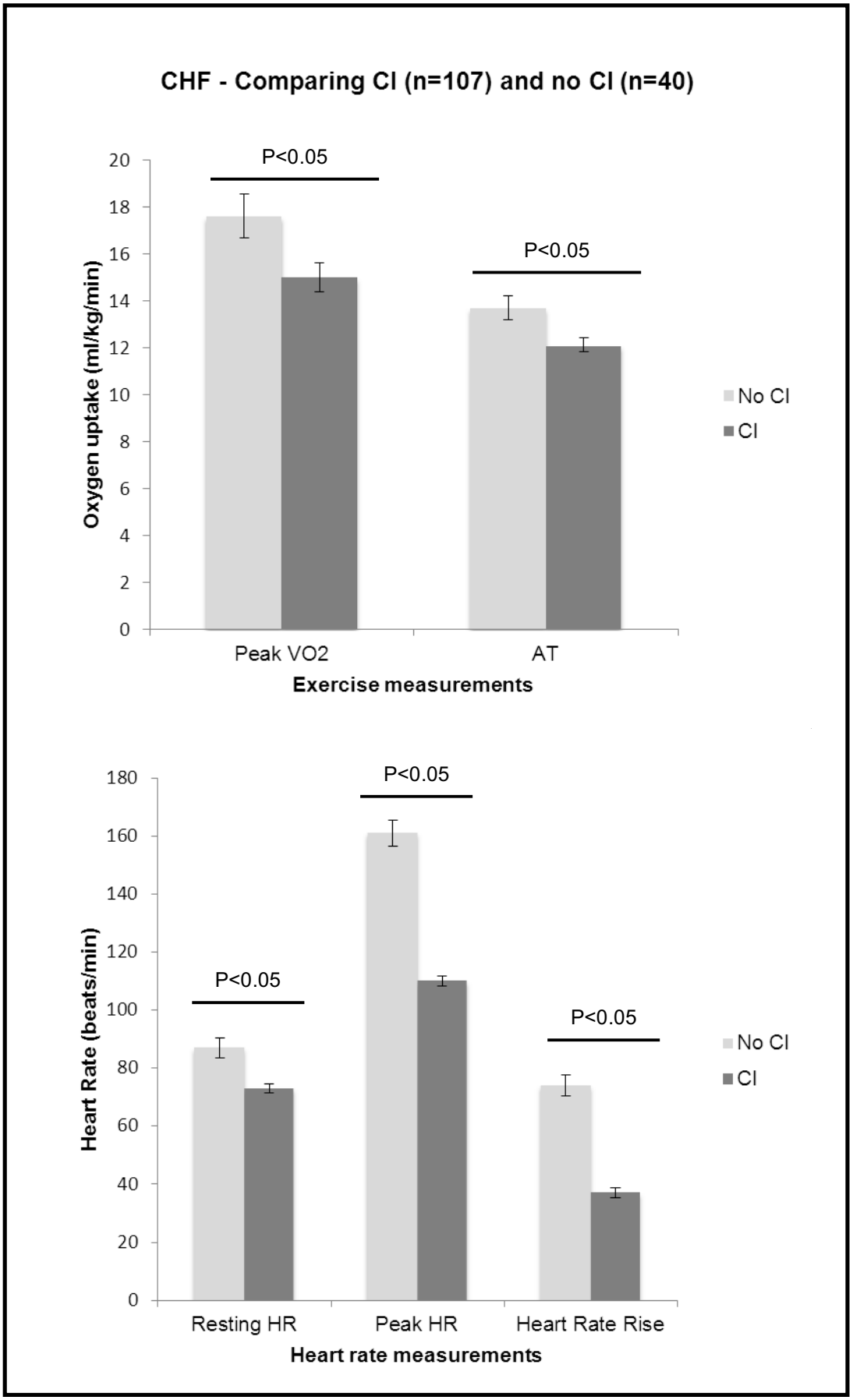


Figure 4.5 Comparing CHF cohorts with and without CI

Demographics (mean (SD)/median (IQR)*)	**No CI (n=43)**	**CI (n=104)**	**P value**
Age	69 (30)	67 (13)	0.834
Male	35 (80%)	80 (78%)	
Height*	172 (19)	170 (10)	0.394
Weight	90 (22)	81 (15)	0.769
BMI	30 (5)	28 (4)	0.636
Ejection Fraction (%)	30 (9)	35 (9)	0.791
LVIDd diameter (mm)	58 (9)	56 (8)	0.989
LVIDs (mm)	48 (12)	46 (9)	0.890
BB* (bisoprolol equivalent, mg)	5 (5)	7.5 (5)	0.475
ACEi/ARB* (ramipril equivalent, mg)	10 (0)	10 (8)	0.569
Peak V_{O_2}* (ml/kg/min)	16.3 (6)	15.9 (6)	<0.05
Exercise Time (s)	477 (217)	382(209)	<0.05
AT (ml/kg/min)	13.7 (3)	12.1 (3)	<0.05
V_E/V_{CO_2} slope (peak)	30 (5)	35 (7)	0.288
V_E/V_{CO_2} slope (AT)	29 (4)	32 (7)	0.329
RER*	1.09 (0)	1.05 (0)	0.484
Rest HR* (bpm)	89 (16)	73 (15)	<0.05
Peak HR (bpm)	159 (28)	109 (19)	<0.05
HR rise (bpm)	73 (23)	36 (16)	<0.05
Peak Predicted HR* (bpm)	144 (19)	149 (13)	0.064
Chronotropic index*	1.07 (0.7)	0.6 (0.3)	<0.05
Rest Systolic BP (mmHg)	125 (25)	128 (22)	0.660
Rest Diastolic BP* (mmHg)	70 (19)	70 (20)	0.690
Peak Systolic BP (mmHg)	141 (27)	150 (29)	0.658
Peak Diastolic BP* (mmHg)	74 (13)	70 (20)	0.286
Ischaemic Heart Disease	21 (48%)	54 (52%)	
Dilated Cardiomyopathy	17 (40%)	34 (33%)	
Coronary Artery Disease	23 (53%)	61 (59%)	
Heart Failure	43 (100%)	104 (100%)	
Diabetes Mellitus	3 (8%)	23 (21%)	
Any pacing device	14 (33%)	63 (60%)	
Bi-ventricular CRT	12 (28%)	56 (53%)	
Atrial fibrillation	22 (55%)	18 (17%)	
LBBB (QRS >120ms)	15 (35%)	56 (53%)	
QRS duration* (ms)	90 (50)	130 (50)	<0.05

All continuous variables are reported as either mean (SD) or median (IQR).*

Key: BMI: body mass index, LVIDd: left ventricular internal diameter in diastole, LVIDs: left ventricular internal diameter in systole, BB, beta-blocker, ACEi/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist, V_{O_2}: oxygen consumption, AT: anaerobic threshold, V_E/V_{CO_2} slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory exchange ratio, HR: heart rate, BP: blood pressure, CRT: cardiac resynchronisation therapy, LBBB: left bundle branch block.

Table 4.4 Comparison between different exertional heart rate rise groups (No CI vs CI).

4.4.7 Stratification of the cohort based on degree of CI

The CI group had worse exercise capacity and lower peak V_{O_2}, despite no difference in BMI, ejection fraction, co-morbidities or medications.

The total heart failure cohort (n=147) was then re-stratified by the degree of CI, as defined by the chronotropic index to assess for any link between worsening CI and exercise capacity, described by the peak V_{O_2} and exercise time. This resulted in seven groups: 1 (Chronotropic Index > 1.2, n=16), 2 (Chronotropic Index > 1, n=8), 3 (Chronotropic Index > 0.8, n=18), 4(Chronotropic Index > 0.6, n=32), 5 (Chronotropic Index > 0.4, n=40), 6 (Chronotropic Index > 0.2, n=23), 7 (Chronotropic Index < 0.2, n=10).

Bisoprolol and ACEi/ARB dose were not normally distributed (Shapiro Wilk test $p<0.05$), and were examined using non-parametric tests, which demonstrated no difference between groups (Table 4.5, bisoprolol $\chi^2=8.7$, $p=0.188$; ACEi/ARB $\chi^2=3.6$, $p=0.727$).

	N	Mean	SD	Minimum	Maximum	Percentiles		
						25th	50th	75th
Bisoprolol	146	5.6507	3.61456	0	10	2.5000	5.0000	10.0000
ACEi/ARB	142	6.70	3.723	0	10	2.50	10.00	10.00

Table 4.5 Bisoprolol and ACEi/ARB doses

ANOVA testing was used to compare the seven groups (results data for each group is available in appendix A). Significance was seen in heart rate rise ($F(6,140) = 47$, $p < 0.05$), exercise time ($F(6,140) = 4.38$, $p < 0.05$),

resting heart rate ($F(6,140) = 9.30$, $p < 0.05$), peak heart rate ($F(6,140) = 101$, $p < 0.05$), peak VO_2 $F(6,140) = 4.5$, $p < 0.05$) and QRS duration ($F(6,127) = 2.8$, $p < 0.05$).

Below an index of 0.8 (group 3), worsening heart rate response was associated with definite and progressive reductions in pVO_2, AT and exercise time (figures 4.6 and 4.7).

There was no difference in ejection fraction, ventricular internal dimensions, anaerobic threshold, VE/VCO_2 slopes at AT and peak or BMI.

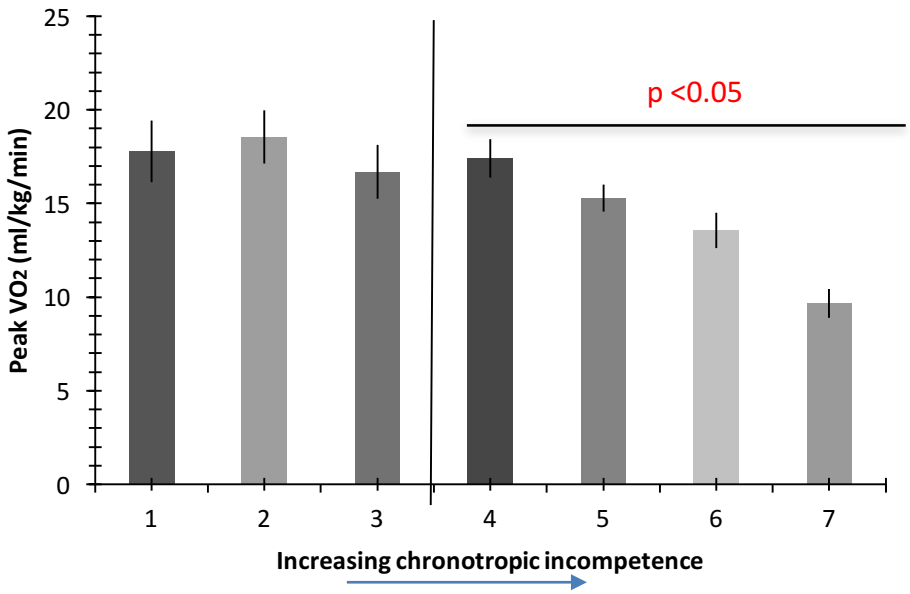


Figure 4.6 Peak oxygen consumption with decreasing chronotropic index

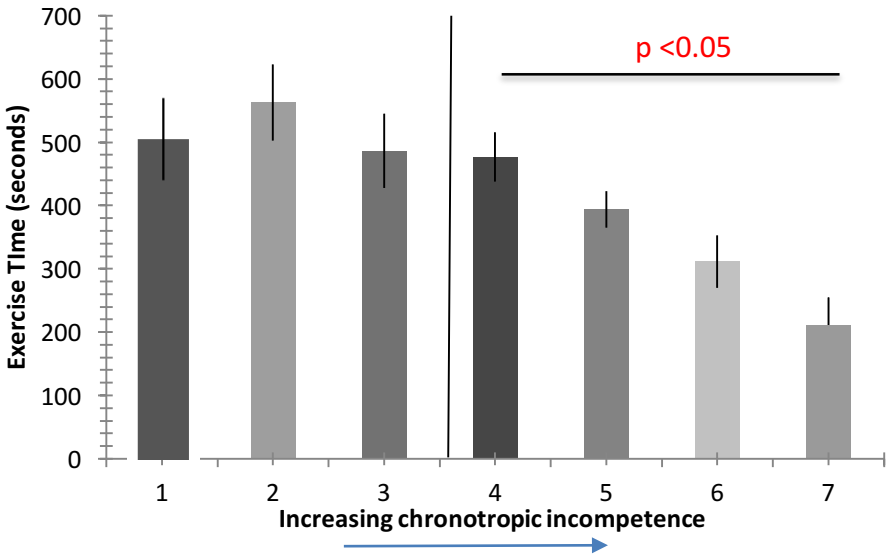


Figure 4.7 Exercise time with decreasing chronotropic index

4.5 Discussion

This retrospective analysis of a cohort of real-world subjects with heart failure of multiple aetiologies undergoing exercise testing for clinical purposes demonstrated that heart rate rise is closely related to exercise capacity in a linear way, but that the slope of this relationship is much reduced in those with severe heart failure.

Furthermore, within the heart failure cohort, the presence of CI was associated with worse exercise capacity, despite there being no difference in cardiac structure or function, co-morbidities, medications, BMI and age.

4.5.1 Cohort selection

The cohorts were selected according to the resting EF on echocardiogram. Multiple studies have shown that although LVSD is associated with reduced functional capacity, there is poor correlation between the severity of LVSD and symptoms as measured by the NYHA functional classification,(326) and also between the severity of LVSD and CPX exercise measures.(207)(327) The findings from this study are in keeping with this.

The degree of LV systolic impairment at rest (ejection fraction) was chosen as the measure by which to group these patients since mechanical alterations are a possible driver behind the pathophysiological changes

leading to impaired HRR with exertion. EF is also widely used, both clinically and in the research setting, to assess systolic function, influence treatment decisions and monitor response,(328)(329) so if in due course management is altered by our findings, grouping patients like this is practical and pragmatic.

Selecting a control group for this study was also challenging, and a hospital based control cohort of convenience was used. This consisted of a healthy subset of hospital patients who underwent outpatient echocardiogram and CPX testing for elective non-cardiac surgery pre-operative assessment. Thus a higher proportion of the control cohort had co-existing IHD, AF or a pacing device in-situ, than would be expected in a totally healthy cohort. This may impact any group comparisons made, however as the presence of these comorbidities would limit exercise capacity, then any difference seen is likely to be an under-estimation.

4.5.2 Relationship between HRR and exercise in controls and heart failure patients

Our data confirm that HRR is strongly associated with peak exercise capacity achieved in control subjects. However, this relationship was weaker in patients with heart failure. There was a potential age related bias with the hospital based controls in that they were younger than the HF cohort. In our analyses we corrected for both age and level of fitness by using the ratio of

HR reserve to metabolic reserve, known as the chronotropic index. This is a more objective measurement for CI than measures that rely on achieving a certain percentage of the age-predicted maximum heart rate. An index of less than 0.8 is considered to represent CI, regardless of age, functional capacity or BMI.

The two LVSD cohorts had lower chronotropic index measures than the control group, and cardio-pulmonary exercise test indices were similarly reduced. However, there was no difference in exercise parameter comparisons between the two heart failure groups.

Although most of the LVSD patients were taking beta-blockers, which could result in an iatrogenic worsening of heart rate rise, we and others have previously shown that although these agents lower peak and resting heart rates, this does not generally adversely alter exercise capacity. Equally, although acute withdrawal of beta-blockers improves PHR there is no increase in exercise capacity or symptoms.(230) (235) Patients with LVSD were also taking ACEi, but ACEi are not known to restrict exercise capacity.(330) In addition, all patients attending for elective outpatient CPX testing in this Cardiology Investigations Unit are routinely instructed to omit all rate-limiting medications on the day of the procedure, and 24 hours prior.

Nonetheless, the data have shown that within the control cohort, there is a strong correlation between HRR and pVO_2, and this association is weakened in the LVSD cohorts, who exhibit an impaired chronotropic response.

4.5.3 CI and LVSD

A significant difference in exercise capacity was demonstrated when the combined LVSD dataset was divided into two groups based on the chronotropic index. The ‘no CI’ group also had a higher resting HR, which could either represent higher sympathetic tone in this group, or be a reflection of the increased prevalence of AF.

The LVSD cohort was further stratified into seven groups based on the chronotropic index. CI commonly develops in association with cardiac dysfunction and seems to worsen with disease progression. Whether this contributes to or is the consequence of lower exercise capacity in CHF is unclear. These results confirm that there is a relationship between peak oxygen consumption and heart rate rise, and that both are reduced in the context of heart failure.

This forms the key principle underpinning this body of research, and the associated hypotheses. These results agree with previous studies that have shown a similar relationship.(331)(332) However, what is not clear from these data, and from previous studies in this area, is whether the reduced HR response is a causative factor in the impaired exercise capacity that is pathognomonic of worsening heart failure, or simply an associated incidental finding that reflects the reduced exertional capability.

4.5.4 Clinical implications

These findings are clinically relevant because they highlight the differences in heart rate response with decreasing resting ejection fraction, in a large cohort with varied co-morbidities. It is widely believed that a limited HRR contributes to exercise intolerance in subjects with CHF. Hence, the correction of CI remains a target to improve functional capacity. This is a reasonable assertion in patients without CHF and as we have seen there is a strong relationship between heart rate rise and peak oxygen consumption.

However, even our observational dataset shows that this relationship is weaker in patients with heart failure and essentially flat in those with the worst heart function. This is likely to be the consequence of the chronic multi-system abnormalities in the respiratory, skeletal and cardiovascular systems, whether directly or indirectly the result of CHF, that could all be contributing to the limited exercise capacity, such that simply increasing HRR and achieving ‘chronotropic competence’ may not result in any improvement in exercise capacity.

Nevertheless, the uncertainty of a causative relationship might contribute to suboptimal use of heart rate reducing agents, for fear of inducing exercise intolerance. Furthermore, despite no conclusive evidence of benefit on exercise time or quality of life in CHF from rate-adaptive pacing,(263) this programming mode with high base rates remains the standard of care for most CHF patients with pacemakers, creating a paradoxical mix of medical

therapy to reduce mean heart rate with rate-adaptive pacing to increase heart rate.

4.5.5 Study limitations

This was a retrospective cohort analysis and prospective studies will necessarily be required in order to confirm these findings and explore the association between heart rate and exercise further. All of the patients in this cohort had been referred for either a clinical indication, functional assessment prior to undergoing vascular surgery, impaired exercise capacity or for heart failure prognostication. Thus, there was a wide mixture of aetiologies and co-morbidities present within this cohort, all of which could impact the overall functional capacity and exercise test results.

Resting ventricular function was used to divide cohorts into controls, mild-moderate LVSD and severe LVSD. EF has been shown to correlate poorly with exercise capacity and as such a better way to discriminate LVSD severity may have been to use questionnaires that assess the activities of daily living, 6-minute walk tests, NYHA status or dose of diuretics required to control the LVSD symptoms. Nonetheless, LVSD treatment guidelines rely on echocardiographic EF measurements to stratify LVSD severity and to guide treatment decisions. Hence, EF was chosen as the measure with which to separate the cohorts, as this information was readily available.

Measurement of BNP would also have been useful for stratification however this was not available in the context of this retrospective analysis. It is also

noteworthy to mention that the controls were a hospital based sample of convenience, comprising of younger asymptomatic individuals with normal ejection fractions attending for elective pre-operative assessment for non-cardiac surgery.

The rationale behind using cardio-pulmonary exercise testing results, rather than six-minute walk tests was to increase reproducibility. The accuracy of the CPX tests and echocardiograms that were carried out clinically may not be to the same standards and rigour as required for research purposes and post-hoc data analysis. Different cardiac physiologists would have carried out the tests, thus creating the potential for errors in data recording and measurement. However, all cardiac physiologists are highly specialised, and each test was supervised and reported by two independent physiologists. All echocardiogram reports in this department are all routinely verified by the senior echosonographer on call for reporting.

Also, all patients underwent an echocardiogram to quantity their ejection fraction, yet other imaging modalities such as cardiac magnetic resonance imaging can produce much more accurate and reproducible ejection fraction measurements, as well as give additional information with regards to cardiac filling and wall stiffness. However, such tests are not widely carried out on all patients undergoing functional assessment in the clinical setting.

The groups were also not matched for height, weight, age or level of training; all of which can affect peak VO_2. There may also have been differences in

the level of motivation within patients or encouragement from the technicians running the tests. There is a suggestion that a proportion of patients in this analysis may not have performed maximal tests as the mean RER for the entire cohort was below 1.1, however this could just be reflection of the multiple co-morbidities that were present within this cohort.

4.6 Conclusion

The study has confirmed that an association exists between CI and exercise capacity in control subjects and albeit less strongly in patients with heart failure. However, a correlation does not necessarily indicate causation.

The close relationship between the heart rate and any measure of exercise capacity makes determining a causal link between CI and poor exercise capacity difficult. Observational data will never be able to answer this question of causality, and it is therefore currently unknown whether CI, intrinsic or iatrogenic, either contributes to or is the consequence of reduced exercise capacity in CHF.

In order to perform a comprehensive analysis of heart rate and exercise capacity in CHF, the roles of both the resting and peak heart rate will need to be investigated, whilst neutralising the potential effects of any contributors to functional capacity such as co-morbidities or medications. Double-blind randomised controlled trials of interventions to increase or reduce heart rate are required in order to determine whether CI actually causes exercise limitation.

Chapter 5: The influence of increasing the heart rate on exercise capacity in chronic heart failure (Opt-RATE 1 Study)

5.1 Abstract

As the observational cohort study has shown (Chapter 4), there is a strong relationship between peak oxygen consumption and heart rate rise (HRR) in controls. This association is decreased in chronic heart failure (CHF), and the presence of more severe chronotropic incompetence (CI) relates to lower functional capacity.

Functional capacity is considered the most consistent prognostic indicator, and a reliable predictor for mortality. Those with reduced functional capacity also tend to have a blunted exertional heart rate response, however whether this is cause or effect has never been directly investigated before.

A total of 118 subjects with pacemaker devices were enrolled into a randomised double blind study of rate adaptive versus fixed base rate pacing. The purpose of this trial was to assess whether 'correcting' chronotropic incompetence by increasing the heart rate response during exercise with a pacemaker device acutely alters exercise capacity in heart failure.

This was a placebo controlled cross-over study where the intervention was rate adaptive pacing and the control was fixed rate pacing to allow intrinsic rate changes. Each subject underwent two symptom-limited maximal treadmill-based cardio-pulmonary exercise tests, and acted as their own controls. Measures of oxygen kinetics were collected throughout the test period. Subjects with exertion-limiting co-morbidities and those who were known to not exhibit any intrinsic heart rate rise were excluded.

Rate-adaptive pacing led to a higher mean (SE) peak HR (128 (3.0) vs 107 (3.9) bpm) but no difference in mean peak oxygen consumption (16.6 (0.7) vs 15.9 (0.6) ml/kg/min, p=0.24), anaerobic threshold (11.7 (0.4) vs 11.3 (0.4) ml/kg/min; p=0.24), exercise time (470 (34) vs 451 (31) s; p=0.33) or perceived exertion level scores.

The study showed that correcting CI and increasing the peak HR achieved during a maximal exercise test did not result in any improvement in exercise capacity.

5.2 Introduction

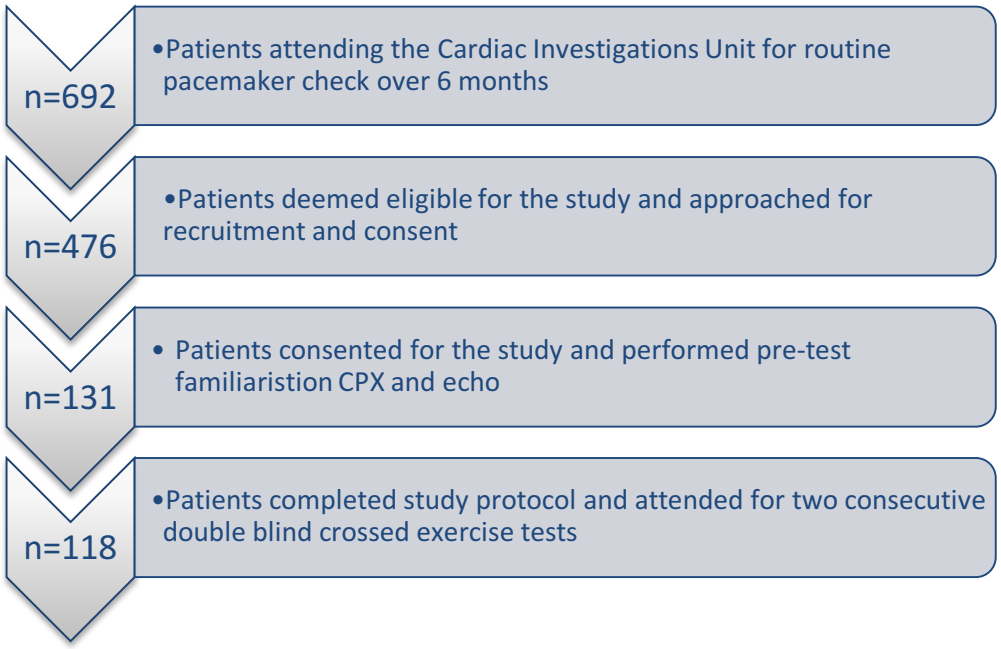
Reduced aerobic exercise capacity is the hallmark of heart failure, and it has been postulated that this may be to be due to an impairment in the ability of the heart to augment cardiac output in response to increasing physical activity demands. This is thought to be as a result of minimal increases in stroke volume and reductions in the peak achievable heart rate. However, it is currently unknown whether the lower peak heart rate is a limiting factor during aerobic exercise, or whether this is simply a reflection of the lower workload achieved prior to the onset of fatigue.

The focus of this investigation is to examine the effects of increasing the heart rate rise and thus correcting CI in patients with CHF on peak and submaximal exercise capacity, by augmenting the heart rate profile throughout exercise, including peak heart rate.

5.3 Methods

5.3.1 Study design

This study was designed as a cross-over study of rate adaptive versus fixed rate pacing with subjects acting as their own controls, thus negating the contribution of all confounding factors except the independent variable, heart rate rise. All subjects were approached at routine outpatient pacemaker follow-up appointments and given information sheets. A pre-test consent appointment was attended by all participants (as described in chapter 3). This study was approved by the National Research Ethics Service (REC reference 13/YH/0144, IRAS project ID 129113, Appendix B).



5.3.2 Study population

Within this cohort of 118 subjects, 79 had CHF due to LVSD (HF group), and 39 had pacing devices with no symptomatic or structural evidence of heart failure (Control group). These cohorts were further divided into those with

sinus rhythm (CHF n= 53; Controls n= 26) and atrial fibrillation (CHF n=28; Controls n = 11). All subjects had a pacing device in situ for a clinical indication, with stable pacemaker device and lead variables for at least six months.

5.3.3 Inclusion and exclusion criteria

The inclusion criteria for the test subjects were CHF due to left ventricular systolic dysfunction (LVSD), (moderate-severe; left ventricular ejection fraction <45% and symptoms of breathlessness or fatigue on exertion), on optimal medical therapy and stable symptoms. They must have had their pacemaker for at least 6 months with stable lead variables and no change in medication or other invasive cardiac procedures for at least three months. All subjects were capable of performing a peak exercise test on a treadmill, and informed written consent was obtained in all subjects.

Subjects who were pacing dependent in the atrium and hence would not exhibit any rise in heart rate during activity were excluded. Other exclusion criteria consisted of the inability to give informed consent and co-morbidities 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.

5.3.4 Exercise testing and randomisation

After at least one week following the familiarisation test, subjects were invited back for the two maximal symptom-limited treadmill crossover exercise tests, which were carried out at least one week apart. Immediately prior to each test, the unblinded pacing technician temporarily programmed the pacemaker to rate-adaptive (RR on) or fixed rate pacing (RR off), with the maximum paced HR determined using the age-predicted peak HR equation (220-age).

A screen was used to separate the heart rate and electrocardiographic monitor, which was only observed by the unblinded technician, from the metabolic cart, which was monitored by the blinded investigator. Resting, peak and recovery blood pressures were measured using a standard manual cuff sphygmomanometer.

5.3.5 Cohort size calculation

The changes due to rate limitation are as yet not investigated in heart failure patients. This part of the study is therefore necessarily exploratory. An additional problem is that assessing sample size to demonstrate statistical equivalence is more difficult than establishing a difference between two groups. However peak oxygen consumption measurement is reliable and reproducible, with a coefficient of variation percentage of 9.73 in this laboratory. A mean of 15 (2) ml/kg/min was expected in CHF subjects in sinus rhythm, and a mean of 13 (2) ml/kg/min for CHF with atrial fibrillation (mean difference 15% lower), with higher peak heart rates achieved in the AF cohort (mean difference 23% higher).

Therefore, in order to demonstrate a clinically important change of 2.0 ml/kg/min with 80% power, and a two sided alpha of 0.05, a minimum of 22 subjects were needed in the atrial fibrillation CHF group, and a minimum of 38 in the sinus CHF group. To allow for drop-outs and to confidently suggest equivalence, the recruitment aims for the HF cohort were a minimum of 25 patients in atrial fibrillation and 50 in sinus rhythm. As controls were expected to achieve higher peak V_{O_2} readings (mean of 24 (3) ml/kg/min for sinus rhythm and 22 (3) ml/kg/min for atrial fibrillation) and heart rates, the recruitment aims were a minimum of 10 subjects with atrial fibrillation and 25 with sinus rhythm.

5.4 Results

5.4.1 Baseline characteristics

5.4.1.1 Entire cohort

The total population for this RCT consisted on 118 subjects. There were 79 subjects with a diagnosis of CHF (symptomatic heart failure with echocardiographic evidence of LV systolic dysfunction), within which 53 were in sinus rhythm and 26 had co-existent permanent atrial fibrillation. The remaining 39 were controls, of which 28 were in sinus rhythm and 11 had atrial fibrillation.

Weight, resting heart rates and resting diastolic blood pressure followed a non-parametric distribution (Shapiro-Wilk normality test; $p<0.05$) and are hence reported as median ± interquartile range. Normally distributed variables are reported as mean (SD). Baseline variables are shown in table 5.1.

	Group 1 Controls AF N=11	Group 2 Controls sinus N=28	Group 3 CHF-AF N=26	Group 4 CHF sinus N=53	F statistic/ Chi-Square	P Value
Height, cm	171 (9)	173 (9)	173 (6)	172 (7)	.437	0.727
Weight, kg	76 (16)	81 (12)	85 (17)	86 (15)	1.439	0.235
Age, years	78 (6)	69 (13)	76 (8)	73 (8)	3.051	0.074
NYHA class	1	1	2	2	-	-
Ejection fraction, %	54 (7)	55 (7)	31 (10)	34 (11)	34.698	0.000
Peak predicted HR, bpm	142 (8)	151 (13)	144 (9)	147 (8)	3.051	0.076
LVIDd, mm	49 (5)	48 (6)	53 (20)	53 (10)	0.408	0.748
LVIDs, mm	35 (4)	35 (6)	46 (21)	43 (11)	2.409	0.081
EA ratio	-	0.96 (0.3)	-	1.4 (1.3)	0.694	0.421
E wave DT, ms	-	234 (48)	-	235 (72)	0.149	0.863
E/E'	-	10 (5)	-	8 (2)	0.903	0.462
Furosemide dose: 0/40/80/≥120 mg (% [n])	0/100/0/0 [0/2/0/0]	0/0/0/0 [0/0/0/0]	23/42/12/23 [6/11/2/6]	42/40/12/6 [22/21/7/3]	26.218	0.000
Diabetes mellitus	9% (1)	18% (5)	39% (10)	32% (17)	5.232	0.156
IHD	9% (1)	32% (9)	39% (10)	42% (22)	4.418	0.220
Hypertension	27% (3)	29% (8)	31% (8)	28% (15)	0.069	0.995
PMH: CABG	0% (0)	18% (5)	27% (7)	23% (12)	3.784	0.286
PMH: PCI	0% (0)	14% (4)	12% (3)	23% (12)	4.258	0.235
PMH: Valve surgery	0% (0)	4% (1)	19% (5)	6% (3)	6.822	0.078
ACEi	27% (3)	29% (8)	62% (16)	53% (28)	10.013	0.124
ARB	0% (0)	11% (3)	35% (9)	36% (19)	15.582	0.016
Beta-blocker	64% (7)	32% (9)	89%(23)	87% (46)	31.717	0.000
Aldosterone antagonist	9% (1)	4% (1)	42% (11)	47% (25)	21.628	0.000
Statin	36% (4)	32% (9)	77% (20)	70% (37)	16.729	0.001
Ca^{2+} channel blocker	18% (2)	11% (3)	8% (2)	8% (4)	1.365	0.714
Digoxin	0% (0)	0% (0)	46% (12)	6% (3)	34.260	0.000

Normally distributed variables shown as mean (SD).

KEY: NYHA: New York Heart Association functional classification, HR: heart rate, LVIDd: left ventricular internal diameter in diastole, LVIDs: left ventricular internal diameter in systole, DT: deceleration time, PMH: past medical history, IHD: ischaemic heart disease, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker.

Table 5.1 Baseline group demographics

5.4.1.2 Groups

There were no differences in all four groups with respect to co-morbidities (table 5.1), thus making it possible to consider some inter-group comparisons. In particular, there were similar percentages of ischaemic heart disease and diabetes mellitus in all groups.

The subgroups within the controls and CHF cohorts (ie: AF and sinus) showed no difference with respect to height, weight, BMI, age, NYHA class, ejection fraction, LV measurements, co-morbidities or medications.

5.4.2 Comparing intrinsic heart rate rise (RR off) to augmented heart rate rise (RR on)

Rate adaptive pacing alters the heart rate profile and cardio-acceleration in response to increasing levels of activity. The four groups exhibited different functional and symptomatic responses.

5.4.2.1 CHF sinus group

In the sinus CHF group (Group 4, n= 53) the use rate-adaptive pacing (RR on) resulted in correction of chronotropic incompetence, with a significant increase in the heart rate achieved at submaximal (HR at AT: 103 (18) v 94 (18) bpm; $p<0.05$), maximal exercise (HR at peak: 125 (24) v 108 (26) bpm, $p<0.05$) and overall heart rate rise (HRR: 83 (20) v 58 (20) bpm, $p<0.05$).

