#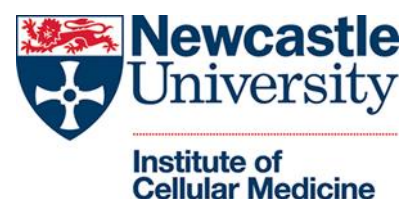 A novel, personalised home-based physical activity intervention for chronic heart failure: exploring feasibility, effectiveness and patient experiences

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A thesis submitted for the degree of Doctor of Philosophy
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Declaration

This thesis is submitted for the degree of Doctor of Philosophy at Newcastle University. I, Nduka Charles Okwose, declare that data and all other information presented in this thesis is the result of my own original research. I confirm that work done by others is clearly acknowledged and any published work is clearly attributed and the source stated. I certify that this thesis contains no material that has been submitted for any other academic degree and published material presented was the result of the research carried out during the course of the present doctoral study.

Abstract

Heart failure (HF) is a clinical syndrome associated with reduced cardiac output at rest and/or in response to stress. Physical activity plays an important role in reducing cardiovascular morbidity and mortality. Patients with chronic heart failure demonstrate reduced physical activity levels. Exercise based cardiac rehabilitation programmes are safe and recommended to improve symptoms and outcomes in HF. Available data suggests that less than 10% of patients with HF in the UK are referred for cardiac rehabilitation. This is secondary to lack of resources and direct exclusion of HF rehabilitation from local commissioning agreements. A personalised home-based physical activity intervention may hold great potential to improve patient outcomes and clinical practice.

This thesis firstly investigates non-invasive methods for evaluation of cardiac function (cardiac output) at rest and in response to cardiopulmonary exercise stress testing. Secondly, is explores the feasibility and physiological effects of a novel, personalised home-based physical activity intervention in HF patients (Active-at-Home-HF), and qualitatively explores barriers and facilitators to uptake and continued participation from a patient perspective.

The major findings and conclusions of the thesis suggest that i) Bioreactance and inert gas rebreathing methods show acceptable levels of agreement for estimating cardiac output at higher levels of metabolic demand. However, they cannot be used interchangeably due to strong disparity in results at rest and low-to-moderate exercise intensity; ii) Inert gas rebreathing method demonstrates acceptable level of test-retest reproducibility for estimating cardiac output at rest and during cardiopulmonary exercise testing at higher metabolic demands; iii) Active-at-Home-HF intervention is safe, feasible and acceptable for patients with chronic HF. It leads to increased daily physical activity levels and may improve quality of life and exercise tolerance; and iv) Lastly, the qualitative study emphasizes the importance of clinicians who advocate physical activity as a management option for heart failure, personalised support to increase and maintain levels of physical activity and that heart failure patients should seek social support from friends and family.

Dedication

This thesis is dedicated to my parents, Christopher C. Okwose and Nkechi M. Okwose

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Although the opinions, interpretations and analyses in this thesis are purely mine, I owe a debt of gratitude to many who contributed directly by giving up their own time and effort or indirectly through less tangible but no less support.

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Above all, I thank God Almighty, the Omniscient one for without you, I surely, will be lost.

Table of Contents

List of Figures

List of Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHF	Acute heart failure
ALT	Alanine aminotransferase
ABPM	Ambulatory based pressure monitoring
ANP	A-type natriuretic peptide
ANS	Autonomic nervous system
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
AV	Atrio-ventricular
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
BPM	Beats per minute
BSA	Body surface area
CABG	Coronary artery bypass graft/grafting
CAD	Coronary artery disease
CCB	Calcium-channel blocker
CI	Cardiac index

CMR	Cardiac magnetic resonance
CO	Cardiac output
CSR	Cheyne-Stokes respiration
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
HbA1c	Glycated haemoglobin
HBPM	Home based pressure monitoring
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	HF with mid-range ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HR	Heart rate
ICD	Implantable cardioverter-defibrillator
IHD	Ischaemic heart disease
IVC	Inferior vena cava
LV	Left ventricular/left ventricle
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction

LVSD	Left ventricular systolic dysfunction
MRA	Mineralocorticoid receptor antagonist
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
Peak VO$_2$	Peak oxygen uptake
QOL	Quality of life
QRS	Q, R, and S waves (combination of three of the graphical deflections)
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SNS	Sympathetic Nervous System
SpO2	Transcutaneous oxygen saturation
TEE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
VE-VCO$_2$	Ventilatory equivalent ratio for carbon dioxide
VT	Ventricular tachycardia

List of Publications and Presentations from Thesis

Manuscripts – published

Okwose NC, Chowdhury S, Houghton D, Trenell MI, Eggett C, Bates M, MacGowan GA and Jakovljevic DG. Comparison of cardiac output estimates by bioreactance and inert gas rebreathing methods during cardiopulmonary exercise testing. *Clinical Physiology and Functional Imaging. 2017* [e-publication ahead of print 02 June 2017 DOI: 10.1111/cpf.12442] (Based on Chapter 3).

Manuscripts – under review

Okwose NC, Zhang J, Chowdhury S, Houghton D, Eggett, Bates MDG, MacGowan GA, Jakovljevic DG. Reproducibility of Inert Gas Rebreathing Method to Estimate Cardiac Output at Rest and During Cardiopulmonary Exercise Stress Testing. *European Journal of Applied Physiology.* Under review 07 February 2018 (Based on chapter 4).

Manuscripts – in preparation

Okwose NC, Charman S, Cassidy S, O'Brien N, Avery L, Bailey K, Skinner J, MacGowan GA, Jakovljevic DG. Feasibility and preliminary evaluation of a novel, personalised, home-based physical activity intervention for chronic heart failure. *BMJ Heart* (to be submitted in March 2018 and is based on chapter 5)

Okwose NC, Cassidy S, Trenell MI, O'Brien N, Bailey K, Skinner J, MacGowan GA, Avery L, Jakovljevic DG. Exploring barriers and facilitators of adults with heart failure to participation in a home-based physical activity programme: A qualitative study. *International Journal of Cardiology* (to be submitted in April 2018, and is based on chapter 6)

Abstracts presented

Okwose NC, Chowdhury S, Houghton D, Trenell MI, Eggett C, Bates M, MacGowan GA, Jakovljevic DG. Inert gas rebreathing is a reproducible method to assess cardiac and metabolic function at rest and during cardiopulmonary exercise stress testing. *The 8th Alliance for Healthy Ageing Conference, Groningen, Netherland, 9-11 November, 2017*

Okwose NC, O'Brien N, Cassidy S, Charman S, Avery L, Jakovljevic DG. Exploring barriers and facilitators of adults with heart failure to participation in a home-based physical activity programme: A qualitative study. *The 7th Interdisciplinary Conference on Ageing, California USA, 3-4th November, 2017*

Okwose NC, Cassidy S, Trenell MI, Bailey K, Skinner J, MacGowan GA, Jakovljevic DG. Feasibility and preliminary evaluation of home-based physical activity intervention for chronic heart failure. *European Society of Cardiology Heart Failure Annual Congress.* Paris, France, 29th April - 2nd May, 2017

Okwose NC, Chowdhury S, Houghton D, Trenell MI, Eggett C, Bates M, MacGowan GA, Jakovljevic DG. Comparison of cardiac output estimated from non-invasive technologies. The 7th International Congress of the African Association of Physiological Sciences, Lagos, Nigeria, 5th-8th September, 2016.

CHAPTER 1: Introduction and literature review

1.0 Introduction

This thesis, structured into nine chapters, provides detailed description of my PhD research programme. **Chapter 1** provides an introduction into thesis and review of the literature. In this section, heart failure (HF) is reviewed in detail highlighting epidemiology, etiology, diagnosis and treatment. **Chapter 2** explores physical activity in heart failure and gives a summary of home based cardiac rehabilitation in heart failure patients. **Chapter 3** highlights the importance of cardiac output measurement in Heart failure and the research methodology and techniques used to collect data. **Chapter 4** describes the aims, objectives and hypothesis of the thesis. **Chapters 5 and 6** evaluate methodological aspects i.e. comparison between inert gas rebreathing and bioreactance methods for monitoring cardiac output and reproducibility of inert gas rebreathing method at rest and in response to cardiopulmonary exercise testing. Both studies were carried out to inform choice of equipment to be used for evaluation of haemodynamic effects of a physical activity intervention (Active-at-Home-HF). **Chapter 7** evaluates feasibility, and clinical effect of a novel, personalised, home-based physical activity intervention (Active-at-Home-HF) which was developed as part of my PhD research programme. **Chapter 8** investigates barriers and facilitators of adults with heart failure to participation in a home-based physical activity programme using qualitative methods. **Chapter 9** provides summary of the main results from all the studies, their limitations and recommendations for future research to improve monitoring, management and care of people living with heart failure.

1.1 Heart failure

1.1.1 *Definition and epidemiology*

'HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or physiological cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress' (Ponikowski *et al* 2016)

In the United Kingdom, it is estimated that around 900,000 people suffer from HF (NICOR 2013) accounting for about 0.9% of men and 0.7% of women. This figure rises to 13.1% of men and 11.9% of women when those over 75 years are accounted for. The sharp increase in prevalence results from ageing population and improved outcomes in coronary artery disease, particularly in acute coronary syndrome (Townsend et al. 2012). HF constitutes a huge economic burden on the NHS and accounts for one million in-patient days and 5% of all emergency hospital admissions (NICE 2010).

Data from European and American studies puts the overall prevalence of HF in the range of 1-12% (Roger 2013). Survival rate is variable with greater outcome and life expectancy shown in patients admitted at specialist cardiology units compared with those admitted at general wards. The UK National HF Audit reported that around one in ten patients die in hospital and for those who survive hospital admission, as many as 25-33% die within one year of their admission (NICOR 2013). Due to the progressive nature of HF, 5-year survival estimate after diagnosis, is 50% (Cowie *et al* 2000, Mosterd *et al* 2001). While this has not changed till date, 10-year survival estimate seems to have improved from 10 % to 30% (Taylor *et al* 2017).

1.1.2 *Aetiology*

HF is a pathophysiologic complex associated with dysfunction of the heart and is a common end point for many diseases of the cardiovascular system. These include hypertension, ischemic heart disease, diabetes, obesity and chronic kidney disease (Roger *et al* 2011, Lloyd-Jones *et al* 2002). Therefore, the underlying cause of the cardiac dysfunction must be determined. Approximately 75% of all HF patients have underlying hypertension and this risk factor alone doubles the risk of developing HF compared to normotensive patients (Lloyd-Jones *et al* 2002). However, some researchers (Jin *et al* 2014) have suggested that hypertension appears not to be associated with adverse clinical outcomes in HF patients but rather, may be a protective factor for reduced HF-related re-hospitalisation. In general, HF

could be caused by (1) inappropriate workloads placed on the heart, e.g. volume or pressure overload (2) restricted filling of the heart (3) myocyte loss or (4) decreased myocyte contractility. Other important but less common causes of HF include, infections (e.g. viral myocarditis, Chagas disease), toxins (alcohol, cytotoxic drugs), valvular disease and prolonged arrhythmias (Kemp and Conte 2012) (Table 1.1).

Table 1.1 Aetiology of heart failure (General Classification)

Coronary artery disease	Progressive atherosclerosis, Acute coronary syndrome
Intrinsic myocardial disease	Dilated cardiomyopathy Hypertrophic cardiomyopathy Restrictive cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy
Valvular heart disease	Congenital Age-related/calcific Infective endocarditis Immunological (e.g. rheumatic fever) Collagen disease (e.g. Marfan's syndrome) Neoplastic (metastases, carcinoid syndrome)
Congenital heart disease	
Hypertension	Systemic and pulmonary
Arrhythmias and cardiac conduction disturbances	Tachyarrhythmias Bradyarrhythmias Intraventricular conduction disturbance
High-output cardiac failure	Anaemia Thyrotoxicosis Pregnancy Arteriovenous fistula Liver cirrhosis Paget's disease Renal cell carcinoma
Pericardial disease	Constrictive pericarditis Pericardial effusion with tamponade
Reproduced from (Pearse and Cowie 2014)	

1.1.3 *Signs and symptoms*

The signs and symptoms of HF usually present as a clinical after-effect of reduced CO and inefficient venous return (Yancy *et al* 2013). Signs and symptoms of HF may vary depending on the type of HF. This will be elaborated on under pathophysiology of HF (Section 1.2). However, general signs and symptoms include dyspnoea, cough, fatigue, wheezing, pulmonary and peripheral oedema and pre-renal failure. Dyspnoea, cough and wheezing, result from increased pressure in the pulmonary capillary bed, a consequence of ineffective forward flow from the left ventricle. Similarly, lower extremity oedema and in some cases peritoneal ascites, occurs when the right ventricle is unable to accommodate systemic venous return (Kemp and Conte 2012). Fatigue is a common complaint as the heart cannot pump enough blood to meet the body's metabolic needs (Kemp and Conte 2012) thus limiting physical activity/exercise tolerance (Yancy *et al* 2013). Furthermore, as the heart tries to compensate for this shortage via a faster heart rate, palpitations can occur. In addition, nausea and a lack of appetite may also be a resultant effect as blood is shifted from the gastrointestinal tract to more vital organs including kidneys, heart and brain. In recent years, most definitions of HF have emphasised the need for correlation between patient symptoms and the physical signs manifested (Dickstein and Cohen-Solal 2008).

1.1.4 *Functional classification*

HF is usually classified using the New York Heart Association (NYHA) mode of classification (Table 1.2). This places the patient into one of four classes depending on the physical disability resulting from the HF (Little 1994). Currently the NYHA classification is used not only to document functional cardiac status but also as an entry criterion for clinical trials.

Table 1.2 NYHA Classification of heart failure

Class I	No symptoms with ordinary activity
Class II	Slight limitation of physical activity Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina
Class III	Marked limitation of physical activity Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina
Class IV	Unable to carry out any physical activity

| | without discomfort |
| | Symptoms of cardiac insufficiency may be present even at rest |

Aside the NYHA classification, the American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly developed a new classification system (Table 1.3) (Hunt *et al* 2001). This system takes into account the pathogenesis and progression of the disease process. It also recognises that there are established risk factors for HF as well as structural prerequisites for the development of HF.

Table 1.3 ACC/AHA classification of heart failure

Stage A	Patient at high risk for developing HF with no structural disorder of the heart
Stage B	Patient with structural disorder of the heart without symptoms of HF
Stage C	Patient with past or current symptoms of HF associated with underlying structural heart disease
Stage D	Patient with end-stage disease who requires specialized treatment strategies i.e. heart transplantation / mechanical circulatory support

1.2 Pathophysiology of HF

The evaluation of HF as a cardiac pathology focusses mainly on ventricular function, particularly the left ventricle. This is because the left ventricle is the primary physiologic pump of the heart. This section will discuss HF under left and right ventricular dysfunction.

1.2.1 *Left ventricular systolic dysfunction*

There are three main categories of left ventricular systolic dysfunction based on values of the left ventricular ejection fraction i.e. HF reduced ejection fraction (HFrEF), HF preserved ejection fraction (HFpEF) and HF mid-range ejection fraction (HFmrEF), as further detailed below (Ponikowski *et al* 2016).

As the name implies, HFrEF is caused by impaired ventricular contraction and ejection of the myocardium. This could be regional e.g. following a myocardial infarction or global (as seen

in cardiomyopathy, or chronic mitral regurgitation). The failing myocardium is unable to eject sufficient blood during ventricular contraction, although the heart may fill properly during diastole (Pearse and Cowie 2014). This leads to dilatation and stretching of the myocardium.

On the other hand, HFpEF is caused by impaired ability of the heart to relax or impaired ventricular filling during diastole, although systolic function is preserved. This can be visualised using Doppler echocardiography to assess flow through the mitral valve and ventricular wall motion during diastole. HFpEF becomes increasingly common with advancing age and is typically associated with a history of hypertension or diabetes (Pearse and Cowie 2014).

Although, there are different causes of HF, reports have shown that approximately 40-50% of patients diagnosed with HF present with have HFrEF (Lilly 2012). In addition, most patients with systolic dysfunction have underlying diastolic dysfunction. Whatever the underlying pathology may be, diagnosis of diastolic or systolic dysfunction currently depend on ejection fraction (EF), which is defined as the amount of blood pumped from the ventricle in one heartbeat. EF of < 40% signifies HFrEF, while EF > 50% connotes HFpEF. Ejection fraction between 40-50% signifies HFmrEF (Ponikowski *et al* 2016).

As noted earlier, the leading cause of HFrEF is loss of functional myocardium due to ischemic disease and infarction. Another important factor is uncontrolled hypertension leading to excessive pressure overload. In addition, volume overload and impaired contractility have been implicated in the pathogenesis of HF as shown in Figure 1.1.
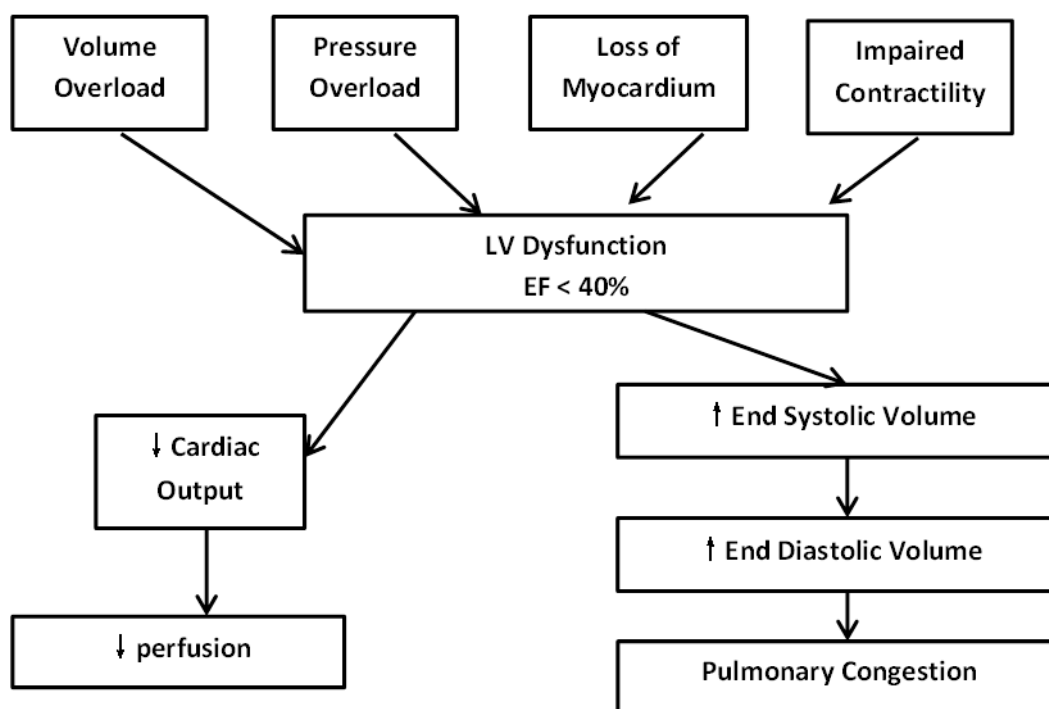
Figure 1.1 Pathophysiology of Left ventricular systolic dysfunction (Kemp & Conte 2012)

The resultant effect is a decrease in CO which in turn leads to a decrease in global perfusion (Kemp and Conte 2012). In addition, left ventricular dysfunction causes a rise in left ventricular blood volume thus leading to an alternate increase in end systolic and diastolic volumes (Johnson 2014). There is an increase in left ventricular end diastolic pressure which in turn leads to elevated left atrial pressure thus resulting in increased pulmonary pressure (Pearse and Cowie 2014). This elevated pressure in the lungs forces fluids out of the pulmonary capillaries and leads to pulmonary congestion. At this point, dyspnoea arises as the major symptom of heart failure (Table 1.4)

Table 1.4 Signs and symptoms of left ventricular heart failure

Signs	Symptoms
Basilar rales	Dyspnoea at rest or on exertion
Pulmonary oedema	Paroxysmal nocturnal Dyspnoea
S_3 Gallop	Tachycardia
Pleural effusion	Haemoptysis
Cheyne-Stokes respiration	

1.2.2 *Right ventricular systolic dysfunction*

Right ventricular failure is usually caused by left ventricular failure (Kemp and Conte 2012). Other causes include congenital heart disease and pulmonary arterial hypertension (Haddad *et al* 2008). Patients with isolated right ventricular failure (pulmonary hypertension or Cor pulmonale) can have a mechanical reason for left ventricular failure (Haddad *et al* 2008). The interventricular septum is usually displaced toward the thinner walled and lower pressure right ventricle (Haddad *et al* 2008). When right ventricular pressure increases relative to the left, the interventricular septum can shift to the left and prevent efficient filling of the left ventricle, which may lead to pulmonary congestion (Haddad *et al* 2008). Progressive failure of the right ventricle leads to build up of blood in the ventricles which in turn leads to elevated right atrial pressure and increased pressure in the superior and inferior vena cava, thus impairing venous drainage from the body (Kemp and Conte 2012). This causes increased pressure in the abdominal viscera affecting the liver, gastrointestinal tract and also the lower extremities. Signs and symptoms include abdominal pain, hepatomegaly and peripheral oedema (Table 1.5)

Table 1.5 Signs and symptoms of right ventricular failure

Signs	Symptoms
Peripheral edema	Abdominal pain
Jugular Venous distension	Anorexia
Abdominal-jugular reflex	Nausea
Hepatomegaly	Bloating
Adapted from (Kemp and Conte 2012)	

1.3 Compensatory mechanisms in HF

Under physiological conditions, hemodynamic equilibrium is attained by the regulation of the amount of blood pumped out of the heart (CO) and the resistance to the ejection of blood (peripheral resistance). This is achieved via several mechanisms which include the Frank-Starling mechanism, neuro-humoral activation and ventricular remodelling. In HF, these mechanisms are also enforced although long term effects of these mechanisms worsen the syndrome in what could be termed as a vicious cycle of events.

1.3.1 *Frank-Starling mechanism*

Frank-Starling mechanism plays an important compensatory role in the early stages of HF. The mechanism proposes that as end diastolic volume increases, the returning blood stretches the walls of the ventricle, which leads to an expansion during diastole. The enlarged ventricular wall causes cardiac myocytes to contract forcefully leading to a greater stroke

volume and CO. This effect is known as the Frank-Starling mechanism (Chaui-Berlinck and Monteiro 2017). At the onset of HF, the ventricles may be able to contract and produce sufficient CO for systemic utilization. However, as HF progresses, there is a continuous inability of the heart to contract effectively. Thus, there is a reduction in stroke volume although end diastolic volume (preload) continues to increase. At this point, compensatory mechanisms fail and the increase in end diastolic volume and end diastolic pressure eventually leads to pulmonary congestion (Westerhof and O'Rourke 1995)

1.3.2 *Neurohumoral activation*

Neurohumoral activation plays an important role in the maintenance of mean arterial pressure (MAP) during early stages of HF. When there is a decrease in MAP, the SNS is activated thus releasing the hormones epinephrine and norepinephrine (Chaggar *et al* 2009). This has a direct effect on the heart and peripheral vasculature. While it increases heart rate and cardiac contractility, it also causes peripheral vascular constriction which leads to increased stroke volume and total peripheral resistance, thereby increasing MAP (Kjaer and Hesse 2001).

Although this is a regulatory mechanism, overstimulation of the SNS via α_1, β_1 and β_2 receptors, leads to myocardial toxicity (Chaggar *et al* 2009). The effects of this resultant toxicity are decreased pumping capability and ejection fraction, arrhythmia and tachycardia (Chaggar *et al* 2009).

In addition, when MAP, is reduced, α_1, and β_1 receptors activate the RAAS. The RAAS is activated in response to reduced renal blood flow arising from a decreased MAP (Rea and Dunlap 2008). The kidneys secrete renin which acts on angiotensinogen in the liver to synthesise angiotensin I. Circulating angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II. Angiotensin II is a potent vasoconstrictor that promotes the secretion of aldosterone. In summary, the end result of the neuro-hormonal activation is the release of norepinephrine, promotion of sodium and water retention and increased myocardial contractility.

Although the stimulation of the SNS and activation of the RAAS system play an important compensatory role in HF (Bernstein *et al* 2011), long term effects of this activation is the remodelling of the ventricles which further hastens myocardial dysfunction (Mann 1998, Packer 1998). In addition, long term RAAS activation has deleterious effects on the kidneys which include the stimulation of inflammatory pathways, fibrosis, increased oxidative stress and endothelial dysfunction (Metra *et al* 2012).

There are other neuro-hormonal mechanisms related to HF. These mechanisms are mediated by compounds produced in the brain e.g. C-type natriuretic peptide (CNP) as well as the heart e.g. atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) to counteract the effects of the above discussed mechanisms. ANP and BNP are found in the atria and Ventricles respectively and are released following atrial or ventricular expansion. CNP is found predominantly in the central nervous system. These hormones act directly to cause vasodilation, electrolyte and water excretion by inhibiting renin, aldosterone and vasopressin activity (Kim and Januzzi 2011). Other compounds involved in HF pathophysiology and regulation include nitrous oxide, bradykinin, prostacyclin and endothelinin I and cytokines (e.g. tumour necrosis factor α, interleukins and interferons) (Chen *et al* 2008, Boulanger 1999). The aforementioned compounds act as biomarkers in the investigation of HF and elevated BNP and NTproBNP levels, in particular, are thought to be one of the first signs of the HF syndrome used to enhance diagnosis and monitor of disease progression (Nice 2010, Gaggin and Januzzi 2014).

1.3.3 *Ventricular remodelling*

There is growing acceptance that ventricular remodelling offers the best compensation to the failing heart (MacIver 2010). Current evidence (Yip *et al* 1999, Abhayaratna *et al* 2006, Hogg *et al* 2004) suggests that HF patients have an increased incidence of hypertension and concentric left ventricular hypertrophy. This has highlighted the possibility that an increased wall thickness might be relevant to the preservation of the left ventricular ejection fraction, stroke volume and CO despite contractile abnormalities. This is especially true as the Frank-Sterling mechanism is exhausted in chronic HF and so elevated end diastolic pressures cannot maintain stroke volume alone (Gill *et al* 2006, Schwinger *et al* 1994). Furthermore, there is an increased likelihood that neurohumoral activation will not produce a sustained positive inotropic and chronotropic effect as there is a down regulation of β_1 adrenergic receptors and the uncoupling of β_2 receptors to efferent neurons (Lohse *et al* 2003).

However, remodelling causes changes in ventricular mass, composition and volume and its overall myocardial morphology changes as it becomes more spherical in shape (Kemp and Conte 2012). As remodelling progresses, it eventually becomes detrimental. The ventricles continue to enlarge and the myocardium hypertrophies. This leads to increased wall tension and fibrosis which eventually impair contractility as a result of myocardial apoptosis and necrosis.

Pathophysiologic changes involved in HF development and progression are associated with changes at the cellular and molecular levels (Table 1.7). These are very complex and include changes in Ca^{2+} handling, adrenergic receptors, contractile mechanisms and myocyte structure (Kusumoto 2013).

Table 1.6 Pathologic changes associated with heart failure

Haemodynamic changes	Decreased output (systolic dysfunction)
	Decreased filling (diastolic dysfunction)
Neurohormonal changes	Sympathetic system activation
	Renin-Angiotensin Aldosterone System
	Vasopressin release
	Cytokine release
Cellular changes	Inefficient intracellular Ca^{2+} handling
	Adrenergic desensitization
	Myocyte hypertrophy
	Re-expression of foetal phenotype proteins
	Cell death
	Fibrosis
Redrawn from (Kusumoto 2013)	

1.4 Assessment and diagnosis of heart failure

The evaluation of patients with suspected HF entails determining more than just whether the syndrome is present or not (Fonseca 2006). According to the National Institute of Clinical Excellence (NICE) guidelines 2010, assessment should begin with detailed documentation of patient's history of symptoms and conducting a physical examination. Furthermore, laboratory and other diagnostic test results are vital to ascertain the severity of disease and also to identify the underlying cardiac pathology exacerbating the disease (Nice 2010). Additional guidelines for the evaluation and management of HF have also been published by the European Society of Cardiology (Ponikowski *et al* 2016) and the American College of Cardiology/American Heart Association (Yancy *et al* 2017). Presently, there is a general consensus that diagnosis of HF is only concrete when patient symptoms bear a positive correlation with physical signs of the disease. According to NICE Guideline, (Nice 2010) diagnostic investigation include an ECG aiming to identify the presence of infarct, ischemia or any conduction or structural abnormality, chest X-ray; to determine the size of the heart and presence of pulmonary congestion or pleural effusion and echocardiogram; to determine

cardiac function and structure i.e. ejection fraction, cardiac geometry, wall thicknesses and valvular abnormalities.

1.4.1 *Electrocardiography*

The electrocardiogram (ECG) is a device which records differences in electrical activity of the heart. The movement of ions inside and across the membrane of cardiac myocytes constitute the flow of electrical charges which the ECG records (Davey 2010). These changes are recorded on ECG graph paper which moves at a speed of 25mm/s. ECG measures duration horizontally while voltage is measured vertically. A typical ECG is made up of a P-wave, QRS complex, ST segment, T wave and a U-wave. The P-wave and QRS complex represent atrial and ventricular excitation respectively and have duration of 0.12-0.20secs for p-wave and 0.04-0.11secs for the QRS complex. On the other hand, the ST segment, T-wave and U-wave stand for the return of the stimulated myocardial cells to rest.

For over a century, the ECG has been used as a standard diagnostic tool for different forms of heart disease. Resting and exercise ECG abnormalities have been shown to be independently associated with CVD (Liao *et al* 1987, De Bacquer *et al* 1998). However, due to the high prevalence of CVD and ECG abnormalities in older adults, other markers should also be incorporated alongside ECG in making better diagnosis (Ashley *et al* 2001).

The ECG has also been used as a screening tool to determine the presence or absence of underlying structural or valvular heart disease with applicability to sports participation (Hevia *et al* 2011, Maron *et al* 2009). Although the ECG is cost effective, safe and widely available (Bauer 2012, Denes *et al* 2007), its low sensitivity of 53% for identifying those who would have future coronary event (Froelicher et al., 1998; Sekhri et al., 2008) is still a cause for concern. According to Barraclough (2008), resting ECG could yield negative results in almost half of patients with clinically significant disease. The ECG however remains a valuable screening tool for subclinical CVD (Bauer 2012).

