Exercise in heart failure

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Abstract

Introduction

In ambulatory patients with chronic stable heart failure, the cardinal symptom of exercise intolerance is not fully resolved despite optimal medical treatment. Identifying other treatments to improve exercise intolerance may improve quality of life.

Methods

I investigated 2 treatments that may improve exercise intolerance in patients with heart failure. First, I conducted a review of oxygen supplementation in cardiovascular disease and then investigated the exercise capacity of 46 patients (mean age 75 years, 63% male and median N-terminal pro-B type natriuretic peptide 1432 (interquartile range: 543-2378 ng/l)) with heart failure and normal ejection fraction (HeFNEF), using different oxygen supplementation (21%, 28% and 40%). Second, I conducted a literature review on the acute effects of water immersion (WI) and swimming in patients with heart failure and reduced ejection fraction (HeFREF) and then investigated the haemodynamic and echocardiographic changes during warm WI in 17 patients with HeFREF (NYHA I and II; mean age 67 years, 88% male and mean left ventricular ejection fraction 33%) and 10 normal subjects.

Results

In patients with HeFREF, high doses of oxygen have negative haemodynamics effects however low doses may improve exercise tolerance. In patients with HeFNEF, increasing oxygen supplementation during exertion leads to a small increase in exercise time. In patients with HeFREF, although exercise in water appears to be safe, the studies conducted have been small, very heterogeneous and inconclusive. In patients with HeFREF, warm WI causes an acute increase in cardiac output and a fall in systemic vascular resistance.

Conclusion

Warm WI is well tolerated; however, whether swimming can be recommended as alternative to other forms of exercise or rehabilitation in patients with HeFREF needs further studies. In patients with HeFNEF, a disproportionate increase in left atrial pressure on exercise contributes to symptoms. However extra-cardiac mechanisms may also contribute to impaired exercise tolerance. Studies should also focus on treatment of co morbidities.

Table of contents

List of Tables

List of Figures

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Author's declaration:

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the university of Hull or the university of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.

I had a substantial and direct contribution to the conception, design of the 2 studies included in this MD thesis. This involved submitting the proposal (protocol, patient information sheets, consent forms) to the local patient advisory group (Trans-Humber consumer research panel), regional ethics committee and to the Health Research Authority. I liaised with the hospital physiotherapy department to organise the hydrotherapy pool sessions and mandatory safety training and with the works and estates department to ensure the safety of electrical equipment for the warm water immersion in patients with chronic heart failure study. I analysed, wrote and interpreted the data to both the studies included in this MD thesis. I also, solely conducted the review in chapter 2 and the review in chapter 4, I had a substantial direct contribution to the conception, design, analysis, writing and interpretation of data.

Publication from the thesis

1. Shah P, Pellicori P, Rimmer S, Rigby AS, Clark AL. Effect of increased inspired oxygen on exercise performance in patients with heart failure and normal ejection fraction. *Int J Cardiol*. 2018;**268**:166-169
2. Shah P, Pellicori P, Macnamara A, Urbinati A, Clark AL. Is Swimming Safe in Heart Failure? A Systematic Review. *Cardiol Rev*. 2017;**25**:321-325
3. Parin Shah, Pierpaolo Pellicori, Anna Kallvikbacka-Bennett, Jufen Zhang, Daniel Pan, Andrew L Clark. Warm water immersion in patients with chronic heart failure: A pilot study. *Clin Res Cardiol*. 2018 [Epub ahead of print]

Abbreviations

LVEF:	left ventricular ejection fraction
HeFREF:	heart failure with reduced ejection fraction
HeFNEF:	heart failure with normal ejection fraction
HIV:	human immunodeficiency virus
HCM:	hypertrophic cardiomyopathy
DCM:	dilated cardiomyopathy
LV:	left ventricle
ARVC:	arrhythmogenic right ventricular cardiomyopathy
BNP:	B-type natriuretic peptide
NTproBNP:	N-terminal pro-B type natriuretic peptide.
ARNI:	angiotensin-aldosterone and the neutral endopeptidase systems
MRI:	magnetic resonance imaging
CI:	cardiac index
CO:	cardiac output
HR:	heart rate
SVR:	systemic vascular resistance
LTOT:	long term oxygen therapy
NYHA:	New York Heart Asssociation
BTS:	British thoracic society
COPD:	chronic obstructive pulmonary disease
ESC:	European society of cardiology
ET:	exercise time
BMI:	body mass index
SBP:	systolic blood pressure

IHD: ischaemic heart disease

Hb: haemoglobin

ECG: electrocardiogram

ECHO: echocardiogram

LA: left atrium

IVS: interventricular septum

FCV: forced vital capacity

FEV1: forced expiratory volume in 1 second

ACEi: Angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker

MRA: mineralocorticoid receptor antagonist

CHF: chronic heart failure

HR: heart rate

SV: stroke volume

Peak VO_2: peak oxygen consumption

LVEDD: left ventricular end diastolic diameter

LVESD: left ventricular end systolic diameter

6 MWT: six minute walk test distance

QOL: quality of life

WI: water immersion

WWI: warm water immersion

FBC: full blood count

BCP: biochemical profile

EDV: end diastolic volume

ESV: end systolic volume

LAD:	left atrial diameter
LAV:	left atrial volume
TAPSE:	tricuspid annular plane systolic excursion
TR:	tricuspid regurgitation
IVC:	inferior vena cava
CRT:	cardiac resynchronization therapy

Chapter 1 Introduction

Heart failure is a clinical syndrome of symptoms and signs of congestion (exercise intolerance, shortness of breath, fatigue, ankle swelling, elevated jugular venous pressure and pulmonary crackles). Heart failure is caused by structural or functional abnormalities of the heart.[1] Identifying the underlying cause is important in the treatment of heart failure as a precise aetiology enables specific treatment. (Table 1) The diagnosis of heart failure is conventionally reached if a patient has symptoms compatible with heart failure with a compatible abnormality of the heart on investigations.

By far the most common cause of heart failure is an abnormality of myocardial function and, for better or worse, the commonest index of myocardial function used is left ventricular ejection fraction (LVEF). Patients with a LVEF of less than 40% are classed as having heart failure with reduced ejection fraction (HeFREF).[1] Some patients who have signs and/or symptoms of heart failure may have a LVEF more than 50%. These patients are classed as heart failure with normal ejection fraction (HeFNEF), if they have some other objective evidence of cardiac dysfunction in the shape of raised natriuretic peptide level and a structural abnormality of the heart (such as left atrial dilation, left ventricular hypertrophy or signs of diastolic dysfunction).[1] Recently the European Society of Cardiology have suggested that patients with heart failure may be divided into three categories; HeFREF (LVEF less than 40%), HeFNEF (LVEF more than 50%) and the new category of heart failure with mid- range ejection fraction.[1] This new category comprises of patient with an LVEF of between 40-49% with a raise natriuretic peptide and structural abnormality

of the heart. It is important to differentiate patients with heart failure according to their LVEF due to the different aetiologies and response to therapies.[2]

Table 1: Causes of heart failure

Causes of heart failure		
Diseased myocardium		
Ischaemic heart disease		
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytotoxic drugs, immunomodulating drugs, antidepressant drugs, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetic drugs
	Radiation	
Immune-mediated and inflammatory damage	Infections	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV).
	Non infectious	Lymphocytic/giant cell myocarditis, autoimmune diseases hypersensitivity and eosinophilic myocarditis.
Infiltrative	Malignancy	
	Not malignancy related	Amyloidosis, sarcoidosis, haemochromatosis, glycogen storage diseases, lysosomal storage diseases.

Table1: Causes of heart failure

Metabolic derangements	Hormonal	Thyroid disease, parathyroid disease, acromegaly, growth hormone deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy
	Nutritional	Deficiency in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition, obesity
Genetic abnormalities		HCM, DCM, LV non- compaction, ARVC, restrictive cardiomyopathy, muscular dystrophies and laminopathies.
Abnormal cardiac loading conditions		
Hypertension		
Valve and myocardium structural defects	Acquired or congenital	Mitral, aortic, tricuspid and pulmonary valve disease. Atrial and ventricular septum defects
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis, Pericardial effusion
	Endomyocardial	Hyper eosinophilic syndrome, endomyocardial fibrosis, endocardial fibro elastosis
High output states		Severe anaemia, sepsis, thyrotoxicosis, Pagets disease, arteriovenous fistula, pregnancy
Volume overload		Renal failure, iatrogenic fluid overload
Arrhythmias		
Tachy-arrhythmias		Atrial, ventricular arrhythmias.
Brady-arrhythmias		Sinus node dysfunctions, conduction disorders.

Abbreviations: HIV: human immunodeficiency virus, HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, LV: left ventricle, ARVC: arrhythmogenic right ventricular cardiomyopathy. Table adapted from the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[1]

1.1 Investigations for the diagnosis and aetiology of heart failure

The investigations typically used to diagnose heart failure are, firstly, imaging of the heart. Echocardiography is the most widely used form of imaging and provides crucial information on cardiac chamber volumes, ventricular systolic and diastolic function, ventricular wall thickness, valve function and estimate pulmonary artery systolic pressure to establish the diagnosis, aetiology and guide appropriate therapy.[3] In more recent years, plasma natriuretic peptides, which have a high negative predictive value but a low positive predictive value for the diagnosis of heart failure, have been used as a "rule out" test when echocardiography is not immediately available.[4] (Upper limit of normal in the non-acute clinical setting; B-type natriuretic peptide (BNP) is 35 pg/ml and N-terminal pro-B type natriuretic peptide. (NTproBNP) is 125 pg/ml; in the acute clinical setting, BNP, 100 pg/ml and NTproBNP, 300 pg/ml)[1]

Other imaging modalities such as cardiac magnetic resonance imaging, single-photon emission computed tomography, radionuclide ventriculography and positron emission tomography may be considered to answer specific clinical questions to aid in the aetiology and management of patients with heart failure.[5,6]

Apart from imaging of the heart, other investigations should be considered during the assessment of patients with suspected heart failure to aid in the aetiology, severity and co morbidities associated with heart failure. An electrocardiogram may provide information on the aetiology of heart failure and indications for therapies (anticoagulation, cardiac resynchronisation therapy), chest X –ray provides signs of severity (pulmonary congestion), pulmonary causes of shortness of breath and blood

tests (full blood count, renal function, liver function tests, thyroid function and ferritin) aid in the monitoring of drug therapy.[1] Other specific investigations, targeted to find the underlying cause of heart failure, are crucial to detect reversible/treatable causes of heart failure when the suspicion arises.[1]

1.2 Epidemiology

Heart failure affects 1- 2% of the adult population in the western world and the prevalence increases with age, peaking at around 7 - 8% in those aged over 75 years.[7,8,9,10,11] Epidemiological studies suggest that roughly half the patients with heart failure have reduced LVEF (<40%) whilst the other half have normal LVEF (LVEF > 50%) [12,13,14] Although in the United Kingdom, the national heart failure audit report for 2014-2015, suggested that over 70% of patients admitted with acute heart failure had reduced LVEF.[15] Prevalence data of patients with heart failure from hospital cohorts may be skewed as patients with HeFNEF have less severe symptoms and tend to have fewer admissions to hospital for cardiovascular problems.[16,17] The proportion of patients with HeFREF and HeFNEF varies depending on the definition of heart failure applied, clinical setting (acute admissions or clinics), type of study (epidemiological or audit) and method and criteria of analysing left ventricular ejection fraction.[12,17,18] The current European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, quotes a wide range, between 22-73%, for the proportion of patients with heart failure who have a normal LVEF.[1]

1.3 Characteristics of patients with heart failure

Although both patients with HeFREF and HeFNEF present with similar symptoms of shortness of breath, reduced exercise tolerance and signs of congestion, their characteristics are different. Compared to patients with HeFREF, patients with HeFNEF tend to be older, more overweight and more likely to be female.[12,19,20,21] Patients with HeFREF and HeFNEF have different co-morbidities, with non-cardiovascular co-morbidities more common in patients with HeFNEF. In the UK national heart failure audit, compared to patients with HeFREF, patients with HeFNEF, were more likely to have hypertension (61% versus 52%), valve disease (33% versus 23%) and chronic obstructive pulmonary disease (19% versus 17%) and less likely to have ischaemic heart disease (40% versus 51%).[15] In epidemiological studies as well, compared to patients with HeFREF, patients with HeFNEF are more commonly have atrial fibrillation, hypertension and chronic obstructive pulmonary disease but ischaemic heart disease was less common.[19,20]

Patients with HeFREF and HeFNEF spend similar length of time in hospital.[17] The most common cause of admission in patients with HeFREF is due to acute heart failure with fluid congestion whilst for patients with HeFNEF it is due to non-cardiovascular causes.[22]

Mortality in patients with heart failure remains high. In the EURObservational programme one year all-cause mortality of ambulatory patients with heart failure was 7% which increased to 17% in patients with heart failure who were hospitalised.[23] Some studies suggest that the mortality is similar between patients with HeFREF and HeFNEF[17] whilst others suggest an increased mortality in patients

with HeFREF.[14,19,23] Patients with HeFNEF tend to die of non-cardiovascular causes whilst patients with HeFREF tend to die of cardiovascular causes.[19]

1.4 Symptoms of heart failure

Patients with heart failure have significantly more symptoms, that hinder their activities of daily living, than any other chronic medical condition.[24] The clinical course of patients with heart failure is one of a gradual decline with intermittent acute episodes of worsening symptoms which tend to need hospital admissions. (Figure 1) Patient's symptoms vary depending on the severity of heart failure.

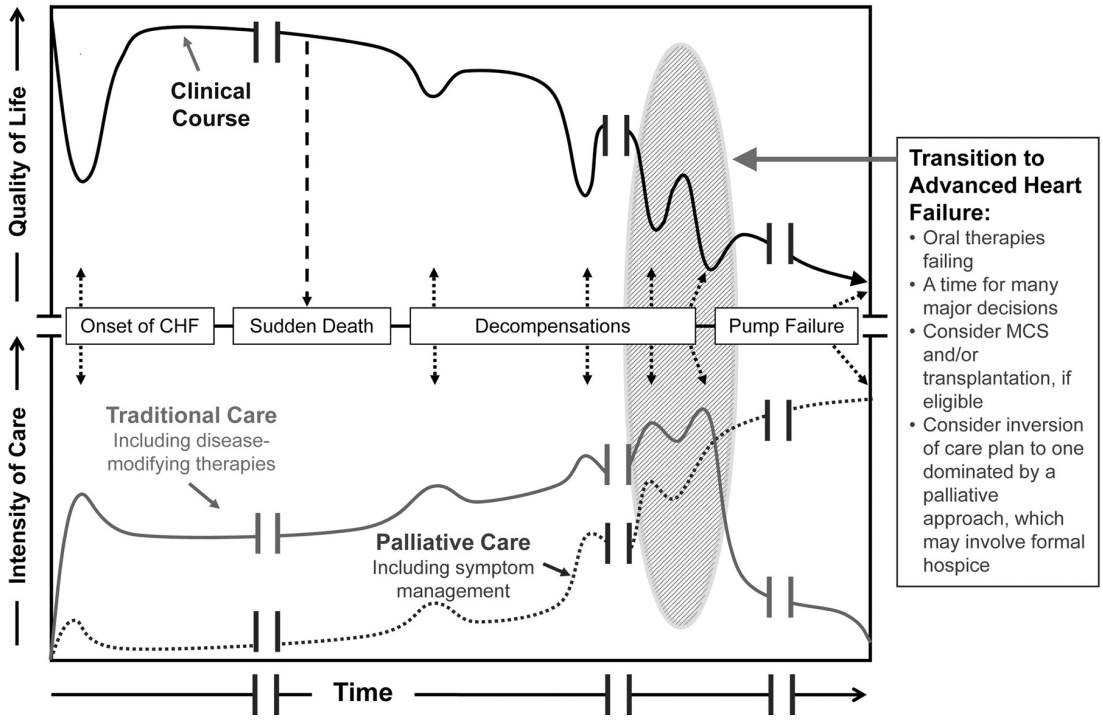

Figure 1: A depiction of the clinical course of heart failure with associated types and intensities of available therapies.[25]

1.4.1 Symptoms of acute heart failure

Acutely, patients may present with a rapid onset or gradual worsening of the symptoms and signs of heart failure, which requires urgent therapy. These symptoms represent either acute pulmonary oedema or a gradual progression of fluid congestion (increasing peripheral oedema and shortness of breath) over the preceding few weeks.[1] The deterioration in symptoms may be caused by a primary cardiac dysfunction (myocardial infarction, valve insufficiency or arrhythmia) or by an extrinsic factor such as infection or non-adherence to diet or medications. An acute presentation of heart failure may be the first presentation of heart failure or worsening of chronic heart failure.[1]

1.4.2 Symptoms of chronic stable heart failure

More commonly, in ambulatory patients with chronic stable heart failure, the cardinal symptom is exercise intolerance due to breathlessness and fatigue.[26,27] Both patients with HeFREF and HeFNEF have reduction in exercise capacity and both have markedly abnormal cardiopulmonary exercise tests which are indistinguishable from each other, even though there is a difference in their LVEF at rest.[28] Despite optimal medical treatment, the symptoms of exercise intolerance have a significant bearing on the lifestyle of patients with heart failure. Both patients with HeFREF and HeFNEF have similar impairment of health related quality of life scores.[29] The mechanisms causing exercise intolerance in patients with heart failure are complex.[30]

1.5 Determinants of exercise capacity in patients with heart failure

1.5.1 Determinants of exercise capacity in patients with HeFREF

In most stable ambulatory patients with HeFREF, haemodynamics at rest are not substantially impaired.[31] Studies in patients with HeFREF, have shown that markers of cardiac dysfunction at rest such as LVEF, left ventricular size, right ventricular ejection fraction and neuro hormonal markers are not determinants of exercise capacity.[32,33,34] In a study by Shelton and colleagues, 42 normal subjects and 23 patients with HeFREF were exercised at increasing workloads of 15, 30, 45 and 60 watts every 3 minutes on a cycle ergometer. Compared to normal subjects, in patients with HeFREF, there was no difference in the increase in cardiac index (measured by inert gas method) or oxygen consumption from rest to peak work load of 60 watts but there was significant lower mixed venous oxygen content on exercise.[31] This implies that the peripheral tissues extract greater quantities of oxygen at much lower levels of exercise in patients with heart failure.[31] The major determinants of exercise in patients with HeFREF appear to lie in the periphery, with abnormal skeletal muscle performance being chiefly implicated.

1.5.2 Determinants of exercise capacity in patients with HeFNEF

The situation may be different in ambulatory patients with HeFNEF: again, haemodynamics at rest may be normal, but during exercise, there is impaired cardiac output[35] and a disproportionate increase in left atrial pressure.[36] In a study by Borlaug and colleagues, of 17 patients with HeFNEF and 19 control subjects, there was no difference in haemodynamic and echocardiographic findings at rest apart from a significantly raised E wave and reduced E/A ratio in patients with HeFNEF.[37]

However during maximal-effort upright cycle stress testing (starting at 25 watts and increasing by 25 watts every 3 minutes until exhaustion), compared to normal control subjects, patients with HeFNEF had a significantly reduced exercise capacity (total exercise time of 180 ±71 versus 455±184 seconds in controls; P<0.001).[37] The determinants of reduced exercise capacity in patient with HeFNEF were impaired arterial vasodilation, blunted increase in heart rate and cardiac output. In another study by Maeder and colleagues, compared to normal subjects, patients with HeFNEF again had a significantly lower exercise time and work load during resistance cycling on a stationary bike (workload was increased by 5-15 watts at 1-minute intervals). In this study determinants of exercise capacity, measured invasively, were a significantly lower peak stroke volume index leading to a reduced peak cardiac index, a significantly higher peak systemic vascular resistance and an early significantly peak in pulmonary capillary wedge pressure.[38] In a recent systemic review of 17 cohorts of patients with HeFNEF, in whom invasive haemodynamic and oxygen consumption was measured during rest and exercise, impaired exercise capacity was related in order of effect size to chronotropic incompetence, elevated pulmonary capillary wedge pressure, blunted augmentation of arteriovenous oxygen content difference and reduced stroke volume reserve.[39] This contributes to symptoms of dyspnoea and fatigue on exertion and is associated with worse long term outcomes.[40]

1.6 Current treatment for patients with chronic stable heart failure

The goal of treatment in patients with heart failure is to improve symptoms and signs, reduce hospital admissions and improve prognosis. Treatments which improve functional capacity are also important to consider especially because heart failure is a chronic disease which significantly affects quality of life. There are various treatments, pharmacological and non-pharmacological, available which have proven to improve symptoms and/or prognosis of patients with heart failure.