There was no associated change in any CPX parameters including pVO_2 (17.0 (5.0) v 16.6 (5.4) ml/kg/min, p=0.345), exercise time (459 (240) v 464 (249) s, p=0.706), AT (12.8 (3.4) v 12.3 (3.6), p=0.073), V_E/VCO_2 slopes (AT and peak) or reported symptoms of breathlessness and fatigue (Borg score (shortness of breath), 2.9 (2) v 2.7 (2), p=0.227; Borg score (leg weakness), 3.1 (2) v 3.1 (2), p=0.856 (figures 5.1 and 5.2A-D; tables 5.2 and 5.3).

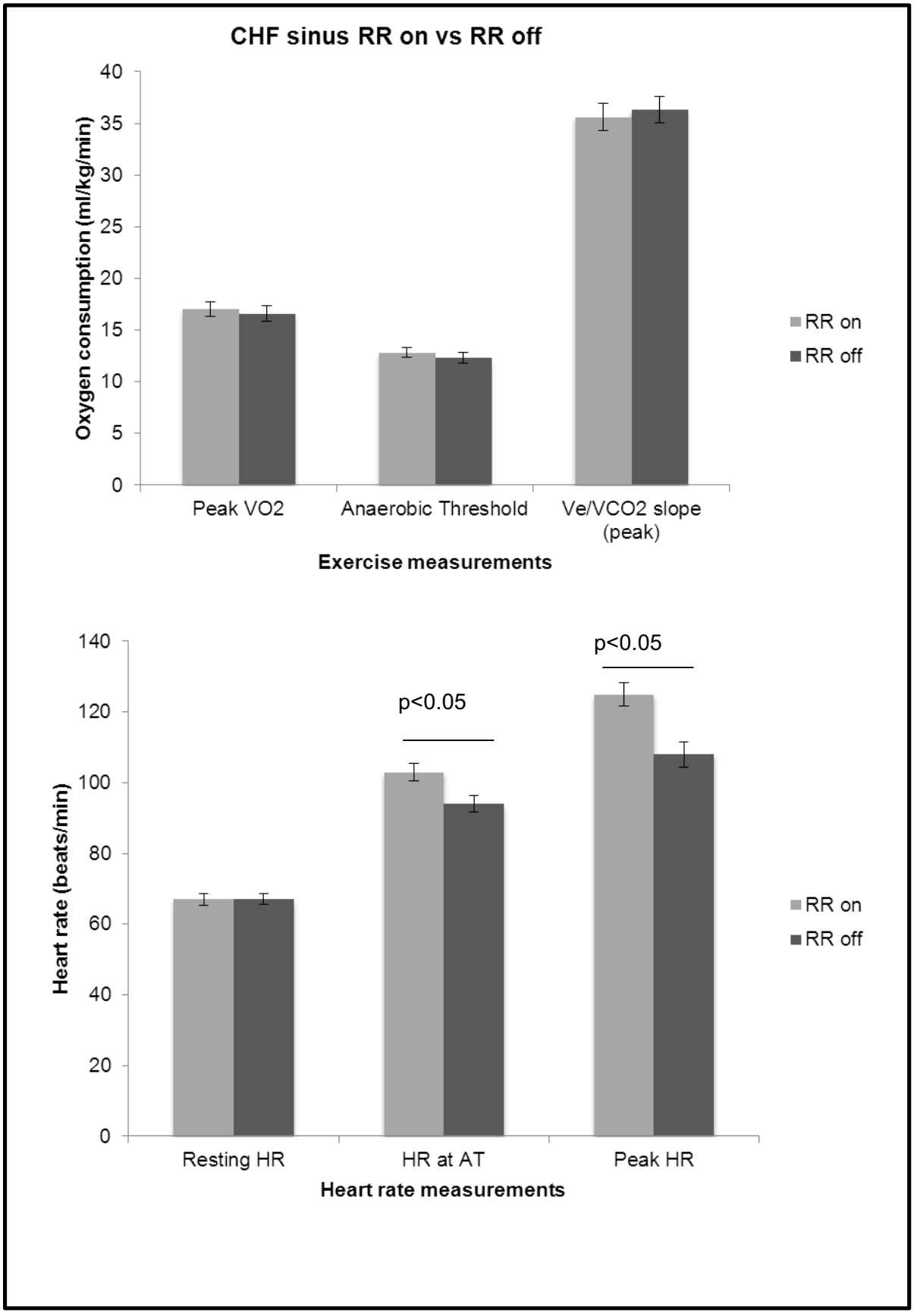


Figure 5.1 RR on vs RR off in sinus CHF cohort

Group (CHF sinus, n=53)		Mean	N	Std. Deviation	Std. Error Mean
Resting HR, bpm	RR on	67.151	53	11.9782	1.6453
	RR off	66.642	53	10.7024	1.4701
Peak HR, bpm	RR on	125.453	53	23.7758	3.2659
	RR off	107.849	53	26.3763	3.6231
Resting systolic blood pressure, mmHg	RR on	122.769	52	17.3958	2.4124
	RR off	119.346	52	18.6725	2.5894
Resting diastolic blood pressure, mmHg	RR on	66.808	52	10.7831	1.4954
	RR off	67.077	52	11.0858	1.5373
Peak systolic blood pressure, mmHg	RR on	147.154	52	28.2603	3.9190
	RR off	143.500	52	22.3865	3.1045
Peak diastolic blood pressure, mmHg	RR on	68.000	52	12.9373	1.7941
	RR off	65.808	52	11.1971	1.5528
Exercise time, seconds	RR on	458.679	53	239.9860	32.9646
	RR off	464.811	53	249.0455	34.2090
pVO_2, ml/kg/min	RR on	17.030	53	5.0202	.6896
	RR off	16.645	53	5.4102	.7431
HR at AT, bpm	RR on	103.48	42	17.904	2.763
	RR off	93.83	42	18.340	2.830
AT, ml/kg/min	RR on	12.99	43	3.441	.525
	RR off	12.44	43	3.632	.554
VE/VCO_2 slope (peak)	RR on	35.6728	53	9.72763	1.33619
	RR off	36.2838	53	10.69304	1.46880
VE/VCO_2 slope (AT)	RR on	29.73	40	6.690	1.058
	RR off	30.70	40	8.925	1.411
Peak RER	RR on	1.1262	53	.11994	.01647
	RR off	1.1306	53	.12185	.01674
OUE slope	RR on	1702.11	51	636.7709	89.1658
	RR off	1707.28	51	721.2726	100.998
MRT	RR on	193.56	15	108.067	27.903
	RR off	187.81	15	126.239	32.595
MRT recovery	RR on	90.44	7	28.894	10.921
	RR off	106.03	7	46.827	17.699
O_2 pulse (peak)	RR on	11.64	14	3.225	.862
	RR off	11.64	14	3.319	.887

KEY: CHF: chronic heart failure, HR: heart rate, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.2 Paired sample statistics (CHF sinus)

Group: CHF sinus (n=53)	Paired Differences					t	df	P value
	Mean	SD	SE	95% Confidence Interval				
				Lower	Upper			
Resting HR, bpm	.5094	10.115	1.3895	-2.2789	3.2977	.367	52	.715
Peak HR, bpm	17.603	19.622	2.6954	12.1951	23.0125	6.531	52	.000
Rest SBP, mmHg	3.4231	16.720	2.3187	-1.2320	8.0782	1.476	51	.146
Rest DBP, mmHg	-.2692	11.334	1.5718	-3.4248	2.8864	-.171	51	.865
Peak SBP, mmHg	3.6538	23.048	3.1963	-2.7630	10.0707	1.143	51	.258
Peak DBP, mmHg	2.1923	14.210	1.9706	-1.7638	6.1484	1.113	51	.271
Exercise time, s	-6.132	117.74	16.173	-38.5859	26.3217	-.379	52	.706
pVO_2, ml/kg/min	.3849	2.9386	.4037	-.4251	1.1949	.954	52	.345
HR at AT, bpm	9.643	15.631	2.412	4.772	14.514	3.998	41	.000
AT, ml/kg/min	.553	1.973	.301	-.054	1.161	1.839	42	.073
VE/VCO_2 slope (peak)	-.6109	6.9987	.96135	-2.54003	1.31814	-.636	52	.528
VE/VCO_2 slope (AT)	-.979	6.328	1.001	-3.003	1.044	-.979	39	.334
Peak RER	-.0043	.12314	.01691	-.03828	.02960	-.257	52	.799
OUE slope	24.835	368.32	51.575	-78.757	128.428	.482	50	.632
MRT	5.747	157.03	40.546	-81.217	92.710	.142	14	.889
MRT recovery	-15.58	34.058	12.873	-47.083	15.914	-1.21	6	.272
O_2 pulse (peak)	.000	2.000	.535	-1.155	1.155	.000	13	1.000

KEY: CHF: chronic heart failure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory exchange ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.3 Paired sample T-tests (CHF sinus)

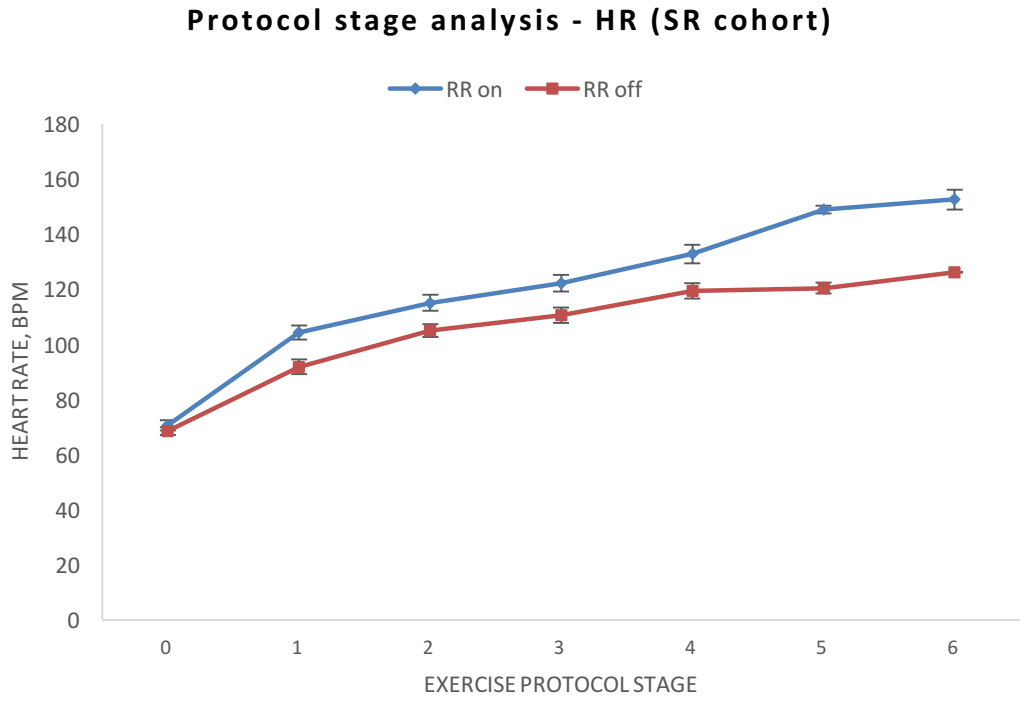


Figure 5.2A Heart rate profile in CHF sinus cohort

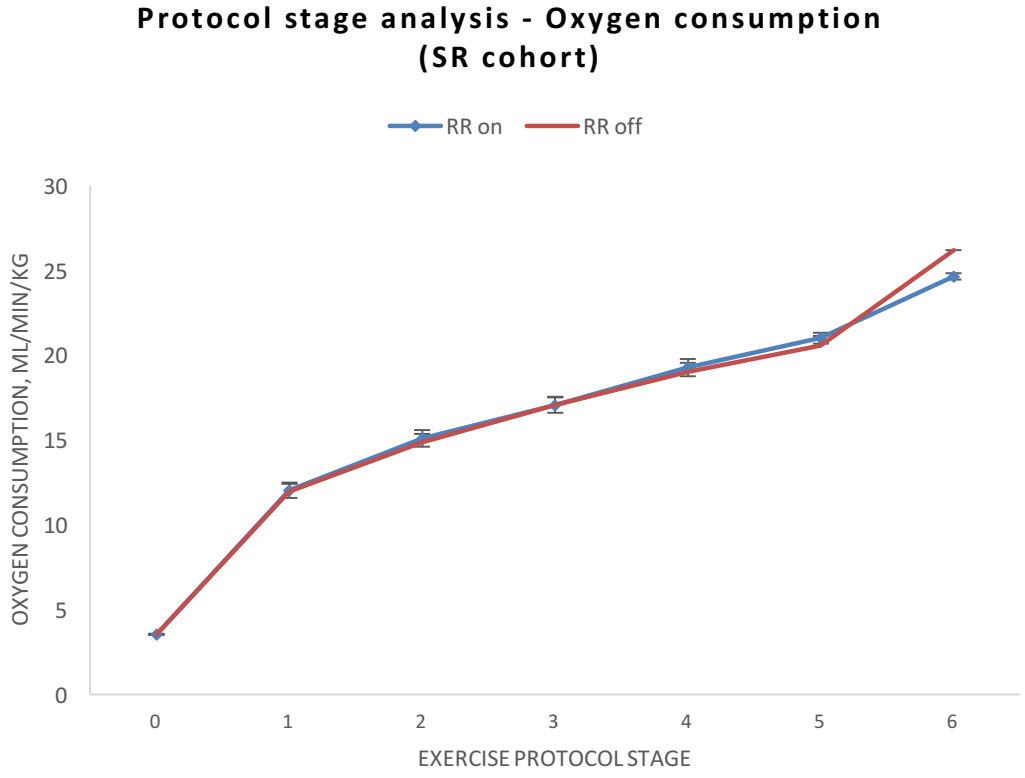


Figure 5.2B Oxygen consumption profile in CHF sinus cohort

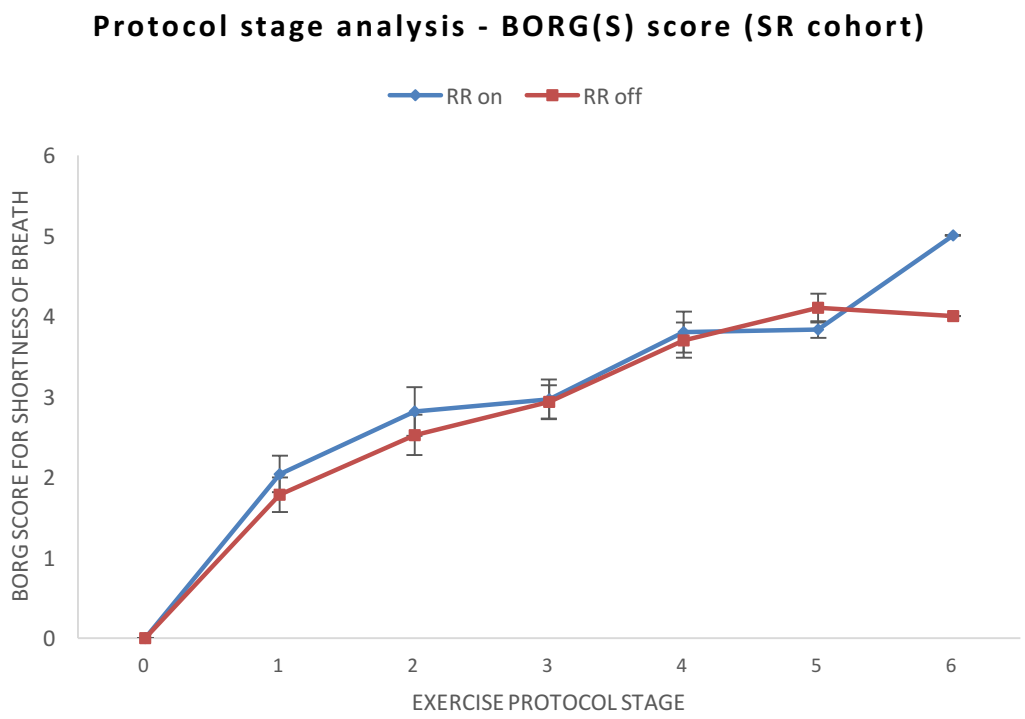


Figure 5.2C Symptom score (shortness of breath) in CHF sinus cohort

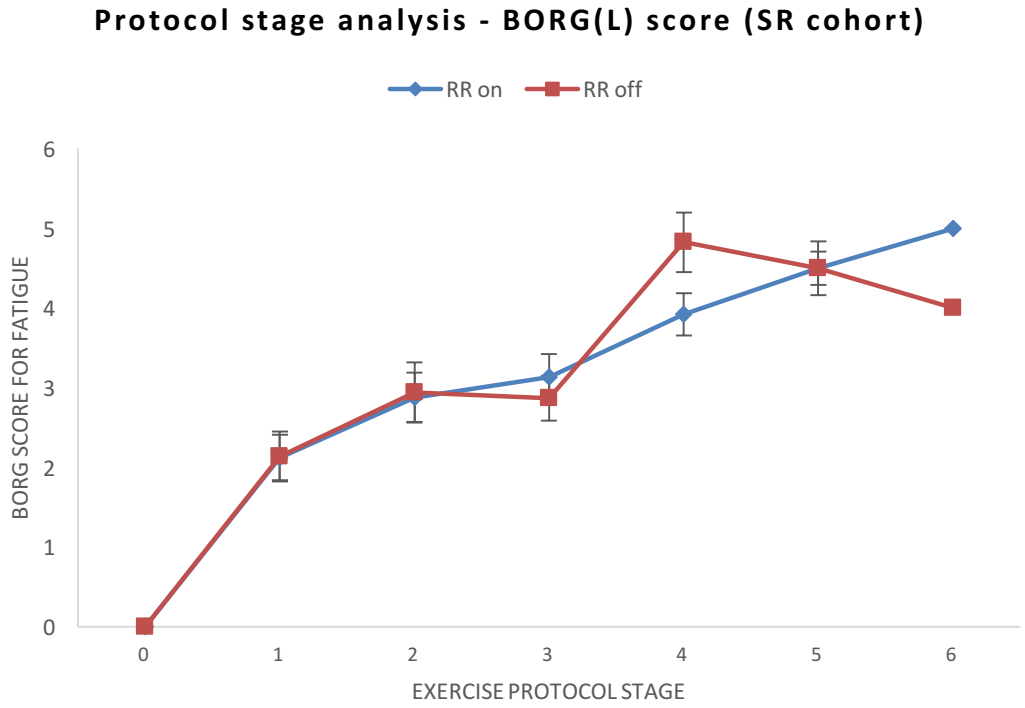


Figure 5.2D Symptom score (leg fatigue) in CHF sinus cohort

5.4.2.2 CHF-AF group

In the subgroup of CHF with concurrent atrial fibrillation (n=26), rate-adaptive pacing led to a higher mean (SD) heart rate at AT (99 (19) v 82 (21) bpm, $p<0.05$) and maximal exercise (121 (20) v 98 (27) bpm, $p<0.05$). The intrinsic heart rate test (RR off) in this cohort exhibited a blunted heart rate response overall. There was an initial brisk HRR, followed by a plateauing at sub-maximal exercise levels and a drop in the heart rate at peak. Rate adaptive pacing in the context of CHF with atrial fibrillation resulted in an increase in the heart rate achieved with each stage of exercise, and correction of the expected heart rate response (figure 5.4A).

This was associated with higher mean pVO_2 (15.3 (3.8) v 14.0 (3.8) ml/kg/min, $p<0.05$) but no change in the AT (11.3 (2.5) v 10.1 (3.5) ml/kg/min, $p=0.177$), exercise time (417 (237) v 373 (210) s, $p=0.197$), VE/VCO_2 slopes (AT and peak) or perceived exertion level scores: shortness of breath scores (3.4 v 3.1, $p=0.919$) or leg fatigue (3.7 v 3.3, $p=0.306$) (figure 5.3, 5.4B-D, table 5.4 and 5.5).

A comparison of those on beta-blockers (n=14) with those on both beta-blockers and digoxin (n=12) revealed similar HRR (55 (18) v 49 (21) bpm, $p=0.211$) and AT (11.9 (3) v 10.6 (4), $p=0.244$), but lower pVO_2 (16.7 (4) v 14.4 (5), ml/kg/min, $p<0.05$) and exercise time (516 (255) v 401 (240) s, $p<0.05$) in the latter sub-group.

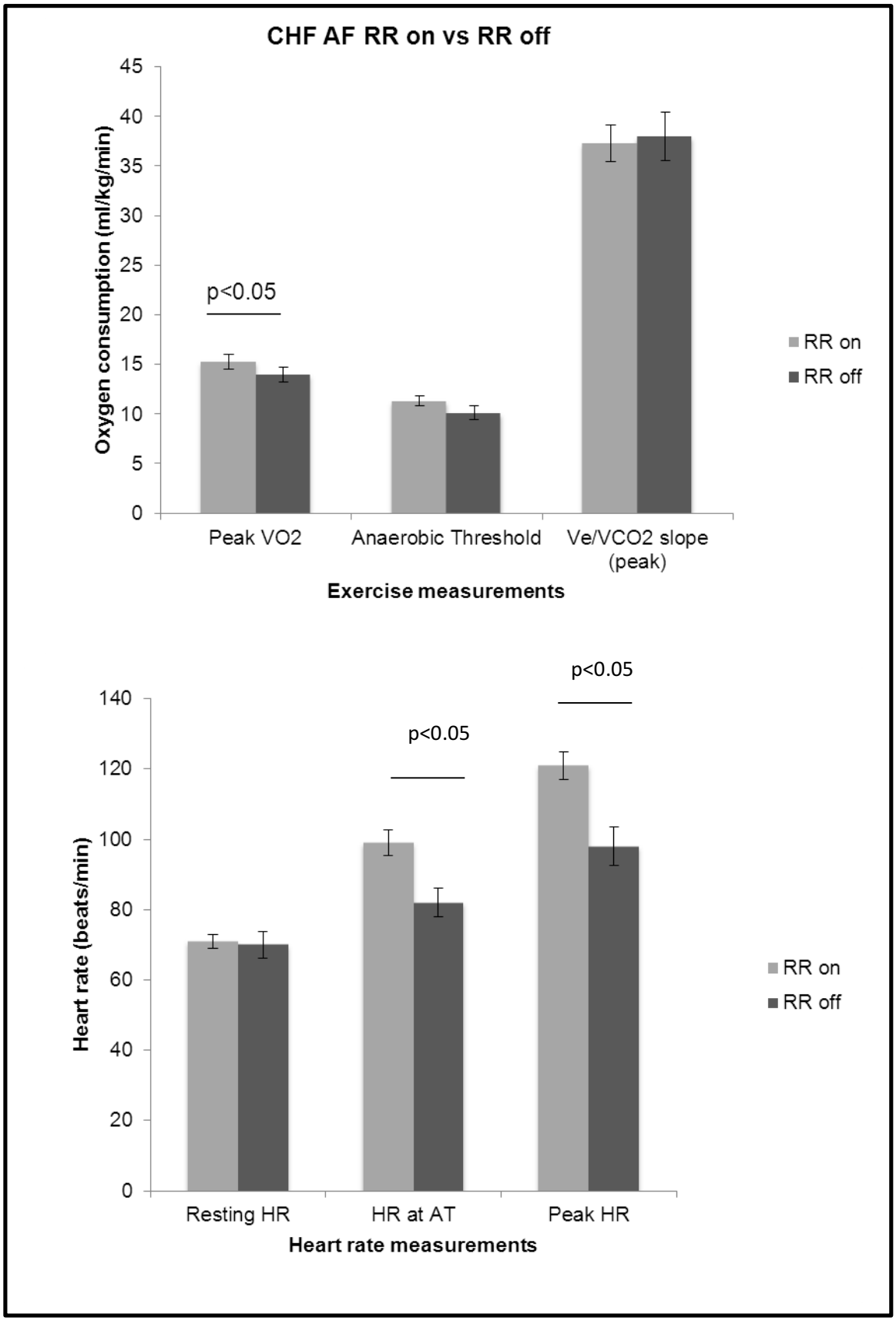


Figure 5.3 RR on and RR off in AF CHF cohort

Group (CHF-AF, n=26)		Mean	N	Std. Deviation	Std. Error Mean
Rest HR, bpm	RR on	71.120	25	10.0471	2.0094
	RR off	68.800	25	11.8462	2.3692
Peak HR, bpm	RR on	121.000	25	20.3695	4.0739
	RR off	98.200	25	27.0201	5.4040
Rest systolic blood pressure, mmHg	RR on	120.240	25	16.1691	3.2338
	RR off	118.320	25	20.5400	4.1080
Rest diastolic blood pressure, mmHg	RR on	65.680	25	9.3217	1.8643
	RR off	64.560	25	11.8957	2.3791
Peak systolic blood pressure, mmHg	RR on	139.120	25	23.8613	4.7723
	RR off	133.120	25	21.6262	4.3252
Peak diastolic blood pressure, mmHg	RR on	65.600	25	10.3441	2.0688
	RR off	62.880	25	11.5337	2.3067
Exercise time, seconds	RR on	417.160	25	229.7406	45.9481
	RR off	373.480	25	205.3568	41.0714
pV_{O_2}, ml/kg/min	RR on	15.260	25	3.8550	.7710
	RR off	14.032	25	3.9088	.7818
HR at AT, bpm	RR on	98.68	22	15.628	3.332
	RR off	81.64	22	18.288	3.899
AT, ml/kg/min	RR on	11.24	22	2.654	.566
	RR off	10.14	22	3.081	.657
V_E/V_{CO_2} slope (peak)	RR on	37.4080	25	9.50166	1.90033
	RR off	39.4440	25	10.33078	2.06616
V_E/V_{CO_2} slope (peak)	RR on	31.85	22	8.824	1.881
	RR off	33.71	22	9.728	2.074
Peak RER	RR on	1.1475	24	.15845	.03234
	RR off	1.1396	24	.14505	.02961
OUE slope	RR on	1501.00	24	375.6624	76.6818
	RR off	1415.79	24	463.0956	94.5290
MRT	RR on	183.83	3	73.206	42.265
	RR off	232.83	3	130.359	75.263
MRT recovery	RR on	64.30	1[a]	.	.
	RR off	64.30	1[a]	.	.
O_2 pulse (peak)	RR on	10.40	5	6.269	2.804
	RR off	10.40	5	5.983	2.676

KEY: CHF: chronic heart failure, HR: heart rate, pV_{O_2}: peak oxygen consumption, AT: anaerobic threshold, V_E/V_{CO_2} slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUE: oxygen uptake efficiency, MRT: mean V_{O_2} response time.

Table 5.4 Paired sample statistics (CHF-AF)

Group: CHF-AF (n=26)	Paired Differences					t	df	P value
	Mean	SD	SE	95% Confidence Interval				
				Lower	Upper			
Resting HR, bpm	4.3200	6.8843	1.3769	1.4783	7.1617	3.138	24	.004
Peak HR, bpm	21.800	25.9037	5.1807	11.1075	32.4925	4.208	24	.000
Rest SBP, mmHg	1.9200	13.6806	2.7361	-3.7271	7.5671	.702	24	.490
Rest DBP, mmHg	1.1200	10.2807	2.0561	-3.1237	5.3637	.545	24	.591
Peak SBP, mmHg	6.0000	22.8035	4.5607	-3.4128	15.4128	1.316	24	.201
Peak DBP, mmHg	2.7200	11.6316	2.3263	-2.0813	7.5213	1.169	24	.254
Exercise time, s	16.680	98.1269	19.625	-23.8248	57.1848	.850	24	.404
pVO_2, ml/kg/min	1.1280	2.7865	.5573	-.0222	2.2782	2.024	24	.054
HR at AT, bpm	12.045	25.688	5.477	.656	23.435	2.199	21	.039
AT, ml/kg/min	1.505	3.355	.715	.018	2.992	2.104	21	.048
VE/VCO_2 slope (peak)	-2.036	6.87222	1.3744	-4.87271	.80071	-1.481	24	.152
VE/VCO_2 slope (AT)	-1.858	4.805	1.024	-3.988	.273	-1.813	21	.084
Peak RER	.01792	.15100	.03082	-.04584	.08168	.581	23	.567
OUE slope	85.208	284.67	58.108	-34.9991	205.4158	1.466	23	.156
MRT	-49.00	69.864	40.336	-222.552	124.552	-1.215	2	.348
MRT recovery	.000	2.550	1.140	-3.166	3.166	.000	4	1.000
O_2 pulse (peak)	4.3200	6.8843	1.3769	1.4783	7.1617	3.138	24	.004

KEY: CHF: chronic heart failure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory exchange ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.5 Paired sample T tests (CHF-AF)

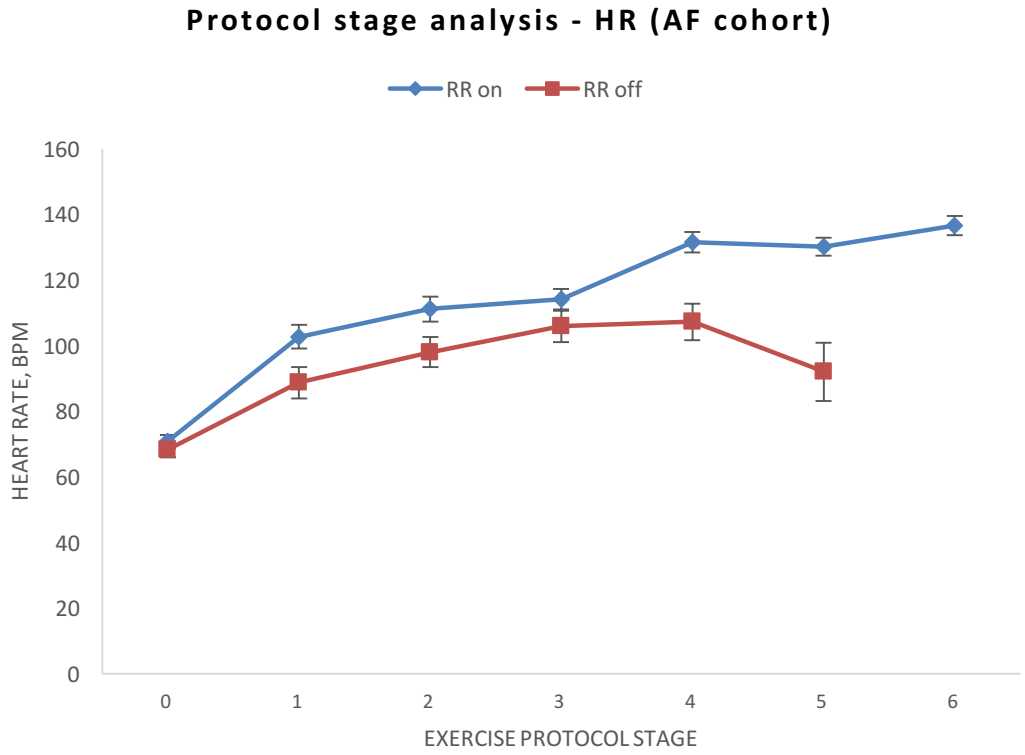


Figure 5.4A Heart rate profile in CHF AF cohort

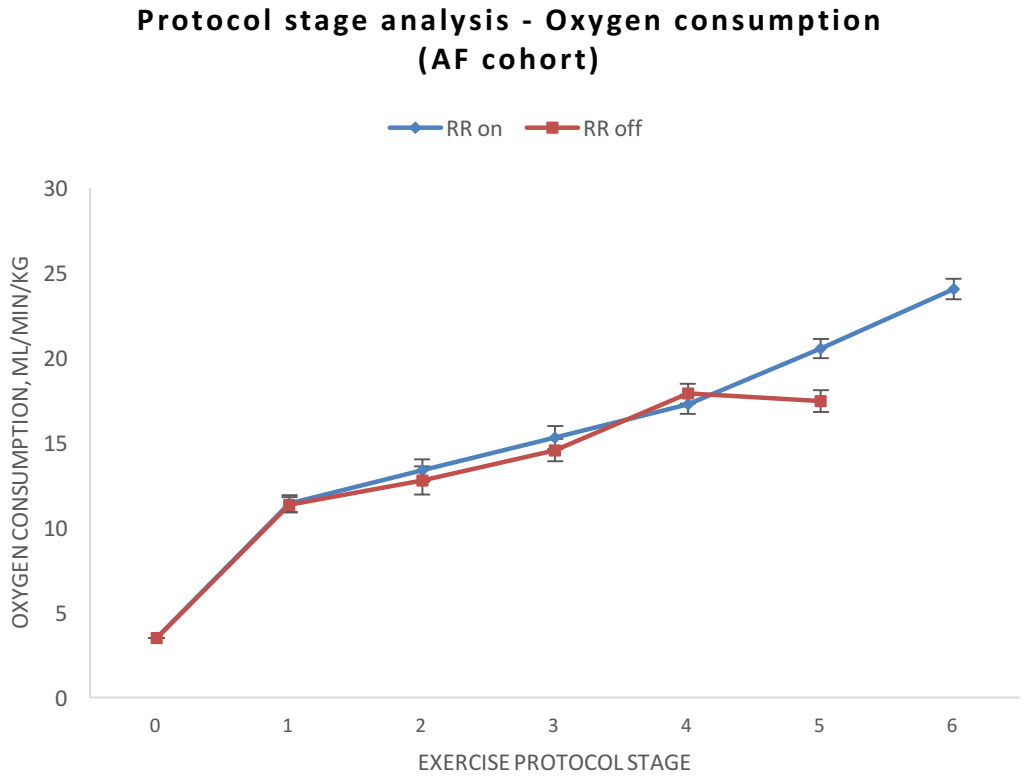


Figure 5.4B Oxygen consumption profile in CHF AF cohort

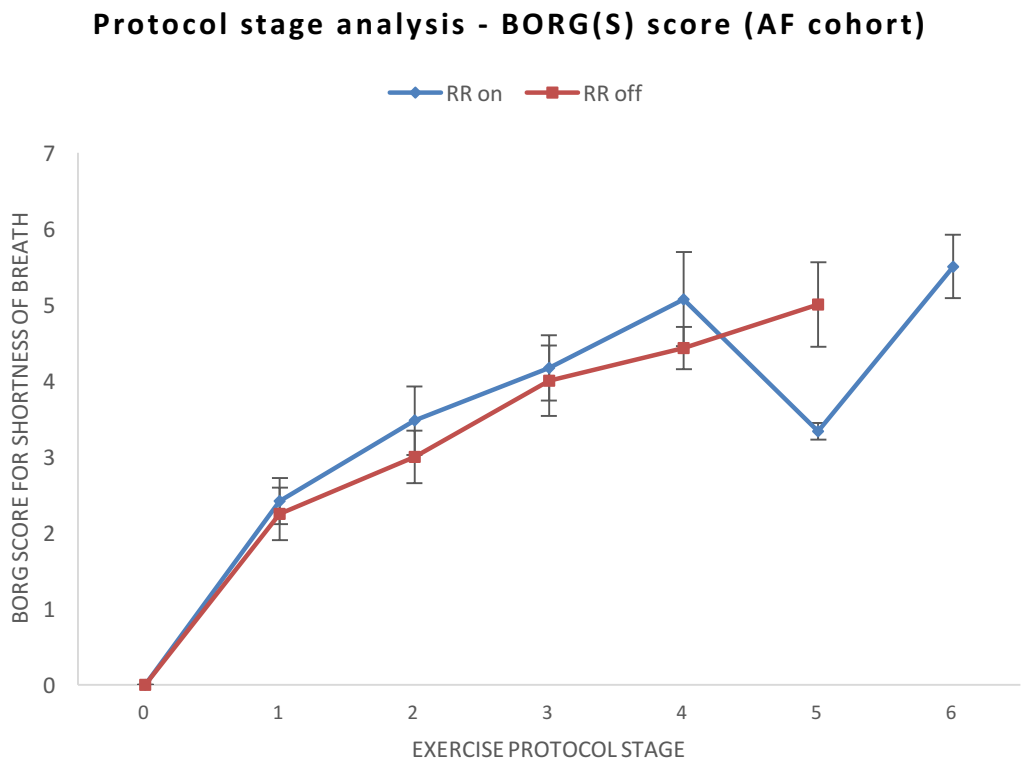


Figure 5.4C Symptom score profile (shortness of breath) for CHF AF cohort

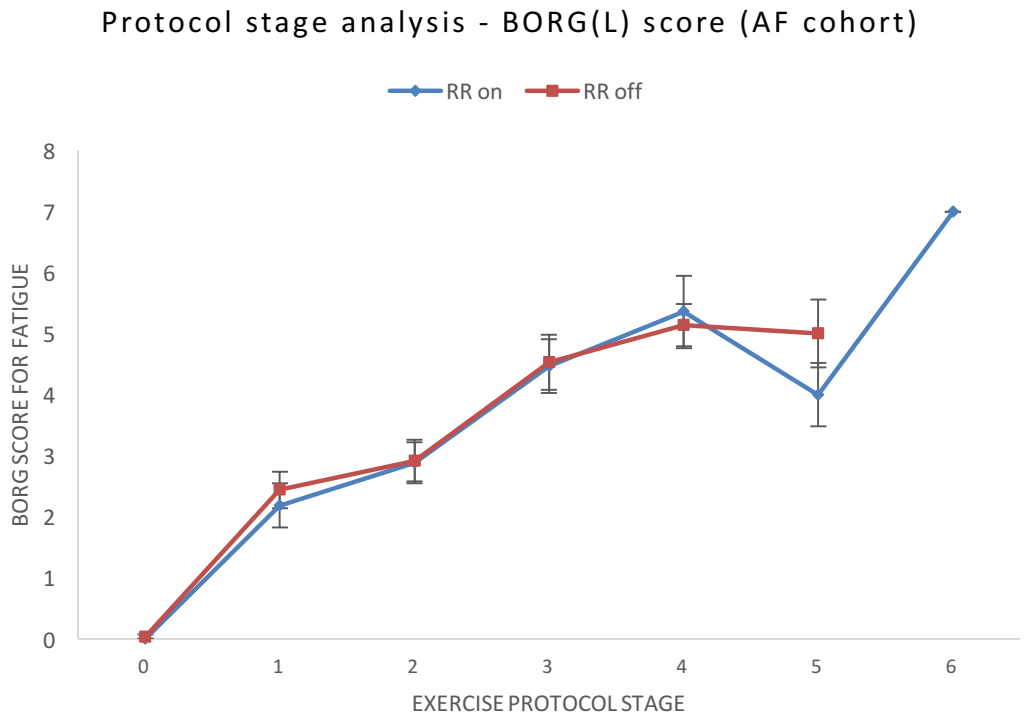


Figure 5.4D Symptom score profile (leg fatigue) for CHF AF cohort

5.4.2.3 Control sinus group

In the control subjects with sinus rhythm (n=28), there was no evidence of chronotropic incompetence with RR off. This group had a normal intrinsic heart rate rise profile, even without rate adaptive pacing (RR off). The peak exertional heart rate achieved in both tests exceeded the 80%PPHR threshold that is traditionally used to define chronotropic incompetence, especially in the absence of heart failure.

