The Effects of Low Frequency Electrical Muscle Stimulation in Advanced Heart Failure

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Abstract Summary

Aims: To investigate Low Frequency Electrical Muscle Stimulation (LF-EMS) in the advanced Chronic Heart Failure (CHF) population: 1) Characterise the physiological stimulus of LF-EMS, 2) Determine the feasibility of a Randomised Controlled Trial (RCT) in the CHF population, 3) Investigate effect of LF-EMS on vascular function.

Methods and Results: Study one*:* Nine healthy males (mean age: 24.0 ± 3.1 yrs) and 6 male patients with CHF (New York Heart Association class III-IV, mean age: 67.7 ± 14.1 yrs) undertook a 45-minute bout of LF-EMS (4Hz, continuous) of the legs. Oxygen uptake (VO_2), was measured at 5-minute intervals along with multiple haemodynamic variables. VO_2 increased in both groups (P<0.001), although patients with CHF demonstrated higher percentage of their maximal VO_2 (5.8% [95%CI: 2.6, 7.9% :P<0.001]). Haemodynamic variables increased in both groups consistent with moderate exercise.

Study two: Sixty participants with CHF were randomised to 8-weeks (5 x 60 minute per week) of LF-EMS (n=30) or 'sham' placebo (n=30). Recruitment, dropout and adherence were measured in addition to Six-Minute Walk Distance (6MWD) and quality of life (QoL). Sixty of 171 eligible participants (35.08%) were recruited, 12 (20%) patients withdrew. Forty-one patients (68.3%), adhered to the protocol (≤70% of sessions). There were no significant differences between groups in 6MWD(P=0.13) and QoL (P=0.55).

Study three: This study measured endothelial function using Flow Mediated Dilation (FMD) and maximal VO_2 in a smaller cohort (LF-EMS n=20, 'sham' n=15). There was some evidence of enhanced FMD following LF-EMS

compared to ‘sham’.

Conclusions: Study one: LF-EMS can elicit a significantly greater cardiovascular response in patients with CHF compared to healthy individuals. **Study two**: People with CHF can be recruited to and tolerate LF-EMS studies; a larger RCT in this population is technically feasible. **Study three**: Patients with CHF using LF-EMS could gain prognostically significant improvements in endothelial function.

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Definition of Terms

Afterload: the ‘load’ against which the LV must eject blood during systole

Arteriovenous oxygen difference: the difference between arterial and venous content of oxygen. It is greater during exercise than at rest, and in trained versus untrained individuals

Augmentation Index (AIx): an indirect measure of arterial stiffness, AIx. describes the amount of additional (augmented) afterload contributed by reflected pulse waves from the arterial tree

Beta-receptor/beta-agonist: beta agonists (e.g. adrenalin, dobutamine) act on beta receptors to stimulate increased heart rate, myocardial contraction and blood pressure

Cardiac myocyte: myocardial muscle cell

Cardiac output: the volume of blood pumped by the heart each minute

Cardiac Rehabilitation (CR): a multidisciplinary approach to restoration and improvement of physical, psychological and social function

Cardiopulmonary Exercise Test (CPET): maximal cycle exercise test with ventilatory gas analysis

Catecholamines: a group of neurotransmitters e.g. adrenalin that act on the sympathetic nervous system to stimulate fight or flight responses such as increased heart rate, blood pressure and blood glucose levels

Chronic Heart failure (CHF): diagnosis with underlying physiology of insufficient cardiac output to meet metabolic demand

Chronotropic incompetence: the inability of the heart to increase its rate in relation to increased activity or demand

Concentric ventricular hypertrophy: a thickening of the walls of the heart with a corresponding reduction in chamber size

Coronary Heart Disease (CHD): reduced coronary artery blood flow due to atherosclerotic stenosis

Diastole: the relaxation phase of the cardiac cycle between aortic valve closure (emptying of the ventricle) and mitral valve closure (filling of the ventricle)

Dyspnoea: breathlessness

Electrical Muscle Stimulation (EMS): also known as neuromuscular electrical stimulation (NMES) or functional electrical stimulation (FES), EMS is the elicitation of muscle contraction using electric impulses

Endocardium: inner layer of LV myocardium

Endothelial dysfunction: a condition in which the endothelial layer (the inner lining) of the small arteries fails to perform all of its important functions normally, primarily vasodilation

Epicardium: outer layer of the LV myocardium

Fibrosis: abnormal formation of fibrous tissue

Flow Mediated Dilatation (FMD): the most commonly used non-invasive assessment of vascular endothelial function in humans, involving artery diameter measurement before and after a reactive hyperaemia stimulus

Heart Rate Reserve (HRR): the difference between an individual's resting heart rate and maximum heart rate

Hyperkalaemia: raised levels of potassium (>5.5mmol/l) in the blood stream which can lead to palpitations and in severe cases cardiac arrest

Left Ventricle (LV): myocardial chamber responsible for systemic circulation

Low Frequency-Electrical Muscle Stimulation (LF-EMS): a sub-tetanic form of EMS developed by Minogue et al (Minogue, Caulfield and Reilly, 2007), that, due to its frequency of 4-5Hz, creates a 'shivering' contraction that can be tolerated continuously

Left Ventricular Ejection Fraction (LVEF) percentage of end diastolic volume ejected during systole

Left ventricular hypertrophy (LVH): enlargement of the LV myocardium

Left Ventricular Systolic Dysfunction (LVSD): impairment of LV systolic function

Mean Arterial Pressure (MAP): the average blood pressure during a single cardiac cycle

Mitral regurgitation: back flow of blood from the left ventricle into the left atrium, due to stenosis of the mitral valve

Muscle ergoreflex: the reflexes initiated by sympathetic mechanical and metabolic changes in a working muscle

Myocardial infarction (MI): cardiac myocyte necrosis following ischemic insult

Myocardium: the muscle middle layer of the heart that allows the wall to contract

Necrosis: cell death

Neurohormonal activation: the compensatory neural and hormonal mechanisms triggered by a drop in cardiac wall pressure, chiefly the sympathetic nervous and renin-aldosterone-angiotensin-systems

Oedema: swelling in the feet, ankles and legs

Peak oxygen uptake (VO_2 peak, ml.kg-1.min-1): the highest O_2 uptake attained during exercise. Preferred to maximal oxygen uptake (VO_2 max) in patient populations as a true VO_2 max is rarely achieved

Pericardium: a double walled sac containing the heart and the roots of the large blood vessels

Preload: the amount of sarcomere stretch experienced by cardiac muscle cells, called cardiomyocytes, at the end of ventricular filling during diastole

Pulmonary congestion: the accumulation of an abnormal amount of blood in the vascular bed of the lungs

Pulse Wave Velocity (PWV): a measure of arterial stiffness, or the rate at which pulses from the heart travel down the circulatory tree

Randomised Clinical Trial (RCT): a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention

Regional Wall Motion Abnormality (RWMA): an abnormal motion of a region of the heart muscle normally caused by recent myocardial infarction. It is a term commonly used in echocardiography

Renin-Angiotensin-Aldosterone System (RAAS): neurohormonal system essential for the maintenance of fluid and sodium balance and cardiovascular haemodynamics

Reverse LV remodelling: any reversal of pathological alterations to LV mass, size, geometry and/or function, either spontaneously or in response to therapy

Stroke Volume (SV): the volume of blood pumped by the left ventricle in each beat

Sympathetic nervous system: branch of the autonomic nervous system responsible for vasoconstriction, increased heart rate and increased LV contractility and relaxation

Systole: contraction phase of the cardiac cycle between mitral valve closure (filling of the ventricle) and aortic valve closure (emptying of the ventricle)

The Fick principle: that cardiac output can be calculated as the quotient of total body oxygen consumption divided by the difference in oxygen content of arterial blood and mixed venous blood

Valvular stenosis: a narrowing or thinning of any of the heart valves

Vasoconstriction: the narrowing of a blood vessel caused by contraction of the muscular walls of the vessel

CHAPTER 1: Introduction

1.1 Thesis Context

Chronic Heart Failure (CHF) is a long-term condition defined by the inability of the chambers of the heart to fill with and pump blood around the body. Following acute or chronic injury to the heart, there is a maladaptive response to maintain cardiac function that progressively leads to reduced cardiac output, muscle weakness and eventual decompensation (failure) of the heart. The main symptoms are fatigue and breathlessness on minimal exertion which impact heavily on quality of life as the disease progresses. This condition has a prevalence of 1–2% of the adult population in developed nations (Mosterd and Hoes, 2007), and affects approximately 26 million people worldwide (Ambrosy *et al.*, 2014). In the UK, it is estimated that 900,000 people suffer from this debilitating condition with as many people undiagnosed (*Chronic heart failure : management of chronic heart failure in adults in primary and secondary care : quick reference guide*, 2010). Despite reductions in mortality of related conditions such as coronary heart disease, the number of patients with CHF are expected to increase over time. Hospital admissions due to CHF are projected to rise by 50% over the next 25 years despite an age adjusted reduction of hospitalisation of 1.5% per annum since 1992 (Mosterd and Hoes, 2007).

Patients with CHF experience frequent hospital admissions that make daily living and social activities difficult, resulting in social isolation and poor quality of life. Furthermore, the disease has a worse prognosis than many other conditions (e.g. cancer); 30- 40% of patients diagnosed with CHF die within a year (2019). As well as the cost to the individual, CHF is an expensive condition to treat. The estimated total annual cost of CHF is 2% of all UK health

care costs (Stewart *et al.*, 2002). Thus, despite considerable progress in the management of patients with CHF, mortality and morbidity remain a major healthcare concern for the national health service in the UK (Corrà *et al.*, 2003).

The 2016 European guidelines (Ponikowski *et al.*, 2016) for the diagnosis and treatment of acute and CHF have incorporated a class IA recommendation (strongly recommended for benefit) for regular aerobic exercise in patients with CHF to improve functional capacity and symptoms. Unfortunately, many patients are unable to gain the considerable benefits of exercise due to the debilitating nature of their condition. Electrical Muscle Stimulation (EMS) involves attaching electrodes to large muscles (normally legs) in order to artificially induce muscle contraction via a battery operated controller. The beneficial effects of EMS as an alternative to exercise training for the CHF population are relatively well documented, including evidence of improved functional capacity, leg strength and quality of life (Harris *et al.*, 2003; Karavidas *et al.*, 2010; Sillen *et al.*, 2009). However, it is uncertain whether the advanced CHF population could practically use or tolerate EMS. Moreover, little is known about the physiological mechanisms by which EMS can mediate benefits. A better understanding of these factors may help develop EMS protocols that maximise benefits to the most debilitated CHF sufferers.

The aim of this thesis was therefore to investigate the efficacy of Low Frequency Electrical Muscle Stimulation (LF-EMS, a novel method of continuous EMS) in patients with advanced CHF. Specifically, three studies were planned and carried out with the following aims:

Study one: characterise the mechanisms by which LF-EMS provides an

aerobic response in the CHF population compared to healthy individuals during an acute bout.

Study two: determine the feasibility of conducting a larger definitive trial into the efficacy of LF-EMS in the advanced CHF population.

Study three: examine the effects of eight weeks of continued LF-EMS use on vascular function in the CHF population.

CHAPTER 2: Review of Literature

2.1. Introduction

Chronic Heart Failure (CHF) is a condition characterised by the reduced ability of the heart to pump blood around the body, leading to muscle weakness, breathlessness and fatigue. It is a debilitating and complex condition with multiple causes making it difficult to treat. As the disease develops, patients are hospitalised more frequently, presenting with 'fluid overload': oedematous ankles, pulmonary congestion and severe dyspnoea caused by insufficient cardiac output. Treatment involves antagonism of the neurohormonal activation of the body (which attempts to maintain cardiac output via water and sodium retention) with medication. There are few treatment options after medication has been optimised and many patients are non-compliant. Exercise has been introduced as a complimentary therapy for this population. The benefits of exercise in CHF are well established. Conventional exercise rehabilitation has been incorporated into American Heart Association (AHA) (Yancy *et al.*, 2017), European Society of Cardiology (ESC) (Ponikowski *et al.*, 2016) and National Institute for Clinical Excellence (NICE) (Taylor, Moore and O'Flynn, 2019) guidance. Regular aerobic exercise in patients with CHF has been shown to reduce symptoms of breathlessness, improve abnormalities in skeletal muscle and lead to a better quality of life (Davies *et al.*, 2010). Unfortunately, those with advanced CHF become so deconditioned they cannot take more than a few steps without becoming breathless, and so are unable to gain the benefits of cardiac rehabilitation (CR). For those CHF patients unwilling or unable to

exercise, EMS may offer an alternative. In the last 20 years, studies into the use of EMS in patients with CHF have shown that it can provide similar benefits to exercise, reducing dyspnoea, improving leg strength and quality of life (Harris *et al.*, 2003; Karavidas *et al.*, 2010; Sillen *et al.*, 2009). However, it is uncertain whether the effects of EMS would be as effective in the advanced CHF population.

The following literature review initially provides an overview of the pathophysiology of CHF, the benefits of exercise training to attenuate this condition, and the barriers to exercise for patients with CHF. Thereafter, the role of EMS is discussed as a possible alternative treatment to exercise in clinical populations. Finally, a review of the physiological effects of EMS and LF-EMS in the advanced CHF population is provided before the presentation of the subsequent aims of this thesis.

2.2. Pathophysiology and Treatment of Chronic Heart Failure

Chronic Heart Failure is a complex clinical syndrome that results from any structural or functional impairment of filling or ejection of blood from the heart (Yancy *et al.*, 2013). There is no single diagnostic test for CHF because it is largely a clinical diagnosis based on a careful history and physical examination. CHF may result from disorders of the pericardium, myocardium, endocardium, heart valves, larger arteries, or from metabolic abnormalities (Fleg *et al.*, 2015). However, most patients with CHF have symptoms resulting from Left Ventricular Systolic Dysfunction (LVSD) i.e. reduced cardiac output (Yancy *et al.*, 2013). The most debilitating symptoms of CHF are dyspnoea, early

muscular fatigue, and fluid retention which may lead to pulmonary congestion and/or peripheral oedema (Hunt *et al.*, 2009). These symptoms can limit exercise tolerance and functional capacity, thus reducing quality of life and the ability to carry out daily tasks of living. A more detailed description of the physiological stages that lead to advanced CHF is provided below in order to explain clearly how treatments and interventions might best attenuate the condition.

2.2.1. Mechanism of Chronic Heart Failure

Many forms of heart disease can lead to CHF, and there is no single mechanistic cause. Instead, a series of maladaptive responses to an insult, injury or remodelling stimuli lead to cardiac dysfunction and ultimately CHF (Sisakian, 2014). Typically, CHF begins with an injury to the heart (Fig. 2.1.) such as an acute Myocardial Infarction (MI). However, other chronic conditions can also cause detrimental remodelling of the heart such as: ischemia, valvular disease, hypertension, inflammation, metabolic derangements, muscular dystrophies, sensitivity and toxic reactions (alcohol, cocaine, and chemotherapy), infiltrative disorders (amyloid) or genetic disorders e.g. hypertrophic cardiomyopathy (Maurer *et al.*, 2007). Describing the pathophysiological processes that drive the progression of CHF illustrates where therapies such as exercise can be beneficial.

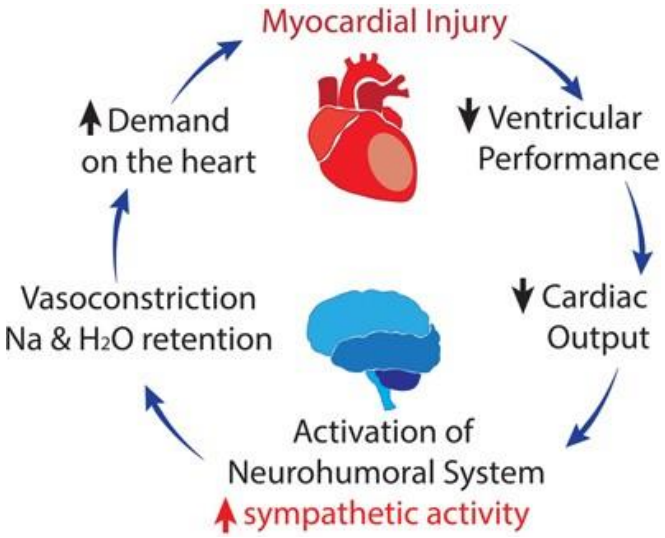


Fig. 2.1. The Vicious Cycle of CHF.

An injury to the myocardium results in reduced cardiac output. The neurohormonal activation of the sympathetic and renin-angiotensin-aldosterone (RAAS) systems compensate initially promoting vasoconstriction, sodium and water retention. However, this ultimately leads to greater demand on the heart, remodelling and deterioration in cardiac function. This can occur quite quickly following acute MI or chronically over several years (Booth, May and Yao, 2015).

2.2.2. Insult/Injury/Remodelling Stimuli

Cardiac dysfunction, which presents as a reduction in Cardiac Output (CO) can be due to both acute and/or chronic causes. For example, acute MI due to an occluded coronary artery can results in necrosis of large portions of the ventricle wall. This section of the ventricle develops areas of regional wall motion abnormality (RWMA) affecting systole i.e. emptying of the ventricle. Conversely, chronic untreated hypertension can lead to increased afterload, valvular stenosis and regurgitation of blood back through the aortic or mitral valves. In both RWMA and valve regurgitation, the heart is unable to contract appropriately, resulting in a reduction in Ejection Fraction (EF), Stroke Volume (SV) and consequently CO. This reduced CO translates into a lowered peak oxygen uptake (VO_2peak) and exercise capacity, exhibited by premature fatigue and dyspnoea. Exercise Interventions like CR can be employed acutely after

MI to minimise the size of infarction by improving coronary circulation to stunned areas of the myocardium, and thus reduce detrimental remodelling. Exercise can also be used preventatively in hypertensive patients to improve vascular function, reduce both peripheral and central blood pressure and slow down the chronic progression of disease (Erbs *et al.*, 2010; Dawson *et al.*, 2008). Unfortunately, exercise/CR at this early stage of CHF is not widely available or adhered to (Karmali *et al.*, 2014) even though it can maintain cardiac function and quality of life for many years before the condition deteriorates (Haykowsky *et al.*, 2007).

2.2.3. Neurohormonal Activation

The fall in CO resulting from the MI is detected by baroreceptors in the aortic arch that detect a drop in arterial wall tension, and this activates several neurohormonal pathways (Piepoli *et al.*, 2010). Although these neurohormonal pathways are initially compensatory and beneficial, eventually they lead to detrimental remodelling of the myocardium (discussed in more detail in 2.2.4.). The three main neurohormonal pathways are: the Sympathetic Nervous System (SNS), the Renin-Angiotensin-Aldosterone-System (RAAS) and Vasopressin; also known as Anti Diuretic Hormone (ADH). The SNS responds first to a fall in CO via baroreceptors in the heart and arteries (Fig. 2.2.), by releasing catecholamines (e.g adrenalin), into the circulation to increase heart rate (HR) and myocardial contractility to compensate for any loss in function (Hosenpud and Greenberg, 2006).

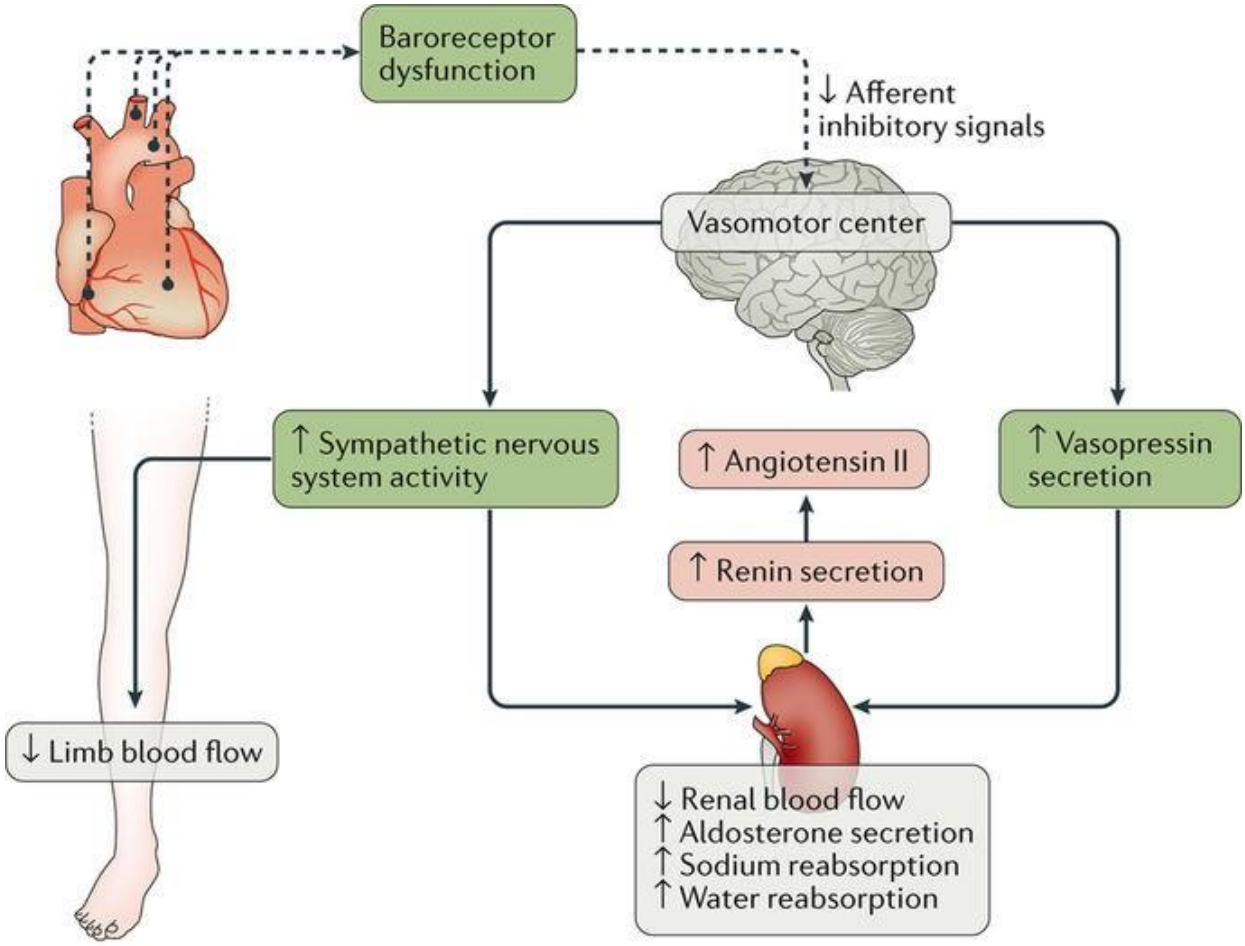


Fig. 2.2. The Neurohormonal Response to Cardiac Dysfunction.
Falling CO is detected by baroreceptors and leads to activation of compensatory mechanisms in order to restore haemodynamic homeostasis (Hartupee and Mann, 2017).