1.4.2 *Echocardiography*

Echocardiography, also called cardiac ultrasound, has become an indispensable diagnostic tool in cardiovascular departments (Bhan *et al* 2010) and is the second most frequently ordered test in evaluation of cardiac patients after the resting ECG. Echocardiography uses sound waves to examine a wide range of cardiac dysfunction such as structural abnormalities, heart wall motion abnormalities, valvular function, ejection fraction, systolic and diastolic function and CO.

The cardiac ultrasound works on the principle that high frequency sound waves generated from parts of the cardiac anatomy return to the echocardiogram providing information regarding the area targeted. Computerized analysis of the returning sound waves makes it possible to identify multiple structures and their relationship to each other. Different techniques have been used to acquire ultrasound information. These methods include transthoracic, trans-esophageal, stress and contrast echocardiography.

Echocardiography is particularly useful for intra-cardiac studies in infants and children but its reliability reduces with age (Marx and Geva 1998). In older adults with cardiorespiratory disease or those with trunk deformity, limited acoustic access and other factors may make transthoracic echocardiography (TTE) difficult, unreliable and occasionally impossible (Hartnell and Notariani 1998). These limitations could be overcome by using trans-esophageal echocardiography (TEE) although it is more invasive, expensive and potentially more hazardous than TTE. TEE is performed using a transducer mounted on the end of a flexible tube which is swallowed. Being closer to the heart than a surface transthoracic transducer allows for better visualization of the atria, interatrial septum, mitral septum, mitral valve, aorta and atrial appendages. TEE also provides useful information on appropriateness of repair during surgery for CHD, leading to changes in management (O'Leary *et al* 1995, Ungerleider *et al* 1995). TEE is however, limited in that there are significant blind spots for imaging the great vessels like the pulmonary artery, veins and the aortic arch (Hartnell and Notariani 1998).

Stress echocardiography combines surface echocardiography and graded exercise testing. Images are obtained at rest and within 1-2 minutes after exercise. For patients who cannot exercise, intravenous dobutamine acts as an alternative to induce increased myocardial oxygen demand. The real-time stress echocardiogram is recorded and compared with resting scans to evaluate changes in heart function under stressful conditions owing to ischemia or myocardial infarction. When conventional echocardiographic techniques provides insufficient information (e.g. detection of intra-cardiac shunts), contrast echocardiography is used. This technique involves the use of radioactive isotopes and has been found useful for augmenting the visibility of right heart structures, detecting and quantitating intra-cardiac shunts (Okura *et al* 1995). However, better echocardiographic technologies e.g. three-dimensional echocardiography, are being developed and improved upon regularly to enhance disease diagnosis and patient care (Lodato *et al* 2009, Bhan *et al* 2010)

1.4.3 *Magnetic Resonance Imaging*

Magnetic resonance imaging (MRI) is a noninvasive medical test used to diagnose and treat medical conditions. MRI uses a powerful magnetic field, radio frequency pulses and a computer to produce detailed pictures of organs, soft tissues, bone and virtually all other internal body structures. Cardiac magnetic resonance (CMR) imagine can provide accurate left ventricular volume change measurements over time which can be converted to left ventricular volume curve to estimate the peak filling rate and time to peak filling (Kinno *et al* 2017). In addition, CMR can precisely and reproducibly quantify LV deformation in systole and diastole (Kinno *et al* 2017). MRI has many advantages compared with x-ray–based diagnostic techniques, including its nonionizing nature and unrivaled ability to discriminate different soft tissues without contrast media (Roguin *et al* 2004). However, MRI is expensive thus limiting its use in routine clinical practice.

1.4.4 *Biomarkers for heart failure diagnosis*

As pointed out in section 1.3, along with the complex series of events occurring in the heart from risk to fully developed HF, there are increasing numbers of compensatory mechanisms and the expression of neuro-humoral activation proteins whose measurements can give important information about HF (Table 1.7). Some of these markers such as the B-type natriuretic peptide (BNP) and N- Terminal proBNP (NT-pro BNP) are well validated and established in their use (Daniels and Maisel 2007, Kim and Januzzi 2011, Parekh and Maisel 2009, Komajda *et al* 2011, Maisel *et al* 2002) and even represent the gold standard biomarkers in the diagnosis of HF (Gaggin and Januzzi 2014), while others are still being explored for potential use in clinical practice. Other vital tests include liver and kidney function tests.

Table 1.7 Biomarkers in heart failure

Myocardial insult	**Neuro-hormonal activation**	**Remodelling**
Myocyte stretch • NT-proBNP, BNP, MR-proANP	Renin angiotensin system •Renin, angiotensinII, aldosterone	Inflammation • C-reactive protein, tumor necrosis factor α, Fas, interleukins, osteoprotegerin, adiponectin
Myocardial Injury • Troponin T, troponin I	SNS •Norepinephrine, Chromogranin A	Hypertrophy/Fibrosis • Matrix metalloproteinases, collagen propeptides, galectin 3, soluble ST2

Oxidative stress	Arginine vasopressin system	Apoptosis
•Myeloperoxidase, oxidized low-density lipoproteins, MR-proADM	• Arginine vasopressin	• GDF-15
BNP=B-type natriuretic peptide, GDF-15=growth differentiation factor-15, MR-proADM=mid-regional pro adrenomedullin, MR-proANP=mid-regional pro atrial natriuretic peptide, NT-proBNP=N-terminal pro B-type natriuretic peptide. (Gaggin and Januzzi 2013)		

Step by step guidance for diagnosing HF according to the European society for Cardiology is detailed in Figure 1.2.
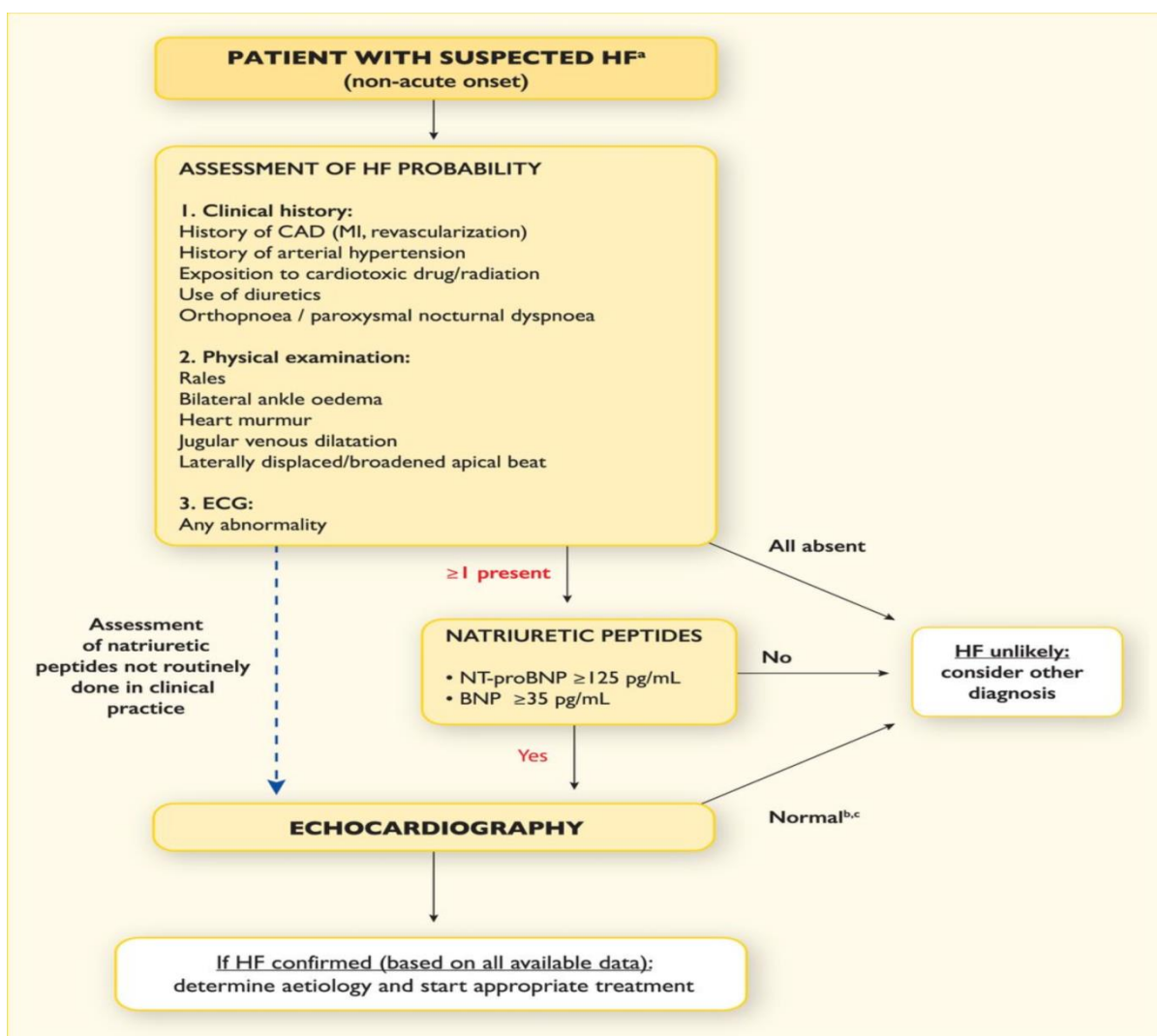
Figure 1.2 Diagnostic Algorithms for CHF (Ponikowski *et al* 2016)
BNP- B-type natriuretic peptide; CAD- coronary artery disease; HF- heart failure; MI-myocardial infarction; NT-proBNP- N-terminal pro-B type natriuretic peptide.
[a]Patient reporting symptoms typical of HF.
[b]Normal ventricular and atrial volumes and function.

1.8 Treatment of HF

Treatment for HF could be achieved via medical/surgical intervention as well as lifestyle modification (Table 1.8).

Table 1.8 General measures for the treatment of HF (Kemp and Conte 2012)

Lifestyle modification	Medical therapy
Weight reduction	Treatment of hypertension, hyperlipidaemia, diabetes and arrhythmias
Smoking cessation	
Avoidance of alcohol and other cardio-toxins	Coronary revascularisation
	Anticoagulation
Exercise/Physical activity	Immunisation
Healthy dieting	Daily weighs and close outpatient monitoring

Patients should be encouraged to improve their lifestyle by losing weight, eating healthy, abstaining from smoking and alcohol and increasing their physical activity as tolerated. Medical therapy includes treatment of hypertension, dyslipidaemia, diabetes, arrhythmia and other co morbidities (Kemp and Conte 2012) .

Pharmacologic treatment of HF involves the use of medications which have been designed to counter the deleterious effects of the compensatory mechanisms previously discussed. For instance, ACE inhibitors (ACEI) block the conversion of angiotensin I to angiotensin II which reduces activation of the RAAS. Angiotensin receptor blockers (ARBs) e.g. valsartan and candesartan and combined angiotensin II receptor blocker neprilysin inhibitors (ARNIs) e.g. are used in patients who cannot tolerate ACEI (Rain and Rada 2015). They work directly on the angiotensin receptors which are the final down-stream target of the RAAS pathway. B-blockers (e.g. atenolol, carvedilol, metoprolol, bisoprolol) are used to protect the heart vasculature from the vicious effects of SNS hyper-stimulation (Metra and Teerlink 2017) by slowing the heart down thus allowing for more efficient contraction. When patients present with arrhythmia, different classes of antiarrhythmic drugs (class I-IV), e.g. nifedipine and diltiazem can also be used to restore cardiac rhythm. Aldosterone antagonists also directly inhibit RAAS and prevent electrolyte and water retention thus lowering blood pressure (Metra and Teerlink 2017). Digoxin is used to enhance cardiac muscle force of contraction. It also

reduces activation of the SNS and the RAAS. Diuretics reverse the action of vasopressin and also inhibit fluid retention thus reducing pulmonary congestion and peripheral oedema (Faris *et al* 2016, Roush *et al* 2014).
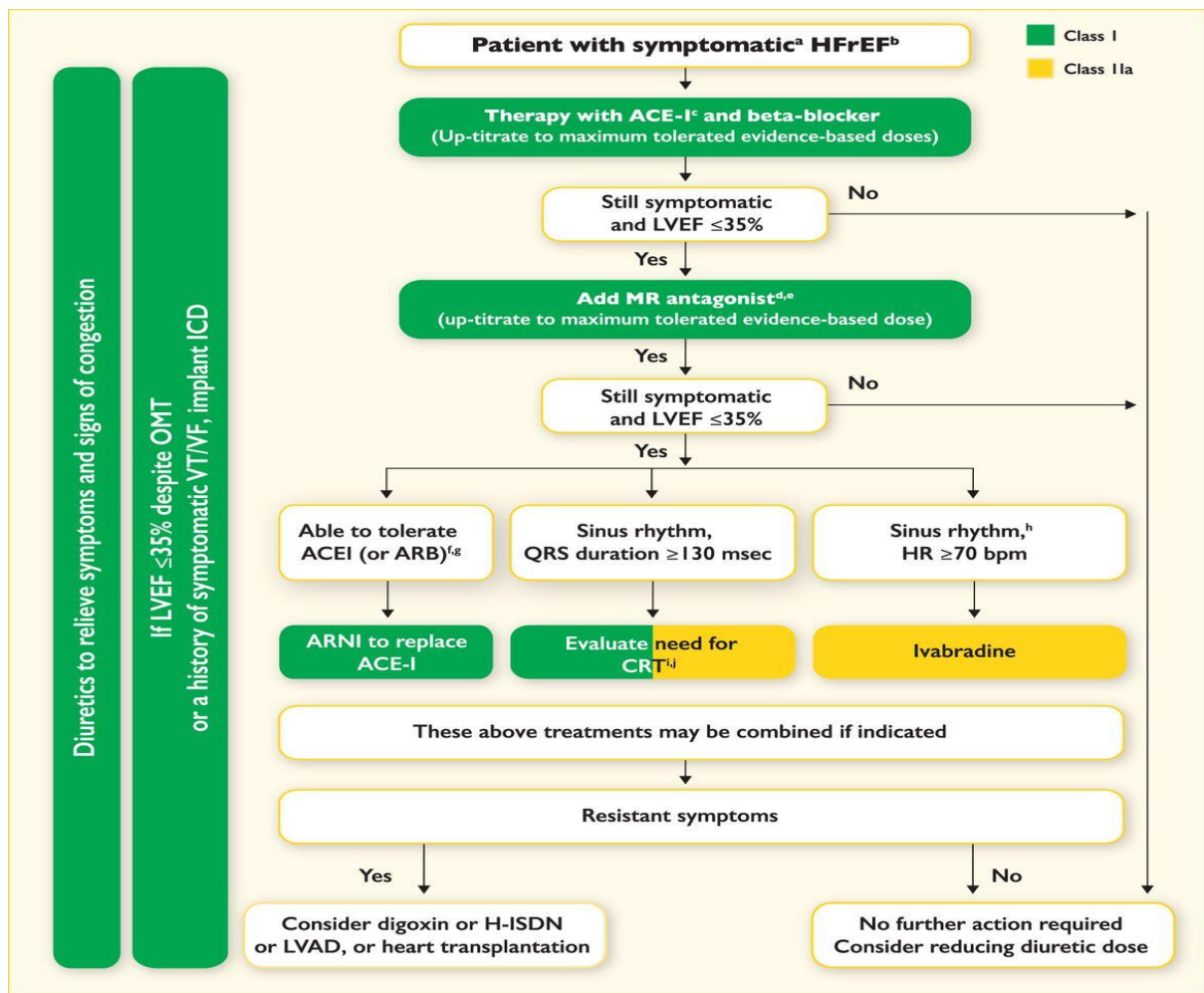
Figure 1.3 Treatment Algorithm for HFrEF patient (Ponikowski *et al* 2016). Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = HF; HFrEF = HF with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. [a]Symptomatic = NYHA Class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contra-indicated, use ARB. [d]If MR antagonist not tolerated/contra-indicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/ml or NTproBNP > 500 pg/ml in men and 750 pg/ml in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g]In doses equivalent to enalapril 10 mg b.i.d. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥ 130 msec and

LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision)

Surgical Management of HF includes Cardiac Resynchronisation Therapy (CRT), coronary revascularisation, Surgical Ventricular Remodelling (SVR), Ventricular Assist Device (VAD) implantation and heart transplantation. CRT is aimed at improving ventricular efficiency by simultaneously pacing both ventricles (Ponikowski *et al* 2016). SVR surgically restores the normal anatomy of the ventricles while VAD augments the decreased CO and heart transplantation replaces the failing heart with a new functional organ. Current guidelines for the treatment of HF is summarised in Figure 1.9.

CHAPTER 2 Physical activity in heart failure

2.0 Physical activity and heart failure

It is well known that lifestyle plays a major role in the way the body functions. It could be detrimental or of immense benefit to whole body homeostasis. Important lifestyle behaviours include physical activity, sedentary lifestyle, sleep, and smoking.

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscles that require energy expenditure above resting level (Wittink *et al* 2011). Physical activity constitutes most activities carried out as part of daily routine and is markedly different from exercise. Exercise is a sub-type of physical activity which is planned and consists of repetitive whole or partial body movements performed to maintain or improve physical fitness (Wittink *et al* 2011).

Although chronic HF is characterized by progressive exercise intolerance and exertional dyspnoea during minimal exercise (Servantes *et al* 2012), available data suggests that exercise is beneficial for HF patients in terms of decreased mortality and morbidity, improved quality of life, functional capacity and cardiac and vascular function (Flynn *et al* 2009, Smart 2010). However, exercise training should be considered as an adjunct in these groups of patients (Downing and Balady 2011).

The relative success of an exercise training programme is commonly determined by comparing changes between baseline and post training fitness markers. Maximal oxygen consumption is the most commonly reported measure of functional capacity in HF patients (Daskapan *et al* 2005) but is rarely achieved in activities of daily living. In carrying out exercise training, it is important to clearly establish the frequency, type, intensity and length of intervention. This perhaps is the reason why programme design is the most important and controversial issue regarding the role of exercise training in HF. Most exercise training programmes have followed the standard prescription of continuous aerobic exercise used in cardiac rehabilitation (Smart 2010), with resistance exercise sometimes added. However continuous aerobic exercise may not optimally stress the peripheral muscles, as they are often atrophied and have fewer fibres, oxidative enzymes, and capillaries in HF patients (Duscha *et al* 2008, Gielen *et al* 2005). Similarly, there has been some controversy on the effect of exercise dose on the efficacy of training. While Morris *et al*., (2002) argue that volume of exercise rather than method of delivery determine improvement in functional capacity, other researchers suggest that programme duration especially those designed to last 12 weeks and beyond, have more influence on functional capacity (Støylen *et al* 2012, Piepoli *et al* 1998, Tabet *et al* 2009).

Previous studies have also yielded conflicting results regarding the benefits of exercise for patients' health status. For example, Coats et al., (1990) reported an improvement in patient-reported symptoms after 8 weeks of exercise training among 11 rigorously selected HF patients. Another randomized trial among 99 HF patients by Belardinelli et al., (1999) revealed improvements in quality of life as measured using the 21- item Minnesota Living With Heart Failure Questionnaire (MLHFQ), after 8 weeks of exercise training compared with usual care, and these improvements were sustained even at 12 months. In contrast, the Exercise Rehabilitation Trial (EXERT) among 181 patients randomly assigned to 3 months of supervised exercise training and followed by 9 months of home-based training or usual care showed no differences in MLHFQ scores (McKelvie *et al* 2002). Further emphasizing the confusion surrounding the association of training-induced improvement in exercise capacity and quality of life is the study by Keteyian et al, (1999) in which 24 weeks of exercise training improved peak oxygen consumption but not quality of life (MLHFQ) scores. Most of these studies were conducted prior to current guideline recommendations for pharmacologic and device therapies, including beta-blockers, biventricular pacemakers, implantable cardioverter-defibrillators and left ventricular assist devices. Thus, critical questions remain about whether exercise training can improve patient-reported health status. However, the 'HF-ACTION' trial (Flynn *et al* 2009), which is one of the largest trial (2331) to examine the effects of exercise training on clinical outcomes in stable HF patients on optimum medical therapy, showed modest but statistically significant improvements in self-reported health status compared with usual care patients without training. This improvement was reported to occur early and persisted over time.

2.1 Cardiac Rehabilitation for Heart Failure Patients in the UK

'*Cardiac rehabilitation is a process by which patients with heart disease, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal health*' (Scottish Intercollegiate Guidelines Network 2002) . In the UK, cardiac rehabilitation is viewed as a 'multidisciplinary intervention for people with heart disease. Its main aims are to help the patient to recover as quickly and completely as possible and then to reduce to a minimum the chance of recurrence of the cardiac illness' (Bethell *et al* 2009). A recent systematic review by Taylor *et al*., (2014) including 33 randomised trials in 4740 individuals with HF showed that participation in exercise-based CR was associated with a significant reduction in the risk of overall hospitalisation (relative risk: 0.75; 0.62 to 0.92, $p=0.005$) and HF-specific hospitalisation (relative risk: 0.61; 0.46 to 0.80, $p=0.0004$) and important improvements in patient health-related quality of life. Based on such evidence, there have

22

been recommendations by NICE and the ESC, for the inclusion of supervised CR for HF patients (Ponikowski *et al* 2016, NICE Guideline 2010).

Despite this recommendation, a 2012 survey indicated that few UK centres (16% of those surveyed) had a specific rehabilitation programme for those with HF (Dalal *et al* 2012). The researchers give two main reasons to explain the suboptimal provision and uptake of CR in HF patients. Firstly, previous guidelines (Remme and Swedberg 2001) provided no specific details for healthcare planners about how and where these cardiac rehabilitation services would best be delivered, and healthcare staff involved in frontline cardiac rehabilitation services are unsure about the safety and benefits of cardiac rehabilitation in people with heart failure (Health Commision 2007). This has led to direct exclusion of HF in local commissioning agreements, even though over half (54%) of the centres visited in the Dalal *et al*., (2012) study expressed confidence in the skill and knowledge of their staff to provide cardiac rehabilitation in heart failure. Furthermore, 65% of centres considered that evidence on safety of CR for HF patients was adequate while 71% did not believe that lack of evidence on clinical benefit was an influencing factor. This uncertainty in safety has led to a direct exclusion of HF in local commissioning agreements and CR is merely taken as an optional lifestyle improver. In other to address this issue, Madden et al., (2011) have suggested that 'Rehabilitation might be perceived differently if presented as part of a treatment programme prescribed by cardiologists' rather than an optional strategy to improve health. Also, looking at the evidence for safety of CR as already stated, It will be in order to say that the focus of CR for heart failure patients should not essentially be based on reduction of mortality, rehospitalisation and peak exercise but rather, a step towards improvement in physical ability of patients to engage in activities of daily living and improvement in quality of life (Cowie *et al* 2012).

Currently, home based exercise programmes which seem to be more accessible and acceptable are being explored (Cowie *et al* 2012). However, there are still concerns of safety, long term training protocol and follow up guidelines. Further details about the role and effect of home based versus centre based physical activity and exercise in heart failure is summarised in Table 2.1.

Table 2.1 Summary of results from physical activity and exercise interventions in heart failure and other cardiac conditions

Authors	Title of study	*N*	Protocol / Volume and Intensity	Results
(Chien *et al* 2011)	Home-based exercise improves the quality of life and physical function but not the psychological status of people with chronic HF: a randomised trial	51	- 30 mins x 3 days/week x 8 weeks - Phone consultation Strength training exercises and walking	Significant improvement in post 6MWT distance and quality of life
(Karapolat *et al* 2009)	Comparison of hospital-based versus home-based exercise training in patients with HF: effects on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters	74	- 3(45mins- 1hr sessions)/week x 8 weeks (flexibility, aerobic and breathing exercises) - 60-70% HRR &VO_{2peak} - 13-15 Borg scale RPE - Hospital based- treadmill - Homebased- Walking	Significant improvement in VO_{2peak} for both groups. No change in AT. Quality of life (Physical function, general health and vitality) also improved significantly in both groups
(Cowie *et al* 2012)	Effects of home versus hospital-based exercise training in chronic HF	60	- 40-60% (HRR) x 2 days/week x 8 weeks.	Significant improvement in post Shuttle walk tet in both home and hospital based

			- 15mins warm up/cool down - 30mins Aerobic exercise - 12-13 RPE Borg scale	groups but no significant improvement in quality of life
(Daskapan et al. 2005)	Comparison of supervised exercise training and Home-based exercise training in chronic HF	22	- 60% HR_{max}, 3days/week x 12 weeks - Supervised Hospital based treadmill - Unsupervised Homebased walking - 5mins warm up/cool down/recovery - 30 mins aerobic walking	Significant improvement in peak exercise work load, speed (Km/hr) and grade for both groups. Post resting heart rate, DBP and VO_2 peak were significantly improved only in the supervised exercise training group
(Piotrowicz *et al* 2010)	A new model of home-based tele monitored cardiac rehabilitation in patients with HF: effectiveness, quality of life, and adherence	152	- 40-70% HRR, 11 RPE on Borg scale - 10-15min session per day gradually increased to 20-30 mins/day. Continuous walking for	For both groups, significant improvement in 6MWT distance, VO_2 peak, exercise time and quality of life

			home based group and intermittent cycling for supervised rehabilitation group	
(Ramadi *et al* 2015)	The Sustainability of Exercise Capacity Changes in Home Versus Center-Based Cardiac Rehabilitation in what patient group	3488	- Centre-Based; 2-3 days/week x 12 weeks aerobic training (treadmill, cycle ergometer, track walking or elliptical trainer) - Homebased; 3-5days/ week self-styled aerobic exercise. - 12-14 RPE - 20-60 min - 45-85% HRR	Significant improvement in exercise capacity to the 1-year follow-up, exercise capacity remained unchanged in home-based CR participants whereas the centre-based CR group demonstrated a decline in exercise capacity.
(Piotrowicz *et al* 2014)	Home-based tele monitored Nordic walking training is well accepted, safe, effective and has high adherence among HF patients, including those with cardiovascular implantable electronic devices: a	111	- 5 times/week x 8 weeks - Home based tele monitored rehabilitation - 5-10min warm up/cool down - 15-45mins Nordic walking	Significant improvement in post training VO2 peak, 6MWT and QoL compared to control group

	randomised controlled study.		gradually increased to 46-60mins after 2 weeks - 40-70HRR	
(Oerkild *et al* 2011)	Home-based cardiac rehabilitation is as effective as centre-based cardiac rehabilitation among elderly with coronary heart disease: results from a randomised clinical trial	75	- Home based: 30mins/day x 6 days/week x 6 weeks - Self-paced brisk walking and stationary bicycling - 11-13 Borg scale - Centre based: 60 mins/day x 2 days/week x 6 weeks - 11-13 Borg Scale	Modest change in VO_2 peak and 6MWT.
(Keast *et al* 2013)	Randomized Trial of Nordic Walking in Patients With Moderate to Severe HF	54	- 15 mins warm up - 30 mins Nordic walking for Nordic walking group or continuous walking for standard	Significant improvement in 6MWT distance in Nordic walking group compared to standard care group but no

			care group	difference in VO_2 peak.
			- 15 min stretching exercise	
			- Additional 200-400 min/week of normal or Nordic walking	
(Jolly *et al* 2009)	A randomized trial of the addition of home-based exercise to specialist HF nurse care: The Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive HF (BRUM-CHF) study	169	- 20 – 30 mins Aerobic walking, 5days/week x 24 weeks - Low intensity strength training (10 repetitions of 8 exercises) - 12-13 Borg scale	Addition of a home-based exercise programme to specialist nurse care did improve the outcomes of a community-based HF population. However, there was higher quality of life at 6 months and reduced psycho-logical distress (HAD scale) at 12 months in exercise group.
6MWT, Six minute walk test; VO_{2peak}, Peak oxygen consumption; DBP, diastolic blood pressure; AT, anaerobic threshold; HRR, heart rate recovery.				

CHAPTER 3: Cardiac output assessment in heart failure (Methods)

3.0 Methods

This chapter describes main clinical technologies and techniques used in the research programme upon which the present thesis is based upon. A key feature of heart failure is impaired CO either at rest or exercise, hence assessment of CO is a crucial part of the diagnostic workup of people with symptoms possibly due to heart failure. This section therefore gives a brief review of available technologies used in cardiac output assessment in HF and a rational for the non-invasive methods used in the thesis.

3.1 Cardiac output assessment in Heart Failure

Cardiac output (CO) is an important measure of cardiac function. It is a measure of the amount of blood pumped out of the heart each minute. CO assessment at rest and during exercise can provide important information about cardiac function and performance, prognosis, risk stratification, diagnosis and guiding therapy (Jhanji *et al* 2008).

Historically, cardiac output was measured via invasive methods however, there are now non-invasive and minimally invasive methods used to measure cardiac output. The following session will describe some of these methods and also highlight the gaps in research which the present thesis will address.

3.2 Invasive Cardiac output Assessment

3.2.1 *Fick's Technique*

In 1870, Adolph Fick (Hoff and Scott 1948) described the first method to estimate CO in humans. Fick postulated that oxygen uptake in the lungs is entirely transferred to the blood. Therefore, CO can be calculated as the ratio between oxygen consumption (VO_2) and arteriovenous difference in oxygen ($AVDO_2$). The Fick principle can be applied to any gas diffusing through the lungs, including carbon dioxide and nitrous oxide. This estimation is accurate when the haemodynamic status is sufficiently stable to allow constant gas diffusion during the mean transit time of blood through the lungs. This method was the reference standard by which all other methods of determining CO were evaluated until the introduction of thermo-dilution using pulmonary artery catheters in the 1970's.