Rate adaptive pacing did result in a further increase in the peak heart rate alone (136 (30) v 126 (32) bpm, $p<0.05$), with no associated changes in any exercise variables, (pVO_2 24.2 (9.3) v 24.3 (9.7) ml/kg/min, $p=0.783$, or exercise time (620 (217) v 584 (258) s, $p=0.189$) (tables 5.6 and 5.7).

There was also no associated change in the stage-by-stage oxygen consumption achieved. However, the use of rate-adaptive pacing did result in a worsening of both shortness of breath and leg fatigue scores in the latter stages of exercise (Stages 5 to 8: ΔBorg (SOB), 2 (2) v 1 (2), $p=0.05$, ΔBorg (Leg Fatigue) 2 (2) v 1 (2), $p<0.05$) (figures 5.5B-D).

Group (Control sinus, n=28)		Mean	N	Std. Deviation	Std. Error Mean
Resting HR, bpm	RR on	62.393	28	9.7841	1.8490
	RR off	62.964	28	10.9019	2.0603
Peak HR, bpm	RR on	136.786	28	29.5263	5.5800
	RR off	125.857	28	32.0910	6.0646
Resting systolic BP, mmHg	RR on	132.462	26	17.9270	3.5158
	RR off	135.846	26	18.3732	3.6033
Resting diastolic BP, mmHg	RR on	71.077	26	10.0754	1.9760
	RR off	72.615	26	10.8188	2.1217
Peak systolic blood pressure, mmHg	RR on	167.308	26	27.9997	5.4912
	RR off	169.923	26	27.3202	5.3579
Peak diastolic blood pressure, mmHg	RR on	70.462	26	16.5632	3.2483
	RR off	69.077	26	11.9897	2.3514
Exercise time, seconds	RR on	620.357	28	216.7993	40.9712
	RR off	583.679	28	257.6517	48.6916
pV_{O_2}, ml/kg/min	RR on	24.218	28	9.3391	1.7649
	RR off	24.346	28	9.6745	1.8283
HR at AT, bpm	RR on	102.48	25	20.514	4.103
	RR off	98.08	25	19.313	3.863
AT, ml/kg/min	RR on	16.36	25	5.128	1.026
	RR off	17.52	25	6.056	1.211
V_E/V_{CO_2} slope (peak)	RR on	32.4714	28	7.41284	1.40090
	RR off	33.0171	28	8.42776	1.59270
V_E/V_{CO_2} slope (peak)	RR on	27.11	25	7.055	1.411
	RR off	27.22	25	6.347	1.269
Peak RER	RR on	1.1293	28	.13018	.02460
	RR off	1.1364	28	.16473	.03113
OUE slope	RR on	2164.53	28	840.3618	158.8135
	RR off	2189.64	28	757.2785	143.1122
MRT	RR on	183.35	18	104.638	24.663
	RR off	159.23	18	100.300	23.641
MRT recovery	RR on	81.49	13	28.582	7.927
	RR off	80.95	13	31.110	8.628
O_2 pulse (peak)	RR on	13.50	18	3.073	.724
	RR off	13.72	18	3.953	.932

KEY: HR: heart rate, BP: blood pressure, pV_{O_2}: peak oxygen consumption, AT: anaerobic threshold, V_E/V_{CO_2} slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUE: oxygen uptake efficiency, MRT: mean V_{O_2} response time.

Table 5.6 Paired samples statistics (Controls sinus)

Group: Control sinus (n=28)	Paired Differences					t	df	P value
	Mean	SD	SE	95% Confidence Interval				
				Lower	Upper			
Resting HR, bpm	-.571	5.4530	1.030	-2.6859	1.5430	-.55	27	.584
Peak HR, bpm	10.92	20.421	3.859	3.0100	18.8471	2.83	27	.009
Rest SBP, mmHg	-3.38	13.899	2.726	-8.9989	2.2297	-1.24	25	.226
Rest DBP, mmHg	-1.53	10.012	1.963	-5.5828	2.5058	-.783	25	.441
Peak SBP, mmHg	-2.61	16.625	3.260	-9.3306	4.0998	-.802	25	.430
Peak DBP, mmHg	1.384	16.769	3.288	-5.3886	8.1578	.421	25	.677
Exercise time, s	36.67	144.14	27.23	-19.2131	92.5703	1.347	27	.189
pVO_2, ml/kg/min	-.128	2.0109	.3800	-.9083	.6512	-.338	27	.738
HR at AT, bpm	4.400	15.281	3.056	-1.908	10.708	1.440	24	.163
AT, ml/kg/min	-1.15	3.710	.742	-2.687	.375	-1.55	24	.132
VE/VCO_2 slope (peak)	-.545	4.8855	.9232	-2.44015	1.34872	-.591	27	.559
VE/VCO_2 slope (AT)	-.108	5.295	1.059	-2.293	2.078	-.102	24	.920
Peak RER	-.007	.11718	.0221	-.05258	.03830	-.323	27	.750
OUE slope	-25.1	369.56	69.84	-168.409	118.1949	-.359	27	.722
MRT	24.12	101.21	23.85	-26.212	74.456	1.011	17	.326
MRT recovery	.545	30.817	8.547	-18.077	19.168	.064	12	.950
O_2 pulse (peak)	-.222	3.318	.782	-1.872	1.428	-.284	17	.780

KEY: HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory exchange ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.7 Paired samples T test (Controls sinus)

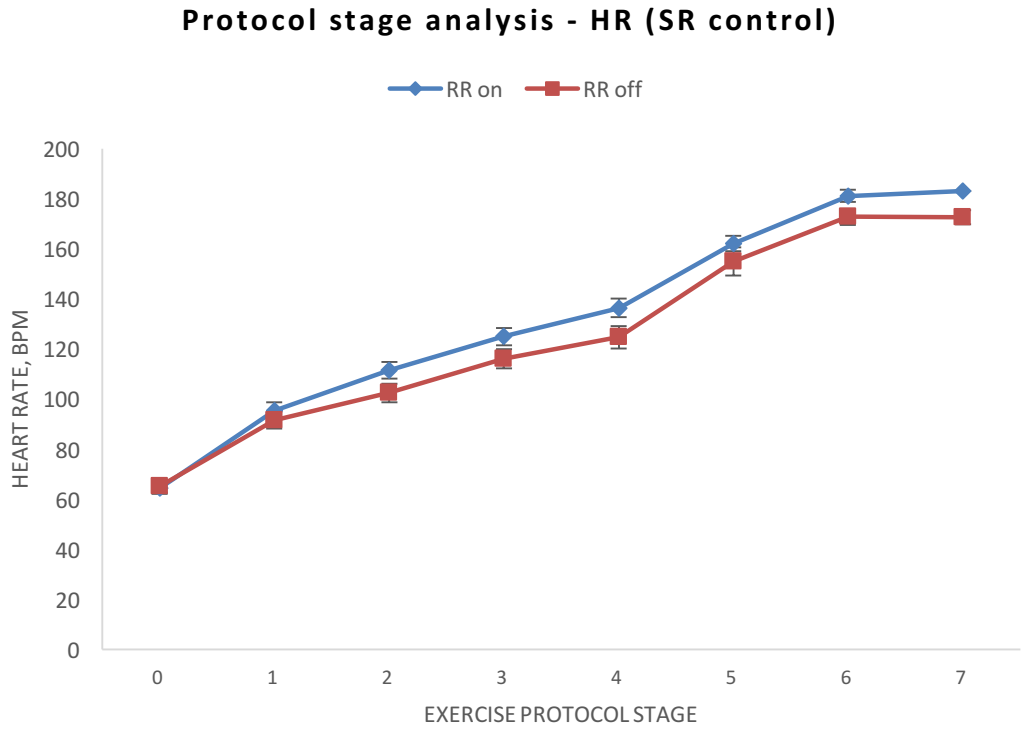


Figure 5.5A Heart rate profile in sinus controls

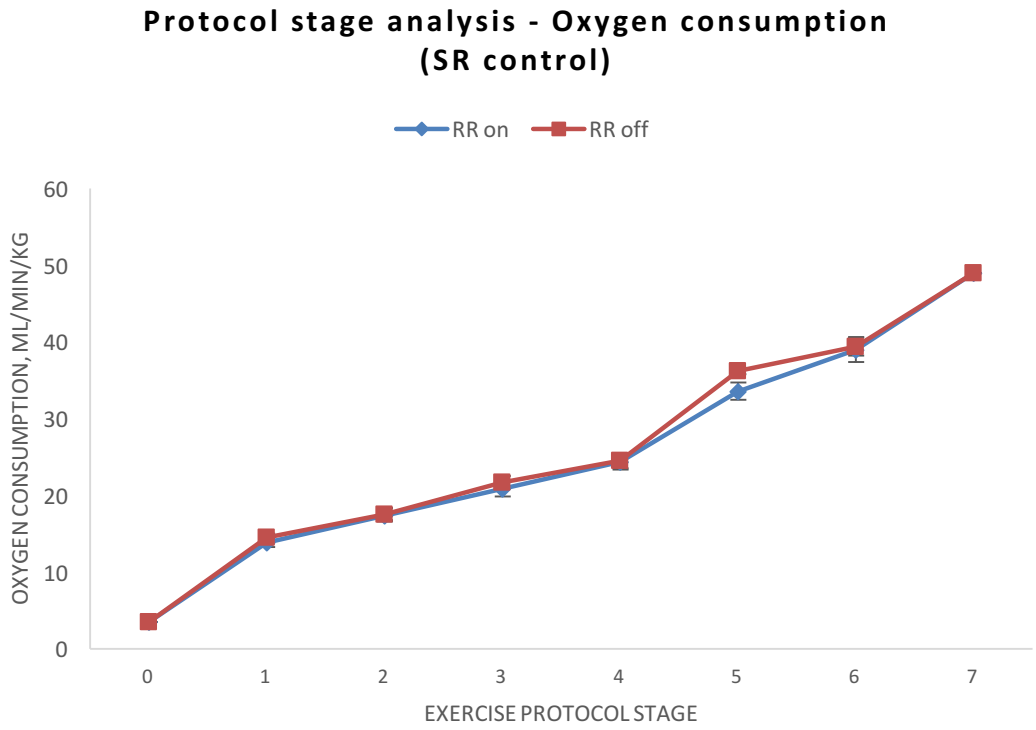


Figure 5.5B Oxygen consumption profile in sinus controls

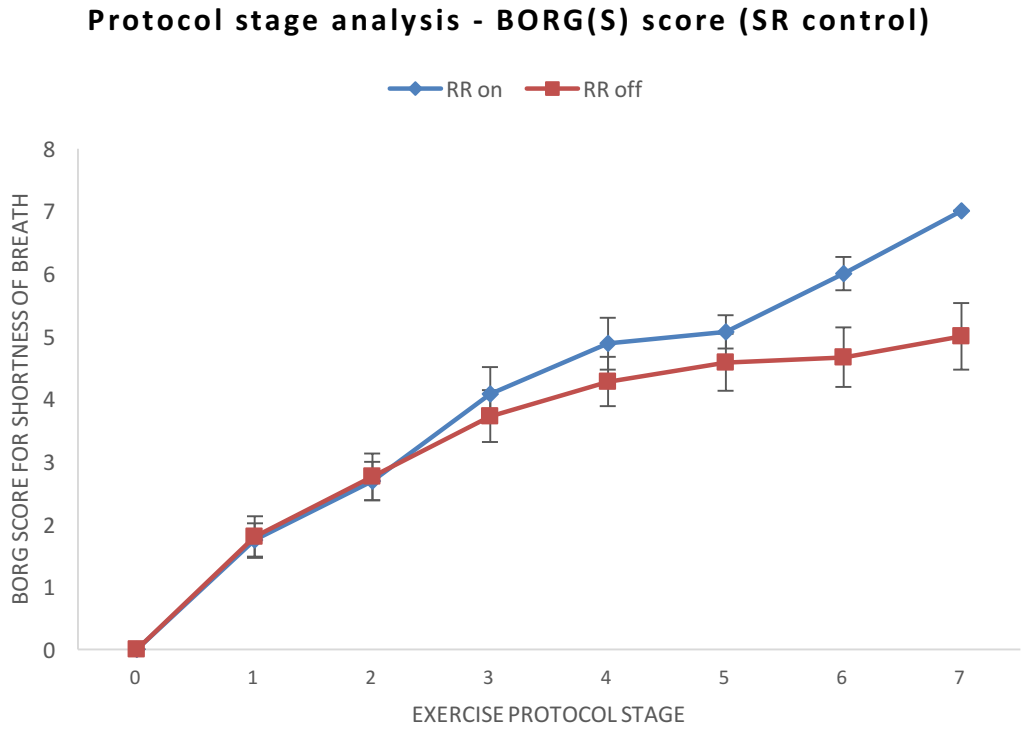


Figure 5.5C Symptom score profile (shortness of breath) in sinus controls

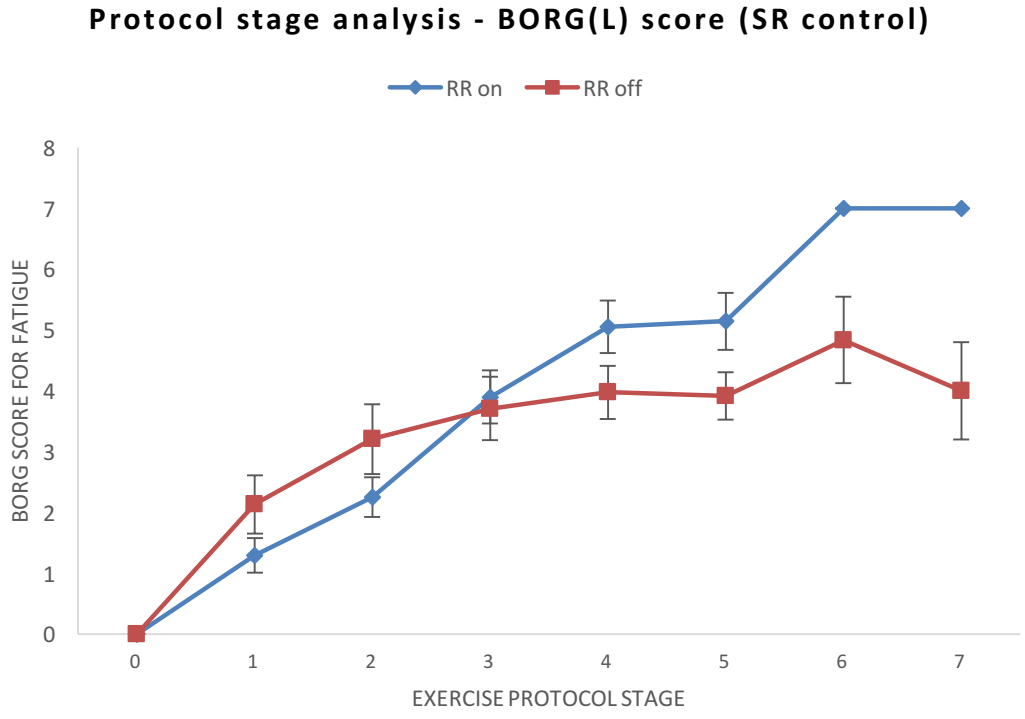


Figure 5.5D Symptom score profile (leg fatigue) in sinus controls

5.4.2.4 Control AF group

In the controls with AF (n=11), there was a blunted HRR with RR off (peak HR: 104 (42) bpm) compared to 80% PPHR (114 bpm). The higher HRR with rate adaptive pacing (RR on) led to no increase in peak V_{O_2} and no change in exercise time (tables 5.8 and 5.9).

Although rate adaptive pacing did increase the heart rate rise during the earlier stages of exercise (HRR (Stage 0 to Stage 4): 76 v 65 bpm, $p<0.05$), this equalised during the latter stages (HRR(Stage 5 to Stage 8): 21 v 30 bpm, $p=0.960$) in those that reached stage 8, and overall there was no difference in profiles when comparing RR on and RR off ($p=0.075$), even though the RR on tests achieved a higher mean peak heart rate overall (figure 5.6A).

Oxygen consumption followed an identical pattern, with an increase seen in the earlier stages (ΔV_{O_2}(Stages 0-4), 19.1(5) v 22.8(5) ml/kg/min, $p=0.052$), and no change from mid exercise to peak (ΔV_{O_2}(Stages5-8), 8.1 v 10.5 ml/kg/min, $p=0.770$). There were no obvious differences in the self-reported symptom profiles with regards to either shortness of breath or leg fatigue (figures 5.6B-D).

Group (Controls AF, n=11)		Mean	N	Std. Deviation	Std. Error Mean
Resting HR, bpm	RR on	64.636	11	8.9249	2.6910
	RR off	60.818	11	4.6004	1.3871
Peak HR, bpm	RR on	133.636	11	27.8039	8.3832
	RR off	103.818	11	42.4919	12.8118
Resting systolic blood pressure, mmHg	RR on	126.364	11	14.3337	4.3218
	RR off	127.273	11	12.7208	3.8355
Resting diastolic blood pressure, mmHg	RR on	68.182	11	9.8165	2.9598
	RR off	69.091	11	7.0065	2.1125
Peak systolic blood pressure, mmHg	RR on	162.182	11	23.7563	7.1628
	RR off	148.545	11	20.8632	6.2905
Peak diastolic blood pressure, mmHg	RR on	70.273	11	7.6693	2.3124
	RR off	64.909	11	10.6344	3.2064
Exercise time, seconds	RR on	482.545	11	332.6723	100.3045
	RR off	450.455	11	269.8834	81.3729
pVO_2, ml/kg/min	RR on	20.173	11	8.8446	2.6667
	RR off	17.500	11	9.0916	2.7412
HR at AT, bpm	RR on	109.50	8	23.078	8.159
	RR off	80.50	8	22.947	8.113
AT, ml/kg/min	RR on	14.29	8	4.934	1.744
	RR off	12.30	8	6.430	2.273
VE/VCO_2 slope (peak)	RR on	34.8545	11	8.45321	2.54874
	RR off	38.3818	11	13.56922	4.09127
VE/VCO_2 slope (peak)	RR on	29.75	8	11.853	4.191
	RR off	30.75	8	6.798	2.403
Peak RER	RR on	1.0991	11	.19076	.05752
	RR off	1.2191	11	.16688	.05032
OUE slope	RR on	1624.27	11	512.7249	154.5924
	RR off	1426.36	11	678.1133	204.4589
MRT	RR on	117.55	2	26.234	18.550
	RR off	115.00	2	29.840	21.100
O_2 pulse (peak)	RR on	12.00[b]	2	.000	.000
	RR off	17.00[b]	2	.000	.000

KEY: HR: heart rate, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.8 Paired samples statistics (Controls AF)

Group: Controls AF (n=26)	Paired Differences					t	df	P value
	Mean	SD	SE	95% Confidence Interval				
				Lower	Upper			
Resting HR, bpm	3.8182	9.1304	2.7529	-2.3157	9.9520	1.387	10	.196
Peak HR, bpm	29.818	35.2925	10.641	6.1083	53.528	2.802	10	.019
Rest SBP, mmHg	-.9091	20.7145	6.2457	-14.825	13.007	-.146	10	.887
Rest DBP, mmHg	-.9091	8.3121	2.5062	-6.4932	4.6750	-.363	10	.724
Peak SBP, mmHg	13.6364	26.5604	8.0083	-4.2072	31.479	1.703	10	.119
Peak DBP, mmHg	5.3636	5.9038	1.7801	1.3974	9.3298	3.013	10	.013
Exercise time, s	32.0909	154.436	46.564	-71.660	135.84	.689	10	.506
pVO_2, ml/kg/min	2.6727	4.3267	1.3045	-.2340	5.5794	2.049	10	.068
HR at AT, bpm	29.000	38.038	13.448	-2.800	60.800	2.156	7	.068
AT, ml/kg/min	1.987	5.118	1.809	-2.291	6.266	1.098	7	.308
VE/VCO_2 slope (peak)	-3.52727	15.6213	4.7100	-14.021	6.9672	-.749	10	.471
VE/VCO_2 slope (AT)	-1.000	11.161	3.946	-10.331	8.331	-.253	7	.807
Peak RER	-.12000	.20586	.06207	-.25830	.01830	-1.933	10	.082
OUE slope	197.909	418.232	126.10	-83.063	478.88	1.569	10	.148
MRT	2.550	3.606	2.550	-29.851	34.951	1.000	1	.500
O_2 pulse (peak)	1.000	4.243	3.000	-37.119	39.119	.333	1	.795

KEY: HR: heart rate, BP: blood pressure, pVO_2: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, RER: respiratory exchange ratio, OUE: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table 5.9 Paired samples T test (Controls AF)

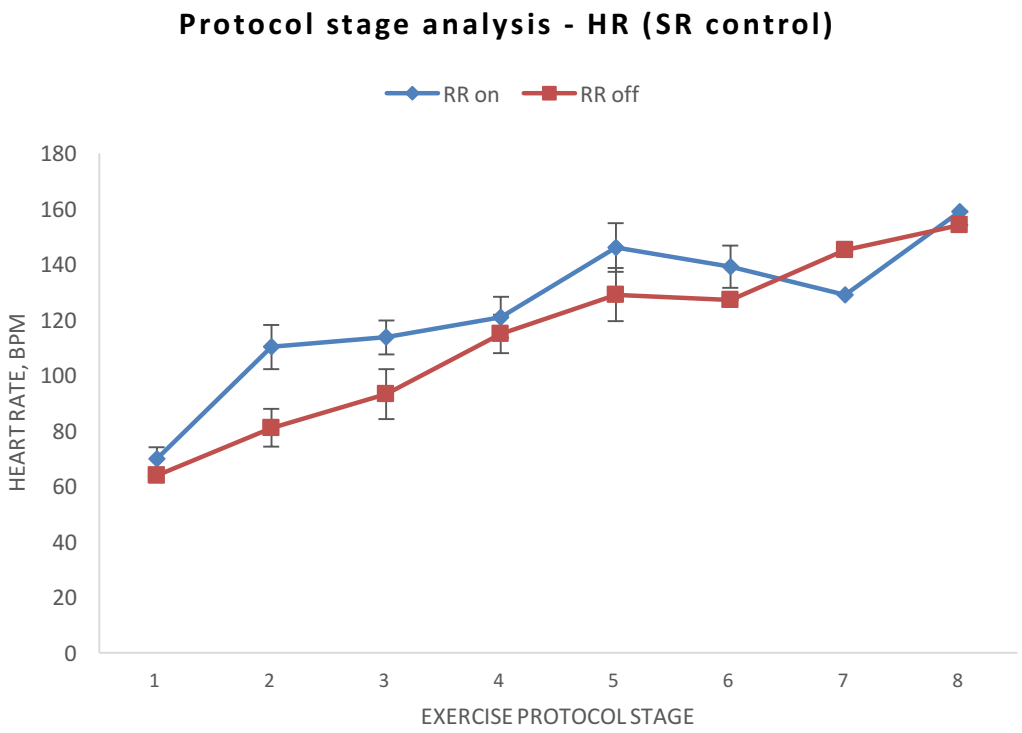


Figure 5.6A Heart rate profile in AF controls

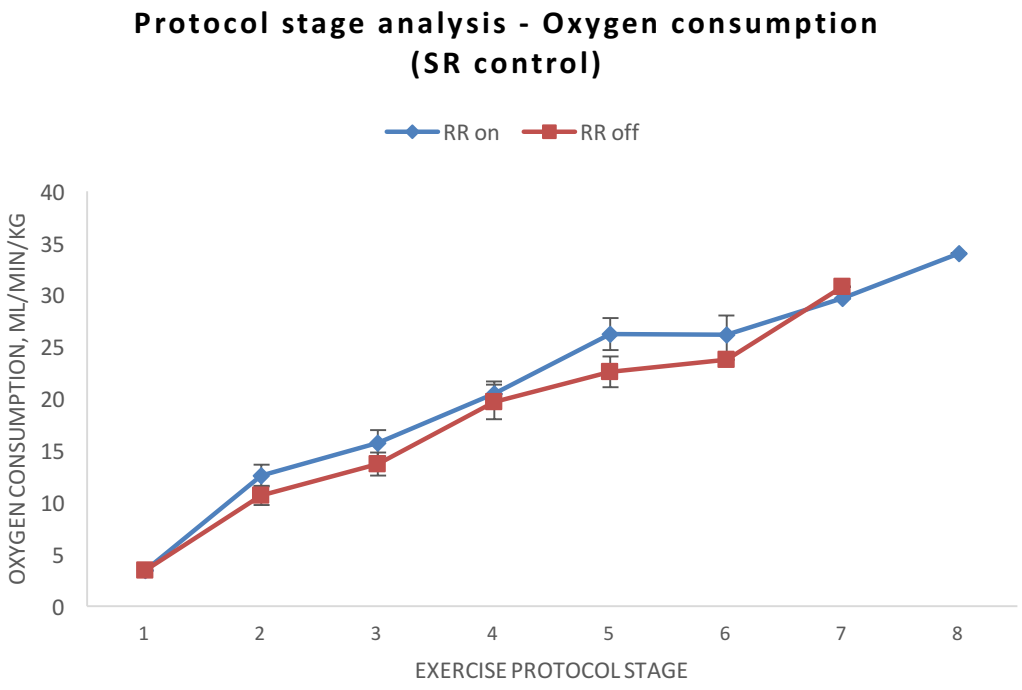


Figure 5.6B Oxygen consumption profile in AF controls

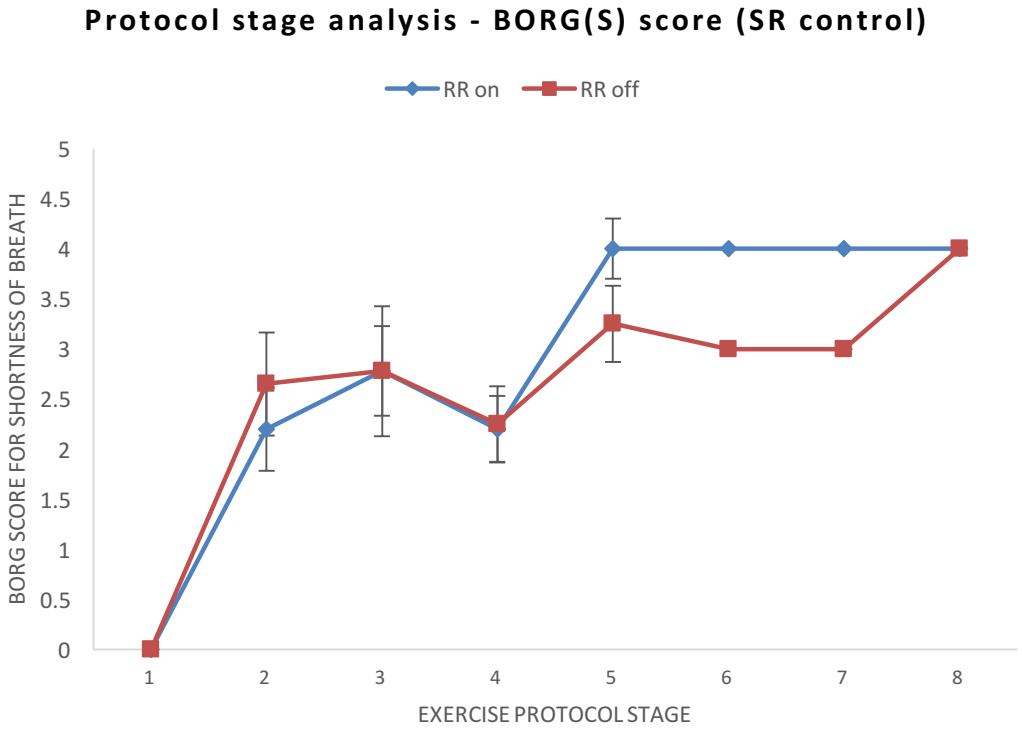


Figure 5.6C Symptom score profile (shortness of breath) in AF controls

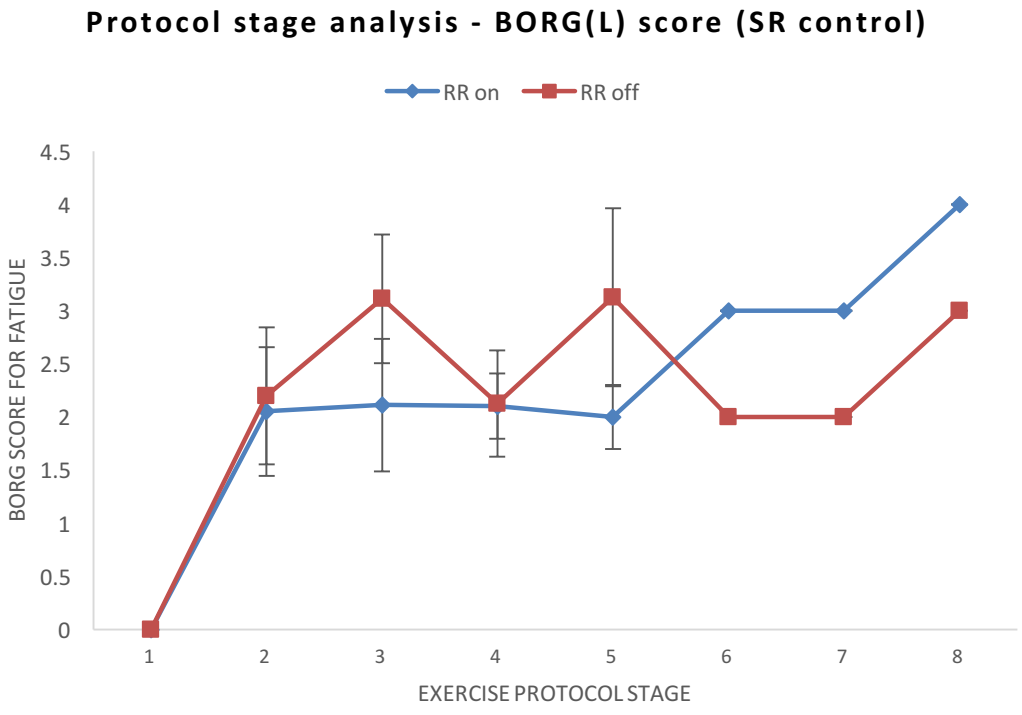


Figure 5.6D Symptom score profile (leg fatigue) in AF controls

5.5 Discussion

If impaired HRR is the limiting factor for exercise capacity, then any increase in the HR response should increase cardiac output, especially in those with CI, and hence improve blood supply to skeletal muscles, allowing longer exercise time, higher peak oxygen consumption and less fatigue. This is an important area for research and has huge clinical implications because exercise intolerance due to breathlessness and fatigue is a cardinal feature of CHF and remains a problem for many patients despite optimal medical and device therapy.