Although increased sympathetic activity initially maintains arterial blood volume and cardiac function, the consequences of the chronic elevations of catecholamines can elicit increased ischemia, provoke arrhythmias, and promote systemic and pulmonary vasoconstriction (Maurer *et al.*, 2003; Maurer *et al.*, 2005). This vasoconstriction increases venous return, maintaining SV via the Frank Starling mechanism (Maurer *et al.*, 2007). However, the increased venous return (preload) whilst beneficial in the short term, has negative effects after many years. The increased peripheral vascular resistance resulting from systemic vasoconstriction causes greater arterial blood pressure (afterload), eventually leading to cardiac and vascular remodelling. Increased sympathetic

activity additionally stimulates the RAAS (Hosenpud and Greenberg, 2006), leading to further arterial vasoconstriction, sodium and water retention and the release of aldosterone. The increased aldosterone levels perpetuate sodium and water retention, causing endothelial dysfunction and ultimately organ fibrosis (Kitzman *et al.*, 2002). Also known as vasopressin, ADH is released by the hypothalamus and is also stimulated by the RAAS in response to low CO. ADH promotes fluid retention, enhances water reabsorption by the kidneys and leads to a fall in plasma sodium concentration (Maurer *et al.*, 2005). These three neurohormonal mechanisms have the combined effect of increasing water and sodium retention and blood volume in patients with CHF whilst reducing endothelial function to limit peripheral blood flow. This ultimately leads to increased peripheral vascular resistance and an increased pressure on the ventricle wall of the heart. Regular physical activity at this stage of the CHF continuum can attenuate these neurohormonal mechanisms (Erbs *et al.*, 2010) by reducing vasoconstriction and hence afterload by increasing blood flow to the skeletal muscles (See section 2.4.3.).

2.2.4. Ventricular Remodelling of the Myocardium

The heart remodels differently depending on the nature of the injury/insult sustained (Fleg *et al.*, 2015). Localised necrosis of the myocardium caused by MI leads to RWMA of the cardiac wall, promoting ongoing remodelling almost immediately. The heart then becomes less elliptical and more spherical, as ventricular mass and volume increase. With chronic pressure overload as in aortic stenosis or hypertension, *concentric ventricular hypertrophy* develops in response to increased ventricular wall stress/afterload caused by sodium/water retention and vasoconstriction over many years. In this condition (Fig. 2.3.a),

the ratio between wall thickness and ventricular cavity size increases, i.e. a thicker wall with a reduced LV chamber size; hypertrophic cardiomyopathy (Passino *et al.*, 2006; Fleg *et al.*, 2015). Another way in which the heart remodels is by *eccentric hypertrophy*, i.e., cavity dilation, (Fig. 2.3.b). This is called dilated cardiomyopathy and can be caused by a genetic predisposition to bacterial/viral infection, pregnancy, toxins or chemotherapy (Yancy *et al.*, 2013).

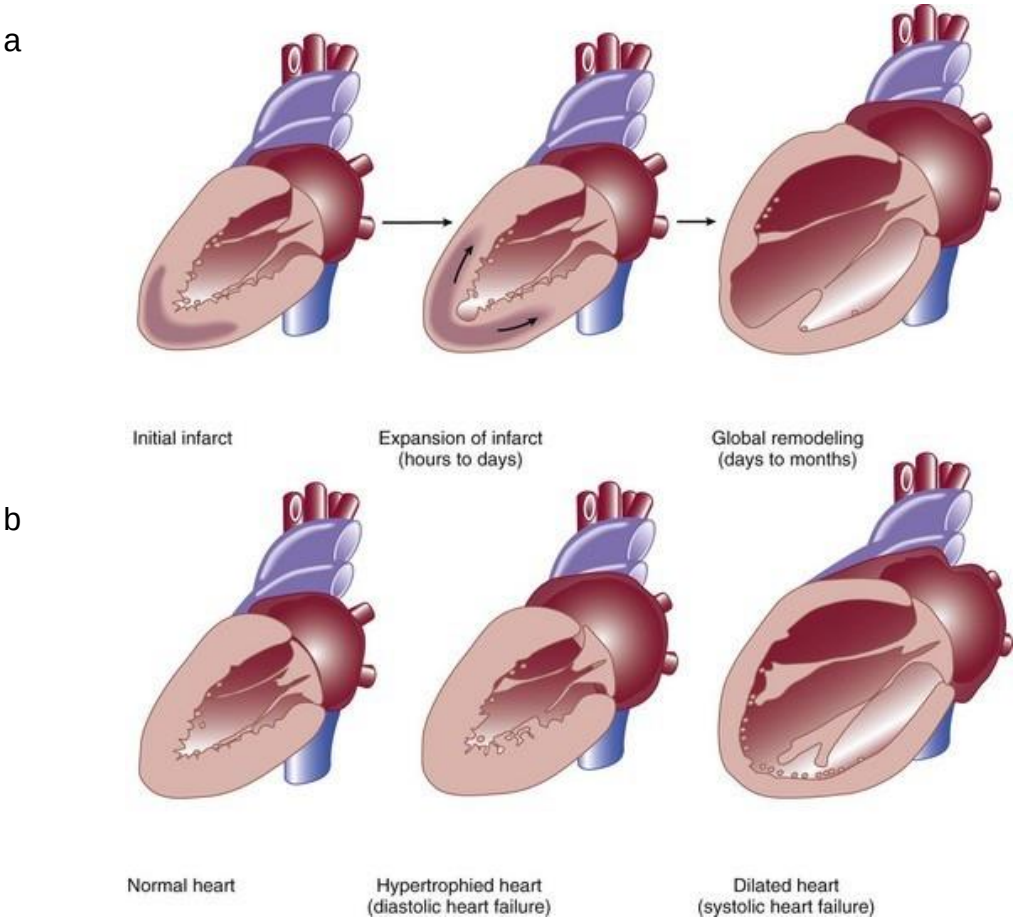


Fig. 2.3. Left Ventricle (LV) Remodelling After Acute Myocardial Infarction. (a) Remodelling after acute MI, resulting in a dilated LV with global systolic dysfunction. (b) Ventricular remodelling in diastolic and systolic CHF. Note the differences in LV morphology in hypertrophied versus dilated cardiomyopathies (Jessup and McCauley, 2003).

Irrespective of acute myocardial necrosis, chronic pressure overload or genetic predisposition, the same stages of the disease outlined above are present and

the outcome is the same on quality of life: cardiac function ultimately deteriorates, leading to the detrimental cycle of decreased exercise capacity, breathlessness and reduced activity level (Piepoli *et al.*, 2010; Fleg *et al.*, 2015). Even at the later stages of the disease, regular exercise can attenuate this remodelling by improving peripheral O_2 efficiency, maintaining cardiovascular function and reducing afterload, to slow down the progression of CHF. Unfortunately, many advanced CHF patients eventually become demotivated or avoidant of activities that bring on symptoms of dyspnoea such as exercise. Therefore alternative therapies are needed for use in this population.

2.2.5. Morbidity and Mortality in the Chronic Heart Failure Population

The compensatory physiological mechanisms described previously i.e. increased sympathetic activation, increased water/sodium retention and ventricular remodelling, can maintain myocardial function and stability for many years. However, in the long-term, CHF patients experience acute decompensation: a sudden worsening of dyspnoea, oedema and fatigue requiring lengthy hospitalisation. The progressive deterioration in cardiac function leads to reduced VO_2peak, further compounded by the avoidance of symptom provoking physical activity. Over time, patients experience muscle atrophy due to inactivity and become more deconditioned, and the cycle of decline gets progressively worse. Eventually this leads to low quality of life, frequent hospitalisation and death (Oeing, Tschöpe and Pieske, 2016; Hosenpud and Greenberg, 2006). Therapies and treatments with the potential to reverse this condition particularly in the most debilitated stages are hence of great importance and urgently required.

2.2.6. Classification of Chronic Heart Failure

Clinical markers of cardiac dysfunction such as EF do not necessarily correlate strongly with diminished exercise capacity or symptoms of breathlessness in CHF patients (Froelicher and Myers, 2006). This is because other factors relating to the efficiency of the peripheral tissues (discussed in more detail in section 2.4.2.) and oxygen utilisation can determine the severity of the condition experienced by patients (Minotti *et al.*, 1991). The New York Heart Association (NYHA) functional classification system was developed to define the degree of limitation /of CHF symptoms and exercise tolerance (New York Heart Association. Criteria Committee. and New York Heart Association., 1979), and is commonly used to distinguish stages of the disease (Table 2.1.).

This system enables mild, moderate and severe CHF patients to be targeted separately (if required) in terms of treatment and clinical research. As stated earlier, this thesis is concerned with the most debilitated group of CHF patients (NYHA III-IV), who have marked limitation in physical activity and are hence unable or unwilling to exercise normally.

Table 2.1. New York Heart Association (NYHA) functional classification system taken from American Heart Association (AHA) guidelines (New York Heart Association. Criteria Committee. and New York Heart Association., 1979).

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of CHF
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of CHF.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of CHF.
IV	Unable to carry on any physical activity without symptoms of CHF, or symptoms of CHF at rest.

2.3. Pharmacological Treatment of Chronic Heart Failure

The goals of treatment in patients with CHF are to improve their clinical status, exercise capacity and quality of life, prevent hospital admission and reduce mortality (Ponikowski *et al.*, 2016). Medications that antagonise the neurohormonal pathways i.e. Angiotensin Converting Enzyme Inhibitors (ACEIs), Mineralocorticoid Receptor Antagonists (MRAs) and beta-blockers (Table 2.2.) have been shown to improve survival in patients with CHF and are recommended for the treatment of symptoms unless contraindicated or not tolerated (Ponikowski *et al.*, 2016; Hunt *et al.*, 2009; Yancy *et al.*, 2013).

Table 2.2. Pharmacological Treatments indicated in Patients with Symptomatic (NYHA Class II-IV) CHF(Ponikowski *et al.*, 2016).

Recommendations	Class[a]	Level[b]	Reference(s)
An ACEI is recommended in addition to a beta-blocker for symptomatic patients with HFrEF to reduce the risk of CHF hospitalisation and death	I	A	(Garg and Yusuf, 1995; Packer *et al.*, 1999; Yusuf *et al.*, 1991)
A beta-blocker is recommended in addition to an ACEI, for patients with stable symptomatic HFrEF to reduce the risk of CHF hospitalisation and death	I	A	(Hjalmarson *et al.*, 2000; Clark *et al.*, 2017; Packer *et al.*, 1996; Packer, 1997; Packer *et al.*, 2001; Packer *et al.*, 2002)
An MRA is recommended for patients with HFrEF who remain symptomatic despite treatment with an ACEI and a beta-blocker, to reduce the risk of CHF hospitalisation and death	I	A	(Pitt *et al.*, 1999; Zannad *et al.*, 2011)

ACEI, angiotensin-converting enzyme inhibitor; CHF, chronic CHF; HFrEF, CHF with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist

[a] Class of recommendation. i.e. I : strong, IIa: moderate, IIb: (weak),III: (no benefit)

[b] Level of evidence. i.e. A: highest quality (systematic review), B-R: moderate quality (randomised controlled trials), B-NR: moderate quality (non-randomised trials), C-LD: observational studies (limited design), C-EO: consensus (expert opinion)

By inhibiting the formation of angiotensin II, ACEIs suppress sympathetic activity, prevent action of the RAAS and sodium and water excretion. This promotes vasodilation, reducing arterial blood volume and pressure as well as ventricular preload and afterload. The combined effect of these actions over time inhibit negative remodelling of the myocardium (Flather *et al.*, 2000). ACEIs have been shown to reduce mortality and morbidity in patients with CHF and are recommended unless contraindicated or not tolerated in all symptomatic patients (Yancy *et al.*, 2017; Teo *et al.*, 2002; Flather *et al.*, 2000). Common adverse effects of ACEI's include dry cough, hyperkalaemia and fatigue (Teo *et al.*, 2002). Consequently, not all patients with CHF can tolerate this treatment.

There is strong evidence that beta-blockers and ACEIs are complementary, and can be started together as soon as CHF is diagnosed (Packer, 1997; Hjalmarson *et al.*, 2000). Beta-blockers inhibit adrenalin and angiotensin release, lowering HR and blood pressure (Packer, 1997). They reduce mortality and morbidity in symptomatic patients with CHF, separately and alongside treatment with an ACEI and, for many patients, a diuretic (Hjalmarson *et al.*, 2000).

Mineralocorticoid/aldosterone receptor antagonists (MRAs) stop the action of receptors that bind to aldosterone and block the RAAS, and with different degrees of efficacy, other steroid hormone (e.g. corticosteroids, androgens) receptors. These medications are recommended in all symptomatic patients (in combination treatment with an ACEI and a beta-blocker) with CHF and EF ≤35%, to reduce mortality and hospitalisation (Ponikowski *et al.*, 2016).

Common side effects including stomach pain and dizziness mean again that not all people with CHF can tolerate this medication (Pitt *et al.*, 1999).

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with CHF. A Cochrane meta-analysis has shown that in patients with CHF, loop and thiazide diuretics appear to reduce the risk of death and worsening CHF compared with placebo (Oeing, Tschöpe and Pieske, 2016; Faris *et al.*, 2012). Compared with control, diuretics appear to improve exercise capacity (Faris *et al.*, 2012; Oeing, Tschöpe and Pieske, 2016).

2.3.1. Non-Adherence to Prescribed Medication in Chronic Heart Failure

Despite the known benefits of medications, non-adherence in the CHF population is high (Fitzgerald *et al.*, 2011). The prevalence of non-adherence is difficult to accurately measure, however, in some reports, only 10% of patients were compliant with CHF therapies (Hauptman, 2008), with up to 64% of readmissions resulting from poor adherence (Leventhal *et al.*, 2005). Reasons for non-adherence in CHF are mainly psychosocial (see section 2.5.2), and can be related to apathy and depression regarding their poor condition and quality of life (Kop, Synowski and Gottlieb, 2011). Programmes of CR are designed to improve exercise capacity, improve confidence (by undertaking exercise safely), reduce isolation and encourage patients to remain compliant with medications. However, the same psychosocial reasons that prevent medication compliance e.g. apathy, depression are a barrier to exercise. A different intervention that could confer similar benefits to exercise and be more easily adhered to would

be beneficial.

In summary, medications that antagonise the neuro-hormonal pathways i.e. ACEIs, beta blockers and MRAs, have strong evidence for attenuating disease progression and improved survival in patients with CHF. However, medications are not always tolerated or complied with and therefore adjuncts/alternatives are required.

2.4. Pathophysiology of Exercise Intolerance in the Chronic Heart Failure Population

Before the benefits of exercise can be fully illustrated, a more detailed description of the mechanisms of exercise intolerance in CHF is required. Exercise intolerance is the primary symptom of CHF due to dyspnoea and fatigue, and is a strong prognostic indicator of morbidity and reduced quality of life (Kitzman *et al.*, 2002). It is normally characterised by a reduction in VO_2peak during maximal effort exercise (Fleg *et al.*, 2015). The Fick equation (below) explains the relationship between exercise capacity and cardiac performance:

$$VO_2 = Q\ (a\text{-}vO_{2\ diff})$$

(VO_2: oxygen consumption; Q: cardiac output; $a\text{-}vO_{2\ diff}$: arteriovenous oxygen difference)

The Fick equation demonstrates that exercise capacity is dependent upon central CO, (Q) as well as peripheral ($a\text{-}vO_{2\ diff}$) O_2 uptake mechanisms. Exercise intolerance in CHF is caused by an impairment in both

musculo-skeletal and cardiac function. In addition, the delivery of oxygen from the heart to the working muscles during exercise is decreased further by endothelial dysfunction (vasodilatory impairment affecting blood flow). Combined, these factors significantly reduce exercise tolerance in CHF patients although each factor may be attenuated with appropriate intervention (Adams and Niebauer, 2015). Below, the role that a dysfunctional central circulation, musculoskeletal system and peripheral vasculature play in exercise response in people with CHF is examined.

2.4.1. Central Limitations of Chronic Heart Failure During Exercise

People with CHF often achieve less than 50% of the maximal CO achieved by healthy individuals during peak exercise (Sullivan and Hawthorne, 1995). The decreased CO in CHF patients at submaximal and peak levels of effort is a result of a reduction in SV coupled with a lower heart rate reserve (HRR) (Sagar *et al.*, 2015; Sullivan *et al.*, 1989). The HRR i.e. the potential HR increase above resting levels, is often reduced (chronotropic incompetence) more substantially (Fig. 2.4). in CHF patients due to the sympathetically-driven elevation in resting HR (Piña *et al.*, 2003). In people with CHF, a decrease in beta-receptor density leads to a diminished sensitivity of the beta-adrenergic pathway and a decrease in beta-agonist stimulated muscle contractility (Bristow *et al.*, 1990). Therefore, people with CHF must rely, to a greater extent, on increases in HR to supplement CO to compensate for their inadequate SV during physical exertion. However, without the parasympathetic ‘ brake’ on resting HR, patients with CHF have less HRR to sustain physical exertion, and

so they reach VO_2peak earlier than their healthy counterparts (Brubaker and Kitzman, 2011).

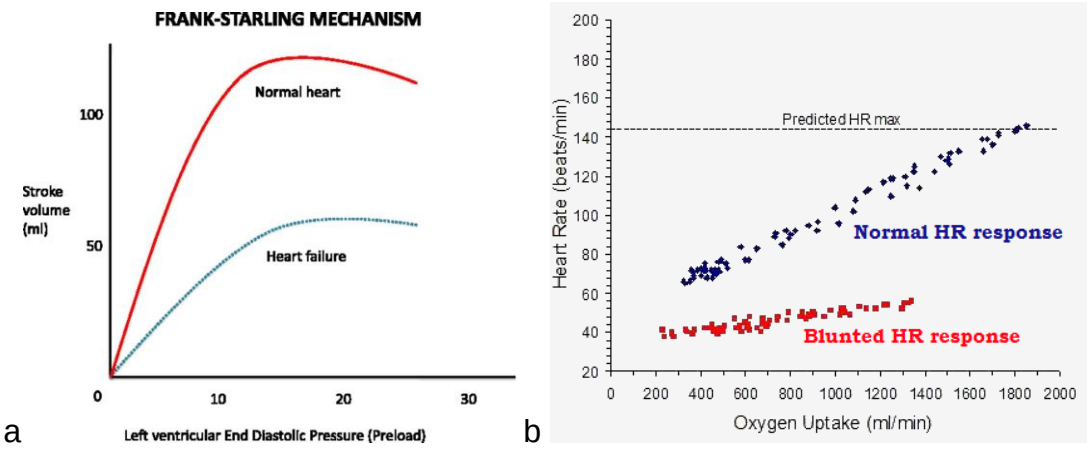


Fig 2.4. (a) Reduced SV and (b) HR in CHF Compared to the Normal Heart (McArdle, Katch and Katch, 2014).

The response of the heart to exercise in CHF is typified by inadequate LV shortening with increases in end-systolic and end-diastolic volumes i.e. increased filling but reduced emptying/low EF (Erbs *et al.*, 2010; Witte and Clark, 2007). The need for an increased left ventricular filling pressure to maintain CO, results in reduced pulmonary diffusion owing to interstitial oedema, which leads to breathlessness and fatigue during exertion (Witte and Clark, 2007). Despite severe cardiac dysfunction, measures of LVSD (EF, CO) relate poorly to exercise capacity and symptoms,(Franciosa, Park and Levine, 1981) suggesting that the limiting symptoms lie in the periphery.

2.4.2. Peripheral Limitations of Chronic Heart Failure During Exercise: Skeletal Muscle

Central limitations on CO reduce the amount of oxygenated blood that can be delivered to active tissues in the periphery. To assist blood flow and maintain sufficient arterial pressure during exercise in CHF patients, the arteries supplying skeletal muscles experience enhanced sympathetic vasoconstriction

(Sullivan *et al.*, 1989). This limits muscle perfusion during exercise (as explained in section 2.4.3.), contributing to a decreased exercise capacity i.e. earlier fatigue of muscle. Chronically this leads to muscle dysfunction (myopathy) and reduced strength, which additionally limits CHF patients during exercise. Key features of the skeletal myopathy of CHF are:

- muscle fibre atrophy (Harrington *et al.*, 1997; Clark, Rafferty and Arbuthnott, 1997).
- fibre type shift from oxidative to glycolytic (Massie *et al.*, 1988; Minotti *et al.*, 1991).
- decreased capillary density (Drexler and Coats, 1996; Schaufelberger *et al.*, 1997).
- rapid depletion of high energy phosphates during exercise (Massie *et al.*, 1988).
- decreased mitochondrial density/oxidative enzyme content (Clark, Poole-Wilson and Coats, 1996; Middlekauff, 2010).

Muscle biopsies of CHF patients have shown this detrimental change from oxidative muscle to anaerobic, quickly fatiguing muscle (Massie *et al.*, 1988; Minotti *et al.*, 1991). Consequently there is an inverse correlation (Mancini *et al.*, 1989) between the percentage of type IIb (fast twitch) fibres in CHF and exercise capacity (Massie *et al.*, 1988). This chronic muscle weakness within CHF may account for the failure of many therapies targeted at the heart to improve exercise tolerance. Low LVEF, increased left atrial pressure, and other haemodynamic determinants measured at rest do not predict exercise capacity in CHF as the primary limiting factor is in the peripheral tissues (Sullivan *et al.*,

1989; Franciosa, Park and Levine, 1981). Adaptations to the skeletal muscle, such as those seen following exercise training (Adamopoulos *et al.*, 1993; Clark, Poole-Wilson and Coats, 1996) are therefore highly desirable, and may be more beneficial to CHF sufferers than conventional medication alone (Clark, Poole-Wilson and Coats, 1996).

2.4.3. Peripheral Limitations of Chronic Heart Failure During Exercise: Endothelial Dysfunction

Markers of skeletal muscle dysfunction i.e. fibre type shift, atrophy, decreased capillary density, are a result of decreased blood flow during exertion caused by chronic sympathetic activation (Middlekauff, 2010). The vascular endothelium plays an important role in the regulation of arterial tone and, hence, blood flow to exercising muscles. This occurs through complex mechanisms that stimulate and control the release of nitric oxide (NO), a potent vasodilator (Gielen *et al.*, 2003). Release of NO is stimulated by increased laminar shear stress, such as that which occurs during physical activity. Decreases in pulsatile blood flow (Birk *et al.*, 2012) caused by chronic inactivity (inherent in CHF) leads to decreased NO levels and lowered vasodilatory function (Harris *et al.*, 2008). Vasoconstriction and reduced blood flow to the exercising muscles in CHF is further compounded by chronic RAAS activation in response to reduced CO (Fleg *et al.*, 2015; Hambrecht *et al.*, 1998). The RAAS activation results in release of angiotensin II resulting in a decrease in the half-life of endothelium-derived NO and subsequent endothelial dysfunction (Sandri *et al.*, 2016). Sympathetic activation causes further peripheral vasoconstriction, as elevated catecholamine levels at rest rise further with exercise in patients with CHF, an indication of advanced disease (Erbs *et al.*, 2010). Endothelial dysfunction in

the CHF population has emerged as an important prognostic indicator (Katz *et al.*, 2005; Shechter *et al.*, 2009) and target for treatment in CHF. Therapies such as exercise that increase shear stress and target oxidative fibres i.e. stimulate an aerobic response, offer potential to preserve vascular function and consequently improve blood flow to skeletal muscle. In this way, regular exercise (if the patient can tolerate it) can preserve and potentially enhance skeletal and vascular dysfunction, increase exercise capacity and lead to improved quality of life.