3.2.2 *Thermodilution*

Thermodilution simply means reduction in temperature of a liquid that occurs when a colder liquid is introduced to it. In clinical settings, it is a method of measuring ventricular blood volume and CO. A bolus of solution of known volume and temperature is injected into the right atrium, and the resultant change in blood temperature downstream over duration of time

is detected by a thermistor previously placed in the pulmonary artery with a catheter. CO is inversely proportional to the mean blood-temperature depression and the duration of transit of cooled blood. Following the introduction of the pulmonary artery catheter (PAC) into clinical practice (Swan *et al* 1970), the single-bolus thermodilution measurement of CO is currently widely accepted as the "clinical invasive standard" for advanced hemodynamic monitoring. More precisely, it is considered to be the clinical gold-standard against which new technologies are validated and compared (Vincent *et al* 2011).

3.3 Non-invasive Cardiac Output Assessment

3.3.1 *Bioimpedance*

Thoracic bioimpedance, often referred to as bioimpedance, is a technique which became popular in the 1990's (Shoemaker *et al* 1994) although first developed in 1966 (Kubicek *et al* 1966). Bioimpedance is used to measure CO and is based on the theory that the thoracic cavity is perfused with blood and has a specific resistivity (Lee *et al* 2011). This hemodynamic resistance is to a high frequency low amplitude current, transmitted from electrodes placed in the thorax is referred to as bioimpedance (Funk *et al* 2009). Usually, two electrodes are placed on either side of the neck and four other electrodes placed on the lower thorax. The current transmitted from the outer surface electrodes is detected by the inner surface electrodes. Impedance (Z_0) is then calculated from voltage change (resulting from cardiac events and aortic blood flow) which is inversely proportional to the volume of fluid in the thorax (Lee *et al* 2011). Stroke volume (SV) is calculated as the product of maximal rate of change of impedance (dZ0/dtmax) and ventricular ejection time.

Several studies have reported conflicting correlation results when bioimpedance was compared with thermodilution, the invasive gold standard for CO measurement. For example, while Clancy *et al.*, (1991), Shoemaker *et al.*, (1998) and Barin *et al.*, (2000), report positive correlation in cardiac catheterization, surgical, critical care and coronary artery bypass graft patients, Spiess *et al.*, (2001), in contrast, Marik et al., (1997) reported poor agreement between both techniques in HF patients. Similarly, there was poor correlation between both techniques during CABG surgery in patients that developed significant cardiac dysrhythmia (Spinale et al., (1995) and also in critically ill and elderly subjects (Keren *et al* 2007). Furthermore, bioimpedance as a technique is affected by electric noise, chest wall edema and increased pleural fluid (Critchley *et al* 2000, Raue *et al* 2009). In addition, it is sensitive to body size, electrode contact on skin and physical factors that impact on electrode conductivity such as temperature and humidity (Wang and Gottlieb 2006)

3.3.2 *Bioreactance*

Bioreactance is a non-invasive measurement of CO which was developed to address the limitations of the bioimpedance technique. The working principle of bioreactance is based on an analysis of beat by beat changes (phase shifts) of an electric current that occur as that current travels through the thoracic cavity (Keren *et al* 2007). Phase shifts occur due to intermittent flow of blood which arises majorly from the aorta. Volume changes in the thoracic cavity produce variations in electrical capacitance and inductance referred to as bioreactance (Lee *et al* 2011). A popular bioreactance device is the NICOM system (Cheetah Medical Inc., Indianapolis USA). The device consists of paired electrodes which are placed on the upper and lower borders on either sides of the thorax. While one end is used to introduce high frequency (75 kHz) current to the body, the other is used by a voltage input amplifier (Figure 3.1).
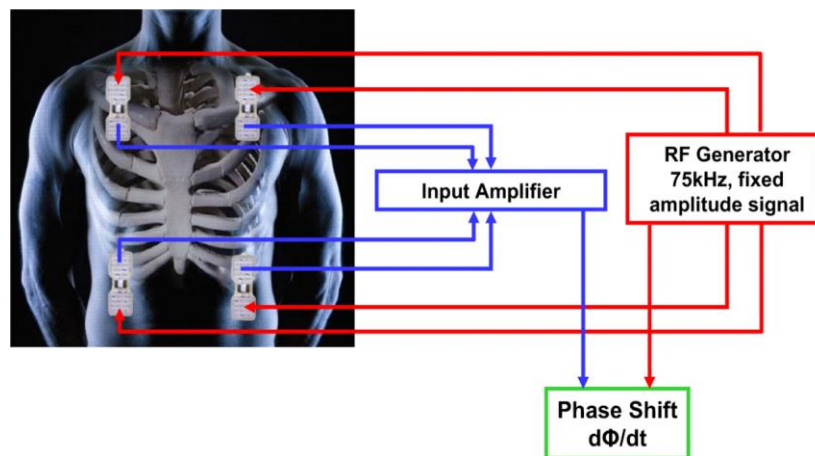
Figure 3.1 NICOM system and its connection to the body (adapted from Keren et al., 2007)

Unlike bioimpedance, bioreactance does not use static impedance and is independent of the distance between electrodes for the calculation of stroke volume and CO. Furthermore, it averages the signals received over one minute thereby allowing precise determination of CO in patients.
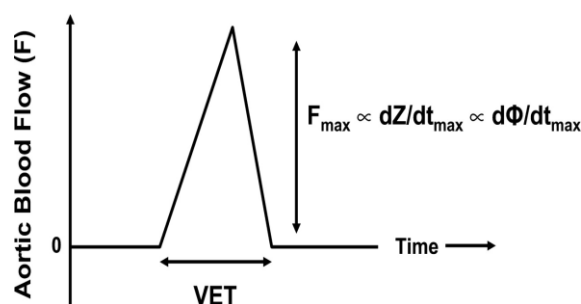
Figure 3.2. Schematic representation of aortic flow as a function of time underlying the basic principle for estimation of stroke volume (SV) from changes in bioimpedance (dZmax/dt) or changes in relative phase shifts (dΦ/dtmax, bioreactance).

Since the aortic flow pulse is relatively triangular in time, SV is proportional to the product of peak flow (Fmax) and ventricular ejection time (VET). Stroke volume can be determined by the relationship of a constant of proportionality 'C', ventricular ejection time and the maximum slope of the phase shift between the applied and the received electrical signals as a function of time.

$$SV= C.VET.d\phi/dt_{max}$$

Start Time	18:24:19	18:24:49	18:25:19
CI	4	3.9	3.9
CO	7.8	7.5	7.7
HR	63	62	62
SV	124.5	122.1	122.7
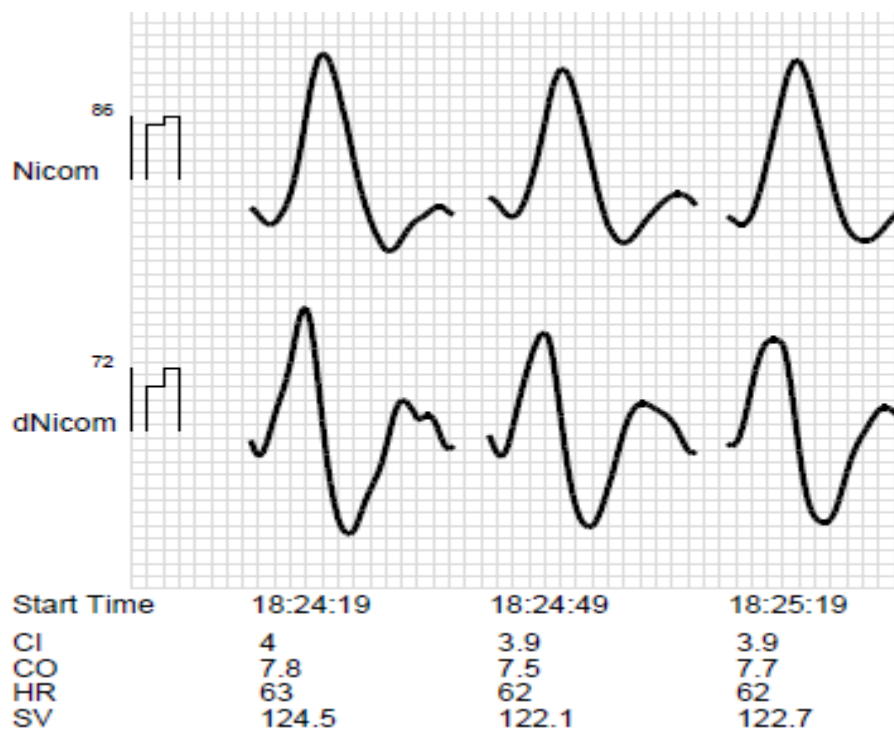
Figure 3.3 Data acquisition from bioreactance using the NICOM device. The top trace represent time-dependent phase shift (F (t), that is a fundamental bioreactance signal) and its first derivative (bottom trace) (dF (t)/dt, which is related to aortic flow). Each column shows tracing that represent 30 seconds signal averages.

3.3.2.1 *Validity and reliability of bioreactance*

Validation studies of bioreactance technique have been conducted over previous years. Initial evaluation of the technique by Keren and colleagues (Keren *et al* 2007) revealed a strong correlation (r = 0.90) between bioreactance CO and CO obtained from the thermodilution. Similarly, Squara *et al.*, (2007) compared the bioreactance technique with CO derived from pulmonary artery catheterisation in 110 post-cardiac surgery patients. They reported a mean

bias of $+0.16 \pm 0.52 \, \text{l/min}$ ($+4.0 \pm 11.3\%$), and relative error of $9.1\% \pm 7.8\%$. Bioreactance precision for determining haemodynamic changes was better than thermodilution (Raval *et al* 2008, Squara *et al* 2007) with both sensitivity and specificity reported to be 93% (Squara *et al* 2007). Rich et al., (2013) also reported that CO measured by bioreactance was significantly more precise than that of thermodilution ($3.5\% \pm 0.3\%$ vs $9.6\% \pm 6.1\%$, $p < 0.001$) when measurements were performed using three different methods (thermodilution, modified Fick's and bioreactance). The mean CO (l/min) at baseline as measured by the three methods was 4.73 ± 1.15 (bioreactance), 5.69 ± 1.74 (thermodilution) and 4.84 ± 1.39 (Fick). Bland-Altman analyses comparing bioreactance to thermodilution and Fick revealed bias and 95% limits of agreement that were comparable to those comparing Fick to thermodilution. Other studies have also shown that CO from bioreactance show good agreement with CO derived from other non-invasive (Jakovljevic *et al* 2012a, 2014, Elliott *et al* 2010, Maurer *et al* 2009, Myers *et al* 2011) and minimally invasive (Keren *et al* 2007, Marqué *et al* 2009, Squara *et al* 2009) methods.

3.3.3 *Inert gas rebreathing*

Inert gas rebreathing (IGR) with continuous analysis of respiratory gases is a safe, reliable and cheap method of measuring pulmonary blood flow from which CO is derived (Agostoni *et al* 2005). The technique, also known as the foreign gas rebreathing method, is non-invasive and suitable for bedside or ambulatory measurements. Foreign gases usually used are physiologically inert, blood soluble gases, e.g. acetylene, ethylene and nitrous oxide (Laszlo 2004). The technique was first proposed by Bornstein in (1910). Bornstein modified the Fick's principle of CO measurement and theorised that if a physiologically inert gas is inhaled, its partial pressure in the pulmonary capillary blood is equal to that in the lungs. The change in the amount of gas in the lungs, in an interval before recirculation occurs, equals its alveolar concentration multiplied by its solubility in blood and the amount of blood to which the gas is exposed during the interval (Reinhart *et al* 1979). IGR works on the principle that when a subject breath a gas mixture containing a non-physiological soluble gas in a closed rebreathing system, the gas is inhaled rapidly and taken up in the pulmonary capillary blood stream at a rate proportional to the effective pulmonary capillary blood flow. When the gas comes in contact with the blood in the pulmonary capillaries, it is dissolved and is then washed out by the blood perfusing the lungs (Dong *et al* 2005). The pulmonary blood flow is therefore proportional to the rate of washout of blood soluble gas, which is measured continuously by a gas analyser (Dong *et al* 2005).

In the past, measurements of pulmonary blood flow and CO by an IGR method have been performed using mass spectrometers (Liu *et al* 1997, Hoeper *et al* 1999). However, mass spectrometers are bulky, difficult to operate and require constant maintenance (Gabrielsen *et al* 2002a). The IGR device currently available is the Innocor (Innovision, Odense, Denmark) system (Figure 1.5). The system consists of a respiratory valve with a mouth piece and a rebreathing bag connected to an infrared photo acoustic gas analyser. CO is measured by rebreathing in a closed system which contains a gas mixture of 0.5% nitrous oxide (N_2O; blood insoluble gas), 0.1% sulphur hexafluoride (SF_6; blood soluble gas) and 28% oxygen (O_2). SF_6 measures volume of lungs, respiratory valve and rebreathing bag while N_2O concentration decreases proportionally to pulmonary blood flow. The first two or three breaths are usually excluded from the analysis due to initial incomplete gas mixing. CO is calculated as the sum of pulmonary blood flow and intrapulmonary shunt. In the absence of pulmonary shunt, CO is calculated as pulmonary blood flow determined by rebreathing (Jakovljevic *et al* 2008). Calculations of cardiorespiratory parameters by the Innocor are based on the assumptions that there is 1). Complete and instantaneous mixing in the volume consisting of alveolar and dead space air bag volume. 2), instantaneous equilibration of the soluble gas between the alveoli and blood, and between alveoli and tissue, 3) constant pulmonary blood flow and constant volume of lung tissue, and 4) Negligible mixed venous concentration of soluble gas throughout the rebreathing period.

IGR is highly reproducible (Reutershan *et al* 2003a) and validation studies have shown this to be true in healthy and cardiac disease patients. (Cattadori *et al* 2009, Christensen *et al* 2000, Gabrielsen *et al* 2002b, Agostoni *et al* 2005). However, accuracy may be reduced in patients with parenchymal lung disease due to intrapulmonary shunting or incomplete gas mixing (Friedman *et al* 1984, Kallay *et al* 1987). Furthermore, rebreathing requires adequate technical skill on the part of the test administrator and active cooperation by patients (Saur *et al* 2009b). Nevertheless, (Farina *et al* 2014) notes that the IGR technique is useful in the after care of pulmonary hypertension patients.
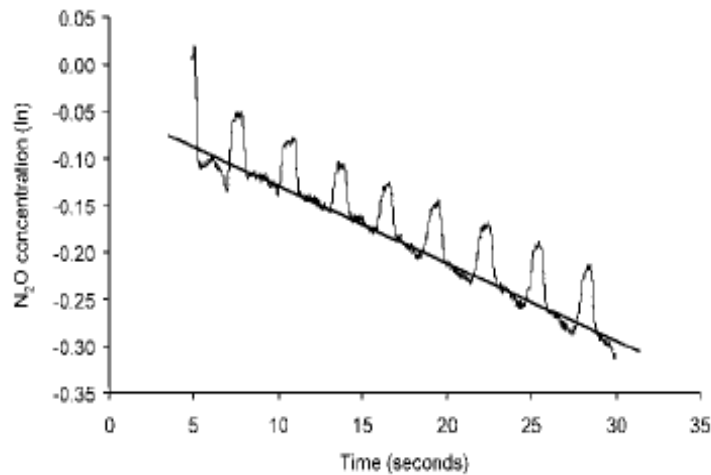
Figure 3.4 Nitrous oxide rebreathing in a closed system. Semilogarithmic plot of the end-expiratory fractional concentrations of nitrous oxide (N_2O) as a function of time (Reutershan *et al* 2003b)

3.3.3.1 *Validity and reliability of IGR method*

A number of studies have reported the validity and reliability of rebreathing using inert gases like acetylene (Barker *et al* 1999, Johnson *et al* 2000, Hoeper *et al* 1999, Liu *et al* 1997). Results show that this technique is good and strongly agrees with the invasive methods. However, this section focusses on IGR using N_2O as test gas.

Gabrielsen and colleagues (2002), compared CO determined by IGR with those obtained from thermodilution and direct Fick's method in 11 patients with HF or pulmonary hypertension. Results showed that in all but three patients, who had shunt flow in areas without significant gas exchange, the mean difference (bias) and limits of agreement (2 S.D.) were 0.6 ± 1.2 l/min when comparing Fick's method and IGR and 0.8 ± 1.3 l/min when comparing Fick's and thermodilution techniques. When correction for intrapulmonary shunt flow was applied in all 11 patients, the bias between Fick's and rebreathing methods was 0.1 ± 0.9 l/min, primarily because agreement improved in the three patients with significant shunt flow. The study suggested that rebreathing method with nitrous oxide provided at least as reliable a measure of CO as did thermodilution especially in the absence of shunt. Similarly, Agostoni et al. (2005) studied the validity and reliability of CO measured at rest and during exercise by IGR, thermodilution and directs Fick's methods. Twenty stable chronic HF patients were recruited for the study. Results (mean $\pm$ SD) showed that CO estimated from IGR was 5.1 ± 1.3 l/min, direct Fick 5.0 ± 1.3 l/min and thermodilution was 4.5 ± 1.2 l/min. Agreement between IGR and Fick's method remained similar at peak exercise (11.3 ± 3.2l/min vs 11.2 ± 3.2 l/min), while thermodilution method overestimated CO (11.7 ± 3.7). Christensen et al. (2000) also

reported a mean difference of 0.01 l/min with upper and lower limits of agreement of $\pm$ 1.19 l/min when rebreathing was compared with thermodilution in fourteen critically ill patients. Dong et al. (2005) also reported a strong correlation (r=0.94) between IGR and thermodilution methods and both devices provided a good estimate of CO. However, Bland-Altman plot showed that thermodilution tended to overestimate CO by 0.66 l/min (P< 0.001)

3.4 Invasive versus non-invasive cardiac output monitoring

With current advancements in research and technological development, there is growing advocacy for the use of non-invasive methods for the assessment of cardiac output in cardiac disease patients. Newer non-invasive technologies have the advantage of being safe, cheaper and could offer frequent monitoring of haemodynamic function with minimal discomfort to patients. These techniques have previously been reviewed in detail elsewhere and include pulse contour analysis, oesophageal doppler, CO_2 rebreathing, thoracic bioimpedance and bioreactance (Marik 2013). Regrettably, whilst these techniques reduce the risk to patients, their acceptability have been limited by inaccuracy and reliability (Mathews and Singh 2008, Critchley *et al* 2010a). Therefore, the choice of the choice of test method depends upon the clinical and research scenario and patient tolerability.

Two novel non-invasive methods for CO monitoring that have received increased clinical and research attention over the previous years are bioreactance and IGR methods (Agostoni *et al* 2005, Jakovljevic *et al* 2014). However, bioreactance and IGR have not being compared with each other neither has the reproducibility of IGR at rest and during different intensities of exercise been studied previously. This thesis addresses both issues in chapters 5 and 6 respectively.

Chapter 4 Aims, objectives and hypothesis

4.1 Aims

Cardiac rehabilitation services have improved with overall uptake from referrals reaching 45% in 2013 compared with 41% in 2009 (Doherty P, Petre C, Onion N, Dale V 2014). Despite these statistics, participation of heart failure patients in cardiac rehabilitation is consistently low. In the UK alone, less than 10% of those with HF participate in cardiac rehabilitation (NICE 2015). Numerous factors account for this with the most common being direct exclusion from local commissioning agreements due to limited funds available for rehabilitation services, inadequate social support and lack of capacity for supervised programmes (Dalal *et al* 2012). In addition, patients do not participate in cardiac rehabilitation due to difficulties in attending hospitals, work or domestic commitments and reluctance to attend group-based classes (Beswick *et al* 2004, Griebsch *et al* 2004).

The barriers highlighted above could be potentially overcome by promoting increased physical activity during daily activities. By assessing daily activity in HF patients, true functional impairment could be measured (Walsh *et al* 1997) as the number of steps and energy expenditures outside the hospital environment is positively correlated with improved exercise capacity (Sato *et al* 2012)

Recognising the above facts, the aim of the present study is to evaluate the feasibility, compliance, and physiological effects of a novel, personalised, home-based, 12-weeks physical activity intervention (Active-at-Home-HF) in chronic HF

4.2 Objectives

In order to achieve the aims of the thesis, four main objectives were considered. These included;

1. Comparison of CO estimated from bioreactance and IGR
2. Assess the reproducibility of IGR for CO measurement
3. Feasibility and acceptability of the Active-at-Home-HF
4. Compliance and physiological effects of the Active-at-Home-HF
5. Barriers and Facilitators to engaging in the Active-at-Home-HF

The rationale behind the first two objectives which constitute chapters 5 and 6 was to determine the more appropriate of two non-invasive CO monitoring devices to be used in the Active-at-Home-HF intervention for the assessment of haemodynamic function.

4.3 Hypothesis

Based on results from previous studies we hypothesize that;

1. Active-at-Home-HF will be feasible and acceptable for chronic HF patients

2. Compliance based on how many people completing the intervention would exceed 70%

3. There would be clinically significant improvement in Quality of life

4. There would be improvement in exercise capacity resulting from significant changes in markers of haemodynamic (CO and stroke volume) and metabolic (VO_2 peak) function

CHAPTER 5: Comparison of cardiac output estimates by bioreactance and inert gas rebreathing methods

Abstract

Purpose. Non-invasive cardiac output (CO) monitoring methods have become increasingly popular for assessing cardiac function. The present study assessed the agreement between CO estimated by inert gas rebreathing (IGR) and bioreactance methods at rest and during exercise.

Methods. Haemodynamic measurements were assessed in 20 healthy individuals (11 females 9 males; aged 32 ± 10 years) using IGR and bioreactance methods. Gas exchange and haemodynamic data were measured at rest and different stages of progressive graded cardiopulmonary exercise stress testing using a cycle ergometer.

Results. At rest, bioreactance produced significantly higher CO values than IGR method (7.8 ± 1.4 vs. 6.5 ± 1.7 L/min, P= 0.01). Under low and moderate exercise intensities (i.e. 30-90 watts), bioreactance continued to produce higher CO values compared with rebreathing method (p<0.05). At workloads of 120W and above, there was no significant difference in estimated CO values between the two methods (p >0.05). There was a strong relationship between the IGR and bioreactance CO (r = 0.82, P= 0.01). Bland-Altman analysis including rest and exercise data showed that IGR reported 1.95 l/min lower CO than bioreactance, with lower and upper limits of agreement of -3.1 to 7.07 l/min.

Conclusion: Bioreactance and inert gas rebreathing methods show acceptable levels of agreement for estimating cardiac output at higher levels of metabolic demand. However, they cannot be used interchangeably due to strong disparity in results at rest and low-to-moderate exercise intensity.

5.1 Introduction

CO measurement provides an indication of systemic oxygen delivery and global tissue perfusion (Marik 2013, Wasserman *et al* 2000). The average CO for a healthy adult is approximately 5-6 L/min (Hall 2010). This value can increase up to four fold in untrained individuals, and in trained athletes, CO may increase seven fold (Hall 2010).

In patients with HF CO obtained during stress testing, coupled with blood pressure, is the strongest predictor of mortality and functional capacity (Roul *et al* 1995, Williams *et al* 2001, Lang *et al* 2009, Bain *et al* 1990). Furthermore, monitoring of CO during surgical procedures reduces post-operative complications and time to hospital discharge (Gan *et al* 2002, Venn *et al* 2002).

The first method for CO evaluation was proposed in 1870 by Adolf Fick (Hoff and Scott 1948), which has since led to the development of more precise and sophisticated methods. Pulmonary artery catheters which use a bolus thermodilution method was introduced a century later (Swan *et al* 1970). This was the first clinical device which enabled bedside CO measurement and is now regarded as the gold standard method for CO measurement alongside the Fick's technique (Critchley *et al* 2010a). However, the use of these techniques and their wide clinical applications have been limited due to their invasive nature, cost, need for specialist expertise and the risks involved (Harvey *et al* 2006, Sandham *et al* 2003). Due to invasive nature of these "gold standard" methods for CO measurements, investigators have tried to identify new technologies that can be used in CO assessment. Regrettably, whilst these techniques reduce the risk to patients, their acceptability have been limited by inaccuracy and reliability (Mathews and Singh 2008, Critchley *et al* 2010a). The ideal CO monitor should be a valid, reliable, non-invasive, cheap and should have a fast response time (de Waal *et al* 2009). Two novel non-invasive methods for CO monitoring that have received increased clinical and research attention over the previous years are bioreactance and IGR methods (Agostoni *et al* 2005, Jakovljevic *et al* 2014). There is only one study that previously compared bioreactance and IGR methods (Elliott *et al* 2010). However, the study was performed in highly trained athletes making its applicability to the general population difficult. In addition the authors reported that there were discrepancies in the results between the two methods. There is a need for further investigation on the performance of both methods, particularly under stress testing.

Therefore the aim of this study was to compare CO values obtained by bioreactance and IGR methods and to assess their agreement.

5.2 Methods

5.2.1 *Participants*

Twenty healthy individuals (11 females and 9 males) participated in the study which was conducted at the Clinical Research Facility of Royal Victoria Infirmary in Newcastle. All participants performed < 60 minutes of moderate to vigorous activity per week (defined as 3-6 and >6 metabolic equivalent of task, respectively, as defined by the Centres for Disease Control and Prevention and the American College of Sports Medicine (ACSM 2014). All participants were non-smokers, normotensive, free from any cardiac and respiratory disorders and on no medication three months prior to study commencement, as determined during screening and consent. Participants were informed of the benefits and potential risks of the study and they subsequently provided a written informed consent. All procedures were according to Declaration of Helsinki and the study was approved by the local research ethics committee. Subjects were instructed to abstain from eating for a >2 h before each test and from vigorous exercise 24 h prior to the test. Subjects were also instructed not to consume alcohol or caffeine containing foods and beverages on test days. Upon arrival at the laboratory participants were asked to lay in a supine position for 10 min. Blood pressure was measured in duplicate in the brachial-artery of participant's non dominant arm. Participants then completed a standardised health screening questionnaire and underwent a resting electrocardiogram.

5.2.2 *Study protocol and measurements*

CO was recorded using bio-reactance and IGR techniques simultaneously at rest and during exercise. In addition, theoretically calculated arterial- venous oxygen difference and consequently CO was also estimated for a given oxygen uptake using equation previously suggested by Stringer and colleagues (Stringer *et al* 1997).

$$C (a\text{-}vDO_2) = 5.72 + 0.105 \text{ x } \%VO_{2max,}$$

Where $C (a\text{-}vDO_2)$ is arterial venous oxygen difference, and $\% VO_{2max}$ is the percentage of measured maximal oxygen uptake. Gas analysis (e.g. oxygen consumption, ventilation, and respiratory exchange ratio were measured using the Innocor device (Innovision, Denmark) and exercise was performed on an electro-magnetically controlled semi-recumbent cycle ergometer (Corival, Lode, Groningen, Netherlands). The test comprised three minutes rest period and progressive exercise of six steady-state stages each lasting 3 min (30, 60, 90, 120, 150 and 180W) with pedal cadence of 60-70 revolutions per minute. CO was monitored continuously using the bioreactance method, whereas the rebreathing maneuver was

performed at the end of three minute stage. Exercise 12-lead ECG was monitored using Custo Diagnostic system (SunTech Medical Inc. NC, USA). Testing was stopped after the 180 W workload stage was completed, or a subject could no longer continue with exercise due to maximal exertion, unable to pedal at a cadence of $60 - 70$ revolutions per minute or voluntarily terminated the test. Data recorded at this point were taken as peak data.

5.2.3 Equipment

5.2.3.1 Bioreactance
Please refer to section 3.3.2

5.2.3.2 Inert gas rebreathing method
Please refer to section 3.3.3

5.2.4 Data Analysis
Data are expressed as mean ± SD unless otherwise stated. Normality of distribution was evaluated using a Kolmogorov-Smirnov test. One-way analysis of variance with a post hoc (tukey) test was used to assess differences between the bioreactance and IGR and theoretically calculated CO values. Pearson's correlation coefficient was used to evaluate the relationship between CO and oxygen uptake measures taken at different time points. Paired t-tests were also used to assess differences between the two methods at different intensities of exercise. Bland-Altman plots were constructed to evaluate the upper and lower limits of agreements (± 2SD of mean difference) between bioreactance and IGR methods (Bland and Altman 1986). All statistical analysis was carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results
Participants were aged 32 ± 10 years, weight 74 ± 10 kg, height 171 ± 8 cm with a maximal oxygen consumption (VO_2max) of 2.17 ± 0.7 L/min. In all subjects a stable bio-reactance signal was obtained at rest, whereas 18 out of 20 participants (90%) successfully carried out the rebreathing procedure at rest. Resting CO estimated by bioreactance and IGR methods were significantly different (7.8 ± 1.4 vs. 6.5 ± 1.7 L/min, P = 0.01, respectively), which is due to the significant difference in stroke volume estimates (Table 5.1). During exercise, the IGR method reported lower CO values compared to bioreactance throughout the test and values were significantly different at low to moderate exercise intensities (P < 0.001, Table 1). However at higher exercise intensities ($120 - 180$ Watts), there was no significant difference in CO, between the two methods (Table 5.2). There was a

strong positive relationship between bioreactance and IGR cardiac outputs at rest and exercise (r= 0.87, p<0.001) (Figure 5.1).
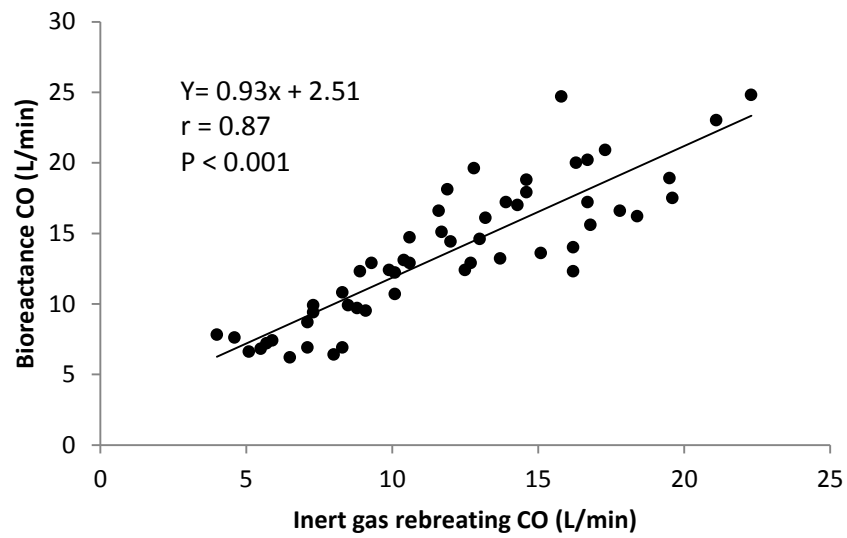
Figure 5.1 Relationship between bioreactance and IGR cardiac outputs (n = 20)

Table 5.1 Comparison of haemodynamic variables by bioreactance and IGR methods under resting condition and low to moderate exercise intensity

	REST [a]			30W [b]			60W [c]			90W [d]		
	BR	IGR	*P*	BR	IGR	*P*	BR	IGR	*P*	BR	IGR	*P*
CO (l/min)	7.8±1.4	6.5±1.7	0.01	12.4±2.4	9.8±2.6	0.01	13.8±2.5	10.7±2.4	<0.01	14.6±2.6	12.3±2.2	<0.01
CI (l/m^2/min)	4.4 ±0.7	3.5 ±0.9	<0.01	6.8±1.4	5.3±1.3	<0.01	7.6±1.2	5.8±1.1	<0.01	8.0±1.2	6.7±1.0	<0.01
SV (ml)	104.3±13.9	90.4±27.7	0.06	134± 22.7	114± 29.2	0.06	132.7± 30.5	105±28.6	0.01	116.8± 29.3	103.9± 29.6	0.10
HR (b/min)	76.0 ±12	76±13	0.89	95± 10	95± 13	0.99	109± 10	108±11	0.78	128±12	128±11	0.97

BR- bio-reactance; IGR- Inet gas rebreathing; CO- cardiac output; CI- Cardiac index; SV- Stroke Volume; HR-Heart rate; Data presented as mean (SD). Subjects [a] n=18, [b] n=14, [c] n=16, [d] n=19, for which concurrent data were available. * P value significant at 95% confidence interval.