This study shows that in CHF, no improvement in functional capacity is seen by increasing the peak HR. This is a clinically important finding that has never been demonstrated in a randomised controlled trial before.

5.5.1 Correcting choronotropic incompetence: sinus rhythm

The results from this study conclusively prove that rate adaptive pacing can successfully improve the heart rate rise and thus restore ‘chronotropic competence’. However, in the CHF sinus cohort, the results of the CPX tests showed that this increase in the heart rate response throughout the period of activity did not result in any improvement in exercise time, peak oxygen consumption, subjective symptom scores, ventilation measurements or measures of submaximal activity (AT).

The peak RER achieved by both arms of this crossover study was lower than expected, with a mean value less than 1.1 (figure 5.7). Greater encouragement from the supervising team may induced patients to try harder and reach a higher RER, however this would have introduced an additional potential bias with regards to the level of motivation given, in what context and by whom.

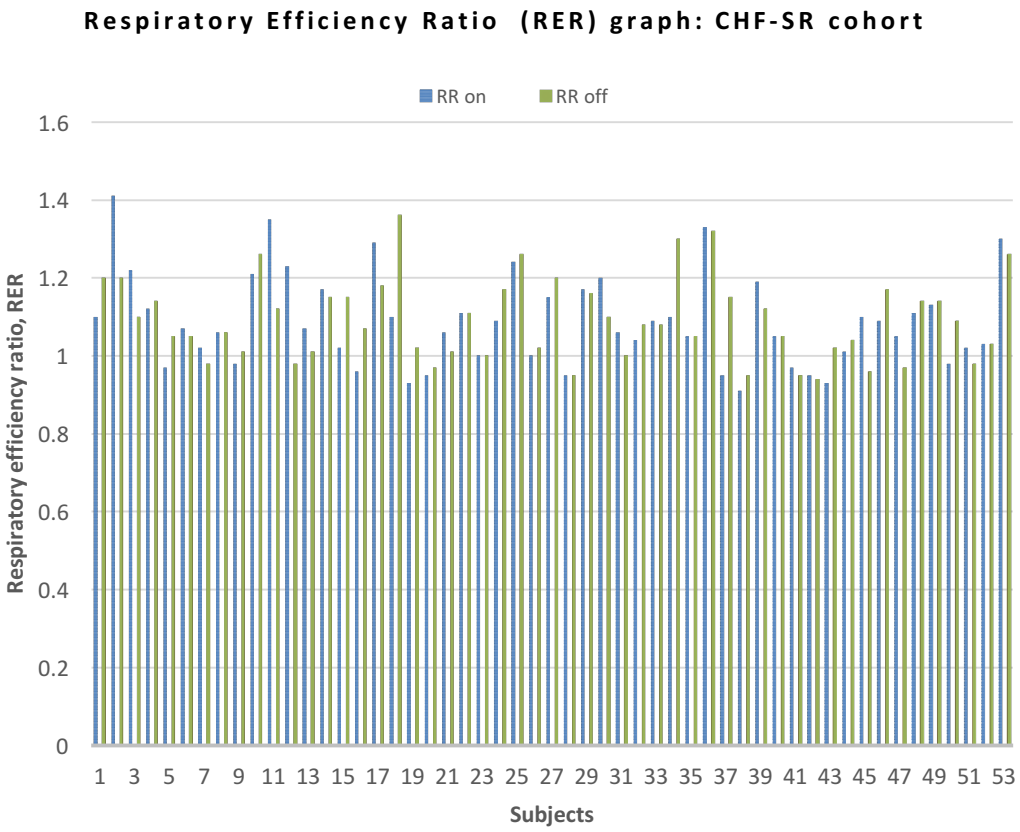


Figure 5.7 RER in the CHF-SR cohort

The purpose of this investigation was to look at the role of the heart rate throughout exercise in a reproducible manner, rather than just the parameters at peak exercise. Thus despite the possible sub-maximal nature of the CPX tests, all patients reached and exceed their anaerobic threshold,

and reported similar symptom scores in both arms. This ensures the validity of my results from the two study arms as being both comparable to one another and also relevant to the general HF population as a whole, given that these patients rarely achieve or aim to reach their absolute peak exercise capacity during usual activities of daily living. The primary concern of this study was whether increasing the rate and magnitude of heart rate rise altered any exercise capacity measures, at either sub-maximal or peak exertion levels. There was no change in either the rate or magnitude of increase in oxygen consumption at each stage of the exercise protocol, nor any change in reported symptoms.

This was a large cohort with varied co-morbidities and medications, and thus it was truly representative of the actual CHF population as seen in the clinical setting. These results are firm evidence that increasing the heart rate throughout exercise in CHF (with sinus rhythm) does not have any effect on either the exercise capacity or patient symptoms.

5.5.2 Correcting chronotropic incompetence: atrial fibrillation

Atrial fibrillation frequently co-exists with CHF, and its presence results in further alteration of the cardiac haemodynamics at rest and during any activity. The irregularly irregular nature of AF at rest, also extends to the way in which cardio-acceleration occurs in these patients during exercise or activity. Thus it is important to study this group separately in order to determine any patterns within the chaotic heart rate response and also to be able to derive useful and practical clinical conclusions.

Intrinsic heart rate response during activity (RR off) followed a different pattern to the sinus CHF group discussed above. Whereas the response in sinus CHF remained linear despite being blunted, in CHF-AF there was a blunted linear rise in heart rate initially, followed by a plateauing of the heart rate response during sub-maximal exercise. Prior to symptom limited termination of exercise a drop in the heart rate response was recorded. This corresponded with a plateauing in the level of oxygen consumption, both occurring within the final stage of the exercise protocol.

The use of rate adaptive pacing (RR on) resulted in a correction of the heart rate response, which then followed a linear increase to its maximum level achieved at peak exercise. The change in heart rate response (due to 'RR on') resulted in an increase in the peak oxygen consumption, with no change in exercise time, symptom perception or ventilatory efficiency measures (V_E/V_{CO_2} slope) at AT or peak. The peak RER achieved in this subgroup was also lower than expected given that the protocol aim was to reach peak exercise (Figure 5.8). However, this does not alter the validity of the results obtained, as my interest lies in the journey the heart rate takes throughout increasing levels of activity rather than simply the destination or peak exercise parameters. Altering the rate and magnitude of heart rate rise did not improve functional capacity.

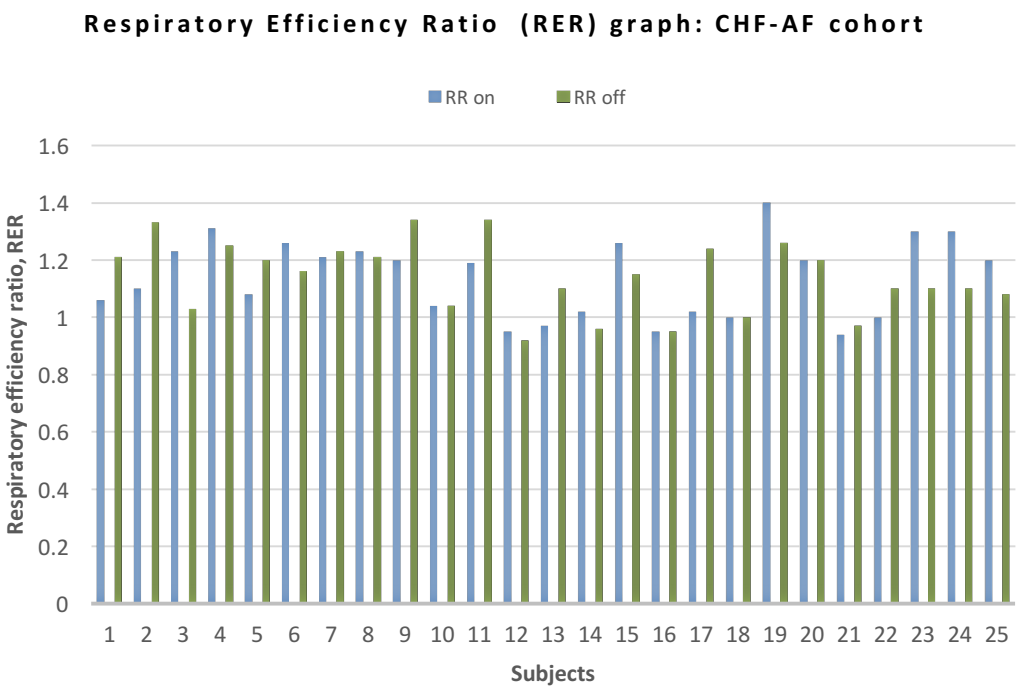


Figure 5.8 RER profile in the CHF-AF cohort

Rate adaptive pacing in the presence of AF, led to an increase in oxygen consumption with no change in overall exercise time, implying 'wasted' metabolic effort. A lower peak heart rate may actually improve the efficiency of the entire system, with similar exercise time but with lower skeletal muscle oxygen consumption.

5.5.3 Correcting chronotropic incompetence in control subjects

The sinus controls did not have chronotropic incompetence and thus did not receive any additional benefit from the increase in heart rate in terms of exercise capacity, symptoms or oxygen consumption.

Unexpectedly, the control subjects with AF did exhibit a blunted heart rate response to activity. The presence of intrinsic impairment in HRR during the incremental CPX test (RR off) suggests that the CI may be more prevalent in the AF population than previously thought, even in the absence of CHF.

Previous studies have shown that controls with chronotropic incompetence might benefit from rate adaptive pacing, although the majority of the evidence is derived from studies that excluded AF.

Rate adaptive pacing (RR on) resulted in an increase in the peak heart rate, which did not lead to any change in peak oxygen consumption, anaerobic threshold, V_E/V_{CO_2} slopes, symptom scores or exercise time.

5.5.4 Clinical relevance

Heart rate rise and exercise capacity are linked closely such that the exact nature of the relationship is difficult to ascertain. On the one hand, a limitation to heart rate rise in controls results in reduced exercise time and increased fatigue, which improves with pacemaker treatment to increase activity related cardio-acceleration. On the other hand, at moderate levels of activity or early termination of exercise due to other causes such as respiratory or skeletal muscle factors, the associated rise in heart rate is reduced. This is particularly the case in patients with HF who often have co-morbidities, such that the limitation to heart rate rise might also be due to peripheral limitation in the skeletal muscles for example.

In this crossover RCT, pacing algorithms in conjunction with built-in movement sensors were utilised to increase heart rate rise. Our data confirm that pacemakers are capable of correcting CI and increasing heart rates throughout exercise. However, the evidence on how to program pacemakers, in terms of the heart rate range, response to exercise and whether or not to activate rate adaptive (RR) modes, is both conflicting and also based on studies in non-CHF sinus cohorts for the most part. It is generally assumed that the origins of the exercise intolerance in HF patients might be similar to those in patients without HF.

5.5.5 Minimising bias

The purpose of this double blind randomised controlled crossover trial was to assess the impact of acutely correcting CI on exercise capacity in four different patient cohorts. The crossover study design allowed each subject to act as their own control, and thus minimized the effects of differences in characteristics or co-morbidities to act as confounders. The double-blind arrangement removed opportunity for bias with regards to exercise duration or motivation.

The relationship between heart rate rise and exercise capacity is both controversial and heavily debated in the clinical setting. Thus in order for this RCT to have far-reaching and general clinical relevance, it was important to keep the inclusion criteria broad and exclusion criteria to a minimum. The

cohort demographics reveal that this strategy was successful in recruiting subjects with a spread of co-morbidities, past medical history and medications into the study. The crossover design, and unselected patient selection, meant that this would still allow for valid comparisons to be made, and the main advantage to this was that any findings would be immediately and directly relevant to a contemporary heart failure population.

The only differentiation that was made was based on the underlying cardiac rhythm. The reason for this was that heart rate is known to vary and respond differently in AF and sinus rhythm, and clinically the treatment approach differs dependent on whether or not the patient is in AF. Different medications, therapies and procedures are utilised, and thus it was felt that the exertional response to altering the heart rate rise would need to be assessed separately.

5.5.6 Current clinical approach

To complicate matters further, pharmacological agents that lower the resting HR and induce or worsen CI are actually proven to improve outcomes for patients with CHF due to LVSD. Trials involving either beta-blockers or sinus node I_f channel antagonists all show that the magnitude of resting heart rate reduction corresponds to the degree of increased survival and clinical improvements.

Due to the current lack of evidence, some CHF patients with pacemakers may be subjected to higher mean heart rates as a result of attempts to increase their exercise capacity by increasing the peak paced HR achieved, whereas patients without pacemakers are treated with maximal heart rate lowering medications in order to ensure resting heart rate is at the lowest tolerated level, in line with grade 1 evidence and international guidance, despite the fact that these agents also reduce the peak exertional HR.

5.6 Conclusion

Our data provide clear evidence that ‘treating’ chronotropic incompetence in the CHF population, by increasing the exercise related heart rate response and peak heart rate achieved, does not improve exercise capacity or symptoms.

However, this study does not clarify the entire role of heart rate on exercise capacity in heart failure. A question still remains as to whether heart rate limitation per se leads to impaired exercise capacity in patients with HF. Thus, further work is necessary in order to investigate whether reducing the resting and peak heart rate pharmacologically worsens exercise capacity.

Chapter 6: The influence of reducing the heart rate on exercise capacity in chronic heart failure (Opt-RATE 2 Study)

6.1 Abstract

Reduction of the heart rate (HR) at rest is associated with improvements in survival for both patients with heart failure and the general population as a whole,(333) however it is currently unknown whether acute pharmacological HR reduction in heart failure results in a worsening of functional capacity or patient symptoms. The aim of this double blind randomised placebo controlled trial was to ascertain whether an acute reduction in HR has any effect on exercise capacity in stable CHF.

A total of 40 HFrEF patients with pacemakers, 26 in sinus rhythm and 14 with concurrent atrial fibrillation (AF), were recruited into this interventional study. Each subject performed two exercise tests one week apart, starting either at their paced or intrinsic resting heart rate, or an iatrogenically lowered starting heart rate. This was done on the day of the visit, and the heart rate profiles were returned to normal following each test. No other interventions were performed and each patient acted as their own control.

Lowering the resting heart rate in either the sinus (65 (13) v 57 (9) bpm) or the AF (65 (14) v 49 (18), bpm) cohort, did not result in any change in the

peak oxygen consumption (pVO_2 - Sinus: 17.4 (5.7) v 17.2 (5.7) ml/kg/min, p=0.584; AF: 14.8 (4) v 14.4 (4) ml/kg/min, p=0.203) or exercise time.

Thus, acutely reducing the resting heart rate in the context of either sinus rhythm or atrial fibrillation is well tolerated, and does not lead to any reduction in functional capacity. This is a novel finding which has far reaching clinical implications for pharmacological and device treatment strategies in the context of significant systolic heart failure.

6.2 Introduction

Exercise intolerance due to breathlessness and fatigue is a key feature of the heart failure syndrome. This often persists despite optimal medical therapy, and objective measures of peak exercise capacity such as exercise time or peak oxygen consumption are powerful and reproducible predictors for prognosis. Controversy exists around the role and impact of heart rate rise (HRR) and peak heart rate (PHR) on exertional capability.

A limitation of either HRR or PHR is termed chronotropic incompetence (CI), which is considered by some to be both a key causal factor and a prognostic marker. However, in the modern era of medical therapy where pharmacological interventions with proven benefits to mortality and morbidity may impact the heart rate profile and cause iatrogenic CI, it remains unclear whether this definitely causes exercise limitation and also whether treatment should be directed to ‘correct’ the heart rate response.

Resting heart rate is a strong predictor for outcomes and slower heart rates have been shown to be strongly associated with increased survival, in both CHF and controls. In contrast the use of pacemaker therapy to increase the resting heart rate results in worsening of outcomes and cardiac function.(334)

In health, the overall heart rate rise during exercise depends on the baseline resting heart rate, and the peak heart rate achieved at maximal exercise. The first interventional study of this investigation into the role of the heart rate on exercise capacity in heart failure (chapter 5: OPT-Rate 1) revealed that augmenting cardio-acceleration and thus increasing the peak heart rate did not result in any change in exercise capacity or symptoms.

Whether the acute reduction in resting heart rate has any effect on exercise capacity in CHF has hitherto remained unexplored. This is an important area for investigation, as the main opposition for aggressive heart rate reduction in this context is the potential impact it could have on symptoms and functional capacity. Thus the aim of this double blind placebo controlled randomised crossover interventional trial was to focus solely on investigating the effect of acutely reducing the resting heart rate on overall exercise performance within a mixed heart failure cohort.

6.3 Methods

This is a proof of concept study whereby the aim is to establish the feasibility of acute heart rate lowering in a population with pacemakers, and to explore the relationship between baseline heart rate reduction and functional capacity. A paced population was chosen for this study in order to ensure safe baseline heart rate reduction, without the risk of excessive or symptomatic bradycardia. This study was approved by the National Research Ethics Service (REC reference 09/H1305/60, Appendix B).

6.3.1 Study design

The study was designed to investigate the effect of reducing the resting heart rate on overall exercise performance. The crossover interventional design of this investigation negated the need for a control cohort, as each subject was randomised to undergo two symptom-limited maximal treadmill-based cardio-pulmonary exercise (CPX) tests, and thus acted as their own controls. The only independent variable that was altered between tests was the resting heart rate. A pre-test consent appointment and familiarisation test were attended by all participants (described in chapter 3).

6.3.1.1 Study population

A total of 40 subjects were enrolled into this double blind placebo controlled randomised trial. All subjects were approached at routine outpatient pacemaker follow-up appointments, and all had a diagnosis of moderate-severe systolic heart failure (ejection fraction less than 45%), a pacing device in situ for a clinical indication, and stable pacemaker device and lead variables for at least six months. The cohort was divided into those with permanent atrial fibrillation (n=14) and those in sinus rhythm (n=26).

6.3.2 Inclusion and exclusion criteria

The inclusion criteria for this study were confirmed CHF due to left ventricular systolic dysfunction (LVSD, moderate-severe; left ventricular ejection fraction <45%, and symptoms of breathlessness or fatigue on exertion), on optimal medical therapy and stable symptoms. They must have had their pacemaker for at least 6 months with stable lead variables and no change in medications or other invasive cardiac procedures for at least three months. All subjects were capable of performing a peak exercise test on a treadmill and giving informed written consent, which was obtained in all subjects.

Subjects with co-morbidities 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 were excluded.

Furthermore, any subjects enrolled into the sinus CHF cohort could not currently be taking the sinus node blocking agent, ivabradine. Other exclusion criteria included any contraindications to ivabradine use such as severe hepatic impairment, significant renal impairment (creatinine clearance <15ml.min^{-1}), and long QT syndrome.

6.3.3 Exercise testing

Each subject was invited back to the exercise laboratory at least one week following the baseline visit and familiarisation test, for two further exercise tests at least one week apart. At the start of each visit, the subject was double blind randomised to either their 'normal' resting heart rate or a lowered resting heart rate, as detailed below. Following this, a maximal symptom-limited treadmill-based exercise test was performed.

A screen was used to separate the heart rate and electrocardiographic monitor, which was only observed by the unblinded technician, from the metabolic cart, which was monitored by the blinded investigator. Resting, peak and recovery blood pressures were measured using a standard manual cuff sphygmomanometer.

6.3.4 Randomisation and heart rate lowering procedures

Both the supervising physician and all subjects were blinded to the allocation order, pacemaker settings and heart rate profiles during the two tests.

6.3.4.1 CHF sinus cohort

In this cohort, heart rate lowering was achieved via a sinus node blocking agent, ivabradine. This is an I_f channel blocker that specifically targets the sinus node leading to a slower heart rate, with no known peripheral effects.(335)(336) The agent is approved and licensed for use in patients with heart failure at the doses used in this study.

In order to ensure double blinding, subjects were randomised by the research pharmacist to receive either a single 7.5mg dose of ivabradine or matching placebo.

Capsules containing ivabradine or placebo were formulated and encapsulated to be exactly identical in shape, size, colour, weight, taste and consistency. The capsule was taken in the presence of the primary investigator and the research technician. The time to peak plasma ivabradine concentration after a single oral dose is between 60 -120 minutes.(337) Thus, the capsule was taken two hours prior to the exercise test.

Immediately prior to the start of exercise, the pacing device was programmed to a minimum base rate of 40 beats per minute. All other pacemaker settings were standardised during the two tests. At the end of each test the pacing device was returned to its original settings.

6.3.4.2 CHF-AF cohort

In the AF cohort, lowering of the resting heart rate was achieved by reducing the programmed pacemaker base rate to 30 beats per minute thus allowing the lower intrinsic heart rate to come through. No other pacemaker settings were altered and the pacing device was returned to its original settings at the end of each test.

6.3.5 Cohort size calculation

Heart rate related changes on exercise capacity have not been fully investigated in heart failure patients, and remain poorly understood. However, the results from the previous RCT were useful for establishing the minimum sample size required in this study. The primary outcome was peak oxygen consumption, which is known to be both reliable and reproducible, with a coefficient of variation percentage of 9.73 in this laboratory. As before, a mean of 15 (2) ml/kg/min was expected in CHF subjects in sinus rhythm, and a mean of 13 (2) ml/kg/min for CHF with atrial fibrillation (mean difference 15% lower), with higher peak heart rates achieved in the AF cohort (mean difference 23% higher).

By factoring in the results obtained from the previous study, the predicted group size required in order to demonstrate a clinically important change of 2.0 ml/kg/min with 80% power, and a two sided alpha of 0.05 was revised. Thus, a minimum of 12 subjects was needed in the atrial fibrillation CHF group, and a minimum of 20 in the sinus CHF group. To allow for drop-outs and to confidently suggest equivalence, the recruitment aims were 15 atrial fibrillation subjects and 25 sinus subjects.

6.4 Results

6.4.1 Baseline characteristics

A total of 40 subjects with CHF and pacemakers were recruited to take part in this randomised controlled trial of intrinsic/usual resting heart rate compared to a lowered resting heart rate.

6.4.2 Comparing demographics between groups

The cohort was divided into two groups: sinus rhythm (n=26) and atrial fibrillation (n=14). Baseline characteristics for each group separately are shown in table 6.1 (parametric data as mean (SD); non-parametric as median±IQR).

	Sinus N=26	**AF N=14**
Height, cm	171 (6)	171 (8)
Weight, kg	86 (17)	86 (21)
Age, years	72 (10)	76 (10)
NYHA class	2	2
Ejection fraction, %	36 (9)	37 (7)
Heart rate drop, bpm	8 (10)	16 (14)
Peak predicted HR, bpm	148 (10)	145 (10)
LVID (diastole), mm	56 (8)	51 (9)
LVID(systole), mm	49 (9)	40 (9)
EA ratio	0.8 (0.2)	-
E wave DT, ms	265 (44)	-
Furosemide dose, mg	53/31/12/4 [14/8/3/1]	29/43/14/14 [4/6/2/2]
Diabetes mellitus	27% (7)	50% (n=7)
Ischaemic heart disease	42% (11)	43% (6)
Hypertension	23% (6)	43% (6)
PMH: CABG	19% (5)	21% (3)
PMH: PCI	19% (5)	21% (3)
PMH: Valve surgery	4% (1)	29% (4)
ACEi/ARB, ramipril equivalent, mg	10±5	10±5
Beta-blocker, bisoprolol equivalent, mg	5±4.25	7.5±7
Aldosterone antagonist	42% (11)	43% (6)
Statin	77% (20)	64% (9)
Calcium channel blocker	0% (0)	7% (1)
Digoxin	11% (3)	29% (4)
Amiodarone	4% (1)	0% (0)
Anticoagulation	19% (5)	86% (12)
Antiplatelets	46% (12)	29% (4)

Normally distributed variables shown as mean (SD).

KEY: AF: atrial fibrillation, NYHA: New York Heart Association, HR: heart rate, LVID: left ventricular internal diameter, DT: deceleration time, PMH: past medical history, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotension II receptor blocker.

Table 6.1 Baseline group demographics

6.4.3 Comparing intrinsic heart rate rise (placebo/base rate 60) to lowered resting heart rate (ivabradine/base rate 30)

6.4.3.1 CHF-SR group

Ivabradine resulted in HR reduction at rest (RHR: 65 (13) v 57 (9) bpm, $p<0.05$), at submaximal exercise (HR at anaerobic threshold: 97 (19) v 92 (11) bpm, $p<0.05$) and at peak (PHR: 113 (23) v 106 (22) bpm, $p<0.05$), with no effect on the overall heart rate rise (HRR: 48 (22) v 49 (24) bpm, $p=0.569$). There was no change in exercise time (534 (242) v 554 (251) s, $p=0.267$) or oxygen consumption at the anaerobic threshold (AT: 14.4 (4.5) v 14.6 (3.2) ml/kg/min, $p=0.708$) and at peak (pVO_2: 17.4 (5.7) v 17.2 (5.7) ml/kg/min, $p=0.584$)(figure 6.1). The symptom score profiles and all other measured CPX parameters were similar in both tests.

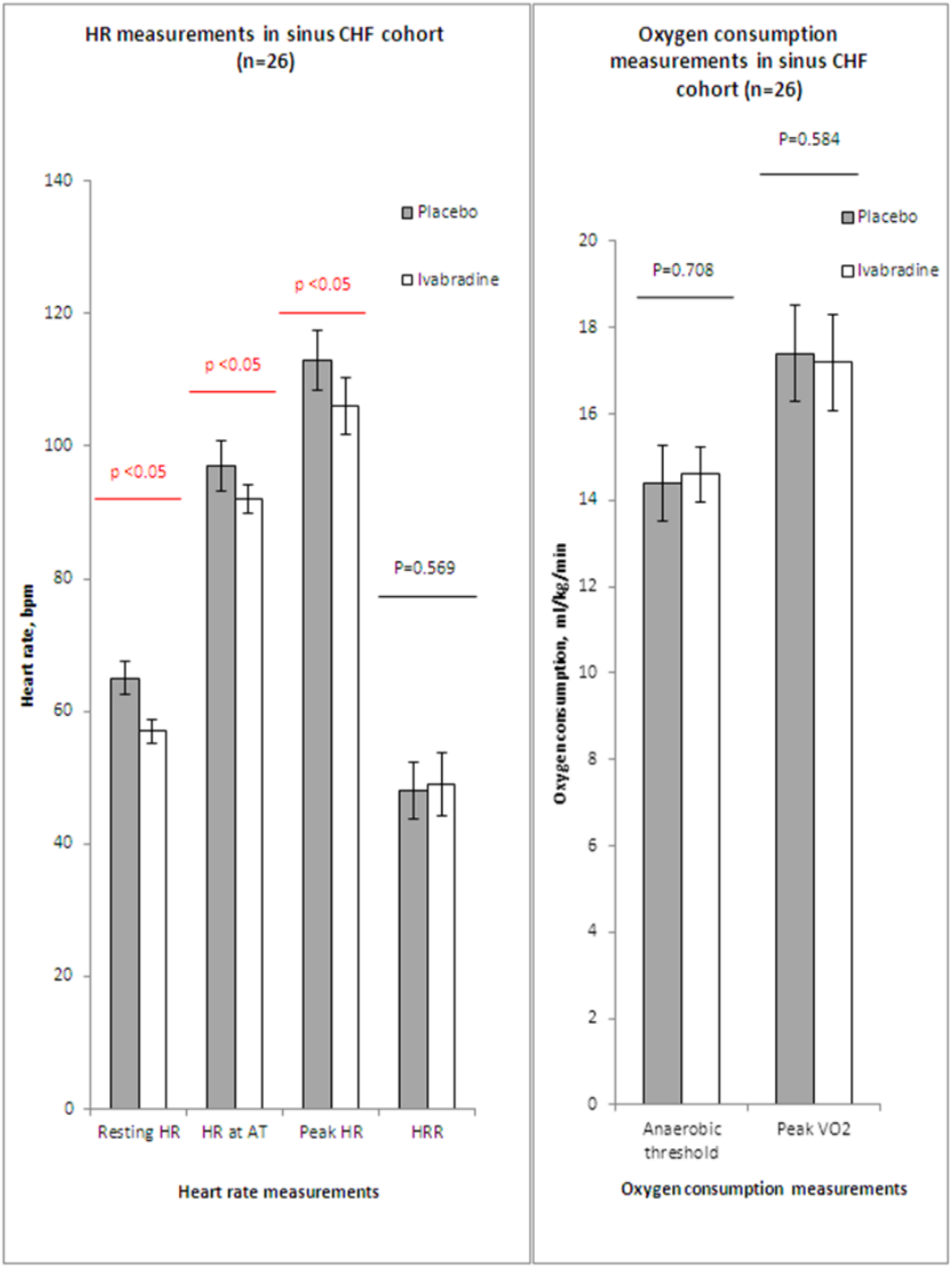


Figure 6.1 Heart rate and oxygen consumption measurements in sinus CHF cohort

6.4.3.1 CHF-AF group

In the CHF-AF group (n=14), starting at a lower resting heart rate by reducing the pacemaker base rate (BR 60 v BR 30) resulted in significant differences in the resting heart rate (65 (14) v 49 (18) bpm, $p<0.05$) and heart rate rise (47 (23) v 59 (20), $p<0.05$). There was no change in the chronotropic index (0.61 (0.3) v 0.66 (0.3), $p=0.600$).

The lower resting heart rate group (BR 30) achieved a better exercise time (BR 60 v BR 30, 434 (225) v 482 (235) s, $p<0.05$) with no change in peak oxygen consumption (pVO_2, 14.4 (4) v14.8 (4) ml/kg/min, $p=0.203$).

There was no difference in heart rate at submaximal exercise (HR at AT, BR 60 v BR 30, 107 (24) v 98 (22) bpm, $p=0.137$), however the anaerobic threshold was lower (AT, 12.8 (3) v 11.5 (3) ml/kg/min, $p<0.05$). A higher peak RER was achieved at the lower base rate setting (BR 60 v BR 30, 1.08 (0.1) v 1.14 (0.1), $p<0.05$)(figure 6.2). All other measured CPX variables were similar within both two settings.

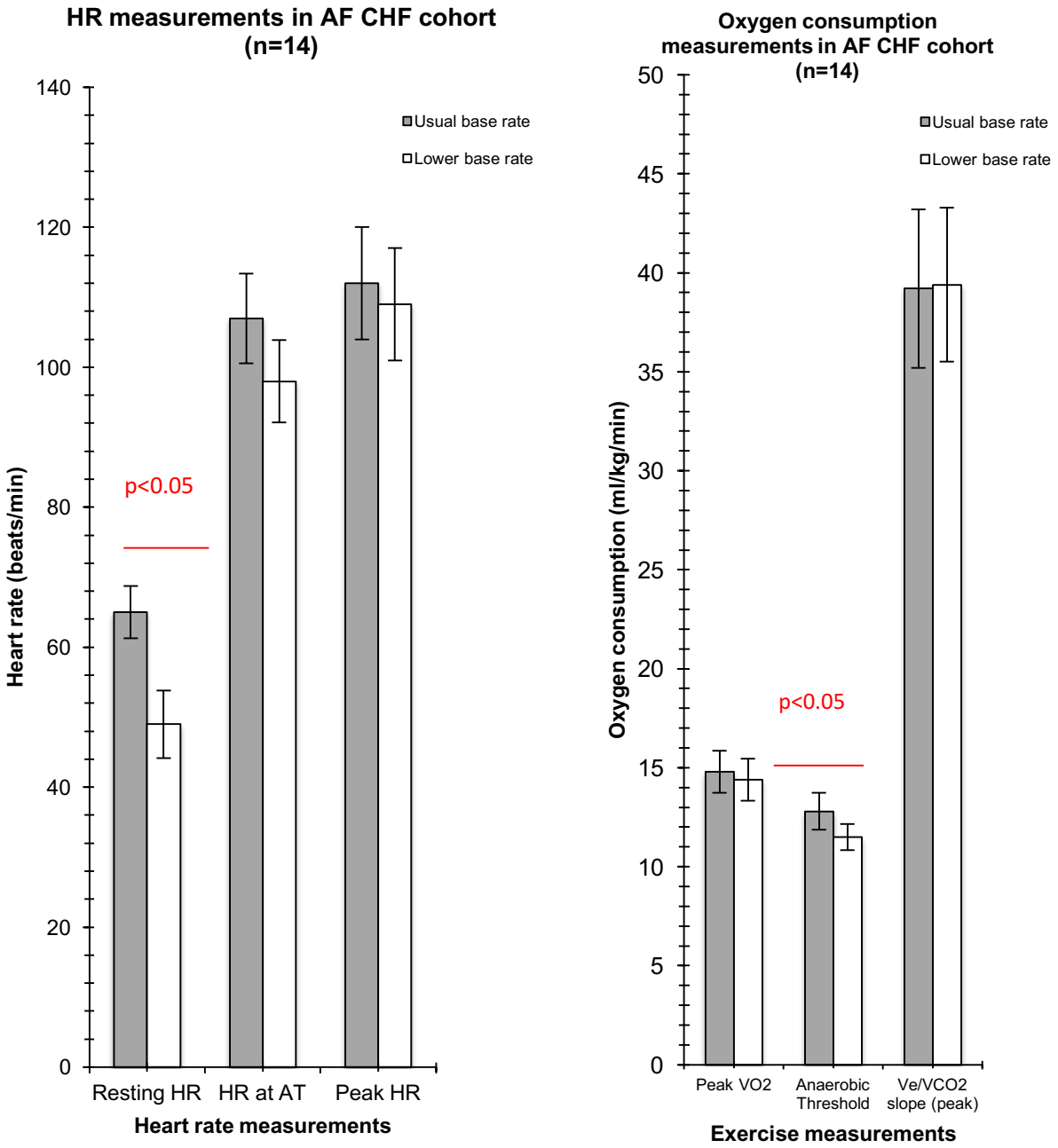


Figure 6.2 Heart rate and oxygen consumption measurements in AF CHF cohort

Starting at a lower resting rate (base rate 30) with the CHF-AF cohort resulted in lower heart rates being achieved throughout the exercise test, compared to the higher base rate ($p<0.05$). The same peak oxygen consumption was achieved in both tests, however starting at a lower resting rate allowed subjects to tolerate higher levels of 'shortness of breath' and 'leg fatigue' (figures 6.3A-D).