2.5. The Benefits of Exercise on Chronic Heart Failure

Based on the potent effects exercise has on peripheral vascular function and central haemodynamics, exercise training is a beneficial treatment for patients with stable CHF and is recommended by the European Society of Cardiology (ESC) (Ponikowski *et al.*, 2016), the American College of Cardiology and the American Heart Association (AHA) (Hunt *et al.*, 2009). Systematic reviews evaluating the efficacy of exercise training in CHF patients (Flynn *et al.*, 2009), report reductions in hospitalisation and improvements in VO_2peak and peak exercise duration (Davies *et al.*, 2010), both of which are positively correlated with prognosis. Subjective symptoms, e.g. perceived dyspnoea and exertion, functional class, and quality of life measures also improve after training (Flynn *et al.*, 2009; Davies *et al.*, 2010). As well as exercise capacity, exercise training In CHF patients can positively affect central haemodynamic function, autonomic nervous system function, peripheral vascular and muscle function (Sagar *et al.*, 2015). These adaptations allow an individual to exercise at a lower HR and level of effort for a given workload and hence perform more tasks of daily living without symptoms (Fletcher *et al.*, 2013).

The effects of exercise on central haemodynamic function in CHF are less well established than the overall effect on exercise capacity and quality of life (Fleg *et al.*, 2015). A meta-analysis of 14 trials (including 812 patients) demonstrated that aerobic exercise at moderate intensity led to small but significant improvements of LVEF (mean difference: 2.59%, 95% confidence interval (CI): 1.44–3.74%), compared with usual care (Passino *et al.*, 2006; Haykowsky *et al.*, 2007). Whether these improvements are clinically meaningful, i.e. improved symptomology or exercise capacity, is hard to determine. Thus, whilst exercise training appears to lead to small central adaptations that potentially slow the deterioration of cardiac function in clinically stable CHF patients, peripheral improvements (in vascular and muscular dysfunction) have greater effects on exercise capacity.

Regular exercise training in CHF patients leads to adaptations that reverse many of the histochemical features of skeletal myopathy listed in section 2.4.2. (Corrà *et al.*, 2003; Hambrecht *et al.*, 1995). These include: decreased skeletal muscle atrophy and fibre type shift (Hambrecht *et al.*, 1995), increased density and oxidative capacity of the mitochondria (Adamopoulos *et al.*, 1993), reduced depletion of phosphocreatine and excessive acidosis during exercise (Conraads *et al.*, 2002). Adaptations have been observed within 2 months of initiation of an exercise programme (Middlekauff, 2010). Regular physical activity counteracts muscle wasting by restoring a favourable anabolic/catabolic balance (Mann and Reid, 2003; Hambrecht *et al.*, 1995), controlling hyperactive muscle ergoreflexes and ultimately improving muscle strength (Piepoli *et al.*,

1996). Exercise training in CHF patients also leads to improved vascular function (Sandri *et al.*, 2016). Studies have demonstrated that regular exercise in the CHF population decreases circulating catecholamine levels (Passino *et al.*, 2006), has anti-inflammatory (Gielen *et al.*, 2003; Conraads *et al.*, 2002) and antioxidative effects (Linke *et al.*, 2005), reduces natriuretic peptide concentrations (Conraads *et al.*, 2004) and increases shear stress and nitric oxide bioavailability (Ennezat *et al.*, 2001). These adaptations cumulatively reduce peripheral vasoconstriction, improve endothelial function (vasodilation), enhance blood flow to skeletal muscle during activity and increase exercise capacity (Davies *et al.*, 2010). Thus, regular exercise can attenuate the symptoms of CHF and make daily activities of living easier e.g. walking, climbing stairs etc.

2.5.1. Effects of Aging, Frailty and Comorbidities on Patients with Chronic Heart Failure

Approximately 88% of CHF deaths and 75% of CHF hospitalisations occur in person's age ≥ 65 years (Fang *et al.*, 2008). Up to 20% of adults over the age of 80 years have CHF (Fang *et al.*, 2008). Because of the natural ageing process and the progression of CHF over time, many older patients become less active. This can lead to muscle atrophy, further deconditioning and reduced exercise capacity that exacerbates their condition (Fleg *et al.*, 2015). Many patients are therefore limited not just by CHF but also by frailty, muscle wasting and comorbidity (sarcopenia, osteoarthritis) that further reduce mobility and balance, making exercise interventions nearly impossible (Murad and Kitzman, 2012; Krumholz, 2013). Interestingly, inactivity alone does not account for all of the skeletal myopathy present in patients with CHF

(Middlekauff, 2010). Muscle atrophy from inactivity affects primarily the postural muscles, and not the muscles of the arms and those involved in breathing, whereas the skeletal myopathy of CHF is systemic (Adamopoulos *et al.*, 1993) and hence more debilitating. Perhaps because of this the prevalence of CHF increases after middle-age (Benjamin *et al.*, 2017) when people become generally less active.

The effects of aging, multiple comorbidities, and frailty make exercise training in older CHF patients even more challenging than in their younger counterparts (Fleg *et al.*, 2015). The discovery of alternative means of exercise therapies for CHF patients too frail to exercise is important to give a viable treatment option after medication has been optimised. However, older patients are significantly under-represented in CHF studies, especially those involving exercise training (Kitzman and Rich, 2010; Fleg *et al.*, 2015; Heiat, Gross and Krumholz, 2002). The average age of CHF patients in the community is currently >77 years, however in an analysis of 59 general CHF trials conducted from 1985–1999 in > 45,000 patients, the average age of participants was only 61.4 years (Heiat, Gross and Krumholz, 2002). Furthermore, in the HF-ACTION trial, the largest trial of exercise training in CHF to date, the mean age of participants was 59.5 years (O'Connor *et al.*, 2009). This is likely because older more advanced patients with CHF show poor uptake adherence to clinical trials due to hospitalisation, frailty and depression (Nieminen *et al.*, 2015). Clinical trials targeting this challenging CHF population are needed to test the efficacy of exercise-based interventions to improve symptoms and prognosis. Importantly, if exercise is too difficult to perform or adhere to, alternative strategies are

required. Investigating the feasibility, tolerance, safety and impact of such alternative interventions for CHF patients are the main aims of this thesis.

2.5.2. Barriers to Adherence of Exercise Programmes

Although the benefits of exercise to the CHF population are considerable, many are unable to tolerate or adhere. The HF-ACTION trial (O'Connor *et al.*, 2009), addressed the efficacy and benefits of exercise training in patients with CHF (O'Connor *et al.*, 2009; Flynn *et al.*, 2009; McKelvie, 2008). This was a multicentre, randomised, controlled trial (RCT) designed to measure the effects of exercise training on clinical outcomes in medically optimised and stable patients with systolic CHF (LVEF ≤35%). The primary endpoint of all-cause mortality was modestly significant (hazard ratio: 0.89; P = 0.03) i.e. exercise was clinically beneficial, but additional analysis revealed no significant difference in mortality (16% vs. 17%) between the exercise and control group, respectively (O'Connor *et al.*, 2009). The impact of the exercise intervention was reduced by the generally low rate of adherence in the training group, where only 30% of individuals exercised at or above the target volume. Potentially effective interventions like exercise are of little use if patients with CHF do not adhere to them. A Cochrane review of the literature since June 2001 (Karmali *et al.*, 2014) evaluating interventions aimed at improving uptake and adherence to CR programmes in CHF found that few practical recommendations could be made (Sagar *et al.*, 2015). Individual barriers to exercise that need to be overcome include physical and psychological comorbidities, frailty caused by muscle atrophy, impaired cognition, sleep disturbances, and poor health literacy

(Kop, Synowski and Gottlieb, 2011). Exercise is introduced to CHF patients as a new behaviour, and as with all behaviour change, many factors are involved in successfully initiating and maintaining it for the long term (Karmali *et al.*, 2014).

Even discounting any recent inactivity due to CHF itself, the majority of CHF patients referred to a CR programme for exercise training begin at a completely sedentary baseline level of activity (Artinian *et al.*, 2002; Kop, Synowski and Gottlieb, 2011), and so find any level of activity hard to tolerate. Many patients therefore, particularly those with advanced CHF, are often so limited that they are unable to gain the holistic benefits of exercise. Alternative interventions that can stimulate the same adaptations as traditional exercise should therefore be investigated for this group.

In summary, medication can be used effectively to manage CHF symptoms although not all patients can tolerate the side effects or do not comply with the recommended dose and or prescribed regime. Exercise can be extremely beneficial for attenuating the progression of the disease, however more elderly or advanced CHF patients become too inactive and frail to exercise, or do not adhere to exercise due to many psycho-social factors. For these reasons, exercise-based studies have excluded patients with more advanced CHF, even though they are arguably more in need of evidence-based interventions. One potentially valuable alternative therapy that has been suggested for this under-represented population is electrical muscle stimulation (EMS). The next section of this review will focus on EMS in more detail.

2.6. Electrical Muscle Stimulation: Key Concepts

Using electrical stimulation to produce muscle contraction is not a novel procedure. In 1790, Luigi Galvani first observed motion after applying electrical wires to the leg muscles severed from the body of frogs, and in 1831, Michael Faraday demonstrated that electrical currents could stimulate nerves to create active movement (Cambridge, 1977). One of the earliest clinical experiments that used electrical stimulation for muscle function in 1961, stimulated the peroneal nerve in the leg in an effort to correct foot drop during ambulation in persons with stroke-related hemiplegia (Liberson *et al.*, 1961). Since then, electrical stimulation parameters have been optimised to treat a wide variety of conditions from spinal cord injuries (SCI) to incontinence (Jones *et al.*, 2016). The following review of EMS starts with a brief description of the main types of electrical stimulation. Following this the various parameters that can be modified are discussed to illustrate appropriate methods of EMS for patients with advanced CHF.

2.6.1. Types of Electrical Stimulation

Transcutaneous Electrical Nerve Stimulation (TENS) is a form of electrical stimulation utilised for pain relief. Historically used at high frequencies, (Deyo *et al.*, 1990) it is now also administered at very low frequencies, (2-10 Hz) (Sluka and Walsh, 2003). TENS propagates along smaller afferent sensory fibres than the larger motor nerves that lie deeper in muscle tissue. This is specifically to override pain impulses e.g. during labour. When very low frequencies are used, TENS specifically targets sensory nerve fibres on the skin surface and does not

activate motor fibres; therefore, no discernible muscle contraction is produced. Functional Electrical Stimulation (FES) has been utilised to reproduce the activation pattern of muscles in persons unable to actively perform these movements. Predominantly the application for FES has been with spinal cord injury or stroke patients (Carty *et al.*, 2012; de Kroon *et al.*, 2005; Eser *et al.*, 2003). FES has been utilised to recreate the activation pattern of lower extremity muscles to produce human gait (Kesar *et al.*, 2010) and cycling (Yeh *et al.*, 2010; Griffin *et al.*, 2009). The use of FES in patients with SCI can improve neural activity below the level of the injured spine, while reducing muscle atrophy, improving CV function (Gibbons *et al.*, 2016) and overall health (Vanderthommen and Duchateau, 2007; Yeh *et al.*, 2010).

Electrical muscle stimulation (EMS) or neuromuscular electrical stimulation (NMES) as it is also termed, is currently used in many forms to facilitate changes in muscle action and performance (Doucet, Lam and Griffin, 2012; Alon and V Smith, 2005). In clinical settings, EMS can be used for improving muscle strength, increasing range of motion, reducing oedema, decreasing atrophy, healing tissue, and decreasing pain (Doucet, Lam and Griffin, 2012). This stimulation (EMS), is specifically designed to produce muscle tetany and contraction that can be used for “functional” purposes and can be found in the literature as early as 1964 (Valenti, 1964). It is termed EMS because of its ability to produce repeated contractions of the ambulatory muscles that has been investigated in populations with muscle weakness, i.e. CHF, cancer, Chronic Obstructive Pulmonary Disease (COPD) (Jones *et al.*, 2016).

2.6.2. Parameters of Electrical Muscle Stimulation

Not all EMS protocols can be considered the same due to the high variability of stimulation parameters (Doucet, Lam and Griffin, 2012). An exploration of how these variables interact is useful to understand how protocols can be manipulated to target different populations and effect different outcomes.

2.6.2.1. Frequency

The frequencies of electrical stimulation used can vary widely depending on the goals of the task or intervention, but most clinical regimens use 20-50Hz patterns (Baker, Bowman and McNeal, 1988; de Groot *et al.*, 2006). This range of frequency stimulation produces a smooth tetanic contraction and avoids excessive fatigue or pain, optimising improvements in muscle strength (Bhadra and Peckham, 1997; Baker, Bowman and McNeal, 1988). Frequencies between 20-50Hz require an on/off stimulation pattern to allow muscles time to recover in between contractions. Recently, Minogue and colleagues (Minogue, Caulfield and Reilly, 2007) have developed a Low Frequency Electrical Muscle Stimulation (LF-EMS, discussed in more detail in section 2.8.) protocol at 4-5Hz that allows continuous sub-tetanic contraction to be tolerated.

2.6.2.2. Pulse Duration

The time span of a single pulse is known as the pulse width or pulse duration. In biphasic pulses (a positive/ negative wave, used in EMS for better comfort/contraction), the pulse duration includes both phases (Fig. 2.5. below) (McLoda and Carmack, 2000). Dynamic quadriceps extensions similar to those used in cycling exhibit pulse durations between 300µs-600µs (Eser *et al.*, 2003; Kebaetse, Turner and Binder-Macleod, 2002).

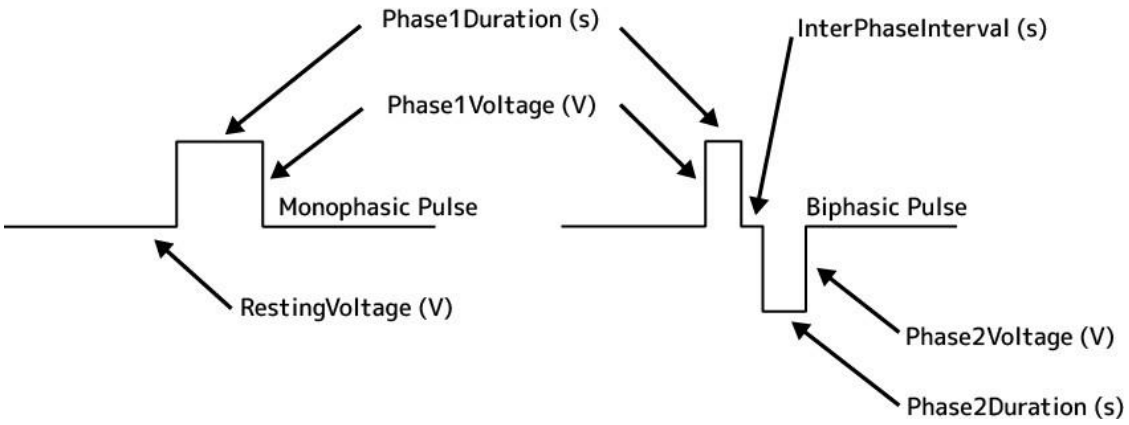


Fig. 2.5. Pulse Parameters (Baker, Bowman and McNeal, 1988)

Investigators have suggested that stimulation with pulse durations that mimic the pulse durations of the human body (300µs-600µs), will fatigue fibres at a slower rate than longer pulses (Kralj, Bajd and Turk, 1988). Much shorter pulse durations (10µs-50µs) appear to limit the number of muscle fibres recruited, but generate a larger maximum torque resulting in a greater stimulus for strength improvement (Gorgey *et al.*, 2009). Conversely, longer pulse durations (500µs-1000µs), can recruit more fibres and thus produce stronger contractions as they penetrate more deeply into subcutaneous tissues, but fatigue muscle fibres more quickly (Kralj, Bajd and Turk, 1988). The optimal pulse duration for muscle strength is therefore currently unclear.

2.6.2.3. Duty Cycle

Cycling pulses on and off (intermittent stimulation) is a common practice at higher (tetanic) frequencies to preserve force of contraction, reduce muscle fatigue and increase tolerance for the patient. Hence, most CHF studies using EMS have employed intermittent stimulation for improving muscle strength. The duty cycle describes the on and off time of the EMS protocol used and is

usually stated in a ratio form, such as 1:2 e.g.10 seconds of contraction, then 20 seconds recovery. Common clinical applications use a 1:3 duty cycle as standard, but this ratio can be modified to accommodate the tolerance of the patient as well as the goals of the treatment (McPhee *et al.*, 2008), e.g. muscle strength or endurance. The sub-tetanic LF-EMS protocol does not require a duty cycle because it can be tolerated continuously. It is the continuous nature of LF-EMS that may have a therapeutic application for CHF patients because it can stimulate an aerobic response and hence stimulate slow oxidative fibres that are dysfunctional in this population (Banerjee *et al.*, 2005).

2.6.2.4. Intensity/Amplitude

Another parameter that contributes to overall fatigue is the strength of the current being administered or the intensity/amplitude (usually reported in milli-amperes, mA) with which the stimulation is delivered. The higher the intensity, the stronger the depolarising effect on the muscle tissues underlying the electrodes (Mesin *et al.*, 2010). Higher intensities can foster greater increases in strength following training with electrical stimulation programmes (Maffiuletti, Pensini and Martin, 2002; Piva *et al.*, 2007; Stevens-Lapsley *et al.*, 2012; Gondin, Cozzone and Bendahan, 2011). Intensity will also influence patient comfort with higher intensities being less well tolerated; however, frequency and intensity inevitably will determine the quality of muscle contraction produced (Gorgey *et al.*, 2009; Baker, 2000). How easily advanced CHF patients tolerate EMS intensities sufficient to enable a training effect is unknown.

2.6.2.5. Stimulation Dose

A review of the use of EMS for muscular strength and recovery after stroke examined several studies and found high variability in the volumes of EMS delivered (de Kroon *et al.*, 2005). The overall length of programme varied from two weeks to three months, with no rationale given for why a particular protocol was chosen. Increasing the period of treatment was not directly related to more successful outcomes in strength: positive benefits were seen with short programmes (two and a half hours/week), and in some trials, limited benefits were seen with longer programmes (21 hours/week). For rehabilitation of ambulatory muscles, most EMS programmes usually consist of three to five hour-long sessions per week for at least four weeks (Thrasher and Popovic, 2008). Banerjee and colleagues (Banerjee *et al.*, 2009) achieved significant improvements in mild CHF patients leg strength and six minute walk distance using a LF-EMS protocol of 5 x 1hr sessions for eight weeks. The feasibility of replicating this dose in patients with more advanced CHF requires confirmation; poor tolerance and adherence of such a protocol in the severely ill could limit the effectiveness of this intervention. It is also possible that with such a low baseline fitness, lower doses of EMS than previous studies maybe effective, particularly if more tolerable in this population. The advanced CHF population demonstrate poor adhere to exercise and pharmaceutical interventions (Fitzgerald *et al.*, 2011; O'Connor *et al.*, 2009) so determining an effective dose of EMS that is practical is important.

2.6.2.6. Electrode Placement

The effectiveness of the EMS current in reaching muscle tissue is highly related

to electrode size and placement, as well as the conductivity of the skin-electrode interface (Livshitz, Mizrahi and Einziger, 2001). Larger surface electrodes will activate more muscle tissue but will disperse the current over a wider surface area, decreasing current density (Sha *et al.*, 2008). Smaller electrodes will concentrate current densities, allowing for focal concentration of current with less chance of stimulation crossover into nearby muscles. However, a more dense current increases discomfort or pain (Sha *et al.*, 2008). Debate about whether the muscle belly or the motor point is the most effective location for electrode placement is widespread throughout the literature (Gobbo *et al.*, 2011; Smans, Korsten and Blom, 1996; Mangold *et al.*, 2005). Variable electrode placement can result in significant differences between users in force of contraction, blood flow and oxygen uptake (Doucet, Lam and Griffin, 2012). Standardisation of electrode placement is crucial therefore to ensure all participants receive the same stimulus. Crognale and colleagues (Crognale *et al.*, 2013) developed larger electrodes that cover both the muscle belly and the motor point for use with LF-EMS (Fig. 2.6. below) to overcome this problem.

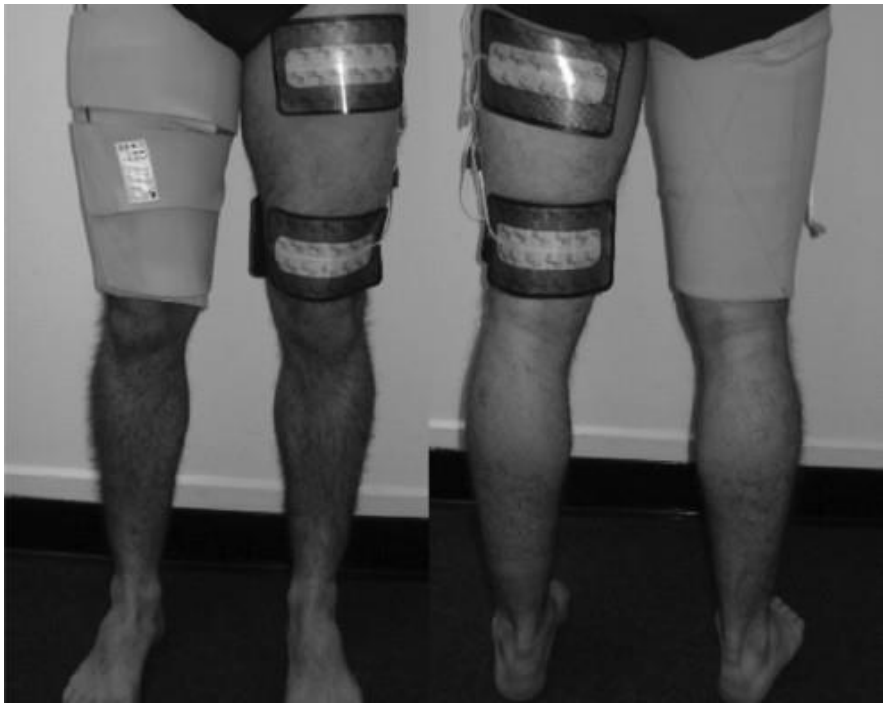


Fig. 2.6. Electrode Placement Utilised During LF-EMS. Crognale and colleagues (Crognale *et al.*, 2013) improved the subjective tolerability of LF-EMS by increasing electrode size by 33% to cover both the nerve trigger points and much of the muscle belly. This was to optimise muscle contraction while minimising skin discomfort.