1.6.1 Pharmacological treatment of patients with HeFREF

In the past 30 years several trials on neuro hormonal antagonists (angiotensin converting enzyme inhibitors, [41,42] mineralocorticoid receptor antagonists[43,44] and beta blockers[45,46]) have shown a benefit of improving symptoms, reducing hospitalization and improving prognosis in patients with HeFREF. (Figure 2 and 3) When used individually their benefits are modest but in combination they reduce 2 year mortality by 50-60%.[47] A new therapeutic class, which acts on the renin-angiotensin-aldosterone and the neutral endopeptidase systems (ARNI), has been introduced. In patients with HeFREF, compared to enalapril, the ARNI, sacubitril-valsartan reduced heart failure admissions, cardiovascular and all-cause mortality.[48] Sacubitril-valsartan treatment is therefore recommended in patients with HeFREF, who remain symptomatic despite optimal medical therapy.[1,49]

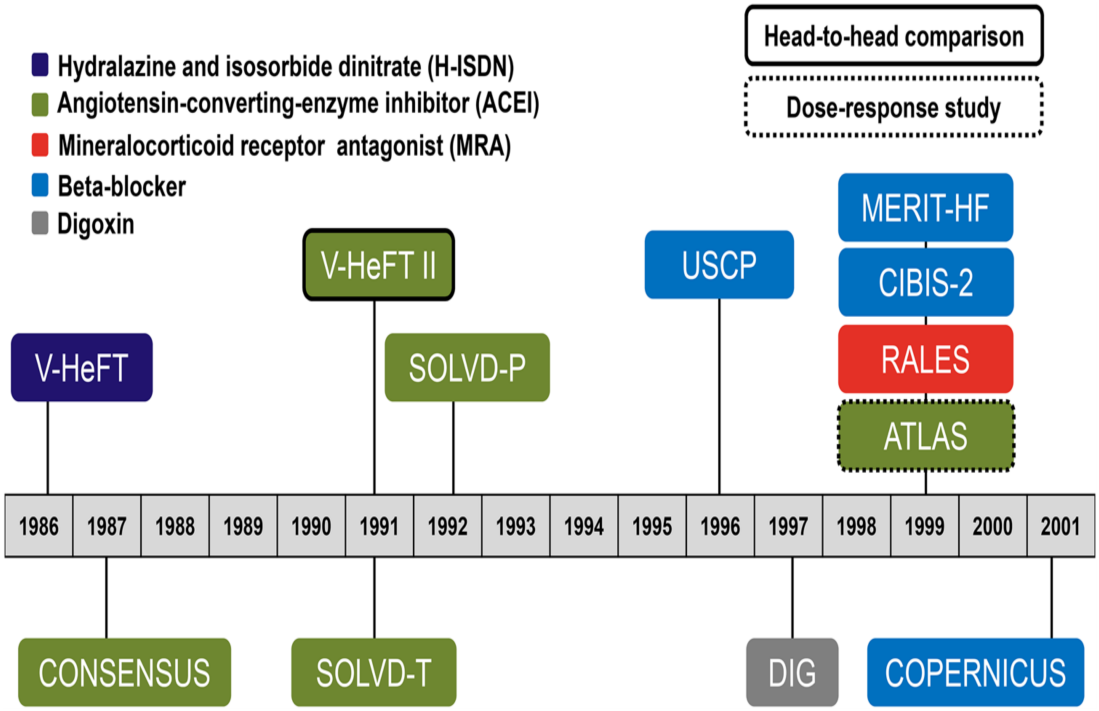

Figure 2: Heart failure-reduced ejection fraction: thirty years of progress – positive drug trials 1986–2001.[50]

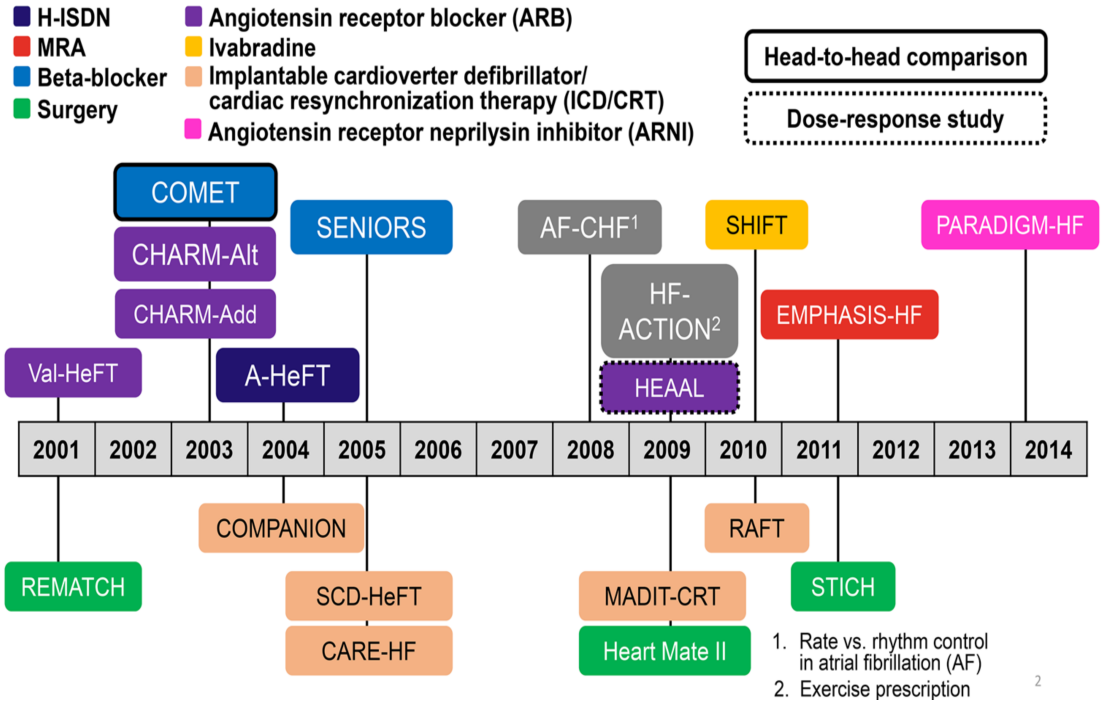

Figure 3: Heart failure-reduced ejection fraction: thirty years of progress - positive drug, device and other trials 2001–2014.[50]

1.6.2 Pharmacological treatment of patients with HeFNEF

The situation is very different for patients with HeFNEF. Considering the prevalence, outcomes, future projections and lack of effective therapies, HeFNEF represents the single largest unmet need in cardiovascular medicine.[51] None of those pharmacotherapies which are beneficial in patients with HeFREF have any mortality or morbidity benefit in patients with HeFNEF.[52,53,54,55,56,57] Only diuretics seem to be helpful in that they relieve congestion.[1] Part of the reason may be that patients with HeFNEF tend to be older and have more co morbidities; the co morbidities make it more difficult to be certain that any symptoms are due to the heart and majority of the symptoms are due to non-cardiovascular causes..[58,59] Only a small proportion of patients with HeFNEF have a specific genetic, pericardial, myocardial, or valvular aetiology to treat.[2] The PARAGON-HF trial is currently looking at cumulative number of cardiovascular deaths and heart failure hospitalizations of valsartan and sacubitril compared to valsartan on its own. (ClinicalTrials.gov Identifier: NCT01920711)

1.7 Exercise in patients with chronic stable heart failure

Cardiovascular disease remains largely a preventable disease. Although there are non-modifiable risk factors (male gender, race and family history), there are other risk factors which are amenable to intervention (blood pressure, abnormal blood sugar, high cholesterol, smoking and obesity). [60] A common modifiable risk factor is sedentary lifestyle, which had been associated with increased cardiovascular events and premature death.[61] Conversely physical activity such as walking, swimming, cycling and even stair climbing reduces many risk factors for cardiovascular disease such as diabetes and also reduces mortality.[62,63,64] Exercise still improves symptoms and outcomes in patients with cardiovascular disease. In patients with coronary artery disease, regular physical exercise improves angina free activity and mortality.[65,66] In a recent study by Howden and colleagues on sixty-one healthy, sedentary, middle-aged participants compared to controls, an exercise programme for 2 years (where increases in training frequency, duration, and intensity progressed over time), increased maximal oxygen uptake, left ventricular end diastolic volume and resting stroke volume.[67] The authors theorised that this improvement in left ventricular compliance and distensibility may provide protection against the future risk of heart failure with a normal ejection fraction.

Traditionally cardiac rehabilitation was mainly prescribed to patients following a myocardial infarction and coronary artery bypass surgery but now the patient scope has widened to include patients with heart failure. Despite the great improvements in treatment during the past 30 years, in patients with HeFREF, many patients with heart failure remain symptomatic. Exercise training improves symptoms in patients with heart failure who are already optimised on heart failure medications and in the

HF-ACTION study there was a signal towards improvement in all-cause mortality, hospitalization, cardiovascular mortality and heart failure hospitalizations.[78] Patients with heart failure frequently report exercise intolerance and/or fatigue, which might not necessarily represent impaired central haemodynamics.[68,69] Abnormalities of peripheral muscle and peripheral haemodynamics play a substantial role in the symptoms reported by many patients.[70] In patients with heart failure, there is a shift from type I to type II skeletal muscle fibres which have a lower concentration of glycogen and are less fatigue resistant; there is loss of muscle mass and fibre atrophy.[71] The changes in peripheral muscle seen in patients with heart failure are similar to those seen in normal subjects who have stopped training.[72]

1.7.1 Exercise in patients with HeFREF

In the past, it was commonly assumed that rest is beneficial in patients with heart failure,[73,74] but clinical trials of exercise training conducted in patients with HeFREF have demonstrated unequivocal benefits in terms of symptom relief, with a suggestion that training might improve prognosis. Current guidelines now all firmly recommend regular physical activity and structured exercise training for patients with HeFREF.[75] Exercise training does not appear to have much effect on central haemodynamics, but rather improves the peripheral muscle bulk and metabolic function.[70,76]

ExTraMATCH was a meta-analysis of 9 trials enrolling a total of 801 patients with HeFREF (mean age 60 ± 9 years, 88% male, mean NYHA class 2.6 ± 0.6, 59% ischaemic heart disease, mean LVEF 28%) randomised patients to exercise programmes between 8 weeks to a year or control (no exercise). The exercise

programmes mainly involved cycling and walking sessions between 50 -80% of peak exercises measure by heart rate or peak oxygen capacity. Studies with a long duration of exercise programme also had home-based exercise programmes included after a period of supervised exercise training session. (table 2) The exercise programmes led to a significant reduction in mortality (exercise arm: 88 (22%) versus control arm 105 (26%) with a hazard ratio of 0.65, 95% confidence interval, 0.46 to 0.92;) and hospital admissions.[77] A Cochrane review in the same year concluded that exercise training improved exercise capacity.[68] The more recent HF–ACTION trial recruited 2331 patients with HeFREF (median LVEF: 25%) from 82 centres across the United States, Canada, and France. Patients were randomised to exercise (supervised exercise training followed by unsupervised exercise training at home, 3 sessions per week of 30-35 minutes each at 70% of heart rate reserve, total of 36 sessions) or usual care. Compared to usual care, exercise training had a 4% absolute risk reduction in the primary event rate at 3 years (death or hospitalization from any cause).[78] Exercise capacity measured by peak oxygen consumption and 6 minute walk test significantly increased in the exercise arm compared to the usual care arm from baseline to 3 months.[78] Regular exercise and organise cardiac rehabilitation should be prescribed as part and parcel of the overall management of patients with HeFREF.

Table 2: Characteristics of studies included in the ExTraMATCH meta-analysis

Study	No in group (exercise/ control)	Duration of programme (days)	Description of exercise programme	Intensity of programme
Belardinelli 1999	50/49	420	Supervised cycling, 60 minutes three days a week for eight weeks, then two days a week	60% peak oxygen consumption
Dubach 1997	24/26	56	Supervised walking, two hours daily; supervised cycling 40 minutes four days a week	80% peak oxygen consumption
Giannuzzi 1997	46/42	168	Supervised cycling, 30 minutes three days a week for two months, then home based 30 minutes for three days a week and walking for 30 minutes	80% peak heart rate
Hambrecht 1995	34/35	168	Supervised and home-based walking, calisthenics, cycling 40-60 minutes a day	70% peak oxygen consumption
Kiilavuori 2000	12/15	182	Supervised cycling 30 minutes three days a week for three months, then home-based training (walking, cycling, rowing, and swimming)	50-60% peak oxygen consumption
McKelvie 2002	90/91	364	Supervised aerobic (cycling, treadmill, arm) and resistance training 30 minutes three days a week for three months, then home based aerobic training three days a week	60-70% peak heart rate
Zanelli 1997	76/79	364	Supervised aerobic (cycling, treadmill, arm) and resistance training 30 minutes two days a week and home based cycling three days a week for two months, then only home based aerobic training five days a week	70% peak oxygen consumption
Wielenga 1999	41/39	84	Supervised cycling, walking, ball game 30 minutes three days a week for eight weeks, then two days a week	60% peak heart rate
Willenheimer 1998	22/30	112	Supervised interval cycling training (90 second exercise and 30 second rest) for 15-45 minutes two days a week	80% peak oxygen consumption or grade 15 Borg scale

Table referenced from the ExTraMATCH meta-analysis.[77]

1.7.2 Exercise in patients with HeFNEF

The predominant symptom that patients with HeFNEF complain of is exercise intolerance. At rest patients with HeFNEF may have normal central haemodynamics, but during exercise, there is a disproportionate increase in left atrial pressure, which contributes to symptoms.[36]

Rather less is known about the long-term effects of training on cardiac haemodynamics in patients with HeFNEF. In a study of 7 patients with HeFNEF, who completed 1 year training (walking or cycling 3 times per week with session times increasing through the year to a maximum of 200mins/week), compared to baseline, exercise training did not significantly change cardiac haemodynamics (blood pressure, heart rate, cardiac output and stroke volume) or echocardiographic measurements (left ventricular volume, LVEF or TDI e).[79]

The effects of exercise training on symptoms and quality of life in patients with HeFNEF have been reviewed in two meta-analyses which included randomised control trials with training programmes for 12 to 24 weeks. In the meta-analysis by Fukuta and colleagues of 5 randomised control trials involving 245 patients with HeFNEF, compared to usual care, exercise training improved peak exercise oxygen uptake (V_{O_2}; weighted mean difference (WMD) 2.283, 95% confidence interval (CI) 1.318–3.248 ml/min/kg), six-minute walk distance (30.275 m (4.315–56.234)), and Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score (8.974 points (3.321–14.627)).[80] In another meta-analysis by Pandey and colleagues of 6 randomised control studies involving 276 patients with HeFNEF, compared to usual

care, exercise training had significantly improved cardiorespiratory fitness (mL/kg per min; weighted mean difference, 2.72; 95% confidence interval, 1.79–3.65) and quality of life (weighted mean difference, −3.97; 95% confidence interval, −7.21 to −0.72)[81] There have been no studies looking at the effect of training on hospitalization or mortality in patients with HeFNEF.

1.7.3 Types of exercise that are beneficial in patients with heart failure

Various exercise programmes have been designed to assess the effect of training on exercise capacity, symptoms and mortality in patients with heart failure. The sorts of exercises that have been shown to be helpful in patients with HeFREF include: aerobic exercise on a treadmill or a cycle at 3-5 times per week at a heart rate of 60-70% of the maximum predicted heart rate; resistance training of peripheral muscles and calisthenics.[68,77,78]

The sort of exercise training that have improved quality of life in patients with HeFNEF are community-based walking intervention with an education program, supervised endurance training on a treadmill, cycle or track walking or a mixture of endurance (cycling) and resistance training. These training programmes lasted anywhere between 12 to 24 weeks with at most 3 sessions per week.[80,81]

The ESC guidelines on acute and chronic heart failure recommends regular aerobic exercise sufficient to provoke mild or moderate breathlessness to improve functional capacity, symptoms and reduce the risk of HF hospitalization and in patients with HeFREF.[1] The guidelines also advice health professional to actively refer patients

with heart failure to a structured exercise programme.[1] The guidelines do to mention any criteria on what exercise to avoid.

1.8 Conclusion and rationale for thesis

The cardinal symptom of ambulatory patients with heart failure is exercise intolerance. In patients with HeFREF, despite optimal treatment with pharmacological agents, exercise intolerance may still persist and impact patient's quality of life. In patients with HeFNEF, no pharmacological treatment has shown any benefit in the mortality, morbidity. In a study by Dunlay and colleagues of patients with heart failure almost 60% of the patients reported difficult with at least one or more activities of daily living. Mortality also increased with the increasing difficulty in activities of daily living.[82]

1.9 Aim and objectives

1.9.1 Aim

Another focus of treatment could be to improve quality of life by improving exercise tolerance. Exercise programmes are an attractive therapeutic option because it improves exercise capacity and quality of life in patients with heart failure.[78]
The overall aim of the thesis is to identify therapies that improve quality of life by improving exercise capacity in patients with heart failure.

1.9.2 Objectives:

1) Use supplemental oxygen to improve symptoms of exercise capacity in patients with heart failure.

2) Swimming as an alternative method of exercise in patients with heart failure

In the next chapter I will discuss the use of oxygen in medicine and in particular cardiovascular disease. In small studies of patients with HeFREF or pulmonary hypertension, increasing inspired oxygen improves exercise tolerance.[83,84,85] In patients with HeFNEF apart from diuretics there are no other treatments which are useful to improve symptoms. The effect of oxygen supplementation has not been studied in ambulatory patients with HeFNEF. Oxygen is widely used and cheaply available. I have reviewed the literature to understand the safety and benefits of oxygen supplementation. This is followed by a study on the use of short-term supplemental oxygen during exercise in patients with HeFNEF in chapter 3.

Many patients with heart failure cannot participate in exercise programmes which are designed around treadmills and stationery cycles due to other co morbidities like arthritis. Swimming may be an ideal form of exercise but whether it is safe in patients with heart failure has not been answered comprehensively in previous studies of water immersion or swimming.[86] In chapter 4, I have reviewed the literature on the safety and benefit of water immersion and swimming and then in chapter 5, I have described a study to assess the safety of immersing patients with heart failure in warm water.

Chapter 2 The use of supplemental oxygen in patients with shortness of breath

Oxygen is cheap, widely available and used in a variety of health care settings to relieve symptoms of shortness of breath and/or treat tissue hypoxia. Annually, the need for supplemental oxygen is projected to be around 800,000 individuals at a cost of 1.8 billion dollars.[87] Oxygen administration is often sub optimal due to poor prescribing, monitoring and inappropriate doses are often administered.[88,89,90] The use of oxygen is embedded in guidelines for the management of acute shortness of breath for a variety of conditions.[91,92] During emergency and resuscitation situations, advanced life support guidelines recommended oxygen to be delivered in high concentrations which may lead to systemic hyperoxia.[93,94] Oxygen is one of the first therapies to be administered when patients are admitted with shortness of breath due to acute heart failure regardless of their oxygen saturations.

Compared to the acute hospital setting, out-patient prescription of oxygen supplementation is more regulated, especially in pulmonary diseases where hyperoxia can cause carbon dioxide retention.[92] Physicians often prescribe long term oxygen therapy (LTOT) to patients with heart failure in the belief that it relieves symptoms of shortness of breath.[95] However there is no compelling evidence for the use of supplemental oxygen in heart failure.[96]

2.1 Effects of hyperoxia on tissues and organs in humans

Oxygen is an essential requirement in the metabolism. Majority of oxygen consumed by the mitochondria is utilized for adenosine triphosphate (ATP) generation.[97] The mitochondrial electron transport chain reduces the elemental molecular oxygen to ionic oxygen by the relay of electrons making oxygen usable for ATP generation, during this process, oxidizing free radicals are generated.[98]

Excess or inappropriate oxygen supplementation, leading to hyperoxia of tissues and organs, may be deleterious, with toxicity increasing with the increase of oxygen partial pressure.[99] Under hyperoxic conditions, a large influx of oxygen free radicals are produced. The mass effect of oxygen free radical elevation, caused by hyperoxia, disrupts the balance between oxidants and antioxidants, and this in turn disrupts homeostasis resulting in damage to cells and tissues.[100] Oxygen supplementation causes a spectrum of lung injury, ranging from mild tracheobronchitis to diffuse alveolar damage. Oxygen supplementation also has toxic effects on the cardiovascular system. In fact, oxygen supplementation has been shown to cause a reduction in heart rate since the early 19th century.[101]

2.2 Methodology of study selection

In this chapter I will discuss the effect of supplemental oxygen on the cardiac haemodynamics in healthy subjects and patients with respiratory and cardiac conditions such as myocardial infarction and heart failure.

The studies discussed in this review were selected by myself to highlight the effects of oxygen on haemodynamics in various conditions. This is not a full review of all studies of oxygen supplementation but a selection of studies to highlight certain methodologies and theories of the effects of oxygen on cardiovascular haemodynamics. In patients with heart failure and reduced ejection fraction, the studies described in this review were divided into two types. First, I will describe studies where cardiac haemodynamics were assessed with oxygen supplementation. Second, I describe studies where exercise capacity was assessed using varying inspired oxygen (FiO_2).

2.3 The effect of supplemental oxygen on cardiac haemodynamics in normal subjects

Oxygen supplementation has been perceived as beneficial but even in healthy individuals, near 100% oxygen supplementation had an adverse effect on cardiac haemodynamics. In a study by Barratt-Boyes and Wood of 26 healthy individuals, compared to room air, 95% inspired oxygen for an average of 78 minutes significantly reduced heart rate, increased stroke index and systemic vascular resistance but there was no change in cardiac index (using Fick's principle).[102] In a study by Eggers and colleagues, of 9 healthy individuals, compared to room air,

100% oxygen supplementation from a 120 litre Tissot spirometer filled with compressed oxygen via a large bore, low resistance, one way valve, rubber spirometer mouthpiece for 30 minutes significantly decreased cardiac output (using Stewart-Hamilton equation and radioactive iodinated serum albumin; 3.09 to 2.72 L/min/m^2, p = < 0.02) and heart rate (62 to 58 bpm), and increased systemic vascular resistance (1103 to 1344 dynes/sec/cm^5) and mean blood arterial pressure (77.9 to 84.0 mmHg).[103] The cardiac haemodynamics changes during oxygen supplementation persisted for a further 40 minutes after stopping oxygen supplementation. In a study by Daly and Bondurant of 15 healthy male subjects, compared to room air, 100% oxygen supplementation via a mouth piece with a low resistance valve, nose clips and a Douglas bag, significantly reduced heart rate (70 ± 8.7 to 64 ± 8.9 bpm) and cardiac index (using indocyanine green dilutional method; 3.01± 0.52 to 2.67± 0.47 L/min/m^2), and increased systemic blood pressure (93.6 ± 9.0 to 95.3 ± 9.0 mmHg) and systemic vascular resistance ((16.3 ± 4.6 to 18.5 ± 2.9 U).[104] (Table 3)

More recent studies, using invasive catheters or magnetic resonance imaging (MRI) had mixed results on the changes in cardiac haemodynamics during oxygen supplementation. In a study by Bodetoft and colleagues of 16 healthy individuals, compared to room air, 100% oxygen supplementation through a standard reservoir bag mask, significantly decreased heart rate by 9% from a baseline of 63 ± 2.7 bpm, cardiac output by 10% from a baseline of 6046 ± 223ml/min and left ventricular perfusion by 23% (measured by dividing coronary blood flow by the measured left ventricular mass on MRI).[105] In contrast, a study by Mak and colleagues, of 12 subjects who had normal left ventricular function, high concentration oxygen for 20

minutes administered via a nonrebreather mask with a reservoir bag filled with 100% oxygen, there was no significant change in heart rate, cardiac output and stroke volume (measured using invasive pressure catheters) but an increased systemic vascular resistance (1626 ± 148 to 1901 ± 181 dynes/sec/cm^5) and left ventricular filling pressures (11 ± 2 to 13 ± 2 mmHg).[106] (Table 3)

Table 3: The effect on cardiac haemodynamics with the administration of near 100% oxygen in healthy volunteers

Use of oxygen in normal subjects							
Authors	**Year**	**N**	**%O_2**	**Method**	**CI/CO**	**HR**	**SVR**
Barrat-Boyes and Wodd	1958	20	95	Fick's technique	No change	↓	-
Eggers et al	1961	8	100	Radioactive indicator	↓	↓	↑
Daly and Bondurant	1961	15	100	Indocyanine green dilution	↓	↓	↑
Mak et al	2001	19	100	Thermodilution	No change	No change	No change
Bodetoft et al	2011	16	100	MRI	↓	↓	-

Abbreviations: N: number of patients, CI: cardiac index, CO: cardiac output, HR: heart rate, SVR: systemic vascular resistance.