Table 5.2 Comparison of haemodynamic variables by bioreactance and IGR methods during higher intensity exercise

	120W [e]			150W [f]			180W [g]		
	BR	IGR	*P*	BR	IGR	*P*	BR	IGR	*P*
CO (l/min)	15.9±2.4	14.7±3.2	0.20	18.1±2.7	17.6± 3.2	0.54	21.6± 3.3	18.5 ± 2.6	0.10
CI (l/m^2/min)	8.6± 0.9	7.9± 1.6	0.10	9.8± 1.1	9.3± 1.6	0.34	10.9± 1.5	9.2 ± 1.8	0.07
SV (ml)	115.5±26.1	114.9±48.7	0.96	140.4±37.3	122.0± 22.5	0.15	124.3±23.4	118.7± 29.5	0.70
HR (b/min)	147.1±10.5	147.1±10.9	1.00	158.8±15.6	157.9±15.4	0.88	173.2±14.3	171.5±15.1	0.77

BR- Bioreactance; IGR- Inert gas rebreathing CO- cardiac output; CI- Cardiac index; SV- Stroke Volume; HR-Heart rate; Data presented as mean ± SD. Subjects [e] n=18, [f] n=15, [g] n=7, for which concurrent data were available. * P value significant at 95% confidence interval.

Similarly, there was a strong positive significant relationship between oxygen uptake and CO for bioreactance and IGR methods (Figure 5.2)
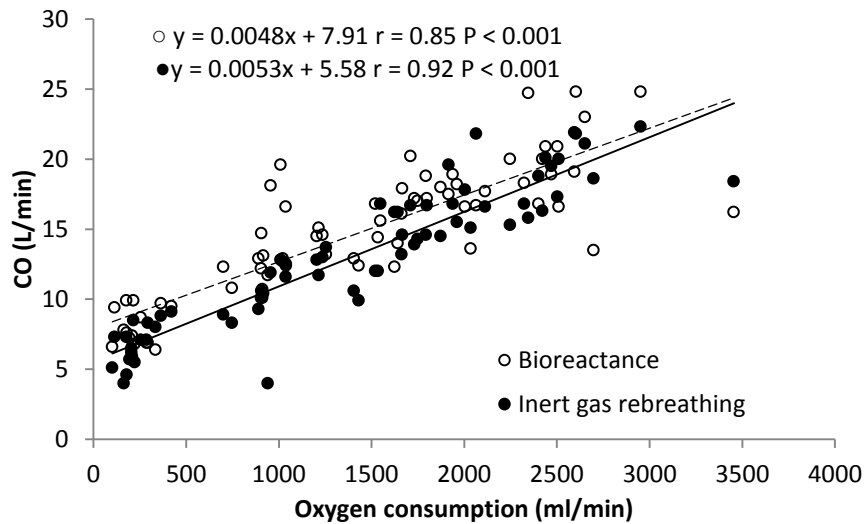
Figure 5.2 Relationship between Bioreactance and IGR COs and oxygen consumption

Using Stringer equation (Stringer *et al* 1997), theoretically calculated arterial-venous oxygen difference and CO at peak exercise were 16.2 ml/dl and 18.0l/min respectively. This did not differ significantly from values obtained by IGR and bioreactance methods; 16.6 ml/dl and 17.1l/min (for IGR) and 15.5ml/dl and 17.9 l/min for bioreactance, (Figure 5.3).
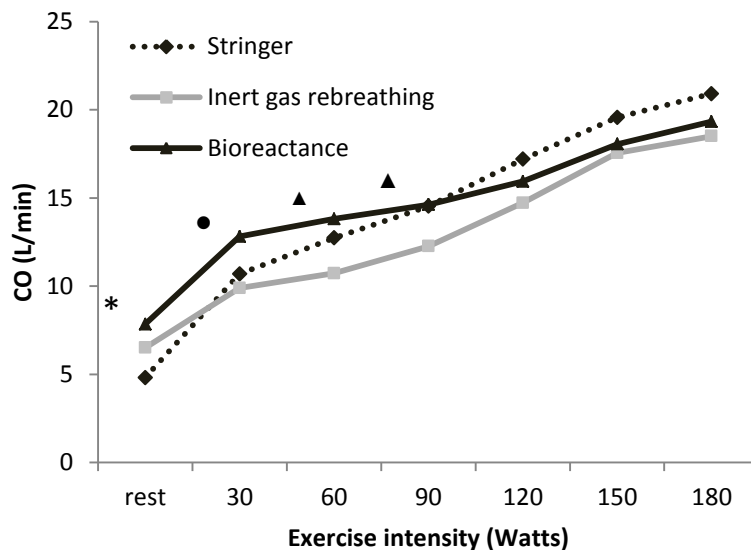
Figure 5.3 Comparison of COs estimated by bioreactance, IGR and theoretically calculated methods at rest and during different exercise intensities * P<0.05 theoretically calculated CO versus rebreathing versus Bioreactance; •P< 0.05 theoretically calculated CO versus Bioreactance, ▲P<0.05 theoretically calculated CO versus IGR (n=20).

Bland-Altman analysis including rest and exercise data demonstrated that IGR method reported 1.95 l/min lower CO than bioreactance, with lower and upper limits of agreement being -3.1 to 7.1 l/min (Figure 5.4). Further analysis showed that much of the difference occurred during low to moderate (up to 90 W) exercise intensities when the mean difference in CO between both techniques was 2.7/min (lower and upper limits of agreement of -1.6 to 7.0 l/min). At higher exercise intensities (120 -180 watts), mean difference between the two techniques was 1.2 l/min (lower and upper limits of agreement -5.03 to 7.4l/min). However, Bland-Altman's analysis for peak exercise data showed a mean difference of 0.4 L/min (lower and upper limits of agreement of -4.9 to 5.7 l/min).
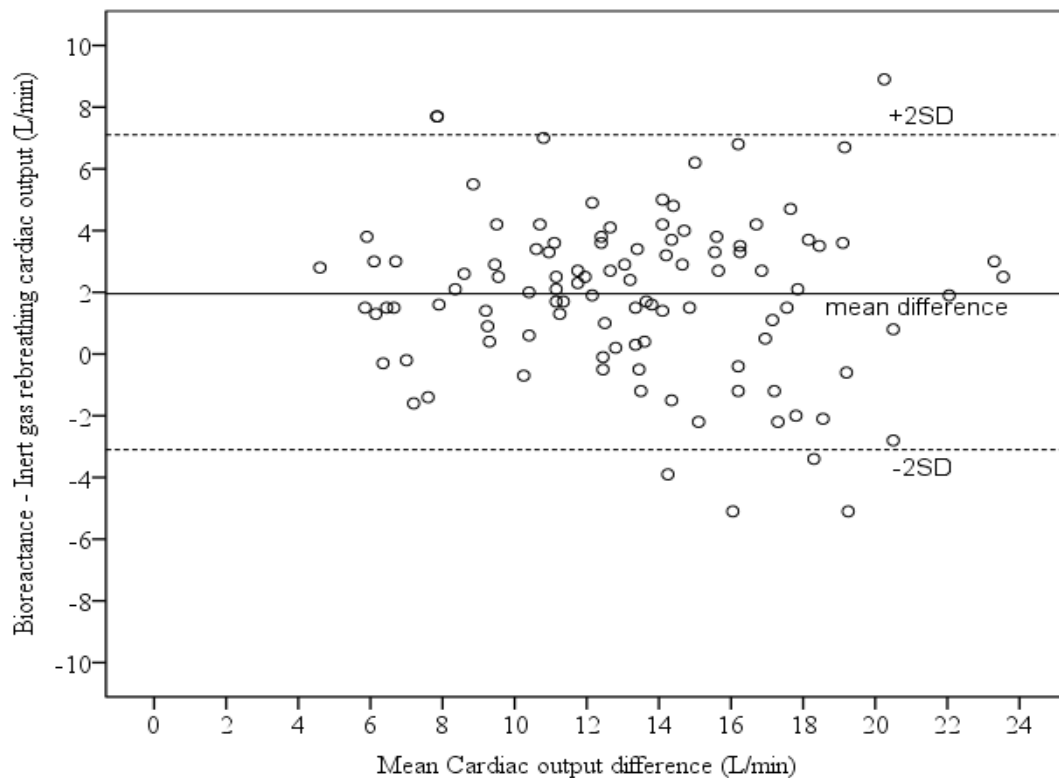
Figure 5.4 Bland-Altman plot to demonstrate limits of agreement between bioreactance and IGR CO measured at rest and during exercise. The solid line represents the mean bias (mean difference) and the dashed lines represent lower and upper limits of agreement.

5.4 Discussion

The purpose of the present study was to compare two non-invasive methods for estimating CO i.e. bioreactance and IGR under rest and exercise stress testing conditions. The major findings suggest that IGR method consistently reported lower CO values than bioreactance at rest and during exercise. These differences were particularly emphasized during low to moderate exercise intensities. However, the difference between the two methods was not significant at higher and peak exercise intensities. In addition, there was strong relationship between the two methods and peak oxygen consumption.

The data presented here are consistent with previous studies that have reported lower CO from the IGR when compared with other non-invasive CO measuring devices e.g. pulse contour analysis, (Bartels *et al* 2011, Siebenmann *et al* 2015). This is probably due to recirculation of N_2O which reduces alveolar-arterial diffusion gradient for N_2O and further attenuate N_2O uptake (Jarvis *et al* 2007, Laszlo 2004). Furthermore, potential incomplete mixing of gases at rest and low intensity exercise may result in an underestimation of CO (Peyton and Thompson 2004, Gabrielsen *et al* 2002a). In contrast to the present findings and previous reports, Elliott et al. 2010, reported a significantly lower CO from bioreactance compared to the IGR when trained athletes were assessed. The authors acknowledged that this was possibly due to interference/movement artefacts and underestimated values of heart rate at high intensity exercise due to loss of electrocardiograph signal using bioreactance method.

An interesting finding from the present study is a lack of significant difference between bioreactance and IGR methods at exercise intensities ≥120 watts. This is in contrast to results from a study which compared bioreactance with bioimpedance, (Jakovljevic *et al* 2012a). Our findings could be explained physiologically by increase in lung volume and blood flow as exercise progressed, thereby leading to adequate mixing of rebreathing gases (Bartels *et al* 2011). Our result thus corroborates the notion that rebreathing methods are more accurate for monitoring CO during increased metabolic demand and higher exercise intensities (Saur *et al* 2009a).

In the current study there was a linear increase in oxygen extraction during incremental exercise, which was proportional to oxygen uptake, as previously suggested (Elliott *et al* 2010). COs obtained by bioreactance and IGR demonstrated a strong positive relationship with oxygen consumption. Stringer et al., 1997 (Stringer *et al* 1997), demonstrated that if oxygen consumption is measured, arterial venous oxygen difference and CO could be calculated with a high degree of

accuracy. Using the Stringer's equation, mean peak exercise CO was 18.0l/min. This value was similar to those estimated by bioreactance (17.9 l/min) and IGR (17.1 l/min).

Both CO measuring techniques were non-invasive and easy to operate, however, the IGR required a high level of subject – operator coordination and familiarization procedure before actual measurements. In contrast to IGR, bioreactance provides continuous CO monitoring. Furthermore it is patient-friendly, and does not require a familiarization procedure and therefore may have wider application, especially in different clinical settings where CO monitoring is warranted. In stark contrast the IGR method is not continuous and only provides CO measurements at specific time points during testing, and is less user friendly for patients. However, inert gas re-breathing is also coupled with gas exchange and respiratory data and thus may provide further insight into cardiovascular pathophysiology underlying exercise intolerance in many clinical conditions (Farina *et al* 2014). Furthermore it could also be used as previously suggested, in setting where bioreactance electrical signal can potentially be diminished due to interference with devices i.e. patients implanted with left ventricular assist device (Jakovljevic et al AJC, 2010; Jakovljevic et al Heart 2010).

In present study the following limitations should be considered. First, the gold standard method for CO assessment was not included. Applying any of the gold standards to this study could have led to heightened risk due to its invasive nature. Secondly, in four subjects, we experienced gas leakage during rebreathing due to inappropriate mask size or the mask going loose but this was corrected immediately by fitting the facemask tightly. The rebreathing maneuver is a discontinuous process and requires extra effort during exercise, which may pose significant challenge in clinical groups.

5.5 Conclusion
Bioreactance and IGR methods provide different CO estimates particularly at rest and during lower intensities of exercise, and therefore cannot be used interchangeably. Technological differences are likely to explain discrepancies in CO estimates between the bioreactance and IGR COs. Future studies are warranted to assess performance of bioreactance and IGR against the gold standard methods in broader clinical settings for example COPD and CHF.

CHAPTER 6: Reproducibility of the inert gas rebreathing method at rest and during cardiopulmonary exercise stress testing

Abstract

Purpose: The present study evaluated reproducibility of the IGR method to estimate cardiac output (CO) at rest and during cardiopulmonary exercise testing.

Methods: Thirteen healthy subjects (range 23-32years) performed maximal graded cardiopulmonary exercise stress test using cycle ergometer on two occasions (Test 1 and Test 2). Participants cycled at 30-watts/3-min increments until peak exercise. Haemodynamic variables were assessed at rest and during different exercise intensities (i.e. 60, 120, 150, 180 watts) using IGR technique.

Results: CO and stroke volume were not significantly different between the two tests at rest (7.4± 1.6 vs. 7.1±1.2 l/min, p=0.54; and 114±28 vs. 108±15 ml/beat, p=0.63) and all stages of exercise. There was a significant positive relationship between Test 1 and Test 2 COs when data obtained at rest and during exercise were combined (r=0.95, p<0.01, coefficient of variation of 6.0%), at rest (r=0.90, p<0.01 coefficient of variation of 5.1%), and during exercise (r=0.89, p<0.01 coefficient of variation 3.3%). The mean difference and upper and lower limits of agreement between repeated measures of CO at rest and peak exercise were 0.4 (-1.1 to 1.8) litre min^{-1} and 0.5 (-2.3 to 3.3) litre min^{-1} respectively.

Conclusion: IGR method demonstrates acceptable level of test-retest reproducibility for estimating CO at rest and during cardiopulmonary exercise testing.

6.1 Introduction

CO and pulmonary blood flow are important parameters of the cardiovascular system function, and provide an indication of systemic oxygen delivery and tissue perfusion. Changes in cardiac function are commonly reported in diseases such as heart failure and/or following pharmacological and physiological interventions (Coats *et al* 1992). Therefore, methods that can accurately detect CO and other haemodynamic changes in response to a clinical intervention are desirable. A large number of studies now support cardiopulmonary exercise testing as a preoperative tool to risk stratify patients for mortality and morbidity (West *et al* 2014, Fernandes *et al* 2011, Moran *et al* 2016, Wijeysundera *et al* 2010). Cardiopulmonary exercise testing sheds a lot of insight into dynamic cardiac performance and is important clinically for a number of reasons. Firstly, haemodynamic parameters obtained from exercise stress testing can identify patients who are at high risk of ischaemic heart disease who may benefit from interventional procedures or even avoid surgery (Fleisher *et al* 2008). Secondly, stress testing can help detect stress induced angina and also guide therapeutic decision making for example, use of β blockers and/or statins for patients with exertional angina or in patients with multiple clinical risk factors, especially in those with stress induced ischaemia (Poldermans *et al* 1999, Lindenauer *et al* 2005). Finally, preoperative testing could be used to identify patients that would require a more robust perioperative clinical haemodynamic management. (Wijeysundera *et al* 2010)

To date, there is no universal consensus on the best method for measuring CO. In addition to being accurate, reproducible, safe, and easy to perform, new technologies in medicine should as well be favourably non-invasive. Current methods include pulse contour and oesophageal Doppler devices, carbon dioxide rebreathing, and bioimpedance. These techniques rely on various assumptions and have limitations which restrict their routine use in clinical practice (Feldman 2009). For instance, pulse contour techniques require calibration manoeuvre and carbon dioxide rebreathing is restricted in intubated patients (Peyton and Chong 2010) while bioimpedance is affected by electrical noise, chest wall edema and increased pleural fluid (Raue *et al* 2009, Critchley *et al* 2000). Furthermore, these devices require expensive single-use components (transducers, probes, or valves) and the significance of the clinical data provided by these methods in influencing patient care and improving outcomes is still debated (Feldman 2009, Funk *et al* 2009). Cardiac magnetic resonance imaging is currently accepted as the non-invasive gold standard method for CO assessment (Hombach *et al* 2010, Hassan *et al* 2017). However, this technique is expensive, time consuming and not applicable in many clinical situations (Saur *et al* 2013) e.g. patients with implantable cardiac devices.

One of the novel, non-invasive approaches for CO measurement at rest and during cardiopulmonary exercise stress testing is inert gas rebreathing method (Innocor, Innovision, Denmark) (Agostoni *et al* 2005). In principle, it functions by measuring the rate of clearance of a physiologically inert gas from the pulmonary capillary circulation, which is directly proportional to pulmonary blood flow (Dong *et al* 2005). If the inert gas completely diffuses into the pulmonary capillary circulation, i.e., in the absence of significant pulmonary shunt flow, pulmonary blood flow would be equal to cardiac output (Saur *et al* 2013). Previous studies have reported promising results for monitoring CO using this method, when compared with the invasive gold standard thermodilution, (Saur *et al* 2009b, Christensen *et al* 2000) and more recently cardiac magnetic resonance imaging (Saur *et al* 2010, Hassan *et al* 2017)

The two most important features of any clinical test are validity and reproducibility. In addition to validity (i.e. the extent to which a test accurately measures what it is supposed to measure), test-retest reproducibility of any technique used in clinical setting is essential. A common method of assuring a reproducible response to cardiopulmonary exercise testing is to have the patient perform two exercise tests on separate days, at the same time of the day, and a test is considered reproducible if functional capacity of the cardiorespiratory system (i.e. peak oxygen uptake) is within 10% on both days(Myers and Froelicher 1990)

Test-retest reproducibility of IGR method was subject to limited number of previous clinical investigations (Agostoni *et al* 2005, Reutershan *et al* 2003a). However, these investigations have been focused on a reproducibility of measurements obtained at rest and/or peak exercise in different clinical groups, which commonly present with diminished cardiac performance. To obtain a better insight into test-retest characteristics of the IGR method, ideally the study design will involve assessment of CO at different levels of metabolic demand. Therefore, we designed the present study with the aim of assessing test-retest reproducibility of IGR method at rest and different stages of graded cardiopulmonary exercise testing.

6.2 Methods

6.2.1 *Participants*

Thirteen participants (10 males) who were non-smokers and free from cardiorespiratory, metabolic, and musculoskeletal diseases were enrolled into the study. The study protocol was approved by local research Ethics Committee and all procedures were in accordance with the Declaration of Helsinki. All participants gave written informed consent. All aspects of the study were conducted at the Clinical Research Facility of the Royal Victoria Infirmary, Newcastle upon Tyne. Participants visited laboratory on two occasions (two days apart, Test 1 and Test 2) and were instructed to abstain from vigorous exercise 24h and from eating for at least 2h prior to each visit. Subjects were also instructed not to consume alcohol or caffeine containing foods and beverages on the test days. Upon arrival at the laboratory participants were asked to complete a standardised health screening questionnaire. This was followed by a 10-min rest period in supine position when blood pressure and ECG were measured.

4.2.2 *Study protocol and measurements*

CO, coupled with gas exchange metabolic and ventilatory data at rest and during exercise was recorded using the Innocor device (Innovision, Odense, Denmark) which uses IGR technique (Agostoni *et al* 2005, Jakovljevic *et al* 2008). Exercise test was performed on an electro-magnetically controlled semi-recumbent cycle ergometer (Corival, Lode, Groningen, Netherlands). The test comprised three minutes rest period followed by a progressive exercise test of six steady-state stages each lasting 3 min (30, 60, 90, 120, 150 and 180 watts). Rebreathing maneuver and CO recording were performed at rest and at 60, 120, 150 and 180 watts. The study participants underwent exercise testing previously and the workload of 120 watts represented ≥70% of their maximum exercise capacity. ECG and blood pressure were monitored throughout exercise using a 12-lead ECG using Custo Diagnostic system (SunTech Medical Inc. NC, USA). The test was terminated when participants were unable to maintain a cadence of 60 – 70 revolutions per minute, or desired to stop. Peak exercise intensity was regarded as the maximum power output (watts) achieved before exercise was stopped.

6.2.3 *Inert gas rebreathing method*

Please see Chapter 3, Section 3.3.3 for detailed description of the inert gas rebreathing method.

6.2.4 *Data analysis*

Data analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean (SD). Reproducibility of haemodynamic and metabolic variables were calculated using coefficient of variation (CV) while linear relationships between repeated measures were assessed using Pearson's correlation coefficient (r). CV was calculated as a

percentage of within person S.D divided by within person average. A CV of ≤6% was considered as good reproducibility while CV of 6-10% and >10% was considered acceptable and poor reproducibility respectively (Jakovljevic *et al* 2012b). Additionally, Bland-Altman plots were constructed to evaluate the upper and lower limits of agreements (± 2SD of mean difference) of CO measured at rest and different intensities of exercise (Bland and Altman 1986). CO trending analysis was done using polar plot method as described by Critchley et al (Critchley *et al* 2010b).

6.3 Results

Physical characteristics of the subjects were: age 27 (23-32) years, weight 69.5±9.7 kg, height 171±7 cm, body mass index 23.5±2.2 kg/m^2 and body surface area 1.8±0.2m^2. All subjects completed each exercise test without any contraindication and a total of 46 paired rebreathing manoeuvres were performed. However, only 8 participants completed the 180 watts stage and peak work load was 160±26 watts. There was no significant difference in resting and exercise metabolic and ventilatory variables between Test 1 and Test 2 (Table 6.1).

Table 6.1 Reproducibility of metabolic measurements at rest and peak exercise.

Variables	Test 1	Test 2	P value	*r*	CV (%)
Rest					
VO_2 (l/min)	0.3±0.1	0.3±0.1	ns	0.43	15.9
VO_2 (ml/kg$^/$min)	4.4±1.7	4.7±1.6	ns	0.65	15.3
VCO_2 (l/min)	0.3±0.1	0.3±0.1	ns	0.44	17.3
VE (l/min)	10.9±3.3	10.9±2.9	ns	0.64	15.4
RER	0.8±0.1	0.8±0.1	ns	0.32	4.5
SPO_2 (%)	97±1	98±1	ns	0.52	0.4
Oxygen pulse (ml/beat)	4.5±1.7	5.0±1.7	ns	0.73	14.0
Peak Exercise					
VO_2 (l/min)	2.2±0.5	2.2±0.5	ns	0.60	8.9
VO_2 (ml/kg$^/$min)	32.5±6.7	32.9 ±6.2	ns	0.95	3.7
VCO_2 (l/min)	2.3±0.6	2.3±0.4	ns	0.38	10.9
VE (l/min)	62±14	57±16	ns	0.75	9.8
RER	1.0±0.1	1.0±0.1	ns	0.85	3.1
SPO_2 (%)	95±3	97±2	ns	0.60	0.9
Oxygen pulse (ml/beat)	19.3±6.3	18.6±6.0	ns	0.84	3.2
VE- minute ventilation, VO2- Oxygen consumption, SPO2- peripheral oxygen saturation, RER- respiratory exchange ratio VCO2- carbon dioxide release. Data are expressed as mean (SD). ns- not significant					

At rest and at all stages of exercise, there were no significant differences in CO values between Test 1 and Test 2 (Figure 4.1).
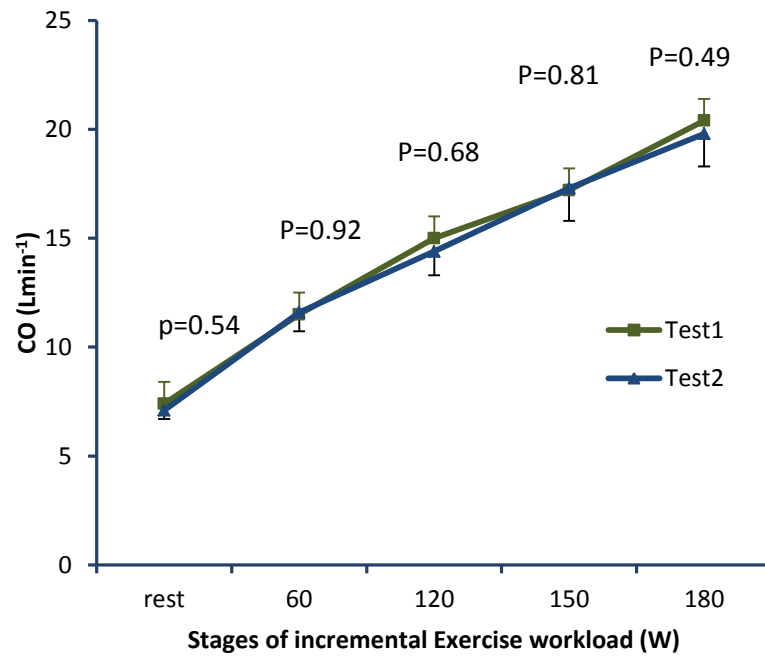
Figure 6.1 Mean CO at rest and at different stages of exercise on two tests

There were no significant differences between repeated measures of haemodynamic variables at rest and during exercise (Table 6.2).

Table 6.2 Reproducibility of haemodynamic measurements at rest and different exercise intensities

Variables	Test 1	Test 2	P	*r*	CV (%)
Rest					
CO (l/min)	7.4±1.6	7.1±1.2	0.54	0.90	6.9
HR (beats/min)	65±7	68±10	0.72	0.85	4.9
SV (ml/beat)	114±28	108±15	0.63	0.61	13.0
VO_2 (ml/kg/min)	4.4±1.7	4.7±1.6	0.69	0.65	15.3
60 watts					
CO (l/min)	11.5±1.9	11.6±2.6	0.92	0.49	12.5
HR (beats/min)	99±10	99±8	0.96	0.83	3.0
SV (ml/beat)	122.3±34.2	122.1±32.4	0.99	0.45	11.9
VO_2 (ml/kg/min)	14.3±1.6	13.7±1.9	0.59	0.65	7.9
120 watts					
CO (l/min)	15.0±3	14.4±3	0.68	0.87	6.3
HR (beats/min)	138±20	138±19	0.99	0.96	1.9
SV (ml/beat)	132±44	134±38	0.94	0.85	5.9
VO_2 (ml/kg/min)	23.4±4	25±5	0.47	0.92	5.3
150 watts					
CO (l/ min)	17.2±4	17.3±4	0.81	0.77	4.3
HR (beats/min)	145±19	147±23	0.88	0.98	2.3
SV (ml/beat)	126±35	123±43	0.89	0.86	5.1
VO2 (ml/kg/min)	27±4	26±5	0.76	0.83	5.6
180 watts					
CO (l/min)	20.4±2.3	19.8±2.6	0.49	0.92	3.8
HR (beats/min)	163±15	160±17	0.86	0.99	1.4
SV (ml/beat)	135±25	132±25	0.89	0.92	4.8
VO_2 (ml/kg/min)	35±1.7	33.4±0.9	0.15	0.75	3.4
CO: CO, HR: Heart Rate, SV: Stroke Volume, VO2: Oxygen Consumption, r: correlation coefficient, CV: coefficient of variation. Data are expressed as mean (SD)					

There was also a strong relationship between Test 1 and Test 2 COs when all data (rest and exercise) were combined together (r=0.95, p < 0.01 Figure 4.2).
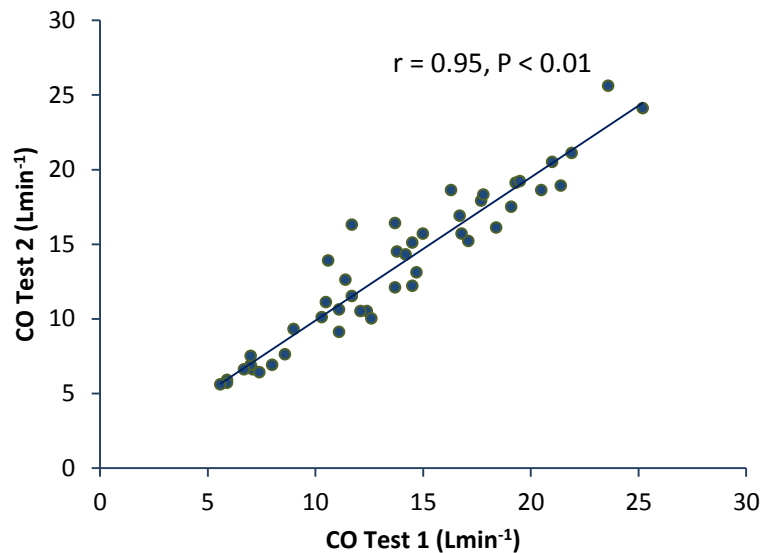
Figure 6.2 Relationship between CO estimates obtained at Test 1 and Test 2 when data from rest and exercise were combined.