2.6.3. Limitations of Electrical Muscle Stimulation

The biggest limitation of EMS in strength improvement in clinical populations i.e. CHF, COPD, cancer, is fatigue of the targeted muscles. Although electrical stimulation has the capacity to produce movement in denervated, paralysed, or spastic muscles, it is inherently less efficient than human movement. There are three main reasons for this: firstly, EMS as an external intervention, alters normal motor unit recruitment order (Vanderthommen and Duchateau, 2007). Ordinarily the smaller, fatigue-resistant motor units are activated first in human movement, which helps to delay fatigue; however, motor unit recruitment in electrically evoked contractions is more random, and this makes the muscles less resistant to fatigue (Gregory and Bickel, 2005). Secondly, muscle fibres being artificially stimulated are done so simultaneously, unlike the normal, incremental, efficient recruitment and de-recruitment process of motor units

observed during voluntary muscle contractions. In voluntary contractions, the human motor system resists fatigue by increasing the firing rate of active motor units and/or recruiting new motor units to replace others that have been de-recruited due to fatigue (Carpentier, Duchateau and Hainaut, 2001). Third, surface electrodes apply current precisely beneath the surface area of the electrode, and the current will encounter resistance by various thicknesses of subcutaneous tissue. The strength of the current will be diminished variably due to individual differences therefore the depth of penetration will be limited. The lack of standardisation for other stimulation parameters preclude comparative analyses between different EMS protocols (Singer, DE Domenico and Strauss, 1987; Halback and Straus, 1980). Electrical current application through the skin results in activation of pain receptors, inevitably inducing discomfort (Halback and Straus, 1980). Given that the individuals' tolerance to electrical current strongly determines the training intensity, there is a considerable inter-individual variability in EMS response between and within studies. The physiological stimulus of EMS must be characterised fully before its efficacy can be properly investigated. Delaying the onset of muscle fatigue is often cited as an important goal linked to EMS clinical efficacy (Ibitoye *et al.*, 2016). This is particularly important for CHF patients who have deconditioned muscle and could benefit from improved muscle strength. Whether muscle fatigue can be reduced enough to allow beneficial doses of EMS to be tolerated in patients with advanced CHF is not currently known.

In summary, EMS can potentially improve muscle strength, but it can also induce excessive neuromuscular fatigue as artificial stimulation inefficiently

recruits motor units within muscle. Researchers have studied frequency, pulse duration, duty cycle, amplitude, electrode placement, and the use of various dosing protocols to determine if muscle fatigue can be reduced through a modification of any of these parameters (Doucet, Lam and Griffin, 2012). The LF-EMS stimulation pattern offers an alternative stimulation protocol that allow continuous stimulation and is worthy of further investigation. Before LF-EMS is discussed in more detail, it is worth considering the research literature using high frequency EMS that has led to its development to identify where LF-EMS could be employed with more debilitated patient groups such as advanced CHF.

2.7. Research on Electrical Muscle Stimulation in Healthy Adults and Chronic Heart Failure

In 1971 the Russian researcher Yakov Kots was the first to introduce EMS as a modality for muscle strengthening and claimed that EMS led to strength gains of up to 40% in elite athletes (Ward and Shkuratova, 2002). However, the corresponding study was poorly described and was not translated into English until 2002 (Gondin, Cozzone and Bendahan, 2011). Nevertheless, it has been largely acknowledged that EMS delivered at intermittent high frequencies can increase maximal isometric voluntary strength (Boutelle, Smith and Malone, 1985; Colson, Martin and Van Hoecke, 2000; Colson, Martin and Van Hoecke, 2009; Currier and Mann, 1983; Duchateau and Hainaut, 1988). This effect has been observed in the biceps (Colson, Martin and Van Hoecke, 2000), triceps (Rich, 1992), abdominals (Alon and V Smith, 2005) but most commonly in the quadriceps, hamstrings and gastrocnemius muscles (Babault *et al.*, 2011;

Cometti, Deley and Babault, 2011; Boutelle, Smith and Malone, 1985; Currier and Mann, 1983; Laughman *et al.*, 1983). The potential applications of EMS in elite sport have been investigated recently; high frequency EMS is less time consuming than voluntary resistance training protocols (i.e., 15–20 vs. 30–60 min) which are advantageous in many high performance sports (Gondin, Cozzone and Bendahan, 2011). In addition EMS can be targeted on a single muscle in order to prevent muscle injury that could be induced by heavy weight training e.g., low back pain in gymnasts/rugby players, (Deley *et al.*, 2011). It is important to recognise however, that EMS alone is less effective than voluntary exercise (Bax, Staes and Verhagen, 2005; Paillard *et al.*, 2010). For those too debilitated to exercise voluntarily, such as CHF, COPD, stroke patients etc, EMS has potential use as a substitute for exercise. Studies presenting data on the efficacy of EMS in CHF form the next part of this review.

2.7.1. Electrical Muscle Stimulation in the Chronic Heart Failure Population

The application of EMS to the CHF population has been the subject of a number of trials in recent years. Several reviews have focused on the effects of EMS in CHF (Smart, Dieberg and Giallauria, 2013; Sillen *et al.*, 2009; Gomes Neto *et al.*, 2016; Sbruzzi *et al.*, 2010), and report beneficial effects in CHF patients. These include: reversal of muscle atrophy and dysfunction, increase in muscle mass (Type I fibres) and oxidative enzyme levels, improved VO_2peak, increased endothelial function, better performance in functional tests and improved quality of life/ reduced depression (Smart, Dieberg and Giallauria, 2013). Dobsak et al., (Dobsák *et al.*, 2006), reported that an eight week EMS training intervention based on a frequency of 10 Hz increased leg strength and

aerobic capacity of CHF patients. Nuhr et al., (Nuhr *et al.*, 2004) have similarly shown that an EMS protocol at 15 Hz applied for four hours per day increased aerobic capacity in CHF patients. Muscle biopsies indicated biochemical markers and structural changes in the muscle consistent with increased oxidative capacity. Deftereos and colleagues (Karavidas *et al.*, 2010; Deftereos *et al.*, 2010), employed a six week 20Hz EMS intervention in NYHA II-III patients that resulted in a 7.5 % improvement in 6 minute walk distance (6MWD) as well as a 38% increase in Flow Mediated Dilation (FMD). However, studies comparing these benefits with those obtained from exercise training or placebo in this patient group reported small sample sizes and conflicting results. The accumulating evidence suggests that if exercise can be tolerated in this group then it's benefits are potentially equal or superior to EMS (Gomes Neto *et al.*, 2016). In practice, however, many CHF patients cannot tolerate or adhere to sufficient exercise doses to gain these benefits (O'Connor *et al.*, 2009) and so there is a large requirement for an alternative treatment such as EMS that can elicit potentially similar health benefits. Importantly, there is a lack of data on the benefits of EMS in the most debilitated CHF patients. In the most recent meta-analysis of 10 RCT's (Smart, Dieberg and Giallauria, 2013) of EMS vs conventional exercise training or placebo control in CHF patients, the trials typically included less symptomatic NYHA class I-III patients. From an aggregate of 300 subjects, only 11 were NYHA IV. No RCT to date has investigated if EMS has a significant impact on people with more advanced CHF(NYHA III/IV). It is possible that LF-EMS may be tolerable and provide improvements in aerobic capacity and vascular function. However, it is not known whether such a trial is feasible if this sick and debilitated population.

2.8. Low Frequency Electrical Muscle Stimulation

There is potentially a strong application in CHF patients for a pattern of EMS stimulation that produces an elevated cardiovascular response. Tetanic EMS muscle contraction of the type traditionally used for muscle strengthening does not stimulate a significant aerobic response (Minogue, Caulfield and Reilly, 2007). This is primarily because the slow type I fibres which are primarily adapted to oxidative metabolism become fatigued (Crognale *et al.*, 2013). In addition, blood flow to muscle is inhibited during isometric contraction (Banerjee *et al.*, 2005; Dobsák *et al.*, 2006), thus interrupting the supply of oxygen and further hastening fatigue. Continuous LF-EMS was developed by Minogue et al. (Minogue, Caulfield and Reilly, 2007), who investigated the optimal stimulation frequency for creating a sustained aerobic response. By measuring O_2 uptake and knee muscle torque across a range of frequencies 1-12Hz, (Fig. 2.7. overleaf), the optimal combination of frequency and contraction force was identified at 4-5Hz. This frequency had the highest torque (force of contraction) that could be tolerated continuously i.e. to produce a prolonged aerobic response (Fig. 2.7. d). Frequencies above this speed create fused twitch summation of the muscle, i.e. full tetany, producing greater force of contraction but quicker fatigue. It also requires an on/off duty cycle which prohibits continuous aerobic exercise.

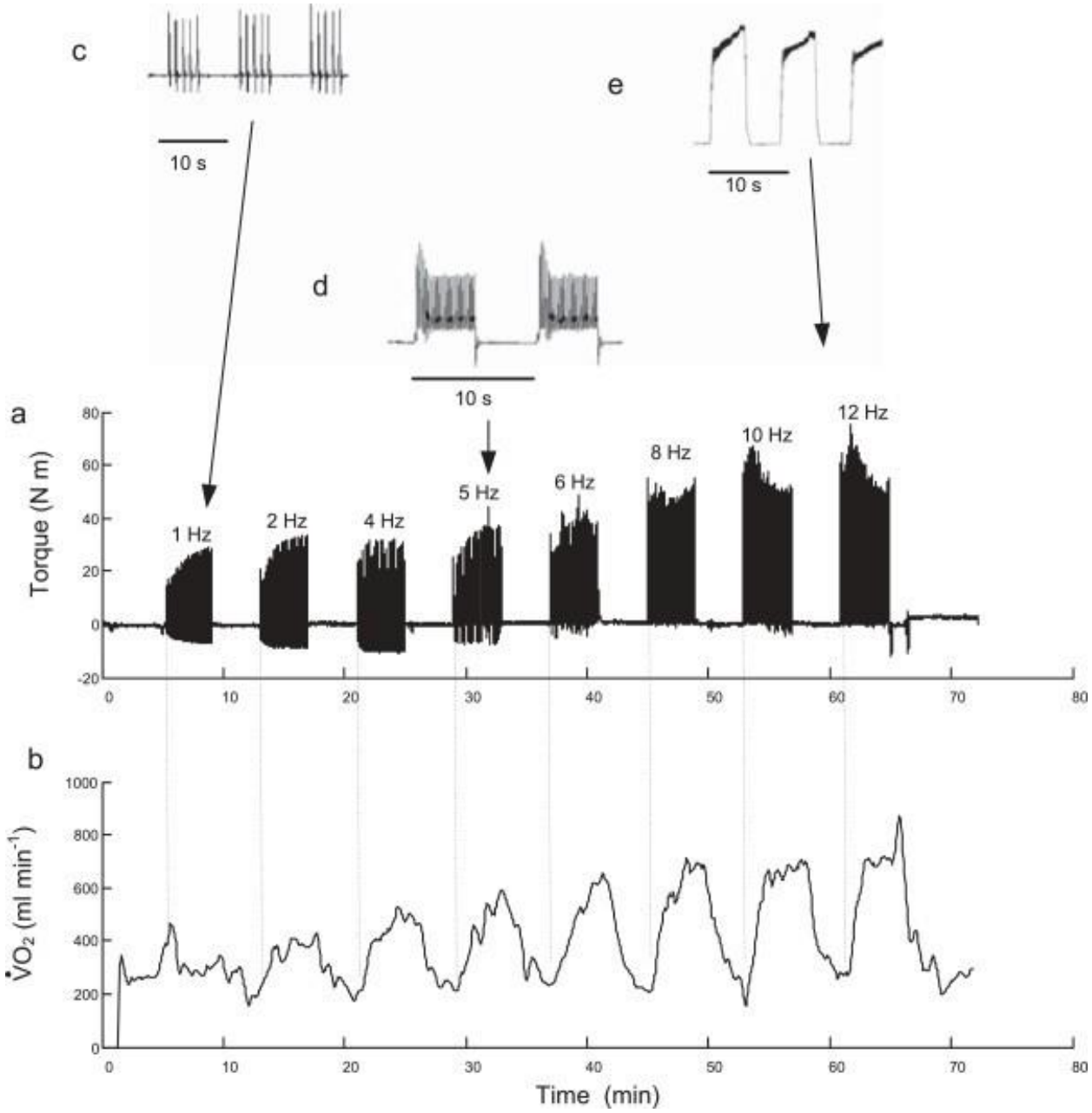


Fig. 2.7. The Measured Joint Torque and Oxygen Consumption Responses for a Typical Subject During a Session of EMS at Different Frequencies. The increasing degree of force fusion as the impulse frequency increases is evident; (a) as is the corresponding increase in VO_2 (b). During the first stimulation bout at 1 Hz (c), individual force twitches can be seen at low VO_2 levels. At a pulse frequency of 12 Hz (e) there is almost complete fusion and VO_2 is higher with no time for relaxation during the 5 second contraction time, but this is unsustainable due to fatigue. At 5 Hz (d), there is a small degree of force fusion allowing fibres to relax sufficiently to be stimulated continuously without fatigue creating aerobic metabolism (Minogue, Caulfield and Lowery, 2014).

Whilst LF-EMS may have the potential to provide cardiovascular as well as muscular benefits, the mechanisms by which an LF-EMS bout alters central and peripheral haemodynamics are only partially known. Previous studies have

reported improved local blood flow to the skeletal muscles during high frequency EMS (Dobsák *et al.*, 2006; Wang *et al.*, 2004; Angelopoulos *et al.*, 2013). Tanaka et al (Tanaka *et al.*, 2016) reported enhanced peripheral vascular function (via peripheral arterial tonometry) but no significant blood pressure, SV or cardiac index (l/min/m^2) responses during a high frequency (50Hz) EMS session in patients recovering from MI. Crognale and colleagues (Banerjee *et al.*, 2005; Crognale *et al.*, 2013), reported a VO_2 of 51% max., HR 71% max. and BLa of 4.7 mMol during LF-EMS in healthy individuals after nine habituation sessions. These studies collectively did not measure vascular/ haemodynamic function during LF-EMS or did not do so in a clinical population. The effects of tetanic high frequency EMS which utilises an on/off stimulation pattern in the Tanaka study (Tanaka *et al.*, 2016), cannot be assumed to have the same effect as continuously tolerable and sub-tetanic LF-EMS. More functionally limited patient groups such as CHF may respond differently to LF-EMS due to impaired left ventricular, endothelial and skeletal muscle function and therefore further research is required.

2.8.1. Low Frequency Electrical Muscle Stimulation Studies in the Chronic Heart Failure Population

Few studies have investigated the effects of LF-EMS in the CHF population. Deley et al. (Deley *et al.*, 2005) compared EMS at 10 Hz with conventional exercise in CHF patients and found similar improvements after 5 weeks: VO_2 peak, 6MWD and quadriceps strength increases were all comparable. However, although 10 Hz is lower than that used in most other studies it still produces tetanic contractions that require an on/off duty cycle. Because of this, a prolonged aerobic stimulus cannot be delivered, and improvements are likely

limited. Banerjee et al (Banerjee *et al.*, 2009) provided proof of concept of LF-EMS in mild to moderate CHF patients. Although the sample was small and an exercise control was not included, CHF patients improved VO_2peak, 6MWD and quadriceps strength following eight weeks (5 x 1hr) of LF-EMS. The effect of LF-EMS on the vascular system, a strong prognostic indicator of risk in the CHF population, has not been the subject of any research to date. Furthermore, the stimulus of LF-EMS has not been fully characterised in a clinical population and so the haemodynamic changes by which this intervention could benefit CHF have not yet been established. The potential of LF-EMS in more advanced CHF patients is substantial, due to the low baseline health and fitness level in this population and the minimal improvement required to make a significant difference to quality of life.

2.9. Overall Summary of Literature Review and Thesis Aims

Advanced CHF is a complex, condition that develops chronically over decades and is characterised by reduced cardiac, muscular and vascular function, as well as retention of sodium and water. This results in patients becoming symptomatic with dyspnoea, lowered exercise capacity, oedema and a poor quality of life. Exercise is a useful addition to medical therapies, negating many symptoms by improving peripheral and central limitations. However, although the benefits of exercise are well acknowledged, many CHF patients cannot tolerate or adhere to exercise as the illness becomes more debilitating. EMS is an alternative to exercise in this population that can improve exercise capacity, and reverses muscle weakness. Numerous meta-analyses involving CHF patients demonstrate that EMS should be considered as a surrogate training

method as well as, or instead of, voluntary exercise training (Smart, Dieberg and Giallauria, 2013; Sillen *et al.*, 2009; Gomes Neto *et al.*, 2016; Sbruzzi *et al.*, 2010). Tetanic EMS at higher frequencies can provide similar improvements in VO_2peak, 6MWD, leg strength and quality of life to conventional exercise, although patients with advanced CHF have not been studied. Muscles fatigue less rapidly during LF-EMS because of its sub-tetanic stimulation pattern and can be tolerated for continuous periods in the same manner as aerobic exercise training. Although Banerjee et al. (Banerjee *et al.*, 2009) demonstrated positive health benefits could be gained in mild CHF patients, a larger trial is required to confirm these findings in advanced CHF patients. There is considerable potential for LF-EMS in the advanced population that have very little treatment options owing to their debilitated condition. The feasibility of the acceptability and adherence of LF-EMS in advanced CHF should be determined before a definitive trial can be planned for this intervention. Furthermore, the response of advanced CHF patients to LF-EMS has not been adequately characterised. Finally, the potential for LF-EMS to improve vascular function, an important prognostic target for CHF, should also be explored.

2.9.1. Thesis Study Objectives

The purpose and specific aims of this thesis were:

1: characterise the physiological stimulus of LF-EMS in the healthy and advanced CHF population

2: determine the feasibility of LF-EMS use in patients with advanced CHF

3. investigate the effect of LF-EMS on vascular function in patients with advanced CHF

To meet these aims, 3 distinct studies were completed:

2.9.2. Study One

The mechanisms by which LF-EMS may act are poorly understood, particularly the manner in which a session of LF-EMS affects central haemodynamics and the peripheral vasculature. The first study of this thesis therefore sought to characterise the central and peripheral physiological responses to a 45-minute LF-EMS bout in CHF patients and compare these to young healthy controls.

2.9.3. Study Two

The objective of the second study was to determine the feasibility of LF-EMS use in advanced CHF patients. This was achieved by monitoring uptake, adherence and tolerance to eight weeks use of the intervention in this population. This study also generated initial data on exercise capacity, physical activity levels and quality of life before and after eight weeks LF-EMS to inform future large clinical trials.

2.9.4. Study Three

The effects of prolonged use of LF-EMS on vascular function and VO_2peak has not been investigated. Flow Mediated Dilation (FMD) Pulse Wave Velocity (PWV), surrogates of vascular function, and VO_2peak are targets for treatment in CHF due to their strong correlation with prognosis. The third study objective was to determine changes in FMD, PWV and VO_2peak following eight weeks of LF-EMS in the advanced CHF population.

CHAPTER 3: The Acute Effects of Low Frequency Electrical Muscle Stimulation on Cardiovascular Haemodynamics; an Exploratory Comparison of Patients With Chronic Heart Failure and Young Healthy Individuals .

3.1. Introduction

Regular participation in exercise improves aerobic capacity and is associated with better long-term health outcomes for healthy and clinical populations alike (Astrand, 1988). Unfortunately, some individuals are unable (due to medical conditions) or unwilling to exercise, and thus do not obtain these beneficial effects. EMS has been employed in patients with CHF (Smart, Dieberg and Giallauria, 2013), COPD (Sillen *et al.*, 2009) and muscle weakness (Jones *et al.*, 2016) as an alternative to traditional exercise. The involuntary muscle contraction of large muscle groups (typically lower limb) produced by EMS interventions can mediate increased leg strength, exercise capacity and quality of life in these populations (Sillen *et al.*, 2009; Jones *et al.*, 2016; Smart, Dieberg and Giallauria, 2013). The EMS employed in the aforementioned reviews and meta analyses, utilised frequencies between 30-50Hz (Tanaka *et al.*, 2016; Bax, Staes and Verhagen, 2005; Balogun *et al.*, 1993), which produce tetanic i.e. full muscle, contractions. An on/off stimulation cycle is required for this type of stimulation as contractions cannot be sustained for more than a few seconds without fatiguing the muscles. Previous research has suggested that there is little or no cardiovascular response during intermittent EMS. For example, Tanaka et al (Tanaka *et al.*, 2016) reported negligible changes in blood pressure, SV or cardiac index during a 50Hz EMS session in patients recovering from MI. It is likely that the intermittent duration of stimulation is not long enough to create changes in cardiovascular haemodynamics (Minogue, Caulfield and Reilly, 2007). Therefore, tetanic EMS at high frequencies may not be the most suitable intervention for clinical populations (i.e. CHF, COPD) with

central limitations where an alternative to aerobic exercise would be beneficial.

With a frequency of 4Hz, LF-EMS has a continuous sub-tetanic pattern, does not fatigue the muscle fibres as quickly as higher frequency EMS and so can be tolerated for longer durations (Minogue, Caulfield and Lowery, 2014). Additionally, LF-EMS has been shown to mediate increases in HR, VO_2 and blood lactate (BLa) to similar levels observed during exercise in healthy individuals (Banerjee *et al.*, 2005). There is therefore potential for LF-EMS to improve muscle/cardiovascular function in populations limited by chronic disease (Jones *et al.*, 2016).

The LF-EMS stimulus sufficient to elicit a haemodynamic benefit has not yet been fully characterised in a healthy population or in those with cardiac dysfunction i.e. CHF. Banerjee et al. (Banerjee *et al.*, 2005), examined the VO_2 and HR response during an acute bout of LF-EMS with incremental stages of increasing amplitude in healthy individuals. They reported VO_2 and HR during the highest intensity stage at 33% and 54% of VO_2peak measured during a CPET, respectively. More recently, Crognale and colleagues (Banerjee *et al.*, 2005; Crognale *et al.*, 2013), measured VO_2 and HR at 51% and 71% respectively of VO_2peak during an incremental LF-EMS protocol to subjective comfort threshold in healthy individuals. Importantly, these two studies did not measure CO, SV, central blood pressure or peripheral vascular function, which are needed to characterise the impact of this stimulus on cardiovascular function. In addition, patients with CHF may respond differently than healthy individuals to LF-EMS due to their impaired left ventricular, endothelial and

skeletal muscle function. They may also be a group that benefit more due to their deconditioned status. Accordingly, the aim of the current study was to characterise the central and peripheral cardiovascular responses to a 45-minute bout of LF-EMS in CHF patients and compare these to young healthy controls.

3.2. Methods

3.2.1. Participants

Fifteen male individuals were recruited; nine young healthy individuals (age: 24 ± 3 yrs) with no history of cardiovascular disease and six patients (age: 67 ± 3.25 yrs) with advanced CHF (NYHA functional class III-IV). Patients with CHF had an LVEF < 40% documented by echocardiography, and were medically stable, defined as no hospital admission or alterations in medical therapy in the two weeks prior to inclusion. All participants were informed of the methods before providing written informed consent (see appendix 1). The study was approved by the Cardiff Metropolitan University and the Edgbaston NHS ethics committee and conformed to the Declaration of Helsinki. Participant characteristics are presented in Table 3.1.