In a recent meta-analysis by Smit and colleagues of 19 studies, where varying concentrations of oxygen was administered to healthy volunteers, heart rate reduced by 6.5% (95% confidence interval (CI) −8.1% to −5.0%), stroke volume decreased by 3% (95% CI −5.7% to −0.3%), cardiac output (CO) reduced by 10.2% (95% CI −12.9% to −7.3%), systemic vascular resistance increased by 12.1% (95% CI 8.6% to 15.7%).[107] Despite these findings oxygen supplementation is blindly administered in patients especially when they are admitted with an acute illness.

2.3.1 Underlying mechanisms of oxygen supplementation causing cardiac haemodynamics changes

The mechanisms underlying the acute cardiovascular effects of oxygen supplementations are unknown, but several mechanisms have been suggested. Increased oxygen supplementation decreases heart rate and cardiac output, increases systemic arterial pressure and systemic vascular resistance, strikingly similar to the cardiovascular effects of certain vasoconstrictors.[108] Hyperoxia, through the brain stem, may induce hyperventilation, which in turn induces hypocapnia and systemic vasoconstriction.[109,110] Another possible sequence of events after oxygen supplementation may be constriction of the peripheral vascular bed centrally via the sympathetic nervous system with a resultant increase in arterial blood pressure and subsequent slowing of the heart rate due to the carotid sinus reflex. With a slower heart rate and with maintenance of the same stroke volume, there would be a decrease in cardiac output.[103] Others have suggested that the decrease in heart rate and subsequent cardiac output may be due to attributed to the chemoreceptor reflex or the baroreceptor reflex.[111]

Nitric oxide plays an important part in cardiovascular function. A decrease in vasodilator endothelial nitric oxide caused by a reaction with oxygen free radicals, may play a role in both the peripheral and the coronary vascular effects of hyperoxia.[112] Increased production of oxygen free radicals have also been implicating in myocardial function. Oxygen free radicals can prolong ventricular relaxation by impairing myocyte calcium homeostasis and cardiac beta-receptor signalling.[113,114] As a result of consumption of endothelial-derived nitric oxide by oxygen free radicals in response to hyperoxia there is an enhancement left ventricular diastolic distensibility.[115,116]

2.4 The use of oxygen in pulmonary conditions

Prescribing LTOT is considered mainly in pulmonary diseases. The current British Thoracic Society (BTS) guidelines recommend LTOT in patients with chronic obstructive pulmonary disease (COPD) who have either a resting partial pressure of oxygen (PaO_2) ≤7.3 kPa or PaO_2 ≤8 kPa with evidence of peripheral oedema, polycythaemia (haematocrit ≥ 55%) or pulmonary hypertension.[96] The use of LTOT in patients with COPD who fit the BTS guideline criteria has been shown to reduce hospitalizations and mortality.[117,118] However, in patients with stable COPD and moderate oxygen desaturations (SpO_2 between 89-93%) or exercise induced desaturation (during 6 minute walk test, a SpO_2 ≥80% for ≥5 minutes and <90% for ≥10 seconds), compared to usual care, LTOT did not change the prognosis, time to first hospitalization, number of COPD exacerbations, quality of life or 6 minute walk test.[119]

In the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of pulmonary hypertension, oxygen supplementation is recommended only in patients with evidence of symptomatic benefit and correctable desaturations on exercise with increased inspired oxygen.[120] The recommendation has been extrapolated from studies using supplemental oxygen for COPD.[121] A more recent study of 22 patients with pulmonary hypertension (idiopathic pulmonary arterial or chronic thrombo-embolic pulmonary hypertension) who were a mean age of 61 ± 14 years and had a mean pulmonary artery pressure of 35 ± 9mmHg underwent bicycle ergospyrometry to exhaustion on different days. Increasing inspired oxygen (FiO_2) from 21% to 50% led to a doubling of exercise time (from 571 ± 443 seconds to 1242 ± 514 seconds) and maximal work rate increased from 113 ± 38 watts to 132 ± 48 watts.[122] Oxygen supplementation improves oxygen availability in muscles and to the brain and there is a reduction of the excessive ventilatory response to exercise thereby enhancing ventilatory efficiency.[122]

2.5 The use of oxygen in cardiac conditions

Oxygen is used liberally in the acute setting when patients present with shortness of breath due to a myocardial infarction or acute pulmonary oedema. The administration of oxygen continues, without reassessment, during the admission especially in patients admitted with acute heart failure. The notion that oxygen does not cause harm has now come into question for various cardiac conditions.

2.5.1 Use of oxygen in myocardial infarction

In the past, studies on the use of oxygen supplementation during a myocardial infarction have shown reduction in infarct size in dogs[123] and in humans (number and magnitude of ST elevation using surface electrodes).[124] Oxygen supplementation also improves symptoms of angina.[125] This led to the wide spread use of supplemental oxygen in patients presenting with suspected myocardial infarction. However, a small study of 6 patients with acute myocardial infarction, cautioned about the negative effect of oxygen supplementation on cardiac haemodynamics. Compared to room air, 10 l/min oxygen supplementation was associated with a decrease in cardiac output and stroke volume with a rise in heart rate.[126] In a recent meta-analysis by Smit and colleagues of 6 studies, administration of oxygen to patients with coronary artery disease, reduced heart rate by −4.7% (95% confidence interval (CI) −7.9% to −1.5%) with no difference in the stroke volume, −2.7% (95% CI −5.7% to 0.4%), but a reduction in cardiac output −9.6% (95% CI −12.3% to −6.9%) and an increase in systemic vascular resistance of 11.4% (95% CI 7.2% to 15.7%).[107]

Other studies assessing the effect of acute oxygen supplementation on left ventricular function and pain relief during an acute presentation of myocardial infarction have had mixed results. In a study by Dekleva and colleagues, of 74 patients admitted with a myocardial infarction, compared to usual care (thrombolysis), patient who had hyperbaric oxygen therapy on top of their usual care improved their left ventricular ejection fraction 3 weeks post myocardial infarction,[127] whereas in the study by Shandling and colleagues of 66 patients who were admitted with myocardial infarction, compared to usual care (thrombolysis),

there was no significant difference in left ventricular ejection fraction with the use of hyperbaric oxygen on top of usual care.[128] Although, Shandling and colleagues reported a shorter time to pain relief and resolution of ST segments in patients who received hyperbaric oxygen.

Most studies of oxygen supplementation were conducted in an era before percutaneous coronary intervention was the standard treatment for patients presenting with ST elevation myocardial infarction. In a study of 136 patients admitted with their first presentation of ST elevation myocardial infarction uncomplicated by cardiogenic shock or hypoxia and treated with primary percutaneous coronary intervention, were randomised to high flow oxygen or titrated oxygen (maintain oxygen saturation of between 93-96%).[129] There was no difference in left ventricular ejection fraction, myocardial infarct mass or troponin levels between patients in the high flow oxygen arm or the titrated oxygen arm. The neutral results may have been due to the small sample size and the study commented on the need for a larger randomised control trial to resolve the clinical uncertainty. In a more recent study by Stub and colleagues on 441 patients, who presented with a ST elevation myocardial infarction, compared to no oxygen supplementation, 8 litres oxygen significantly increased creatinine kinase, recurrent myocardial infarction, arrhythmias and myocardial infarct size (on cardiac MRI at 6 months).[130]

A Cochrane review on oxygen therapy in acute myocardial infarction concluded no benefit in the routine use of supplemental oxygen but could not rule out any harmful effects with supplemental oxygen.[131] The current ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment

elevation myocardial infarction recommend oxygen supplementation in patients who present with a myocardial infarction when they are breathless, hypoxic, or have signs and/or symptoms of acute heart failure.[132] Majority if the patients presenting with a ST elevation myocardial infarction will have shortness of breath associated with chest pain however their oxygen saturations will be normal. Non-invasive monitoring of blood oxygen saturation greatly helps when deciding on the need to administer oxygen or ventilatory support.

2.5.2 Use of oxygen in heart failure

Unlike the situation for patients with severe COPD, in whom oxygen improves survival, the use of oxygen in patients with chronic heart failure has not been as well evidenced with a lack of systematic research. Thus, guidelines from different societies differ in their recommendations on the prescription of oxygen to patients with heart failure.

The current BTS guidelines for home oxygen use in adults recommend oxygen therapy in patients with "advanced" heart failure.[96] Although, the guidelines mention that there is no evidence for the use of supplemental oxygen, they recommend its use in patients with heart failure with a resting arterial partial pressure PaO_2 ≤7.3 kPa, or a higher PaO_2 of ≤8 kPa in the presence of peripheral oedema, polycythaemia (haematocrit ≥55%) or evidence of pulmonary hypertension.[96] Patients with heart failure who have nocturnal hypoxaemia but no significant daytime hypoxia due to obstructive or central sleep apnoea. The BTS guidelines recommends prescribed nocturnal oxygen therapy at 1-2 L/min and assessment for other modalities of ventilatory support. Administration of nocturnal oxygen improves sleep study

variables (apnoea hypopnoea index, reduced duration of central sleep apnoea and reduction in the duration of sleep disordered breathing) with no significant improvement in left ventricular ejection fraction, New York Heart Association (NYHA) functional class, or frequency of ventricular arrhythmias during sleep.[96]
In a study by Clark and colleagues of 114 patients with HeFREF who had severe symptoms (breathlessness either at rest or on minimal exertion) and at least moderate LV systolic dysfunction, compared to optimal medical treatment only, patients who received LTOT (15 hours a day, 28% oxygen using opened labelled containers), there was no difference in the Minnesota living with heart failure score, 6-minute walk test distance, NTproBNP level and left ventricular ejection fraction.[133]
Although, the study was stopped early due to poor patient adherence to the oxygen prescription. As most patients seem to have a positive placebo effect with the use of oxygen supplementation, the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure only recommend the use of oxygen in patients with heart failure for palliative treatment in order to provide relief from dyspnoea.[1,134]

2.5.2.1 The effect of oxygen on acute haemodynamics in patients with heart failure

The failing heart requires a higher filling pressure. The higher the filling pressure, the worse the cardiac function – hence an intervention causing a rise in filling pressure is deleterious. In a study by Haque and colleagues, of 10 patients with severe heart failure (NYHA class III or IV) admitted for the assessment and consideration of an orthopotic heart transplant, compared to room air, 100% oxygen administered for 20 minutes decreased cardiac output (from 3.7 ± 0.3 to 3.1 ± 0.4 litres/min [mean ± SE], $p < 0.01$) and stroke volume (from 46 ± 4 to 38 ± 5 ml/beat

per min, $p < 0.01$), increased pulmonary capillary wedge pressure (from 25 ± 2 to 29 ± 3 mm Hg, $p < 0.05$) and systemic vascular resistance (from 1,628 ± 154 to 2,203 ± 199 dynes's/cm5, $p < 0.01$) with no change in pulmonary vascular resistance.[135] (Table 4) In a study by Mak and colleagues, of 16 patients with heart failure with mild to moderate symptoms (NYHA class I or II), compared to room air, 100% oxygen administered for 20 minutes decreased cardiac output (from 4.6 ± 0.4 to 4.1 ± 0.3 liters/min; $p <0.05$) and stroke volume (from 64 ± 6 to 57 ± 5 ml/beat, $p < 0.05$), increased systemic vascular resistance (from 1,626 ± 148 to 1909 ± 181 dynes's/cm^5, $p < 0.05$) and LV end-diastolic pressure (from 21 ± 3 to 25 ±3 mmHg).[106] These cardiac haemodynamics changes may further impair blood flow and hence oxygen delivery to tissues.[88]

Table 4: studies on use of oxygen in patients with heart failure.

Use of oxygen in patients with heart failure							
Authors	**Year**	**N**	**%O_2**	**Method**	**CI/CO**	**HR**	**SVR**
Haque et al	1996	10	100	Thermodilution	↓	No change	↑
Mak et al	2001	16	100	Thermodilution	↓	No change	↑

Abbreviations: N: number of patients, CI: cardiac index, CO: cardiac output, HR: heart rate, SVR: systemic vascular resistance.

Although high concentrations of oxygen have negative haemodynamic effects on patients with heart failure, lower doses of supplemental oxygen do not significantly change cardiac haemodynamics. In a study by Park and colleagues on 13 patients with heart failure, compared to room air, 40% oxygen for 15 minutes did not significantly affect cardiac output, heart rate, blood pressure or systemic vascular resistance.[136] In the HOT trial sub study of 19 patients with heart failure (mean age 59 ± 14 years, 37% male and mean LVEF of 24 ± 10% in NYHA class III/IV), acute haemodynamics changes of 28% oxygen were assessed invasively using cardiac catheterization. Compared to room air, inhaling 10 minutes of 28% oxygen caused an increase in cardiac output (from 3.9 ± 1 to 4.2 ± 1 litres/min; $p < 0.05$), increased and LV end-diastolic pressure (from 21 ± 3 to 25 ±3 mmHg) but no change in heart rate (76 ± 13 to 77 ±14 bpm; $p = 0.35$), stroke volume (from 51 ± 16 to 55 ± 17 ml/beat, $p = 0.11$) and systemic vascular resistance (from 20.0 ± 4.8 to 18.7 ± 3.6 woods units, p).[133] As there are few data available from previous studies, the sample size was largely empirical. The study was stopped after 19 patients when it became apparent that oxygen had very few effects.[133] Despite these mixed results on the benefits of oxygen in patients with heart failure, LTOT is still being prescribed.[95]

2.5.2.2 The effect of oxygen on exercise capacity in patients with heart failure

Ambulatory patients with heart failure mainly complain of symptoms of dyspnoea and fatigue during exertion. Trials of oxygen supplementation during exercise in patients with HeFREF have yielded mixed results. Moore and colleagues reported a dose dependent increase in exercise time from 548 ± 275 seconds on room air to 632 ±288 seconds with FiO_2 of 50% in 12 patients with HeFREF during resistance cycling on a stationary bike to maximum capacity (workload was increased by 15

watts at 2-minute intervals).[83] In contrast, in a study by Russell and colleagues compared to 21% FiO_2 in 16 patients with HeFREF (LVEF <35%), there was no effect of increasing FiO_2 to 60% on exercise time (21% = 595 ± 179 seconds and 60% oxygen = 602 ± 181 seconds) during symptom limiting resistance cycling on a stationary bike (2-minute resting period followed by increasing workloads of 25 watts every 3 minutes).[137] Although there was a trend toward a decrease in venous lactate with 60% oxygen, this was not significant (p = 0.11). In a study by Restrick of 12 patients with stable chronic heart failure, there was no difference in 6 minute walking distance with room air or oxygen delivered at 2 and 4 l/min (288m, 201; -133 to 45m, 220; -97 to 53m respectively).[138] In a study by Koshy and colleagues of 31 patients with HeFREF (mean LVEF 31%) who undertook maximal incremental exercise tests (workload increased by 10 watts every minute), exercise time increased from 501 ± 25 seconds on room air to 525 ± 25.1 seconds and 536 ± 24 seconds, with FiO2 of 28% and 40%, respectively. Maximal metabolic equivalents were 3.5 ± 0.2 on room air and 3.7 ± 0.2 and 3.7 ± 0.2 on 28% and 40% oxygen, respectively. Maximal workload was 78 ± 5 Watts on room air and 83 ± 4 and 84 ± 4 on 28% and 40% oxygen, respectively.[84] (Table 5)

Table 5: Characteristics of studies of oxygen supplementation in HeFREF

Study	No of pts	Age	NYHA	FiO_2	Delivery of oxygen	Exercise
Moore 1992	12	55	II/III	Air/ 30%/ 50%	Non- rebreathe valve Douglas bag (inspiratory reservoir 500 L) Parkinson-Cowan gas meter	Bicycle ergometer exercise tests at 15W increments every 2 mins to maximum capacity
Restrick 1992	12	64	III	Air/ 24%	Portable oxygen cylinder (230L capacity) via nasal cannualae	6-minute walk test with/ without carrying oxygen cylinder
Russel 1999	16	56	II/III	Air/ 60%	Hans-Ru- Dolph 3-way nonrebreathing valve, a 170L nondiffusable reservoir bag, a humidifier, and interchangeable tanks of 21% or 60% oxygen	staged, symptom-limited cycle ergometry (25W every 3 minutes)
Koshy 2018	31	68	II/III	Air/ 28%/ 40%	Venturi mask connected to an oxygen supply	Bicylcle ergometer test at 10W increments every minute to maximum capacity

2.6 How does increased oxygen supplementation cause haemodynamic changes in patients with heart failure

The mechanisms that limit exercise tolerance in patients with heart failure are not certain, however the symptoms that limit patients are dyspnoea and muscle fatigue. Moore and colleagues theorised a number of reasons why oxygen may help improve exercise capacity. Increased oxygen supplementation may divert blood from respiratory muscles to the exercising limbs which may improve oxygen delivery to active muscle. Oxygen enrichment by supplementation of oxygen was accompanied by a fall in ventilation and in dyspnoea score, possibly mediated by carotid-body chemoreceptors.[83]

An increased exercise ventilatory response in patients with heart failure is accompanied by an increase in physiological dead space to tidal volume ratio. A reduction in exercise ventilation by oxygen enrichment of inspired air may be achieved by increased oxygen supplementation because increased alveolar oxygen partial pressure will improve oxygen transfer in poorly ventilated lung regions, with a consequent improvement in arterial saturation.[83] Restrick and colleagues also theorised that the reduced exercise capacity may due to a ventilation- perfusion mismatch however unlike in patients with chronic lung disease, patients with heart failure do not benefit from oxygen supplementation in terms of exercise capacity despite some improvement in oxygen saturations.[138] Russell and colleagues suggested that the increased oxygen supplementation did not significantly increase peripheral oxygen saturations. Moreover, the small increase in arterial oxygen delivery to the legs did not enhance limb oxygen uptake because venous oxygen content also increased.[137]

All the studies on the effect of oxygen in patients with heart failure were in reduced LVEF. Pharmacological therapies in patients with HeFNEF have not been shown to be of any benefit. Another important aim of treatment in patients with HeFNEF is to alleviate symptoms and to improve wellbeing.[1] The clinical hallmark of HeFNEF is exercise intolerance due to shortness of breath and/fatigue, at least partially due to an abnormal increase in left atrial pressure during exercise.[139] Reduction in delivery of oxygen to the periphery and myocardium might contribute to, and aggravate, breathlessness and fatigue.[139]

In a recent meta-analysis by Pandey and colleagues of peak oxygen uptake and hemodynamic or echocardiographic parameters during exercise, compared to normal subjects, patients with HeFNEF had a significantly lower peak oxygen uptake. Compared to normal subjects, patients with HeFNEF had significant impairment in haemodynamics during exercise; reduced chronotropic response reserve, exaggerated increase in pulmonary capillary wedge pressure, blunted augmentation of arteriovenous oxygen content difference and reduced stroke volume reserve.[140]

2.7 Limitations

This is not a systematic review of the use of supplemental oxygen in cardiovascular disease. The studies here are selected to highlight the merits and pitfalls of the use of oxygen in patients with cardiovascular disease. Studies were also selected to emphasize the study methodology and practicality of the use of supplemental oxygen.

2.8 Conclusion

The use of high flow oxygen lead to unwanted haemodynamic effects in patients with HeFREF. Lower doses of oxygen (less than 40% inspired oxygen) did not have any objective symptomatic benefit when administered over 15 hours but studies using oxygen during exercise had mixed results in improving exercise capacity. This may be of benefit to patients with HeFNEF in terms of exercise capacity. In the next chapter I aim to assess the effects of increasing inspired oxygen fraction (FiO_2) on exercise capacity in patients with HeFNEF.

Chapter 3 Effect of increased inspired oxygen on exercise performance in patients with heart failure and normal ejection fraction

3.1 Introduction

Clinical trials in patients with HeFNEF have failed to demonstrate any pharmacological treatment that improves morbidity and mortality.[52,53,54,55,56,57] The failure may be due to the inclusion of patients who may have symptoms pre dominantly due to other causes such as breathlessness due to respiratory diseases or obesity.[141,142] Other reasons, why clinical trials have failed, is that patients with HeFNEF may have a transitory phase of symptoms and a lower rate of cardiovascular events.[143] Patients with HeFNEF have a lower rate of mortality and admissions with acute heart failure compared to patients with HeFREF but higher than patients those with other cardiovascular diseases (coronary artery disease and hypertension and diabetes.[144]

Another focus of treatment may be to alleviate symptoms and to improve wellbeing.[1] Patients with HeFNEF and HeFREF have similar symptoms and reduction in quality life.[145,146] The cardinal symptom of ambulatory patients with HeFNEF is exercise intolerance. Improving symptoms of exercise intolerance may improve patient's quality of life.[147,148]

3.2 Aim of the study

Trials of oxygen supplementation during exercise in patients with HeFREF have yielded mixed results.[83,84,137,138] (Table 6) There have been no studies on the effect of increased inspired oxygen on exercise capacity in patients with HeFNEF. The aim of the study was to assess the effects of increasing inspired oxygen fraction (FiO_2) on exercise capacity in patients with HeFNEF.

Table 6: Studies that investigated the effect of increasing FiO_2 on exercise capacity in patients with HeFREF.