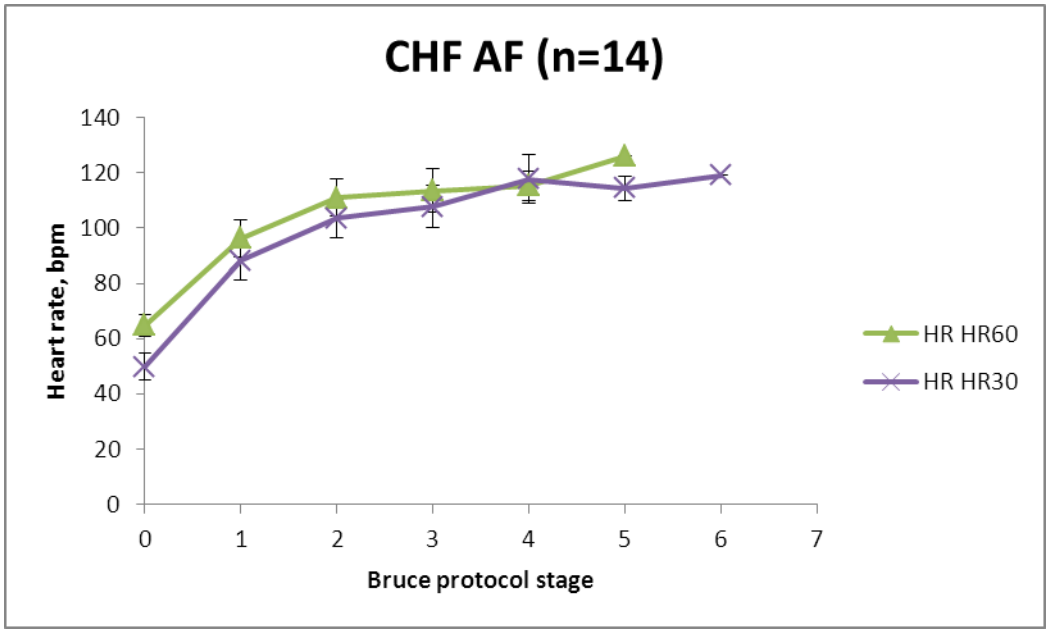


Figure 6.3A AF heart rate profile

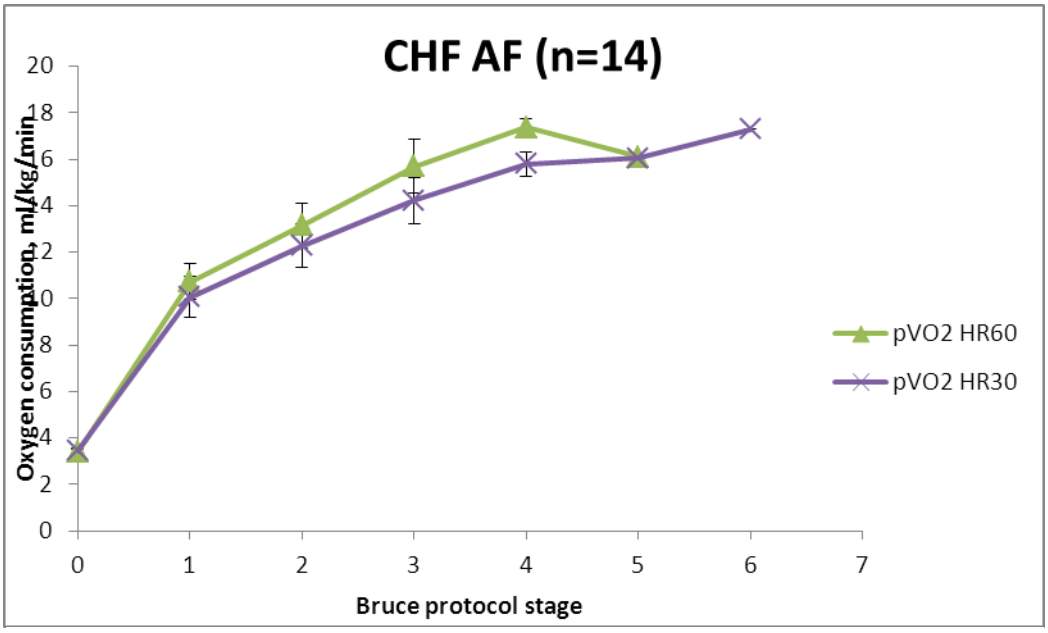


Figure 6.3B AF oxygen consumption profile

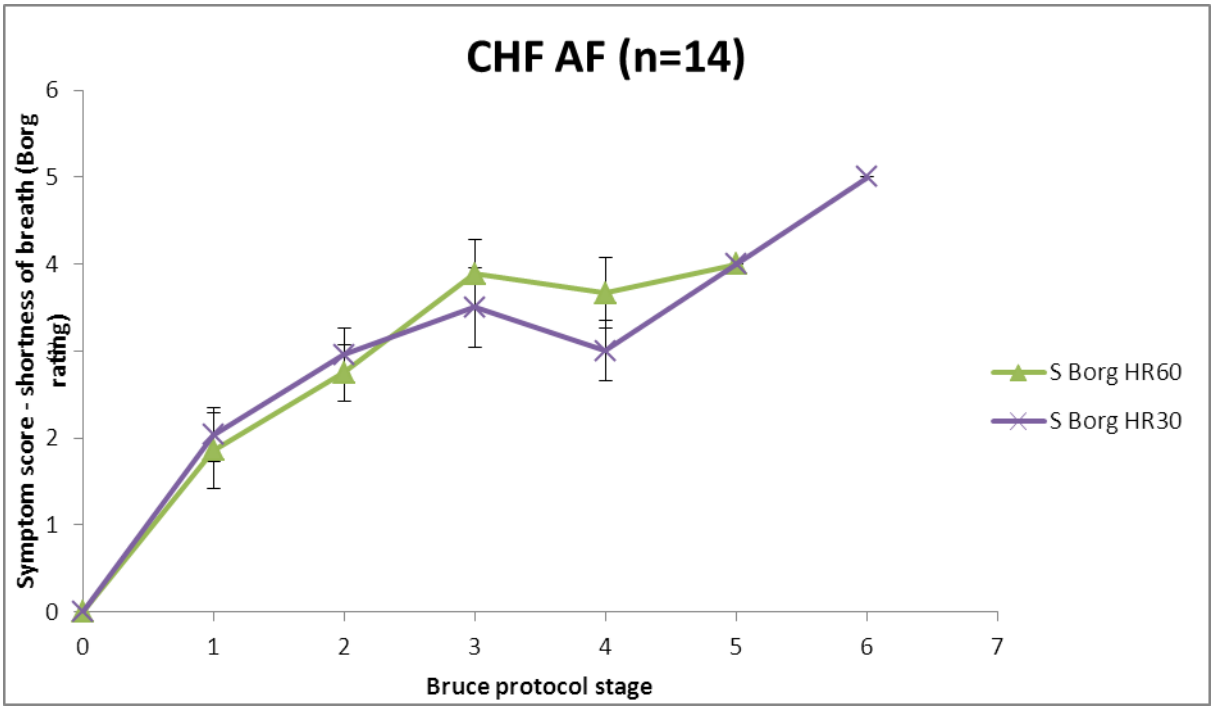


Figure 6.3C AF symptom score profile (shortness of breath)

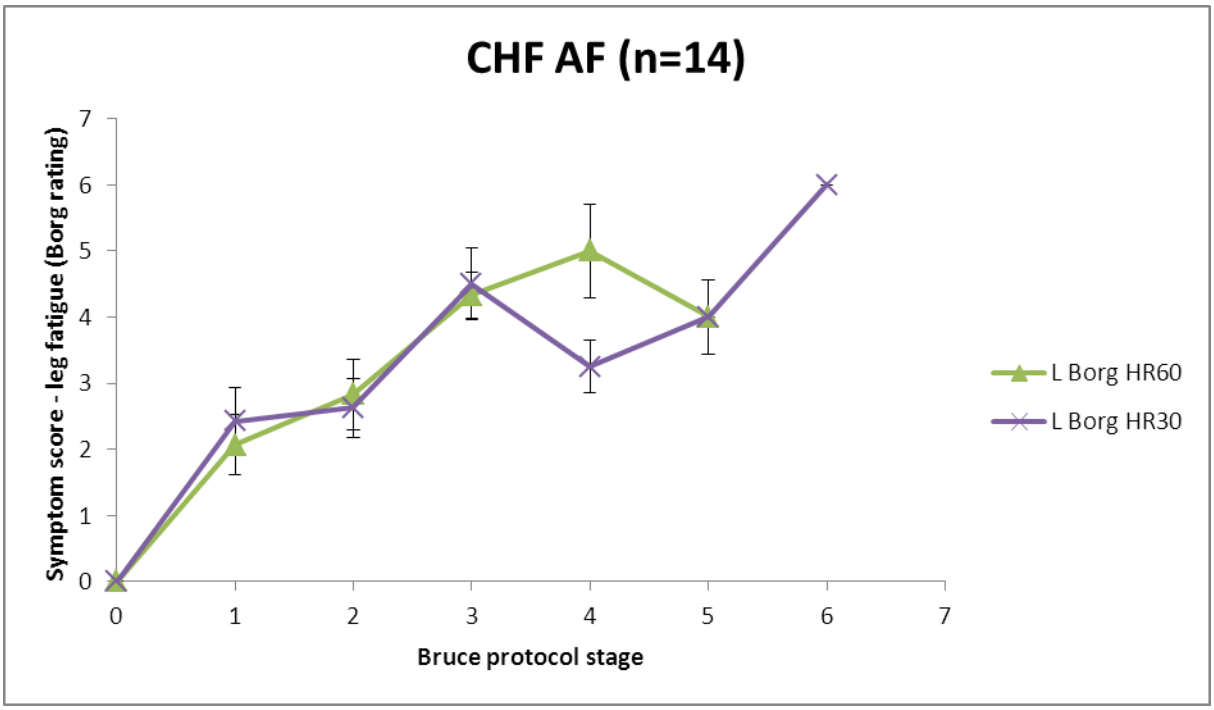


Figure 6.3D AF symptom score profile (leg fatigue)

6.5 Discussion

This study showed that lowering the resting and peak heart rates did not result in any worsening of peak oxygen consumption, reported symptoms or exercise time.

Acute administration of ivabradine in the CHF cohort in sinus rhythm, resulted in a reduction in both the resting and peak heart rates, such that the heart rate rise (HRR) remained unchanged. This blunting of the heart rate profile, and iatrogenic worsening of CI did not impact oxygen consumption or exercise time.

These data conclusively prove that while CI is a marker of poor prognosis in CHF, it does not cause exercise tolerance. Correcting CI (Chapter 5, OPT-Rate 1) or worsening CI in this context makes no difference to either the peak oxygen consumption achieved or the total exercise time. Ivabradine use was safe in the acute setting in a paced CHF cohort, regardless of the pre-dose resting HR, and did not alter functional capacity or symptoms.

In addition, acute reduction in the pacemaker baseline heart rate in the CHF-AF cohort did not result in any worsening of symptoms or exercise capacity. Surprisingly, this resulted in a higher HRR, and allowed subjects to tolerate higher levels of shortness of breath and fatigue, so achieving both a higher peak RER and a better exercise time with the lower base rate, yet still reaching the same peak oxygen consumption level.

Thus lowering the resting heart rate in a cohort of AF patients with LVSD, resulted in an increase in exercise efficiency, allowing the participants to achieve significantly longer exercise times with the same level of skeletal muscle oxygen consumption at peak exercise.

Lowering the resting heart rate in AF did not result in fatigue, and actually allowed subjects to tolerate exercise for longer, at higher reported symptom score levels. These results demonstrate that heart rate reduction in a CHF cohort with atrial fibrillation does not affect peak oxygen consumption or symptoms, and CI may actually represent an adaptation that increases both exercise capacity and tolerance.

6.5.1 Clinical implications

Resting heart rate is a prognostic factor in heart failure due to LVSD. It is also a recognised risk factor for cardiovascular events in heart failure secondary to systolic dysfunction. This situation exists because the resting heart rate is a marker of underlying neuro-hormonal activity, excessive activation of which is associated with adverse outcomes.(264) Thus reducing the resting HR is seen as the aim of pharmacological therapy and a marker of treatment success.

The extent of resting heart rate reduction has been shown to be prognostically significant in trials involving beta-blockers and sinus node blocking agents. Conversely, every beat per minute increase in the baseline

heart rate in heart failure is associated with an increase in cardiovascular death and heart failure hospital admissions. This relationship was first postulated on the basis of meta-regression analyses on heart rate in comparison to other outcome variables, which revealed a strong correlation between heart rate reduction and improvements in both mortality and left ventricular ejection fraction.(269)

These findings were confirmed more recently in SHIFT (Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial), a randomised placebo controlled study whereby heart rate reduction with long-term use of a pure heart-rate lowering agent ivabradine, which is an inhibitor of the I_f current in the sinoatrial node with no peripheral activity or blood pressure effects, resulted in a significant reduction in heart failure related deaths and hospitalisations.(258)

The long-term prognostic effects of reducing the baseline heart rate in chronic heart failure have been well established. However, heart rate, in conjunction with stroke volume, determines cardiac output and hence oxygen availability for both myocardial and skeletal metabolism. So any agents that lower the resting heart rate will also affect the heart rate profile during exercise, and may impact on overall performance.

CI has long been established as a marker of poor prognosis and reduced functional capacity in heart failure. However, whether CI is a causal factor for exercise intolerance and poor prognosis has been a long-standing topic of debate and conflicting opinions, with no evidence to back either claim.

Regardless of biological plausibility, in order to establish a prognostic marker as a causal factor, it is necessary to demonstrate not only that an outcome is quantitatively related to the factor, but also that modification of the alleged risk factor will alter the outcome.

The unique combination of a double blind randomised controlled crossover study design along with therapeutic modalities that alter heart rate, and hence CI, in isolation, such as the pacemaker and ivabradine, to reduce the heart rate, has made it possible to study the effects of worsening CI without changing any other cardiovascular parameters.

Baseline characteristics of the population show that this RCT cohort is well representative of the 'typical' heart failure patient. All patients had a pacemaker device and the majority were taking ACEi/ARBs (92.5%), beta-blockers (95%) and loop diuretics (55%). One third had concurrent diabetes and a high proportion also had either hypertension (30%) or ischaemic heart disease (45%), all in keeping with global heart failure and diabetes statistics.(338) No adverse events were reported during any test, thus confirming the safety of such an approach to induce bradycardia clinically, in a pacemaker population.

6.6 Conclusion

Previous studies have suggested that a potential therapeutic target to improve symptoms in HF may be to increase the heart rate response during exercise.(339) In addition it is commonly assumed that the heart rate lowering achieved by contemporary therapies to improve outcomes in HF induces exercise intolerance.

This interventional RCT has shown that acutely inducing iatrogenic bradycardia, and worsening CI by reducing both the resting heart rate and the heart rate response does not worsen exercise capacity, suggesting that exercise intolerance might more likely be due to peripheral factors relating to CHF, and that CI might not be a causal factor in the symptoms expressed by patients.

Chapter 7: Investigating the relationship between heart rate and cardiac contractility (Opt-RATE 3 Study)

7.1 Abstract

Increases in cardiac contractility during exercise are under two major influences: depolarisation-rate dependent (heart rate dependent; force frequency relationship (FFR)), and catecholamine-dependent. The FFR is thought to be impaired in chronic heart failure (CHF) such that contractility does not rise normally with increases in heart rate.(340) It is not known whether an optimal heart rate range exists in CHF, and whether this is related to cardiac function, levels of symptoms and exercise capacity, or indeed whether modifying heart rates in CHF patients can positively influence cardiac contractility.

The aim of this double-blind case-control pilot study was to measure the FFR in at least 10 controls with normal cardiac function and 15 subjects with moderate to severe heart failure (left ventricular ejection fraction <45%), pacemaker devices, in sinus rhythm on optimally tolerated medical and pacemaker therapy. The subjects remained at rest throughout the testing period, with heart rate increases driven solely through atrial/bi-ventricular pacing, in 10 beats/minutes increments from the minimum underlying heart rate. The FFR was calculated non-invasively using blood pressure and echocardiographic measures.

The results showed clear differences in the relationship between heart rate and contractility in healthy patients and patients with CHF. Contractility increased in both groups as the heart rate was increased, albeit at different rates, however FFR was blunted in CHF and fell beyond heart rates of 100 bpm.

This provides a mechanistic basis to explain the results of the two previous RCTs (OPT-Rate 1 and 2), wherein altering the peak heart rate did not influence functional capacity.

7.2 Introduction

Cardiac output is dependent on heart rate and stroke volume, which is the difference between end diastolic left ventricular volume and end systolic ventricular volume. These three factors are interdependent, and continuously increasing the heart rate will affect the stroke volume by reducing the filling time and hence the end diastolic volume. (341)

Simply increasing the heart rate in response to increased metabolic demands during exercise is not sufficient to allow maintenance of cardiac output. The role of contractility in exercise is to ensure that cardiac output matches venous return. Increasing the cardiac output by increasing the heart rate and reducing the end systolic volume is energetically more favourable initially, rather than increasing the end diastolic volume, which requires greater energy in order to achieve the necessary pressure and wall tension.(342)

The depolarisation-rate dependent (catecholamine-independent) mechanism whereby increases in heart rate lead to increases in the force of contraction is known as the Treppe phenomenon, or the force frequency relationship (FFR). This frequency-dependent up-regulation of contractility is rapid and intrinsic to the myocardial cell with no external involvement from neuronal or hormonal controls. The FFR is vital because when heart rate increases,

diastolic filling time is reduced. Hence contractility must increase to avoid a paradoxical fall in cardiac output.

The FFR is thought to be impaired in CHF such that contractility in heart failure does not rise normally with increases in heart rate.(343) This raises the possibility that there may be a lower optimal heart rate range for cardiac contraction in CHF patients than in control subjects.

The aim of this study is to measure cardiac contractility non-invasively and thus examine the FFR throughout the full range of heart rates achievable via pacemaker programming, independent of activity, cardiac loading or catecholamine activity.

7.3 Methods

7.3.1 Study population

A total of 31 subjects were enrolled into this study. All participants were approached at routine outpatient pacemaker follow-up appointments and given information sheets. This study was approved by the National Research Ethics Service (REC reference 12/YH/0097, Appendix B).

Controls (n=13) were selected on the basis of no diagnosis or symptoms of heart failure and normal heart function on echocardiogram.

The HF subjects (n=18) had a known diagnosis of moderate-severe systolic heart failure (ejection fraction less than 45%), a pacing device in situ for a clinical indication, and were clinically stable on optimally tolerated medical and pacemaker therapy for at least six months.

7.3.2 Inclusion and exclusion criteria

The inclusion criteria for controls in this study were no known diagnosis of heart failure, no signs or symptoms consistent with HF and no abnormalities on echocardiogram.

Inclusion in the HF cohort required confirmed CHF due to left ventricular systolic dysfunction on echocardiogram (LVSD, moderate-severe; left ventricular ejection fraction <45%, and symptoms of breathlessness or

fatigue on exertion), on optimal medical therapy and stable symptoms. They must have had their pacemaker for at least six months with stable lead variables and no change in medications or other invasive cardiac procedures for at least three months. All subjects were capable lying in a supine recumbent position for the duration of the test and of giving informed written consent, which was obtained in all subjects.

Subjects unable to give informed consent or with co-morbidities that prevented lying flat comfortably for the duration of the test, such as severe obstructive or restrictive respiratory conditions, uncontrolled symptomatic heart failure, uncontrolled angina or musculoskeletal conditions, were excluded.

7.3.3 Testing

7.3.3.1 Pre-test data collection

Each subject attended the research department for a single visit. Height and weight were measured to allow FFR measures to be adjusted for body-surface-area (BSA (m^2) = SQRT([Height(cm) x Weight(kg)]/ 3600)).

Information was also collected regarding co-morbidities, past medical history, medication types and dosages, pacemaker settings, NYHA symptom class and activities of daily living. A symptom limited treadmill based maximal cardio-pulmonary exercise test was also performed at baseline. All data were stored in a secure anonymised electronic database.

7.3.3.2 Test procedure

The subjects remained at rest throughout the testing period, with heart rate increases driven solely through atrial/bi-ventricular pacing, in 10 beat/minute increments starting at either a paced base rate of 30 beats per minute or the underlying intrinsic heart rate (if above 30 bpm). The FFR was calculated non-invasively using the systolic blood pressure and the end systolic volume index, as described previously in chapter 3.

Blood pressures were measured at each heart rate setting using a standard manual cuff sphygmomanometer and a standard stethoscope by the blinded clinician. The systolic pressure was recorded as the point where the first tapping sound occurred for 2 consecutive beats. Echocardiographic images were recorded by a blinded echosonographer. Heart rate was increased at 10 beat increments by the unblinded technician, who also monitored the ECG throughout the test. The patient was not made aware of the heart rate, blood pressure or echocardiographic measures at any stage of the testing process.

7.3.3.3 Data collection

Heart rate settings were recorded and adjusted by the unblinded pacing technician. Prior to starting the test, the technician positioned the patient on the echocardiogram couch, attached ECG monitoring and determined the lowest tolerated heart rate by reducing the pacemaker base rate to 40 bpm. The two key measurements for determining contractility non-invasively are the end-systolic volume and systolic blood pressure, which is used as a surrogate for end-systolic LV pressure. The end systolic volume was determined using the Simpsons bi-plane method using two dimensional

echocardiographic images. This was collected by the blinded echosonographer, and analysed by two independent senior echosonographers off-line. Heart rate (HR, bpm) was increased at 10 bpm increments by the unblinded technician, who would alter the pacing rate, wait for exactly one minute and then instruct the echosonographer to begin image acquisition.

Systolic blood pressure readings were taken manually by the blinded physician at the same time as the recording of end systolic images to ensure maximum accuracy of the resulting contractility measure. Blood pressure readings were taken twice during that time period, and an average was recorded on the data capture form. Serial measures were taken in this way until either the peak predicted heart rate was achieved, the patient complained of any discomfort or the unblinded technician detected any ischaemic ECG changes. All pacemaker settings were returned to baseline following the test. Five minutes after the end of the test, a final set of images and a blood pressure were recorded.

7.3.4 Cohort size calculation

Heart rate related changes in contractility have not been previously investigated in paced controls or heart failure patients, using a non-invasive incremental study protocol. This part of the study is therefore necessarily exploratory. However previous studies have demonstrated that non-invasive

contractility measures using the end-systolic volume (adjusted to BSA) and the systolic blood pressure are reliable and reproducible. Moreover, all major previous studies looking at contractility and Treppe have been able to demonstrate significance using HF cohorts of 11 ± 4 and control cohorts of 8 ± 3.(313)

Therefore, in order to demonstrate a clinically important change in contractility, a minimum of 8 subjects were needed in the control group, and a minimum of 11 in the CHF group. To allow for drop-outs and to confidently suggest equivalence, the recruitment aims were a minimum of 10 controls and 15 CHF subjects.

7.4 Results

7.4.1 Baseline characteristics for entire cohort

A total of 31 participants were recruited in to this study (CHF n=19, Controls n=12). Weight, body surface area, ejection fraction, pVO_2, furosemide dose, NYHA status and age followed a non-parametric distribution (Shapiro-Wilk normality test; $p<0.05$) and are hence reported as median ± interquartile range (table 7.1).

	Full cohort (n=31)
Height, cm	173 (8)
Weight, kg	78 ± 18
Age, years	77 (15)
Body Surface Area, m^2	1.95 ± 0.2
NYHA class 1	90% (28)
NYHA class 2	10% (3)
Ejection fraction, %	45 (19)
Exercise Time, second	526 (266)
pVO_2, ml/kg/min	18.2 ± 10
Baseline HR, bpm	50 (13)
Syst BP (SP)	125 (19)
Diast BP (DP)	70 (11)
Furosemide	32% (10)
Diabetes mellitus	20% (6)
Ischaemic heart disease	29% (9)
Hypertension	10% (3)
PMH: CABG	13% (4)
PMH: PCI	3% (1)
PMH: Valve surgery	7% (2)
ACEi/ARB	68% (21)
Beta-blocker	68% (21)
Spironolactone	23% (7)
Statin	52% (16)
Calcium channel blocker	3% (1)
Digoxin	10% (3)
Amiodarone	10% (3)
Anticoagulation	45% (14)
Antiplatelet	29% (9)

Non-parametric variables reported as median ± interquartile range. Normally distributed variables as mean (SD).

KEY: NYHA: New York Heart Association, HR: heart rate, BP: blood pressure, pVO_2: peak oxygen consumption,, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotension II receptor blocker.

Table 7.1 Baseline characteristics

7.4.2 Comparing demographics between groups

Baseline characteristics for each group separately are shown in table 7.1 (parametric data as mean (SD); non-parametric as median±IQR).

	CHF (n=19)	Controls (n=12)	P value
Height, cm	172 (7)	175 (8)	0.450
Weight, kg	83 ± 16	76 ± 10	0.068
Age, years	77 (9)	70 (16)	0.183
Body Surface Area, m^2	2.0 ± 0.2	1.9 ± 0.2	0.134
NYHA class 1	84% (16)	100% (12)	0.148
NYHA class 2	16% (3)	0	
Ejection fraction, %	34 (7)	55 (5)	<0.05
Exercise Time, second	441 (233)	639 (275)	0.050
pVO_2, ml/kg/min	15.8 (4)	26.7 (11)	<0.05
Baseline heart rate, bpm	49 (13)	53 (13)	0.434
Systolic BP, mmHg	121 (23)	129 (13)	0.171
Diastolic BP, mmHg	68 (12)	71 (10)	0.317
Furosemide dose, mg	20 ± 70	0	<0.05
Diabetes mellitus	21% (4)	17% (2)	0.763
Ischaemic heart disease	42% (8)	8% (1)	<0.05
Hypertension	6% (1)	17% (2)	0.296
PMH: CABG	16% (3)	8% (1)	0.546
PMH: PCI	5% (1)	0% (0)	0.419
PMH: Valve surgery	11% (2)	0% (0)	0.245
ACEi	53% (10)	25% (3)	0.129
ARB	42% (8)	8% (1)	<0.05
Beta-blocker	95% (18)	25% (3)	<0.05
Spironolactone	37% (7)	0% (0)	<0.05
Statin	74% (14)	17% (2)	<0.05
Calcium channel blocker	5% (1)	0% (0)	0.419
Digoxin	16% (3)	0% (0)	0.148
Amiodarone	16% (3)	0% (0)	0.148
Anticoagulation	63% (12)	17% (2)	<0.05
Antiplatelet	32% (6)	25% (3)	0.694

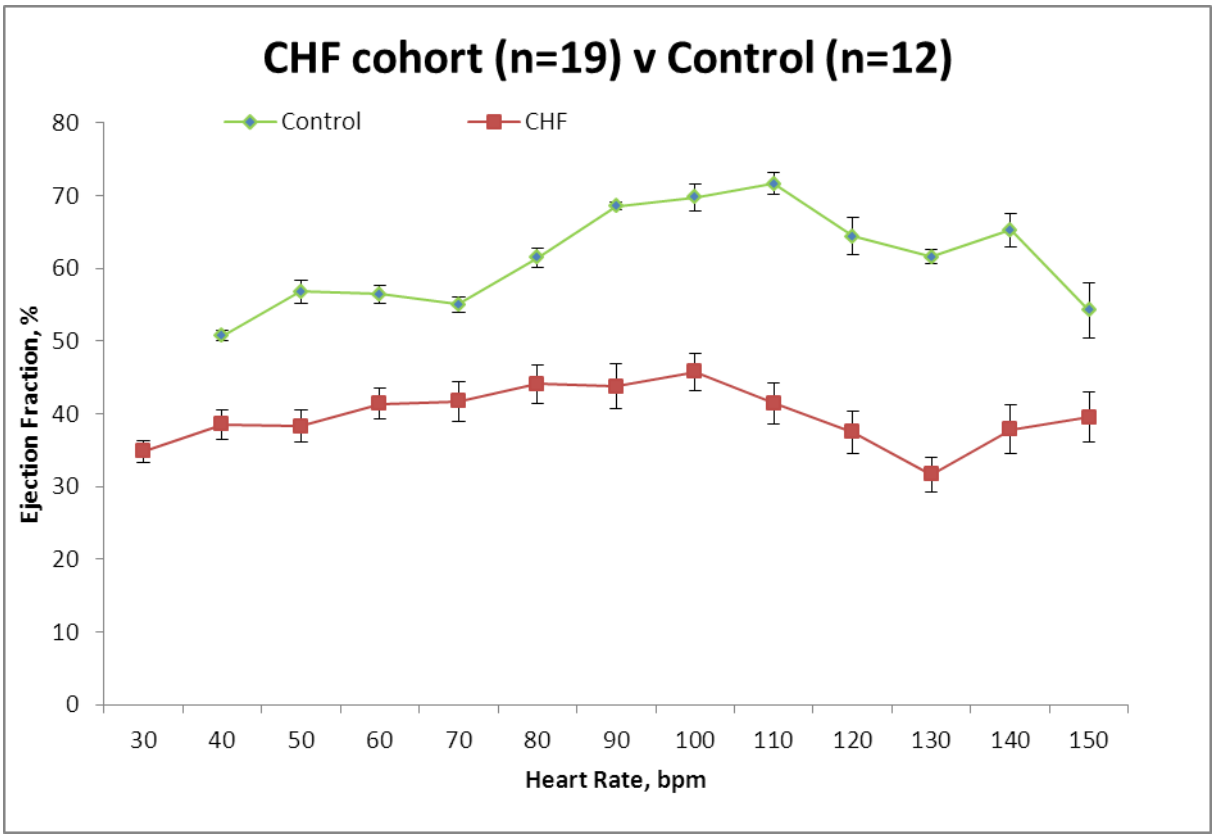
KEY: NYHA: New York Heart Association, HR: heart rate, BP: blood pressure, pVO_2: peak oxygen consumption,, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotension II receptor. blocker.

Table 7.2 Group demographics

7.4.3 Comparing echocardiographic measures

A comparison was made of the ejection fraction (calculated using the Simpson's bi-plane method), left ventricular internal diameter in systole, left ventricular internal diameter in diastole, the estimated cardiac output and the aortic pre-ejection time. The data was analysed by two independent echosonographers, and the mean of the values obtained was used in all subsequent analyses after performing a Bland-Altman test to assess the level of agreement, using measurements and calculations on the resting pre-test echocardiogram (correlation $R=0.712$, $p<0.05$).

Both the control and the CHF cohort exhibited a similar relationship in these measures with increasing heart rates, albeit worse in the CHF group (Figure 7.1A-E).