Table 3.1. Baseline Demographic and Clinical Characteristics of the Young Healthy and CHF Groups. All participants were male. Data presented as mean ± SD

Demographics	**Young Healthy (n=9)**	**CHF (n=6)**
Age (yrs)	24.0 ± 3.1	67.7 ± 14.1
BMI kg/m^2	24.8 ± 2.9	27.4 ± 4.8
Clinical		
BP_{sys} (mm Hg)	113 ± 9	124 ± 21
BP_{dia} (mm Hg)	65 ± 8	73 ± 10
Resting HR (beats.min^{-1})	54 ± 13	72 ± 14
Max values		
VO_{2peak} (ml. kg^{-1} min $^{-1}$)	48.1 ± 9.3	16.0 ± 2.9
HR peak (beats.min^{-1})	178 ± 8	133 ± 20
mA during LF-EMS	92.4 ± 15	101.5 ± 22

BMI, Body Mass index; BP_{sys} (mmHg), systolic blood pressure; BP_{dia} (mmHg), diastolic blood pressure; HR, heart rate; CPET, cardiopulmonary exercise test; VO_2 peak, peak oxygen uptake; mA, milliamps;LF-EMS, low frequency electrical muscle stimulation.

3.2.2. Experimental Design

Participants reported to the laboratory on three occasions over a two week period. The first visit was to perform a CPET, followed by a familiarisation

session with the LF-EMS equipment. The second visit consisted of a further supervised familiarisation session and on the third visit the experimental protocol was performed, which included a 45-minute bout of lower limb LF-EMS. Immediately prior to and following the 45-minute bout of LF-EMS, brachial artery FMD and aortic pulse wave velocity (aPWV) were measured. During the 45-minute bout of LF-EMS, VO_2, BLa, brachial artery diameter and blood flow, Mean Arterial Pressure (MAP), HR, SV, CO and Rating of Perceived Exertion (RPE) and Pain (Borg, 1998) were recorded every 5-minutes or continuously (Fig. 3.1.).

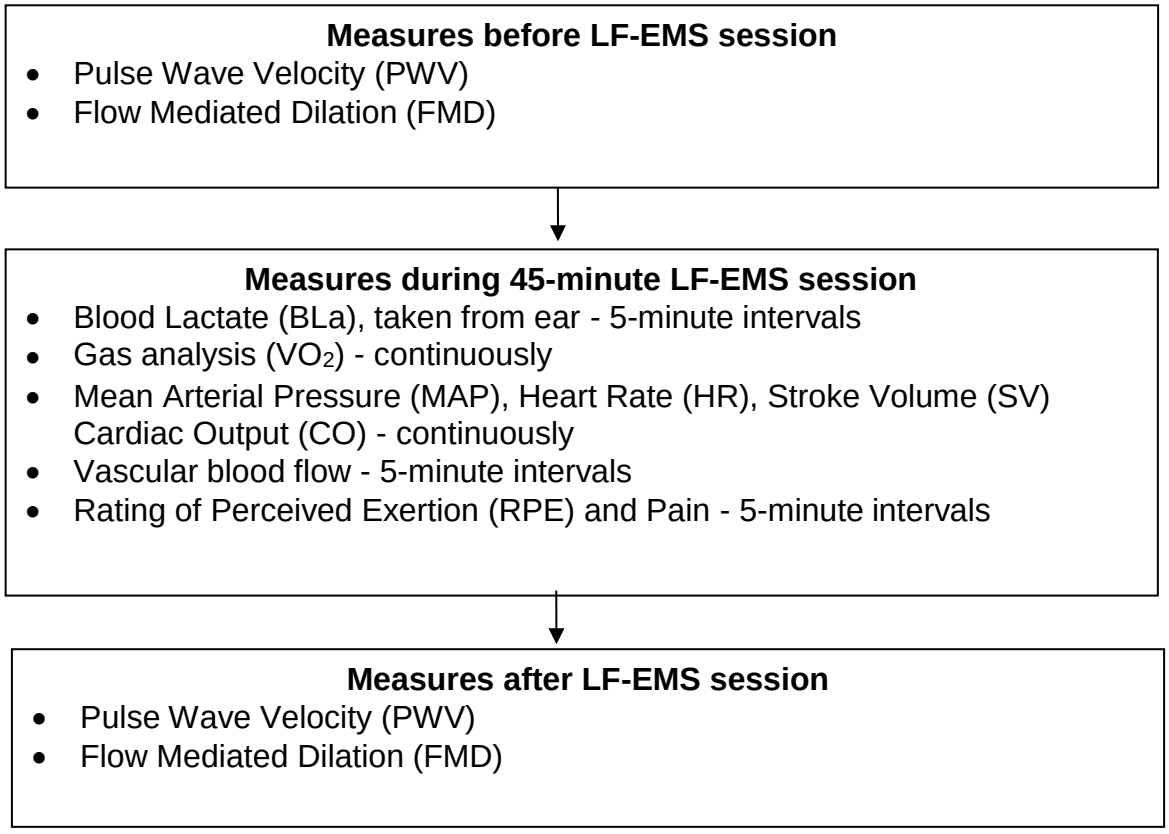


Fig. 3.1. Experimental Protocol for Acute Study
Measures were taken before during and after the 45-minute LF-EMS bout

3.2.3. Maximal Cardio-Pulmonary Exercise Test

Participants completed a maximal effort CPET in accordance with American Thoracic Society (ATS) guidelines (Society and Physicians, 2003). Briefly, a

ramp protocol on a cycle ergometer was calculated to ensure optimal test duration of nine to twelve minutes and a Respiratory Exchange Ratio (RER) of >1.10 to indicate maximal effort. Continuous measurements of VO_2, carbon dioxide production (VCO_2) and minute ventilation (VE) were recorded (Oxycon Pro, Jeager, Warwick, Warwickshire, UK). VO_2peak was calculated as an average of the last 30 seconds of the CPET (Fig. 3.2a) when a plateau in VO_2 could be observed (Society and Physicians, 2003). Blood pressure and RPE/pain scale were monitored at regular intervals throughout (Borg, 1998).

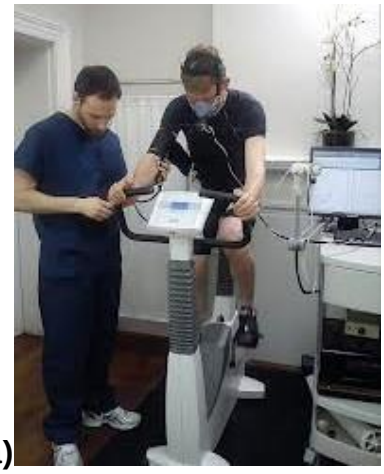
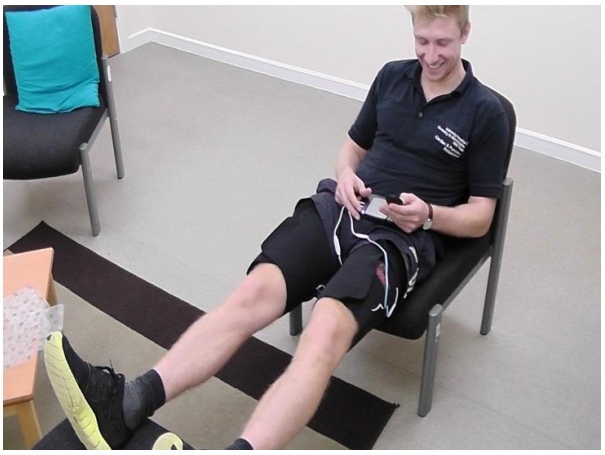
(a)  **(b)** 

Fig. 3.2. Visit 1 (a) Cardiopulmonary Exercise Test (CPET) Followed by (b) LF-EMS Familiarisation Session.
NB All photo subjects granted permission to use their images in this thesis.

3.2.4. Low Frequency Electrical Muscle Stimulation Familiarisation

After a one-hour recovery period from the CPET test, participants then completed 30-minutes of LF-EMS familiarisation (Fig. 3.2b). The LF-EMS equipment consisted of 4 large (10 x 17 cm) adhesive electrodes (Biomedical Research Limited, Galway, Ireland) applied to the quadriceps and hamstring muscles. The equipment is CE marked under the European Medical Device Directive. The stimulator current waveform was designed to produce rhythmical

contractions in the leg muscle groups occurring at a pulse frequency of 4-5Hz (pulse width: 620μs). The LF-EMS device produced a continuous current waveform at a frequency of 5Hz, and a maximum peak output of 140mA. The current amplitudes were gradually increased as tolerated by each individual. Participants were instructed to increase the current as much as they could tolerate without being in 'severe' discomfort using the Borg rating of perceived discomfort scale (Borg, 1998). A second 30-minute LF-EMS familiarisation was completed by all participants three to five days later (visit 2).

3.2.5. Experimental Protocol

Participants arrived at the laboratory having not performed exercise or consumed alcohol for a least 24 hours, abstained from caffeine and fasted for five hours. Upon arrival participants rested in a reclined position (Fig. 3.3. overleaf), on an examination bed for ten minutes. Brachial artery FMD and PWV measurements were performed, then the EMS straps were positioned (as described above) and participants completed a five minute warm-up at an amplitude that induced visible muscle contraction. During the warm-up, the intensity was gradually increased until the participant reached their maximum tolerable intensity as determined previously during the familiarisation sessions. This intensity was maintained for a period of 45-minutes. During the LF-EMS bout, VO_2, BLa, brachial artery diameter and blood velocity, MAP, HR, SV, CO, pain rating and RPE were recorded. At the end of the 45-minute bout FMD and PWV measurements were repeated immediately.

3.2.6. Measurements

Flow mediated dilation: Brachial artery endothelium-dependent function was measured using the FMD technique (Thijssen *et al.*, 2011). Measurements were performed in the supine position following 20 minutes of rest, on the right arm with the cuff placed distal to the olecranon process. A 15-MHz multi-frequency linear array probe, attached to a high-resolution ultrasound machine (T3000; Terason, Burlington, MA) was then used to image the brachial artery in the distal third of the upper arm. Images were optimised, and settings were identical between FMD assessments.

(a)

(b

Fig 3.3. Experimental Protocol Set Up for (a) Healthy Individuals and (b) Advanced CHF Patients.
NB All photo subjects granted permission to use their images in this thesis.

Following a one minute recording period of diameter and flow, the cuff was inflated (>200 mmHg) for five minutes (D.E. Hokanson, Bellevue, WA). Diameter and flow recordings resumed 30-seconds prior to cuff deflation and continued for three minutes thereafter, in accordance with amended technical specifications (Thijssen *et al.*, 2011).

Pulse wave velocity: aPWV was determined using applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia) by sequentially recording ECG-gated carotid and femoral artery waveforms as described previously (Wilkinson *et al.*, 1998). Brachial and whole body PWV (bPWV, wPWV,) were determined from the carotid, radial and dorsalis pedis waveforms for regional comparisons. Foot-to-foot transit time between the respective pressure waves was calculated from the integrated software. The distance measurements were taken using measuring tape from the suprasternal notch to the carotid, radial, femoral and dorsalis pedis arteries. Velocities were adjusted for MAP to allow between group comparisons pre and post LF-EMS.

Respiratory measurements: Continuous respiratory measurements of VO_2, VCO_2 and VE were recorded using a metabolic cart continuously during the LF-EMS bout (Oxycon Pro, Jaeger, Warwick, Warwickshire, UK). As well as providing oxygen uptake levels attained during the LF-EMS relative to body weight (ml. kg^{-1} min^{-1}), they were also calculated as a percentage of the maximum values attained during CPET:

$$\mathbf{(VO_{2\ LF\text{-}EMS} \div VO_{2peak}) \times 100 = VO_{2peak}\ \%}$$

This was done in order to demonstrate the intensity of the bout relative to maximal values.

Blood lactate: A capillary blood sample (20 µl) was taken at five minute intervals

from the ear lobe. The sample BLa level was immediately analysed with the Biosen C-Line Sport lactate analyser (EKF-Diagnostic, Barleban, Magdeburg, Germany).

Vascular blood flow: During LF-EMS, brachial artery diameter and blood velocity were measured with a linear array probe attached to a high-resolution ultrasound machine (T3000: Terason, Burlington, MA). The probe was placed on the distal third of the upper arm for image consistency. Blood flow velocity was measured with an isonation angle <60 °. Measurements were taken for 30-seconds at each time point every five minutes.

Haemodynamics: Continuous beat-by-beat arterial blood pressure was estimated from digit wave form analysis (Finapres, Amsterdam, Netherlands). Calculations of SV, CO and MAP were calculated using the BP waveform using the Model Flow method, incorporating age, height, sex and weight (Beatscope, TNO, Biomedical Instruments). To verify continuous BP, intermittent arterial BP was also measured by brachial auscultation using an automated sphygmomanometer (Dinamap, Germany). For the duration of the 45-minute LF-EMS session, 30-second averages were calculated retrospectively at five minute intervals.

Brachial artery diameter and blood flow analysis.

Custom designed edge-detection software was used to analyse all vascular ultrasound recordings. This method allowed analysis to be performed largely independent of investigator bias. Blood flow was calculated at a sampling rate of 30 Hz. Shear rate (independent of viscosity) was calculated as four x mean blood velocity/vessel diameter. The semi-automated software, compared with manual methods, significantly reduces observer error and has shown previous

intra-observer coefficients of variation (CoV) of 6.7% (Thijssen *et al.*, 2011). All files were analysed by the author (S.E.) to minimise variability between subjects. Baseline diameter measured before the introduction of hyperaemia in each test of FMD was also taken into account and controlled for in subsequent calculations. The allometric approach is more accurate for scaling changes in diameter than simple percentage change, which makes implicit assumptions about the relationship between baseline diameter and peak diameter (Erbs *et al.*, 2010; Thijssen *et al.*, 2011).

3.2.7. Statistical Analysis

Given that this was an exploratory study, no *a priori* sample size was calculated. Changes in all variables during the LF-EMS bout were compared using general linear models for both (a) the repeated measures during the 45-minute LF-EMS bout (10 time points and 2 groups) and (b) the pre/post measures taken before and after the LF-EMS bout (2 times points and 2 groups), using Statistical Package for the Social Sciences (SPSS,Version 20: SPSS Inc., Chicago, IL). Data are presented in the text as mean and 95% confidence intervals (95%CI) with P values <0.05 set a priori as statistically significant.

3.3 Results

3.3.1. Oxygen Uptake

Mean VO_2 increased by 5.7ml. kg^{-1} min^{-1} (95%CI: 4.1, 7.3) during the 45-minute LF-EMS (P<0.001) across both groups. There was a significant group*time interaction with the healthy group showing a 5.3 ml. $kg^{-1}.min^{-1}$ (2.7, 7.9) higher VO_2 than the patients with CHF (P<0.001, Fig. 3.4.a). When the VO_2 data was expressed as a percentage of VO_2peak from the CPET test (Fig. 3.4.b), there was a significant group*time interaction with the healthy individuals working at a 5.8% (2.6, 7.9) lower VO_2 than the patients with CHF (P<0.001).

3.3.2. Blood Lactate

Blood lactate levels increased by 0.6mmol/L (0.2, 0.9) during the 45-minute LF-EMS bout (P<0.001). There was a significant group*time interaction with the healthy individuals showing lower BLa levels (group mean difference: 0.9 mmol/L, -0.18,1.8), during the LF-EMS than the patients with CHF (P<0.001, Fig. 3.4.c).

3.3.3. Heart Rate

Mean HR increased by 24 beats.min^{-1}(15, 32) during the 45-minute LF-EMS (P<0.001, Fig. 3.4.d). There was no significant group*time interaction.

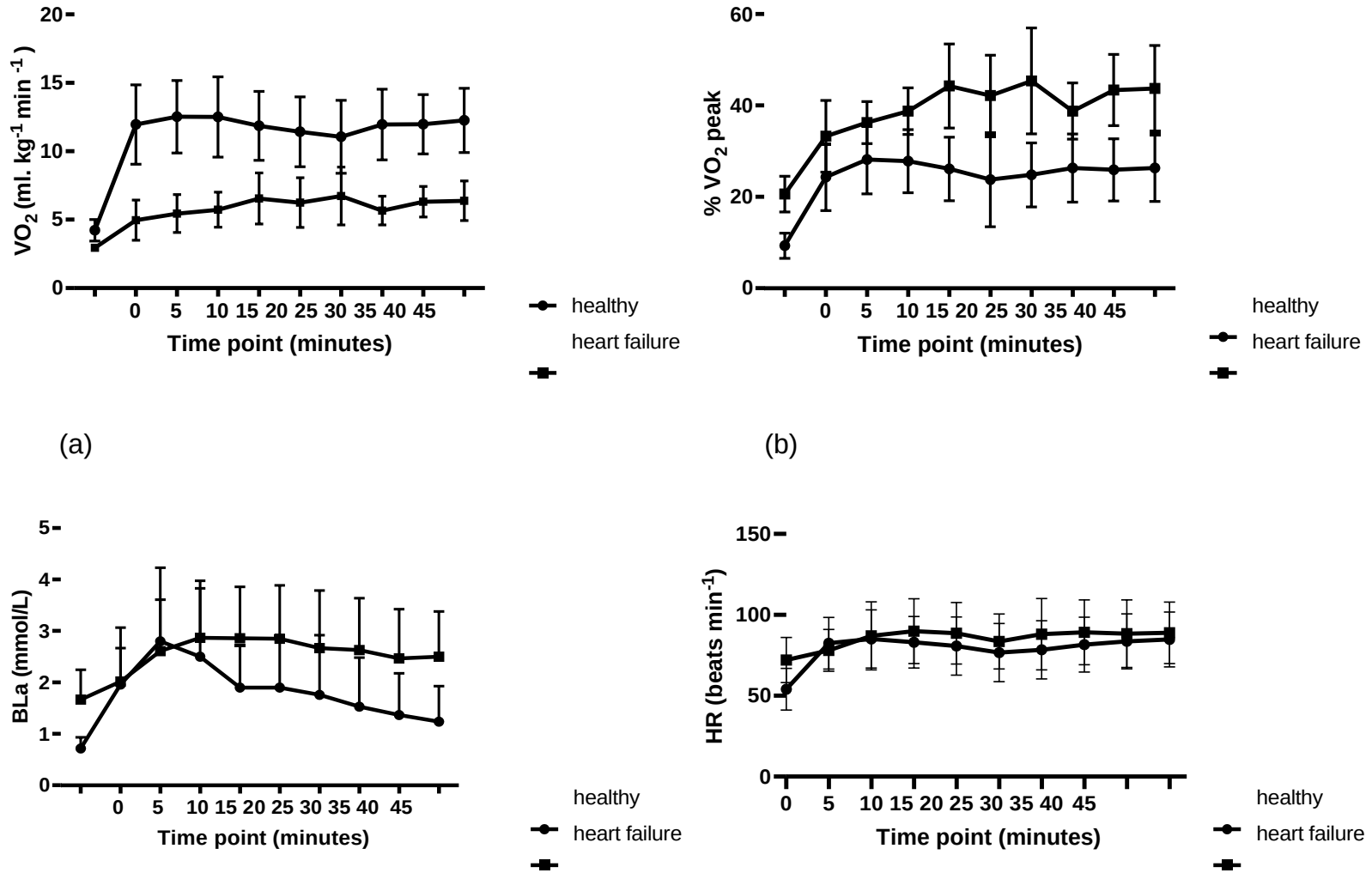
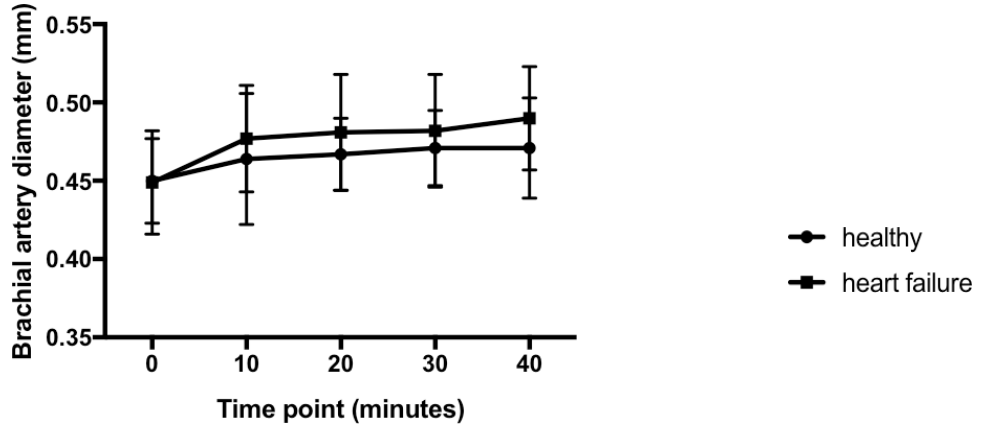


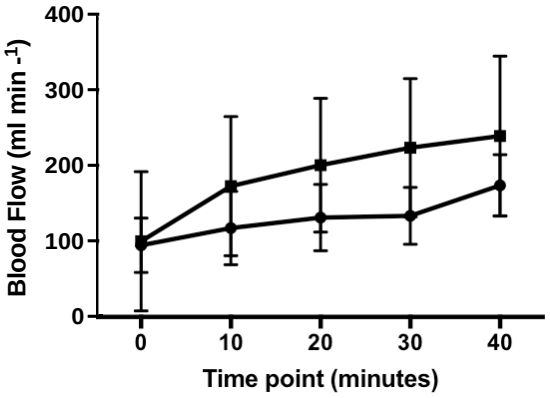
Fig.3.4. (a) O_2 Uptake, (b) O_2 Uptake Expressed as Percentage of VO_2peak, (c) Blood Lactate (BLa) and (d) Heart Rate Response During LF-EMS.

3.3.4. Blood Flow

Brachial artery diameter, blood flow, and shear rate increased from rest by 0.3 mm (± 0.03 mm), 1.03 ml/min (± 0.43) and 2704 s^{-1} (± 2365) respectively, during the LF-EMS bout (P<0.001) in both groups (Fig. 3.5. below). There was no group*time interaction (P>0.05).



(a)



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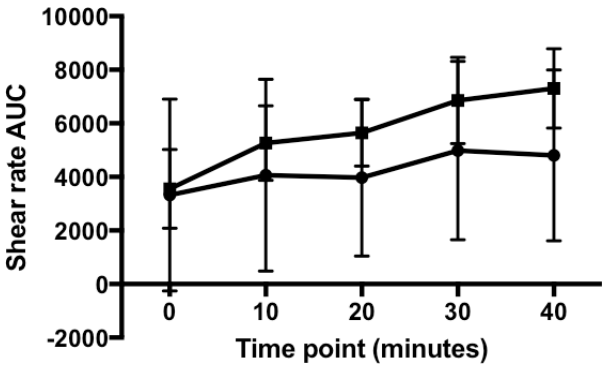

(c)

Fig.3.5 Brachial Artery Diameter (a), Blood Flow (b), and Shear Rate AUC (c) During LF-EMS

3.3.5. Haemodynamics and Pain/Perceived Exertion

For all participants, MAP, SV, CO, pain scale and RPE increased significantly during the LF-EMS ($P<0.001$). There was no main effect of group or group*time interaction in HR, SBP, MAP, pain or RPE (Table 3.2.). However, CO did show a significant group*time interaction at 5-minutes (3.79 ml/min, (0.02, 7.57)) reflecting a greater initial CO response in the healthy group compared to patients with CHF.