Authors	Year	Type of exercise test	Method of O_2 delivery	Control	Inspired FiO_2
Moore et al[83]	1992	Bicycle ergometry	-	21%	30%, 50%
Restrick et al[138]	1992	6 minute walk test	Nasal cannulae	21%	2l, 4l oxygen
Russell et al[137]	1999	Bicycle ergometry	Mouth piece connected to Hans-Rudolph 3-way nonrebreathing valve	21%	60%
Koshy et al[84]	2016	Bicycle ergometry	Venturi mask	21%	28%, 40%

Abbreviations: O_2: oxygen, FiO_2: inspired oxygen, l: litres

3.3 Methods

This was a single centre, randomised, single-blinded, cross-over trial in patients with HeFNEF.

3.3.1 Patient identification and inclusion and exclusion criteria

Ambulatory patients older than 50 years of age attending a community heart failure clinic were considered for the study if they had a clinical diagnosis of heart failure with a left ventricular ejection fraction (LVEF) by echocardiography $\geq$ 45% and a plasma concentration of amino terminal pro brain type natriuretic peptide (NTproBNP) $\geq$ 220 ng/l within the last 12 months.[149] If a patient did not have an echocardiography or NTproBNP in last 12 months this was repeated by the echocardiographer at the screening visit. Patients had to be taking a diuretic.

Patients unable to exercise, and those who had severe mitral or aortic valve disease on echocardiography in the last 12 months, haemoglobin < 100 g/l, estimated glomerular filtration rate <30 ml/min/1.73m^2) in the last 3 months, or severe chronic obstructive pulmonary disease (FEV_1 less than 50% predicted) were excluded from the study. Patients who had a myocardial infarction or cerebrovascular event within the preceding month were also excluded from the study.

Around 5000 patients are enrolled and followed up in the local heart failure clinic from a single centre. Of these, around 45% of the patients have HeFNEF. Suitable patients were identified in clinic and from the database, and invited for an initial screening visit. These patients had already been consented to enable the investigators

to contact them regarding clinical trials. The cohort has electronic notes with all the relevant diagnosis, investigations and treatments which would make it more efficient to identify the potential patients for the trial.

Suitable patients received a patient information leaflet and were invited for a screening visit. At the screening visit the rationale of the study was explained, number of visits and contact details of the study team in case of any further queries were given. All patients gave written informed consent after patients had read the information leaflet and any queries had been answered. The patients then had a full history and clinical examination which was performed by myself to ensure patients had signs and symptoms of heart failure and there were no contraindications to the study.

The research conforms to the Helsinki declaration. Ethics approval was granted by an external research ethics committee (research and ethics committee number 16/YH/0272). The trial was registered on the ClinicalTrials.gov website (Identifier: NCT02949531). The study design, protocol, patient leaflets were presented to the local Trans-Humber consumer research panel. The panel included lay people whose advice was valuable in amending the protocol.

3.3.2 Randomization and blinding

The randomisation was generated using computer software. Patients were randomised by a member of the research team on the day of signed consent to one of three groups.

- Group 1: 21% oxygen, 28% oxygen, 40% oxygen;

- Group 2: 28% oxygen, 40% oxygen, 21% oxygen;
- Group 3: 40% oxygen, 21% oxygen, 28% oxygen

All three oxygen concentrations were delivered via a Venturi mask. This allowed the investigator to control the oxygen concentration administered from the wall mounted oxygen supply which was situated behind the patient. The oxygen supply was connected to the Venturi mask via a long tube. The patients and the technicians conducting the test were blinded to FiO_2 administered. Blinding of oxygen supplementation to patient is important to avoid bias at the patient level.

3.3.3 Exercise protocol

The study was conducted in the same exercise room using the same equipment for every patient and at all visits. A stationery cycle was used as the equipment for exercise testing as it offers the convenience of a stable sitting position.[150] A ramp protocol was used where the patients cycled at 60 revolutions per minute starting from 0 watts for 4 minutes; subsequently, resistance increased gradually by 10 watts/minute. This protocol was selected as it would assess a patient's maximal or near maximal function with a high degree of confidence and reproducibility.[150] Patients undertook three maximal incremental exercise tests on a stationary cycle using a standardised exercise protocol with a different FiO_2 at each exercise test in random order. Patients were encouraged to exercise to their maximum capacity. At the end of the exercise test, patients were assisted off the cycle and sat on a chair.

The reason for stopping and modified Borg scale score were recorded after 5 minutes of stopping the exercise test. Modified Borg scale is a uni-dimensional, numerical

scale with verbal anchors relating to the numbers.[151,152] The modified Borg scale score assess symptom intensity in response to a specific stimulus, in this case maximal symptom limiting maximum exercise test.[153,154]

Inspired oxygen fraction was administered at different concentrations (21%, 28% and 40%) in a random sequence which was computer generated. There have been no studies assessing the effect of increased FiO_2 on the exercise capacity of patients with HeFNEF but there have been studies that have investigated the effect of FiO_2 used in on the exercise capacity of patients with HeFREF. (Table 4) The control was taken as 21% (room air) which was administered via the Venturi mask. 28% and 40% were selected as the increased FiO_2 as they are commonly used in clinical practice and these concentrations have also shown to be of benefit in improving exercise capacity in patients with HeFREF. The Venturi mask was the chosen mode of delivery of FiO_2 as it is able to deliver this increase FiO_2 reliably and in a blinded fashion.

During the exercise test, patients had a blood pressure cuff attached on the left arm, pulse oximeter attached to the index finger of the right hand and 12 lead ECG attached to the chest to continuously monitor blood pressure, oxygen saturation, heart rate and rhythm respectively. The three exercise tests were conducted at approximately weekly intervals.

3.3.4 Primary and secondary endpoints

The primary endpoint was exercise time (ET; seconds). Secondary end points included: peak workload (watts), peak heart rate (beats per minute), and peak arterial oxygen saturation (O_2 saturation; percentage).

3.3.5 Statistical analysis

There have been no studies conducted on the effect of increased FiO_2 in patients with HeFNEF therefore a power calculation was not conducted. An estimate of the sample size was derived from previous studies in which the effect of increased FiO_2 was assessed in patients with HeFREF where a sample size of between 12 and 36 patients showed significant difference in exercise capacity with increased FiO_2.[83,84,137,138] A larger sample size of 50 patients was chosen to assess the effect of increased FiO_2 because patients with HeFNEF have multiple co-morbidities which affect their exercise capacity.

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± standard deviation (SD) and non-normally distributed continuous variables as median and interquartile range.

Between-group means of the primary and secondary endpoints were compared using analysis of variance (ANOVA). The method uses 'least squares' to fit linear models. We used one-way ANOVA with repeated measures on dose-group. An underlying assumption of the F test is independence of observations. In a repeated measures design, this assumption is almost certainly violated (observations from the same subject are likely to be correlated). To overcome this, we used a correction factor to the degrees-of-freedom for the F test. We chose one developed by Box which is conservative in a statistical sense (if significant by Box it will be significant by the rest).[155] Other assumptions of ANOVA were met. Paired t-tests were then used to compare the primary and secondary endpoints between exercise tests.

Sub-group analysis of the primary and secondary endpoints were pre-specified and used to explore the relation between age, haemoglobin, creatinine, NTproBNP, body mass index (BMI), sex, the use of a walking aid and heart rhythm (atrial fibrillation vs sinus rhythm) and the end points. Continuous variables were compared with the primary and secondary endpoints using Pearson correlation coefficient. The difference in primary and secondary outcome between the different strengths of inspired oxygen was compared with between sex, use of walking aid and heart rhythm. The current European Society of Cardiology guidelines on heart failure set a LVEF cut-off at 50% for diagnosing HeFNEF, so we re-analysed the primary and secondary endpoints separately for patients above and below this LVEF cut-off. Primary and secondary endpoints are shown in box plots. All analyses were performed on SPSS (V 23.0) and Stata statistical computer packages. A statistical significance was assumed at $P<0.05$ (two tailed).

There were no missing values for exercise time so an analysis of missing data by multiple imputations was unnecessary.[156]

3.3.6 Results

3.3.7 Screening for eligible patients

217 patients with a diagnosis of HeFNEF were screened. 116 of the patients either declined to participate or were unable to be contacted. 25 patients were unable to exercise due to mobility issues such as previous strokes or arthritis. 10 patients were excluded as they are enrolled in another study. 3 patients had died on review of their medical records. 13 patients did not meet the inclusion and exclusion criteria for the study; 5 had an NTproBNP of less than 220 ng/L, 4 patients were found to have an LVEF of < 45%, 2 patients were not on any diuretics, and 2 had severe COPD. (Figure 4)

Of the 50 patients who were eligible to participate and signed the consent form, 46 patients completed the three visits, and 4 withdrew, as shown in figure 4. Compared to previous clinical trials that included patients with HeFNEF, this study had similar demographic character, this study had patient with a higher NTproBNP and more patients had atrial fibrillation. Compared to other trials in HEFNEF, patients in this study were more likely to be on an ACEi, beta-blocker or MRA. (Table 7)

Table 7: Baseline demography compared with other clinical trials

	All patients (N = 46)	**I-PRESERVE (N = 2067)**	**CHARM- Preserved (N = 1514)**	**PEP-CHF (N = 424)**
Age (yrs)	75 (8)	72 (7)	67 (11)	75
Male Sex (%)	29 (63)	840 (41%)	920 (61%)	46%
SBP (mmHg)	146 (23)	137 (15)	136 (19)	138
Heart rate (bpm)	69 (11)	72 (11)	71 (12)	74
BMI (kg/m^2)	31 (7)	30 (5)	29 (6)	27.5
II (%)	37 (80)	426 (21)	931 (62)	
III (%)	5 (11)	1582 (77)	556 (67)	
Hypertension (%)	28 (61)	1834 (89)	984 (69)	333 (79%)
Diabetes (%)	16 (35)	570 (28)	434 (29)	88 (21%)
IHD (%)	20 (44)			
Stroke (%)	3 (7)	198 (10)	140 (9)	
NTproBNP (ng/l)	1432 (543 – 2378)	360 (139-987)		335
Hb (g/l)	12.9 (1.7)	14 (2)		
Creatinine(µmol/l)	102 (80-137)	100 (32)		95
Sinus rhythm (%)	21 (46)	1714 (83%)	1075 (71)	345 (81%)
Mean LVEF (%)	54 (7)	59 (0.9)		65%
LA size (cm)	4.3 (0.6)			4.5
IVS (cm)	1.1 (0.2)			1.3
Beta blocker (%)	37 (80)	1225 (59)	847 (56)	235 (55%)
ACEi (%)	30 (65)	538 (26)	296 (20)	
Loop diuretics (%)	39 (89)	1078 (52)	1138 (75)	198 (47%)
MRA (%)	23 (50)	320 (15)	171 (11)	37 (9%)
Digoxin (%)	8 (17)	291 (14)	432 (29)	45 (11%)
Statin (%)	34 (74)	656 (32)	617 (41)	151 (36%)
Aspirin (%)	14 (30)	1222 (59)	875 (5)	283 (67%)
Anticoagulant (%)	28 (61)	392 (19)	378 (29)	71 (17%)

Abbreviations: SBP: systolic blood pressure, BMI: body mass index; NYHA: New York Hear Association, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, NTproBNP: Amino terminal pro brain natriuretic peptide, Hb: haemoglobin, ECG: electrocardiogram, ECHO: echocardiography, LVEF: left ventricular ejection fraction, LA: left atrial; IVS: interventricular septum, FCV: forced vital capacity, FEV1: forced expiratory volume in 1 second, ACEi: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist. Categorical variables are expressed as number (percentage) and continuous variables are expressed as mean (standard deviation) or median (interquartile range) depending on distribution. *P values significant (<0.05) between LVEF $\geq$ 50% and 45-49%.

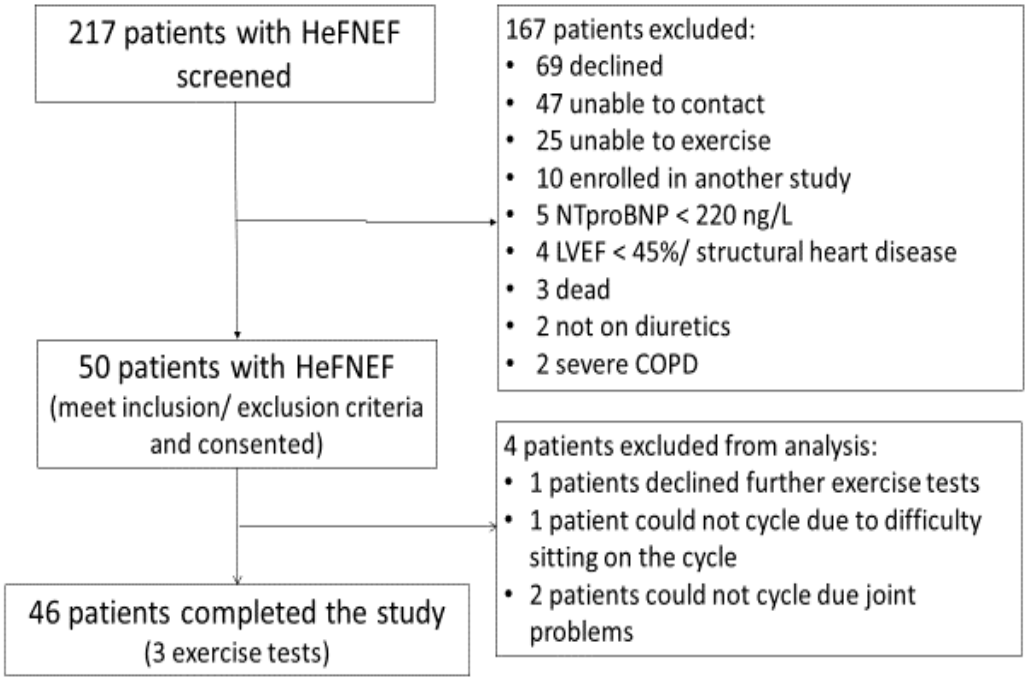

Figure 4: Total number of patients consented and completed all three visits of the study

3.3.8 Baseline characteristics of patients enrolled in study

The baseline characteristics of the 46 patients who completed the study are shown in table 8. Most patients were men, overweight and had NYHA class II symptoms. Compared to patients with LVEF > 50%, patients with LVEF between 45 and 49% had a significantly higher NTproBNP and creatinine, and a lower haemoglobin.

Table 8: Baseline characteristics for all patients and divided according to LVEF (≥ 50% or between 45-49%).

Baseline characteristics			
	All patients (N = 46)	**LVEF ≥ 50% (N= 29)**	**LVEF 45-49% (N= 17)**
Demographics			
Age (yrs)	75 (8)	76 (8)	75 (8)
Male Sex (%)	29 (63)	18 (62)	11 (65)
SBP (mmHg)	146 (23)	150 (23)	140 (23)
Heart rate (bpm)	69 (11)	70 (11)	68 (11)
BMI (kg/m^2)	31 (7)	32 (8)	31 (6)
Weight (kg)	90 (25)	91 (28)	91 (18)
NYHA function class			
I (%)	4 (9)	3 (10)	1 (6)
II (%)	37 (80)	23 (79)	14 (82)
III (%)	5 (11)	3 (10)	2 (12)
Medical history			
Hypertension (%)	28 (61)	19 (66)	9 (53)
Diabetes (%)	16 (35)	10 (35)	6 (35)
IHD (%)	20 (44)	13 (45)	7 (41)
Stroke (%)	3 (7)	3 (10)	0 (0)
Asthma/ COPD (%)	10 (22)	8 (28)	2 (12)
Walking aids (%)	14 (30)	9 (31)	5 (29)
Medical therapy			
Beta blocker (%)	37 (80)	23 (79)	14 (82)
ACEi (%)	30 (65)	17 (59)	13 (77)
ARB (%)	10 (22)	7 (24)	3 (18)
Loop diuretics (%)	39 (89)	26 (90)	13 (77)
MRA (%)	23 (50)	13 (45)	10 (59)
Diuretic (%)	46 (100)	29 (100)	17 (100)
Digoxin (%)	8 (17)	8 (28)	0 (0)*
Statin (%)	34 (74)	22 (76)	12 (71)
Aspirin (%)	14 (30)	10 (35)	4 (24)
Anticoagulant (%)	28 (61)	16 (55)	12 (71)

Table 8: Baseline characteristics for all patients and divided according to LVEF (≥ 50% or between 45-49%).

Blood test			
NTproBNP (ng/l)	1432 (543 – 2378)	1282 (443 – 2244)	2184 (1372 – 2501)*
Hb (g/l)	12.9 (1.7)	13.5 (1.7)	12.0 (1.5)*
Creatinine (µmol/l)	102 (80 – 137)	98 (75 – 125)	125 (95 – 155)*
ECG and ECHO			
Sinus rhythm (%)	21 (46)	15 (52)	6 (35)
Mean LVEF (%)	54 (7)	58 (5)	47 (1)*
LA size (cm)	4.3 (0.6)	4.2 (0.6)	4.5 (0.5)
IVS (cm)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Spirometry			
FCV % predicted	70 (17)	69 (21)	71 (12)
FEV1 % predicted	75 (20)	77 (23)	73 (17)

Abbreviations: SBP: systolic blood pressure, BMI: body mass index; NYHA: New York Hear Association, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, NTproBNP: Amino terminal pro brain natriuretic peptide, Hb: haemoglobin, ECG: electrocardiogram, ECHO: echocardiography, LVEF: left ventricular ejection fraction, LA: left atrial; IVS: interventricular septum, FCV: forced vital capacity, FEV1: forced expiratory volume in 1 second, ACEi: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist. Categorical variables are expressed as number (percentage) and continuous variables are expressed as mean (standard deviation) or median (interquartile range) depending on distribution. *P values significant (<0.05) between LVEF ≥ 50% and 45-49%.

3.3.9 Results of primary and secondary endpoints

Increasing FiO_2 led to an increase in exercise time of approximately 20 seconds (P=0.04). There was no dose response relation: exercise time was increased by the same amount during both tests with increased FiO_2 compared with 21% FiO_2. (Table 9, Figure 5) Increasing FiO_2 had no effect on peak workload (P=0.50). (Table 9, Figure 6) There was no effect of increasing FiO_2 on heart rate during exercise (P=0.65), although arterial oxygen saturation throughout exercise was higher with increasing FiO_2 (P=0.03). (Table 9, Figure 8 and 9)

At the end of the exercise tests patients scored on how breathless they were using the modified BORG score. The perceived dyspnoea was similar regardless of the FiO_2. (FIGURE 7)

Table 9: Changes in primary and secondary endpoints with increasing oxygen concentration

Variable	21% oxygen	28% oxygen	40% oxygen	P value
Mean exercise time (seconds)	522 (180)	543 (176)*	542 (177)*	0.04
Peak workload (watts)	57 (25)	58 (25)	58 (25)	0.50
Peak heart rate (bpm)	104 (26)	105 (21)	105 (26)	0.65
Peak oxygen saturation (%)	96 (5)	97 (3)	98 (3)*	0.03

* P value significant (<0.05) compared to 21% oxygen.

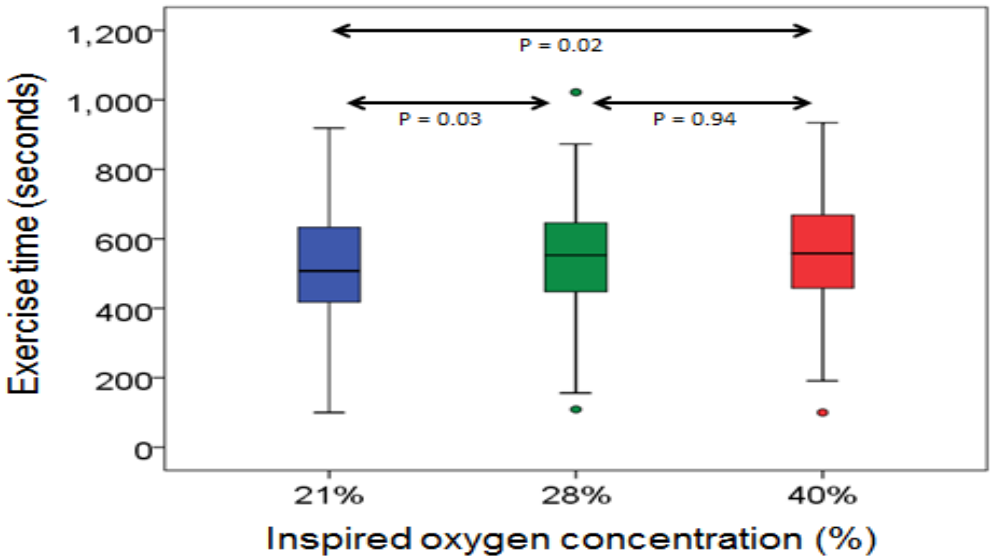

Figure 5: Increasing FiO_2 resulted in a small increased mean exercise time without a significant difference found between 28% and 40% as presented by arrows.