When all data were combined (rest and exercise), coefficient of variation for CO, stroke volume and oxygen consumption were 6.0%, 11.1% and 5.7% respectively. Coefficients of correlations and variations for resting and each exercise stage haemodynamic data are presented in Table 6.2.

Resting CO (7.4±1.5) vs 7.1±1.1) litres/min) and peak CO 18.7± 3.6) vs 18.2±4.1) litres min) between both tests were not significantly different. The agreement between CO estimates at Test 1 and Test 2 are shown using Bland-Altman analyses (Figure 6.3A-D). Rest and peak exercise COs between Test 1 and Test 2 showed mean difference and limits of agreement of 0.4 (-1.1 to 1.8 litres/min, Figure 6.3B) and 0.9 (-0.9 to 2.6 litres/min, Figure 6.3D). Further analysis including rest and exercise data together demonstrated a mean difference (limits of agreement) of 0.3 (-2.64 to 3.24 litres/min, Figure 6.3A), while the mean difference of low intensity (60 watts) and higher intensities (120-180 watts) were -0.1(-5.0 to 4.8 litres/min) and 0.3 (-2.43-3.02 litres/min, Figure 6.3C) respectively.
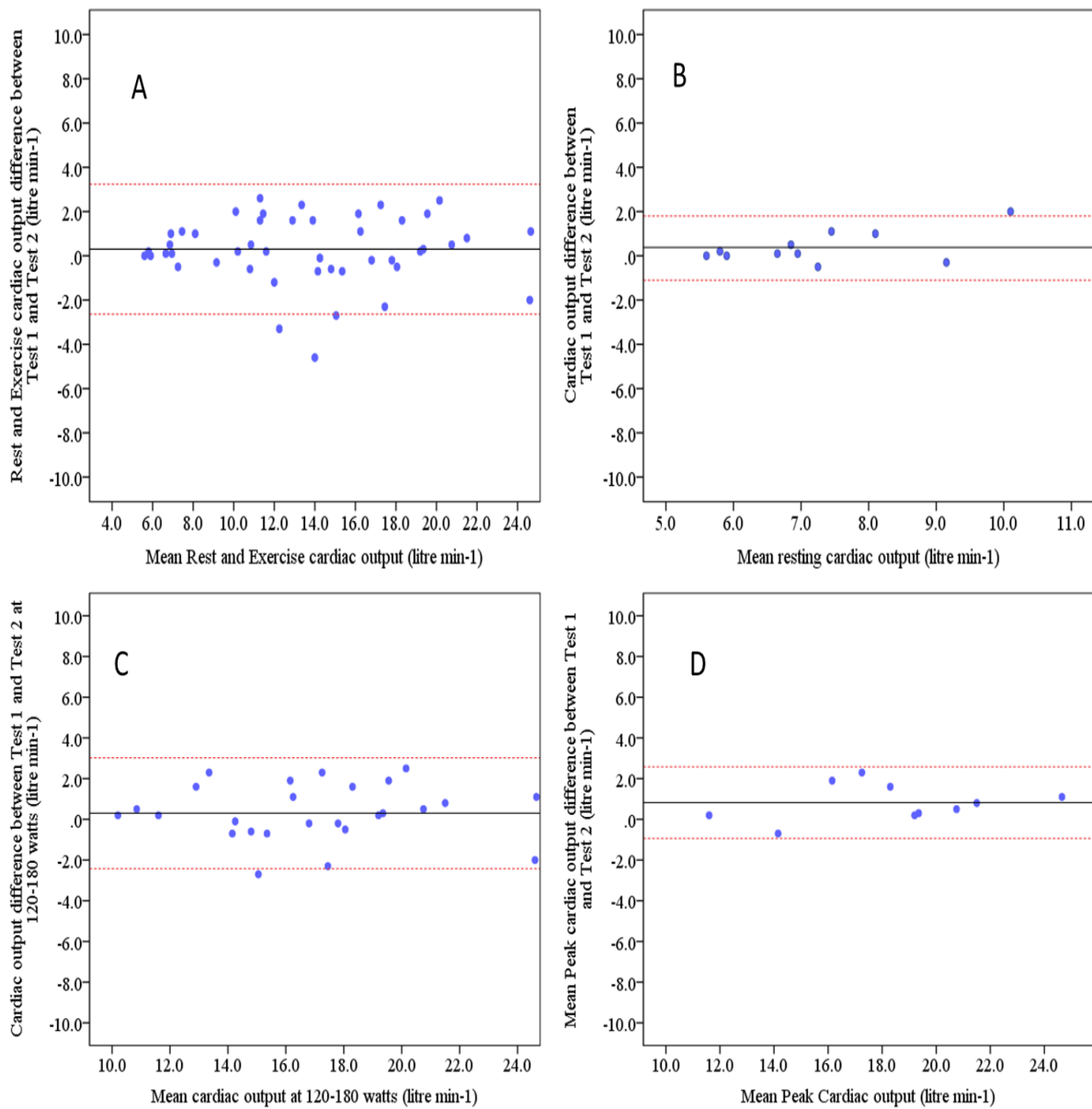
Figure 6.3 Bland-Altman plots to demonstrate limits of agreement between Test 1 and Test 2 at rest and exercise (combined data, A); at rest (B); high intensities (120-180watts, C); and at peak exercise (D). The solid line represents the mean difference and the dashed lines represent lower and upper limits of agreement between Test 1 and Test 2

Polar analysis after central exclusion showed a mean polar angle of 3.07 degrees, radial limits of agreement of less than $\pm30^\circ$ and a concordance rate of 87%. Centrally occurring data was excluded when change in CO was analysed (Figure 4.4). This was because small changes in CO represent statistical noise which makes detection of true CO changes difficult.
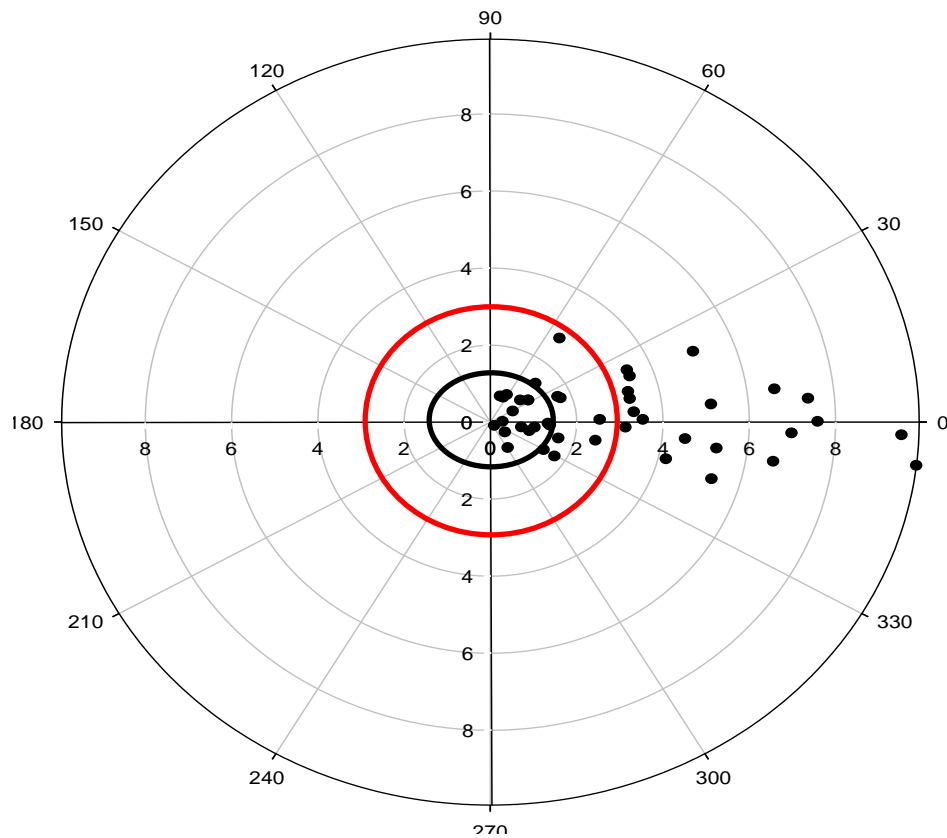
Figure 6.4 Polar plot to show cardiac output trending ability between test 1 and test 2. The innermost dark circle represent the zone of central exclusion and was set at 1.35 according to our data set which represent 10% of mean cardiac output. The red circle represents the polar angle of 3.07 degrees.

There was a strong positive relationship between CO and oxygen consumption for both tests ($r > 0.91$, $P < 0.05$) signifying that with increasing metabolic demand, there was increased ejection of blood to meet oxygen and nutritional demand of exercise muscles. However, only a moderate positive relationship was seen between peak exercise stoke volume and oxygen pulse although this was not significant ($r = 0.49$, $p = 0.18$)

6.4 Discussion

The present study assessed the test-retest reproducibility of resting and exercise hemodynamic and metabolic parameters in healthy individuals using IGR. The data show that IGR method demonstrates acceptable level of reproducibility in estimating CO. Assessment of pulmonary blood flow and thus CO from uptake of nitrous oxide using IGR is safe and feasible.

Reproducibility is usually assessed by performing two or more tests at different time intervals using a particular technique and maintaining similar testing conditions. A technique is assumed to be reproducible if the coefficient of variation of that test parameter was within 10% on repeated tests (Myers and Froelicher 1990). Limited number of studies reported reproducibility of rebreathing methods for measuring CO in clinical conditions (Reutershan *et al* 2003a, Agostoni *et al* 2005, Jakovljevic *et al* 2008, 2012b) In contrast with these previous investigations, the present study is the first to assess reproducibility of IGR method not only at rest and peak exercise, but at different exercise intensities and metabolic demands, providing further insight into the performance of IGR method.

Major findings of the present study suggest acceptable reproducibility of IGR method in estimating CO with mean CV of 6.9% and 6.2% for rest and exercise measurements respectively. These data are consistent with previous studies which reported reproducibility of resting or peak exercise measurements in HF patients with a CV between 3.4% and 11% (Jakovljevic *et al* 2012b, Christensen *et al* 2000, Agostoni *et al* 2005). At low exercise intensity i.e. 60 watts in the present study, reproducibility of CO from IGR was poorer than at rest and higher exercise intensities (CV, 12.5%). This was possibly due to constant fluctuations in stroke volume which showed a high CV of 11.9% in response to onset of exercise whereas the heart rate remained fairly stable with a low CV of 3%. Fontana *et al.,* (2010) noted that at exercise intensities below 70% of an individual's maximal capacity, there was a significant difference in repeated measures of stroke volume. They also suggested better stroke volume reproducibility during higher exercise intensities. This may shed some insight on the use of IGR method for clinical cardiopulmonary exercise testing. Based on our current findings and those of Fontana *et al.* (2010) it seems reasonable to suggest that improved reproducibility can be obtained at high exercise intensities due to better reproducibility of the stroke volume.. Interpretation of IGR CO data obtained at the beginning of cardiopulmonary exercise testing and low exercise intensities should be considered with caution when suggesting a potential effect of clinical interventions on cardiac function. This is clinically relevant as haemodynamic response to dynamic exercise especially at high intensities and peak exercise defines overall function and performance of the heart and can

help explain the mechanisms underlying exercise intolerance (Roul *et al* 1995, Williams *et al* 2001, Lang *et al* 2009).

The present results showed very good reproducibility of IGR method with increased metabolic demand. When CO was analysed at peak exercise, reproducibility was even better with coefficient of variation of 3.3%. At rest and at low intensity exercise, it is possible that not all parts of the lungs are perfused and also ventilated. This means there is incomplete mixing of gases may result in variation of CO values as previously suggested (Peyton and Thompson 2004) As exercise intensity increases, increase in lung volume and pulmonary blood flow progresses, thereby leading to adequate mixing and uptake of rebreathing gases (Bartels *et al* 2011). Findings from the present study corroborates the notion that rebreathing methods are more accurate for monitoring CO during increased metabolic demand and higher exercise intensities (Saur *et al* 2009a). Although there is a paucity of data on reproducibility of IGR during different exercise intensities, our findings are in agreement with one previous study conducted in patients with HF demonstrating low CV and acceptable reproducibility (Jakovljevic *et al* 2012b). Only one study (Agostoni *et al* 2005) has investigated the reproducibility of CO measured by IGR at rest and during different stages of graded exercise. Unlike the present study which showed better reproducibility as exercise intensity increased, Agostoni et al. reported a CV ranging between 9 and 11% for all exercise intensities. Cardiopulmonary exercise testing was performed in chronic heart failure patients who demonstrate significantly reduced exercise tolerance.

It has been previously suggested that resting CO values in healthy adults may range between 5 and 8 l/min. Similar values as in the present study have previously been reported by Fontana *et al*. (Fontana *et al* 2010) and Reutershan *et al*. (Reutershan *et al* 2003a). It is recognised that the rebreathing manoeuvre require increased metabolic demand and consequently may lead to increased values of CO at rest, as previously suggested (Ohlsson and Wranne 1986). This may be due to the increased breathing frequency and tidal volume required for successful rebreathing, which increases oxygen demand from respiratory muscles and in turn increases CO (Jakovljevic *et al* 2008). Other studies have reported an underestimation of CO by rebreathing technique compared to other techniques at rest and during exercise (Okwose *et al* 2017, Siebenmann *et al* 2015) with significant number of recorded values lower than what was considered possible (Siebenmann *et al* 2015). This is possibly due to recirculation of nitrous oxide (Jarvis *et al* 2007) which could reduce the alveolar-arterial diffusion gradient for nitrious oxude and attenuate its further uptake (Laszlo 2004).

Similarly, data presented here show good reproducibility of metabolic variables at rest and during exercise. Metabolic parameters showed very good reproducibility throughout exercise. Reproducibility of peak oxygen consumption per body weight was 3.7%, which is similar to previous studies using non-invasive gas exchange measurement systems (Jakovljevic *et al* 2012b, Keteyian *et al* 2010). Bland-Altman analysis for both CO and metabolic data show low mean differences between Test 1 and Test 2 and acceptable limits of agreement.

Although Bland-Altman analysis has been used extensively to show agreement between comparative CO measurements, it has been criticised as it does not provide useful standard parameter such as percentage error for which the quality of repeated measurement could be based upon (Critchley *et al* 2011). Therefore to verify results from coefficients of variation and Bland-Altman analyses and also ascertain CO trending capability, polar plots were constructed. Results showed mean polar angle of 3 degrees, radial limits of agreement of 19 degrees and a concordance rate of 87%. These results are significant as Critchley and colleagues (Critchley *et al* 2011) note that for good trending to occur, mean polar angle or angular bias must be less than $\pm 5^{\circ}$, radial limits of agreement should be within $\pm 30^{\circ}$ and a concordance rate of 95%. Therefore, it is reasonable to suggest that IGR shows acceptable CO trending. The concordance rate in the present study was lower than expected perhaps due to 30 data points used in analysis after central data exclusion.

The current study is not without limitations. Firstly, relatively small sample size of healthy volunteers can potentially reduce generalisation of the study findings. However, by collecting data at rest and during different levels of exercise intensity provide sufficient data points for study to adequately assess reproducibility between repeated measures. Secondly, the feature of the rebreathing method is that it requires a subject to 'learn how to perform rebreathing manoeuvre' i.e. a learning effect. Detailed explanation and familiarisation with the rebreathing procedures was carried out with each study participants resulting in a valid rebreathing manoeuvre being performed. Thirdly, the number of female participants in the present study was small i.e. three. Considering gender-related differences in cardiovascular function and its response to stress, the present study would benefit from including more participants of a female gender.

6.5 Conclusion

The findings of the present study suggest that IGR method demonstrates acceptable test-retest reproducibility in measuring CO at rest, during and at peak exercise when metabolic demand is significantly increased. The present study encourages integration of non-invasive CO

monitoring in cardiopulmonary exercise stress testing procedures as cardiac and metabolic data generated during exercise could help improve understanding of pathophysiology of exercise intolerance. Future prospective studies are warranted to define clinical (i.e. diagnostic and prognostic) and cost-effectiveness of non-invasive cardiac output assessment in clinical practice.

CHAPTER 7: Feasibility and preliminary evaluation of a novel, personalised, home-based physical activity intervention for chronic heart failure (Active-at-Home-HF): a pilot study

Abstract

Purpose: Exercise-based cardiac rehabilitation programmes are safe and recommended to improve outcomes in chronic heart failure (CHF). However <10% of CHF patients participate in cardiac rehabilitation programmes. An effective home-based physical activity intervention may improve current clinical practice and benefit patients. The aim of the present study was to evaluate safety, compliance, and physiological effects of a novel, personalised, home based physical activity intervention (Active-at-Home-HF) in CHF.

Methods: A single-centre feasibility and pilot study recruited 20 patients (mean age 68±7 years) with stable CHF due to reduced left ventricular ejection fraction (LVEF=31±8). At baseline patients underwent maximal graded cardiopulmonary exercise testing with non-invasive bioreactance CO monitoring, assessment of quality of life, NTproBNP and physical activity level over a 7-day period using pedometers. Following initial assessments, patients commenced the Active-at-Home-HF physical activity intervention. The aim was to increase and maintain daily physical activity levels by at least 2000 steps per day from baseline for 12 weeks. This increment has been shown to be associated with a significant 10% reduction in cardiovascular events in high risk patients. All patients were monitored weekly via telephone calls and average daily activity levels were recorded using diaries. During the follow-up visit, all assessments performed at baseline were repeated.

Results: Seventeen patients (85%) completed the study, achieved and maintained the targeted physical activity level. Number of steps increased significantly from baseline to 3 weeks by 2546 (5108±3064 to 7654±3849 steps/day, p=0.03) and was maintained and further increased until week 12 (9022±3942 steps/day). No adverse reactions to this increased activity level were reported. Quality of life scores decreased by 15% following the intervention (26±18 vs. 22±19, p=0.50). There was no clinically relevant change in NTproBNP (876±1106 vs 832±1164 ng/L, p=0.95) and O_2 consumption at peak exercise (16.8±3.8 vs. 17.6±4.2 ml/kg/min, p=0.54), whereas peak exercise workload and cardiac index increased by 11% and 11.8% respectively (82±10 vs. 91±19 watts, p=0.21; and 6.8±1.5 vs. 7.6±2.0 L/min/m^2, p=0.19). Workload and O_2 consumption at anaerobic threshold increased by 20% (49±16 vs. 59±14 watts, p=0.01) and 11% (11.5±2.9 vs. 12.8±2.2 ml/mg/min, p=0.39) following completion of the intervention.

Conclusion: The personalised home-based Active-at-Home-HF intervention that aimed to increase daily physical activity was found to be safe, feasible and acceptable for patients with CHF. It may improve quality of life and exercise tolerance.

7.1 Introduction

The benefits of cardiac rehabilitation in HF have been well documented (Zwisler *et al* 2016a, Safiyari-Hafizi *et al* 2016, Taylor *et al* 2015). Evidence-based clinical guidelines recommend that physical activity should be integrated into cardiac rehabilitation programmes as a cornerstone of clinical management of HF (Ponikowski *et al* 2016, Nice 2010). Furthermore, meta-analyses show that increased physical activity can improve functional capacity, quality of life, reduce symptom burden, reduce likelihood of hospitalisation (Piepoli *et al* 2004, Belardinelli *et al* 1999, Lewinter *et al* 2015, Taylor *et al* 2014, Dalal *et al* 2010) and can also improve cardiac function (Haykowsky *et al* 2007, Mezzani *et al* 2008a, Hambrecht *et al* 2000). In addition, regular physical activity can reduce HF related NHS costs as it decreases HF related hospitalisation by 30% (£2,231 per admission) (NICE 2010). Considering the estimated reduction in the number of hospital admissions and the current costs of rehabilitation services (£500 per patient) (Mant *et al* 2011, NICE 2015), NICE suggest a potential net saving of approximately £19,000 per 100,000 chronic heart failure patients as a consequence of regular participation in physical activity (Mant *et al* 2011). As such, current guidelines now include physical activity training as an important component of cardiac rehabilitation in addition to patient education, psychological support and drug therapy (Ponikowski et al. 2016; Nice 2010; Yancy et al. 2013).

Despite the benefits referred to above, participation of heart failure patients in cardiac rehabilitation is consistently low. In the UK alone, less than 10% of those with HF participate in cardiac rehabilitation (NICE 2015). Numerous factors account for this with the most common being direct exclusion from local commissioning agreements due to limited funds available for rehabilitation services, inadequate social support and lack of capacity for supervised programmes (Dalal *et al* 2012). Furthermore, priority is often given to patients with coronary artery disease (i.e. following heart attack), In addition, patients do not participate in cardiac rehabilitation due to difficulties in attending hospitals, work or domestic commitments and reluctance to attend group-based classes (Beswick *et al* 2004, Griebsch *et al* 2004).

The barriers highlighted above could be potentially overcome by promoting increased physical activity during daily activities. By assessing daily activity in HF patients, true functional impairment could be measured (Walsh *et al* 1997) as the number of steps and energy expenditures outside the hospital environment is positively correlated with improved exercise capacity (Sato *et al* 2012). This type of assessment is valuable in identifying patients at high risk and provides an objective measure of incapacity during normal daily life. Walking

intensity in particular is an independent predictor in discriminating patients with advanced HF (Jehn *et al* 2009). Previous studies evaluating the effect of physical activity suggest that interventions with long duration and frequency of sessions, that use monitoring tools are effective for improving quality of life and function in HF (Taylor *et al* 2014). Outdoor walking interventions (Piotrowicz *et al* 2014, Keast *et al* 2013, Lejczak *et al* 2011) and the use of step-counting devices (pedometers) (Harris *et al* 2013) have demonstrated to be an effective way to increase physical activity in middle-aged and older adults with chronic disease. With respect to 'optimal' amount of daily physical activity, a large cohort study published in the Lancet suggested that every 2000 steps/day increment in daily physical activity was associated with a 10% lower risk of a cardiovascular events (Yates *et al* 2014).

Home-based physical activity interventions are becoming a popular option as a means to increasing physical activity and are reported to be safe (O'Connor *et al* 2009) and equally effective as hospital-based programmes in patients with coronary artery disease (Dalal et al. 2010; Taylor et al. 2015) especially among older patients (Oerkild *et al* 2011, Crawford-Faucher 2010). Home based physical activity is cheaper for patients, often more convenient and can provide an opportunity for patients with CVD to engage in physical activity (i.e. those who might find it difficult to attend hospital-based services). It remains to be determined however whether home-based interventions can benefit HF patients as limited evidence exists on the effectiveness of such an intervention programme in the context of chronic HF. Table 2.1 provides a brief summary of results from exercise and physical activity interventions in HF and other cardiac conditions comparing home based and centre based programmes. A previous UK based trial failed to demonstrate benefits of a home-based physical activity intervention on quality of life and functional capacity due to low adherence and high attrition at follow up (Jolly *et al* 2009). Furthermore, an ongoing NIHR funded trial; REACH-HF has been designed to develop and evaluate a healthcare professional facilitated home-based manual rehabilitation intervention to improve self-care and quality of life in people with HF and their caregivers (Greaves *et al* 2016) but little information is available with regards to the physical activity component incorporated in the trial.

The aim of the present study was to evaluate the feasibility, compliance, and physiological effects of a novel, personalised, home-based, 12-weeks physical activity intervention (Active-at-Home-HF) in chronic HF. Prior to the start of the study, a focus group discussion was held with a group of HF patients to seek their opinions and input in the content of a physical activity intervention designed for HF patients. The views of the focus group participants were incorporated in the final design of the intervention used in the present study in order to

improve adherence and engagement. A detailed description of the methodological procedures used, analyses and findings of the focus group discussions are presented in Chapter 8

7.2 Methods

7.2.1 *Study design*

A single arm, pilot feasibility study design was used to assess the effect of a home-based physical activity intervention in adults with chronic HF with reduced ejection fraction (HFrEF). Eligible participants attended the NIHR Clinical Research facility of the Royal Victoria Infirmary for two separate visits i.e. before and after the 12 week intervention. Participants were contacted via email, telephone or spoken to in person to discuss the project and were taken through the information sheet to ensure they understood the nature of the study. Each visit lasted about four hours.

7.2.1.1 *Participants*

Participants were recruited from HF Clinics at the Royal Victoria Infirmary and Freeman Hospitals in Newcastle upon Tyne. All participants were screened prior to commencement of the study to assess eligibility. Patients with HFrEF i.e. left ventricular ejection fraction $\leq 40\%$ (as defined in the European Society of Cardiology guidelines) (Ponikowski *et al* 2016) diagnosed for at least three months prior taking part in the study, classified according to the New York Heart Association (NYHA) class II – IV, who were clinically stable and receiving an optimal medical treatment were eligible to take part. Patients were required to have no contraindications to physical activity and had to be capable of walking and performing activities of daily living independently. Participants were excluded if they had mild to severe aortic stenosis, uncontrolled cardiac arrhythmias, myocardial infarction, percutaneous coronary intervention and/or bypass graft surgery over the past 3 months, severely obese (i.e. body mass index >40), implanted with left ventricular assist device, were currently participating in a cardiac rehabilitation programme and were unable to provide informed written consent. The study was approved by the Health Research Authority (North East Tyne and Wear South Research Ethics Committee). Each Patient provided written informed consent and all procedures were conducted in accordance with Declaration of Helsinki.

7.2.1.2 *The home-based physical activity programme (Active-at-Home-HF)*

The Active-at-Home-HF intervention was designed as part of the present research programme for patients with chronic heart failure to encourage an increase in their overall daily physical activity level. The intervention aimed to increase the daily number of steps by at least 2000 comparable to baseline. Once patients enrolled on to the study they were supported by weekly telephone calls designed to initiate, increase and maintain their activity levels. This was achieved with behavioural goal setting where the patient would agree a goal with a member of

the person providing the telephone support and discuss barriers to achieving that goal with a view to identifying ways to overcome those barriers. Patients were encouraged to consider times in the past where they had been more physically active as a means of increasing confidence and motivation. Self-monitoring was used to encourage participants to continue being physically active and they were prompted to involve family members and friends in their attempts to increase physical activity levels as a means of social support. At the end of each day, the aim was that the pedometer used to monitor physical activity should indicate at least 2000 steps more than the average daily number of steps obtained at baseline. This increase is associated with 10% reduction in cardiovascular events in patients with high risk of cardiovascular mortality and morbidity (Yates *et al* 2014). Participants were provided with a pedometer (Omron Healthcare, Japan) that allowed them to self-monitor, record and report their steps over a 7-day period. Participants also completed a paper-based daily physical activity diary that was discussed on a weekly basis with a member of the research team (please see appendix 7). The data recorded was also analysed. The physical activity prescription was progressed individually as conditioning took place, with the emphasis on volume of activity i.e. duration and number of steps rather than intensity.

7.2.2 *Clinical assessment*
All participants underwent the following assessments before and after the 12-week physical activity intervention. Clinical examinations and assessment included venous blood sampling, cardiac autonomic function test, arterial stiffness, cardiopulmonary pulmonary exercise test couples with non-invasive haemodynamic assessment and quality of life (QoL). Participants' ejection fraction data were obtained from medical records from the most recent echocardiography assessment performed within 3 months prior study.

7.2.2.1 *Assessment of quality of life*
The Minnesota Living with HF 21 item disease specific questionnaire assessing physical, socioeconomic, and psychological impairment related to HF was used to assess quality of life. Score is based on how each person ranks each item on a common scale and it is used to quantify how much HF has influenced aspects of a participants daily life during the previous month and how it is affected by therapeutic intervention. Scores range from 0 to 105 points with lower scores indicating less effect from HF symptoms and thus a better quality of life (Bilbao *et al* 2016, Rector and Cohn 1992). Change in the score of 5 is considered to be a clinically relevant change/improvement in a patients quality of life (Riegel *et al* 2002).

7.2.2.2 *Assessment of Haemodynamic Function*

Based on the results from chapters 5 and 6, bioreactance was the preferred method for estimating haemodynamic parameters such as cardiac output and stroke volume. Bioreactance offers continuous cardiac output monitoring, is patient and operator friendly, simple to use and does not require familiarization procedure unlike IGR. Also at increased exercise intensities, rebreathing manoeuvre was quite difficult to achieve in healthy participants and this challenge could potentially be increased in HF patients. This limitation was the primary rational for choosing bioreactance over IGR for haemodynamic monitoring in the Active-at-Home-HF intervention.

7.2.2.3 *Cardiopulmonary exercise test*

A progressive exercise test using an electro magnetically braked semi recumbent cycle ergometer (Corival, Lode & Groningen, Netherlands) was performed with simultaneous gas exchange measurements (Cortex metalyser 3B, Leipzig, Germany) and non-invasive haemodynamics using bioreactance method (NICOM®, Cheetah Medical, Delaware, USA) previously described (Keren *et al* 2007, Jakovljevic *et al* 2014). The ECG (Custo Diagnostic system) and an automated blood pressure (SunTech Tango, SunTech Medical, Inc., Morrisville, USA) were determined at rest, during and at peak exercise. The progressive exercise test involved maintaining a pedal frequency of 60-70 revolutions per minutes with workload increasing at the rate of 10 watts per minute. Test was terminated when one of the following criteria was met: i) maximal exertion was achieved (RER>1.15), ii) a patient was unable to maintained required cycling cadence, or iii) patient desire to stop.