Table 3.2. Haemodynamic, Subjective Effort and Pain and Measures During LF-EMS. Data presented as mean ± SD

Time point	Resting	5minute	10minute	15minute	20minute	25minute	30minute	35minute	40minute	45minute
Healthy SV (ml)	95.7 ± 12.3	109.4 ± 16	117.8 ± 18.5	123.6 ± 19.7	117.8 ± 15	121.4 ± 18.1	118.1 ± 15.3	120.4 ± 14	116 ± 13.5	117 ± 14.3
Healthy CO (l/min)	6.16 ± 2	9.94 ± 2.83	10.94 ± 2.93	11.16 ± 2.67	10.43 ± 2.74	10.30 ± 2.4	9.95 ± 2.29	10.46 ± 2.14	10.46 ± 2.56	10.47 ± 2.41
Healthy MAP (mm/Hg)	111.5 ± 15.5	123.5 ± 27.2	121.0 ± 22.2	125.6 ± 39.2	114.9 ± 24.6	105.1 ± 16.8	110.6 ± 22.2	105.2 ± 17	111.1 ± 19.2	111.1 ± 23.9
Healthy Pain	0.0 ± 0	3. 6 ± 0.7	3.5 ± 0.7	3.0 ± 0.7	2.6 ± 0.7	2.3 ± 0.7	2.1 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.6 ± 0.7
Healthy RPE	6.0 ± 0	12.4 ± 0.7	12.3 ± 1.2	11.9 ± 1.4	11.5 ± 1.4	10.9 ± 1.6	11.0 ± 1.6	11.1 ± 1.5	10.8 ± 1.6	10.6 ± 1.4
CHF SV (ml)	74.2 ± 29.7	85.4 ± 35	84 ± 33.2	85.6 ± 29.8	86.9 ± 27.9	88.3 ± 33.7	87.1 ± 30.7	88.3 ± 30.3	87.8 ± 33.8	88.7 (± 30.8
CHF CO (l/min)	5.65 ± 1.67	6.46 ± 2.28	7.16 ± 2.49	7.23 ± 3.03	7.64 ± 2.64	7.40 ± 2.61	7.28 ± 2.26	7.62 ± 2.46	7.89 ± 2.58	7.64 ± 2.27
CHF MAP (mm/Hg)	94.1 ± 14.8	104.3 ± 12.3	114.7 ± 15.7	109.7 ± 13.8	105.5 ± 13.4	102.8 ± 10	101.5 ± 13.2	102.6 ± 12	99.0 ± 14.8	97.0 ± 14.3
CHF Pain	0.0 ± 0	4.0 ± 0.9	3.8 ± 1	3.8 ± 1	3.4 ± 0.8	3.4 ± 0.8	3.4 ± 0.8	3.2 ± 1	3.2 ± 1	3.2 ± 1
CHF RPE	6.0 ± 0	12.2 ± 0.9	12.0 ± 0.8	11.7 ± 0.7	11.3 ± 0.5	11.3 ± 0.5	11.3 ± 0.5	10.8 ± 0.9	10.7 ± 0.7	10.7 ± 0.7

CHF, chronic CHF group; SV, stroke volume; CO, cardiac output; MAP, mean arterial pressure RPE, rating of perceived exertion; Pain, pain rating

3.3.6. Pre/Post Measures: Flow Mediated Dilation and Pulse Wave Velocity

FMD decreased by 1.89% (1.04, 2.74) following the LF-EMS (P<0.001). There were no group*time interaction or group main effects (P>0.05). Baseline diameter and time to peak increased following the LF-EMS (P<0.05). Shear rate was decreased following LF-EMS (P<0.05) and there was no change in peak diameter (Table 3.3. below).

There was no change of PWV in the carotid-radial, carotid-femoral and carotid-dorsalis pedis arterial segments after LF-EMS (P>0.05). However, patients with CHF group displayed significantly higher baseline pulse wave velocities (Table 3) for the carotid-radial (P<0.05), carotid-femoral (P<0.01) and carotid-dorsalis pedis (P<0.05) arterial segments.

Table 3.3. Flow Mediated Dilation (FMD) and Pulse Wave Velocity (PWV) Prior to and Following the LF-EMS Bout

	Healthy (n=9)		**CHF (n=6)**	
Endothelial function	**Pre-LF-EMS**	**Post-LF-EMS**	**Pre-LF-EMS**	**Post-LF-EMS**
FMD (%)	7.51 ± 2.05	5.42 ± 1.67	6.51 ± 2.15	4.93 ± 1.09
Baseline diameter (cm)	0.44 ± 0.05	0.45 ± 0.05	0.44 ± 0.03	0.45 ± 0.03
Peak Diameter (cm)	0.47 ± 0.05	0.48 ± 0.05	0.46 ± 0.04	0.47 ± 0.03
SR (AUC)	13067 ± 6544	11149 ± 5591	10567 ± 8012	9833 ± 6546
Time to peak (secs)	50 ± 27	67 ± 25	68 ± 23	90 ± 42
Arterial stiffness				
Carotid-radial PWV (m/s)	6.8 ± 0.8	6.6 ± 0.6	8.83 ± 2.1 †	9.44 ± 1.4
Carotid-femoral PWV (m/s)	5.63 ± 0.85	6.09 ± 1	11.12 ± 4†	11.11 ± 4.8
Carotid-dorsalis pedis PWV (m/s)	7.39 ± 0.94	7.34 ± 0.57	10.41 ± 2.1†	9.89 ± 2.4

FMD, Flow Mediated Dilation; PWV, Pulse Wave Velocity; SR (AUC), Shear Rate, Area Under the Curve.
† Significant difference (P<0.05) between groups

3.4. Discussion

The aim of the study was to characterise cardiovascular responses mediated by an acute bout of LF-EMS. The main findings were: 1) LF-EMS stimulates significant increases in oxygen uptake and large artery blood flow in both young healthy individuals and patients with CHF, 2) patients with CHF had greater lactate levels and used a higher percentage of their VO_2peak, suggesting that the LF-EMS created a greater physiological stimulus in patients with CHF. To the authors knowledge, this is the first study that has demonstrated higher relative aerobic response during LF-EMS in patients with CHF when compared with young healthy individuals. Mean intensities between 40-45% VO_2peak for the majority of the 45-minute LF-EMS bout can be considered equivalent to those recommended for exercise by the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR). (*ACPICR standards : standards for physical activity and exercise in the cardiovascular population*) (*ACPICR standards : standards for physical activity and exercise in the cardiovascular population*) These findings provide preliminary evidence that a bout of LF-EMS could be used therapeutically to mediate cardio-metabolic changes to the same degree as exercise.

3.4.1. Metabolic Response to Low Frequency Electrical Muscle Stimulation.

The finding that LF-EMS can stimulate significant increases in oxygen uptake, blood lactate and large artery blood flow in both young healthy individuals and patients with CHF, is in accordance with previous studies (Banerjee *et al.*, 2005; Banerjee *et al.*, 2009; Crognale *et al.*, 2013). The second important finding was

that the CHF group displayed higher relative VO_2 and BLa responses to the young healthy group. This may be explained by the reduced HR and VO_2 reserve of the CHF population that leads to exercise intolerance (Kemps *et al.*, 2009; Fülster *et al.*, 2013). Long term reductions in CO results in a higher sympathetic HR response at rest in patients with CHF (Clark, Poole-Wilson and Coats, 1996),

and consequently, they become fatigued at levels of exertion not much greater than resting. Anaerobic threshold is also lowered due to the shift in muscle fibre type from oxidative to anaerobic in response to reduced blood flow, and chronic vasoconstriction (Sullivan and Hawthorne, 1995). Hence, levels of BLa remained significantly elevated in the CHF group throughout the LF-EMS bout. Both young healthy and CHF groups appeared to tolerate similar levels of current intensity and had similar pain and RPE responses to the LF-EMS. It may have been expected that the older CHF patients would exhibit lower tolerance due to muscle dysfunction/weakness, but perhaps the opposite is true; ageing and disease causes neural degeneration (Fülster *et al.*, 2013) which could decrease pain levels and improve tolerance. Following additional habituation, participants in both groups may have been able to tolerate a higher stimulation intensity and thus shown a greater cardiovascular response, underlining the importance of LF-EMS familiarisation for optimal results (Crognale *et al.*, 2013). Collectively, these data show that at similar levels of stimulation, CHF patients can receive relatively higher doses of therapy than healthy individuals, and this could lead to beneficial metabolic adaptations with continued use.

3.4.2. Vascular Function During Low Frequency Electrical Muscle Stimulation

To the authors knowledge this is the first study to report a peripheral vascular response to LF-EMS. Enhanced blood flow and shear rate in the brachial artery was observed during the LF-EMS bout. Given that the LF-EMS was administered on the lower limbs, this finding suggests the LF-EMS provides a stimulus large enough to cause a systemic vascular response. Previous studies have reported increased local blood flow during high frequency EMS i.e. in limbs where the skeletal muscles are directly stimulated, in CHF (Dobsák *et al.*, 2006) stroke patients (Wang *et al.*, 2004) and the critically ill (Angelopoulos *et al.*, 2013), but have not attempted to measure a systemic vascular response. This is most likely because high frequency EMS muscle contraction used for muscle strengthening is intermittent and not intended to provide a prolonged aerobic response (Minogue, Caulfield and Reilly, 2007). The subtetanic LF-EMS stimulus by contrast, is continuous, creating oxygen demand that must be matched by increased CO consistent with steady state ‘aerobic exercise’. Thus LF-EMS has shown similar peripheral blood flow patterns e.g. acute systemic increases in shear rate and blood flow (Thijssen *et al.*, 2009), to moderate cycling and walking.

In support of LF-EMS producing similar responses to an acute bout of exercise, the current findings show a reduction in FMD post LF-EMS. Whilst not all exercise bouts mediate an immediate reduction in FMD (Dawson *et al.*, 2013), the majority of studies do show a reduction following an intense or prolonged bout of exercise, normally cycling (Birk *et al.*, 2013) or running (Harris *et al.*, 2008). An immediate decrease in FMD occurs soon after exercise cessation and this maybe explained by low NO bioavailability and result in adaptive long-

term improvement in endothelial function(Dawson *et al.*, 2013). Taken together, the results of the current study suggest that the LF-EMS mediates responses that are comparable to an acute bout of exercise, and may represent an effective stimulus for long-term adaptation.

3.4.3. Central Response to Low Frequency Electrical Muscle Stimulation

This is the first study to describe increases in SV, MAP and CO during LF-EMS. Utilising high frequency (50Hz) EMS, Tanaka and colleagues (Tanaka *et al.*, 2016) reported no change in systolic blood pressure, SV or cardiac index (l/min/m^2) after 30-minutes. The sub-tetanic nature of LF-EMS that allows continuous use to be tolerated could explain this finding (Crognale *et al.*, 2013; Minogue, Caulfield and Lowery, 2014). At 5Hz muscles are given time to relax between contractions in LF-EMS, extending the time before muscles fatigue and sustaining steady state aerobic respiration throughout the whole body (Minogue, Caulfield and Lowery, 2014).

3.4.4. Implications

The findings from the present study suggest that LF-EMS creates an aerobic and vascular stimulus in healthy individuals and CHF patients. The steady state cardiovascular response was comparable to moderate levels of physical activity recommended during CR(*ACPICR standards : standards for physical activity and exercise in the cardiovascular population*)(*ACPICR standards : standards for physical activity and exercise in the cardiovascular population*).

The higher relative VO_2 uptake evoked by LF-EMS in the CHF population combined with the potential benefits on blood flow during exercise and vascular function suggests that this modality of muscle stimulation could be a valuable alternative to traditional exercise for those too debilitated to exercise. Further larger studies should concentrate on the long-term effects on VO_2peak and vascular function after continued use of LF-EMS in CHF patients unable or unwilling to exercise regularly.

3.4.5. Limitations

Notable limitations include a small sample size and unmatched groups for age. Therefore, the findings of the current study are considered preliminary. A larger sample of age-matched participants within a non-laboratory setting is required to confirm these preliminary findings. A strength of this study is that gold standard measures of VO_2 uptake and vascular function (FMD, PWV) were reliably taken before during and after the LF-EMS intervention.

3.5. Conclusion

In summary, an acute bout of LF-EMS produced a significant increase in VO_2 and a systemic vasodilatory blood flow response in patients with CHF and healthy individuals. Furthermore, LF-EMS produced a higher percentage of VO_2peak in patients with CHF suggesting that this method of EMS could be used as alternative means for reversing exercise intolerance in this population.

This therapy may therefore have potential for enhancing endothelial function and cardiovascular fitness in the CHF population.

CHAPTER 4: Randomised Feasibility Trial Into the Effects of Low Frequency Electrical Muscle Stimulation in Advanced Chronic Heart Failure Patients[1]

[1] This study has been published in the British Medical Journal Open access library: Ennis, S., McGregor, G., Hamborg, T., Jones, H., Shave, R., Singh, S. J. and Banerjee, P. (2017) 'Randomised feasibility trial into the effects of low-frequency electrical muscle stimulation in advanced heart failure patients', *BMJ Open,* 7(8), pp. e016148.

4.1. Introduction

Approximately 26 million people are diagnosed with CHF worldwide, (Ambrosy *et al.*, 2014) and the condition is associated with a poor prognosis; 30- 40% of patients die within a year (*Chronic heart failure : management of chronic heart failure in adults in primary and secondary care : quick reference guide*, 2010). Patients in NYHA class III/IV are unable to perform the simplest daily activities, become depressed and have a poor quality of life (Kop, Synowski and Gottlieb, 2011).

Regular aerobic exercise reduces breathlessness and muscle dysfunction for individuals with CHF whilst improving exercise capacity (Sagar *et al.*, 2015; Piepoli *et al.*, 2011; Höllriegel *et al.*, 2016). According to the ExTraMATCH meta-analysis (Piepoli *et al.*, 2004), exercise training leads to a 35% relative reduction in mortality, similar to the effects of beta-blockers (Sallach and Goldstein, 2003) and ACE inhibitors (Flather *et al.*, 2000). However, those with advanced CHF are often so limited that they are unable to gain the holistic benefits of exercise (Piepoli *et al.*, 2011).

Electrical Muscle Stimulation (EMS) may provide an alternative rehabilitative therapy for this group. In patients with mild to moderate CHF, EMS can improve muscle strength of the legs, exercise capacity and quality of life (Smart, Dieberg and Giallauria, 2013; Nuhr *et al.*, 2004; Dobsák *et al.*, 2006). Low frequency (4-5Hz) electrical muscle stimulation (LF-EMS) produces shivering-

like sub-tetanic muscle contractions that can stimulate an aerobic response equivalent to 51% of maximal oxygen uptake (Crognale *et al.*, 2013). The first study in this thesis (chapter 3) demonstrated that therapeutic levels of aerobic exercise can be achieved passively by LF-EMS, supporting previous research,(Minogue, Caulfield and Lowery, 2014). In addition LF-EMS is well tolerated in healthy individuals and those with mild to moderate CHF(Banerjee *et al.*, 2005; Banerjee *et al.*, 2009). However, the effects of long-term use of LF-EMS in advanced CHF (NYHA class III/IV) patients is currently unknown. As advanced CHF patients have shown poor uptake and adherence to intervention studies (Nieminen *et al.*, 2015), a preliminary study was needed to determine the feasibility of LF-EMS in this patient cohort prior to the development of a large-scale definitive trial.

Based upon recommendations for good practice in the design of pilot and feasibility studies (Thabane *et al.*, 2010), this study was undertaken with the following aims: to (a), test the robustness of the study protocol for a potential future trial (b), estimate rates of recruitment, consent and retention (c), determine the tolerability of the LF-EMS intervention and the effectiveness of a 'sham' placebo in the NYHA III/IV CHF population, and (d) gain initial estimates of the efficacy of LF-EMS for all potential primary outcomes. These can then be used for sample size calculations in future substantive trials.

4.2. Methods

Funding

This study was funded by a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) award in 2012. The successful application was made by the author on behalf of chief investigator Dr Prithwish Banerjee, heart failure lead at University Hospital Coventry and Warwickshire, (UHCW) Hospital NHS Trust. The application also involved the co-authors of the resulting publication (Ennis *et al.*, 2017).

4.2.1. Experimental Design

This feasibility study used a double-blind parallel group randomised control design. Participants were randomised to either LF-EMS or 'sham' placebo for a period of eight weeks and blinded to group allocation. Outcomes were assessed at baseline (pre randomisation), eight weeks and 20 weeks follow-up.

4.2.2. Recruitment and Screening

Between October 2013 and March 2015, UHCW Hospital NHS Trust CHF clinics lists were screened for patients fulfilling the eligibility criteria for the study. Sixty eligible participants were recruited. The study conformed to the Declaration of Helsinki and was approved by the local NHS Ethics Committee. All participants provided written informed consent, (see appendix 2).

4.2.3. Randomisation

The trial statistician, Thomas Hamborg, in conjunction with Warwick Clinical Trials Unit generated the randomisation sequence remotely (by computer) using permuted block randomisation. Group allocation was concealed from outcomes assessors and participants.

4.2.4. Participants

Male and female adults, >18 years old, with stable CHF, documented by echocardiography of left ventricular systolic dysfunction (LVEF< 40%) were eligible for the study. All participants had NYHA functional class III-IV symptoms as judged by an experienced CHF cardiologist. Participants were required to be medically stable, defined as the absence of hospital admission or alterations in medical therapy within the preceding two weeks. Exclusion criteria for safety and practical reasons were: (1) presence of implantable cardiac devices, (2) serious cardiac arrhythmias, (3) neurological disorders or previous stroke significant enough to limit exercise, (4) orthopaedic problems that prevented walking, (5) neuromuscular disease, (6) dementia or (7) a mid-thigh circumference of more than 50cm (due to the size of the LF-EMS straps).

4.2.5. Low Frequency Electrical Muscle Stimulation

The LF-EMS equipment (Biomedical Research Limited, Galway, Ireland) consisted of a pair of neoprene straps containing built-in adhesive gel electrodes. The stimulator current waveform was designed to produce rhythmical contractions in the leg muscle groups occurring at a pulse frequency of 4-5Hz (pulse width: 620μs). The maximum peak output pulse current used

was 140mA.

4.2.6. Low Frequency Electrical Muscle Stimulation Intervention

Participants used the LF-EMS or 'sham' placebo for one hour, five times a week, for eight consecutive weeks. Of the five hourly sessions per week, four were completed unsupervised in the participant's own home. The remaining session was conducted in a cardiac rehabilitation outpatient setting under the supervision of an exercise physiologist. The LF-EMS technology was retrospectively interrogated (at the weekly supervised sessions) to report date, frequency, duration and stimulation intensity.

4.2.7. 'Sham' Placebo Intervention

In the 'sham' arm of the study, participants were provided with identical straps and electrodes. In contrast to the LF-EMS group, the controller was programmed to deliver a very low level of stimulation (frequency: 99Hz, pulse width: 150µs, maximum current amplitude: 7.3mA). This provided sensory input to the skin surface but little or no muscle activation. Participants in the 'sham' group had the same induction, supervision and follow-up as the intervention arm.

4.2.8. Outcome Measures

4.2.8.1. Feasibility Criteria

In relation to the design of pilot and feasibility studies, Thabane (Eldridge *et al.*, 2016), recommends stipulating criteria for success '*a priori'*. The feasibility

criteria were:

1. *Recruitment rate* – at least 40% of eligible participants could be recruited to the trial
2. *Retention* – no more than 33% of participants drop out during the intervention period.
3. *Adherence* – 66% of participants tolerate the intervention and adhere to the protocol for ≥70% of the intervention period.
4. *Placebo efficacy*- participants would be able to guess their group allocation no more often than would be expected by chance.

4.2.8.2. Primary Outcome

Six Minute Walk Distance

The 6MWD was conducted in accordance with ATS guidelines (Holland *et al.*, 2014). Participants were instructed to walk as far as possible in six minutes along a 30 metre, flat, obstacle free corridor, turning 180 degrees at the end of every length. Standardised instructions and verbal encouragement were given.

4.2.8.3. Secondary Outcomes

Isometric Muscle Strength

A hand held dynamometer (MicroFET2 Torque/Force indicator, Hoggan Health Industries, Utah, US) validated for assessing functional leg strength in elderly populations was used (Schaubert and Bohannon, 2005). Participants sat in an elevated chair and were instructed to maximally extend the knee while the assessor provided an equal and opposite resistive force, against the lower shin. Mean force generated was measured in Newtons.

Quality of Life: Minnesota Living with Heart Failure Questionnaire

The MLWHF questionnaire is a disease validated questionnaire (Rector and Cohn, 1992) that has been extensively used in CHF studies. Questionnaire scores range from 0 to 105, with higher scores reflecting lower quality of life. Participants were asked to answer each question based on their perception of health in the week previous to testing.

Physical Activity Levels

Physical activity levels were measured by the Bodymedia© SenseWear Pro3 Armband. The multi-plane accelerometer was worn continuously for the seven days prior to testing to determine Total Energy Expenditure (TEE) used as the main indicator of physical activity.

Low Frequency Electrical Muscle Stimulation Acceptability Questionnaire

At the end of the trial participants were given a brief questionnaire used in previous LF-EMS studies (Crognale *et al.*, 2013; Minogue, Caulfield and Lowery, 2014) to collect feedback on the acceptability of using LF-EMS regularly. Questions used the likert scale to discern cognitive and affective components of attitudes (Likert, 1932) about ease of use, comfort, tolerability and overall satisfaction.

Safety: Blood test

Venous blood samples were taken at baseline, four weeks and eight weeks to assess creatine kinase (CK), urea and electrolytes, and were analysed by the UHCW biochemistry department. Participants discontinued the trial if levels exceeded the upper limit of normal reference ranges

4.2.9. Data Analysis

Data analyses for the feasibility objectives of this study were descriptive, based on the pre-determined criteria needed to conduct a full RCT specified above. Confidence intervals (CI) set at 95%) were calculated for all secondary outcome measures in both groups and paired two-sample t-test conducted for between group comparisons. Intent-to-treat (ITT) analysis was employed in this study as is recommended for clinical trials (Alshurafa *et al.*, 2012) .

4.3. Results

4.3.1. Feasibility Criteria Outcomes

4.3.1.1. Recruitment

There were 171 eligible participants identified in the Coventry and Warwickshire area from November 2013 - April 2015. Sixty of 171 eligible participants (35.08%) were recruited to the trial. Participants were randomised and started on the trial during this period and were followed up until data collection finished in August 2015. Participant characteristics are presented in Table 4.1.

Table 4.1. Baseline Demographic and Clinical Characteristics of the LF-EMS and 'Sham' Placebo Groups. Data presented as mean ± SD or absolute number and percent.