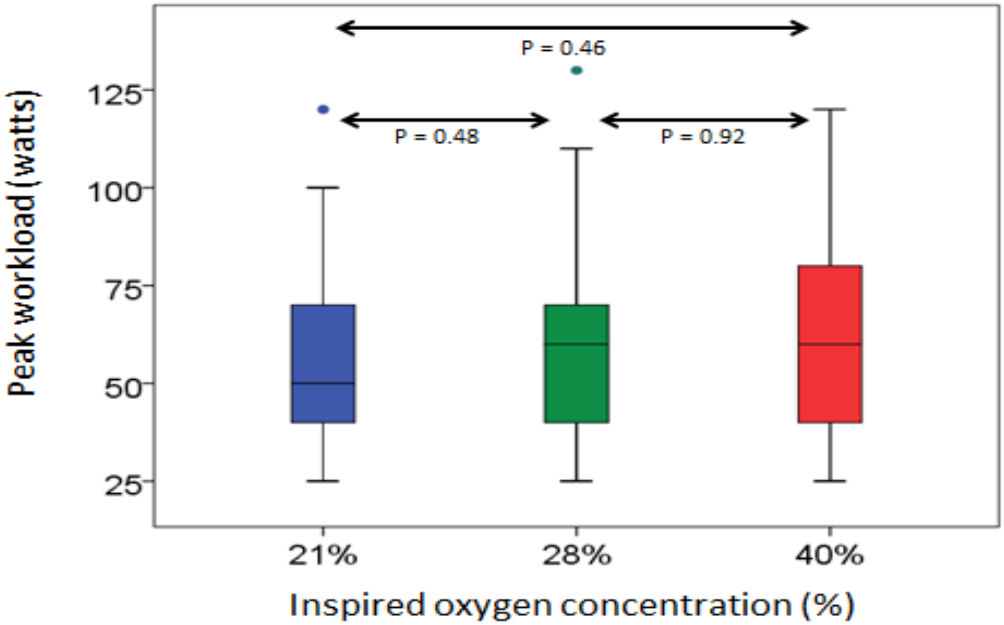

Figure 6: Increasing FiO_2 did not significantly change mean peak workload

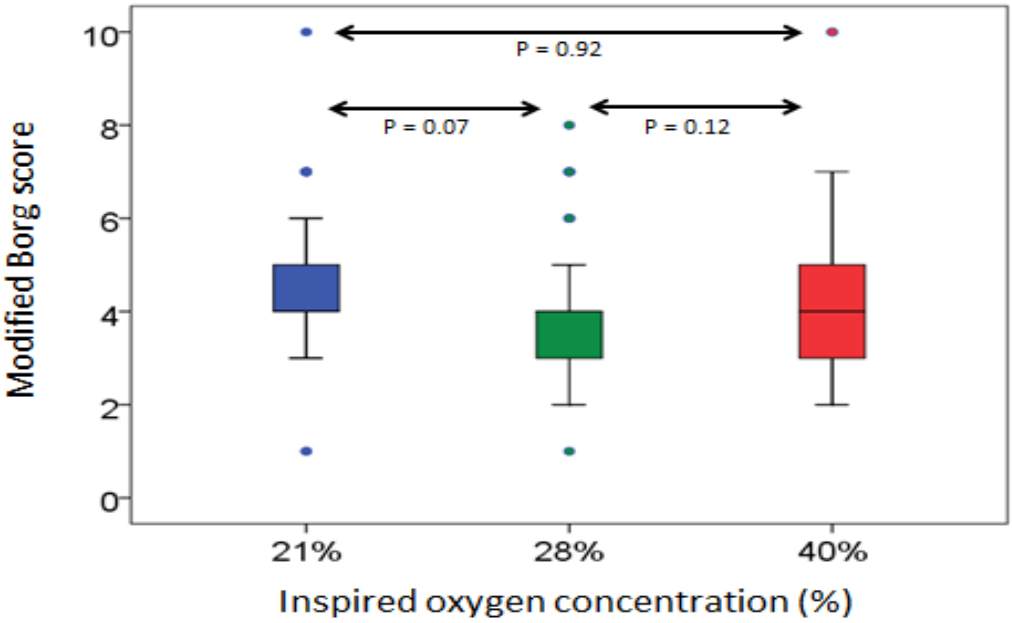

Figure 7 : Increasing FiO_2 did not significantly change mean modified Borg score

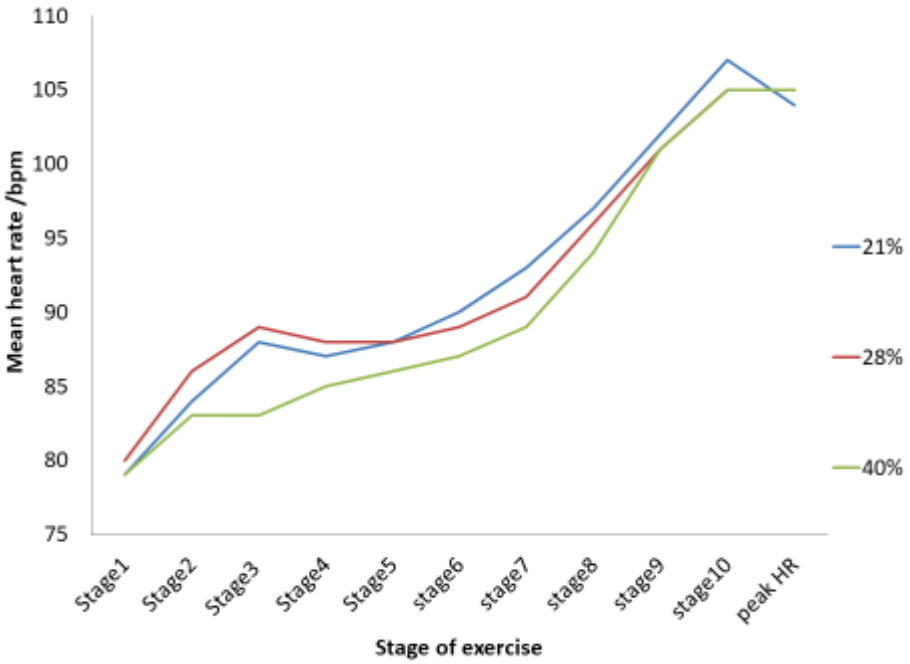

Figure 8: Mean heart rate during exercise

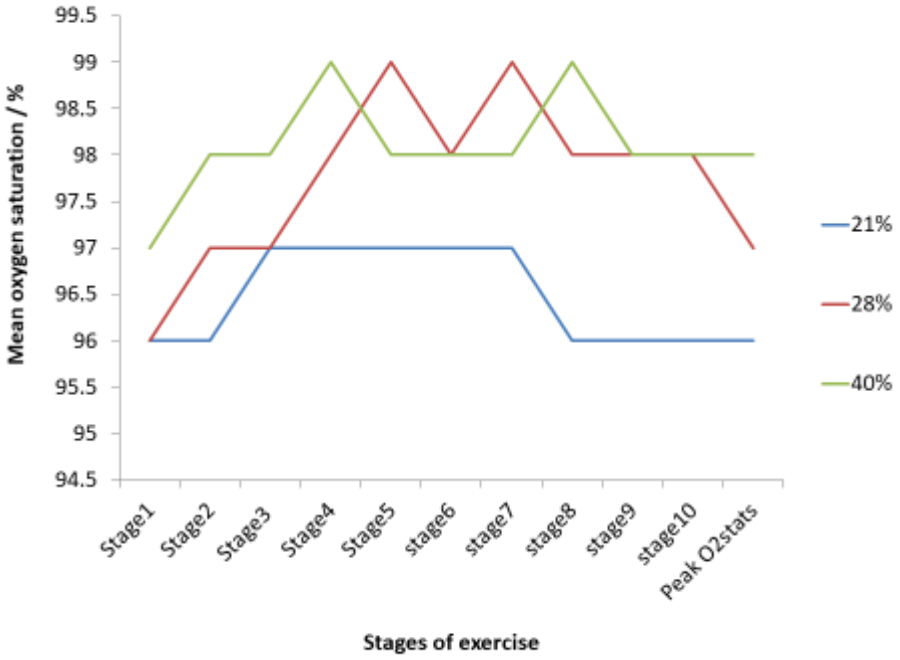

Figure 9: Mean oxygen saturations during exercise

3.3.10 Primary and secondary outcomes according to LVEF.

Patients with LVEF $\geq$ 50% had a significantly lower exercise time and peak workload than those with LVEF between 45-49%. However, patients with LVEF> 50% had a slightly greater increase in exercise time and peak work load with the increase in FiO_2 from 21% to 28%. (Table 10) Compared to patients with LVEF of between 45-49%, patients with LVEF > 50% were more likely to have asthma or COPD.

Table 10: Changes in primary and secondary endpoints with the use of supplementary oxygen in patients with LVEF ≥50% or LVEF between 45-49%.

Variable	LVEF	21% FiO_2	28% FiO_2	40% FiO_2
Mean exercise time (seconds)	LVEF ≥50	482 (168)	509 (158)*	504 (170)
	LVEF 45-49%	592 (184)	600 (194)	607 (173)
P value		0.04	0.09	0.05
Peak workload (watts)	LVEF ≥50	50 (19)	54 (19)*	53 (20)*
	LVEF 45-49%	68 (31)	65 (32)	66 (30)
P value		0.02	0.15	0.10
modified Borg score	LVEF ≥50	4.4 (1.9)	3.9 (1.4)*	4.3 (2.0)
	LVEF 45-49%	4.6 (1.4)	4.7 (1.6)	4.7 (1.8)
P value		0.66	0.07	0.55
Peak heart rate (bpm)	LVEF ≥50	101 (18)	103 (18)	101 (23)
	LVEF 45-49%	110 (36)	110 (26)	111 (30)
P value		0.25	0.26	0.20
Peak oxygen saturations (%)	LVEF ≥50	96 (3)	97 (3)	98 (3)*
	LVEF 45-49%	96 (5)	98 (3)	98 (3)
P value		0.25	0.52	0.93

Abbreviations: FiO_2: concentration of inspired oxygen, LVEF: Left ventricular ejection fraction, bpm: beats per minute. * P values significant (<0.05) compared to 21% oxygen.

3.3.11 Correlation between endpoints and patient characteristics

There was a positive correlation between the difference in exercise time between FiO_2 of 21% and 40% and age, but not with BMI, haemoglobin, creatinine or NTproBNP level. (Table 11) There was no difference in exercise capacity, peak work load or modified Borg scale score with increasing FiO_2 between males and females, whether patients used walking sticks, whether they had sinus or atrial fibrillation or whether they were on a diuretic or not. (Table 12)

Table 11: correlations between primary and secondary endpoints with patient demographics and blood variables.

	Pearson Correlation - R (P value)				
	Age	**BMI**	**Hb**	**Log Creatinine**	**Log NTproBNP**
Difference in ET between FiO_2 28-21%	0.24 (0.10)	-0.06 (0.68)	0.04 (0.78)	0.11 (0.48)	0.09 (0.57)
Difference in ET between FiO_2 40-21%	0.32 (0.03)	-0.04 (0.80)	-0.02 (0.90)	0.09 (0.58)	0.06 (0.67)
Difference in Watts between FiO_2 28-21%	0.02 (0.87)	0.15 (0.31)	0.29 (0.05)	0.08 (0.60)	0.02 (0.89)
Difference in Watts between FiO_2 40-21%	-0.02 (0.89)	0.23 (0.12)	0.26 (0.08)	0.04 (0.77)	-0.04 (0.78)
Difference in modified Borg between FiO_2 28-21%	0.14 (0.37)	-0.07 (0.64)	-0.06 (0.70)	-0.07 (0.65)	0.17 (0.25)
Difference in modified Borg between FiO_2 40-21%	-0.14 (0.37)	0.07 (0.64)	0.06 (0.70)	0.07 (0.65)	-0.17 (0.25)

Abbreviations: ET: exercise time, FiO2: inspired oxygen, BMI: body mass index, Hb: haemoglobin, NTproBNP: amino terminal pro brain natriuretic peptide.

Table 12: Effect of categorical variables on primary and secondary endpoints

	Sex			Walking stick			Heart rhythm			Loop diuretic		
	Male (N= 29)	**Female (N= 17)**	**P value**	**Yes (N= 14)**	**No (N= 32)**	**P value**	**Sinus (N= 21)**	**AF (N= 25)**	**P value**	**Yes (N= 39)**	**No (N= 7)**	**P value**
Difference in ET between FiO_2 28- 21% (seconds)	19 (69)	22 (44)	0.89	31 (64)	15 (59)	0.43	19 (65)	21 (58)	0.93	16 (62)	41 (52)	0.34
Difference in ET between FiO_2 40 – 21% (seconds)	10 (55)	36 (44)	0.10	24 (66)	18 (47)	0.70	27 (57)	13 (48)	0.38	21 (54)	14 (43)	0.77
Difference in Watts between FiO_2 28- 21% (watts)	3 (12)	-1 (16)	0.38	-1 (20)	3 (10)	0.35	0 (17)	3 (9)	0.45	1 (14)	5 (8)	0.45
Difference in Watts between FiO_2 40 – 21% (watts)	2 (9)	0 (16)	0.66	-2 (18)	3 (8)	0.25	1 (16)	2 (7)	0.76	2 (13)	0 (6)	0.76
Difference in modified Borg between FiO_2 28- 21%	0 (1)	0 (1)	0.46	0 (1)	0 (2)	0.77	0 (1)	0 (1)	0.76	0 (1)	0 (2)	0.96
Difference in modified Borg between FiO_2 40 – 21%	0 (1)	0 (1)	0.46	0 (1)	0 (2)	0.77	0 (1)	0 (1)	0.76	0 (1)	0 (2)	0.96

Abbreviations:. ET: exercise time, FiO_2: inspired oxygen, AF: atrial fibrillation.

3.4 Discussion

In patients with HeFNEF, increasing oxygen concentration during exercise lead to a small increase in exercise time but had no effect on peak work load. There are no previous trials of supplementary oxygen during exercise in patients with HeFNEF. Trials of oxygen supplementation during exercise in patients with heart failure with reduced ejection fraction (HeFREF) have yielded mixed results.[83,84,137,138]

3.4.1 The mechanisms causing exercise intolerance in HeFNEF

The mechanisms causing exercise intolerance in patients with heart failure are complex.[157] In most stable ambulatory patients with HeFREF, haemodynamics at rest are not substantially impaired.[158] Major determinants of exercise capacity appear to lie in the periphery, with abnormal skeletal muscle performance being chiefly implicated. The situation may be different in patients with HeFNEF: again, haemodynamics at rest may be normal, but during exercise, there is a disproportionate increase in left atrial pressure,[159] which contributes to symptoms and is associated with worse long term outcomes.[160] However there is growing evidence that extracardiac abnormalities impair exercise capacity in patients with HeFNEF. In a pooled meta-analysis by Pandey and colleagues of 17 unique cohorts of patient with HeFNEF (910 patients with HeFNEF and 476 control subjects) where resting and exercise cardiovascular hemodynamic variables in patients with HeFNEF versus normal subjects were measured.[161] Compared to normal subjects, patients with HeFNEF had a larger impairment in chronotropic response reserve, increased pulmonary capillary wedge pressure, arteriovenous oxygen difference reserve and stroke volume during exercise.[161] In a study by Houstis and colleagues of 79 patients with HeFNEF, who performed cardiopulmonary exercise testing with invasive

monitoring to measure haemodynamics, blood gases, and gas exchange during exercise. Compared to healthy controls, patients with HeFNEF had a reduction in oxygen delivery due to reduction in cardiac output (27±3%; P<0.001), haemoglobin concentration (5±2%; P=0.02, alveolar ventilation (36±3%; P<0.001) and lung diffusion (31±3%; P<0.001), total oxygen extracted by the periphery (difference between arterial and venous oxygen content; 8±2%; P=0.01) and skeletal muscle diffusion capacity (36±2%; P<0.001).[162] All patients harboured multiple O2 pathway defects. When multiple O2 pathway defects coexist, quantifying causal effects is no longer straightforward because defects interact. Trials in patients with HeFNEF which have exercise capacity as a primary endpoint may be likely to fail due to the heterogeneity of the condition

3.4.2 Oxygen supplementation for HeFNEF

Why should increasing Fi_{O_2} improve exercise performance in patients with HeFREF, but not make a substantial difference in those with HeFNEF? Part of the explanation may be that HeFNEF is something of a diagnostic rag-bag. Extra-cardiac mechanisms may significantly contribute to impaired exercise tolerance in patients with HeFNEF. Those with HeFNEF tend to be older than those with HeFREF, are more likely to be overweight or obese and have chronic lung problems (and other co morbidities including anaemia).[163,164] Sarcopenia and loss of muscle bulk are common in older people and particularly in patients with HeFNEF.[165] Patients with HeFNEF are thus, perhaps, more likely to have conditions other than their heart failure that limits exercise, and hence oxygen is less likely to help their exercise performance.

Another reason for the neutral results of this study may be due to the fact that these patients may not have heart failure since the diagnosis is not straight forward and can mimic other conditions. Unlike HeFREF, there is no robust or agreed diagnostic criteria for HeFNEF. In this study the baseline NTproBNP was much higher than what is consider for the diagnosis of heart failure with reduced or preserved ejection fraction. I also only included patients who were taking diuretics which added further to the evidence that these patients suffered with symptoms due to congestion needing treatment.

In the present study, overall I found no relation between cardiac rhythm or plasma NTproBNP and exercise time. I found, perhaps paradoxically, that patients with LVEF between 45-49% had a longer ET than those with higher LVEF (≥50%), despite having a significantly greater plasma NTproBNP and lower haemoglobin level. Patients with LVEF between 45-49% may represent patients who truly have lower exercise capacity due to heart failure (which might therefore respond to oxygen therapy) rather than those with LVEF >50% whose exercise performance might not be related to the heart.[166]

Treatment may need to be focused on other co-morbidities which limit exercise capacity in patients with HeFNEF.[167]

3.5 Limitations

We only enrolled patients able to exercise. We also only included patients treated with a diuretic; this might have led to a population of patients with HeFNEF with a more severe disease profile.[168] Monitoring central haemodynamics during exercise testing might have added to the understanding of the causes of exercise intolerance in patients with HeFNEF.

We included some patients who had an LVEF 45 - 49% on echocardiography. According to the current ESC HF guidelines, these patients would fall into the newly introduced category of "heart failure with mid-range ejection fraction" (HFmrEF).[1] Such patients might represent a separate phenotype from patients with HeFNEF.

Despite using pure oxygen, the actual administered fraction of oxygen through a mask may vary because of mixing with air in the absence of a perfect seal. Even when using the same mask and ventilation system, intra-individual variation in the resulting arterial oxygen tension can exist.

3.6 Conclusions

Increasing Fi_{O_2} during exertion leads to a small increase in exercise time in patients with HeFNEF which is unlikely to be clinically significant. Oxygen supplementation would require patient to wheel an oxygen cylinder which in itself would reduce exercise capacity.

Chapter 4 : Review of water immersion and swimming in patients with heart failure

4.1 Introduction

All current guidelines recommend regular exercise as an integral part of the management of patients with heart failure not only to improve exercise capacity but also for its beneficial effects on morbidity and mortality.[1,169,170,171] Factors such as advanced age,[172,173] and co morbidities such as osteoarthritis, hinder exercise training on a treadmill or a cycle in patients with heart failure.

Swimming is common in the United Kingdom and has the advantage of providing buoyancy to reduce impact on joints.[174] Patients with many different conditions do swim regularly.[175] Swimming in patients with arthritis improves mobility, strength and cardiovascular fitness without any joint discomfort.[176]

However, whether swimming is either safe or beneficial in patients with heart failure is not clear. Most guidelines steer clear of discussing swimming. Only the Scottish guidelines mention swimming in order to warn against it in patients with NYHA class III and IV symptoms.[171] The guidelines are cautious about advice on swimming because even when healthy individuals are immersed up to the neck in water, the hydrostatic pressure forces approximately 700ml of blood pooled in the periphery to the cardiothoracic space.[177] The increased preload to the heart increases stroke volume by 34% - 50% in normal subjects.[177,178] However this increased preload to the failing heart may precipitate pulmonary oedema. In patients with heart failure to

compensate for decreased myocardial contractility and to maintain an adequate cardiac output, the left ventricular end-diastolic volume increases according to the Frank–Starling mechanism. Furthermore, increased diastolic distensibility leads to increased end-diastolic volume tolerance in order to avoid end-diastolic pressure rise, which could lead to pulmonary oedema. Therefore, an increase in central volume, as they occur during water immersion, might potentially overstrain these compensatory mechanisms and as a consequence lead to a decrease in stroke volume, a further rise in the end-diastolic pressure and the occurrence of pulmonary congestion.[184] Whether swimming is a safe exercise rehabilitation treatment for people with heart failure is not clear. In this chapter the literature for studies of water immersion or swimming in patients with heart failure is reviewed.

4.2 Methods

4.2.1 Search strategy and study selection

Publications on swimming and heart failure were searched on Pub Med until January 2016. The search criteria included a specific population of patients with HeFREF. Two types of studies were considered in this review; firstly studies that immersed patient in water and second, studies that included swimming as part of exercise rehabilitation. The studies had to have measurements comparing the change in haemodynamic variables. For the water immersion studies this should have been compared between resting to during water immersion and for the studies of swimming as part of exercise rehabilitation this should be compared between the start and end of rehabilitation. Randomised controlled trials, controlled trials, and observational studies were included.

The words “heart failure”, “ventricular dysfunction” or “cardiomyopathy” in combination with “swimming”, “water immersion”, “hydrotherapy”, “aquatic exercise”, “water exercise” and “water based exercise therapy” were used as search criteria.

Studies performed in animals, in patients with heart conditions apart from patients with HeFREF and studies performed only in normal subjects were excluded. Studies not reported in English, reviews and case reports were also excluded.

4.2.2 Outcome measures

Haemodynamic, echocardiographic and respiratory variables measured during water immersion and swimming rehabilitation were: heart rate (HR), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), peak oxygen consumption (V_{O_2}), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) and left ventricular ejection fraction (LVEF). A further two outcomes reported for swimming rehabilitation were: quality of life (QOL) and six minute walk test distance (6 MWT).

The eligible studies were divided into acute haemodymanic effects of water immersion or swimming as a form of rehabilitation. If a study measured both the acute haemodynamic effects of water immersion and haemodynamic effects after swimming rehabilitation, it would be considered in both analyses. Studies meeting the eligible criteria were then scrutinised for their method and duration of immersion and rehabilitation, equipment used to measure haemodynamics. The outcomes were not combined as the studies were too heterogeneous. The results are presented as a narrative only.

4.3 Results

41 publications in English were identified. Studies on animals (n=10), in conditions other than heart failure (n=4), reviews, case reports or letters to editors (n=12) were excluded. Fifteen eligible publications were thus considered (Figure 10 and 11).