7.2.2.4 *Cardiac autonomic function and arterial stiffness*

Cardiac autonomic function (i.e. heart rate and blood pressure variability) were assessed using non-invasive methods integrated into the Task Force device (CNSystems, Graz, Austria). Using electrocardiogram and continuous blood pressure monitoring with a finger cuff under resting supine condition, the system assessed heart rate variability, blood pressure variability and Baroreceptor sensitivity. Arterial stiffness was assessed using the SphygmoCor device (AtCor Medical, NSW, Australia) by applying a tonometer to the radial artery and measuring pressure changes in blood flow. Augmentation index which is a measure of arterial stiffness was then assessed.

7.2.2.5 *Venous blood sampling*

Following an overnight fast, a blood sample was taken from the right or left median cubital vein. The blood sample was assessed for brain natriuretic peptides (NTproBNP), lipid profile

(total cholesterol, HDL-cholesterol, LDL-cholesterol), triglycerides, fasting glucose, HbA1c and renal function (glomerular filtration rate).

7.2.3 *Outcomes*

The primary outcomes of interest were feasibility/acceptability and adherence to the intervention. Secondary outcomes were changes in functional capacity assessed by peak exercise oxygen consumption and power outputs, quality of life, haemodynamic function and changes in NTproBNP. Feasibility/acceptability was defined as willingness and ability of patients to undertake the Active-at-Home-HF intervention. Adherence was defined as the percentage of patients who completed intervention, and was assessed from weekly telephone contacts and records of daily activity reported by the participants.

7.2.4 *Statistical analysis*

The main aim of the present study was to assess feasibility of the intervention. It is generally accepted that pilot/feasibility studies may not require a formal power calculation (Moore *et al* 2011). Nonetheless, it was estimated that a sample size of 20 patients would provide sufficient (β=0.82) to detect clinically desired change / increase in VO$_2$ peak of 3 ml/min/kg after the intervention, at the significance level of 5% (α=0.05). Normality of distribution was assessed using a Kolmogorov-Smirnov test. Student T-test for paired samples was used to assess the effect of the intervention on quantitative outcomes of interest. The relationship between physical activity, clinical and physiological variables was assessed using Pearson's product moment coefficient of correlation or Spearman's rank correlation coefficient, as appropriate based on whether the data met the assumptions for a parametric or non-parametric test. Statistical significance was indicated if $P<0.05$. All statistical analyses were carried out using SPSS version 17.0 (SPSS, Chicago, IL, USA).

7.3 Results

Out of 43 HF patients initially screened by telephone, 20 participants met the study inclusion criteria and were subsequently recruited. Patients were excluded (n=23) because they were already physically active and met recommended guidelines (n=4); too ill to participate (n=5) or refused to participate for personal reasons (n=14). Recruited patients' demographic and clinical characteristics are presented in Table 7.1.

Table 7.1 Mean and SD (±) patients' demographic and clinical characteristics (n=20)

Parameter	
Age (years)	68±7
Men/women	18/2
Weight (kg)	84±15
Height (cm)	1.72±0.1
Aetiology of HF (IHD/DCM)	10/10
LVEF (%)	31±8
Medication	
ACE inhibitors	15
B- blockers	20
ARBs	5
Diuretics	13
Anti-arrhythmic	3
NSAIDs/Pain Killers	6
Warfarin	5
ICD/Pacemakers	13
Comorbidities	1
COPD	5
Type 2 Diabetes	2
Depression	1
Arthritis	

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; NSAID, non-steroid anti-inflammatory drugs; IHD, ischaemic heart disease; DCM, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; ICD, Implantable cardioverter defibrillator

The average number of steps increased significantly by 2546 (from 5108±3064 to 7654±3849 steps/day, p=0.03) from baseline to 3 weeks, and was maintained and further increased until week 12 (8890±3713 steps/day, Figure 7.1). One participant was unable to undergo final clinical examination due to a scheduled surgery, although this was unrelated to HF. Two patients dropped out of the study for undisclosed reasons and one participant discontinued in the study due to ICD malfunction.
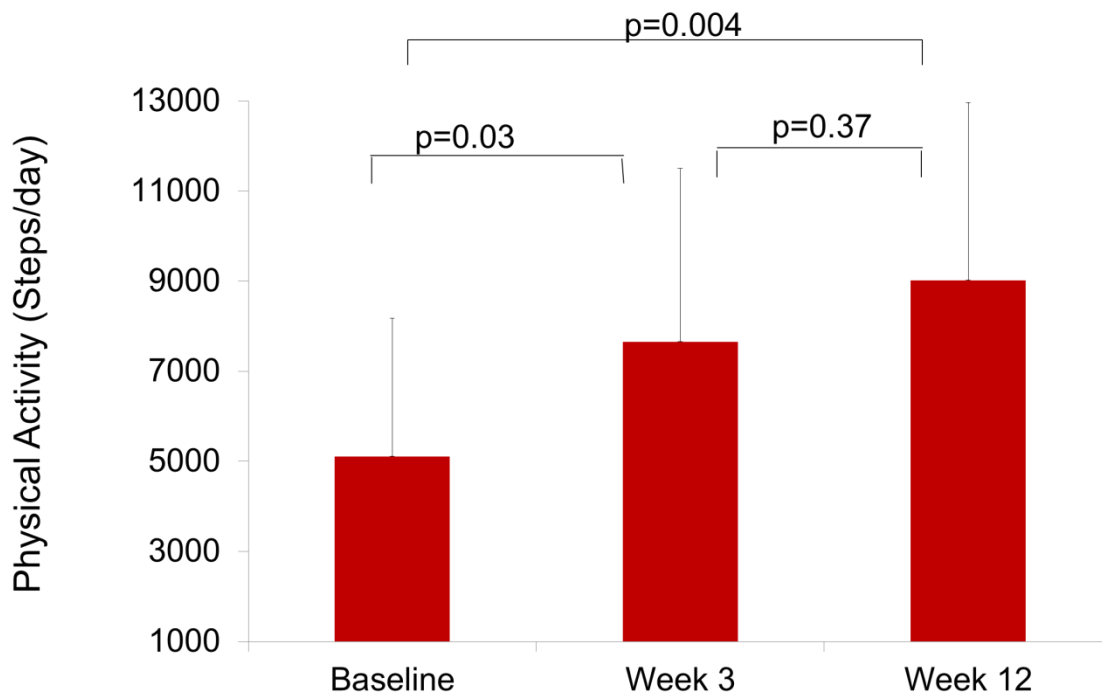
Figure 7.1 Mean (+SD) number of steps achieved at baseline and weeks 3 and 12 of physical activity intervention

7.3.1 *Primary outcome measure*

7.3.1.1 *Feasibility and Adherence*

The intervention was considered feasible with a completion rate of 85% (n=17). No adverse events occurred as a result of participating in the intervention/study. Seventeen participants completed the 12-week physical activity intervention. However, two patients were unable to meet or sustain the required minimum target of 2000 steps above baseline. In situations where patients expressed concerns about their arrhythmias or ischaemia, they were further assessed by the team's consultant cardiologist and were reassured about safety of participation in the intervention before they took part in the study. No patient developed musculoskeletal injury as a result of the study although three participants had arthritis as comorbidity but that did not prevent them from completing the intervention. There was no report of ICD malfunction in HF studies due to increased ambulation or upper body stress.

7.3.2 *Secondary outcome measures*
7.3.2.1 *Metabolic   changes*

There was no statistically significant change in maximal exercise tolerance with peak oxygen consumption and peak workload increasing after the intervention by 4.8% and 11% respectively. Workload and oxygen consumption at submaximal exercise i.e. anaerobic threshold however increased by 20% (49 ± 16 vs 59 ± 14 watts, P=0.01) and 11% (11.5 ± 2.9 vs 12.8 ± 2.2 ml/kg/min, P=0.39) after the intervention (Table 7.2)

7.3.2.2 *Haemodynamic changes*

The Active-at-Home-HF intervention resulted in significant improvements in peak exercise stroke volume (126.5±33.8 vs 150.8±33.5 ml/beat, P= 0.05) and stroke volume index (64.6±14 vs 75.2 ±17 ml/beat/m^2, P=0.04). There was also 10-15% improvement in peak exercise cardiac output and cardiac index although these were not significant (Table 7.2).

Table 7.2 Cardio-metabolic changes (mean ± SD) following 12 weeks of Active-at-Home-HF intervention

	Pre intervention	Post intervention	P Value	% Change
Measurements at Rest				
Oxygen Consumption (ml/kg/min)	3.8 ± 1.0	4.1 ± 0.8	ns	7.9
Respiratory Exchange Ratio	0.85 ± 0.1	0.85 ± 0.1	ns	0
Heart Rate (beats/min)	67 ± 7	70 ± 7	ns	4.5
Stroke Volume Index (ml/beat)	48 ± 9	49 ± 8	ns	2.0
Cardiac Output (l/min)	6.1 ± 1	6.6 ± 1	ns	8.2
Systolic Blood Pressure (mmHg)	118 ± 18	124 ± 18	ns	4.0
Diastolic Blood pressure (mmHg)	74 ± 8	76 ± 12	ns	2.6
Mean Arterial Pressure (mmHg)	90 ± 9	92 ± 13	ns	2.2
Measurements at Peak Exercise				
Oxygen Consumption (ml/kg/min)	16.8 ± 3.8	17.6 ± 4.2	ns	4.8
Respiratory Exchange Ratio	1.05 ± 0.1	1.07 ± 0.1	ns	1.9
Heart Rate (beats/min)	106 ± 19	107 ± 16	ns	1.0
Stroke Volume (ml/beat)	127 ± 34	151 ± 34*	0.05	18.9
Stroke Volume Index (ml/beat/m^2)	64 ± 14	75 ± 17*	0.04	17.2
Cardiac Output (l/min)	13.4 ± 4	15.3 ± 4.9	ns	14.2
Cardiac Index (l/min/m^2)	6.8 ± 1.5	7.6 ± 2.0	ns	11.7

Systolic Blood Pressure (mmHg)	155 ± 30	150 ± 30	ns	3.2
Diastolic Blood pressure (mmHg)	80 ± 8	79 ±8	ns	1.3
Mean Arterial Pressure (mmHg)	103 ± 13	102 ±13	ns	1.0
Peak exercise workload (watts)	82 ± 10	91 ± 19	ns	11
Exercise workload at anaerobic threshold (watts)	49 ± 16	59 ± 14*	0.01	20
Oxygen consumption at anaerobic threshold (ml/kg/min)	11.5 ± 2.9	12.8 ± 2.2	ns	11.3
Rate of perceived exertion	16 ± 2.4	17 ± 2.3	ns	6.3

7.3.2.3 *Blood biomarkers and Quality of life*

There were no significant changes in metabolic controls, lipid profile and biomarkers following completion of the intervention. A 15% reduction in quality of life score was noted suggesting improvement in quality of life (Table 7.3) however, step count had a weak positive correlation with quality of life score ($r = 0.21$) and this did not differ with improved activity at post intervention.

Table 7.3 Blood biomarkers and quality of life (mean ± SD) pre and post intervention

	Pre Intervention	Post Intervention	P Value	% Change
Cholesterol (mmol/L)	4.0 ± 0.9	3.9 ± 0.9	ns	2.5
Triglyceride (mmol/L)	1.5 ± 0.7	1.8 ± 0.9	ns	20
HDL (mmol/L)	1.2 ± 0.3	1.1 ± 0.3	ns	8.3
LDL (mmol/L)	2.1± 0.7	1.9 ± 0.7	ns	9.5
HbA1c (mmol/mol)	49.2 ± 17.3	47.5 ± 12	ns	3.5
FBG (mmol/L)	6.2 ± 2.9	7.0 ± 3.8	ns	12.9
NT proBNP (pg/ml)	823 ± 1085	876 ± 1114	ns	6.4
Renal function eGFR	65.4 ± 18.6	61.4 ± 17.4	ns	6.1
QoL	26 ± 18	22 ± 23	ns	15.4

HDL, high density lipoprotein; LDL, low density lipoprotein; HBA1c, glycated Haemoglobin; FBG, fasting blood glucose; NT proBNP, N-terminal brain natriuretic peptide; QoL, quality of life; eGFR, glomerular filtration rate

7.3.2.4 *Cardiac Autonomic function and arterial stiffness*

There were no significant changes in cardiac autonomic function following completion of the intervention, however results suggest a reduction in parasympathetic activity from HFnu values of heart rate and blood pressure variability. There were no significant changes in arterial stiffness as demonstrated with no significant change in augmentation index (Table 7.4).

Table 7.4 Resting cardiac autonomic and arterial stiffness measures (mean ± SD)

	Pre Intervention	Post Intervention	P-Value	% Change
Heart Rate Variability				
Mean RRI (ms)	875 ± 124	899 ± 120	0.59	2.7
LFnu- RRI	34 ± 18	39 ± 16	0.42	14.7
HFnu-RRI	66 ± 18	61 ± 16	0.42	7.6
LF/HF ratio RRI	0.7 ± 0.6	0.9 ± 0.8	0.48	28.6
Blood Pressure Variability				
SBP LFnu	25 ± 14	24 ± 7	0.81	4.0
SBP HFnu	43 ± 20	39 ± 15	0.58	9.3
SPB LF/HF ratio	0.7 ± 0.5	0.6 ± 0.3	0.60	14.3
DPB LFnu	23 ± 12	25 ± 11	0.74	8.7
DBP HFnu	44 ± 24	44 ± 24	0.96	0
DBP LF/HF ratio	0.7 ± 0.5	0.9 ± 0.7	0.34	28.6
Baroreceptor Reflex Sensitivity				
Total slope mean (ms/mmhg)	13 ± 12	17 ± 14	0.49	30.7
Arterial Stiffness				
Augmentation index (mmHg)	24 ± 8	25 ± 10	0.69	4.2
RRI, R–R interval; LFnu, LF normalized units; HFnu, HF normalized units				

There was a positive relationship observed between daily number of steps and peak oxygen consumption i.e. pre-intervention (r=0.39, P=0.08), and post-intervention (r=0.58, P=0.01), suggesting that daily physical activity is positively associated with functional capacity (exercise tolerance) in active but not sedentary patients with chronic HF (Figure 5.2).
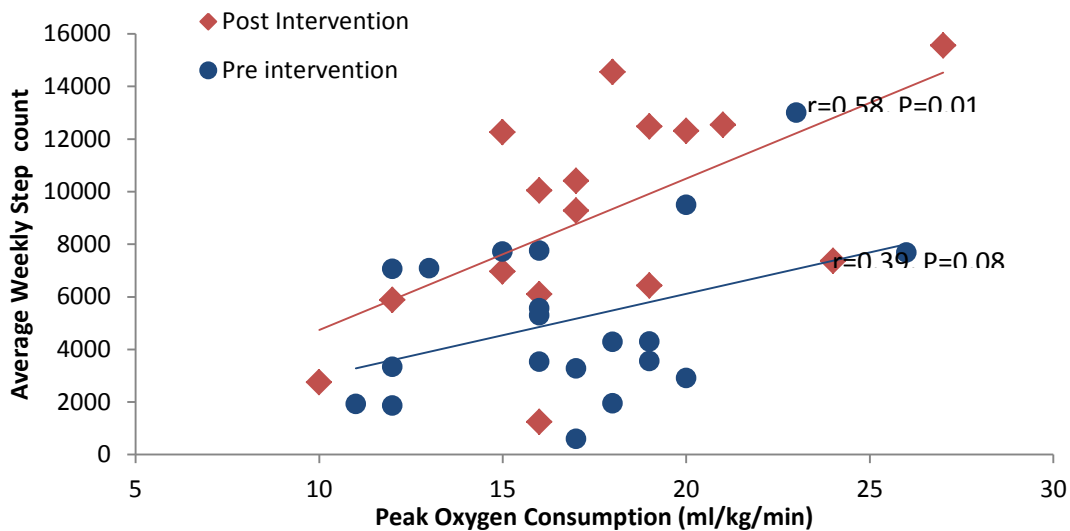
Figure 7.2 Relationship between number of steps and peak oxygen consumption pre and post intervention

7.4 Discussion

The major findings of this study suggest that the Active-at-Home-HF intervention is safe and feasible/acceptable and can potentially lead to functional and haemodynamic improvements in patients with chronic HF.

7.4.1 *Feasibility and adherence*

The findings of this study suggest that physical activity is feasible and acceptable by patients. The findings of this intervention study align with other studies that have reported physical activity to be safe and achievable in HF patients (O'Connor *et al* 2009, Piotrowicz *et al* 2014, Keast *et al* 2013).

7.4.2 *Quality of life*

Patients with HF often experience a decline in health related quality of life (Karapolat *et al* 2009). In addition to clinical presentation, psychological distress can limit activity thereby leading to a decline in quality of life (Ades *et al* 2013). Exercise training has been shown to improve quality of life in HF (Keteyian 2006) and a reduction of 5 points or more in the Minnesota living with HF questionnaire (MLHF) has been previously shown to be of clinical significance (Riegel *et al* 2002). The present pilot study showed a 15% (4 points) reduction in quality of life score. This improvement in quality of life bore a weak positive correlation with step count and did not differ with pre intervention. Considering the Riegel et al's. criteria, the present results are not clinically significant and do not support other studies which have reported a significant improvement in quality of life resulting from an exercise intervention

(Karapolat *et al* 2009, Piotrowicz *et al* 2010, 2014, Chien *et al* 2011, Jolly *et al* 2009, Oka *et al* 2000). However, a 15% improvement in quality of life as shown in the present study is remarkable. Considering the mean age of study participants, it could be argued from the data that participants had a fairly good quality of life prior to the study with mean values of 26 points out of a possible highest score of 105 points in the MLHF questionnaire. Cowie et al., (Cowie *et al* 2012) also reported no change in quality of life in HF patients following home-based or hospital-based intervention, even though there was a significant improvement in exercise capacity. They further suggested that in older HF patients, maintaining quality of life might be a realistic aim for a physical activity or rehabilitation programme.

7.4.3 *Haemodynamic function*

Limited number of studies evaluated the effect of physical activity interventions on haemodynamic response to exercise. In the present study, daily walking resulted in a 14.2% increase in peak exercise cardiac output and a significant 18.9% increase in peak stroke volume. Our results suggest positive adaptation to the intervention and the improvement of systemic oxygen delivery. Other studies have also reported significant improvements in stroke volume as a result of long term (above 12 weeks) exercise training (Giannuzzi *et al* 2003, Lee and Oh 2016). The capacity to increase physical activity depends on the ability of the heart to generate adequate CO and the ability of skeletal muscles to utilise the oxygen delivered (Pina *et al* 2003, McCoy *et al* 2017). This therefore provides a strong evidence for the assessment of cardiac output in response to a physical activity intervention. Stroke volume needs to be maintained by more complete left ventricular emptying via increased left ventricular contraction to reduce end systolic but increased end-diastolic volume, and also via increased peripheral vasodilation. With CVDs and ageing, the heart is less able to reduce left ventricular end systolic volume and relies instead on a greater preload (Pina *et al* 2003). This is probably why previous studies have attributed exercise intolerance in HF to diastolic dysfunction rather than systolic function (Lapu-Bula *et al* 1999, Parthenakis *et al* 2000). Hambrecht et al. showed that a reduction in resting LV end-diastolic volume and an increase in peak exercise stroke volume resulting from aerobic training was related to the decline in resting and peak exercise systemic vascular resistance (Hambrecht *et al* 2000). These findings have been extended by other studies which demonstrated that aerobic training also improves diastolic filling, myocardial contractility and left ventricular ejection fraction in individuals with ischemic cardiomyopathy (Belardinelli *et al* 1998), severe left ventricular systolic dysfunction (Belardinelli *et al* 1996) and HF (Haykowsky *et al* 2007, Giannuzzi *et al* 2003, Maiorana *et al* 2003, Karapolat *et al* 2009, Mezzani *et al* 2008b). Based on the results of the current study

and evidence from the above mentioned studies, it is reasonable to suggest that physical activity in HF can improve cardiac contractility and stroke volume, potentially leading to reverse remodelling in HF.

7.4.4 *Exercise-related outcomes*

Peak oxygen consumption, exercise duration and walking distance are traditionally used as outcome measures in the evaluation of functional capacity (Downing and Balady 2011, Piotrowicz *et al* 2010). The present study found that increased physical activity as recorded from step counts following the Active-at-Home-HF intervention had a stronger correlation with peak oxygen consumption compared with lower step counts (sedentary behaviour) recorded prior to the intervention. This had been demonstrated previously by Jehn et al., who reported a positive correlation between the times spent in light activity/exercise (≤ 3 METs) and improved peak oxygen consumption (Jehn et al. 2009). The results of this study may be of therapeutic importance in the management of HF patients especially older adults as most patients have concomitant exercise-limiting morbidities such as neuromuscular or orthopaedic problems, therefore it may be appropriate to encourage such patients to exercise at a lower intensity than has been considered necessary to increase maximal exercise capacity. The findings of this study have also demonstrated a ~5% non-significant improvement in peak exercise oxygen consumption following the intervention. Most trials involving home-based or centre-based interventions have reported a higher effect of physical activity on peak oxygen consumption (Marchionni *et al* 2003, Sparks *et al* 1993) with an increase of around 15-20% reported in HF (Coats 2000; Karapolat et al. 2009). However, the present results are similar to previous studies (Daskapan *et al* 2005, Dracup *et al* 2007, Corvera-Tindel *et al* 2004) who have reported no change in peak oxygen consumption after a home based walking programme. The following reasons can potentially explain these findings. Firstly, only 16 participants completed the post exercise test and this number did not provide sufficient power to show significance. Secondly, the target population of the current study was older and a sub-group had co morbidities such as COPD, arthritis, and type 2 diabetes which are all factors well known to limit exercise capacity. Thirdly, the focus of the intervention was to increase volume (number of steps), rather than intensity (speed of walking). Based on previous literature, it may be expected that the physical activity performed of higher intensity can lead to more cardiovascular and neuromuscular adaptations (Wisloff *et al* 2007). Nonetheless, the results of this study showed that at anaerobic threshold, participants were able to tolerate greater workload (17% increase) compared to baseline with data. This finding is similar to a previous study (Giannuzzi *et al* 2003) that also reported a significant increase in power output

at anaerobic threshold. This might indicate better utilisation of muscle metabolites and a potential increase in lower extremity muscle mass and strength. In addition other studies have reported that exercise training in patients with chronic HF delays anaerobic threshold and improves submaximal exercise performance. This was also demonstrated in the present study (van Tol *et al* 2006, Sullivan *et al* 1989).

7.4.5 *Autonomic function*

Exercise training have been suggested to improve markers of autonomic function in healthy (Kingsley and Figueroa 2016) and clinical populations (Sandercock *et al* 2007, Jakovljevic *et al* 2013). In particular, exercise training have been found to favourably impact cardiac autonomic function by significantly increasing heart rate variability (HRV) in patients with HF (Murad *et al* 2012, Hsu *et al* 2015, Larsen *et al* 2004, Selig *et al* 2004, Malfatto *et al* 2002). Although HRV does not directly measure autonomic nervous activity, it is considered a significant prognostic indicator of mortality in chronic HF (Nolan *et al* 1998). HRV is defined as beat-to-beat variations in heart rate of an individual during sinus rhythm (Malik *et al* 1996). It is a non-invasive, reproducible, and easy-to-obtain assessment of cardiac autonomic nervous system function and its response to environmental changes (Kleiger *et al* 2005, Malik *et al* 1996). Reduced HRV is an indicator of attenuated autonomic regulation of cardiac pacemaker, or failure of the pacemaker to respond to such regulation (Malik et al. 1996). The findings from the present study demonstrated a 2.7% increase in heart rate variability following increased physical activity, although this failed to reach significance. One possible explanation for this finding could be atrial fibrillation observed in 70% of participants. Previous studies (Puglisi *et al.*, 2008) have reported that persistent atrial fibrillation worsens heart rate variability and in heart failure patients, HRV is further reduced following ICD shocks (Battipaglia *et al* 2010). The time domain HRV parameter (mean RRI, ms) reflect overall autonomic modulation with parasympathetic components. In frequency domain HRV analysis, it is generally accepted that the high frequency (HF) is reflective of parasympathetic activity, while the low frequency (LF) reflects both sympathetic and parasympathetic activity and is now believed to represent baroreflex sensitivity instead of sympathetic modulation (Moak *et al* 2009). Sympathovagal balance can be determined by assessing LF/HF ratio representing the relationship between baroreflex sensitivity and vagal modulation rather than sympathovagal balance (Cygankiewicz and Zareba 2013). There is no HRV parameter reflecting directly sympathetic activation modulation. The results here demonstrate that the physical activity intervention in HF patients had limited effect on improving parasympathetic activity (reduction in heart rate and blood pressure) with no effect

on modulation of sympathovagal balance. The mechanism by which physical activity improves HRV is not very well understood. However, potential mechanisms have been suggested including increased vagal tone which reduces sympathetic cardiac influence, resulting in improvement in HRV (Routledge *et al* 2010, Carter *et al* 2003). At least two mediators (i.e. nitrous oxide (NO) and angiotensin II) are thought to play a role in increasing cardiac vagal tone in response to exercise training. NO is thought to have a direct effect on cardiac vagal tone and an indirect effect on sympathetic cardiac influence (Chowdhary and Townend 1999). Exercise training improves NO bioavailability and endothelial function while angiotensin II, is a known inhibitor of cardiac vagal activity (Townend *et al* 1995). Although athletes and physically trained individuals have been shown to have lower levels of plasma renin activity, and therefore lower angiotensin II levels, than nonathletic and untrained individuals (Fagard *et al* 1985), the present study did not determine nitrous oxide levels and is unable to assess endothelial function.

7.4.6 *Arterial stiffness*

Arterial stiffening is a mark of ageing and is closely associated with many pathological conditions including CVDs, diabetes and chronic kidney disease (Shirwany and Zou 2010). Reduced arterial compliance (i.e. increased stiffness) leads to faster reflection of the systolic wave from the peripheral small arteries to the heart, causing augmentation of the central aortic pressure (Cavalcante *et al* 2011). This augmentation in central pressure leads to increased ventricular afterload and reduced coronary perfusion pressure which, eventually, may cause myocardial hypertrophy, ischaemia and infarction (Sakuragi and Abhayaratna 2010). Thus, arterial stiffness appears to contribute to the complex aetiology of CVD and is regarded as a predictor of increased risk and all-cause mortality (Laurent and Boutouyrie 2007, Mitchell *et al* 2010).

Assessment of vascular function is one commonly used method recognised as an important prognostic index and a potential target for therapeutic intervention in HF (DeLoach and Townsend 2008). In the present study, there was no difference in augmentation index following the physical activity intervention. The mean value for augmentation index post intervention was 25% and this value is similar to augmentation index of 27% which was previously reported in a study involving healthy elderly people (Houghton *et al* 2016). The participants in the current study had augmentation index in the normal range for their age (Kuznetsova *et al* 2014, Chung *et al* 2010) moreover, they were optimally medicated with vasodilators. Therefore, it was unlikely that a physical activity intervention would have an added effect on arterial function in this group of participants. However, other studies have

reported an improvement in vascular compliance resulting from different forms of exercise (Hornig *et al* 1996, Parnell *et al* 2002).

7.4.7 *Other outcomes*

Results from the present study showed no change in NTproBNP; one of the current biomarkers used to diagnose and assess HF progression. In contrast, others have reported a significant reduction in NTproBNP levels following exercise training (Passino *et al* 2006, Guazzi *et al* 2012, Conraads *et al* 2004, Smart and Steele 2010). However, improvement might depend on the design of the intervention as group based exercise training had previously been reported to have no effect on NTproBNP levels in HF (Nilsson *et al* 2010) even though there might be improvements in peak oxygen consumption (Arad *et al* 2008). Significant reductions in brain natriuretic peptides levels with exercise training correlates positively with improvement in VO_{2peak} (Passino *et al* 2006) and ventilatory efficiency (VE/VCO_2 slope) (Guazzi *et al* 2012) suggesting that improvement in peak exercise fitness may serve as a gauge for neuro-hormonal improvement following exercise training, linking pathophysiology to functional capacity.

5.4.8 *Limitations*

The present study has a number of limitations. Firstly, it is possible that small sample size limits the effect training has on clinical and physiological outcomes. However, considering that this was a feasibility/pilot study, results demonstrate that the proposed physical activity intervention is feasible and acceptable by patients. Secondly, the training intensity for the study was low compared with other studies and there was no way of assessing this throughout the intervention period. A future intervention will add an intensity monitoring component using the Borg Scale (0-20) where patients will be advised to reach the moderate intensity effort as indicated on the scale as 13-15 ('somewhat hard to hard') intensity. Furthermore step counts were self-reported limiting the accuracy of results obtained. This will be addressed in future studies by the use of pedometer which blind participants to their step counts. Lastly, only two female patients were recruited into the study limiting generalisability of the study findings. Thus future investigations warrant inclusion of greater numbers of female participants to determine, acceptability and clinical effectiveness of the Active-at-Home-HF intervention in this sub-group.

7.5 Conclusion

The present study shows that the Active-at-Home-HF intervention is a feasible intervention that can provide clinical and physiological benefits to people living with HF. The intervention is associated with increased functional capacity and haemodynamic response to exercise. It may also lead to improved quality of life for patients. Significant changes in response to the Active-at-Home-HF intervention were observed in oxygen consumption and workload at anaerobic threshold (submaximal exercise) and cardiac function response to maximal exercise with increased peak cardiac index and stroke volume.

Future directions

Further evaluation of the Active-at-Home-HF intervention is warranted in a large randomised control trial. Our centre is currently establishing collaborations at a national level which will lead to a joint funding application to the National Institute for Health Research or British Heart Foundation which will aim to define clinical- and cost-effectiveness of the home-based physical activity intervention in patients with chronic HF.

CHAPTER 8: Exploring barriers and facilitators of adults living with heart failure to participation in a home-based physical activity programme: A qualitative study

Abstract

Purpose: Referrals to physical activity and exercise programmes for heart failure patients is suboptimal and this is coupled with a high dropout for patients undergoing rehabilitation programmes especially those which are centre or hospital based. Home-based programmes have now gained popularity to curb dropout however, individual experiences are believed to impact uptake and dropout but knowledge about heart failure patients' experiences of physical activity interventions is limited. The aim of the present study was to explore barriers and facilitators to engaging in a home-based physical activity programme in adults with chronic heart failure.