Demographics	**LF-EMS (n=30)**	**'Sham' (n=30)**
n Male	20 (66%)	22 (73%)
Age (yrs)	66.5 ± 7.8	66.8 ± 13.5
Body Mass Index (kg/m^2)	30.1 ± 4.9	27.8 ± 4.8
Comorbidities		
Prev MI/PCI/CABG	17 (56%)	11 (36%)
Diabetes	12 (40%)	10 (33%)
COPD	9 (30%)	8 (26%)
AF	20 (66%)	16 (53%)
Hypertension	13 (43%)	10 (33%
CKD	5 (16%)	13 (43%)
Clinical		
NT-pro-BNP (pg/mL)	3086 ± 3746	2046 ± 2545
Creatinine (μmol/L)	108 ± 49	113 ± 39
LVEF %	39 ± 11*	22 ± 12**
BP_{sys} (mmHg)	118 ± 16	126 ± 17
BP_{dia} (mmHg)	69 ± 9	74 ± 14
NYHA III	24 (80%)	22 (73%)
NYHA IV	6 (20%)	8 (26%)

NT-pro-BNP (pg/mL),N-terminal pro B-type natriuretic peptide; LVEF; left ventricular ejection fraction; BP_{sys} (mmHg), systolic blood pressure; BP_{dia} (mmHg), diastolic blood pressure; NYHA, New York Heart association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease;

***n=10. Ejection fraction could not be accurately assessed in most patients due to poor body habitus/atrial fibrillation. An experienced cardiac sonographer made an 'eyeball' assessment, confirming poor left ventricular function for all other participants**
****n=5. See previous comments.**

4.3.1.2. Retention

Twelve of the 60 participants (4 LF-EMS, 8 ‘sham’; 20%) withdrew and did not finish the intervention period. Of these, only three found the intervention intolerable (1 LF-EMS, 2 ‘sham’). Other reasons for dropout were: deterioration in health (n=6), family problems (n=2) and implantation of a cardioverter defibrillator (n=1). Only 22 (45%) of those completing the intervention period returned for follow-up testing at 20 weeks (See Fig 4.1.). Reasons for non-follow-up were: deterioration in health (n=9), excluded due to implantation of cardiac resynchronisation therapy device (n=2), declined to take part without further explanation (n=13), and could not be contacted after repeated attempts (n= 3).

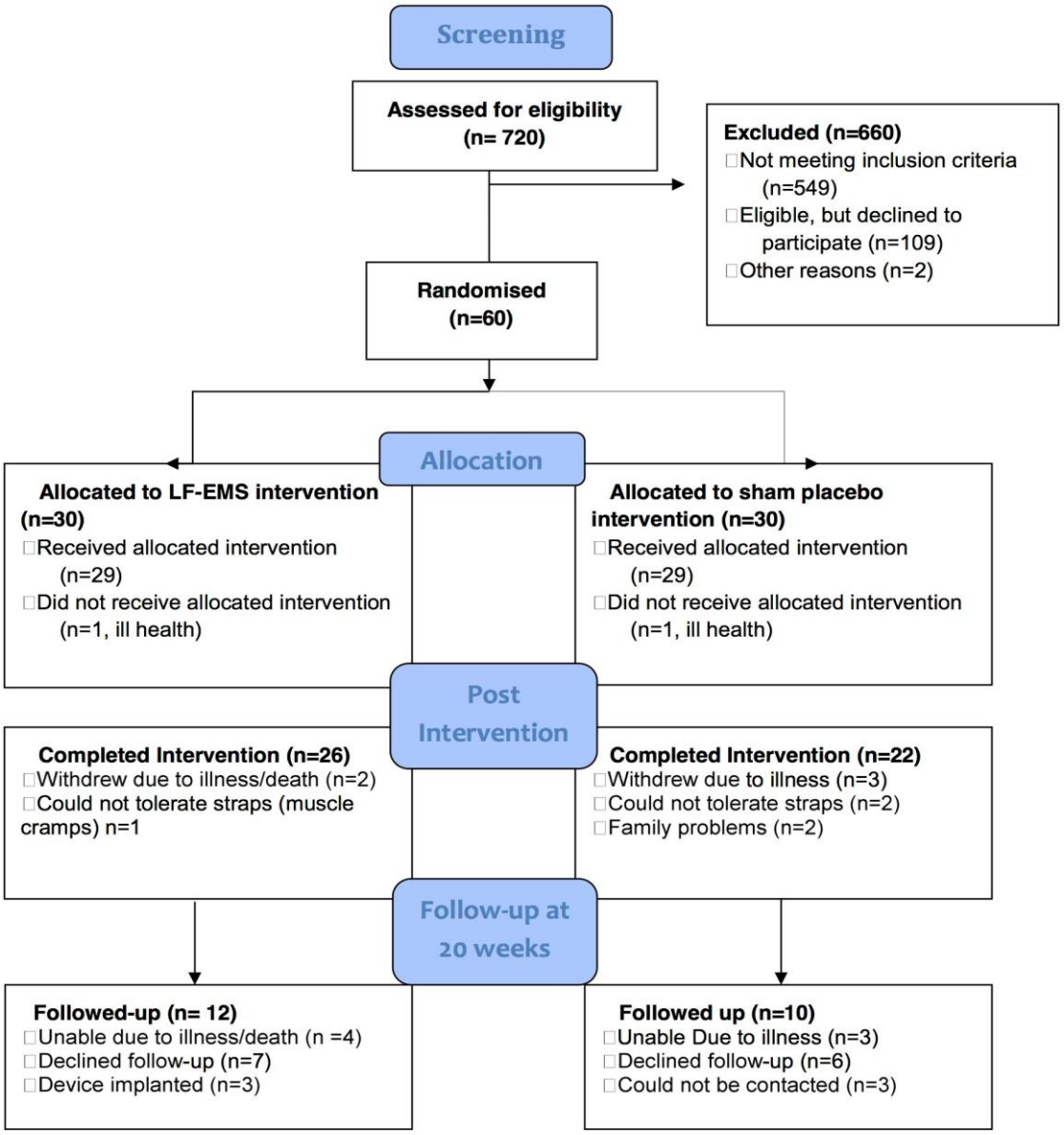

Fig. 4.1. CONSORT Flow Diagram of a Single Centre Blinded Parallel Group Randomised Feasibility Trial of LF-EMS Versus 'Sham' Placebo in Advanced CHF Patients

4.3.1.3. Adherence

Forty one (85.4%) of the 48 participants (22-LF-EMS, 19-'sham') who completed the intervention period (68.3% of the total sample) adhered to the strict protocol for the majority (>70%) of the eight weeks. Interrogation of the LF-EMS controllers revealed that participants in the LF-EMS group became more tolerant to the intervention; mean stimulation intensity increased from 57.79mA (95%CI: 51.16 to 64.42) during week 1 of the study to 84.86mA (95%CI: 75.44 to 94.28) by week 8, a relative improvement of 46.5%.

4.3.1.4. 'Sham' Placebo

The 'sham' placebo for the study appeared to be convincing as only 61% of participants guessed their treatment group correctly. The 95% CI for the proportion of participants guessing correctly was 46% to 74% and thus not significantly different from 50% which would be expected by chance. Participants demonstrated an inclination to guess that they were randomised to LF-EMS regardless of group allocation.

4.3.1.5. Safety

No abnormalities were detected in CK, urea or electrolytes taken before, during or after the study. Likewise, no adverse events due to the intervention were recorded in either group.

4.3.2. Primary Outcome: 6-Minute Walk Distance

Non-significant improvements after LF-EMS (8-week time point) and 'sham' groups were observed in 6MWD with a mean increase from baseline of 24 metres (P=0.13) in the LF-EMS group (Table 4.2.).

Table 4.2.: Mean Outcome Measurements at Each of the Three Time Points with 95% CIs

Outcome	Time point	LF-EMS	'sham'
Mean 6 MWD (metres) [95% CI]	Baseline	283 (237 to 328)	290 (243 to 337)
	(n)	29	29
	8 weeks	312 (262 to 362)	318 (270 to 365)
	(n)	26	22
	20 weeks	257 (173 to 342)	226 (126 to 325)
	(n)	12	10
Mean Leg strength (newtons) [95% CI]	Baseline	234 (196 to 272)	297 (253 to 342)
	(n)	29	29
	8 weeks	224 (187 to 262)	321 (267 to 374)
	(n)	25	22
	20 weeks	181 (131 to 231)	207 (148 to 265)
	(n)	11	10
Mean QoL (score) [95% CI]	Baseline	53.1(42.7 to 63.5)	50 (40 to 60.1)
	(n)	28	29
	8 weeks	43.9 (34.2 to 53.5)	43.1 (30.9 to 55.3)
	(n)	25	22
	20 weeks	51.7 (31.6 to 71.8)	37.0 (16.9 to 57)
	(n)	12	10
Mean TEE (joules) [95% CI]	Baseline	63,438 (56,170 to 70,705)	65,371 (59675 to 71,067)
	(n)	25	27
	8 weeks	59,783 (51,094 to 68,471)	59,687 (50,630 to 68,745)
	(n)	19	17
	20 weeks	61,878 (53,345 to 70,410)	63,541 (55,795 to 71,287)
	(n)	7	6

6 MWD, 6-minute walk distance, QoL, quality of life; TEE, Total Energy Expenditure

4.3.3. Secondary Outcomes

There were no significant differences between groups in the change from baseline for any of the secondary outcome variables (Table 4.3.). There was a non-significant improvement in quality of life in both groups.

Table 4.3: Mean Changes from Baseline Outcomes with 95% CIs

Outcome	Time point	LF-EMS	'sham'	P value
Mean 6 MWD (metres) [95% CI]	Baseline to 8 weeks *(n)*	24 (9 to 40) 26	9 (-4 to 22) 22	0.1366
	Baseline to 20 weeks *(n)*	0 (-32 to 31) 12	-26.3 (-63 to 11) 10	0.2409
(Mean leg strength (newtons) [95% CI]	Baseline to 8 weeks *(n)*	-9.2 (-28.9 to 10.5) 25	6.0 (-19.3 to 31.4) 22	0.3244
	Baseline to 20 weeks *(n)*	-43.4 (-78.7 to -8.2) 11	-74.1(-116.3 to -31.9) 10	0.2223
Mean QoL (score) [95% CI]	Baseline to 8 weeks *(n)*	-7.6 (-15.5 to 0.3) 25	-4.7 (-10.5 to 1.0) 22	0.5505
	Baseline to 20 weeks *(n)*	1.5 (-12.5 to 15.7) 12	-14.0 (-34 to 6) 10	0.1610
Mean TEE (joules) [95% CI]	Baseline to 8 weeks *(n)*	-4635 (-3963 to 4692) 19	-8168 (-14,342 to -1995) 17	0.5108
	Baseline to 20 weeks *(n)*	1686 (-6435 to 9809) 7	4177 (-7695 to 16,050) 6	0.6634

6 MWD, 6 minute walk distance; QoL, quality of life; TEE, Total Energy Expenditure

Acceptability questionnaire

Participant's responses to the LF-EMS acceptability questionnaire are summarised in Table 4.4. The mean response to putting on the straps was 2 (quite easy) and the overall mean satisfaction of participants with the intervention was 6 out of 10. Mean responses to comfort, sensation, tolerability and continued use of LF-EMS were between 3 (medium) and 4 (quite hard/unpleasant).

Table 4.4. Mean Responses to Acceptability Questionnaire and Standard Deviations (SD)

Question	Mean Response	SD
1. I found putting on the straps (1-easy, 5-hard)	2.0	±1.17
2. At the highest intensity I found the comfort level (1-acceptable, 5-unacceptable)	3.5	±1.19
3. Overall I found the sensation (1-pleasant, 5-unpleasant)	3.3	±1.13
4. I found putting on the LF-EMS for an hour (1-easy, 5-hard)	3.1	±1.08
5. I think I would find staying on a LF-EMS training routine (1-easy, 5-hard)	3.4	±1.29
6. Overall satisfaction with LF-EMS as a way of improving your fitness (1-none,10 extremely satisfied)	6.0	±1.94

4.4. Sample Size Calculation

The point estimate from the study and the upper CI limit of this estimate were calculated. The upper CI limit was used for the sample size calculation. For detecting the observed difference of 13.4 metres in this study a sample size of 240 patients per group would be required. However, a recent study (Täger *et al.*, 2014) suggested that the minimal clinically important difference for 6MWD is 36 metres in mild-moderate CHF patients. The clinical benefit of the effect size in this study should be considered before proceeding with a larger trial.

4.5. Discussion

The predetermined criteria for proceeding to a larger trial were achieved for dropout (20%), adherence (68%) and 'sham' placebo efficacy (62% participants guessed correctly). However, only 35% of eligible patients were recruited, below the target of 40%. Initial outcome measures revealed no significant difference between intervention and placebo groups, although there was a non-significant improvement in 6MWD and quality of life after LF-EMS.

4.5.1. Feasibility Outcomes

4.5.1.1. Recruitment

Percentage uptake (35%) of eligible patients in the study was below the predetermined criteria of 40%. This is similar to the poor uptake of conventional cardiac rehabilitation (CR) nationally in the UK: less than 40% of eligible CHF patients accessed CR in the most recent National Audit of Cardiac Rehabilitation (Rehabilitation, 2017).

4.5.1.2. Retention/Adherence/Tolerance

One strength of this study is the good level of adherence (68%) and retention (80%) compared with other clinical studies; In the HF-ACTION trial (O'Connor *et al.*, 2009), only 40% of patients in the exercise group (n=1159), reported adherence to recommended training volumes after three months. This may have been because of the ease of independent use at home of LF-EMS, in combination with the weekly supervised sessions with an exercise physiologist. The patients recruited in the present trial were more debilitated yet they

engaged more with LF-EMS than those in the HF-ACTION trial (Atchley *et al.*, 2009), suggesting that LF-EMS maybe more acceptable to this population than conventional exercise.

The dropout at three months follow-up was higher than expected due to ill health, device implantation and apathy, and would be challenging to overcome in a larger trial. Strategies to combat dropout could include combining assessment with clinical patient appointments to ensure compliance or arranging home visits for some assessments.

Feedback from the acceptability questionnaires may also be useful in curtailing dropout in a larger trial: the LF-EMS group generally thought that wearing the straps for an hour was 'medium' to 'quite hard/unpleasant'. Continued use of a LF-EMS was deemed challenging also, so it is possible that a reduced frequency of LF-EMS whilst still maintaining a sufficient dose e.g. 3 x 1 hr a week may enhance long-term adherence.

Tolerance to the LF-EMS intervention improved during the study. Mean current intensity increased by 46% from week one to week eight. This tolerance effect is in keeping with an earlier study (Crognale *et al.*, 2013), that showed a 20% increase in healthy active adults. The healthy active adults tolerated higher absolute stimulation levels than in this study, both before and after habituation, suggesting that advanced CHF patients are subjectively less tolerant to LF-EMS than a healthy population. In addition, the user feedback collected seems to support this view. Vivodtzev and colleagues (Vivodtzev *et al.*, 2014), examined factors determining tolerance of EMS in pulmonary patients. The study reported that lower tolerance to EMS was associated with greater severity of condition, fat free mass and inflammatory response. It is possible that the same

is true in the CHF population, but more research is needed to confirm this.

4.5.2. Outcome Measures

Baseline 6MWD was higher in the study sample than in other advanced CHF studies (Reeves *et al.*, 2017). This may have been due to high variability because of a few outliers in each group. This reflects the subjective nature of the NYHA classification system. However, signs and symptoms of advanced CHF were primarily the eligibility criteria for this study and not 6MWD. In addition, the ≤300-m distance cut-off (below which our baseline mean falls) is often cited as prognostically important and reflective of advanced disease in many investigations (Guazzi *et al.*, 2009; Arslan *et al.*, 2007; Rostagno *et al.*, 2003). The non-significant improvements in exercise capacity as measured by 6MWD were smaller than those in a meta-analysis of EMS in CHF patients by Smart, Dieberg and Gialluria (Smart, Dieberg and Giallauria, 2013). These authors reported a combined improvement in 6MWD of 47 metres vs usual care or placebo, compared to the effect size of 13 metres in the current study. However, patients in the current study were more symptomatic than those included in the meta-analysis (Smart, Dieberg and Giallauria, 2013), and thus had a lower baseline exercise capacity (286 vs 342 metres). Nevertheless, the mean relative increase (5%) in walk distance of participants in the LF-EMS group is within the measurement error associated with this test (Zugck *et al.*, 2000) and probably should not be considered clinically significant (Täger *et al.*, 2014). The extrapolation from these results that advanced CHF patients are beyond help from EMS maybe premature; a longer training period maybe required to show meaningful changes in exercise capacity, particularly as some

participants took longer to tolerate meaningful EMS intensities than others. Quality of life (MLHFQ) improved in both groups after the intervention. This may, in part, relate to the psychosocial benefits of engaging with researchers regularly in the cardiac rehabilitation facility (Jeon *et al.*, 2010). The placebo effect of both interventions and its influence on patients' perception of well-being should not be underestimated.

Based on previous research by Banerjee et al (Banerjee *et al.*, 2005; Banerjee *et al.*, 2009), and numerous high frequency EMS studies (Nuhr *et al.*, 2004; Harris *et al.*, 2003; Dobsák *et al.*, 2006), improvement in leg strength after use of LF-EMS was expected. The current trial however, demonstrated no significant change in muscle strength. Muscle wasting, prevalent in many advanced CHF patients (Fülster *et al.*, 2013), could explain this observation. The chronic impairment of muscle tissue caused by CHF affects the muscle and skin nerve receptors and hence contractility of the weakened muscle (Rullman *et al.*, 2013). Participants with more functional leg muscles, therefore, may have received greater stimulus to muscle tissue that others did for the same level of current intensity. This suggests that LF-EMS may not be effective for all advanced CHF patients.

4.5.3. Limitations

The sample for this study was small as is recommended for feasibility studies (Thabane *et al.*, 2010) and this limits the external validity of our findings. Participants were deemed eligible for the study based on the judgment of experienced CHF clinicians using available knowledge. This may have led to

greater variability in disease severity/limitation than was intended. The current amplitude (mA) stimulus intensity that participants chose to use was a limitation to the study design. Participants were instructed to adhere to the ‘maximum tolerable intensity’ during LF-EMS sessions. Due to considerable individual differences in the subjective perception of discomfort associated with EMS, It is likely that there was variability in the intensity that individuals received.

4.6. Conclusion

As all but one of the predetermined feasibility criteria were met in this trial, a larger study into the effects of LF-EMS on advanced CHF patients could be undertaken. However, this 'difficult to engage with' patient group would be very challenging to recruit and follow-up in sufficient numbers to provide definitive data on its efficacy. The improvements seen in this study in 6MWD, and quality of life measures, were not statistically significant. Leg strength and physical activity levels showed no meaningful change. A longer intervention period than eight weeks could be considered, to give participants more time to adjust to the intervention. More research is required to determine which CHF patients are unresponsive to LF-EMS due to severe muscle dysfunction. A larger trial may be feasible with this difficult population: however, it is unlikely that the non-significant improvement in exercise capacity and quality of life found in this pilot study justifies a larger pragmatic trial.

CHAPTER 5: Can a Low Frequency Electrical Muscle Stimulation Intervention Improve Endothelial Function in Advanced Chronic Heart Failure Patients?[2]

[2] This study has been published in the ESC Heart Failure Open access library: Ennis, S., McGregor, G., Shave, R., McDonnell, B., Thompson, A., Banerjee, P. and Jones, H. (2018) 'Low frequency electrical muscle stimulation and endothelial function in advanced heart failure patients', *ESC Heart Fail,* 5(4), pp. 727-731.

5.1. Introduction

The longitudinal feasibility study discussed in chapter four gave the opportunity to investigate other important clinical measures for the CHF population, such as endothelial function and VO_2peak, as a subset study.

Advanced CHF patients (NYHA class III/IV) are unable to perform simple activities of daily living despite usual clinical care (Kop, Synowski and Gottlieb, 2011). Exercise capacity (Aslanger *et al.*, 2015) and endothelial function (Katz *et al.*, 2005) are predictors of mortality in CHF and are therefore useful targets for treatment. Advanced NYHA class III/IV patients cannot tolerate exercise; thus, EMS has been explored as a potential therapy which can improve fitness and endothelial function in mild CHF patients (Smart, Dieberg and Giallauria, 2013; Dobsák *et al.*, 2006; Nuhr *et al.*, 2004). Improvements in exercise capacity and endothelial function with LF-EMS in patients with advanced CHF (NYHA class III/IV) could reduce the incidence of all-cause mortality (Shechter *et al.*, 2009) and improve overall quality of life. The aim of this study was to examine the effect of eight weeks of LF-EMS on brachial endothelial function and VO_2peak in advanced CHF patients compared with a 'sham' placebo.

5.2. Methods

5.2.1. Research Design

The study was a double blind, parallel group, randomised controlled trial. Sixty participants with stable CHF and NYHA functional class III-IV symptoms, documented by echocardiography (ejection fraction < 40%) were randomised to

either LF-EMS (n=29) or ‘sham’ placebo (n=29) for a period of eight weeks (Ennis *et al.*, 2017). Patients with implantable cardiac devices, life threatening cardiac arrhythmias, or neurological disorders were excluded. The study was approved by a locally appointed ethics committee in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants (see appendix 2).

5.2.2. Low Frequency Electrical Muscle/ ‘Sham’ Stimulation

A detailed description of the LF-EMS and ‘sham’ interventions is given in chapter four. Briefly, the LF-EMS equipment (Biomedical Research Limited, Galway, Ireland) containing built-in adhesive gel electrodes was worn on the upper legs. The LF-EMS group received stimulation at a pulse frequency of 4-5 Hz (pulse width: 620 µs, maximum current amplitude 140 mA). The ‘sham’ group experienced a very low level of stimulation (frequency: 99 Hz, pulse width: 150 µs, maximum current amplitude: 7.3 mA). Participants used the LF-EMS or ‘sham’ for one hour, five times a week, for eight consecutive weeks. Four of the five sessions were at home and one under supervision, usage was recorded by the device.

5.2.3. Brachial Artery Flow Mediated Dilation and Cardiopulmonary Exercise Test

Brachial artery FMD was assessed using high-resolution ultrasound, (Acuson P50, Siemens Medical, Camberley, UK). Change in arterial diameter in response to a five minute ischemic stimulus induced by forearm cuff inflation to 220 mm Hg was assessed following recommended guidelines (Thijssen *et al.*,

2011). Baseline diameter was controlled for using an allometric approach (Atkinson and Batterham, 2013). Maximal CPET testing was performed in accordance with ATS guidelines (Society and Physicians, 2003) on an upright cycle ergometer with an exercise respiratory gas analysis system.

5.2.4. Statistical Analysis

Delta changes (∆) from pre-intervention were calculated for each group and entered as the dependent variable in a linear mixed model, with pre-intervention data entered as a covariate. Data are presented in the text for intervention adjusted effects as mean and 95% CIs and exact P values are cited. Data were analysed using SSPS, (Version 20: SPSS Inc., Chicago, IL).

5.3. Results

Participant characteristics are presented in table 5.1. below.

Table 5.1. Baseline Demographic and Clinical Characteristics of the LF-EMS and 'Sham' Placebo Groups. Data presented as mean ± SD or absolute number and percent.