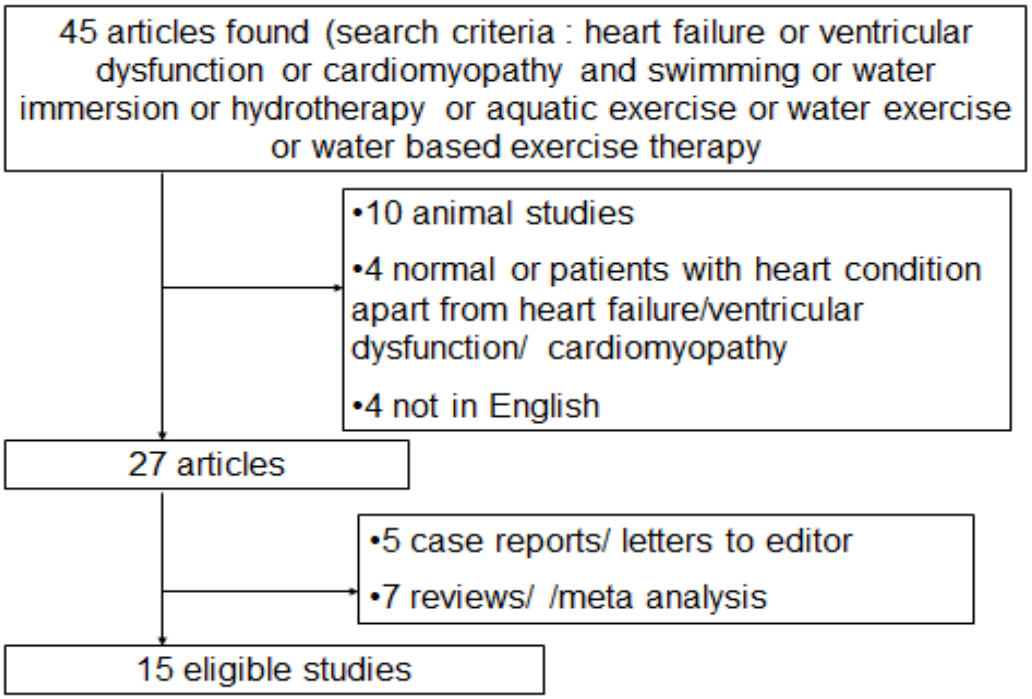

Figure 10: breakdown of studies considered in the review

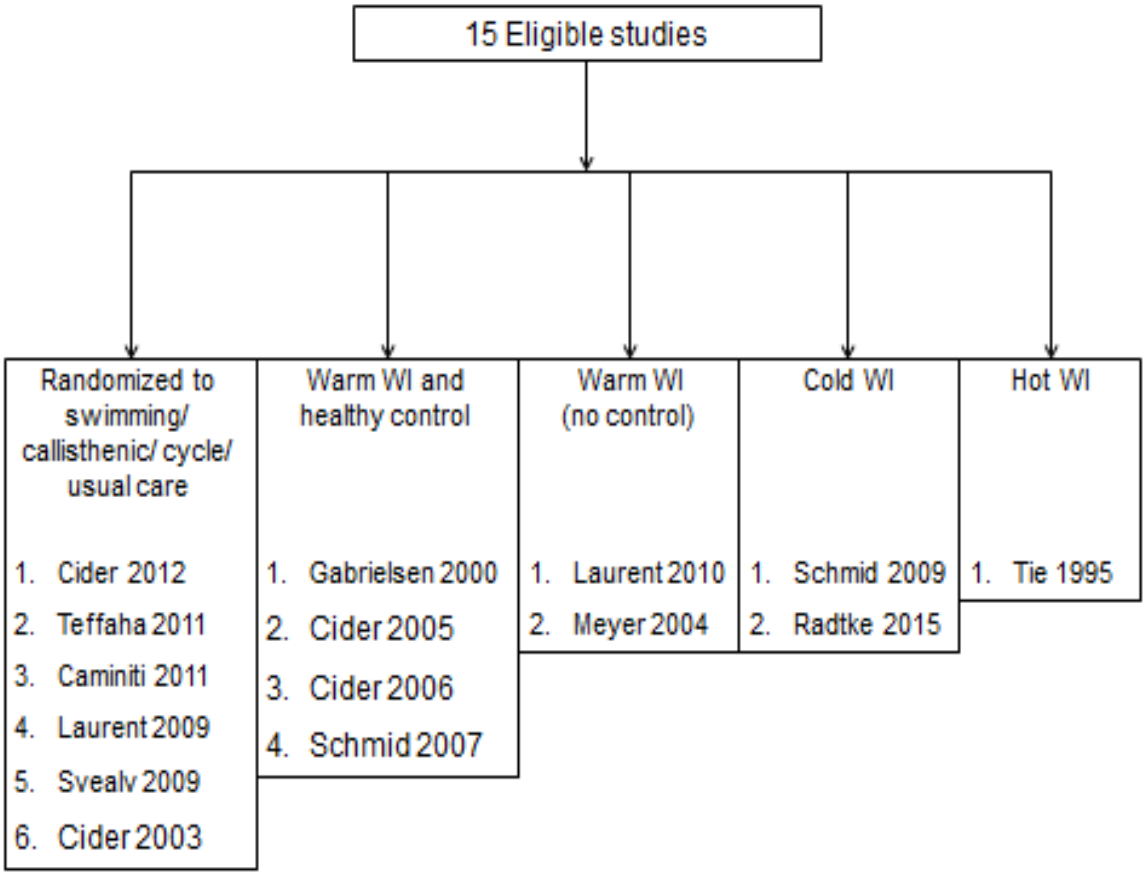

Figure 11: breakdown of eligible studies: WI: water immersion

4.3.1 Acute haemodynamic effects of water immersion

There were 10 studies examining the acute haemodynamic effects of water immersion with a total of 155 patients with heart failure (average age 60 years; 86% male; mean LVEF 29%).[179,180,181,182,183,184,185,186,187,188] Seven were in warm water (32-35°C) with a total of 97 patients (average age of 61 years; 85% male; mean LVEF 30%). Four of these seven compared the responses of patients with normal subjects and the remaining 3 were in patients alone.[179,180,181,182,183,184,185] Two were in cold water (12-22°C) with a total of 24 patients (average age of 60 years; mean LVEF 31%).[187,188] One study compared the responses of patients with normal

subjects and one was in patients alone. There was a single study of hot water immersion (41°C) with 34 patients (average age 58 years; 76% male; mean LVEF 25%).[186] (Table 10; Figure 11)

Table 13: Studies of water immersion in patients with heart failure

Author	Control	Pts	Severity of HF	Immersion	Study outcome	Equipment	Duration of water immersion
Warm water immersion							
Meyer K	None	18	Mod CHF	Graded immersion procedure was performed in upright position up to neck	Central haemo - dynamic response	Subxiphoid Echo, TOE	Graded immersion
		5	Severe CHF				
Cider A	Normal subjects	12	NYHA II – III	Immersed in sitting position up to neck	cardiorespiratory reaction during immersion	continuous gas analyses	5 mins
Svealv BG	None	18	NYHA I – III	Immersed in standing position up to neck	Acute effect of water immersion	Echo	20-30 mins
Gabrielsen A	Normal subjects	9	NHA II – III	Sitting position but to xiphoid process	Cardio-vascular and neuro - endocrine responses to water immersion	Central venous catheter, Echo	30 mins
Cider A	Normal subjects	13	NYHA II – III	Immersed in standing position up to neck	Haemo - dynamic responses during warm water immersion	Echo	5 mins

Table 10: Studies of water immersion in patients with heart failure

Schmid JP	Normal subjects	10	CHF	Immersed in standing position up to chest	Haemo - dynamic response to water immersion	Inert gas rebreathing,	Immediately
Mourot L	None	12	CHF	Immersed in standing position up to neck	Haemo - dynamic adaptations triggered water immersion	Non invasive haemodynamics and echo	15 mins
Hot water immersion							
Tei C	None	34	NYHA II – IV	Semi recumbent position at 45 degrees	Hemo - dynamic effects of hot-water	Thermo dilution Swan-Ganz catheter	10 mins
Cold water immersion							
Schmid JP	None	12	NYHA II	Immersed in standing position up to the neck	cold water immersion, on haemo - dynamic variables	Inert gas re breathing system	35 mins
Radtke T	Normal subjects	12	NYHA I – III	Immersed in standing position up to the neck	cold water immersion on haemo - dynamic variables,	Inert gas re breathing	Few seconds

Abbreviations: Pts: patients, HF: heart failure, CHF: chronic heart failure, Echo: echocardiography, TOE: transesophageal echocardiography, NYHA: New York Heart Association, min: minutes

4.3.2 Warm water immersion

In the 7 studies which compared haemodynamics at baseline to warm WI: 6 studies measured HR, which reduced by a mean of 7% (range: 2 to - 15%).[180,181,182,183,184,185] Five studies measured SV, which increased in most patients by a mean of 32% (range: 13 to 41%),[179,181,183,184,185] apart from in a sub-population of patients with severe heart failure in one study in whom SV decreased by 4%.[179] Five studies measured CO, which increased by a mean of 22% (range 7 to 37%).[181,182,183,184,185] Three studies measured SVR, which decreased by a mean of 9% (range 3 to 21%).[181,184,185] (Figure 12)

In 3 studies which compared echocardiographic changes at baseline to warm WI: 2 studies measured left ventricular end diastolic volume, which increased by a mean of 16% (range 6 to 24%) and LVEF, which increased by a mean of 13% (range 12 to 13%).[181,183] One study showed a greater increase in left ventricular end diastolic diameter (LVEDD) in patients with moderate heart failure (19%) compared to severe heart failure (5%).[179] (Figure 12)

4 studies examined the change in haemodynamics from baseline to during warm WI in patients with CHF compared with healthy subjects: the changes were of similar magnitude in both groups. In 4 studies, HR decreased in both groups by a mean of 7% (range 2 to -15%) in CHF and by a mean of 11% (range -1 to -22) in healthy subjects. [180,182,183,184] In 2 studies, SV increased in both groups by a mean of 28% (range 17 to 37%) in CHF and by a mean of 50% (range 30 to 65%) in healthy subjects.[183,184] In 3 studies, CO increased in both groups by a mean of 20% (range 14 to 37%) in CHF and by a mean of 26% (range 19 to 31%) in healthy

subjects.[182,183,184] In 1 study, SVR decreased in both groups by a mean of 21% in CHF and by a mean of 28% in healthy individuals.[184] (Figure 12)

4.3.3 Physiology underlying the effects of warm water immersion

The haemodynamic effects of warm water immersion, mainly due to the extra central venous return from the periphery due to the hydrostatic pressure, are due to several reflex mechanisms, all interfering with each other. Firstly, the increased venous return increase the left atrial volume and thus left atrial pressure, triggering the Bainbridge reflex which increases the heart rate to increase the cardiac output.[184] However the increased venous also increases the right atrial volume which the according to the Frank-Starling mechanism increases stroke volume and blood pressure. The increased blood pressure activates the arterial baroreceptor control system located in the wall of the internal carotid arteries, the carotid sinus and the aortic arch. This excitation of the vagal centre, finally leads to a decrease in heart rate and venous and arteriolar tone over-ruling, therefore the Bainbridge reflex.[184] Despite patients with heart failure characterised as having the lowest heart rate, stroke volume, blood pressure but the highest peripheral vascular resistance the reflexes mechanisms are still intact and improve cardiac haemodynamics.[184] Central blood volume expansion in compensated heart failure suppresses the activity of the renin–angiotensin–aldosterone system, increases the release of atrial natriuretic peptide and elicits a natriuresis, which is enhanced when angiotensin II and aldosterone concentrations are suppressed by ACE inhibitor treatment.[182]

The second important haemodynamic change noted when patients with heart failure are immersed in water is caused by distention of the peripheral vessels in thermoneutral water which in turn causes a reduction in systemic vascular resistance, arginine, vasopressin, renin and norepinephrine. The reduction in SVR causes activation of cardiac mechanoreceptors which leads to reflex adjustments of water and electrolyte excretions from the kidney.[189]

4.3.4 Hot water immersion

In the single study of hot water immersion, HR increased (33%), SV increased (16%), CO increased (50%) and SVR decreased (41%).[186] On echocardiography, LVEDV (2.4%) and left ventricular end systolic diameter (5.4%) both decreased, but LVEF increased (23%).[186] (Figure 12)

The haemodynamic effects seen by hot water immersion are caused not only by the hydrostatic pressure exerted but also by the thermal vasodilatation which decreases systemic and pulmonary vascular resistances, improving left and right ventricular function and increasing cardiac and stroke indexes. Hot water immersion also dilates the venous system. The redistribution of blood from the intrathoracic compartment toward the peripheral venous system with thermal venous dilatation results in a decrease in pulmonary congestion.[186]

4.3.5 Cold water immersion

In the 2 studies which compared haemodynamics at baseline to cold WI: both studies measured CO which increased, both measured heart rate with inconsistent results and one study measured SVR, which fell.[187,188] (Figure 12) Cold water immersion increases sympathetic tone mediated by thermoreceptors on the skin. This increase in sympathetic tone increases blood pressure on an already hyperdynamic circulation. In theory this increased strain on the circulatory system may be of concern in patients with heart failure however in the study by Schmid and colleagues in cold water (22°C) did not have a detrimental haemodynamic effect in patients with heart failure.[188]

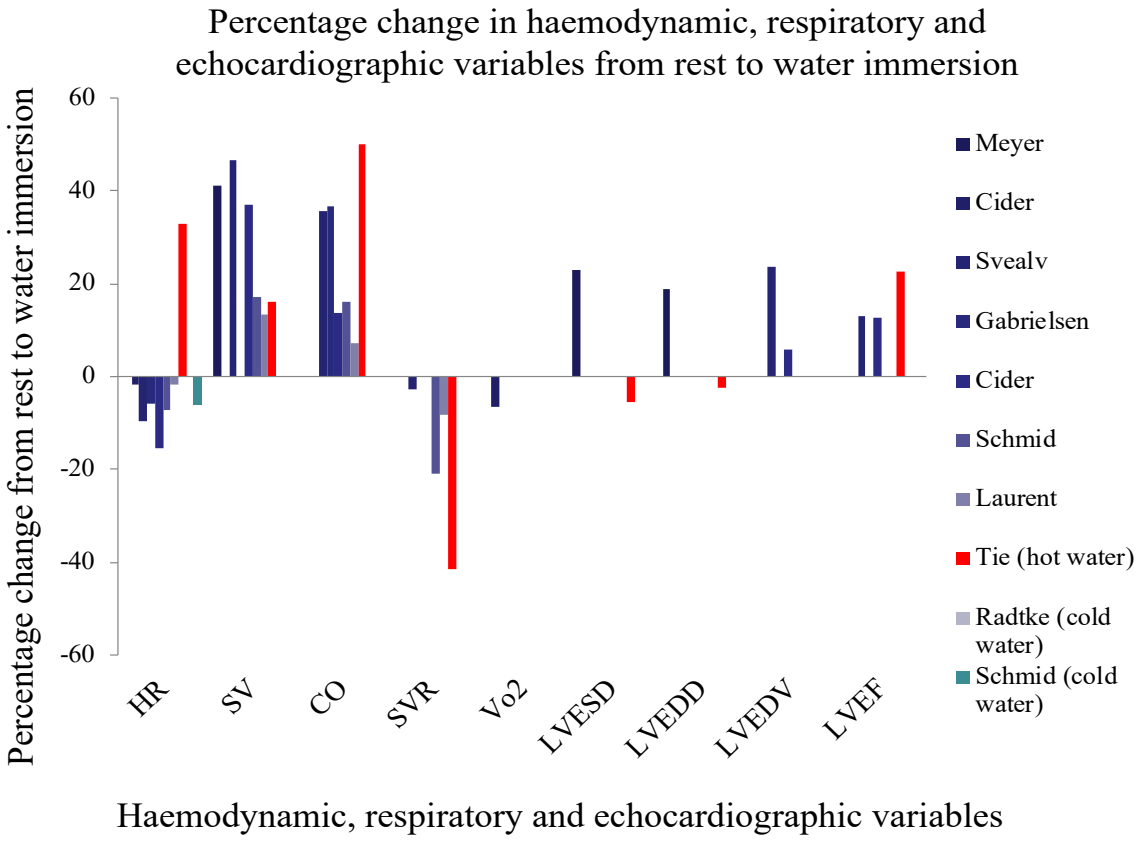

Figure 12: Percentage change in haemodynamic, respiratory and echocardiographic variables from rest to water immersion. HR: heart rate, SV: stroke volume, CO: cardiac output, SVR: systemic vascular resistance, V_{O_2}: peak oxygen uptake, LVESD: left ventricular end systolic diameter, LVEDD: left ventricular end diastolic diameter, LVEF: left ventricular ejection fraction.

4.4 Swimming as a form of rehabilitation in patients with heart failure

There were 6 trials of exercise training with patients. (Figure 11) Three studies randomised patients to either swimming or continued medical therapy (67 patients, mean age of 70, 73% male, mean LVEF of 32%).[181,190,191] Two studies randomised patients to either a combination of swimming and aerobic exercise or aerobic training only (45 patients, mean age of 60, mean LVEF of 31%).[192193] One study randomised patients to either gymnastics on land or in water in combination with cycle training in both groups (24 patients, mean age of 54, mean LVEF 30%).[194] (Table 11)

Table 14: Types of swimming exercises

Study	No of patients	Type of swimming exercise	Intensity of exercise	Duration of session	Duration of study
Swimming training compared to medical management only					
Svealv 2009	18		40- 70% of maximal heart rate reserve	45 minutes – 2 times per week	8 weeks
Cider 2003	25	Peripheral muscle and central circulatory exercises	40 to 75% of maximal heart rate reserve	45 minutes – 3 times per week	8 weeks
Cider 2012	20	Peripheral muscle and central circulatory exercises	40 to 75% of maximal heart rate reserve	45 minutes – 3 times per week	8 weeks
Cycle training compared to a combination of swimming and cycling training					
Laurent 2009	24	Cycling on land and Gymnastic exercise in water	Cycling: 60–70% of the patient heart rate reserve	Cycling 30 minutes – 5 times per week plus Gymnastics: 50 minutes – 5 times per week	3 weeks
Aerobic training compared to a combination of swimming and aerobic training					
Teffaha 2011	24	land endurance and water callisthenic exercises	Cycling: at an individualized target intensity heart rate	Cycling 30 minutes – 5 times per week plus Calisthenics 50 minutes 5 times per week	3 weeks
Caminiti 2011	21	Endurance training: aerobic exercise with cycling or treadmill at hydrotherapy: callisthenic exercises involving muscle groups of the lower and the upper limbs and torso (three sets of 10 repetitions for each exercise)	60–70% VO2 max.	Endurance training: 30 minutes – 3 times per week	24 weeks

4.4.1 Types of swimming exercises

Various types of exercises in water were compared with exercise on land or with medical therapy. All the studies involved some form of callisthenics. All but one used a target heart rate as a measure of exercise intensity. All the studies had at least 2 sessions of exercise per week and each session was between 30 and 45 minutes. The study exercise programme lasted from 3 – 24 weeks. (table 14)

Table 15: randomised controlled trials of rehabilitation comparing swimming with either medical treatment only or in combination with cycling or aerobic exercise.

Study	No. of pts	Age - yrs	Sex - % Male	NYHA class	Swimming/ control	Percentage change from baseline to end of rehabilitation / %								
						HR	SV	CO	SVR	VO_2	LVEDD	LVESD	LVEF	6MWT
Cider 2012	24	67	80	II-III	Swimming					↑ 14				↑13
					Medical					↓7				0
Cider 2003	25	72	68	II – III	Swimming					↑7				↑7
					Medical					↓12				↑2
Svealv 2009	18	69	72	II – III	Swimming	No change	No change		No change	No change	↑			
					Medical	No change	No change		No change	No change				
Teffaha 2011	24	53	100	II - III	Swimming + aerobics	↓	↑				No change	No change	↑	
					Aerobics	↓	↑				No change	No change	↑	

Caminiti 2011	21	68	N/A	II - III	Swimming + aerobics	↓19	↑34	↑28	↓54		↓3	↓9	↑9	↑70
					Aerobics	↑5	↑15	↑9	↓19		↓5	↓2	↑6	↑32
Laurent 2009	24	54	100	N/A	Swimming + cycling	↓16	↑23	No No change	↑15	↑6				
					Cycling	↓8	↑10	↑7	↓15	↑11				

Table 15: randomised controlled trials of rehabilitation comparing swimming with either medical treatment only or in combination with cycling or aerobic exercise.

Abbreviations: Pts: patients, yrs: years, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, HR: heart rate, SV: stroke volume, CO: cardiac output, SVR: systemic vascular resistance, V_{O_2}: Maximum volume of oxygen, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, 6MWT: 6 minute walk test. N/A: not available.

4.4.2 Swimming training compared to medical management only

Three studies compared swimming training with medical management only.[181,190,191] At the end of follow up (8 weeks): in one study, there were no changes in HR, SV, CO or SVR at rest.[181] In 2 studies,[190,191] there was an increase in peak V_{O_2} by a mean 1 ml/kg/min (range: 1 to 2 ml/kg/min) in swimming training versus a reduction by a mean -1 ml/kg/min (range: -1 to -2 ml/kg/min) in medical management) whilst there was no change in peak V_{O_2} in the third study.[181] In 2 studies,[190,191] there was a greater increase in 6 MWT with swimming, by a mean of 35m (range: 30 – 40m) in swimming training versus increase by a mean of 3m (range 1to 6m) in medical management. There was no consistent pattern in quality of life in the 2 studies where it was measured.[190,191] (Table 15)

4.4.3 Cycle training compared to a combination of swimming and cycling training

In a study which compared haemodynamics and peak V_{O_2} between cycle training and gymnastics on land or in water: there was a greater reduction in resting HR (-10 bpm swimming and cycling vs. -5 bpm cycling only), greater increase in resting SV (17 ml/beat swimming and cycling vs. 8 ml/beat cycling only), no change in CO at rest, an increase in resting SVR (206 dyne sec/cm^5 swimming and cycling vs. – 248 dyne sec/cm^5 cycling only) and an increased peak V_{O_2} (2 ml/kg/min swimming and cycling vs. 1 ml/kg/min cycling).[194] (Table 15)

4.4.4 Aerobic training compared to a combination of swimming and aerobic training

In 2 studies which compared haemodynamics between aerobic exercise training only or a combination of swimming and aerobic exercise, at the end of follow up (range 3-24 weeks): there was a greater reduction HR (-12 bpm swimming and aerobic exercise vs. +3 bpm aerobic exercise only) in both studies [193,192] greater increase in SV (16 ml/beat swimming and aerobic exercise vs. 7 ml/beat aerobic exercise only) in both studies. [193,192] In one study there was a greater increased CO at rest (1 l/min swimming and aerobic exercise vs. 0.6 l/min aerobic exercise only) and greater reduction SVR (-23 mm Hg/l/min swimming and aerobic exercise vs. -8 mm Hg/l/min aerobic exercise only).[193] (Table 15

The echocardiographic findings were: LVEDD reduced (-2 cm swimming and aerobic exercise vs. -3 cm aerobic exercise only) in one study[193] but no difference in the second;[192] LVESD reduced (-4 cm swimming and aerobic exercise vs. -1 cm aerobic exercise only) in one study[193] no change in the second;[192] with a similar increase in resting LVEF in both studies (3% swimming and aerobic exercise vs. 2% aerobic exercise). (Table 15))

One study reported six minute walk test distance, and found that there was a greater increase following swimming and aerobic exercise (increased by 150 m) than following aerobic exercise alone (increased by 100 m).[193] (Table 15)

4.5 Discussion

Water immersion up to the neck is well tolerated in stable patients with heart failure, particularly when the water is warm. From the limited studies in both cold and hot water immersion it may cause adverse haemodynamic effects, whereas warm water immersion appeared helpful. The most consistent effects were a fall in resting heart rate and systemic vascular resistance. Exercise in water has effects similar to other forms of exercise training with a similar improvement in exercise capacity. Exercise in water in stable patients with heart failure in NYHA class II-III symptoms was well tolerated with no adverse effects.