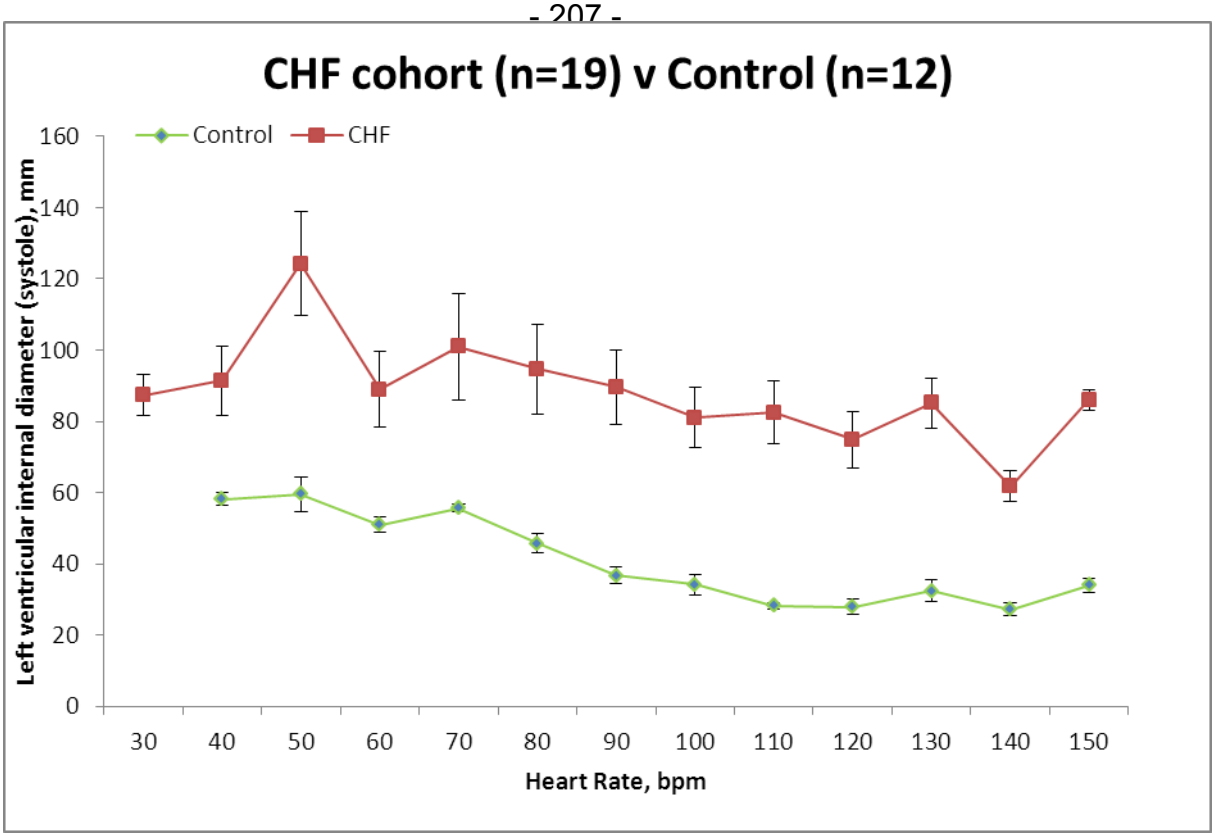


Figure 7.1B Left ventricular internal diameter (systole)

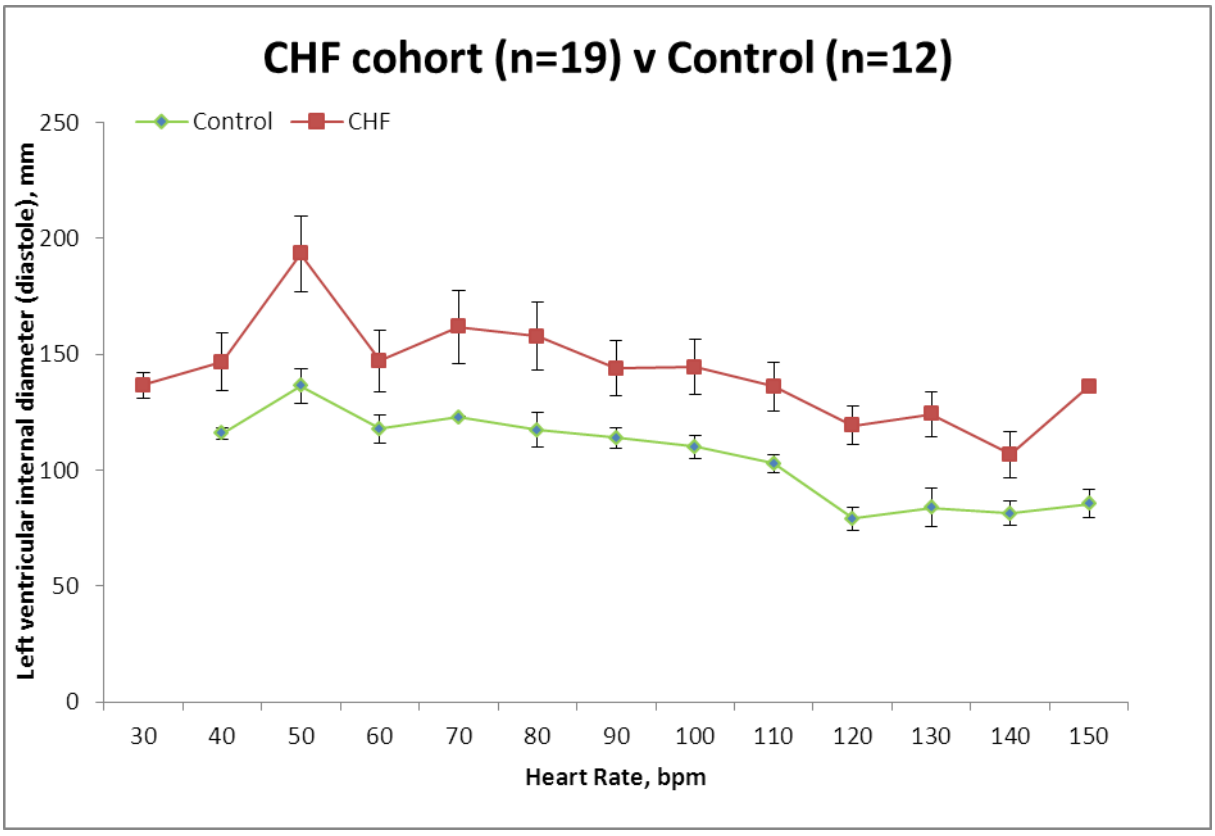


Figure 7.1C Left ventricular internal diameter (diastole)

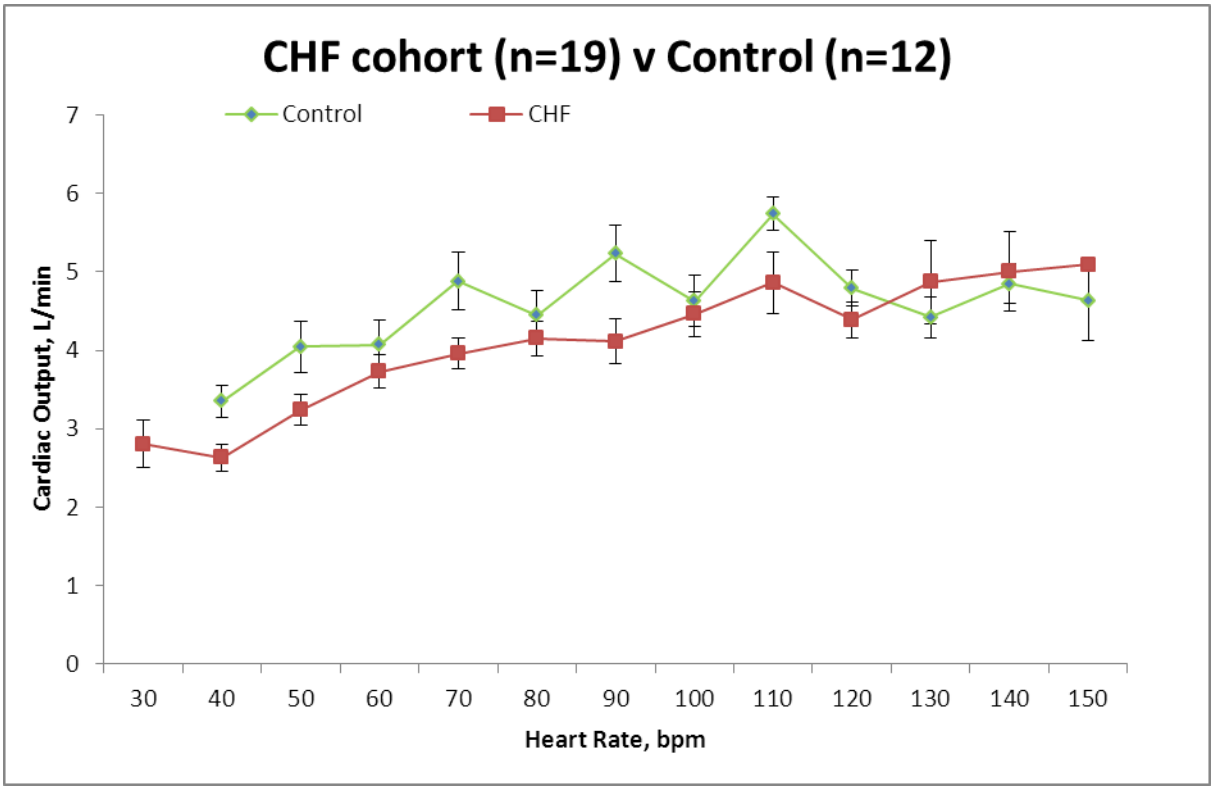


Figure 7.1D Cardiac output

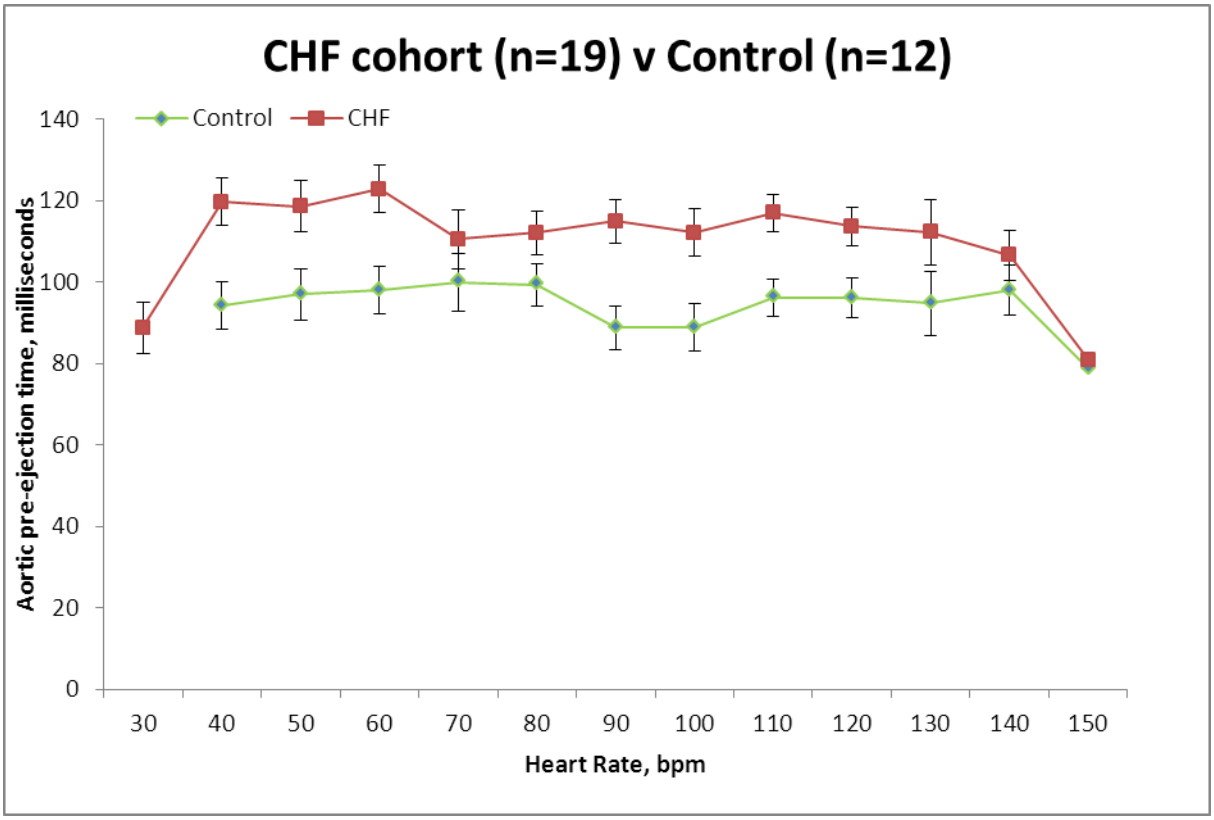


Figure 7.1E Aortic pre-ejection time

7.4.4 Contractility

The end-systolic volume index and systolic blood pressure reading was used to non-invasively estimate the cardiac contractility at each heart rate for the participants. The resultant data is shown in Figure 7.2.

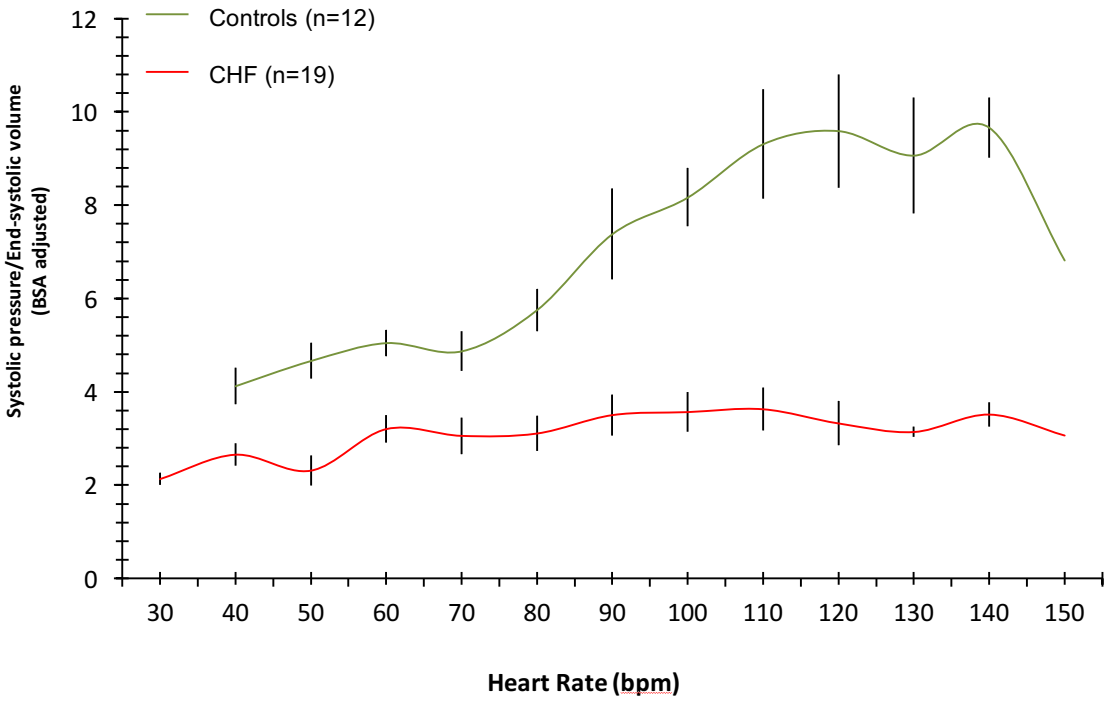


Figure 7.2 Contractility measures

A clear difference was seen in the relationship between heart rate and contractility in healthy controls and patients with CHF (figure 7.3). Examining the relationship in linear regression models (dashed lines) showed that there was evidence of a quadratic relationship in each group of patients:

- Controls: 0.04638×HR−0.0002112×HR2+0.9288
- CHF: 0.1682009×HR−0.0006316×HR2−2.4876

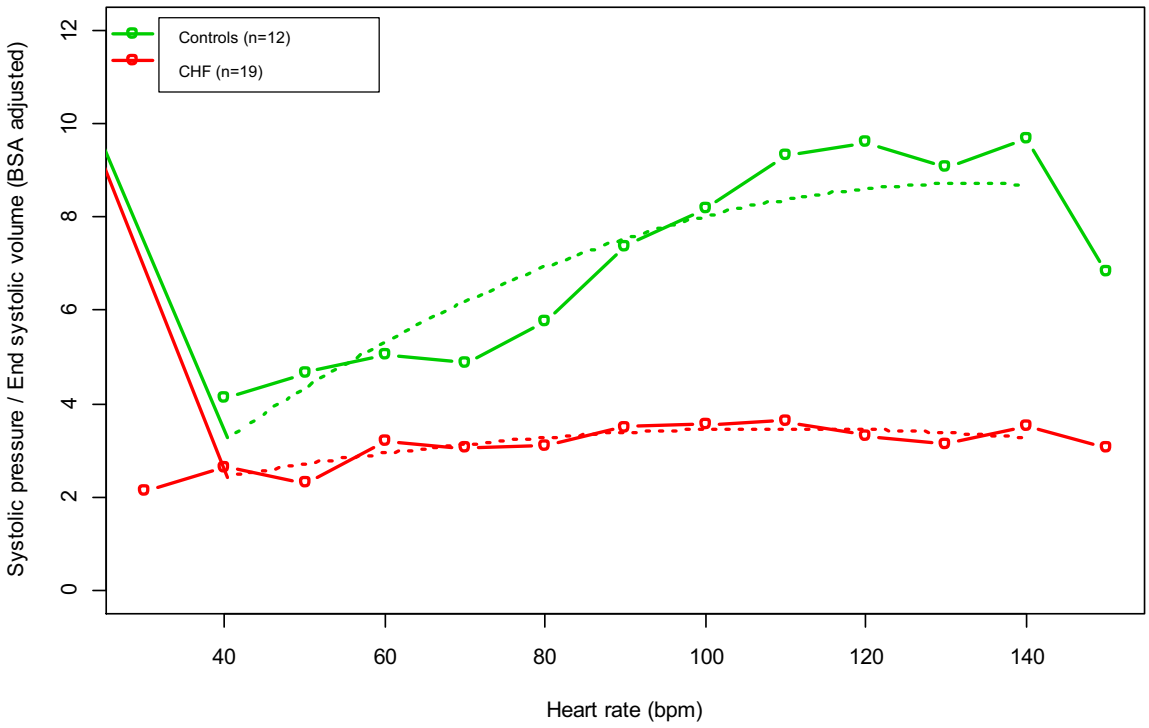


Figure 7.3 Contractility linear regression model

In each model the linear term was significant ($p<0.05$) and the quadratic term at least borderline significant ($p=0.001$ for controls and $p=0.06$ for CHF).

Separate models were required for each group, as compared to considering the data overall. This was confirmed by a likelihood ratio test for a saturated model compared to a simple additive model for HR, HR^2 and patient group ($\chi^2_3=38.96$, $p<0.05$).

7.5 Discussion

The results obtained in this study explain one of the potential mechanisms underlying the relationship between heart rate and exercise capacity in CHF. While heart rate plays an important role in increasing cardiac output during activity in health, this relationship between heart rate and heart function is different in CHF, as a result of a blunted FFR response.

Heart rate is a fundamental modulator of cardiac output, and increases therein are physiologically essential in order to meet the increased metabolic demands of activity and exercise. Cardiac output is dependent on both heart rate and stroke volume. These two factors are interdependent as a result of the Treppe phenomenon.

Increases in heart rate are normally linked to increases in cardiac contractility, via a positive FFR. One of the restrictions to achieving increased cardiac output during exercise in patients with heart failure might be the limited rise in cardiac contractility with increases in heart rate, as shown by this study.

It is clear from this study that contractility increases as heart rate increases in both groups, but the rate of the change is very different in patients with CHF as compared to controls. In the control group, contractility continues to increase until very high heart rates are achieved, up to 140 beats per minute. However, the contractility response is slow in CHF, and a decrease

in the contractility slope occurs at heart rates over 100 bpm. Thus higher heart rates are not energetically favourable in CHF, and increasing the peak heart rate above 100 bpm does not result in any increase in cardiac contractility.

7.5.1 Clinical relevance

Not only does this explain why worsening CHF is associated with increasing CI, but also why correcting CI by augmenting cardio-acceleration does not increase exercise capacity. This has definite and far-reaching clinical implications with regards to treatment goals in CHF with pharmacological and pacemaker device therapy.

In addressing the heart rate clinically, heart failure physicians are faced with a conflicting dilemma. Evidence from numerous large studies, as well as international guidelines all encourage the use of medications to lower the resting heart rate, as this intervention is known to improve patient survival. However, all CHF patients are functionally limited to varying extents, and the origin of this limitation has hitherto been unclear.

Chronotropic incompetence has been proposed by many as being the major cause, and therein lies the conflict. Lowering the resting heart rate to improve mortality will necessarily worsen heart rate rise (HRR) and will lower the peak heart rate achieved. In contrast using a pacemaker to treat CI or reducing HR lowering medications will improve HRR, but has a negative effect on overall survival and mortality.

These results show that there is no favorable HR related change in cardiac contractility at heart rates above 100 bpm in the context of CHF. Thus, there is no symptomatic or functional benefit to be gained from treating CI with

higher pacemaker resting heart rate settings, rate adaptive pacing or suboptimal utilisation of prognostically beneficial pharmacological agents such as beta-blockers or sinus node I_f current blockers, that induce an iatrogenic bradycardia and may limit HRR.

The presence of CI is neither the causal factor for exercise intolerance, nor a target for treatment. Rather it may be an intrinsic cardio-protective measure that ensures the heart rate range does not increase to such a degree that contractility, as hence cardiac function, declines during physical activity. Myocardial perfusion also predominantly occurs in diastole, and the lower HRR in CI may be a physiological response to improve myocardial oxygenation by ensuring longer diastolic time.(344)

7.6 Conclusion

Our data show that in controls, higher heart rates lead to greater contractility, and thus greater potential for cardiac output to increase in response to increasing activity. In CHF, the FFR is blunted so that contractility does not increase to the same degree or in the same manner, as in the control group.

As the force-frequency relationship is different in controls and CHF patients with increasing heart rates, independent of cardiac loading or physical activity levels. These two groups cannot be subjected to the same treatment rationale when it comes to resting heart rate, peak heart rate and exertion related heart rate rise.

Chapter 8: The role of the heart rate on exercise capacity in chronic heart failure: association or contribution?

8.1 Introduction

The constant beating of our heart; it is the very first and also the very last thing any of us will ever experience. The very presence of a heartbeat signifies the presence of life, and its absence marks its end. Heart rate is the metronome of our existence and it regulates the level of overall energy consumption. This vital and familiar life companion is unappreciated, misunderstood and often overlooked. Yet even when the heart starts to fail, the heart rate will adapt to compensate and thus keep us alive. This investigation is an attempt at reconciliation, and its purpose is to show appreciation to the heart rate by exploring, expounding and clarifying its role during activity in the context of heart failure.

8.2 Overview

Exercise capacity refers to the maximum degree of physical exertion attainable. This can be affected by functional abnormalities in the cardiovascular, respiratory and skeletal muscle systems. Exercise intolerance is pathognomonic of chronic heart failure (CHF). This is considered to be the result of reduced cardiac output at rest because of myocardial contractile impairment and impaired increase in cardiac output with exercise, resulting in lower oxygen consumption, exercise intolerance and fatigue. Cardiac output is dependent on alterations in heart rate (HR) and stroke volume, both of which are impaired in the context of CHF. The focus of this investigation was to assess the role of HR on exercise capacity in heart failure.

An overall estimate of exercise capacity can be expressed by measuring the maximal symptom-limited oxygen uptake (peak VO_2) in an incremental exercise regime with breath-by-breath analysis of oxygen uptake and carbon dioxide release. Peak VO_2 is known to be lower in patients with heart failure compared to healthy controls, in reflection of the lower exercise tolerance. Patients with CHF also commonly have a blunted heart rate rise, known as chronotropic incompetence (CI). This refers to an inability of the HR to increase in proportion to the level of physical exertion or metabolic demand. There is conflicting evidence as to whether CI contributes to, or is the result of, the reduced exercise capacity that is characteristic of worsening heart failure.

The degree of CI relates to both the severity of LVSD and the level of exercise limitation, although it is unclear as to whether this is merely an association or a causative link.(235) Multiple studies have explored the relationship between CI and exercise capacity with conflicting results that demonstrate a strong association but no definite causation. (229)(230)(236)(231)(237) A negative force-frequency association may also exist within failing myocardium cells.(35)(265)

As heart rate lowering agents can affect both the resting and the peak HR, there is controversy as to whether these could worsen symptoms by increasing the level of CI, despite the likelihood of long-term mortality benefits. Conversely, perhaps the reduced heart rates seen in CHF throughout exercise is form of chronotropic adaptation (CA), which favours energy kinetics by reducing the resting myocardial oxygen demand, resulting in less cardiac ischaemia and a better contractile response at lower heart rates.

8.3 Resting heart rate

Resting heart rate (RHR) has been established as both a marker of prognosis, and a viable treatment objective in multiple large epidemiological studies.(63)(258) RHR becomes increasingly elevated in heart failure as the disease progresses. Pharmacological targeting to lower RHR results in improvements in both mortality and morbidity.(269)(345) However, despite the burden of evidence showing all-cause mortality benefits with reducing the RHR, there is a failure to achieve recommended doses in a large proportion of patients,(346) and mortality remains high with a 5-year survival rate of around 40%.(338)

Some of these cases may be due to contraindications or poor tolerance, however there is also a great degree of reluctance in using high dose beta-blockers or aggressive RHR lowering through combination with other pharmacological agents such as sinus node blockers, due to a fear of inducing exercise intolerance, severe symptomatic bradycardia and increasing symptoms of breathlessness and fatigue.

In those patients with pacemakers or bi-ventricular devices in-situ, higher doses of rate-limiting agents can be safely used without risk of inducing severe RHR lowering. One of the indications for pacemaker implantation is prevention of excessive bradycardia, hence devices are often set to maintain a higher HR than what the current evidence shows to be optimal for CHF.

Thus devices are seldom programmed in a way to allow pharmacologically induced, prognostically beneficial bradycardia.

A recent pilot study of patients with systolic dysfunction and pacemakers showed an improvement in cardiac function with the lower base rate of 55 beats/min compared to 75 beats/min.(347) However, the situation becomes more complicated when considering the cardiac response to exertion within LVSD, and whether altering the HR profile affects fatigability and exercise capacity.

8.4 Peak heat rate

A key feature of HR in moderate-severe LVSD is the inability to achieve the maximum predicted peak HR (PHR), known as chronotropic incompetence (CI). The increased peripheral demand during exercise results in an increase in the heart rate via the autonomic nervous system. In the non-diseased heart, myocardial contractility will increase in response to the increased rate. This is known as the force-frequency relationship, or the Bowditch effect.(194) CI refers to an inability of the heart rate to increase in proportion to the level of physical exertion or metabolic demand. Rate-adaptive cardiac pacing was developed as an attempt to optimise exercise tolerance in patients with CI.(348)(349)

Pacemakers can be programmed to deliver either fixed rate pacing or utilise a rate-adaptive pacing algorithm, where the heart rate is altered in proportion to the level of activity as detected by internal device sensors. Rate-adaptive pacing in people without CHF is associated with an increase in cardiac output during exercise (252) and better quality of life (253)(254)(255) but inconsistent (256)(257) improvements in exercise capacity, when compared to fixed rate pacing. Using pacemakers to increase PHR in CHF has been shown to worsen prognosis and cardiac function.(259)(260)

8.5 Clinical implications

There is no conclusive evidence of benefit on exercise time or quality of life in CHF from increasing the mean and peak HR with rate-adaptive pacing.(263) Despite this, rate-adaptive pacing with high base rates remains the standard of care for all patients with pacemakers including those with CHF, creating a paradox that medical therapy to reduce mean heart rate is proven and applied, yet those with a pacemaker may be inadvertently subjected to higher mean heart rates, thus missing a therapeutic opportunity.

8.6 Investigation Rationale

The close relationship between the heart rate and exercise capacity, and limited techniques to detach one from the other means that published data are inconclusive. Although an association between exercise capacity and CI is both plausible and coherent through analogous comparisons with controls, in order to prove causality, it is necessary to also determine strength of association, biological gradient, temporality, consistency and specificity through carefully designed and controlled experimental studies. The Bradford-Hill criteria for causality act as guidelines to help determine whether an observed relationship is merely associatory, or actually contributory (Table 8.1).(350)

Bradford-Hill criteria	**Explored/Tested in:**
Plausibility	Background
Coherence	Background
Analogy	Observational study
Strength of association	Observational study
Biological gradient	Observational study
Experiment	Interventional RCT 1 and 2
Temporality	Interventional RCT 1 and 2
Consistency	Interventional RCT 1 and 2
Specificity	Case-control contractility study

Table 8.1 Bradford-Hill Criteria

In heart failure, the force-frequency relationship is greatly reduced. Furthermore, the higher HR in CHF is associated with reduced cardiac efficiency and increased myocardial oxygen demands. An impaired Bowditch effect during exertion may not only result in declining functional capacity, but also an overall reduction in cardiac function.(194) HR reduction would prolong diastole and thus increase efficiency by improving FFR and reducing energy consumption.(264)

There is a pathophysiological argument to be made in support of the haemodynamically optimal heart rate range in heart failure being different to that expected from controls, with a lower optimal peak heart rate beyond which there is no improvement in exercise capacity.(351)

8.7 Observational study

Thus, this investigation started with a retrospective cohort analysis in order to explore some of these factors. In particular, the observational data were analysed for the existence and strength of any association between the presence of CI and limited exercise capacity, and the possibility of a biological gradient between the degree of CI and severity of exercise intolerance.

This involved analysis of clinical, echocardiographic and cardio-pulmonary exercise test (CPX) data from 195 consecutive patients. There was a strong correlation between HRR and peak oxygen consumption in the control group (n=48). This association was much weaker in the CHF cohort (n=147), within which both the presence and degree of CI was associated with worsening exercise capacity. Therefore both an association and a biological gradient (dose-response relationship) were present within the CHF cohort.

8.8 Interventional studies

In order to determine causality, further experiments were required to also demonstrate temporality, consistency and specificity.

8.8.1 Increasing the heart rate during exercise

If the presence of CI caused a limitation in exercise capacity, then correcting CI by increasing the heart rate rise achieved during exercise should result in improved exercise capacity.

In our study, increasing the peak HR achieved during a maximal exercise test on subjects with CHF did not result in any improvement in exercise capacity. The results of this RCT demonstrate that ‘correcting’ chronotropic incompetence in patients with CHF, or unnecessarily activating rate adaptive pacing in patients with a pacemaker and no LV dysfunction, does not result in any improvement in oxygen consumption, exercise capacity, exercise time or symptoms.

The situation differed in the presence of AF. Here, rate adaptive pacing resulted in higher peak oxygen consumption, despite no change in exercise time or anaerobic threshold implying ‘wasted’ metabolic effort. Thus a lower peak heart rate may actually improve skeletal or cardiac muscle efficiency in CHF with AF, as the same output is delivered (exercise time) but with lower oxygen consumption. These findings offer a possibility of future work to

consider whether the CI in HF patients might be beneficially adaptive, rather than as commonly considered, maladaptive.

Overall, our data suggest that a temporal relationship does not exist, whereby correcting the HRR results in any change in total exercise capacity.

8.8.2 Decreasing the heart rate during exercise

A further randomised controlled trial was carried out in order to demonstrate whether a dose-response relationship or any specificity existed such that worsening CI by reducing the resting heart rate could result in any reduction of exercise capacity. To ensure consistency, the same selection criteria were used to identify a different cohort of patients for this study.

A total of 40 patients were recruited into this interventional double blind cross-over randomised controlled trial, of which 14 had concurrent atrial fibrillation and 26 were in sinus rhythm. Each participant performed two cardiopulmonary treadmill based exercise tests at either the normal resting HR (using usual pacemaker settings in the AF cohort, or placebo in the sinus cohort) or a reduced resting HR (pacemaker resting rate reduced to 30 in the AF cohort, or pharmacological heart rate lowering in the sinus group with a sinus node blocking agent, ivabradine). Reducing the resting heart rate did not result in any worsening of exercise capacity in either cohort. In fact, starting at a lower resting heart rate in the AF cohort resulted in an increase

in exercise efficiency, with a higher HRR and longer exercise time, despite achieving the same peak oxygen consumption.

8.8.3 Mechanistic study

Data from the previous studies prompted a further interventional case-control study to explore the cardiac force-frequency relationship (FFR) in heart failure (Treppe phenomenon), in order to understand why both lowering the resting heart rate and increasing the peak heart rate had no effect on functional capacity.

A double blind interventional case-control study was carried out on 31 patients with pacemakers (CHF n=19, Controls n=12) in order to determine a mechanistic basis and suggest an optimal heart rate range for moderate-severe CHF.

Linear regression modelling of cardiac contractility measures (systolic blood pressure/end-systolic volume index) across a range of pacemaker-induced heart rates revealed a different relationship between heart rate and contractility in healthy patients and patients with CHF. In controls, higher heart rates led to greater contractility throughout the full range of measurements. In CHF, the FFR was blunted with only modest increases at a lower heart rate range (40 to 100 beats per minute), with flattening thereafter.

8.9 Discussion

This investigation provides persuasive evidence that CI is simply a marker of exercise intolerance that fails to meet the minimum criteria to infer causality, namely lacking a temporal relationship, consistency or any dose-response effect. Furthermore, there is clinical benefit to be gained from lowering the resting heart rate both in terms of exercise capacity acutely, and prognostic benefits long term.

The unique combination of a double blind randomised controlled cross-over study design along with therapeutic modalities that can alter the heart rate in isolation, and hence manipulate the chronotropic response, such as rate adaptive pacing to increase the heart rate and ivabradine, a pharmacological sinus node I_f current blocking agent that induces bradycardia with no peripheral effects, to reduce the heart rate, has made it possible to study the effects of modifying CI without changing any other cardiovascular parameters. Non-invasive measurement of the force-frequency relationship independently of cardiac loading or catecholamine activity throughout the full range of heart rates achievable in a CHF cohort has provided a mechanistic basis to explain the RCT results.

8.10 Clinical implications

In addressing the heart rate clinically, heart failure physicians are faced with a conflicting dilemma. Evidence from numerous large studies, as well as international guidelines all encourage the use of medication to lower the resting heart rate, as this intervention is known to improve patient survival. However, all CHF patients are functionally limited to varying extents, and the origin of this limitation is unclear.

Chronotropic incompetence has been proposed by many as being the major cause, and therein exists the conflict. Lowering the resting heart rate to improve mortality will necessarily worsen heart rate rise and will lower the peak heart rate achieved. In contrast using a pacemaker to treat CI or reducing the dosage of HR lowering medications will improve heart rate rise, but will have a negative effect on overall survival and mortality.

The novel findings reported here have clinical implications for both pharmacological and device treatment strategies in the context of significant systolic heart failure. Even though the presence of CI in CHF relates to reduced functional capacity, correcting this may be unnecessary as it will not improve oxygen consumption, symptoms or exercise time in CHF. This leads to the conclusion that CI does not play a causal role within the exercise intolerance seen in CHF.

Heart rate rise is not a limiting factor for peak exercise capacity, and is thus precluded from being a potential therapeutic target. The reduced heart rate increase seen in CHF corresponds to the HR range where the contractility response is positive, which raises the possibility that the ‘chronotropic adaptation’ seen in worsening CHF is likely a cardio-protective measure, in order to maximise contractile response and exertional cardiac output.

Exercise capacity is also not worsened by reducing the resting HR, in both sinus and AF heart failure patients. As such, pharmacological goals and pacemaker programming should be different in moderate-severe LVSD, compared to those with normal LV function.

A tailored patient specific approach is necessary when utilising interventions that may alter the heart rate. Further research is required in order to explore whether using FFR estimation to determine a tailored optimal heart rate range to guide personalisation of treatment strategies for each CHF patient could improve exercise capacity in the short term, and mortality in the long term, by mimicking the natural chronotropic adaptation observed in CHF rather than attempting to exceed it.

8.11 Future Research

If contractility does not respond normally to increases in heart rate in CHF patients and plateaus or indeed worsens with increasing heart rate, there may be a lower optimal heart rate range for cardiac contraction in CHF patients, with respect to improving functional capacity and symptoms. Thus the next step will be to use these findings as the basis for programming pacemakers based on the optimal heart rate range in relation to each individual's FFR profile and contractility response within a large-scale randomised controlled trial. The non-invasive echocardiography techniques used in the current investigation would be utilised to calculate the optimal HR range to achieve peak contractility. The study participants would then be double-blind randomised to have two treadmill-based cardiopulmonary exercise tests one week apart, with either the usual pacing settings, or tailored pacemaker HR settings with a lower peak HR, in order to optimise the FFR response. The aim would be to determine whether such an approach could reduce symptoms and increase functional capacity in moderate-severe CHF.