Demographics	**EMS intervention (n=20)**	**'sham'(n=15)**	**P value**
n Male	13 (65%)	10 (66.6%)	0.92
Age (yrs)	68.6 ± 9.4	66.7 ± 6.8	0.5
BMI kg/m $^{-2}$	29.5 ± 4.7	27.8 ±5.4	0.1
Clinical			
NT-pro-BNP (pg/mL)	3052 ± 3398	2132 ± 2012	0.23
Creatinine (μmol/L)	101 ± 47	109 ± 41	0.45
LVEF %	39 ± 11	22 ± 12	0.42
BP_{sys} (mmHg)	116 ± 19	123 ± 14	0.16
BP_{dia} (mmHg)	67 ± 11	70 ± 8	0.23
NYHA III	14 (70%)	11 (73.3%)	0.83
NYHA IV	6 (30%)	4 (26.7%)	0.83
Comorbidities			
Prev MI/PCI/CABG	13 (65%)	8 (53.3%)	0.49
Diabetes	10 (50%)	7 (46.6%)	0.84
COPD	5 (25%)	3 (20%)	0.73
AF	14 (68%)	9 (60%)	0.62
Hypertension	9 (45%)	7 (46.6%)	0.92
CKD	5 (25%)	9 (60%)	0.03

NT-pro-BNP (pg/mL),N-terminal pro B-type natriuretic peptide; LVEF; left ventricular ejection fraction; BP_{sys} (mmHg), systolic blood pressure; BP_{dia} (mmHg), diastolic blood pressure; NYHA, New York Heart association; MI, myocardial infarction; PCI,

percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease;

This study measured endothelial function and VO_2peak on a smaller cohort (LF-EMS n=20, 'sham' n=15) from the larger trial (Ennis *et al.*, 2017), as some of the participants were too ill, unable or unwilling to complete the FMD and CPET measures (Fig. 5.1.).

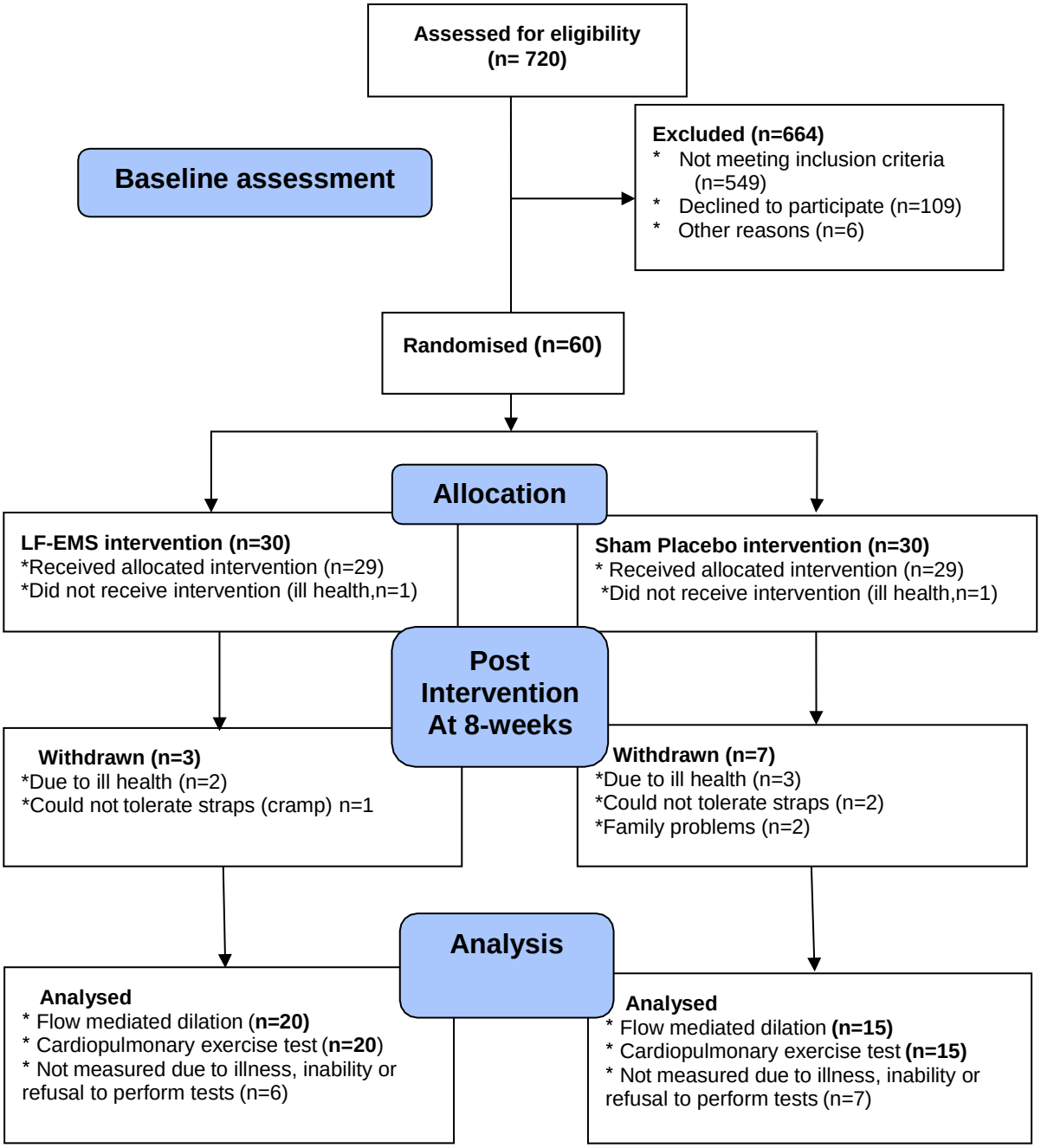

Fig. 5.1. CONSORT Flow Diagram of the Study; LF-EMS Versus 'Sham' Placebo in Advanced CHF Patients

5.3.1. Brachial Artery Flow Mediated Dilation

Brachial artery FMD improved by 2.81% (95%CI: 1.34 to 4.28) with LF-EMS compared with 1.26 (95%CI: -0.44 to 2.95) with 'sham' (Fig.5.2) but this did not reach statistical significance (P=0.07).

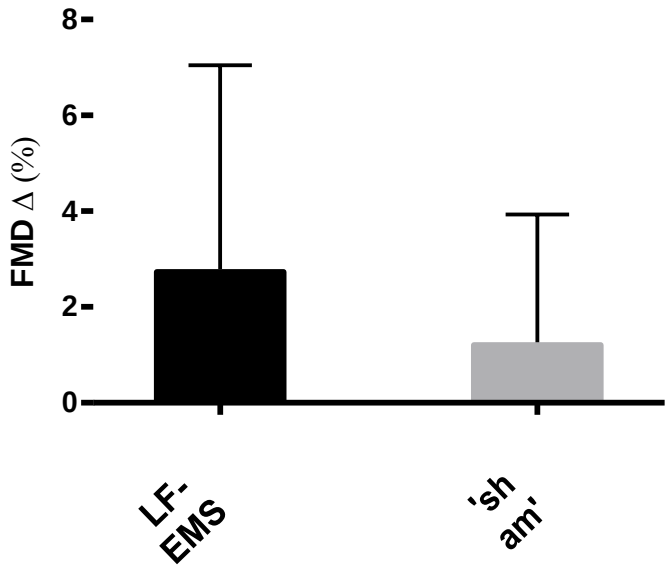

Fig. 5.2. Mean FMD Change After Eight Weeks LF-EMS or 'Sham'. Error bars are SD

There was also a trend towards a smaller arterial diameter (Table 5.2.) with 'sham' vs LF-EMS (P=0.08). There were no notable intervention mediated changes in peak arterial diameter or shear rate and time to peak.

Table 5.2. Changes in Endothelial Function and CPET Performance After Eight Weeks LF-EMS or 'Sham' Intervention.
Data was analysed using general estimating equations and presented as mean (95% CI). Delta (Δ) change from baseline values (95%CI)

Endothelial function	Pre LF-EMS	LF-EMS Δ	Pre 'sham'	'sham' Δ	P
FMD (%)	5.48 (4.34 to 6.32)	2.79 (0.8 to1.99)	5.43 (3.47 to 7.39)	1.26 (-0.22 to 2.7)	**0.075**
Baseline diameter(cm)	0.43 (0.39 to 0.47)	0.00 (-0.02 to 0.01)	0.46 (0.42 to 0.5)	-0.01(-0.04 to 0.02)	**0.086**
Peak diameter (cm)	0.46 (0.42 to 0.49)	0.01 (-0.01 to 0.03)	0.48 (0.45 to 0.52)	0.00 (-0.03 to 0.03')	**0.268**
Shear rate $_{AUC}$	14048.71 (10127.903 to 17969.52	-2735.94 (-7148.93 to 1677.07)	12700.18 (7269.49 to 18130.87)	1127.39 (-5262.84 to7517.63')	**0.953**
Time to peak (s)	73.45 (57.52 to 89.37)	-11.00 (-31.83 to 9.82)	70.04 (48.94 to 91.13)	4.09 (-28.16 to 36.34)	**0.887**
Maximal O_2 uptake					
VO_2 peak (ml. kg^{-1} min^{-1})	13.87 (12.47 to 15.26)	-0.19 (-1.05 to 0.69)	12.87 (10.99 to 14.75)	0.06 (-0.75 to 0.87)	**0.922**
Max watts output	67.25 (56.12 to 78.38)	-1.70 (-9.01 to 5.61)	69.12 (53.94 to 84.29)	-2.29 (-7.64 to 3.05)	**0.999**
Anaerobic Threshold (ml. kg^{-1} min^{-1})	8.84 (7.31 to 10.38)	-0.11 (-0.2 to 2.3)	8.05 (6.21 to 9.89)	0.64 (0.18 to 0.32)	**0.893**

5.3.2. Cardiopulmonary Exercise Test

There were negligible changes in VO_2peak in both groups following the eight week intervention period (Table 5.2).

5.4. Discussion

Data from this study provide preliminary evidence of enhanced endothelial function measured using FMD following LF-EMS compared to 'sham' in NYHA III/IV CHF patients. Despite this, no notable changes in VO_2peak were observed. These data suggest that LF-EMS intervention could be useful in improving vascular function in advanced CHF.

This is the first study to assess the impact of LF-EMS on endothelial function in NYHA III/IV patients. The novel finding of the current study is that FMD can be

improved in advanced CHF patients. The observed improvement in vascular function corresponds to a meaningful decrease in mortality risk, previously a 1% increase in FMD has been associated with a 20% decreased mortality in CHF patients (Katz *et al.*, 2005; Shechter *et al.*, 2009). This group of patients is physically debilitated by their condition and is therefore not generally referred for exercise based cardiac rehabilitation. It is possible that LF-EMS may offer an alternative means to conventional exercise in altering blood flow (shear) stress patterns against the artery walls to improve vascular function.

Whilst a change in artery diameter with LF-EMS was not evident in the current study there was evidence of a decrease in artery size in the 'sham' intervention. The change in artery size may suggest that the health of the artery is deteriorating possibly related to persistent physical inactivity (de Groot *et al.*, 2006). Whilst it should be acknowledged that compensatory outward arterial remodelling is also possible in response to atherosclerosis (Heusch *et al.*, 2014) LF-EMS may prevent detrimental remodelling of the artery.

We observed a minimal improvement in 6MWD in chapter four but no improvements in VO_2peak were evident. Whilst, a larger dose and duration of LF-EMS may be required to improve fitness, the measurement of VO_2peak is challenging in this population. Many were unable to meet the requirements for peak oxygen uptake including Respiratory Exchange Ratio (e.g. 52% lower than 1.10 at baseline) and test duration (<eight minutes) (Society and Physicians, 2003) suggesting that they were limited by their CHF induced musculo-skeletal issues rather than oxygen uptake. The 6MWD is probably a better indicator of

change in functional capacity for trials due to its ease of use and standardisation.

This study had a small sample size and was exploratory in nature. The findings should therefore be considered preliminary. Future larger studies are required to confirm these results in the advanced CHF population. In summary, LF-EMS could be useful in improving vascular function in NYHA III/IV patients and may have a protective effect to reduce the risk of mortality in this population (Ennis *et al.*, 2017).

CHAPTER 6: General Discussion

6.1. Aims and Objectives

The research work described in the current thesis was designed to investigate the feasibility and acceptability of LF-EMS in the advanced CHF population, and to examine the changes in physiological and clinical variables that LF-EMS could mediate in this high-risk group of patients with limited treatment options. This was investigated in three distinct studies with the aims to: 1) characterise the physiological stimulus of LF-EMS; 2) determine the feasibility of a randomised controlled trial of LF-EMS in a CHF patient population; and 3) examine the effect of the LF-EMS intervention on vascular function as an outcome variable.

6.2. Summary of Main Findings and Implications

6.2.1. Low Frequency Electrical Muscle Stimulation May Have Therapeutic Benefits for Enhancing Cardiovascular Function.

The studies in the present thesis provide evidence that an acute bout of LF-EMS can stimulate a central and peripheral cardiovascular response (study one) in healthy individuals and importantly in patients with CHF. The blood flow and oxygen uptake changes mediated by a bout of LF-EMS may explain the evidence of improvements in endothelial function following regular (5 x 1 hr per week for eight weeks) LF-EMS use (study three). Whilst peripheral blood flow and endothelial function are not routinely measured as part of clinical practice in patients with CHF, nor form part of the clinical diagnosis, endothelial function is relevant in this patient group as it provides prognostic information and is implicated in the pathophysiological process of CHF (Katz *et al.*, 2005).

Study one also indicated aerobic responses to LF-EMS, which could explain the increases in functional capacity (study two), a surrogate of fitness, which is employed in clinical practice in patients with CHF. The improvements in functional capacity with eight weeks of LF-EMS were small, but it is important to consider how much improvement can be expected from any intervention in advanced CHF patients, who are largely breathless at rest and too limited to walk more than a few steps. It is likely that many of the participants were in the 'end stage' of CHF (23% of the sample were classified as NYHA IV, which is usually when they receive palliative care) and therefore small changes in functional capacity might be physiologically meaningful to this group of patients. Based on the assumption that advanced CHF patients can improve their functional capacity, potentially increasing the dose of LF-EMS (i.e. a longer intervention) could lead to larger changes that could translate into long-term benefits. Taken together, the studies in the current thesis provide preliminary evidence of physiological improvements with LF-EMS in the advanced CHF population.

6.2.2. Low Frequency Electrical Muscle Stimulation is Feasible and Acceptable in the Advanced Chronic Heart Failure Population

Study two demonstrated that patients with advanced CHF can be recruited to a RCT and tolerate the LF-EMS intervention. Given the poor compliance of this population to other interventions, including medication, these findings are promising. Patients with advanced CHF demonstrated good compliance to this potentially useful intervention. The adherence to LF-EMS could have been

helped by the fact that the intervention was tolerable and could be performed at home. Another positive finding of study two was that advanced CHF patients are willing to take part in randomised control trials to improve their health. Summarily these findings show that LF-EMS is a possible alternative to exercise for patients with advanced CHF for improving prognosis.

6.2.3. Feasibility of Performing a Definitive Randomised Controlled Trial to Test the Efficacy of Low Frequency Electrical Muscle Stimulation

Study two of the thesis was a feasibility trial funded by National Institute of Health Research (NIHR) Research for Patient Benefit (RfPB) scheme. The NIHR encourages feasibility studies to refine trial design, recruitment and outcomes so that the main study, if appropriate, will have a better chance of success. The feasibility study found that the 'a priori 'criteria for a larger trial was fulfilled except for a slightly lower uptake (35%) than was stipulated (40%) suggesting that a fully powered RCT aimed at establishing the effectiveness of LF-EMS is possible. Nevertheless, there are several important recruitment, protocol and outcome measurement issues to consider before progressing to a full trial.

6.2.3.1. Recruitment For a Definitive Randomised Controlled Trial

For detecting the observed difference of 13 metres extra distance walked during the 6MWT in the feasibility study, a sample size of 240 patients per group would be required. Over the 18-month recruitment period 171 eligible patients were found within the Coventry and Warwickshire NHS trust, of which 60 were recruited. At this rate of recruitment, it would take over ten years to complete a

larger study at a single site. Therefore, a multi-site approach would be needed with several sites contributing participants simultaneously in order to recruit at least 40% of eligible patients or higher. Another way to increase recruitment rate would be to opt for a 2:1 recruitment approach where for every participant randomised to the 'sham' control arm, two are randomised to the intervention. Advocates for 2:1 allocation claim that this improves recruitment rate as participants perceive they have more chance of receiving the active intervention (Avins, 1998). However this method has been criticised for introducing bias via 'therapeutic misinformation' i.e. unreasonable expectations about therapeutic benefit (Hey and Kimmelman, 2014).

6.2.3.2. Outcome Measures For a Definitive Randomised Controlled Trial

The primary outcome of 6MWD defined in the feasibility study only demonstrated minor improvements which required a large sample size to power the full trial. Whilst the 6MWD is used clinically in CHF patients to define functional capacity, more recent research studies (Reeves *et al.*, 2017) have employed the Short Physical Performance Battery (SPPB), which involves a combined score for balance, walking speed and the five times sit to stand tests. This score has been shown to be strongly correlated with physical function in older adults (Volpato *et al.*, 2011) and is becoming widely used in recent CHF research studies (Pavasini *et al.*, 2016; Reeves *et al.*, 2017). The SPPB may more accurately capture improvements in functional mobility due to LF-EMS than 6MWD combined with leg strength assessment as was utilised in the feasibility study. One recommendation from the feasibility study therefore is to replace the leg strength assessment with the SPPB in a full trial. Additionally,

the findings of study one and three in the current thesis, which were not part of the NIHR grant, suggest that LF-EMS has an impact on peripheral blood flow and consequently, endothelial function. Given this preliminary evidence, incorporation of FMD as an outcome measure to future trials is recommended. The measure of Health Related Quality of Life (HRQOL) was the Minnesota Living with CHF (MLWHF) questionnaire which is a valid and reliable tool for measuring HRQOL in this population (Napier *et al.*, 2018; Rector and Cohn, 1992). The Kansas city cardiomyopathy questionnaire (KCCQ) is also valid and reliable, though recent studies (Napier *et al.*, 2018) suggest the MLWHF is more responsive to improvements in 6MWD. The MLWHF questionnaire is still recommended therefore as it was sensitive enough to show a (non-significant) improvement following LF-EMS in our study.

6.2.3.3. Changes to the Low Frequency Electrical Muscle Stimulation Protocol For a Definitive Randomised Controlled Trial

The feasibility study also provided information about the intervention itself. After reviewing the memory of LF-EMS units following each participant's intervention, it was evident that optimal current intensities were not reached (even with encouragement from supervisors) until performing the LF-EMS for two weeks. Therefore, another recommendation for a larger trial would be to extend the intervention period. Given that NICE recommends 12 weeks minimum for CHF cardiac rehabilitation programmes, it seems logical that alternative therapies should mirror this time period. In addition, the questionnaire feedback received from participants suggested that patients could not tolerate continued use of one hour of LF-EMS for five days a week. The mean response to continued use of LF-EMS was 3.4, between 3 (medium) and 4 (quite hard/unpleasant)

(Ennis *et al.*, 2017). Therefore, it is recommended to reduce the frequency to 3 or 4 sessions a week while increasing the duration of the intervention period to 12 weeks. This would allow participants to gain better tolerance to LF-EMS and improve on the gains in 6MWD and quality of life observed in the feasibility study.

6.3. Implications for Clinicians, Practitioners and Patients

NICE guidelines recommend cardiac rehabilitation programmes as a second line treatment for CHF patients. Electrical muscle stimulation is not yet recognised as a treatment option for CHF. The findings from this thesis, whilst requiring further substantive studies, suggest some cardiovascular benefit to CHF patients. There are very few other options available for the advanced CHF population without potentially high risk procedures (transplant, left ventricular assist device), which are also costly to the NHS. Therefore, LF-EMS remains one of the few practical solutions for this cohort. The data from this thesis suggest that LF-EMS does no harm (evidenced by safety data in study 2), so could be recommended to patients within the bounds of the current intervention, duration, intensity and frequency. Nevertheless, it is clear that further studies showing larger improvements on clinical and physiological outcomes are necessary before this can be included as part of routine clinical practice and included in NICE recommendations for CHF patients.

6.4. Future Studies

Further studies need to be performed comparing the acute effects of LF-EMS in CHF compared to age matched controls to allow more accurate interpretation of the initial findings in study one. One interesting avenue of study would be to combine the use of LF-EMS with traditional EMS in this population. One EMS programme including high and low frequency stimulation could lead to optimal improvements of muscle strength and muscle endurance. Those patients that appeared to have denervated muscles could simultaneously receive tetanic contractions needed for adaptation during the intervention period. Participants could also alternate the use of high and low frequency muscle stimulation on different days in the same way that athletes combine strength and endurance training to optimise improvements in exercise capacity. The impact of LF-EMS on cardiac function after a longer intervention period should also be measured if possible as it would be informative regarding the utility of LF-EMS in attenuating central dysfunction in this population.

6.5. Limitations

One of the main limitations in studying LF-EMS was the challenge of standardising the stimulus, in particular the intensity that patients chose. Each participant had to self-select their ‘maximal tolerable intensity’ and this would typically increase over the first 2-4 weeks until levelling off for the rest of the study duration. The maximum current level was dictated by individual differences in pain threshold, viable muscle mass, subcutaneous fat level, electrode placement and intrinsic motivation. Hence conclusions about the

efficacy of LF-EMS are limited by this high variability in current amplitude. Furthermore, individuals that could tolerate the same intensity as others, did not get similar results probably due to the different degree of muscle denervation between participants.

6.6. Summary and Conclusion

In summary, LF-EMS has the potential to stimulate a moderate exercise response in those with advanced CHF. It has been shown in this thesis that LF-EMS to the muscles of the upper legs increases systemic blood flow which has potential for reversing vascular dysfunction. A definitive RCT to determine the efficacy of LF-EMS in the CHF population is feasible. However, the feasibility study showed only minor improvements in 6 MWD, leg strength or quality of life. Reasons for this could include the need for a longer intervention period to enable optimal intensity tolerance and hence larger increases in fitness. Finally, endothelial function showed signs of improvement following eight weeks LF-EMS use and should be measured in any substantive RCT. This thesis concludes that more studies are required to confirm the benefit of this intriguing technological intervention in the advanced CHF population.

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Appendices

Appendix 1: Study One Informed Consent Form

PARTICIPANT CONSENT FORM

UWIC Ethics Reference Number:

Participant Name:…….. Date…….

Title of Project: Acute cardiovascular responses to low frequency electrical muscle stimulation (EMS) in healthy individuals.

Name of Researcher: Stuart Ennis

Participant to complete this section: **Please initial each box.**

1. I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

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

3. I agree to take part in the above study. ☐

_____ _____
Signature of Participant Date

_____ _____
Name of person taking consent Date

_____
Signature of person taking consent

Note: When completed, 1 copy for participant and 1 copy for researcher site file.

Appendix 2: Study Two and Three Informed Consent Form

University Hospitals Coventry and Warwickshire NHS Trust

Patient ID Number: _____

Trial: *The Effects of Electrical Muscle Stimulation in Patients with Chronic Heart Failure 'Magic Pants': A Pilot Study*

Please initial the boxes if you agree with each section:

Initial box

1- I confirm that I have read and understood the information sheet dated August 2013 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

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

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

4- I agree to give samples of blood for research in this study. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time. ☐

5- I understand that my GP will be informed of my participation and also if any of the results of tests done as part of the research are important for my health. ☐

6- I agree to take part in the above study. ☐

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Name of patient	Date	Signature
……..	……..	……

Name of person taking consent Role/Title	Date	Signature
…….. …….....	…….	…….....

Original for Investigator Site File/Researcher, 1 copy for participant, 1 copy for medical record/hospital notes (delete/amend as appropriate)