4.5.1 Haemodynamic effects of water immersion

The mechanical properties of water are considerably different to air; there are several changes in haemodynamics and fluid shift even when healthy subjects are immersed in water. During WI up to the neck, approximately 700 ml of peripheral blood pools centrally (of which 180-240 ml accumulates in the heart) due to the hydrostatic pressure exerted on the body.[195,196] As a consequence, in healthy subjects, there is an increase in left ventricular volume and an increase in LVEF resulting in increased stroke volume and blood pressure.[197,198] In healthy subjects, cycling in water leads to a greater increase in cardiac output (CO) than cycling in air by an average of 0.7 l/min.[199] Stroke volume (SV) increases by 49% in air compared to 34% in water.[197]

4.5.2 SIPE: swimming induced pulmonary oedema

Guidelines are cautious about water immersion and swimming in patients with heart failure because of the potential to precipitate pulmonary oedema secondary to the mobilisation of peripheral fluid into the central circulation. Reports of swimming-induced pulmonary oedema (SIPE) are rare, and confined to athletes usually undertaking extreme exercises. SIPE was first described by Wilmshurst and colleagues in eleven divers with no demonstrable cardiac abnormality who had up to seven episodes when swimming or scuba diving.[200] The prevalence of SIPE is not clear and possibly unreported as patients present with subtle symptoms which may be put down to the strenuous exercise just undertaken.[201] However, in healthy athletes competing in triathlons or in people who scuba dive a prevalence of between 1.1 and 1.8% has been found.[202,203,204]

The pathophysiology of SIPE is not well understood but factors such as the central shift of fluid during water immersion, vasoconstriction due to cold water and over hydration may increase right-sided cardiac pressures leading to pulmonary oedema.[205,206]

In a study by Weiler-Ravell and colleagues on 30 young men on a military fitness programme, swimming in cold water at 23°C caused pronounced shortness of breath in 8 subjects.[206] Five subjects stopped swimming early. They needed oxygen supplementation and in the more severe cases intravenous diuretics.[206] Subjects with a history of SIPE have higher pulmonary artery pressure (previous SIPE = 34 mmHg versus control = 22 mmHg, p=0.004) and pulmonary artery wedge pressure

(previous SIPE = 19 mmHg versus control = 11 mmHg, p=0.028) when exercised in cold water on a cycle than those who do not.[205]

None of the studies of water immersion or swimming rehabilitation in patients with heart failure reported SIPE. However, all the studies found were small, involving at most 34 patients. The majority of patients were male and were young compared to the general population of patients with heart failure. Most of the studies which looked at swimming rehabilitation did not prescribe swimming on its own but in conjunction with aerobic exercise on land and so it is difficult to assess the effects of swimming training alone on cardiac function and exercise performance.

4.5.3 Swimming as a form of exercise

What is perhaps surprising is how few patients have been included in studies of swimming. In the United Kingdom, swimming is the most popular sport with over 3 million people taking part in at least a session per week. This is a million more people per week than play football, which is often considered to be the United Kingdom's national sport.[207] Swimming may be more popular than other forms of exercise because it is a low impact activity suitable for people with disability, poor mobility or frailty.[208] Given how common swimming is, it must be the case that patients with heart failure are swimming regularly.[179] The data we have found (and perhaps the lack of reports in the literature) suggest that swimming is probably safe in patients with heart failure. Given that patients with heart failure are often frail and have other co-morbidities (which reduce mobility), swimming is perhaps the ideal way to encourage exercise without the difficulty of weight-bearing exercise on land. However, further studies are needed to assess the safety and larger studies are needed

to assess the potential benefits of swimming compared to conventional heart failure rehabilitation.

4.6 Conclusion

Although exercise in water appears to be safe, the studies conducted have been small, very heterogeneous and inconclusive. Patients with HeFREF can swim safely and in fact may improve symptoms of heart failure with regular swimming.

Chapter 5 : Warm water immersion in patients with chronic heart failure

5.1 Introduction

Whether swimming is safe in patients with heart failure has not been answered comprehensively in previous studies of water immersion or swimming.[209] Most guidelines steer clear of discussing swimming.[1,169,170,171] Only the Scottish guidelines mention swimming in order to warn against it in patients with NYHA class III and IV symptoms.[171]

Patients with chronic stable heart failure mainly complain of exercise intolerance despite optimal medical treatment. Exercise improves symptoms of shortness of breath on exertion and fatigue in patients with heart failure. Some patients with heart failure may consider swimming for exercise or as a recreational activity; however they do not receive advice from health care professionals regarding the safety and benefits of swimming.

5.1.1 Aim of study

Patients with heart failure are understandably concerned about their health and what activities are safe for them to undertake. Patients with heart failure may seek their doctors' advice about different modes of exercise, including swimming or hydrotherapy programmes but doctors may not feel confident in how to advise their patients.

The aim of this study was to investigate the effects of warm water immersion and exercise on cardiac haemodynamics in patients with HeFREF. This chapter, describes the design and results of the single centre study conducted to assess the acute hemodynamic, echocardiographic and NTproBNP changes during warm water immersion (WWI) in patients with heart failure.

5.2 Methods

5.2.1 Patient identification and inclusion and exclusion criteria

Around 5000 patients are enrolled and followed up in the local heart failure clinic from a single centre. Of these, around 55% have HeFREF. Ambulatory patients with an established diagnosis of HeFREF, on stable treatment for more than 3 months were enrolled from a community heart failure clinic. Suitable patients were identified in clinic and from the database, and invited for an initial screening visit. These patients had already consented to be contacted by investigators regarding clinical trials. The cohort has electronic notes with all the relevant diagnosis, investigations and treatments which made it more efficient to identify the potential patients for the trial.

Controls were normal subjects, over 60 years of age, who were already consented to take part as healthy volunteers in a local observational research program. Normal subjects had to have a LVEF $\geq$ 50% on echocardiography.

Patients with severe symptoms (NYHA class IV), weight over 120 kilograms, hospitalised within last 6 weeks or with a contraindication to WWI (epilepsy, recent hypoglycaemia, intravenous line or urinary catheter) were excluded from the study.

The research conforms to the Helsinki declaration and ethics approval was granted by an external research ethics committee. The trial was registered on the ClinicalTrials.gov website (Identifier: NCT02949544) and all participants gave their written informed consent.

5.2.2 Screening for eligible patients

Suitable participants were invited for a screening visit. Participants received patient information leaflets, were explained the rationale of the study, number of visits and given contact details of the study team in case of any further queries.

The screening visit involved the following assessments:

First a research nurse conducted observations, bloods and ECG:

- Weight using standard scales
- Sitting, resting sitting blood pressure and heart rate
- Blood tests: full blood count (FBC), biochemical profile (BCP) and NTproBNP
- Supine resting 12 lead ECG

I assessed the patients in the heart failure clinic:

- Symptom assessment for heart failure and their NYHA class was recorded by the clinic doctor
- Physical examination (presence of peripheral oedema, assessment of jugular venous pressure and auscultation of lung bases) was also conducted by the doctor

The qualified echocardiographer conducted:

- A full transthoracic echocardiography using the British Echocardiography Society guidelines.[210]

Eligible patients who consented for the participation to the study were then invited for the study day.

5.2.3 Water immersion protocol

The study was conducted in a hydrotherapy pool on the hospital site. The pool was checked daily to maintain a temperature between 33- 35°C and the ambient temperature of the room was maintained at 21°C. A metal bed designed to be immersed in water was attached to a manual hoist fixed next to the pool. Participants changed into suitable clothing/swimwear and were shown the equipment being used for the study. Participants then lay in supine position on the bed throughout the study and were immersed and removed from the water using the hoist. (Figure 13) Baseline measurements, including a blood sample for NTproBNP analysis, and echocardiography (GE Vivid E9, Hatfield, Hertfordshire, UK) were conducted after participants were comfortable on the bed for 10-15 minutes.

A non-invasive haemodynamic monitoring device (Nexfin, BMeye, Amsterdam, Netherlands) with an inflatable finger cuff was attached to the mid finger of participant's left hand (Figure 13) and during immersion the left hand was rested on a floater to ensure the device remained out of the water. The reference level for the non-invasive haemodynamic device was at the surface of the water throughout and thus very slightly higher than the level of the heart. The measurements outside the pool were made with the reference level in the same relative position before

immersion. The device continuously recorded cardiac haemodynamics from baseline to the end of the study. This device has been validated against invasive methods of monitoring cardiac haemodynamics in studies of patients with heart failure and critically ill patients.[211,212,213]

Another non-invasive device (VENUS 2000 CVP monitor, Mespere LifeScience Inc, Waterloo, Canada) was used to measure central venous pressure (CVP) using a small adhesive neck sensor placed over the external jugular vein. The device uses near infrared spectroscopy to determine the pressure in the external jugular vein.[214] Its clinical use has been validated in critically ill patients with cardiovascular conditions, and in out-patients setting for patient with heart failure.[215,216,217]

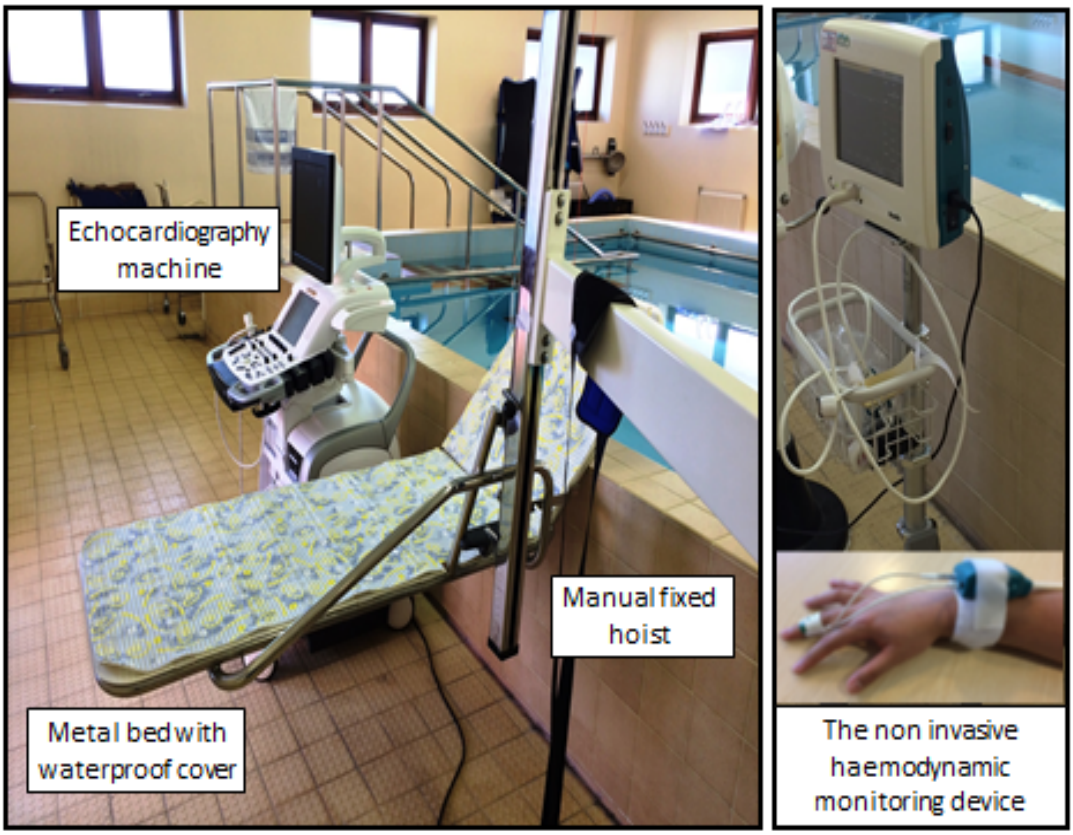

Figure 13: Study equipment. Echocardiography: GE Vivid E9. Non-invasive haemodynamic monitoring device, Nexfin, BMeye

The participants were then gradually immersed up to their neck in supine position into the hydrotherapy pool. Echocardiography was repeated at 1 and 15 minutes following WWI with the ultrasound probe covered with a light polythene bag to ensure it remained water proof. After 15 minutes of WWI, the participants were asked to perform gentle exercise (3 minutes of kicking at a speed of 60 repetitions per minute) whilst remaining in supine position on the bed. The exercise performed was hip extension and flexion with a straight leg. At the end of 3 minutes of exercise, echocardiography was repeated. Once all the echocardiographic and haemodynamic readings were recorded the participants were lifted out of the water. Haemodynamic readings, symptom scores, blood sample for NTproBNP and echocardiography were

repeated whilst participants remained in supine position on the bed 3 minutes after emerging from the hydrotherapy pool.

5.2.4 Safety assessments prior to start of the study

Safety assessments have been performed by the Estates Department and Medical Physics department, both based in Castle Hill Hospital, Cottingham, UK.
The Estates Department assessed the safety of using extension leads and electrical equipment in the pool environment. For the purposes of the study, the Estates department installed a "Safe Supply Unit" made by Blakley Electrics, which is designed for environments with water and mains voltage electricity in close proximity, for example birthing pools or school science laboratories.

The Medical Physics department assessed each individual piece of equipment used for the study and ensured it was safe for use around water. In order to minimise the risk of equipment getting wet, the department provided custom built platform to rest the screen of the non-invasive central venous pressure device screen.

Patients' safety in the pool has been approved by the physiotherapy department. In the event of a patient becoming acutely unwell whilst in the pool, there are specific evacuation procedures. All investigators and support staff were trained to safely and efficient evacuate patients from the pool to a bed next to the pool in case of a medical emergency. The team were aware of the emergency and cardiac arrest numbers of the hospital and the doctors conducting the study had advanced life support training.

5.2.5 Outcome measures

From the non-invasive haemodynamic monitoring device, the following variables were recorded at baseline, 1 minute WWI, 15 minutes WWI, 3 minutes after exercise and after 3 minutes recovery: heart rate (HR), blood pressure (BP), stroke volume (SV), cardiac output (CO), cardiac index (CI) and systemic vascular resistance (SVR). An average of 5 measured values for each haemodynamic variable was taken. From the central venous pressure monitoring device the measurement of jugular venous pressure was recorded at baseline, 1 minute WWI, 15 minutes WWI, 3 minutes after exercise and after 3 minutes recovery. Echocardiographic images were acquired by an expert technician and stored on DVDs. The images were reviewed off-line by a single experienced operator blind to the various phases of the study. The following echocardiographic variables were measured at baseline, 1 minute WWI, 15 minutes WWI, 3 minutes after exercise and after 3 minutes recovery: left ventricular end diastolic volume (EDV) and end systolic volumes (ESV), left ventricular ejection fraction (LVEF), left atrial diameter (LAD) and volume (LAV) tricuspid annular plane systolic excursion (TAPSE), systolic tricuspid regurgitation (TR) pressure gradient, inferior vena cava (IVC) diameter.

Patient's symptoms of shortness of breath and angina were objectively assessed at baseline and recovery using two questionnaires; Modified Borg score and Canadian cardiovascular society angina grading scale. Modified Borg scale is a uni-dimensional, numerical scale with verbal anchors relating to the numbers.[151,152] The modified BORG scale score assesses symptom intensity in response to a specific stimulus, in this case the assessment of shortness of breath after warm water immersion.[153,154] The Canadian Cardiovascular Society classification of angina is an internationally recognised scale to determine the severity of angina. It was first

published in 1976 and till today remains the standardised objective assessment of severity of angina.[218,219] This assessment was used to objectively assess any worsening of angina with warm water immersion.

The research conforms to the Helsinki declaration. Ethics approval was granted by an external research ethics committee (research and ethics committee number 16/NE/0194). The trial was registered on the ClinicalTrials.gov website (Identifier: NCT02949544). The study design, protocol, patient leaflets were presented to the local Trans-Humber consumer research panel. The panel included lay people whose advice was valuable in amending the protocol.

5.2.6 Statistical analysis

This was an exploratory pilot study with two groups using new non-invasive haemodynamic monitoring devices; therefore no power calculations have been made. There was no data upon which to base any sort of sample size calculation.
Categorical data are presented as numbers and percentages; normally distributed continuous data as mean ± standard deviation (SD) and non-normally distributed continuous variables as median and interquartile range. Log transformation of NTproBNP was used, given its not normal distribution.
The repeated measures ANOVA was used to assess the overall difference between related means of each variable and the Bonferroni correction was used for multiple testing errors. Primary and secondary endpoints are shown in graphs. All analyses were performed on SPSS (V.23.0), and statistical significance was assumed at $P<0.05$ (two tailed).

5.3 Results

5.3.1 Patient recruitment

Forty patients with a diagnosis of HeFREF were screened. 10 patients either declined to participate or were unable to be contacted, 8 patients had poor echocardiographic windows and 2 had other ongoing medical problems. (Figure 14) Forty seven normal subjects were screened of which 10 agreed to take part.

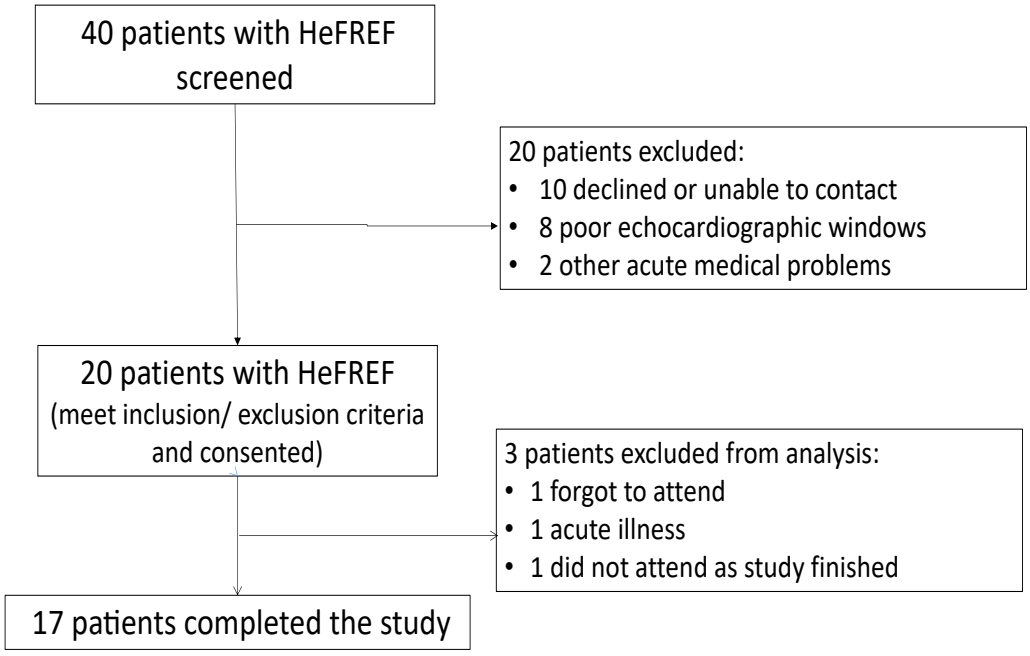

Figure 14: Total number of patients with HeFREF screened.

5.3.2 Baseline characteristics of patients with CHF and normal subjects.

Baseline characteristics of patients with heart failure and normal subjects are shown in table 12. All but one of the patients had NYHA class II symptoms. Normal subjects were of a similar age, 90% were male and baseline cardiac haemodynamics were similar to patients with heart failure.

Table 16: baseline characteristics of patients with heart failure and normal subjects.

Variables	Patients with HF (N = 17)	Normal subjects (N= 10)	P value
Demographics			
Age	67 (12)	70 (10)	0.39
Male (%)	15 (88)	9 (90)	0.89
Weight (kg)	78 (13)	73 (10)	0.37
BMI (kg/m^2)	26 (3)	24 (3)	0.19
SBP (mm Hg)	129 (16)	143 (30)	0.14
NYHA class			
I (%)	1 (6)	10 (100)	<0.001
II (%)	16 (94)	0 (0)	
Medical history			
Hypertension (%)	4 (24)	2 (20)	0.84
IHD (%)	12 (71)	1 (10)	<0.01
Diabetes (%)	2 (12)	3 (30)	0.26
COPD (%)	2 (12)	0 (0)	0.28
Electrocardiogram			
Sinus	14 (82)	10 (100)	0.17
HR (beats/min)	65 (10)	66 (12)	0.87
Echocardiography			
LVEDV (ml)	189 (64)	88 (37)	<0.001
LVEF (%)	33 (9)	58 (8)	<0.001
LAD (mm)	4 (3.5)	3.5 (0.6)	0.15
LAV (ml)	57 (44)	36 (22)	0.20
TAPSE (mm)	1.9 (0.6)	2.7 (0.5)	0.001
Peak TR gradient (mmHg)	18 (9)	15 (8)	0.49
IVC (cm)	1.6 (0.5)	1.4 (0.4)	0.31
Blood results			
Hb (g/L)	13.4 (1.3)	14.2 (1.2)	0.09
Creatinine (µmol/L)	114 (24)	73 (13)	<0.001
NTproBNP (ng/L)	558 (323 – 1140)	82 (42 – 119)	<0.01

Table 15: baseline characteristics of patients with heart failure and normal subjects.