8.12 Conclusion

The clinical implications of this series of investigations are clear. Even though the presence of CI in CHF relates to reduced functional capacity, correcting this in the CHF population is futile and unnecessary as it will not improve oxygen consumption, symptoms or exercise time. Also, lowering the resting HR does not worsen exercise capacity. This leads to the conclusion that CI does not play a major role within the exercise intolerance seen in CHF, and may instead be a cardio-protective 'chronotropic adaptation' response. The rationale for this lies in the blunted FFR seen with moderate-severe CHF, whereby no improvement in contractility is seen with heart rates over 110 beats per minute.

This thesis has expounded the role of the heart rate on exercise capacity in heart failure, and provides evidence that chronotropic incompetence is neither a limiting nor a causal factor for exertional intolerance in CHF.

Instead, the findings of these interventional studies demonstrate that the seemingly counter-intuitive approach of lowering the HR, which is known to improve mortality, does not negatively impact functional capacity. The chronotropic adaptation seen with worsening heart failure should be supported, with the aim to maintain the exertional heart rate rise between an optimal range of 50 to 110 beats per minute.

List of Abbreviations

ACC/AHA	American College of Cardiology
ACEi	angiotensin converting enzyme inhibitor
ADL	activities of daily living
AF	atrial fibrillation
AHA	American Heart Association
ARB	angiotensin II receptor blocker
AT	lactate/anaerobic threshold
ATP	adenosine triphosphatase
AV	atrio-ventricular
BMI	body mass index
BNP	brain natriuretic peptide
BSE	British Society of Echocardiography
Ca^{2+}	calcium ions
CABG	coronary artery bypass grafting
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CHF	chronic heart failure
CI	chronotropic incompetence
CO	cardiac output
CPX	cardiopulmonary exercise test
ECC	excitation-contraction coupling
ECG	electrocardiogram
EDV	end diastolic left ventricular volume
EF	ejection fraction
ESC	European Society of Cardiology

ESP	end-systolic pressure
ESPVR	end-systolic pressure volume ratio
ESV	end systolic left ventricular volume
FFR	force-frequency relationship
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HRR	heart rate rise
I_{Ca}	calcium influx current
IHD	ischaemic heart disease
IQR	interquartile range
LTCC	L-type calcium channels
LVEF	left ventricular ejection fraction
LVESV	end systolic left ventricular volume
LVESVi	end systolic left ventricular volume index
LVIDd	left ventricular internal diameter in diastole
LVIDs	left ventricular internal diameter in systole
LVSD	left ventricular systolic dysfunction
MI	myocardial infarction
MRT	mean response time
MyBP-C	myosin binding protein C
NCX	sodium–calcium exchange protein
NT-proBNP	N- terminal brain natriuretic peptide prohormone
NYHA	New York Heart Association
OUES	oxygen uptake efficiency slope
PCI	percutaneous coronary intervention
$PetCO_2$	partial pressure of end tidal CO_2
PHR	peak heart rate
PKA	protein kinase A

PLB	phospholamban
PMH	past medical history
RCT	randomised controlled trial
RER	respiratory exchange ratio (ratio of V_{CO_2} to V_{O_2})
RHR	resting heart rate
RR	respiratory rate
RV	right ventricle
RyR2	ryanodine receptors
SD	standard deviation
SE	standard error
SND	sinus node disease
SR	sarcoplasmic reticulum
Tm	tropomysin
TnC	troponin C
TnI	troponin I
TTE	transthoracic echocardiogram
VE	ventilation
V_E/V_{CO_2} slope	slope relating ventilation rate to carbon dioxide output
V_{O_2}	oxygen uptake/consumption
Vt	tidal volume

Appendix A Detailed statistical analyses data

Appendix A.1 Stratified cohort data comparing worsening degrees of chronotropic incompetence (study 1, chapter 4, section 4.3.3)

		N	Mean	SD	SE	95% Confidence Interval for Mean	
						Lower Bound	Upper Bound
Age, years	1	16	68.063	13.0255	3.2564	61.122	75.003
	2	8	70.500	11.2504	3.9776	61.094	79.906
	3	18	72.611	15.9268	3.7540	64.691	80.531
	4	32	68.813	9.5087	1.6809	65.384	72.241
	5	40	70.650	11.4703	1.8136	66.982	74.318
	6	23	71.522	11.9197	2.4854	66.367	76.676
	7	10	67.700	12.4012	3.9216	58.829	76.571
	Total	147	70.136	11.8603	.9782	68.203	72.069
PPHR, bpm	1	16	151.94	13.025	3.256	145.00	158.88
	2	8	149.50	11.250	3.978	140.09	158.91
	3	18	147.39	15.927	3.754	139.47	155.31
	4	32	151.19	9.509	1.681	147.76	154.62
	5	40	149.35	11.470	1.814	145.68	153.02
	6	23	148.48	11.920	2.485	143.32	153.63
	7	10	152.30	12.401	3.922	143.43	161.17
	Total	147	149.86	11.860	.978	147.93	151.80
HRR, bpm	1	16	82.13	29.111	7.278	66.61	97.64
	2	8	73.00	11.588	4.097	63.31	82.69
	3	18	63.44	19.515	4.600	53.74	73.15
	4	32	53.44	12.941	2.288	48.77	58.10
	5	40	37.70	8.683	1.373	34.92	40.48
	6	23	23.22	7.299	1.522	20.06	26.37
	7	10	12.10	4.654	1.472	8.77	15.43
	Total	147	47.03	24.775	2.043	42.99	51.07
Height, cm	1	16	175.125	9.7271	2.4318	169.942	180.308
	2	7	170.500	10.6575	4.0282	160.643	180.357
	3	16	166.088	11.6694	2.9174	159.869	172.306
	4	32	163.516	31.2819	5.5299	152.237	174.794
	5	38	171.416	8.1858	1.3279	168.725	174.106

	6	23	168.452	6.1106	1.2741	165.810	171.095
	7	10	170.200	8.8544	2.8000	163.866	176.534
	Total	142	168.842	16.9352	1.4212	166.033	171.652
Weight, kg	1	16	90.813	16.9763	4.2441	81.766	99.859
	2	7	85.400	20.5101	7.7521	66.431	104.369
	3	16	76.899	19.3668	4.8417	66.580	87.219
	4	32	81.089	24.3065	4.2968	72.325	89.852
	5	38	85.091	16.7138	2.7113	79.597	90.584
	6	23	82.630	17.3270	3.6129	75.138	90.123
	7	10	88.960	18.1838	5.7502	75.952	101.968
	Total	142	83.800	19.3636	1.6250	80.587	87.012
Exercise time, s	1	16	417.56	200.239	50.060	310.86	524.26
	2	8	562.88	169.978	60.096	420.77	704.98
	3	18	486.44	247.336	58.298	363.45	609.44
	4	32	476.88	218.714	38.663	398.02	555.73
	5	40	393.53	182.723	28.891	335.09	451.96
	6	23	311.52	198.020	41.290	225.89	397.15
	7	10	211.70	136.042	43.020	114.38	309.02
	Total	147	409.68	214.559	17.697	374.71	444.65
AT, ml/kg/min	1	10	13.80	4.827	1.527	10.35	17.25
	2	6	13.93	3.561	1.454	10.20	17.67
	3	14	13.32	3.577	.956	11.26	15.39
	4	21	12.67	2.843	.620	11.38	13.97
	5	23	11.87	2.753	.574	10.68	13.06
	6	7	12.49	4.640	1.754	8.19	16.78
	7	2	8.05	2.333	1.650	-12.92	29.02
	Total	83	12.66	3.472	.381	11.90	13.42
RER	1	16	1.11	.122	.031	1.04	1.17
	2	8	1.13	.139	.049	1.02	1.25
	3	16	1.06	.123	.031	1.00	1.13
	4	31	1.12	.131	.023	1.07	1.16
	5	38	1.07	.119	.019	1.03	1.11
	6	23	.99	.118	.025	.94	1.04
	7	9	1.08	.205	.068	.92	1.23
	Total	141	1.07	.135	.011	1.05	1.10
V_E/V_{CO_2} slope (AT)	1	12	28.46	6.014	1.736	24.64	32.28
	2	8	31.68	5.163	1.825	27.36	36.00
	3	15	30.59	5.188	1.340	27.72	33.47
	4	25	30.50	6.362	1.272	27.88	33.13
	5	28	30.92	7.938	1.500	27.85	34.00
	6	11	35.58	5.083	1.533	32.17	39.00
	7	3	31.15	10.031	5.791	6.23	56.07
	Total	102	31.05	6.611	.655	29.75	32.35

V_E/V_{CO_2} slope (Peak)	1	16	35.85	14.555	3.639	28.09	43.61
	2	8	33.48	5.681	2.009	28.73	38.23
	3	18	34.75	9.254	2.181	30.15	39.36
	4	31	34.55	11.214	2.014	30.44	38.67
	5	40	36.49	10.103	1.597	33.26	39.72
	6	22	40.08	9.567	2.040	35.84	44.33
	7	10	41.96	12.459	3.940	33.05	50.87
	Total	145	36.55	10.790	.896	34.78	38.32
Resting HR, bpm	1	16	103.25	18.760	4.690	93.25	113.25
	2	8	81.25	11.997	4.242	71.22	91.28
	3	18	74.94	16.917	3.987	66.53	83.36
	4	32	73.94	13.907	2.459	68.92	78.95
	5	40	72.45	15.332	2.424	67.55	77.35
	6	23	72.13	16.966	3.538	64.79	79.47
	7	10	69.70	10.884	3.442	61.91	77.49
	Total	147	76.67	17.971	1.482	73.74	79.60
Peak HR, bpm	1	16	185.38	23.309	5.827	172.95	197.80
	2	8	154.25	13.079	4.624	143.32	165.18
	3	18	138.39	15.790	3.722	130.54	146.24
	4	32	127.38	9.517	1.682	123.94	130.81
	5	40	110.15	12.209	1.930	106.25	114.05
	6	23	95.35	12.737	2.656	89.84	100.86
	7	10	81.80	11.094	3.508	73.86	89.74
	Total	147	123.70	31.287	2.580	118.60	128.80
EF, %	1	16	33.94	11.204	2.801	27.97	39.91
	2	8	31.00	7.578	2.679	24.66	37.34
	3	18	34.56	9.044	2.132	30.06	39.05
	4	32	34.09	8.880	1.570	30.89	37.30
	5	40	33.50	10.201	1.613	30.24	36.76
	6	22	30.77	11.980	2.554	25.46	36.08
	7	10	34.80	6.746	2.133	29.97	39.63
	Total	146	33.35	9.778	.809	31.75	34.95
LVIDd, mm	1	15	56.07	9.625	2.485	50.74	61.40
	2	8	61.50	9.274	3.279	53.75	69.25
	3	15	55.20	8.760	2.262	50.35	60.05
	4	25	56.12	8.343	1.669	52.68	59.56
	5	36	57.64	9.523	1.587	54.42	60.86
	6	18	61.11	7.136	1.682	57.56	64.66
	7	9	55.67	5.545	1.848	51.40	59.93
	Total	126	57.46	8.709	.776	55.92	59.00
LVIDs, mm	1	7	47.00	12.014	4.541	35.89	58.11
	2	6	54.33	11.396	4.652	42.37	66.29
	3	5	41.40	7.197	3.219	32.46	50.34

	4	16	44.31	6.770	1.692	40.71	47.92
	5	17	49.65	11.710	2.840	43.63	55.67
	6	12	50.58	9.317	2.690	44.66	56.50
	7	4	53.50	4.655	2.327	46.09	60.91
	Total	67	48.30	9.961	1.217	45.87	50.73
pVO_2, ml/kg/min	1	16	17.7875	6.55885	1.63971	14.2925	21.2825
	2	8	18.5500	3.98676	1.40953	15.2170	21.8830
	3	18	16.6889	6.08149	1.43342	13.6646	19.7131
	4	32	17.4081	5.81436	1.02784	15.3118	19.5044
	5	40	15.2980	4.55806	.72069	13.8403	16.7557
	6	23	13.5652	4.53437	.94548	11.6044	15.5260
	7	10	9.6600	2.39824	.75839	7.9444	11.3756
	Total	147	15.7210	5.53281	.45634	14.8191	16.6228
QRS duration, ms	1	16	98.00	14.823	3.706	90.10	105.90
	2	8	123.75	29.769	10.525	98.86	148.64
	3	15	121.73	31.594	8.158	104.24	139.23
	4	28	119.61	29.700	5.613	108.09	131.12
	5	37	126.51	24.986	4.108	118.18	134.84
	6	21	129.19	21.507	4.693	119.40	138.98
	7	9	120.67	24.062	8.021	102.17	139.16
	Total	134	120.99	26.694	2.306	116.43	125.55

Key: N: number of patients in each sub-cohort, SD: standard deviation, SE: standard error, PPHR: peak predicted heart rate, HRR: heart rate rise, AT: anaerobic threshold, RER respiratory exchange ratio, VE/VCO_2 slope: slope relating ventilation rate to carbon dioxide output, HR: heart rate, EF: ejection fraction, LVIDd: left ventricular internal diameter in diastole, LVIDs: left ventricular internal diameter in systole, pVO_2: peak oxygen consumption.

Table A.1 Stratified cohort data comparing worsening degrees of chronotropic incompetence (study 1, chapter 4, section 4.3.3)

Appendix A.2 Paired sample statistics, CHF-AF (Study 2, chapter 5, section 6.3.3.1)

Group 1 – CHF-AF (n=14)		Mean	N	SD	SE
Resting HR, bpm	BR 60	64.786	14	14.1431	3.7799
	BR 30	49.214	14	18.2385	4.8744
Peak HR, bpm	BR 60	111.857	14	30.2626	8.0880
	BR 30	108.500	14	30.2903	8.0954
Heart rate rise, bpm	BR 60	47.07	14	22.923	6.126
	BR 30	59.29	14	20.496	5.478
%Predicted Peak HR	BR 60	.778	14	.213	.05744
	BR 30	.753	14	.208	.05567
Rest systolic BP, mmHg	BR 60	117.286	14	13.3037	3.5556
	BR 30	114.857	14	15.7229	4.2021
Rest diastolic BP, mmHg	BR 60	64.000	14	6.6564	1.7790
	BR 30	59.143	14	8.1037	2.1658
PP (rest), mmHg	BR 60	53.29	14	14.024	3.748
	BR 30	55.71	14	11.658	3.116
Peak systolic BP, mmHg	BR 60	131.571	14	21.5432	5.7577
	BR 30	135.857	14	19.2548	5.1461
PP BP, mmHg	BR 60	61.143	14	6.2124	1.6603
	BR 30	61.000	14	9.9460	2.6582
Pulse pressure (peak), mmHg	BR 60	70.43	14	20.429	5.460
	BR 30	74.86	14	18.576	4.965
Exercise time, seconds	BR 60	434.357	14	224.6521	60.0408
	BR 30	482.714	14	235.0743	62.8262
pVO_2, ml/kg/min	BR 60	14.836	14	4.3143	1.1530
	BR 30	14.393	14	4.0189	1.0741
HR at AT, bpm	BR 60	107.00	13	23.759	6.590
	BR 30	97.69	13	22.429	6.221
AT, ml/kg/min	BR 60	12.8377	13	3.46787	.96181
	BR 30	11.5146	13	2.54400	.70558
V_E/VCO_2 slope (peak)	BR 60	39.186	14	14.7624	3.9454
	BR 30	39.4071	14	14.52999	3.88330
V_E/VCO_2 slope (AT)	BR 60	32.50	13	12.094	3.354
	BR 30	36.30	13	12.961	3.595
Peak RER	BR 60	1.0764	14	.12701	.03395
	BR 30	1.1400	14	.12848	.03434
OUE slope	BR 60	1498.214	14	521.3492	139.3364
	BR 30	1454.071	14	473.4275	126.5288
MRT	BR 60	177.58	5	104.181	46.591
	BR 30	202.20	5	113.632	50.818
MRT recovery	BR 60	73.97	3	15.646	9.033
	BR 30	81.67	3	5.686	3.283
O_2 pulse (peak)	BR 60	12.500	10	5.1694	1.6347
	BR 30	12.900	10	4.6296	1.4640
O_2 pulse (AT)	BR 60	10.67	9	2.828	.943
	BR 30	10.33	9	2.449	.816

Key: N: number of entries, SD: standard deviation, SE: standard error, HR: heart rate, BP: blood pressure, PP: pulse pressure, pVO_2: peak oxygen consumption, AT: anaerobic threshold, V_E/VCO_2: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUES: oxygen uptake efficiency, MRT: mean VO_2 response time.

Table A.2 Paired sample statistics, CHF-AF, Study 2, chapter 5, section 6.3.3.1

Appendix A.3 Paired samples tests - CHF-AF (Study 2, chapter 5, section 6.3.3.1)

Paired Samples Test								
Group 1 (AF CHF)	**Paired Differences**					**t**	**df**	**Sig. (2-tail)**
	Mean	**SD**	**SE**	**95% Confidence Interval**				
				Lower	**Upper**			
Resting HR, bpm	15.571	14.4952	3.8740	7.2022	23.9407	4.019	13	.001
Peak HR, bpm	3.3571	13.5056	3.6095	-4.4408	11.1550	.930	13	.369
Heart rate rise, bpm	-12.21	17.894	4.782	-22.546	-1.883	-2.554	13	.024
%Predicted Peak HR	.0247	.0957	.0255	-.0305	.0800	.967	13	.351
Resting systolic BP, mmHg	2.4286	18.2492	4.8773	-8.1082	12.9653	.498	13	.627
Resting diastolic BP, mmHg	4.8571	9.9139	2.6496	-.8670	10.5813	1.833	13	.090
PP (rest), mmHg	-2.429	16.402	4.384	-11.899	7.042	-.554	13	.589
Peak systolic BP, mmHg	-4.285	13.8532	3.7024	-12.2843	3.7129	-1.158	13	.268
Peak diastolic BP, mmHg	.1429	7.7842	2.0804	-4.3516	4.6373	.069	13	.946
PP (peak), mmHg	-4.429	12.358	3.303	-11.564	2.707	-1.341	13	.203
Exercise time, seconds	-48.35	80.8699	21.6134	-95.0500	-1.6643	-2.237	13	.043
pV_{O_2}, ml/kg/min	.4429	1.2364	.3305	-.2710	1.1568	1.340	13	.203
HR at AT, bpm	9.308	18.250	5.062	-1.721	20.336	1.839	12	.091
AT, ml/kg/min	1.3230	1.93372	.53632	.15454	2.49161	2.467	12	.030
V_E/V_{CO_2} slope (peak)	-.2214	6.01283	1.60700	-3.69313	3.25028	-.138	13	.893
V_E/V_{CO_2} slope (AT)	-3.800	10.391	2.882	-10.079	2.479	-1.319	12	.212
Peak RER	-.0635	.10263	.02743	-.12283	-.00432	-2.318	13	.037
OUE slope	44.142	161.3676	43.1273	-49.0280	137.3138	1.024	13	.325
MRT	-24.62	190.019	84.979	-260.560	211.320	-.290	4	.786
MRT recovery	-7.700	21.184	12.231	-60.324	44.924	-.630	2	.593
O_2 pulse (peak)	-.4000	1.5776	.4989	-1.5286	.7286	-.802	9	.443
O_2 pulse (AT)	.333	1.803	.601	-1.052	1.719	.555	8	.594

Key: SD: standard deviation, SE: standard error, HR: heart rate, BP: blood pressure, PP: pulse pressure, pV_{O_2}: peak oxygen consumption, AT: anaerobic threshold, V_E/V_{CO_2}: slope relating ventilation rate to carbon dioxide output, RER: respiratory efficiency ratio, OUES: oxygen uptake efficiency, MRT: mean V_{O_2} response time.

Table A.3 Paired samples tests - CHF-AF, Study 2, chapter 5 section 6.3.3.1

Appendix B Research ethics paperwork

NHS
Health Research Authority
National Research Ethics Service

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07 June 2013

Dr Klaus Witte
Senior Lecturer in Cardiology
University of Leeds
LIGHT building,
Clarendon Road
Leeds
LS2 9JT

Dear Dr Witte

Study Title: **Iatrogenic chronotropic incompetence and exercise tolerance in heart failure**
REC reference: **13/YH/0144**
IRAS project ID: **129113**

The Research Ethics Committee reviewed the above application at the meeting held on 29 May 2013.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering Letter		22 April 2013
Evidence of insurance or indemnity		21 September 2012
GP/Consultant Information Sheets	1.0	24 February 2013
Investigator CV - Dr Klaus Witte		12 January 2012
Investigator CV - Haqeel Jamil		25 September 2012
Other: Certificate: Patient Consent for Clinical Trials		20 June 2012
Other: Email from MHRA confirming non-CTIMP		04 April 2013
Participant Consent Form	1.0	27 March 2013
Participant Information Sheet: Simus rhythm	1.0	24 February 2013
Participant Information Sheet: Atrial fibrillation	1.0	24 February 2013
Protocol	1.4	23 March 2013
REC application	3.5	22 April 2013

Provisional opinion

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

1. The Committee questioned why the research team had not adapted an opt-in approach.

2. The GP Letter states the visits will be one week apart although there is no mention of this in the participant information sheet. Please provide clarification and documentation should be amended accordingly.

3. The Committee questioned why the paragraph regarding compensation was highlighted in bold.

4. The Committee would like to see the Participant Information Sheet revised as follows:
    a. Ensure they are rewritten using the standard template which can found on the National Research Ethics Service website at the following link: http://www.nres.nhs.uk/applications/guidance/consent-guidance-and-forms/ paying particular attention to the first part of the form, you should also ensure they are rewritten in less technical language.
    b. Under the heading 'Do I have to take part' should say 'No, it is up to you….'
    c. Under the heading 'What will happen to me if I take part' this should be broken down in to two parts, detailing what will happen at visit 1 and visit 2.
    d. Explain in more detail what will happen during the exercise test, how long each stage will last.
    e. Should state whether the mouthpiece used to measure the levels of oxygen will be used throughout the exercise programme.
    f. Explain the method of recruitment; this should be made clear and in lay language.
    g. Under the heading 'Who has reviewed the study?' Should say the study has been reviewed by NRES Committee Yorkshire and Humber – Humber Bridge REC.

5. The Committee suggests the Participant Information Sheets are reviewed by a patient representative to ensure the understandability of language.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Diane Catterall whose contact details are on this letter.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 07 July 2013.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Dr Ian Woollands declared that he was the lead reviewer on a previous study submitted, but it was agreed that as he does not have any knowledge or interest in the study he should take part in the review and decision making process.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

13/YH/0144	**Please quote this number on all correspondence**

Yours sincerely

Dr Lynn Cawkwell
Chair

Email: nrescommittee.yorkandhumber-humberbridge@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.

Copy to: Clare Skinner, University of Leeds
Mrs Amanda Burd, Research & Development LTHT

NRES Committee Yorkshire & The Humber - Humber Bridge

Attendance at Committee meeting on 29 May 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Reverend Annabel Barber	Lay Member	Yes	
Dr Stephen Beer	Consultant Physician	Yes	
Mrs Kate Bollington	Customer Services Manager	Yes	
Dr Lynn Cawkwell	Senior Lecturer in Cancer Genetics	No	
Dr Fiona Cowdell	Senior Research Fellow	Yes	
Mr Michael Davidson	Retired Senior Personnel Manager	Yes	
Dr Karen Dunderdale	Chief Nurse	No	
Mr Michael Hockey	Consultant in Accident & Emergency	No	
Dr Sandeep Kapoor	Consultant Paediatrician	No	
Mrs Wendy Witter	Farm Administrator	Yes	
Dr Ian Woollands	Independent Medical Practitioner	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Diane Catterall	Coordinator

Health Research Authority
National Research Ethics Service

NRES Committee Yorkshire & The Humber - Humber Bridge
HRA NRES Centre North West
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7816
Facsimile: 0161 625 7299

12 June 2013

Dr Klaus Witte
Senior Lecturer in Cardiology
University of Leeds
LIGHT building,
Clarendon Road
Leeds
LS2 9JT

Dear Dr Witte

Study title:	**Iatrogenic chronotropic incompetence and exercise tolerance in heart failure**
REC reference:	**13/YH/0144**
IRAS project ID:	**129113**

Thank you for your email of 08 June 2013, 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 Vice-Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Diane Catterall, nrescommittee.yorkandhumber-humberbridge@nhs.net.

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

Conditions of the favourable opinion

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

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		22 April 2013
Evidence of insurance or indemnity		21 September 2012
GP/Consultant Information Sheets	1.0	24 February 2013
Investigator CV - Dr Klaus Witte		12 January 2012
Investigator CV - Haqeel Jamil		25 September 2012
Other: Certificate: Patient Consent for Clinical Trials		20 June 2012
Other: Email from MHRA confirming non-CTIMP		04 April 2013
Participant Consent Form	1.0	27 March 2013
Participant Information Sheet: Atrial fibrillation	1.1	07 June 2013
Participant Information Sheet: Sinus rhythm	1.1	07 June 2013
Protocol	1.4	23 March 2013
REC application	3.5	22 April 2013
Response to Request for Further Information		07 June 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed 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

13/YH/0144	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

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

Yours sincerely

Dr Lynn Cawkwell
Chair

Email:nrescommittee.yorkandhumber-humberbridge@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Clare Skinner, University of Leeds
Mrs Amanda Burd, Research & Development LTHT

The Leeds Teaching Hospitals NHS
NHS Trust

Amanda Burd

12/08/2013

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

Dr Klaus Witte
LIGHT building,
Clarendon Road
University of Leeds
LS2 9JT

Dear Dr Klaus Witte

Re: NHS Permission at LTHT for: Latrogenic Chronotropic Incompetence and exercise tolerance in heart failure
LTHT R&D Number: CD13/10799
REC: 13/YH/0144

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/academic/research-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

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust

only accepts liability for research activity that has been managerially approved by the R&D Department.

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

pp **Dr D R Norfolk**
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	3.5	16/06/2013
SSI Form	3.5	21/06/2013
Directorate Approval		09/08/2013
Insurance/ Indemnity	Hendersons	21/09/2012
REC Letter confirming favourable opinion		12/06/2013
MHRA E mail		04/04/2013
Protocol	V1.4	23/03/2013
Patient information sheet: Atrial and Sinus PIS	V1.1	07/06/2013
Consent form	V1.1	07/06/2013
GP/Consultant information sheets	V1.0	24/02/2013

Conditions of NHS Permission for Research:

- Permission from your Directorate must be obtained before starting the study.
- Favourable Opinion of the appropriate Research Ethics Committee, where necessary, must be obtained before starting the study.
- Arrangements must be made to ensure that all members of the research team, where applicable, have appropriate employment contracts or letter of agreement to carry out their work in the Trust.
- Agreements must be in place with appropriate support departments regarding the services required to undertake the project and arrangements must be in place to recompense them for the costs of their services.
- Arrangements must be in place for the management of financial and other resources provided for the study, including intellectual property arising from the work.
- Priority should be given at all times to the dignity, rights, safety and well being of participants in the study
- Healthcare staff should be suitably informed about the research their patients are taking part in and information specifically relevant to their care arising from the study should be communicated promptly.
- Each member of the research team must be qualified by education, training and experience to discharge his/her role in the study. Students and new researchers must have adequate supervision, support and training.
- The research must follow the protocol approved by the relevant research ethics committee. Any proposed amendments to or deviations from the protocol must be submitted for review by the Research Ethics Committee, the Research Sponsor, regulatory authority and any other appropriate body. The R&D Department should be informed where the amendment has resource implications within the Directorate and the Directorate research lead/clinical director notified.
- Adverse Events in clinical trials of investigational medicinal products must be reported in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004.
- Complete and return Study Status Reports, when requested, to the R&D Department within 28 days of receipt as requested. (NB Failure to comply to such request with the requirement will lead to suspension of NHS Permission.)
- Procedures should be in place to ensure collection of high quality, accurate data and the integrity and confidentiality of data during processing and storage.

- Arrangements must be made for the appropriate archiving of data when the research has finished. Records must normally be kept for 15 years.

- All data and documentation associated with the study must be available for audit at the request of the appropriate auditing authority. Projects are randomly selected for audit by the R&D Department. You will be informed by letter if your study is selected.

- Findings from the study should be disseminated promptly and fed back as agreed to research participants.

- Findings from the study should be exposed to critical review through accepted scientific and professional channels.

- All members of the research team must ensure that the process of informed consent adheres to the standards GCP outlined in the UK Clinical Trials Regulations. Investigators are directed to the R&D website for further information and training availability.

- Where applicable, this NHS Permission includes aspects of the study previously covered by the NRES Site Specific Assessment (SSA) process.

- Appropriate permissions must be in place for studies which are covered by the Human Tissue Act.

- Patient Information Sheet and Consent form must be on The Leeds Teaching Hospitals headed paper and include local contact details.

NIHR Benchmarks for Performance in Initiating & Delivering Clinical Research

- Provide recruitment information when requested by R&D on the Clinical Trial Tracker (available on Trust Sharepoint)

- Work with R&D to resolve blocks and delays on trials to ensure that LTHT meets the NIHR benchmarks.

If you are not able to comply with these requirements, NHS permission to conduct the research in LTHT will be suspended.

Commercially Sponsored Trials

If the study is commercially sponsored, NHS Permission is given subject to provision of the following documents.

- Clinical Trials Agreement - agreed and signed off by the R&D Department (on behalf of the Leeds Teaching Hospitals NHS Trust) and the Sponsor. Investigators do not have the authority to sign contract on behalf of the Trust.

- Indemnity agreement, if not included in the Clinical Trials Agreement- (standard ABPI no fault arrangements apply) signed by the R&D Department and the Sponsor

It is essential that all the responsibilities set out in the Research Governance Framework, including those outlined above are fulfilled. The Trust reserves the right to withdraw NHS Permission where the above criteria are not being met. The Trust will not accept liability for any activity where NHS Permission has not been granted.

NEW **Condition of Approval** NEW

Clinical Trials Performance Management

NIHR Benchmarks for Performance in Initiating & Delivering Clinical Research

LTHT clinical trial performance is now measured against 2 national benchmarks to improve the initiation and delivery of clinical trials approved by the Trust. From April 2013 NIHR funding to the Trust will be conditional on meeting these benchmarks.

- **Initiation** – it should take no more than 70 days from receipt of a valid research application (signed SSI form) by the R&I Department to the recruitment of (ie consenting) the 1st patient to the trial

- **Delivery** – for all commercial trials hosted by the Trust the agreed number of patients must be recruited within the agreed recruitment period

The Trust now has to submit quarterly performance reports to the Department of Health setting out our performance.

NHS permission for this project to be carried out in the Trust is therefore granted on the understanding that you:

- **Provide recruitment information when requested by R&D on the Clinical Trial Tracker (available on Trust Sharepoint)**

- **Work with R&D to resolve blocks and delays on trials to ensure that LTHT meets the NIHR benchmarks.**

If you are not able to comply with these requirements, NHS permission to conduct the research in LTHT will be suspended. These new conditions of approval are in addition to the "conditions of approval" listed in the attached NHS permission letter.

For more information about the new benchmarks and the work we are doing to support clinical trial management please see the R&D website.
http://www.leedsth.nhs.uk/academic/research-development/

The Leeds Teaching Hospitals NHS
NHS Trust

Amanda Burd

12/08/2013

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
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r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dr Klaus Witte
LIGHT building,
Clarendon Road
University of Leeds
LS2 9JT

Dear Dr Klaus Witte

Re: NHS Permission at LTHT for: Latrogenic Chronotropic Incompetence and exercise tolerance in heart failure
LTHT R&D Number: CD13/10799
REC: 13/YH/0144

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/academic/research-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

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust

National Research Ethics Service
South Humber Research Ethics Committee
Room FC27
Coniston House
Trust Headquarters
Willerby Hill Business Park
Willerby
HULL
HU10 6ED

Telephone: 01482 389157
Facsimile: 01482 303916

18 January 2010

Dr Klaus K Witte
Senior Lecturer in Cardiology
Leeds University
LIGHT building
Clarendon Road
LS1 9JT

Dear Dr Witte

Study Title: **The influence of chronotropic incompetence on exercise tolerance in pacemaker patients (with and without heart failure).**
REC reference number: **09/H1305/60**
Protocol number: **Version 1.2**

Thank you for your letter of 18 January 2010, 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

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).

Conditions of the favourable opinion

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

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research

governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		02 November 2009
REC application		25 November 2009
Investigator CV	Dr K Witte	02 November 2009
Participant Consent Form	v1.0	02 November 2009
GP/Consultant Information Sheets	GP letter v1.0	02 November 2009
Evidence of insurance or indemnity	Henderson Corporate	08 October 2009
Protocol	Version 1.2	18 January 2010
Participant Information Sheet: CRT	Version 1.3	18 January 2010
Participant Information Sheet	Version 1.3	18 January 2010
Response to Request for Further Information	Version 1	18 January 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

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.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- 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.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1305/60	Please quote this number on all correspondence

Yours sincerely

pp K. Waltham

Dr Ian G Woollands
Chair – South Humber REC

Email: karen.waltham@humber.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *[SL-AR1 for CTIMPs, SL- AR2 for other studies]*

Copy to: *Mrs Rachel DeSouza*
[R&D office for NHS care organisation at lead site]

ClinicalTrials.gov PRS
Protocol Registration and Results System

Protocol Registration Receipt
09/29/2014

The Influence of Heart Rate Limitation on Exercise Tolerance in Pacemaker Patients. (TREPPE)

This study is currently recruiting participants.
Verified by Haqeel Jamil, University of Leeds, September 2014

Sponsor:	University of Leeds
Collaborators:	
Information provided by (Responsible Party):	Haqeel Jamil, University of Leeds
ClinicalTrials.gov Identifier:	NCT02247245

Purpose

To examine the effects of heart rate reduction on exercise capacity in control subjects and patients with chronic heart failure.

Condition	Intervention	Phase
Chronic Heart Failure Atrial Fibrillation Arrhythmia, Sinus	Drug: Ivabradine Atrial fibrillation	N/A

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: The Influence of Iatrogenic Chronotropic Incompetence on Exercise Tolerance in Pacemaker Patients With Chronic Heart Failure.