Methods: Three focus groups were conducted and attended by 17 participants (14 males and 3 females, age: 68 ±7 years). Sixteen participants were people living with heart failure (≥9 years duration of disease) and had agreed to participate in a home-based physical activity programme (Active-at-Home) while one person was the partner of a participant. Barriers and potential enabling factors were firstly explored for participation in a personalised home-based physical activity programme. The second and third focus groups explored information on participant's experiences during the personalised home-based physical activity programme. Focus groups were analysed thematically using an inductive approach.

Results: Aspects that influenced motivation and participation were linked to eleven themes. These themes present information on participant's fear of engaging in physical activity, family influences on activity habits and choices, care and support from rehabilitation and clinical staff, and self-motivation resulting from confidence built upon as a result of participating in a personalised programme.

Conclusion: The present study emphasizes the importance of personalised support for heart failure patients. Strategies aimed at improving physical activity in heart failure patients should strive to incorporate family members and also develop social support groups in communities to improve self-confidence, learning and adaptation to physical activity in everyday life.

8.1 Introduction

Increasing levels of physical activity has been advocated as a strategy to improve cardio-metabolic and psychological wellbeing (O'Donovan *et al* 2013, Colberg 2012, Josefsson *et al* 2013). To enhance overall health benefits, it has been suggested that individuals should strive for an increase in the amount of time they spend being physically active and reduce the amount of time spent sedentary (Dunstan *et al* 2012). For people living with chronic conditions such as cardiovascular disease, medical support in terms of rehabilitation seems to be on the increase.

Recent data from the British Heart Foundation suggest that cardiac rehabilitation services have improved with overall uptake from referrals reaching 45% in 2013 compared with 41% in 2009 (Doherty P, Petre C, Onion N, Dale V 2014). However, these figures provide a generalised perspective because for some cardiac conditions, referral is still very low. For example, only 2% of cardiac rehabilitation referrals are due to heart failure (NICE 2015). Furthermore, the success of heart failure patient referrals to rehabilitation services is marred by an increase in dropout rates (Yohannes *et al* 2007).

A potential solution to help improve physical activity and reduce sedentary behaviour is a home-based programme. Home-based cardiac rehabilitation and physical activity programmes have been shown to elicit similar improvements as centre based programmes and could be used as a strategy to reduce dropout rates thus improving participation (Zwisler *et al* 2016b, Oerkild *et al* 2011). This could be particularly beneficial where barriers for non-participation include lack of transport, proximity of cardiac rehabilitation services and where the preference for the individual is to increase activity at home and not in a group environment. Chapter 7 presented the findings of a pilot study that assessed the effect of a home-based physical activity programme on outcomes including safety, adherence, quality of life and exercise capacity in adults with heart failure. The present chapter reports on an embedded qualitative study designed to explore the barriers and facilitators to participation in the home-based physical activity programme with the aim to identify ways in which the intervention could be integrated into the routine clinical care pathway for people with heart failure. This included identifying ways in which the intervention could be improved or any additional support that might be required to maximise adherence. Discussions between health psychologists, exercise physiologists and heart failure cardiologists informed the behavioural content and structure on which the overall home-based physical activity intervention was designed.

The home-based physical activity programme was designed to support participants to increase their overall daily activity by at least 2000 steps per day (i.e. walking at low intensity for approximately 30 minutes) from baseline for 12 weeks. Three team members, who were exercise specialists, acted as behavior change coaches and worked with participants to identify ways to increase the likelihood that physical activity levels were increased and sustained. The coaches were also responsible for reviewing participant's health status and answering questions that arose concerning participation in the study. Physical activity goals were modified individually depending on the participants' progress from the previous week, capability and preferences and with an emphasis on volume of physical activity (i.e. duration, rather than intensity).

The aim of the present study was to explore barriers and facilitators to engaging in a home-based physical activity programme (Active-at-Home-HF) in adults with chronic heart failure.

8.2 Methods

8.2.1 Design
Three focus group discussions were held at different stages during the pilot study. The first focus group was held prior to the start of the intervention. Cardiologists, who were part of the research team sent out invitations to the first focus group. The primary aim of the first focus group was to elicit barriers and enabling factors to taking part in a home-based physical activity intervention programme for older adults with CHF, in order to generate further information that would strengthen a pre-designed intervention for these patients. Participants were also asked about the type of support they would require to take part and continue to take part in a home-based programme.

8.2.2 Participants
All participants taking part in the first focus group had previously participated in cardiac rehabilitation and had a basic knowledge on the importance of staying active as a means to improve quality of life while living with heart failure. The first focus group was held in December 2015 at the rehabilitation department of the hospital, which was the main recruiting site for the pilot physical activity study. Six participants attended the group. Although not all participants in the first focus group discussion went on to take part in the intervention, it was important to gather as much information as possible from heart failure patients in relation to their motivations for participation or non-participation (i.e. the aim was to better understand why members of the group had elected not to take part in the intervention). The second focus group was held in June 2016 at the clinical research facility (CRF) of the Royal Victoria

Infirmary, Newcastle upon Tyne. The group was attended by six study participants; 1 participant was at the beginning of the home-based physical activity intervention (3 weeks into the study), four participants were mid-intervention (7 - 10 weeks into the study); and 1 participant had completed the intervention. One participant attending focus group 2 had also attended focus group 1. The final focus group was conducted in December 2016 and was attended by 5 participants, three of whom had completed the study, one who was still participating and was in their eleventh week, and the final participant was the partner of another participant and provided their views as a partner rather than an individual with heart failure. The aim of the second and third focus groups was to obtain views from participants on their experiences of the Active-at-Home-HF intervention, including barriers and enabling factors to continued participation and whether the outcome of participation was meeting their expectations. Participants who attended either the second or third focus group were contacted by a member of the study team to invite them to participate. These groups were held in a seminar room located at the CRF where all clinical assessments detailed in Chapters 2 and 5, were carried out were carried out. This location was chosen to ensure easy access and to put participants at ease, as they were already familiar with that particular environment.

8.2.3 *Study Procedure*
Focus group discussions were facilitated by two chartered health psychologists with expertise in health behaviour change and who were experienced in qualitative research methods in the context of lifestyle interventions. Both health psychologists facilitated the first focus group and only one was present at focus groups 2 and 3. Prior to commencement of the focus group, facilitators described the aims, purpose and format of the group discussion. Participants were also notified that the discussions would be audio recorded, transcribed and the information generated would be anonymised and stored securely at Newcastle University. The study received research ethics committee approval and all participants provided informed written consent prior to participation in focus group discussions.

8.2.4 *Materials*
A topic guide was used by the focus group facilitators to help structure the discussion and ensure that a range of topics were covered (please see Appendix 5). Topics included participant thoughts about completing a physical activity programme at home/outside of the hospital environment; type of support needed to complete a physical activity programme at home; potential obstacles to completing a physical activity programme at home; hopes regarding possible benefits of completing a programme of physical activity at home/outside the hospital environment; impact of the intervention on their social and physical wellbeing

and; whether their experiences of the programme would mean they would promote the intervention to other people living with heart failure. All questions were open ended and prompts were used to generate a deeper understanding of participants' views and experiences. Each focus group lasted approximately one hour in duration.

8.2.5 *Methodological Quality*

To maximise methodological quality of the research conducted, the consolidated criteria for reporting qualitative research (COREQ) checklist (Tong *et al* 2007) was used as a guide. To reduce bias from responders, members of the team involved in participant clinic visits and behaviour change coaching did not attend the focus group discussions. There was one exception to this where a study team member (coach) attended the second focus group meeting to take consent and coordinate participants' travel. The focus group facilitators were not involved in participants' clinic visits and coaching and had not been in any form of contact with the participants prior to the focus group discussions. All focus group audio recordings were transcribed by a reputable external organisation recommended by Newcastle University.

8.2.6 *Data Analysis*

Given the exploratory nature of the present study, an inductive approach to data analysis was adopted (Braun and Clarke 2006). Thematic analysis was used because it is a flexible method that allowed themes to emerge freely from the data obtained (Braun and Clarke 2006). Data from recorded focus groups were transcribed verbatim and audio files carefully stored in a password-protected folder. Once audio files were securely stored they were deleted from the recording device. Transcribed data were crosschecked for accuracy during code generation. The first researcher (NO) read the transcripts multiple times in order to become adequately familiarised with the data. As reading progressed, codes were generated and corresponding comments placed in relevant sections. A second researcher (LA) independently coded one transcript and findings were compared and discussed and consensus on interpretation reached. Due to the large volume of data generated from the focus group discussions, several initial codes were generated and were later cut down to a final set. All codes and participants' semantic expressions were further reviewed by the first two researchers to ensure uniformity of ideas. The final codes were collated and this formed the basis from which subthemes were conceptualised. The subthemes and associated data were further analysed and compressed into groups from which themes emerged. A third researcher (NO'B) reviewed themes and sub-themes generated to check interpretation. Key statements that represented participants'

experiences were also extracted and used as reference statements to support the themes and subthemes generated.

8.3 Results

Overall, seventeen individuals participated in the focus group discussions. All but one participant were patients with stable chronic heart failure who had either completed the home-based physical activity programme (4 participants), had participated in the study for more than 3 weeks (7 participants), or did not participate in the home-based intervention (5 participants), i.e. they declined to participate in the intervention for personal reasons but expressed a desire to provide their views in a qualitative research study (i.e. they were advocates of physical activity and wanted to contribute to a discussion about what would promote participation). One participant was the partner of a participant with heart failure. Ten participants had implanted cardiac defibrillators (ICDs). Fifteen of the sixteen responders were retired from active work, while one was still involved in part-time work as a heavy duty truck driver in a recycling site. Thematic analysis resulted in 11 main themes and 7 subthemes related to participants' views on heart failure, physical activity, cardiac rehabilitation and the home-based physical activity intervention. Table 6.1 provides details of themes and subthemes emerging from the focus group discussions. To add context and support to the themes, direct quotes from participants have been provided alongside.

Table 8.1 Themes and subthemes derived from thematic analyses of focus group transcripts

Theme	Sub-theme
1. Having heart failure makes you apprehensive about undertaking physical activity	1.1 There is a fear that physical activity will result in negative consequences 1.2 Having heart failure can reduce your motivation to be active
2. Family members influence your physical activity efforts	2.1 Family members can be a barrier to physical activity 2.2 Family members can be a facilitator to physical activity by providing support
3. Positive influence and support of healthcare professionals facilitates participation in physical activity	3.1 The consultant and other healthcare professionals advising participation in physical activity/exercise served as an endorsement that family members accepted
4. Participation in a cardiac rehabilitation programme increased my fitness and confidence to undertake a physical activity programme at home	
5. Having a coach while participating in the intervention made it easier to get motivated and keep going	
6. A credible study team increased the	

likelihood of engagement with the intervention	
7. Having weekly agreed step targets increased confidence and motivation	
8. The surrounding environment can be a barrier to participating in and maintaining physical activity/exercise	
9. Participation in the intervention has been beneficial	9.1 Participation in this intervention has encouraged me to consider ways to increase my everyday levels of physical activity 9.2 The intervention has led to improvements in my general health and well being
10. A follow-up by a healthcare professional or other qualified individual once the intervention has ended would be beneficial	
11. A group to facilitate social support would be beneficial and could facilitate maintenance of physical activity/exercise	

Theme 1: Having heart failure makes you apprehensive about undertaking physical activity.

Sub theme 1.1: There is a fear that physical activity will result in negative consequences

Once diagnosed with heart failure or any other heart condition, some participants reported having the feeling of being sentenced to death and only living on borrowed time.

> 'If you've had a heart problem, you just feel you're going to drop down dead any minute, you know. You're nervous to do anything' (*Male aged 70, focus group 1*)

Others thought the biggest challenge was getting over the fear and apprehension associated with the diagnosis and having the assurance that they could still live a healthy and normal life.

> 'I think the biggest problem facing anyone who's had heart problems is getting over the fear factor' *(Male, aged 78, Focus group 1)*

Similarly, other participants reported that they could still engage in physical activity, however there was still the nagging question of whether they were doing too much (i.e. whether too much activity could be detrimental). This was considered to be a serious limiting factor/barrier to increasing physical activity levels.

'It's frightening when you've gone too far. Something's always holding me back from going that little bit further, you know. I'm frightened of doing things. 'I'm not confident when I go out on my own. I'm frightened I'm going to collapse.' *(Male, aged 57, Focus group 1)*

Sub theme 1.2 : Having heart failure can reduce your motivation to be active

One of the consequences of being diagnosed with heart failure was a lack of motivation to being active. Many participants reported feeling breathless and sometimes experiencing falls when they were out walking by themselves. This reduced confidence and caused a loss of motivation to becoming active in order to reduce health risks.

'I think the heart attack or the heart failure can be the very thing that removes some of the motivation [to undertake physical activity]. It did with me. I suppose what I'm saying is my mental and physical reaction to the heart failure was to be demotivated completely' *(Female, aged 62, Focus group 2; completed study)*

I'm not confident when I go out on my own. I'm frightened I'm going to collapse *(Male, aged 57, Focus group 1)*

Theme 2 : Family members influence your physical activity efforts

Sub theme 2.1: Family members can be a barrier to physical activity

Data generated highlighted that family plays a significant role in decision making for participants. Some participants noted that as their family wanted them to get better and not incur repeated cardiac incidents, this meant restricting them from engaging in physical activity for fear of harm, even though the participants themselves wanted to be more active.

' I've got a wife who's not happy if I say I'm going out for a walk for an hour.., going out in 20 minutes… because she thinks that's too much. "No, you can't do that," and I say, "I can. [She] has got her mind made up……. what she's interested in is that I don't over-exercise and something happens. That's what she thinks of, ... she's worried in case something happens so far as she's concerned..' *(Male, aged 67, focus group 2; 3weeks into study)*

However, there was a consensus from participants that in situations when family members placed restrictions on their physical activity, it was done out of care.

'It's actually family support as well. Sometimes, your family don't want you to do it, not because they're being horrible, it's because they're concerned about you' *(Male, aged 78, Focus group 1)*

Sub-theme 2.2: Family members can be a facilitator to physical activity by providing support

Although family members could be a barrier to increase physical activity, there were instances where family support was a strong motivating factor to improve activity levels.

'I needed motivation which I got from the family, which is great. I appreciate not everybody has family around them to do that and I don't know how I would have fared without family' *(Female, aged 62, Focus group 2; completed study)*

For some participants, family support went beyond words of encouragement. Having a partner or close relatives to support and participate in the new activity routines was reported as very beneficial.

'I think it does help if you've got a supportive partner. My husband has come out with me for all my walks right from the start. When I went for rehabilitation class…, he came too. I asked him to come. I think it's good if your partners can be involved and then they realise, don't they, how they can help' *(Female, aged 62, Focus group 2; completed study)*

Theme 3: Positive influence and support of healthcare professionals facilitates participation in physical activity

Sub-theme 3.1: The consultant and other healthcare professionals advising participation in physical activity/exercise served as an endorsement that family members accepted.

As noted previously, there was a strong tendency for family members to hinder activity plans of participants due to fears that it could lead to worsening of their heart condition. However, this was reversed when family members witnessed healthcare professionals recommending increasing levels of physical activity and explaining that it was effective for maintaining improved cardiac function.

'I think my biggest breakthrough was . . . I was doing more and more but, again, family was saying, "Take it easy." Fortunately, my wife was with me on one occasion

when I saw Dr "XX" and he asked what I'd been doing, and he said, "Well, do more." I said, "How do you mean by that?" He said, "Just do more and more until you feel you can't and then back off a bit." So, fortunately, my wife was there and she heard him say it. So, I've had no peace since then' *(Male, aged 78, Focus group 1)*

Not only do healthcare professionals help in assuring family members of the benefits of physical activity, participants also reported how the rapport they had with their consultant, nurses and other care providers helped them to increase their activity levels.

'I found everybody very professional and friendly and explained things and gave you confidence and obviously were concerned for your welfare and wellbeing…' *(Male, aged 69, focus group 2; week 9 of study)*

'To say more about everybody we've met here, speaking for myself, they've been brilliant. The people are nice, the nurses and everybody are fantastic. They're always happy, cheerful and they'll do out for you' *(Male, aged 78, Focus group 1)*

'My nurse certainly was interested [in my physical activity habits] and when I went last time, was aware of what I was doing and obviously encouraging' *(Female, aged 62, Focus group 2; completed study)*

Theme 4: Participation in a cardiac rehabilitation programme increased my fitness and confidence to undertake a physical activity programme at home

Cardiac rehabilitation was showcased in this theme as playing a pivotal role in confidence building among heart failure patients. Cardiac rehabilitation was seen as a holistic form of care where patients not only learn about physical activity, but also receive additional information about heart failure, medication and safety, and emergency actions to take when they notice changes within their body function. Participants remarked that the education they received from rehabilitation gave them the confidence and motivation to continue with activities of daily living.

'I think the most important thing sorry when you've had a heart attack is to have the confidence to do it at all. I think the cardiac rehabilitation that I had gave me the confidence and then you can move on to do other things. I think if you had just had a heart attack and someone says, "Right, you've got to go for a walk every day," it would be difficult to do. I think it would. So it's like a step in the process' *(Male, aged 71, focus group 2; week 9 of study)*

Some others saw the rehabilitation classes as a step in the right direction to build the confidence needed to re-establish social interaction with friends and also get to the level where they felt they were psychologically ready to become physically active.

'Obviously, coming here to rehab and the like, it all just gradually built because I lost social confidence and mental confidence for the want of better terms. It wasn't just getting my body back on track, it was getting the whole of me back on track' *(Female, aged 62, Focus group 2; completed study)*

Some participants expressed their dismay on finishing the rehabilitation course. The rehabilitation programme was seen as an avenue for social interaction and combatting loneliness and not only to improve health. As such the home-based physical activity programme provided (for some) a continuation of this.

'I was really upset when it [cardiac rehabilitation] finished. I had somewhere to go. I'm sat at home by myself all day, so coming here on a Wednesday, it was like bloody Christmas all over again, you know. It was great, wasn't it? It's smashing; it's been really nice' *(Male, aged 57, focus group 1)*

Theme 5: Having a coach while participating in the intervention made it easier to get motivated and keep going

Participants reported that having someone who checked up on them and who cared about the effort they were making to improve their activity levels and who was there to offer support and advice to ensure continuity of habits was a significant bonus. Some participants noted that the connection between them and their coaches meant they had to give up being lazy so not to disappoint the coach.

'When somebody is monitoring you, it makes you get up and go out, doesn't it? I mean if you go to the gym yourself, some mornings you might say, "I'm not going to go today," but it's helping you, isn't it?' *(Male, aged 62 focus group 3; completed study)*

'[having your coach call you] encourages you to keep up with it, definitely, because I think if you didn't get the phone calls, I think you might just go, "It's not very nice out today, I'll not bother going. I mean I got to the point where even when the weather was bad, one day it was thunder and lightning and all sorts, I've got a big table, I was walking round the table in the house. Crazy!! *(Female, aged 62, Focus group 2; completed study)*

The coaches were physical activity/exercise specialists and were trained by a health psychologist in the use of specific behaviour change techniques (e.g., goal setting, barrier identification, problem solving) designed to increase motivation of participants and support adherence once physical activity levels were increased. Furthermore, the personality of the coaches also played an important role in keeping participants motivated. One participant reported that having regular communication with their coach brightened up their day, especially when he felt moody and lonely.

> 'I think they [the coach] are beneficial because you've got that connection. There's another person there who you're connecting with and so on and so forth. I would find that good myself. Of course talking to [the coach] was an experience on its own. He's a great character. That's where this connection comes in, if you're talking to someone that you like it boosts you up a little bit. It takes a lot of the boredom away from the day or whatever if you're on your own' *(Male, aged 73, focus group 3; completed study)*

Theme 6: A credible study team increased the likelihood of participation

Participants acknowledged that one of the incentives to engaging in the Active-at-Home-HF intervention which involved walking at least 2000 steps more than baseline, was the awareness that the study team was made up of experts in the field of heart failure and physical activity and that they had a successful track record of running such interventions.

> 'I think the fact that people like yourselves who are specialists in this sort of area take such an interest in us people. I think that gives you the boost again. I think it does boost people when you've got people who are really even higher than your GP and what not in that specific area of cardiac problems' *(Male, aged 78, focus group 2; week 11 of study)*

Others were also aware that it was a specialist area and they were more likely to participate assured that they were monitored by specialists in the field.

> 'Well I think this is a speciality subject, what you're doing and all the stuff here that we've been doing. I think it's better in that situation to get the right advice' *(Male, aged 67, focus group 2; 3 weeks into study)*

Theme 7: Having weekly agreed targets increased confidence and motivation

Goal setting was seen as an important way to increase motivation among participants. This was particularly useful as weekly goals were agreed between the participant and coach, making it realistic and attainable for participants to intrinsically motivate themselves. Goals created some form of structure and direction for participants. It was also a fulfilling experience when these goals were achieved.

> 'I think if you were told increase to 12,000 and I come back in 12 weeks' time and we talk about it, you would go... but what's good is on Tuesday [my coach] rings me and goes through all the information, we get an average and then he'll ask me how I'm feeling, etc., etc., and say, "Right, let's try and take that 12,000 up to 12,500." That's on a weekly basis. You know for a fact that someone's interested in what's been happening for the past week and we can take that from where we are now to try and improve things.' *(Male, aged 69, focus group 2; week 9 of study)*

Some participants were not only satisfied with weekly targets as part of the intervention, but also expressed optimism that they would continue to give themselves daily or weekly goals after the intervention/study period.

> 'It's a target as everyone's saying and you want to do it and you feel very enthusiastic about doing it and I will certainly continue after the 12 weeks because it would be pointless stopping all together wouldn't it? It would waste the benefit sort of thing' *(Male, aged 70, focus group 2; 7 weeks into study)*

Other participants expressed anxiety as to whether they could keep up with the increased levels of motivation and physical activity after the intervention was finished.

> 'I think it gives you motivation to go out and do it when you know that somebody's going to phone you up and ask you how many steps you've done. What I'm concerned now is about keeping it going. Like the other night I got home at 10 o'clock and I discovered I hadn't done enough steps so I walked round the block. If I hadn't been on the programme, I wouldn't have done that' *(Male, aged 71, focus group 2; week 9 of study)*

Theme 8: The surrounding environment can be a barrier to participating in and maintaining physical activity/exercise

Participants reported that environmental factors could have severe negative impact on wanting to engage in physical activity. For example, although participants were living with heart failure and currently optimally managed through medication, they reported that the rate of recovery and adaptation to physical activity was different for everyone thus making it particularly challenging for participants who live in hilly areas.

> 'I think another …. difficulty… trying to get people motivated is the area that they live in. Now if you've got a bit of countryside, open fields and that, it opens you to more space unlike just got solid concrete, trying to get people motivated to walk down the same street or go a particular… way, that's going to be difficult I think. If you're going to motivate people you're going to have to think where they actually live because people need different types of motivation. For people who live near the coast and the countryside, people living smack bang in the middle of a built-up area etc.' *(Male, aged 67, focus group 2; 3weeks into study)*

> 'To me, I'm okay most of the time on the flat, but it's any incline. The littlest incline in the world kills me' *(Male, aged 78, focus group 2; week 11 of study)*

For other participants, climatic conditions imposed the greatest challenge. While some participants were involved in the intervention during the summer, others participated during the winter. But due to the constant fluctuations in weather conditions, participants did acknowledge that during cold and rainy conditions, it was a difficulty going for a walk.

> 'I think some of the benefit was the climate as well, because it was through the summer because he struggles in wind and rain' *(Female, wife of participant, focus group 3)*

Theme 9: Participation in the intervention has been beneficial

Sub theme 1: Participation in this intervention has encouraged me to consider ways to increase my everyday levels of physical activity

The intervention was reported to be mentally stimulating. Participants sought ways to improve their levels of physical activity by modifying their everyday behaviours and activities. One participant reported how the intervention prompted him to spend more time

than usual with his grandchildren, thereby positively affecting social connections with his family

> 'But the main easiest way I've found of getting your steps up, I get the grandchildren three days a week and they certainly keep you going and you realise that you've done more steps because having to go round the park in all weathers and things like that does become a little bit...' *(Male, aged 69, focus group 2; week 9 of study)*

There was also a change in attitude with regards to the way participants did their shopping. Some participants noted making multiple trips to their local shop just to ensure increased activity levels.

> 'So when I go to the shop for my paper in the morning, I get The Daily Mail. I come back in the afternoon to get The Chronicle' *(Male, aged 70, focus group 2; 7 weeks into study)*

Others reported that whenever they had to drive to get their shopping, they parked further away. Although this was done to increase their step count, it also meant it was a conscious and deliberate action by the participants and was geared towards improving their health.

> 'What I do now is I have to drive to the supermarket but I park in the furthest corner of the car park and I walk round the car park. Then on rainy days what I've been doing is going into the supermarket and going round it twice before I start my shopping. The people must think you're mad if they look at you on the CCTV' *(Male, aged 71, focus group 2; week 9 of study)*

Sub theme 2: The intervention has led to improvements in general health and well being

Involvement in the home-based physical activity intervention had a positive impact on the participants' lives. Some described how their fitness had improved and that they were generally feeling well. They also reported that their consultants could see the change and the work they had put into living a healthier lifestyle had prompted a reduction in the frequency of medical check-ups.

> 'I haven't been back to see my specialist at the Freeman [hospital], because he doesn't want to see me for 12 months because I'm too fit for him. I said, "Are you sick of me?" he said, "No." It was six months before and then I went for the last check sometime last year, he said, "Right, I don't want to see you for 12 months, John. I said, have you gone off me?' *(Male, aged 71, focus group 2; week 9 of study)*

For the majority of participants, the intervention brought about improvement in cardiac function (see Chapter 5). For some, this improvement resulted in halting some invasive procedures that would have been carried out prior to the study.

> 'When they were taking all the tests and things like that, [my doctor] said, "Whatever you've been doing, keep on doing it because it's remarkable. You heart muscle is actually working much better." He said, "Forget the defibrillator, you don't need it' *(Female, aged 64, Focus group 3; completed study)*

> 'I think it's got to work doing exercise. I mean they brought me in here; they're going on about putting a defibrillator in. Now when he saw me, how my heart had changed just through doing things, he decided he wouldn't put one in' *(Male, aged 62, focus group 3; completed study)*

Other participants reported that the intervention had not only helped to improve cardiac function, but it also helped them to control other co-morbidities and their general state of health.

> 'Well since I've completed the course [the physical activity intervention], I've been diabetic for 30 years, my blood sugar levels have never been as normal as an ordinary person's in my life' *(Male, aged 78, focus group 2; week 11 of study)*

> 'The only thing I've got, when I went to the hospital and they said it was remarkable, they were gobsmacked at how well I was and all this and that, I've come out of there thinking is this too good to be true?. I'm frightened [although] I've never felt ill' *(Female, aged 64, Focus group 3; completed study)*

> 'Every time I go and see [the consultant], he says, you're a champion, you're no bother' *(Male, aged 69, Focus group 3; week 11 of study)*

Theme 10: A follow-up by a healthcare professional or other qualified individual once the intervention has ended would be beneficial

Post study follow was considered important and necessary for psychological and emotional wellbeing. Participants received a lot of support from their coaches throughout the intervention period via weekly telephone calls and expressed some form anxiety of being left alone to at the end of the study.

'Do you know, that's the worst thing, when you've finished your course and the following Wednesday there's no phone call. It's horrendous isn't it?' *(Male, aged 67, focus group 2; 3 weeks into study)*

Some also felt that if there was some sort of follow up, they would feel more valued and get better satisfaction from participating in the intervention rather than having the feeling of being used and dumped.

'I think a follow up is a good idea. You need some sort of follow up after you've finished. How they do it, whether it's a phone call or a meeting with your doctor or whatever, your GP or anybody like that, I don't know how they would do it. But I think that's quite important that. Then you wouldn't feel as if you've been chucked on the scrap heap type of thing, you've finished, it's done. I think a good follow up would be beneficial to everybody' *(Male, aged 73, focus group 3; completed study)*

Theme 11: A group to facilitate social support would be beneficial and could facilitate maintenance of physical activity

Having participated in the home-based physical activity intervention and meeting fellow participants for the first time during focus group discussions, there was a general consensus that having frequent meetings among participants was vital as a means of peer support.

'I know it's just the start of this programme …, this is your first sort of thing on it but obviously there's things you'll find you can improve on. As far as feedback on it is concerned, maybe something about halfway through, maybe six weeks you could have a little meeting with some of the people just for half an hour, just have a little chat and see who's there, what's what, talk to people, something like that anyway. A little informal meeting or a social evening or whatever you want to call it. It lets everybody else know that it's not just you or another two or three people, it might be 20 people'*(Male, aged 73, focus group 3; completed study)*

The focus groups allowed participants to discuss their experiences of the intervention and their coping mechanisms, and allowed them to challenge their own and others' views.

'That [participants meeting up] might be good, after a couple of weeks, two, three, four weeks or whatever, see how people are getting on, what they think about it and what their progression is going to be. As I say, I've never met these folks until today' *(Male, aged 69, Focus group 3; week 11 of study)*

The idea of creating a walking group as a consequence of having frequent meetings with fellow participants was also seen as a possibility.

> 'You never know, out of that [participants meeting up] people might say, "Well I'm going out walking such and such," maybe get together to go out for a walk' *(Female, aged 64, Focus group 3; completed study)*

8.4 Discussion

The present qualitative study investigated the experiences of chronic heart failure patients participating in the Active-at-Home-HF intervention. Specifically, the aim was to identify barriers and facilitators to participation in this home-based physical activity intervention and overall adherence. Our findings suggested that there is a significant need for professional support for patient's living with heart failure in the context of lifestyle behaviour change.