Medications and devices			
ACEi/ ARB (%)	15 (88)	1 (10)	<0.001
Beta blocker (%)	15 (88)	0 (0)	<0.001
MRA (%)	13 (77)	0 (0)	<0.001
Loop diuretic (%)	14 (82)	0 (0)	<0.001
CRT (%)	7 (41)	0 (0)	0.02

Abbreviations: HF: heart failure, BMI: body mass index, SBP: systolic blood pressure, NYHA: New York Heart Association, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, HR: heart rate, LVEDV: left ventricular end diastolic volume, LVEF: left ventricular ejection fraction, LAD: left atrial diameter, LAV: left atrial volume, TAPSE: Tricuspid annular plane systolic excursion, TR: tricuspid regurgitation, IVC: inferior vena cava, Hb: haemoglobin, NTproBNP: amino terminal pro brain type natriuretic peptide, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist, CRT: cardiac resynchronization therapy.

5.3.3 Haemodynamic changes with warm water immersion and exercise

In patients with CHF, and compared to baseline measurements, WWI caused a significant, immediate (1 minute) and sustained (after 15 minutes) increase in SV, CO, CI and decrease in BP and SVR, with no change in HR or CVP. The 3 minutes of kicking led to a further increase in HR, BP, CI and CO, with no change in SV, SVR or CVP. (Figures 15 and 16)

In normal subjects, WWI caused a significant, immediate (1 minute) and sustained (15 minutes) increase in SV, CO and CI with no change in HR, BP, SVR or CVP. The 3 minutes of kicking led to an increase in HR, CO and CVP with no change in BP, SV, CI or SVR. (Figure 15 and 16)

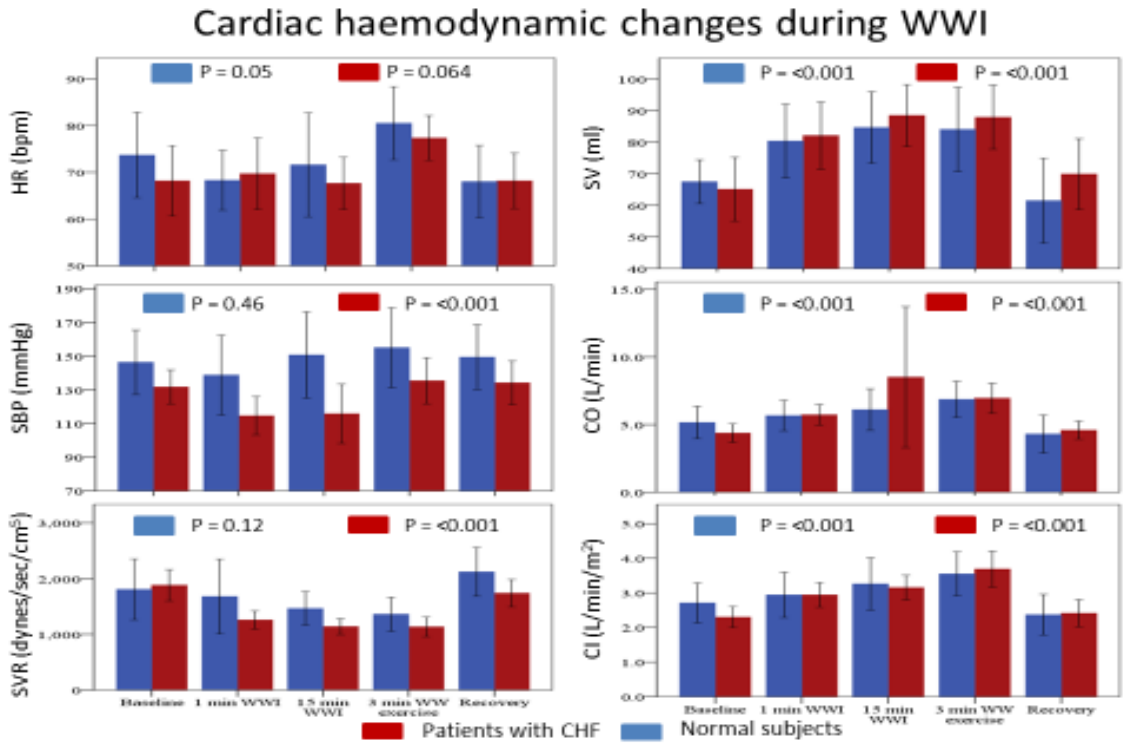

Figure 15: effect of warm water immersion and 3 minutes warm water exercise on cardiac haemodynamics. HR: heart rate, SBP: systolic blood pressure, SVR: systemic vascular resistance, SV: stroke volume, CO: cardiac output, CI: cardiac index, WWI: warm water immersion, CHF: chronic heart failure

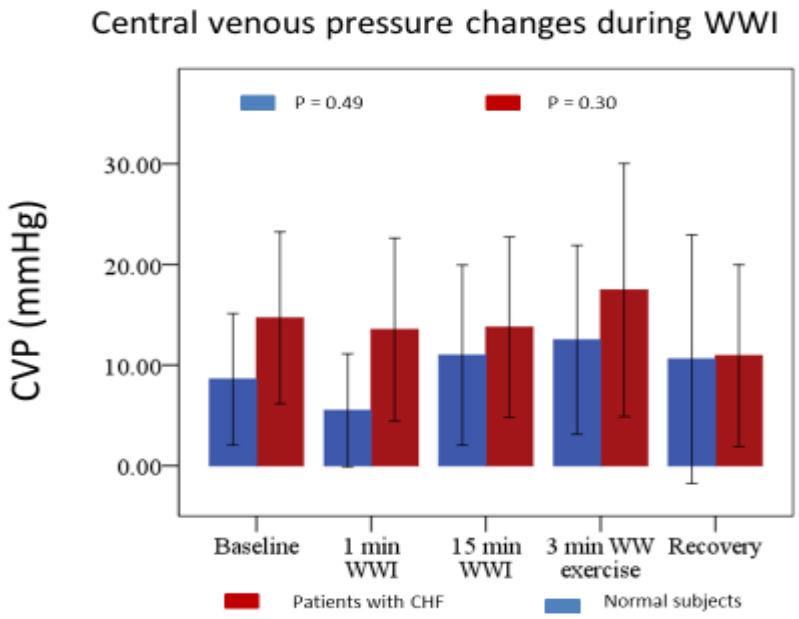

Figure 16: effect of warm water immersion and 3 minutes warm water exercise on CVP. CVP: central venous pressure, WWI: warm water immersion, WW: warm water, CHF: chronic heart failure

5.3.4 Echocardiographic changes with warm water immersion and exercise

In patients with CHF, WWI for 15 minutes led to a significant increase in LAV. The 3 minutes of kicking led to an increase in estimated pulmonary artery systolic pressure. (Figures 17 and 18)

In normal subjects, WWI for 15 minutes significantly increased left ventricular EDV. There were no significant changes in echocardiographic variables after 3 minutes of kicking. (Figures 17 and 18)

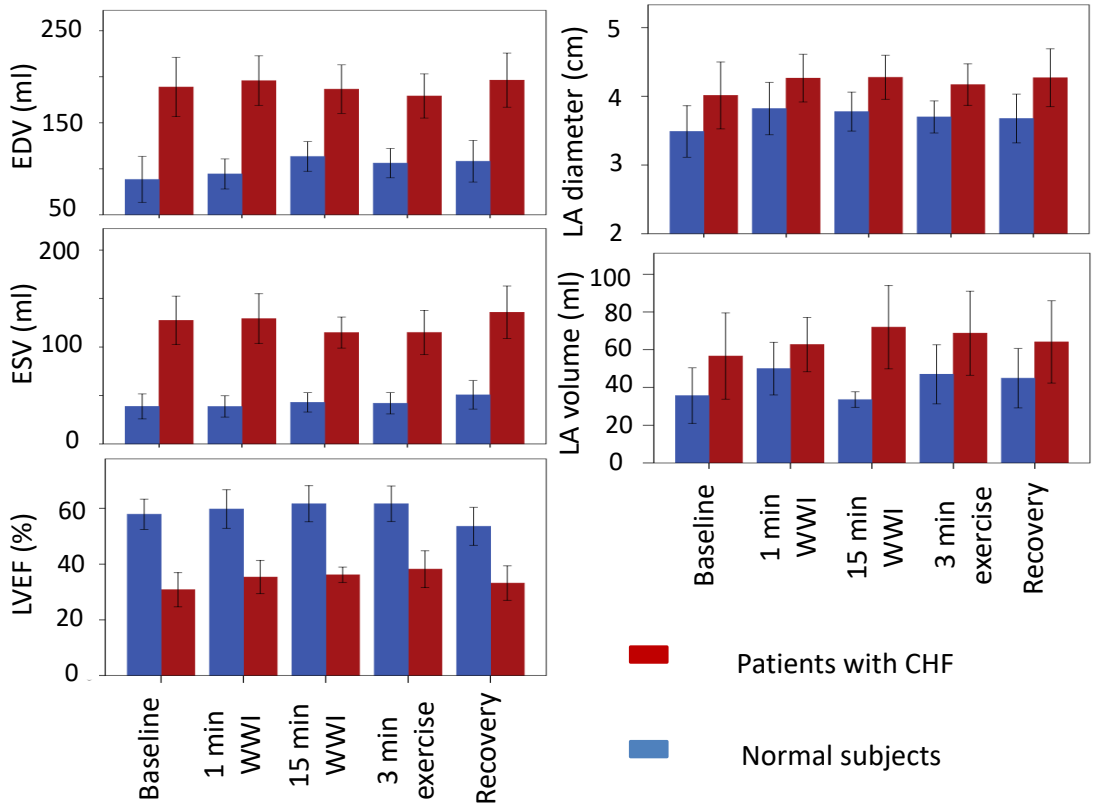

Figure 17: effect of warm water immersion and 3 minutes warm water exercise on left sided echocardiographic variables. EDV: end diastolic volume, ESV: end systolic volume, LVEF: left ventricular ejection fraction, LA: left atrial, WWI: warm water immersion, WW: warm water, CHF: chronic heart failure

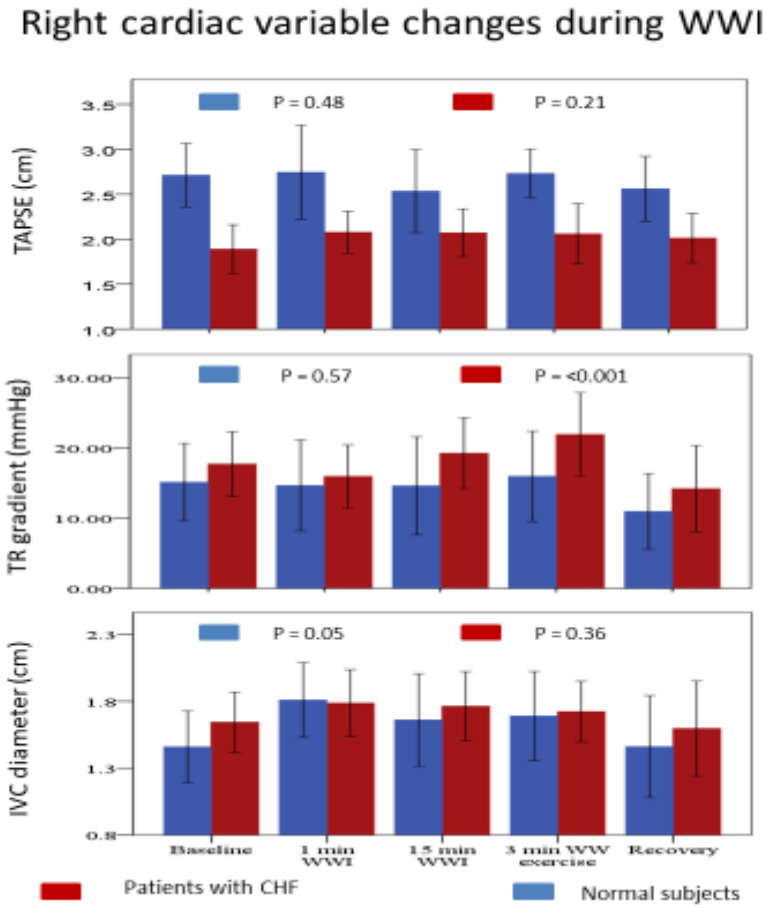

Figure 18: effect of warm water immersion and 3 minutes warm water exercise on right sided echocardiographic variables. TAPSE: tricuspid annular plane systolic excursion, TR: tricuspid regurgitation, IVC: inferior venacava, WWI: warm water immersion, WW: warm water, CHF: chronic heart failure

5.3.5 NTproBNP and symptom changes with warm water immersion and exercise

There was no significant difference in NTproBNP levels between baseline and recovery in patients with HeFREF (558 (IQR: 323 – 1140) to 642 (IQR: 309 – 1187) ng/L, P=0.21) or normal subjects (82 (42 – 119) to 84 (43 – 118) ng/L, P=0.08). None of the subjects experienced any adverse events during water immersion. None of the patients reported any change in any symptom (shortness of breath, chest pain or fatigue) during immersion or recovery.

5.4 Discussion

We found that WWI in patients with HeFREF increases cardiac output. The mechanism for the haemodynamic changes is presumably that hydrostatic pressure increased cardiac preload and atrial volumes. WWI also caused systemic vasodilatation, leading to a fall in blood pressure which, in turn, causes a decreased left ventricular afterload.

Our results are similar to those reported by other researchers. In a study of 9 patients with CHF, WWI (34°C) up to the xiphoid process increased left atrial diameter (by echocardiography), CI and SV index with a decrease in SVR, similar to our study however they also showed an increase in central venous pressure which was not evident in this study.[220] In a study of 13 patients with CHF (mean LVEF 32%) and more severe symptoms (77% in NYHA class 3), WWI (33-34°C) up to the sternal notch increased LVEF, SV and CO but also worsened left ventricular diastolic function (increasing trans mitral Doppler E/A ratio), with no effect on blood pressure.[221] Five minutes of seated reciprocal unilateral knee-extensions in water increased CO, SBP and HR, and was tolerated by patients.[221] Similarly, in a study of 18 patients with CHF (LVEF 31%, 50% in NYHA class 3), WWI (34°C) significantly increased SV and CO but decreased HR, BP and SVR. WWI also led to an increase in left ventricular end diastolic and systolic volumes, estimated pulmonary capillary wedge pressure and left ventricular ejection fraction.[222]
In our study during warm water immersion, normal subjects had a raise in blood pressure but a decrease in SVR, however in patients with HeFREF there was a lower blood pressure at baseline and then a further drop in blood pressure and SVR. The medications prescribed for the treatment of heart failure in patients with HeFREF

were continued during on the study day and therefore may have exacerbated the reduction in blood pressure during warm water immersion.

This study has a number of differences compared to the previous studies in warm water immersion. All the previous studies of WWI on cardiac haemodynamic had patients in sitting or standing positions during WWI. We positioned the participants in supine position because this better replicates the posture during swimming.[220,221,222] This supine position was maintained throughout the study to ensure consist haemodynamic readings. This study used validated novel non-invasive method to measure haemodynamic changes during warm water immersion.

Warmer or colder water temperatures might lead to more pronounced, or different effects, on cardiac haemodynamics and heart function. Hot water immersion (41°C) for 10 minutes significantly decreased left ventricular and atrial size, increased LVEF and decreased mitral regurgitation in a study of 34 patients with CHF and severe symptoms (LVEF 25%, 94% in NYHA class III/IV). The changes persisted for 30 minutes after emerging from water.[223] Mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and mean right atrial pressure rose substantially during hot water immersion but did not cause any symptoms. In two studies, cold water immersion (12°C to 22°C) for a few seconds increased cardiac output and blood pressure but change in heart rate was variable.[224,225]

In previous studies, warm water immersion up to the neck in standing position for 5 to 10 minutes, has increased central venous pressure.[226,227] We found that central venous pressure did not increase and pulmonary artery systolic pressure increases

only after 3 minutes of gentle exercise in patients with HeFREF (without precipitating any symptoms), but not in normal subjects. The pulmonary artery systolic pressure rapidly returned to baseline after WWI.

Reassuringly, the haemodynamic changes did not lead to an increase in NTproBNP plasma levels. In studies looking at the effect of WWI on natriuretic peptides in normal subjects, atrial natriuretic peptide significantly increased without any change in brain natriuretic peptide.[228,229] There have been no studies looking at the acute change in natriuretic peptides during water immersion in patients with heart failure. Whether prolonged immersion or swimming causes a more sustained increase in systolic pulmonary pressure and symptoms in patients with CHF requires further studies.

5.4.1 Limitations

Our study was conducted in a controlled, indoor thermo neutral hydrotherapy pool and therefore the results cannot be translated to swimming in different environmental conditions. The studied population was small, and patients had only mild symptoms; thus, results of this study cannot be generalised to all patients with CHF, particularly to those with more severe disease. Although majority of the patients swim in prone, we were limited to investigate patients in supine position to enable echocardiography. The workload was not standardized and not adjusted for maximal exercise capacity. It was chosen to allow all participants to be able to conduct 3 min of exercise with continuous haemodynamic monitoring. We did not measure NTproBNP levels after a few hours from completing the study, or troponin levels,

which might have provided further information about any delayed effect of WWI with exercise on the myocardium.

5.5 Conclusion

In patients with CHF, WWI causes an acute increase in cardiac output and a fall in vascular resistance. The changes were well-tolerated and patients with HeFREF can immerse in warm water safely. Whether swimming can be recommended as alternative to other forms of exercise or rehabilitation in patients with CHF needs to be studied further.

Chapter 6 Conclusion

Patients with heart failure have significantly more symptoms that hinder their activities of daily living than any other chronic medical condition.[24] In ambulatory patients with chronic stable heart failure, the cardinal symptom is exercise intolerance due to breathlessness and fatigue.[26,27] In the past 30 years several trials on neuro hormonal antagonists (angiotensin converting enzyme inhibitors, mineralocorticoid receptor antagonists and beta blockers) have shown a benefit of improving symptoms, reducing hospitalization and improving prognosis in patients with HeFREF.[41,42,43,44,45,46,47] The situation is very different for patients with HeFNEF. None of those pharmacotherapies which are beneficial in patients with HeFREF have any mortality or morbidity benefit in patients with HeFNEF.[52,53,54,55,56] Only diuretics seem to be helpful in that they relieve congestion.[1]

Despite the improvements in medical treatment, patients with heart failure still remain symptomatic. Another focus of treatment could be to improve quality of life by improving exercise tolerance. Exercise programmes are an attractive therapeutic option because it improves exercise capacity and quality of life in patients with heart failure.

I therefore undertook a project to seek out further treatments to improve quality of life by targeting treatments that may improve symptoms and exercise capacity in patients with heart failure.

The first therapy I investigated was oxygen supplementation, which is cheap, widely available and used in a variety of health care settings, in ambulatory patients with HeFNEF. It is liberally used in the acute and chronic settings in a variety of conditions in the belief that this will improve symptoms of shortness of breath.[96,121,132] However even in normal subjects oxygen supplementation impairs cardiac haemodynamics.[102,103,104] Trials of oxygen supplementation during exercise in patients with HeFREF have yielded mixed results.[83,84,137,138]

There have been no studies on the effect of increased inspired oxygen on exercise capacity in patients with HeFNEF. I therefore designed a study with the aim to assess the effects of increasing inspired oxygen fraction on exercise capacity in patients with HeFNEF. I found that in patients with HeFNEF, increasing oxygen concentration during exercise lead to a small (20 seconds) and clinically meaningless increase in exercise time but had no effect on peak work load.

Although oxygen supplementation in patients with HeFNEF may improve exercise time, it does not seem practical to wheel around an oxygen cylinder, which in itself would hamper and reduced exercise capacity. The prevalence of patients with HeFNEF is increasing and they have the largest unmet need for evidenced based treatment. These patients are a diagnostic rag-bag and they have other extra cardiac co-morbidities that hinder exercise capacity. Treatment may need to be focused on other co-morbidities which limit exercise capacity in patients with HeFNEF.

The second therapy I investigated was warm water immersion in patients with HeFREF. Factors such as advanced age and co morbidities such as osteoarthritis,

hinder exercise training on a treadmill or a cycle in patients with CHF and swimming is a common form of exercise in the UK. However, whether swimming is either safe or beneficial in patients with heart failure is not clear. I first conducted a literature review for studies of water immersion or swimming in patients with heart failure. I found that in small studies of warm water immersion, up to the neck, is well tolerated in stable patients with chronic heart failure but both cold and hot water immersion caused adverse haemodynamic effects. Exercise in water has effects similar to other forms of exercise training with a similar improvement in exercise capacity however these studies were small and swimming was only part of an exercise programme. I therefore designed a study to investigate the changes in cardiac haemodynamics during warm water immersion in patients with HeFREF whilst in supine position using non-invasive devices to measure cardiac haemodynamics and central venous pressure. I found that warm water immersion had favourable changes in cardiac haemodynamics even in the spine position with no changes in central venous pressures.

Cardiac rehabilitation for patients with heart failure has shown to improve symptoms however the uptake is low due to other co morbidities. I have shown that warm water immersion is not only safe but also improves cardiac haemodynamics, at least whilst immersed in water. Swimming is a common sport in the UK and therefore designing cardiac rehabilitation in swimming pools may attract more patients with HeFREF, however the long term benefit need to be demonstrated in further studies.

In summary, I found that patients with heart failure have symptoms of exercise intolerance despite optimal medical treatment. Cardiac rehabilitation has added benefits and improving participation in cardiac rehabilitation is key. I found that warm water immersion is safe and has positive haemodynamic effects in patients HeFREF. Further studies are needed to assess the effect of warm water immersion in patients with HeFNEF and the benefit of swimming alone as a form of cardiac rehabilitation. However, I also found that oxygen supplementation does not clinically improve the exercise capacity of patients with HeFNEF. HeFNEF remains a difficult condition to treat because it is not well defined and co-morbidities may play a significant role in symptoms.

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