Further study details as provided by Haqeel Jamil, University of Leeds:

Primary Outcome Measure:

- Change in exercise capacity [Time Frame: 2 weeks] [Designated as safety issue: No]
  Comparing cardiopulmonary exercise testing performance

Estimated Enrollment: 50
Study Start Date: September 2014
Estimated Study Completion Date: July 2016
Estimated Primary Completion Date: September 2015

Arms	Assigned Interventions
Placebo Comparator: Placebo Subjects are given a placebo capsule (double-blinded) to take 90 minutes prior to the cardiopulmonary exercise test.	
Active Comparator: Ivabradine Subjects are given an ivabradine capsule (double-blinded) to take 90 minutes prior to the cardiopulmonary exercise test.	Drug: Ivabradine Ivabradine 7.5mg Other Names: Precorolan
Experimental: Atrial fibrillation Subjects are (double blind) randomised to either a low base pacing rate (30) or a standard base rate (60), with rate adaptive algortithms switched on.	Atrial fibrillation Pacemaker base rate alteration

Original proposal: Does iatrogenic chronotropic incompetence lead to impaired exercise capacity in patients with CHF

Aim The aim of this proposal is to examine the effects of iatrogenic CI on exercise capacity in control subjects and patients with chronic heart failure.

Hypothesis Iatrogenic chronotropic incompetence does not contribute significantly to reductions in exercise capacity in patients with heart failure or control subjects with pacemakers.

Methods REDUCING HEART RATE AT REST AND EXERCISE In patients with sinus rhythm, the present proposal utilizes a heart failure medication called ivabradine. This agent, an If channel blocker, specifically targets the sinus node leading to a slower heart rate. The agent is approved and licensed for use in patients with heart failure at the doses proposed. Ivabradine slows the sinus rate with none of the peripheral effects of beta-blockers. Heart rate lowering with ivabradine improves cardiac function, and outcomes related to the degree of bradycardia achieved.

In patients with atrial fibrillation, the present proposal will recruit patients with CRT and atrial fibrillation that have undergone atrio-ventricular node (AVN) ablation to improve the efficacy of CRT. Patients who have undergone AVN ablation are dependent upon their pacemaker, and we can therefore control their heart rate accurately.

SUBJECT SELECTION Inclusion criteria We will only include patients able to give informed written consent, which will be obtained in all subjects, and those capable of performing a peak exercise test. Since we are performing the study on three groups of patients, further inclusion criteria for each group are outlined below.

Inclusion criteria – CRT-sinus rhythm group We will enrol 25 patients with severe CHF on otherwise optimally tolerated medical therapy who have undergone cardiac resynchronisation therapy at least 3 months previously. These individuals will be on optimal medical therapy for their heart failure with no change in medication or exacerbation for the preceding 3 months. They will not currently be taking ivabradine.

Inclusion criteria – CRT-atrial fibrillation group We will enrol 25 patients with severe CHF on otherwise optimally tolerated medical therapy who have undergone cardiac resynchronisation therapy at least 3 months previously. All patients will be previously pacemaker dependant or have ‘blocked’ atrial fibrillation either due to medical therapy or previous atrio-ventricular nodal ablation.

Inclusion criteria – control group The control subjects (n=25) will be recruited from the general pacemaker clinic. They will undergo echocardiography to exclude structural heart disease. They will have no contraindications to exercise testing or ivabradine.

Exclusion criteria We will exclude subjects with musculoskeletal disorders limiting exercise capacity, patients with peripheral vascular disease, those with inflammatory disorders such as rheumatoid arthritis, and airways disease. Other exclusions include contraindications to ivabradine use such as severe hepatic impairment, significant renal impairment (creatinine clearance <15ml.min-1), and long QT syndrome. We will only include patients able to give informed written consent, which will be obtained in all subjects.

ECHOCARDIOGRAPHY Each subject will undergo a full echocardiographic examination. The images will be stored on a commercially available database, (Echopac PC, GE-Vingmed, USA) and analysed offline. We will assess LV systolic and diastolic function variables, mitral regurgitation, and pulmonary artery pressure.

EXERCISE TESTING Patients will describe their own NYHA symptom class at the beginning of each exercise session. Each individual will be invited for a familiarization test once agreeing to the study. At least one week following the familiarization test, heart failure patients and controls will return to the exercise laboratory and will be randomised to either ivabradine (7.5mg) or placebo. The following week they will return for the second arm. The randomization will be carried out in pharmacy to ensure blinding of the subject, the technician and the investigator. After ingesting the capsule, the subject will be asked to wait for an hour before the exercise test commences.

Prior to the start of exercise, patients’ devices will be programmed to a base rate of 40 bts/min and they will then be they will be randomised to have their device programmed to either rate response on or off. A screen will separate the electrocardiographic monitor, which will be observed by the unblinded technician, from the metabolic cart, which will be observed by the blinded physician. The following week the other mode will be activated. At the end of each test the device will be returned to its original setting.

For the treadmill tests we will use the Bruce protocol modified by the addition of a ‘stage 0’ at onset consisting of 3 minutes of exercise at 1.61km/hr (1mile/hour) with a 5% gradient. During each test, expired air will be collected continuously and metabolic gas exchange analysis performed (Vmax 29, Sensormedics, USA). The system will be recalibrated prior to each test. Subjects will be encouraged to exercise to exhaustion, and a respiratory exchange ratio (RER), (VCO2/VO2) greater than 1.1 will be taken to suggest a maximal effort. The anaerobic threshold for each test will be calculated using the VO2/VCO2 slope method. At the end of each stage and at peak exercise subjects will be asked to indicate their score for dyspnoea or fatigue on a scale from 0 (no symptoms) to 10 (maximal symptoms) using the standardised Borg scoring system. The slope relating symptom

scores against ventilation (Borg/VE) for each subject can then be plotted. We will also examine other ventilatory variables such as tidal volume (VT) and frequency (f) of ventilation.

Eligibility

Ages Eligible for Study: 18 Years to 90 Years
Genders Eligible for Study: Both

Inclusion criteria:

We will only include patients able to give informed written consent, which will be obtained in all subjects, and those capable of performing a peak exercise test. Since we are performing the study on three groups of patients, further inclusion criteria for each group are outlined below.

Inclusion criteria – CRT-sinus rhythm group We will enrol 25 patients with severe CHF on otherwise optimally tolerated medical therapy who have undergone cardiac resynchronisation therapy at least 3 months previously. These individuals will be on optimal medical therapy for their heart failure with no change in medication or exacerbation for the preceding 3 months. They will not currently be taking ivabradine.

Inclusion criteria – CRT-atrial fibrillation group We will enrol 25 patients with severe CHF on otherwise optimally tolerated medical therapy who have undergone cardiac resynchronisation therapy at least 3 months previously. All patients will be previously pacemaker dependant or have ‘blocked’ atrial fibrillation either due to medical therapy or previous atrio-ventricular nodal ablation.

Inclusion criteria – control group The control subjects (n=25) will be recruited from the general pacemaker clinic. They will undergo echocardiography to exclude structural heart disease. They will have no contraindications to exercise testing or ivabradine.

Exclusion Criteria:

We will exclude subjects with musculoskeletal disorders limiting exercise capacity, patients with peripheral vascular disease, those with inflammatory disorders such as rheumatoid arthritis, and airways disease. Other exclusions include contraindications to ivabradine use such as severe hepatic impairment, significant renal impairment (creatinine clearance <15ml.min-1), and long QT syndrome. We will only include patients able to give informed written consent, which will be obtained in all subjects.

-

Contacts and Locations

Contacts

Haqeel A Jamil, MbChB MRCP	01133923131 Ext. 23131	haqeel@doctors.net.uk
Klaus K Witte, FRCP MD	01133923131 Ext. 23131	k.k.witte@leeds.ac.uk

Locations

United Kingdom

Leeds Institute of Cardiovascular and Metabolic Medicine — Recruiting
Leeds, West Yorkshire, United Kingdom, LS13ex

Contact: Haqeel Jamil, MbChB 01133923131 Ext. 23131 haqeel.jamil@leedsth.nhs.uk
Contact: Klaus Witte, MBBS 01133923131 Ext. 23131 k.k.witte@leeds.ac.uk

Investigators

Principal Investigator:	Klaus K Witte, FRCP MD	University of Leeds
Principal Investigator:	Haqeel A Jamil, MbChB MRCP	University of Leeds

More Information

Responsible Party:	Haqeel Jamil, Cardiology Registrar and Clinical Research Fellow, University of Leeds
Study ID Numbers:	LIGHT-TREPPE-1
Health Authority:	United Kingdom: National Health Service United Kingdom: Research Ethics Committee

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amanda 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".

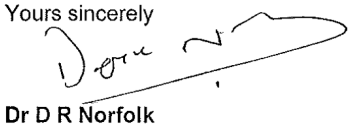
If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

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

Document	*Version*	*Date of document*
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

Conditions of NHS Permission for Research:

- Permission from your Directorate must be obtained before starting the study.
- Favourable Opinion of the appropriate Research Ethics Committee, where necessary, must be obtained before starting the study.
- Arrangements must be made to ensure that all members of the research team, where applicable, have appropriate employment contracts or letter of agreement to carry out their work in the Trust.
- Agreements must be in place with appropriate support departments regarding the services required to undertake the project and arrangements must be in place to recompense them for the costs of their services.
- Arrangements must be in place for the management of financial and other resources provided for the study, including intellectual property arising from the work.
- Priority should be given at all times to the dignity, rights, safety and well being of participants in the study
- Healthcare staff should be suitably informed about the research their patients are taking part in and information specifically relevant to their care arising from the study should be communicated promptly.
- Each member of the research team must be qualified by education, training and experience to discharge his/her role in the study. Students and new researchers must have adequate supervision, support and training.
- The research must follow the protocol approved by the relevant research ethics committee. Any proposed amendments to or deviations from the protocol must be submitted for review by the Research Ethics Committee, the Research Sponsor, regulatory authority and any other appropriate body. The R&D Department should be informed where the amendment has resource implications within the Directorate and the Directorate research lead/clinical director notified.
- Adverse Events in clinical trials of investigational medicinal products must be reported in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004.
- Complete and return Study Status Reports, when requested, to the R&D Department within 28 days of receipt as requested. (NB Failure to comply to such request with the requirement will lead to suspension of NHS Permission.)
- Procedures should be in place to ensure collection of high quality, accurate data and the integrity and confidentiality of data during processing and storage.

- Arrangements must be made for the appropriate archiving of data when the research has finished. Records must normally be kept for 15 years.

- All data and documentation associated with the study must be available for audit at the request of the appropriate auditing authority. Projects are randomly selected for audit by the R&D Department. You will be informed by letter if your study is selected.

- Findings from the study should be disseminated promptly and fed back as agreed to research participants.

- Findings from the study should be exposed to critical review through accepted scientific and professional channels.

- All members of the research team must ensure that the process of informed consent adheres to the standards GCP outlined in the UK Clinical Trials Regulations. Investigators are directed to the R&D website for further information and training availability.

- Where applicable, this NHS Permission includes aspects of the study previously covered by the NRES Site Specific Assessment (SSA) process.

- Appropriate permissions must be in place for studies which are covered by the Human Tissue Act.

- Patient Information Sheet and Consent form must be on The Leeds Teaching Hospitals headed paper and include local contact details.

Commercially Sponsored Trials
If the study is commercially sponsored, NHS Permission is given subject to provision of the following documents.

- Clinical Trials Agreement - agreed and signed off by the R&D Department (on behalf of the Leeds Teaching Hospitals NHS Trust) and the Sponsor. Investigators do not have the authority to sign contract on behalf of the Trust.

- Indemnity agreement, if not included in the Clinical Trials Agreement- (standard ABPI no fault arrangements apply) signed by the R&D Department and the Sponsor

It is essential that all the responsibilities set out in the Research Governance Framework, including those outlined above are fulfilled. The Trust reserves the right to withdraw NHS Permission where the above criteria are not being met. The Trust will not accept liability for any activity where NHS Permission has not been granted.

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Bradford
Yorkshire & Humber REC Office
Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 30 50128
Facsimile: 0113 85 56191

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 C GP letters and Patient Information leaflets

The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

Date:

Dear Dr

Re:

Our joint patient has consented to participate in a study examining the influence of heart rate on exercise capacity in patients with pacemakers.
The study involves two exercise tests with metabolic gas exchange on consecutive weeks. The tests will follow the transient reprogramming of their pacemaker to investigate whether increases in heart rate improve acute exercise capacity. The pacemaker will be reprogrammed to its usual settings after each exercise session.

The study has no implication for the daily management of the patient, and the pacemaker will be returned to its original settings at the end of each visit. Any unexpected results achieved during the tests will be forwarded to you.

If you have any additional questions please do not hesitate to contact me at 0113 3926642.

Best regards

Dr Klaus Witte MRCP, FESC, FACC, MD

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Information sheet – Heart failure Opt PACE 1

Chief Investigator: Dr. Klaus K Witte (Tel: 0113 3923131)

Title: The influence of heart rate limitation on exercise tolerance in pacemaker patients.

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

During exercise, heart rate increases. In some patients with heart failure, the increase in heart rate during exercise might be less than normal. It is possible that this contributes to the symptoms of heart failure during exercise and might reduce the amount of exercise patients can do. It is unknown to what extent heart rate increases contribute to the ability to exercise.

Your pacemaker has as one of its programming options, the capacity to control the increase in your heart rate as you exercise. We want to find out if allowing the

pacemaker to control your heart rate, alters the amount of exercise you can do. This will help establish how important heart rate increases are both in normal people and patients with heart problems.

Why have I been invited to take part?

We have invited you take part in this study because we know your exercise tolerance is limited based upon your previous exercise test and because your pacemaker has the capacity to be programmed in different ways.

Do I have to take part?

It is up to you to decide. Dr Witte (the principle investigator) will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will ask you to attend the exercise laboratory on two occasions. At the first visit, we might repeat the echocardiogram (heart scan) if you have not had one recently (within three months). On each occasion, we will ask you to come having had just a light breakfast. You will perform two study exercise tests on the treadmill. Prior to each test we will interrogate the pacemaker. At one of the visits we will keep the heart rate-response program activated in order that your heart rate increases as you exercise. For the other test this function will be de-activated and your heart rate increase during the test might be less. The order in which we do this will be randomised and neither you nor your doctor will know in which order your pacemaker will be reprogrammed. This is called ‘blinding’ and is common in studies. **At the end of each test the pacemaker will be set back to its original setting.**

During each test we will sample the air you breathe in and out through a mouthpiece to measure the levels of oxygen and carbon dioxide. This is an accurate way to measure your exercise capacity. We will ask you to exercise until you can no longer

continue and also to score your level of breathlessness at each stage during the exercise.

Each test will take less than one hour, and we would aim to complete all of the tests at your convenience, but generally at the same time of the day.

Risks

The risk of any adverse event with this level of exercise is small (less than 1 percent). The adverse effects could include the development of chest pain, hypotension (low blood pressure) or arrhythmias (irregular or abnormal heart beats). A physician will be present to supervise all testing.

Benefits

We want to learn about why patients fell tired and breathless during exercise. It may be that by examining the effects of heart rate limitation on exercise we can alter the way medication is prescribed to patients with heart problems. You are unlikely to personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about your condition, based upon the results of the tests. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What if I don't want to carry on with the study?

You can withdraw from the study but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3923131). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will however make your General Practitioner aware that you are participating in this study.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Leeds West Research Ethics Committee.

Questions

If you have any further questions about the study, or would like to be included in this research, please call Dr Klaus K Witte's Research Team on **0113 3923131** or his secretary on 0113 3926285 quoting 'Chronotropy: The influence of heart rate limitation on exercise tolerance in patients with chronic heart failure' or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Information sheet – Controls Opt PACE 1

Chief Investigator: Dr. Klaus K Witte (Tel: 0113 3923131)

Title: The influence of heart rate limitation on exercise tolerance in pacemaker patients.

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

During exercise, heart rate increases. In some patients with heart failure, the increase in heart rate during exercise might be less than normal. It is possible that this contributes to the symptoms of heart failure during exercise and might reduce the amount of exercise patients can do. It is unknown to what extent heart rate increases contribute to the ability to exercise.

Your pacemaker has as one of its programming options, the capacity to control the increase in your heart rate as you exercise. We want to find out if allowing the pacemaker to control your heart rate, alters the amount of exercise you can do. This will help establish how important heart rate increases are both in normal people and patients with heart problems.

Why have I been invited to take part?

We have invited you take part in this study because we know your pacemaker controls your heart rate during exercise and can be programmed to different modes.

Do I have to take part?

It is up to you to decide. Dr Witte (the principle investigator) will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will ask you to attend the exercise laboratory on two occasions. At the first visit, we might repeat the echocardiogram (heart scan) if you have not had one recently. (within three months). On each occasion, we will ask you to come having had just a light breakfast. You will perform two study exercise tests on the treadmill. Prior to each test we will interrogate the pacemaker. At one of the visits we will keep the heart rate-response program activated in order that your heart rate increases as you exercise. For the other test this function will be de-activated and your heart rate increase during the test might be less. The order in which we do this will be randomised and neither you nor your doctor will know in which order your pacemaker will be reprogrammed. This is called ‘blinding’ and is common in studies. **At the end of each test the pacemaker will be set back to its original setting.**

During each test we will sample the air you breathe in and out through a mouthpiece to measure the levels of oxygen and carbon dioxide. This is an accurate way to measure your exercise capacity. We will ask you to exercise until you can no longer continue and also to score your level of breathlessness at each stage during the exercise.

Each test will take less than one hour, and we would aim to complete all of the tests at your convenience, but generally at the same time of the day.

Risks

The risk of any adverse event with this level of exercise is small (less than 1 percent). The adverse effects could include the development of chest pain, hypotension (low blood pressure) or arrhythmias (irregular or abnormal heart beats). A physician will be present to supervise all testing.

Benefits

We want to learn about why patients fell tired and breathless during exercise. It may be that by examining the effects of heart rate limitation on exercise we can alter the way medication is prescribed to patients with heart problems. You are unlikely to benefit personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve

the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about your condition, based upon the results of the tests. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What if I don't want to carry on with the study?

You can withdraw from the study but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3923131). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will however make your General Practitioner aware that you are participating in this study.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Leeds West Research Ethics Committee.

Questions

If you have any further questions about the study, or would like to be included in this research please call Dr Klaus K Witte's Research Team on 0113 3923131 or his secretary on 0113 3926642 quoting 'The influence of heart rate limitation on exercise tolerance in patients with chronic heart failure' or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

Date:

Dear Dr

Re:

Our joint patient has consented to participate in a study examining the influence of heart rate on exercise capacity in patients with pacemakers.
The study involves two exercise tests with metabolic gas exchange on consecutive weeks following a single dose of ivabradine (Procoralan) or placebo. Ivabradine is a commonly prescribed anti-anginal with heart rate lowering effects. We are using the agent to study the effects of heart rate limitation on exercise capacity. Since all patients will have a pacemaker, there are no concerns that their hearts will go ‘too slow’.

The study has no implication for the daily management of the patient, and the pacemaker will be returned to its original settings at the end of each visit. Any unexpected results achieved during the tests will be forwarded to you.

If you have any additional questions please do not hesitate to contact me at 0113 3926642.

Best regards

Dr Klaus Witte MRCP, FESC, FACC, MD

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Information sheet – Sinus rhythm Opt PACE 2

Chief Investigator: Dr. Klaus K Witte (**Tel: 0113 3923131**)

Title: The influence of heart rate limitation on exercise tolerance in pacemaker patients.

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

During exercise, heart rate increases. This increase in heart rate during exercise might be less than normal in some patients. It is possible that this contributes to the symptoms during exercise and might reduce the amount of exercise patients can do. It is unknown to what extent heart rate increases contribute to the ability to exercise.

Many of the tablets used for angina and other heart conditions are designed to slow the heart down. It is thought that this might adversely affect exercise capacity but it is not known for sure. The presence of a pacemaker allows us to find out whether slowing the heart rate impairs exercise capacity at no risk that it will go too slowly because your pacemaker has a back up rate to prevent this. This therefore allows us to examine the effects of heart rate slowing on exercise capacity and will help establish how important heart rate increases are in determining exercise capacity in patients and normal people.

Why have I been invited to take part?

We have invited you take part in this study because you have a pacemaker.

Do I have to take part?

Not at all. It is up to you to decide. Dr Witte (the principle investigator) or one of his team will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will ask you to attend the exercise laboratory at Leeds General Infirmary on two occasions a week apart for about two hours having had **no caffeine for 16 hours before your visit**. You can eat and drink normally before you arrive except for caffeine-containing drinks.

At the first visit, we might repeat the echocardiogram (heart scan) if you have not had one recently (within three months).

At each visit, we will also first check the pacemaker to make sure that it is functioning normally and set the heart rate to 60 beats per minute.

Once we have done this we will ask you to take a capsule that may or may not contain an approved medication that slows the heart down. This medication is routinely used in patients with angina and heart failure. Neither you nor the team will know whether the capsule contains the heart slowing medication or a blank tablet. So you may receive the medication at the first visit and the blank at the second, or vice-versa. This is called blinding and is common in studies. It is important to reduce bias when the results are interpreted. Our pharmacy will know in which order you received the active medication and the blank and these codes can be made available to any team caring for you subsequently.

We will ask you to then wait for 90 minutes. You are welcome to bring something to read while you wait and you can go to the coffee shop on B-floor of Jubilee Wing as long as you **avoid caffeine-containing drinks.** The pacemaker will provide any back up if the medication slows your own heart rate, and the medication is designed specifically not to lower blood pressure so you should not notice anything at all.

When you come back, we will ask you to perform an exercise test on the treadmill as described below. Prior to the test we will turn down the rate of the pacemaker a little to a rate of 45 beats per minute. This will allow your heart rate to drop gradually. **At the end of each test the pacemaker will be set back to its original setting.**

The exercise tests at both visits will be on a treadmill. The speed of the treadmill will increase gradually during the test and we will ask you to exercise until you can no longer continue and also to score your level of breathlessness at each stage during the exercise.Throughout each test we will continuously sample the air you breathe in and out through a mouthpiece to measure the levels of oxygen and carbon dioxide. This is an accurate way to measure your exercise capacity.

Each test will take about two hours of your time, and we will aim to complete both of the tests at your convenience, but generally at the same time of the day one week apart.

Risks

The risk of any adverse event with this level of exercise is small (less than 1 percent). The adverse effects could include the development of chest pain, hypotension (low blood pressure) or arrhythmias (irregular or abnormal heart beats). A physician will be present to supervise all testing. The heart slowing tablet is approved for use in people with heart failure and angina and has few side effects. Your pacemaker will prevent the heart from going too slow. We do not expect there to be any lasting effects from the single dose that you will take at one of the visits.

Benefits

We want to learn about why patients fell tired and breathless during exercise. It may be that by examining the effects of heart rate limitation on exercise we can alter the way medication is prescribed to patients with heart problems. You are unlikely to benefit personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about your condition, based upon the results of the tests. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What if I don't want to carry on with the study?

You can withdraw from the study but keep in contact with us to let us know your progress. Information collected may still be used.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3928106). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will make your General Practitioner aware that you are participating in this study.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by NRES Committee Yorkshire and Humber – Humber Bridge REC.

Questions

If you have any further questions about the study, or would like to be included in this research, please call Dr Klaus K Witte on **0113 3923131** quoting 'The influence of heart rate limitation on exercise tolerance in patients with chronic heart failure' or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

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The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Academic Unit of Cardiovascular Medicine
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

Information sheet – Atrial fibrillation Opt PACE 2

Chief Investigator: Dr. Klaus K Witte (Tel: 0113 3926642)

Title: The influence of heart rate limitation on exercise tolerance in pacemaker patients.

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

During exercise, heart rate increases. This increase in heart rate during exercise might be less than normal in some patients. It is possible that this contributes to the symptoms during exercise and might reduce the amount of exercise patients can do. It is unknown to what extent heart rate increases contribute to the ability to exercise.

Many of the tablets used for angina and other heart conditions are designed to slow the heart down. It is thought that this might adversely affect exercise capacity but it is not known for sure. The presence of a pacemaker allows us to find out whether slowing the heart rate impairs exercise capacity at no risk that it will go too slowly because your pacemaker has a back up rate to prevent this. This therefore allows us to examine the effects of heart rate slowing on exercise capacity and will help establish how important heart rate increases are in determining exercise capacity in patients and normal people.

Why have I been invited to take part?

We have invited you take part in this study because you have a pacemaker.

Do I have to take part?

Not at all. It is up to you to decide. Dr Witte (the principle investigator) or one of his team will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will ask you to attend the exercise laboratory at Leeds General Infirmary on two occasions a week apart for about one hour. having had **no caffeine for 16 hours before your visit**.

You can eat and drink normally before you arrive except for caffeine-containing drinks.

At the first visit, we might repeat the echocardiogram (heart scan) if you have not had one recently (within three months).

At each visit, we will also first check the pacemaker to make sure that it is functioning normally. We will then slowly reduce the rate setting of the pacemaker to 45 beats per minute. This will allow your heart rate to drop gradually.

At one of the visits we will keep the heart rate-response program activated in order that your pacemaker makes the heart beat faster as you exercise. For the other test this function will be de-activated and your heart rate will increase less during this test. The order in which we do this will be randomised and neither you nor your doctor will know in which order your pacemaker will be reprogrammed. This is called ‘blinding’ and is common in studies. **At the end of each test the pacemaker will be set back to its original setting.**

The exercise tests at both visits will be on a treadmill. The speed of the treadmill will increase gradually during the test and we will ask you to exercise until you can no longer continue and also to score your level of breathlessness at each stage during the exercise.Throughout each test we will continuously sample the air you breathe in and out through a mouthpiece to measure the levels of oxygen and carbon dioxide. This is an accurate way to measure your exercise capacity.

Each visit will take about one hour of your time, and we will aim to complete both of the tests at your convenience, but generally at the same time of the day, one week apart.

Risks

The risk of any adverse event with this level of exercise is small (less than 1 percent). The adverse effects could include the development of chest pain, hypotension (low blood pressure) or arrhythmias (irregular or abnormal heart beats). A physician will be present to supervise all testing. Your pacemaker

will prevent the heart from going too slow. We do not expect there to be any lasting effects from participation in this study.

Benefits

We want to learn about why patients feel tired and breathless during exercise. It may be that by examining the effects of heart rate on exercise we can alter the way medication is prescribed to patients with heart problems. You are unlikely to benefit personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about your condition, based upon the results of the tests. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What if I don’t want to carry on with the study?

You can withdraw from the study but keep in contact with us to let us know your progress. Information collected may still be used.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3928106). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will make your General Practitioner aware that you are participating in this study.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and

given a favourable opinion by NRES Committee Yorkshire and Humber – Humber Bridge REC.

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Questions

If you have any further questions about the study, or would like to be included in this research, please call Dr Klaus K Witte on 0113 3923131 quoting ‘The influence of heart rate limitation on exercise tolerance in patients with chronic heart failure’ or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

5th September 2011

Dear Dr

Re:

Our joint patient has consented to participate in a study exploring cardiac contractility.

The study will involve two or three extra visits to the cardiology department where the patient will undergo echocardiography with the increased heart rate being stimulated by their pacemaker. There are unlikely to be any consequences, but if you have any questions, please feel free to contact me through the hospital switchboard, or my secretary on 01133926642.

Best regards

Dr Klaus Witte MRCP, FESC, MD

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The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Academic Unit of Cardiovascular Medicine
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
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Leeds LS2 9JT

Information sheet – Controls Opt PACE 3

Chief Investigator: Dr. Klaus K Witte (Tel: 0113 3926642)

Title: Defining the optimal heart rate in chronic heart failure

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

We have invited you to take part in this study as a ‘control subject’. In other words information we get from you will be compared with information from patients with heart failure in order to know what is normal and what is abnormal.

Chronic heart failure is a condition most people associate with a weakened heart. However, most patients are comfortable at rest, but develop symptoms of breathlessness and fatigue during activity. This might be due to the fact that in people with heart failure, as the heart rate increases, the power (contractility) of each beat, rather than increasing, as is normal, is reduced. This causes a reversal of the normal response to exercise, where, as activity intensifies cardiac contractile function reduces. This can have a major effect on patients’ ability to exercise, but might also contribute to long term deterioration in heart function.

It is possible therefore that conventional wisdom suggesting we need to make sure that the heart rate goes up more in people with heart failure is wrong. It might be better for people with heart failure to have a lower than usual heart rate to maintain optimal heart contraction.

We want to examine in detail the heart’s contraction in response to increases in heart rate. In order to do this we would like to do an echocardiogram (ultrasound of the heart) during three further visits to the cardiology department while your heart is beating faster. We will make your heart speed up either by asking you to exercise while lying down, during the infusion of a stimulant or while we program the pacemaker to beat faster.

Why have I been invited to take part?

We have invited you take part in this study because you do not have heart failure.

Do I have to take part?

It is up to you to decide. Dr Witte (the principle investigator) will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take

part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will invite you to come to the Cardiology Department at Leeds General Infirmary.

We will program the pacemaker to faster heart rates while we take heart images. The pacemaker will be reprogrammed to its usual settings once this visit is completed.

The visit should take less than 45 minutes to complete.

Risks

The risk of any adverse event with this project is very small. You will be able to stop each of the tests if you develop shortness of breath or angina. An echocardiogram is a very safe test done routinely in the NHS.

Benefits

We want to learn about why patients with heart failure feel tired and breathless during exercise. It may be that by examining the effects of heart rate on heart contraction that we can tailor patients' heart rates to them as an individual. You are unlikely to benefit personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this

consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3926642). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will however make your General Practitioner aware that you are participating in this study and of any important information that comes out of it.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Bradford Research Ethics Committee.

Questions

If you have any further questions about the study, or would like to be included in this research, please call Dr Klaus K Witte on 0113 3926642 or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

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NHS Trust

Dr Klaus Witte
Academic Unit of Cardiovascular Medicine
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The LIGHT Laboratories
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Leeds LS2 9JT

Information sheet – Heart failure Opt PACE 3

Chief Investigator: Dr. Klaus K Witte (Tel: 0113 3926642; 0113 3926285; 0113 3923131)

Title: Defining the optimal heart rate in chronic heart failure.

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't

understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing the consent form.

Purpose

Chronic heart failure is a condition most people associate with a weakened heart. However, most patients are comfortable at rest, but develop symptoms of breathlessness and fatigue during activity. This might be due to the fact that in people with heart failure, as the heart rate increases, the power (contractility) of each beat, rather than increasing, as is normal, is reduced. This causes a reversal of the normal response to exercise, where, as activity intensifies cardiac contractile function reduces. This can have a major effect on patients' ability to exercise, but might also contribute to long term deterioration in heart function.

It is possible therefore that conventional wisdom suggesting we need to make sure that the heart rate goes up more in people with heart failure is wrong. It might be better for people with heart failure to have a lower than usual heart rate to maintain optimal heart contraction.

We want to examine in detail the heart's contraction in response to increases in heart rate. In order to do this we would like to do an echocardiogram (ultrasound of the heart) during two (or three) further visits to the cardiology department while your heart is beating faster. We will make your heart speed up either by asking you to exercise while lying down, during the infusion of a stimulant or (if you have a pacemaker) while we program the pacemaker to beat faster.

Why have I been invited to take part?

We have invited you take part in this study because you have heart failure.

Do I have to take part?

It is up to you to decide. Dr Witte (the principle investigator) will telephone you in a week to allow you the opportunity to ask questions, but there are telephone numbers at the end of this information sheet if you wish to call yourself. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take

part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you agree to participate in this study, we will invite you to come to the Cardiology Department at Leeds General Infirmary.

We will program the pacemaker to faster heart rates while we take heart images. The pacemaker will be reprogrammed to its usual settings once this visit is completed.

The visit should take less than 45 minutes to complete.

Risks

The risk of any adverse event with this project is very small. You will be able to stop each of the tests if you develop shortness of breath or angina. An echocardiogram is a very safe test done routinely in the NHS.

Benefits

We want to learn about why patients with heart failure feel tired and breathless during exercise. It may be that by examining the effects of heart rate on heart contraction that we can tailor patients' heart rates to them as an individual. You are unlikely to benefit personally benefit from participation in this study. However, information learned may benefit future patients with heart problems.

Participation

Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care. There will be compensation for reasonable for travel expenses.

Compensation

If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Part 2

Complaints

If you have a concern about any aspect of this study, you should ask to speak to Dr Klaus Witte who will do his best to answer your questions (0113 3926642; 0113 3926285). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds University or Leeds Teaching Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study. During the regular monitoring of your study or in the event of an audit, your medical record may be reviewed by the Hospital Research Ethics Board. We will however make your General Practitioner aware that you are participating in this study and of any important information that comes out of it.

What will happen to the results of the study?

We will inform all participants of the results of the study and the results will be published in international peer-reviewed journals.

Who has reviewed the study?

All research in the NHS and the University of Leeds is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Bradford Research Ethics Committee.

Questions

If you have any further questions about the study, or would like to be included in this research, please call Dr Klaus K Witte on 0113 3926642 (Research office numbers: 0113 3926285; 0113 3923131), or write to Dr Witte at the Cardiology Department, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX.

Appendix D Consent forms

The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

Centre Number: 1

Study Number: 1

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: The influence of chronotropic incompetence on exercise tolerance in pacemaker patients.

Name of Investigator: Dr Klaus Witte

Please initial box

1. I confirm that I have read and understand the information sheet dated 18th January 2010 (version 1.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Subject	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

The Leeds Teaching Hospitals NHS
NHS Trust

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

Centre Number: 1

Study Number: 1

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: The influence of heart rate limitation on exercise tolerance in pacemaker patients.

Name of Investigators: Dr Klaus Witte

Please initial box

1. I confirm that I have read and understand the information sheet dated 7th June 2013 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

☐

4. I agree to my GP being informed of my participation in the study

5. I agree to take part in the above study.

☐

_____	_____	
Name of Subject	Date	Signature
_____	_____	
Name of Person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Dr Klaus Witte
Division of Cardiovascular and Diabetes Research
Leeds Institute for Genetics, Health and Therapeutics
The LIGHT Laboratories
University of Leeds
Leeds LS2 9JT

The Leeds Teaching Hospitals NHS
NHS Trust

Centre Number: 1

Study Number: 1

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Defining the optimal heart rate in heart failure.

Name of Investigator: Dr Klaus Witte

Please initial box

1. I confirm that I have read and understand the information sheet dated 3rd March (version 1.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Subject	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

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