Although physical activity is widely advocated for improved health, it is viewed as a very challenging and scary task for people living with chronic conditions. A particular issue of concern for the group of participants taking part in this study was the fear of falling (FOF) or collapsing and this was in line with previous research. FOF is thought to include concerns that normal activities of daily living could not be performed without falling, lack of confidence in maintaining gait during normal activities and being frightened of falling (Jung, 2008; Jefferis et al., 2014). FOF affects about 20-50% of the older adult population (Austin et al., 2007; Mendes da Costa et al., 2012) and may be a rational psychological response to previous falls, but is also reported by people who have not experienced a fall (Zijlstra et al., 2007). Fear was reported in the present study to be more of a psychological issue, although there were other limiting health conditions for example, arthritis. Family members and loved ones sometimes compound this fear by placing restrictions on what people with heart failure could or could not do.

Participating in cardiac rehabilitation was reported to reduce some of the psychological stress and fear associated with increasing and maintaining levels of physical activity. This was achieved by personal contacts with specialist doctors and cardiac rehabilitation staff who play an important role in patient education, motivation and confidence building. Just like community or clinic based cardiac rehabilitation, it is important for home-based interventions which target increased physical activity to be as holistic as possible (Haase et al., 2010). Duda et al., 2014 (Duda et al., 2014) noted that the outcomes of an exercise intervention depended on the intensity and type of support offered.

Having a lifestyle coach who was a qualified clinical exercise physiologist, trained in the use of behaviour change techniques and who understood the participants' condition thus providing personalised support was crucial in this study as it positively affected participants' motivation (O'Sullivan et al., 2010) and reduced anxiety thus improving adherence (Moore, Moore and Murphy, 2011). Coaches were available on scheduled appointments; usually weekly, to motivate participants with improving activity.

The presence of health and behavioural coaches has previously been reported to provide a sense of safety and comfort with an empathetic approach to coaching increasing trust (Winward et al., 2011; Desveaux et al., 2014, 2017). The positive feedback from the coach when participants achieved physical activity targets helped increase their self-confidence and assured them that they were capable of achieving goals they set out for themselves. The coaches were also useful in supporting participants to think of ways in which they could modify their everyday lifestyles to enhance activity and improve their general health.

When physical activity goals were achieved, participants reported noticing the changes in their general health and had a deep sense of pride in their achievements. Some participants noted they were now ready to reintegrate into society as they felt they had been given the right information and exposure to adequately take care of themselves independently without having to be afraid of an emergency.

The present study has also shown that integrating qualified medical personnel to support improved activity at home for patients with heart failure is vital and this adds credibility. Currently, cardiac rehabilitation in hospitals or community centres is the only option available to heart failure patients. This involves increased transportation costs that could be a barrier to participation, especially for people who may have limited financial resources or who are unable to drive.

The present intervention therefore comes as a timely alternative to help overcome this barrier and improve participation in activities of daily living. However, there are other factors which could serve as 'de-motivators' to home-based physical activity. In the UK where climatic conditions are quite unpredictable, having to go for walks in wet and windy or snowy conditions is perceived as a challenge. Furthermore, the location participants lived seemed to contribute to how little or how much activity couldbe maintained. Hilly areas were seen as a big hindrance for walking making patients very tired with onset of activity. The above limitations are particularly significant to our study population as heart failure patients often

have other comorbidities that may impair respiratory and metabolic function thus limiting exercise capacity.

In the present intervention, the coaches and participants worked out plans to overcome this challenge as much as possible. For instance, for some participants, the plan was to do more walking around their houses and local housing estates rather than walking further afield. For others, being chauffeured to the park where they found it more convenient and then walking back home afterwards seemed to be a better option.

Having a study follow up opportunity was reported as one of the ways in which improved activity could be sustained. Some participants expressed fear that they might not have the motivation to keep up their activity levels at the end of the study. This makes follow up particularly important considering approximately fifty percent of those who participate in physical activity programmes relapse and return to their previous physical activity states within six months (Dishman, 1991).

Furthermore, previous studies have reported that booster calls and follow ups are an effective way to motivate people to continue engaging in physical activity especially people who still have low level of physical functioning after cardiac rehabilitation (Yates et al., 2005) . In the present study, it was almost a unanimous idea from participants that some sort of walking group for heart failure patients would be beneficial for patients and could facilitate maintenance of physical activity / exercise. This notion had been previously emphasized by Moore et al., 2011 (Moore, Moore and Murphy, 2011) who described these groups as a strong form of social support where long term friendships were developed. This friendship was viewed as a strong support system for engagement and encouragement. In addition, these groups comprising friends with similar conditions can generate a sense of obligation to commit from one member to other members of the group thereby facilitating adherence to the intervention (Podlog and Dionigi, 2009).

Strengths and limitations

This qualitative study has several strengths. Firstly, the study was able to meet its aims by identifying barriers and facilitators to participation and adherence to the Active-at-Home-HF intervention. Although several qualitative studies have reported on the barriers and facilitators to self-care in chronic heart failure (Martensson, Karlsson and Fridlund, 1997; Rogers et al., 2000; De Lusignan et al., 2001; KN, BJ and SE, 2006; Riegel et al., 2009; Klersy et al., 2011;

Siabani, Leeder and Davidson, 2013), they were not specifically tailored towards physical activity.

To the best of our knowledge, this is the first study to adequately explore experiences of heart failure patients taking part in a home-based physical activity intervention. Desveaux et al., (2017) explored the experiences of COPD and Heart failure patients referred to community based exercise programmes following cardiopulmonary rehabilitation. Tierney and colleagues (Tierney et al., 2011) sought to understand the barriers and facilitators of physical activity among patients with heart failure. In line with the findings of this current qualitative study, the two studies referred to above reported themes which reflect fear and anxiety when engaging in physical activity, the role of family and health care professionals in boosting activity and bad weather being a significant barrier to engaging in outdoor activities. However, the latter study (Tierney et al., 2011) was a qualitative review of previous studies and did not provide a detailed account of the actual physical activity experiences of heart failure patients thus making our current findings timely in providing insights in this area. Another strength of the present study is the rigor in which it was conducted (i.e. the methodological quality). In order to increase trustworthiness of the data obtained, the study was designed and reported according to the 'consolidated criteria for reporting qualitative research COREQ' (Tong, Sainsbury and Craig, 2007) checklist. This involves utilising a number of methodological and reporting techniques/processes to increase the trustworthiness of the findings. In addition to this, it was felt that data saturation was reached from the number of focus group discussions conducted and data obtained (i.e. no deviant cases or themes emerged that were not later followed up on in subsequent discussions). In terms of the intervention, adherence was supported by provision of coaches who were exercise specialists, trained in the use of specific behaviour change techniques to support initiation and maintenance of physical activity, and they were experienced in working with clinical populations.

The sample of participants included those who had previously participated in a cardiac rehabilitation programme. This could be regarded as a limitation because it could be argued that these individuals were aware of the benefits of physical activity and may have offered bias views in this regard. However, this intervention was home-based and relied upon participants being motivated to continue outside of the supervised, group-based environment. Therefore, their views were valid in this regard. Furthermore, inclusion of individuals who had already completed a cardiac rehabilitation programme provided evidence for the usefulness of the programme as a means of supporting increased physical activity long-term.

The focus group facilitators had vast experience in running focus groups with participants involved in physical activity and exercise interventions. Their familiarity with this area of research may have set a nice ambience for participants to communicate freely without fear of being judged or misinterpreted, but this could also have prompted themes, which reflect the facilitators' personal preconceptions and biases. However, the facilitators were not involved in delivery of the intervention and had no participant contact except for focus group discussions. The findings from this study could be applied to a variety of chronic conditions and clinical settings, in order to improve care. However, the clinical team in the present study comprised of people who are advocates of physical activity. In clinical centres where physical activity is not adequately advocated, this could be a significant barrier to initial referrals to the programme and impact upon the likelihood that patients take up the offer of the programme and adhere to it in the long-term. Furthermore, it was clear from the responses generated from this qualitative study that enthusiastic clinicians who were advocates of physical activity in the context of heart failure were clear facilitators of initial uptake of the programme and continued participation. Patients were keen to continue following positive feedback from clinicians during routine appointments.

8.5 Conclusion

This study showed that participants with heart failure were willing and able to participate and remain in the Active-at-Home-HF (home-based physical activity) intervention and reported several facilitating factors. These included having the support of family members, health care professionals and a behavioural coach. Barriers included bad weather conditions, lethargy and other side effects from medications and limitations resulting from comorbidities such as arthritis. Levels of motivation may vary at different times and seasons of the year and is markedly different from person to person thus, support should be frequently available to ensure sustained motivation. The current study reinforces the importance of health care professionals being a source of motivation to patients (i.e. they should be advocates of physical activity and provide positive reinforcing feedback for continued participation) and the integration of regular behavioural change support (coaching) for heart failure patients in other to prevent relapse. The Active-at home- HF programme offers patients who cannot or who do not wish to travel to gyms and other community-based exercise facilities and services an option to increase their levels of physical activity at home either as a standalone programme or as a way of maintaining levels of physical activity post cardiac rehabilitation once that programme has come to an end. Patients often report that as a downside of such programmes (i.e. no continued support). Although physical activity programmes have to be

standardised to ensure they can be replicated and audited, it is important that the programmes maintain an individualised approach to patient care and mentoring so that maximal outcomes of these interventions can be achieved. In summary, the patients taking part in the Active-at-home HF programme reported it to be an acceptable intervention that helped them to overcome several barriers to increased physical activity. Most salient facilitators included seeing a clinician who advocated use of such a programme and who provided positive feedback; a programme that was tailored to the needs of individuals in terms of the amount and type of physical activity undertaken; and provision of a trained lifestyle coach who supported maintenance of increased physical activity. Barriers included other health conditions where patients were unsure whether increased physical activity could make either their condition or levels of fatigue worse or both.

A multicentre study trialling the current Active-at-Home programme in a number of clinical centres is required to determine whether this programme is acceptable across a range of clinical settings and to identify any issues to implementation. Findings from the present study will be used to support refinements to an intervention and to inform a prospective multicentre trial with an overall aim to integrate the Active-at-Home HF programme into the routine clinical care pathway.

CHAPTER 9: General discussion

The present thesis explored physical activity in HF, patient adherence, physiological benefits, patient experiences and how modern technologies may fit into routine clinical investigation for the purpose of patient assessment and monitoring.

Chapters 1through 3 described introduction, literature review of heart failure and physical activity in heart failure and methodology used in the research programme. Chapter 5 of the thesis investigated how two non-invasive technologies for assessment of cardiac output (Inert gas rebreathing and Bioreactance) compared with each other for assessing cardiac function at rest and in response to stress. To date, there has not been a consensus on the best technology to assess cardiac output non-invasively especially for routine use in clinical practice. Most studies which compared gas rebreathing with either invasive gold standard i.e. thermodilution (Gabrielsen *et al* 2002b) or non-invasive gold standard magnetic resonance imaging (Hassan *et al* 2017) confirmed that inert gas rebreathing is a valid method. Similarly, bioreactance has also been shown to be valid method for cardiac output monitoring (Raval *et al* 2008). With the results from the above studies, one would expect excellent agreement between the inert gas rebreathing and bioreactance methods when compared directly against each other. The present study, contained in Chapter 3, does not support this notion as it reveals significantly different cardiac output values at rest and during low exercise intensity (Okwose *et al* 2017) However, at higher intensities, both techniques showed comparable cardiac output values with acceptable limits of agreement. It can be suggested that the use of either inert gas rebreathing or bioreactance method for routine monitoring of cardiac output in clinical practice will depend on convenience and cost available to rehabilitation or other care services. While bioreactance is more convenient to use, it only measures cardiac and haemodynamic parameters and would need additional technology to measure metabolic/aerobic fitness unlike inert gas rebreathing, which is cheaper and can measure both metabolic and cardiac parameters although significant communication is warranted between patient and test coordinator.

Chapter 6 investigated the reproducibility of inert gas rebreathing for monitoring cardiac output at rest and different intensities of cardiopulmonary exercise test. Excellent reproducibility of bioreactance was previously demonstrated by our group (Jones *et al* 2015). The present research programme evaluated of reproducibility of the inert gas rebreathing method at rest and different levels of metabolic demand (exercise intensities). Results showed excellent reproducibility at rest and at peak exercise. The coefficient of variation for cardiac output and stroke volume was, however, >10% for cardiac output and stroke volume at low and submaximal exercise intensities. Based on these findings as well as simplicity-to-use, the

bioreactance was the method of choice for evaluating haemodynamic effect of Active-at-Home-HF intervention proposed in Chapter 5.

Chapter 7 described, feasibility and effectiveness of a novel, personalised home-based physical activity intervention (Active-at-Home-HF) in chronic heart failure. Using a pilot study design, data showed that is the intervention is safe, feasible and could lead to improvement in physical and haemodynamic function in patients with chronic heart failure. – Results demonstrated a significant increase in peak exercise stroke volume and submaximal exercise tolerance. Quality of life was also improved even though patients in the present study already had a relatively good quality of life compared to what might be expected from patients with chronic heart failure. A previous study (Cowie *et al* 2012) suggested that in older HF patients, maintaining quality of life might be a realistic aim for a physical activity or rehabilitation programme. Our results show great potential for Active-at-Home-HF to be used as an adjunct in HF management.

Chapter 8 explored experiences of HF patients participating in cardiac rehabilitation and the physical activity intervention. Information from patients was collected during the initial focus group meeting with the specific aim of identifying barriers and facilitators to uptake and continued participation in the programme. Two focus group discussions held during the intervention period together with the first focus group meeting showed that a personalised approach to an intervention aiming to increase physical activity in heart failure would yield positive results. Coaching was also reported as a facilitator to increasing levels of physical activity over time. Barriers included environments, i.e., places in which participants lived in terms of whether the area was suitable and safe for walking, poor weather conditions and other health conditions that may hinder physical activity attempts.

9.1 Implications for patients, practice and future research

The present thesis has proven to be timely and important because it i) provides a novel, personalised approach to help people living with heart failure improve and maintain their daily physical activity levels which may lead to improved quality of life, physical and cardiac function; ii) will provide health care teams with an additional tool to better manage their patients; and iii) can shape heart failure services in the NHS providing an effective, home-based solution. Thus, the studies in this thesis have the potential to impact on the health of those with HF, and on NHS resource use. There is a high level of interest currently amongst clinical care teams and commissioners about how to effectively support increase in physical activity in patients with long-term chronic conditions including heart failure.

Results of the present pilot study have informed development of an adequately powered clinical trial aiming to assess clinical and cost-effectiveness of the Active-at-Home-HF, which is currently subject to development, and submission of the NIHR Programme Development Grant application, which will lead to the Programme Grant. If clinical and cost-effectiveness of the Active-at-Home-HF are to be confirmed, it will be implemented into heart failure clinical care pathway. This will improve clinical practice, patient management and outcomes while leading to significant savings for the NHS, through reduction in heart failure associated hospital admissions, which can be expected because of increased physical activity in patients.

Patient Identification number for this trial:

<div align="center">

CONSENT FORM

</div>

Title of Project: Evaluation of inert gas rebreathing and bioreactance methods for assessment of cardiac output

Name of researchers: Mr Nduka Okwose, Mr Shakir Chowdhury, Dr David Houghton, Dr Djordje Jakovljevic Professor Michael Trenell.

Please initial box

1. I confirm that I have read and understand the information sheet dated …
   for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time,
   without giving any reason, without my medical care or legal rights being affected.

3. I agree to my GP being informed of my participation in the study.

4. I understand that my results will be kept completely anonymous.

5. I understand that my results will be confidential.

6. I understand that my data will be stored securely.

7. I understand that relevant sections of my medical notes may be looked at
   by individuals from the Research Team where it is relevant to my taking
   part in this study.

8. Any regulatory bodies who may audit at the CRF, Movelab
   may have access to my records.

9. I agree to take part in the above study.

_____   _____   _____
Name of patient   Date   Signature

_____   _____   _____
Name of person taking consent   Date   Signature
(If different from researcher)

_____   _____   _____
Researcher   Date   Signature

<div align="center">

1 for patient; 1 for researcher; 1 to be kept with hospital notes

</div>

Patient Identification number for this trial:

CONSENT FORM

Title of Project: Reproducibility of the inert gas rebreathing method for measuring cardiac output

Name of researchers: Mr Nduka Okwose, Mr Shakir Chowdhury, Dr Djordje Jakovljevic, Professor Michael Trenell.

Please initial box

1   I confirm that I have read and understand the information sheet dated …………… for the above study and have had the opportunity to ask questions.

2   I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my legal rights being affected.

3   I agree to my GP being informed of my participation in the study.

4   I understand that my results will be kept completely anonymous.

5   I understand that my results will be confidential.

6   I understand that my data will be stored securely.

7   I understand that relevant sections of my medical notes may be looked at by individuals from the Research Team where it is relevant to my taking part in this study.

8   Any regulatory bodies who may audit at the CRF, Movelab may have access to my records.

9   I agree to take part in the above study.

_____   _____   _____
Name of patient   Date   Signature

_____   _____   _____
Name of person taking consent   Date   Signature
(If different from researcher)

_____   _____   _____
Researcher   Date   Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Patient Identification number for this trial:

CONSENT FORM

Title of Project: Physical Activity in heart failure

Name of researchers: Dr Djordje Jakovljevic, Dr Jane Skinner, Dr Guy MacGowan, Dr Kristian Bailey, Dr Sarah Moore, Dr Leah Avery, Dr Nicki O'Brien, Dr Christopher Eggett, Nduka Okwose

Please initial box

1   I confirm that I have read and understand the information sheet dated 4th April 2016 (version 3.0) for the above study and have had the opportunity to ask questions.

2   I understand that my participant is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3   I agree to my GP being informed of my participation in the study.

4   I understand that my results will be kept confidential.

5   I understand that my data will be stored securely.

6   I understand that relevant sections of my medical notes and data collected during the study, may be looked at by members of the research team or individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

7   I agree to take part in the above study.

8   I agree, that if asked I will take part in a focus group discussion with the member of the research team and other participants recruited to the study for the purpose of this research.

_____   _____   _____
Name of patient   Date   Signature

_____   _____   _____
Name of person taking consent Date   Signature
(if different from researcher)

_____   _____   _____
Researcher   Date   Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept within medical records

Personalised home-based physical activity intervention

for older adults with HF:

Barriers and enabling factors to participation

Topic Guide

1	What are your thoughts about completing a physical activity programme at home/outside of the hospital environment?
2	Do you have any experiences of completing a physical activity programme at home/outside of the hospital environment?
3	What information would you need to help you decide whether or not to complete a physical activity programme at home? (Prompt: PA targets/prescription; those taking part in hospital rehabilitation, is this something they would consider afterwards?)
4	What type of support would you need to complete a physical activity programme at home?
5	What type of equipment, if any do you think you would need to complete a physical activity programme at home? (Prompt: clothing, shoes, activity monitors)
6	What are your thoughts about undergoing a series of examinations before and after completing a physical activity programme at home? (Prompt: advantages/disadvantages; would they provide reassurance?)
7	What would be the potential obstacles to completing a physical activity programme at home? (Prompt: other health problems; time, costs, need for support [practical/emotional])
8	How do you feel about completing a physical activity programme at home via the internet or using other technology such as a mobile phone? (Prompt: having to enter data regularly; self-monitoring progress [steps], receiving feedback and reminders)
9	Would you have any anxieties about completing a physical activity programme outside the hospital environment?
10	What would you hope to achieve by completing a programme of physical activity at home/outside the hospital environment?

Personalised home-based physical activity intervention

for older adults with HF:

Barriers and enabling factors to participation

<u>**Topic Guide: Group 2 (15th June 2016)**</u>

1	Could I start by asking you to share your thoughts about completing a physical activity programme at home? (How did you find it?)
2	Was there anything that you particularly liked or disliked about the programme?
3	What do you feel kept you motivated to keep going with the programme?
4	If you were asked to complete a physical activity programme at home, what sort of information would you need to help you decide whether or not to do it? (Prompt: PA information [why it would be good to do it], PA targets/prescription; those taking part in hospital rehabilitation, is this something they would consider afterwards?)
5	Did anyone need any extra support to complete the physical activity programme at home (Prompt: who/where from)?
6	Did anyone use any sort of equipment while taking part in the programme? (Prompt: clothing, shoes, activity monitors). What else might be needed?
7	What are your thoughts about undergoing a series of examinations before and after completing a physical activity programme at home? (Prompt: advantages/disadvantages; would they provide reassurance; are they needed long-term?)
8	Are there any obstacles to completing a physical activity programme at home? (Prompt: other health problems; time, costs, need for support [practical/emotional])
9	How do you feel about completing a physical activity programme at home via the internet or using other technology such as a mobile phone? (Prompt: having to enter data regularly; self-monitoring progress [steps], receiving feedback and reminders)
10	Did anyone have any anxieties about completing a physical activity programme outside the hospital environment?
11	What did you/do you hope to achieve by completing a programme of physical activity at home?
12	Would you recommend this programme to anyone else with HF? (Prompt: If yes, why? If no, why not?)

Appendix 3

MINNESOTA LIVING WITH HF® QUESTIONNAIRE

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

Did your HF prevent
you from living as you wanted during
the past month (4 weeks) by -

	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Appendix 4   Physical Examination Form

Name: _____   *DOB:* __/__/____

Body weight (kg):   _____   **Waist Circumference** (cm):   _____

%Fat Free Mass: _____   **% Fat Mass**:   _____

Apical pulse rate(min):   _____   **Rhythm**:   OK / Not OK

Resting blood pressure, seated.   ___ / ____

Auscultation of the lungs *with specific attention to uniformity of breath sounds in all areas (absence of rales and wheezes)*	OK / Not OK *Comment:*_____ _____	
Palpation of cardiac apical impulse *point of maximal impulse*	OK / Not OK *Comment:*_____ _____	
Auscultation of the heart *with specific attention to murmurs, gallops, clicks and rubs.*	OK / Not OK *Comment:*_____ _____	
Evaluation of the abdomen *Bowel sounds, masses, visceromegaly, and tenderness.*	OK / Not OK *Comment:*_____ _____	
Evaluation of lower extremities *Oedema and presence of arterial pulse.*	OK / Not OK *Comment:*_____ _____	
Inspection of the skin focus on lower extremities in people with diabetes.	OK / Not OK *Comment:* _____	
Neurologic function *Reflexes*	OK / Not OK *Comment:*_____	
Any orthopedic or medical condition that would limit exercise.	YES / NO *Comment:*_____	
Ventricular tachycardia	OK / Not OK *Comment:*_____	
ST elevation (+1.0 mm) in leads without diagnostic Q-waves (other than V_1 or aVR)	OK / Not OK *Comment:*_____ _____	
ST or QRS changes *such as excessive ST suppression >2mm horizontal or down sloping ST-segment depression*	OK / Not OK *Comment:*_____ _____	
Arrhythmias other than: *sustained ventricular tachycardia, including multiple PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias.*	OK / Not OK *Comment:*_____ _____ _____.	

Cleared to start exercise test   **YES / NO**
Competed by: _____   Date   _____

Physical examination (page 2 on reverse of page 1)

Exercise Stress Testing
Exercise Protocol: _____

Absolute indicators for terminating the Exercise Stress test:

Drop in blood pressure of >10mm Hg *from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia.*	OK / Not OK *Comment:*_____ _____ _____
Any form of chest pain or shortness of breath	OK / Not OK *Comment:*_____ _____
Increasing nervous system symptoms (e.g. ataxia, dizziness or near syncope)	OK / Not OK *Comment:*_____ _____
Technical difficulties monitoring ECG or blood pressure	OK / Not OK *Comment:*_____ _____
Ventricular tachycardia	OK / Not OK *Comment:*_____
ST elevation (+1.0 mm) in leads without diagnostic Q-waves (other than V_1 or aVR)	OK / Not OK *Comment:*_____ _____
ST or QRS changes *such as excessive ST suppression >2mm horizontal or down sloping ST-segment depression*	OK / Not OK *Comment:*_____ _____
Arrhythmias other than: *sustained ventricular tachycardia, including multiple PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias.*	OK / Not OK *Comment:*_____ _____ _____
Fatigue, shortness of breath, wheezing, leg cramps, or patient develops discomfort.	OK / Not OK *Comment:*_____ _____
Development of bundle-branch block or intraventricular conduction delay *that cannot be distinguished from ventricular tachycardia*	OK / Not OK *Comment:*_____ _____
Hypertensive response Systolic blood pressure of > 250 mm Hg and / or diastolic pressure of >115 mm Hg	OK / Not OK *Comment:*_____ _____

Comments:

_____
_____
_____

Adverse reaction to exercise: **YES / NO**
Cleared to start exercise: **YES / NO**
Competed by: _____   Date _____

Appendix 5 Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire
Name: _____

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Date of Birth: _____

Please choose

1. Has your doctor ever said that you have a heart condition and that   YES
    you should only do physical activity recommended by a doctor?   NO

2. Do you ever feel pain in your chest when you do physical activity?   YES
                                                                           NO

3. Have you ever had chest pain when you are not doing physical activity? YES

                                                                           NO

4. Do you ever feel faint or have spells of dizziness?   YES
                                                                           NO

5. Do you have a joint problem (also back problem) that could be made   YES
    worse by exercise?   NO

6. Have you ever been told that you have high blood pressure?   YES
                                                                           NO

7. Do you have any breathing problems?   YES
                                                                           NO

8. Do you have any problems with your liver, thyroid, kidneys or   YES
    have diabetes?   NO

9. Are you currently taking any medication?   YES
    If so, what? _____ Reason _____   NO

10. Are you pregnant, have you had a baby in the last 6 months,   YES
    or do you plan to have a baby this year?   NO

11. Has your mother or father had any heart problems?   YES
                                                                           NO

12. How many times a week do you do exercise: _____   YES
                                                                           NO

13. Is there any other reason why you should not participate in physical activity? YES
    If so, what? _____   NO

Signed by (staff): _____ Print: _____
Date: _____

Appendix 6 Evaluation of Medical History

Medical Diagnosis:

History of cardiovascular disease	YES	NO
Peripheral vascular disease	YES	NO
Hypertension	YES	NO
Diabetes	YES	NO
Pulmonary disease	YES	NO

Previous Physical Examination

Have you had anything reported previously
from a physical examination?   YES   NO

History of symptoms

Discomfort in the chest, jaw, neck, back or arms
(e.g. *pressure, tingling, pain, heaviness,*
burning, tightness, squeezing or numbness)   YES   NO

Light headedness , dizziness or faint?   YES   NO

Recent Illness

Hospitalisation, new medical diagnosis, surgery   YES   NO
Details   _____
        _____

Orthopaedic problems

Arthritis, joint swelling,
anything which would make exercise difficult   YES   NO

Medication use

Medication   YES   NO
Details   _____
        _____

Allergies
Details   _____
        _____

Other habits

Caffeine	YES	NO	if yes, units per week	___
Alcohol	YES	NO	if yes, units per week	___
Tobacco	YES	NO	if yes, units per week	___

Exercise history

Frequency (/week)	1	2	3	4	5	6	7	8
Duration per session (min)		10	20	30	40	50	60	70

Work history

Focus on current of expected physical demands

Family history

Cardiac	YES	NO
Pulmonary	YES	NO
Metabolic disease	YES	NO
Stroke	YES	NO
Sudden death	YES	NO

Comments:
        _____

_____

Competed by   _____   Date   _____

Appendix 6   Telephone Record Sheet

Patient ID _____ Researcher _____

Week of intervention _____ Today's date ____/_____/_____

Time call started _____ Time call finished_____ Duration _____

Self-monitoring

Steps each day (record day of week)

Day 1 _____ Day 2 _____ Day 3 _____ Day 4 _____

Day 5 _____ Day 6 _____ Day 7 _____

Goal setting

Agreed goal
Look at days of the week (weekday vs. weekend day). Active days?
Ideally, we would like you to achieve 2000 steps more that what you would do normally each day
How do you feel about this target? Achievable? Experience any problems? Positive reinforcement
(i.e. any increase is positive, but how do you think you could increase further?).
Reflect upon baseline. May need to reassess goal, record new goal

Agreed goal: Try where possible to record the t**ype of activity** undertaken, **how much** (number of steps/minutes) where, **how often** and **with who.** Encouraging this level of detail will increase the

Reassessment of goal: Check if the person is happy with what they are **currently achieving** (if reaching their target for instance) and **ask would you like to make any changes to your goal?** They might say 'no, I'm happy with it as it is' close by saying something like,

Barrier identification and problem solving

Barriers to increasing activity? Friends/Family?	Problem solving: If they don't identify
Can you think of a solution? Get patient to think about this rather than providing the answer	any solutions to problems, and you struggle to help them, simply ask them to
You may want to go back over this in the follow up calls	have a **think about how they could overcome those problems for next time.**

Prompt review of behavioural goals

Pedometer information	Goals: To increase self-efficacy comment on **how close a person is**
Calculate if patient is meeting targets	**to their goal even if they aren't**
Are any changes needed?	**reaching it** – i.e. they've made progress from last time – how could they increase further next time? Does the person want to **amend their goal to attain a higher target** when things are going well, or a more realistic target when they are having trouble reaching their previous goal.

Patient to reflect	Success: Use this to
Increased levels of activity through cardiac rehab? Refer back to cardiac rehab techniques to increasing levels of activity.	reassure participants they can succeed again.
When I was succeeding… I can do it again	

Planning social support

Patient planning their future physical activity/exercise
Will this involve partner/family/friends/community support?
Emotional support of others?

Summary

Go through agreed action points	As well as making sure the patient has
Make sure patient has understood – reflected upon issues	understood, summarise to check with the patient that you have understood.
Patient has agreed to the summarised points	By briefly summarising what has been agreed, you show that you have listened. Use phases like, 'you said you weren't a fan of XXX activity, therefore you're going to give XXX a go instead. Have I got that right?

Appendix 7

Activity Planner

DAY	GOAL Minutes / Steps / Other	ACTIVITY When? Where? Who with? How long for?	ACHIEVED Minutes / Steps / Other
MONDAY			
TUESDAY			
WEDNESDAY			
THURSDAY			
FRIDAY			
SATURDAY			
SUNDAY			

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