Effect of Eccentric Exercise on Quality of Life and Functional Capacity in People with Chronic Heart Failure

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List of abbreviations

1-RM	One-repetition maximum
ACE	Angiotensin converting enzyme
AICD	Automated implantable cardioverter-defibrillator
AMED	Allied and Complementary Medicine database
ARNI	Angiotensin receptor-neprilysin inhibitor
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CK	Creatinine kinase
cm	centimetres
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
$\bar{d}$	Mean differences between measures
DEFS	Dutch Exertion Fatigue Scale
DOMS	Delayed onset muscle soreness
e.g.	exempli gratia; for example.

FEV_1	Forced expiratory volume in one second
FEV_6	Forced expiratory volume in six seconds
FVC	Forced vital capacity
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
ICC	Intra-class correlation coefficient
kg	Kilograms
LOA	Levels of agreement
m	Metres
MRA	Mineralocorticoid receptor antagonists
n	Number
NT proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PEDro	Physiotherapy evidence database
PRISMA	Preferred Reporting for Systematic Reviews and Meta-Analysis
r	Pearson's correlation coefficient
RR	Risk ratio
SDdiff	Standard deviation of the difference
TiDieR	Template for Intervention Description and Replication

TM	Trademark
VAS	Visual analogue scale
VO_2	Oxygen consumption
vs	Versus
W	Power

Note- additional abbreviations used in tables are included as a footnote to each table.

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Summary

Eccentric exercise is a low energy cost form of exercise that may be suitable for people with difficulties exercising such as people with chronic heart failure. This thesis comprises three studies that investigated the effect of eccentric exercise on people with chronic heart failure.

A systematic review found eccentric exercise was safe, well-tolerated and comparable to traditional (concentric) exercise in improving walking and muscle strength for people with chronic cardiorespiratory diseases such as chronic heart failure, chronic obstructive pulmonary disease and coronary artery disease.

A reliability study examined the inter and intra-rater reliability of a one-repetition maximum strength test in people with chronic heart failure and showed it to be a reliable measure. Given large limits of agreement for inter-rater reliability, assessment by the same rater on each testing occasion was recommended.

A randomised controlled trial investigated the effect of eccentric exercise on quality of life and functional capacity in people with chronic heart failure. The results found that eccentric exercise was not superior to concentric exercise or a waitlist control group. No adverse events were reported, and the per-protocol analysis showed improvement in quality of life measures favouring the eccentric exercise group. The study conclusions were limited by insufficient power, due to the inability to recruit the proposed sample

size. Important clinical findings from this trial include difficulty progressing exercises sufficiently to elicit maximum training effect, and limitations in widespread implementation due the specificity of equipment required to complete eccentric exercise.

The findings of this thesis suggest eccentric exercise may be completed safely by people with chronic heart failure, but it is comparable to traditional rehabilitation in improving functional outcomes. Eccentric exercise may be considered where an adjunct to therapy or alternative exercise regimen is sought.

Statement of authorship

This thesis includes work by the author that has been published as described in the text. Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma.

No other person's work has been used without due acknowledgment in the main text of the thesis.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

Signed: Rachel Elizabeth Ellis  8th November 2020

Preface

This thesis comprises a series of published and unpublished chapters. Each chapter may be read independently or in the order they appear as part of the overall thesis. Chapters 2 and 3 are presented in their published format. Permission was granted by each journal to include the published article in this thesis (Appendix 3). Chapter 4 has been accepted for publication and is presented in the manuscript format that it was submitted to the journal.

All chapters (published papers, unpublished papers and other chapters) are written in Australian English and use a numerical referencing style as was required by the journals of the published papers.

The contribution of the Doctoral candidate, Rachel Ellis, towards each paper is outlined in the publication statements (Appendix 4).

Research procedures reported in the thesis were approved by the La Trobe University Human Ethics Committee, and the Northern Health Human Ethics Committees (Appendix 2).

List of publications

Chapter 2

Ellis R, Shields N, Lim K, Dodd KJ. Eccentric exercise in adults with cardiorespiratory disease: a systematic review. Clinical rehabilitation. 2015;29(12):1178-1197.

Chapter 3

Ellis R, Holland AE, Dodd K, Shields N. Reliability of one-repetition maximum performance in people with chronic heart failure. Disability and Rehabilitation. 2019;41(14):1706-1710.

Chapter 4

Ellis R, Dodd K, Holland AE, Lim, K, Tacey M, Shields N. Effect of eccentric exercise on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial. Disability and Rehabilitation. In press. Accepted 11th October 2020.

Chapter 1: Introduction

1.1 Problem Statement

Chronic heart failure requires substantial health care service usage and impacts people's functional ability and quality of life. Despite exercise being recommended, engagement in rehabilitation programs is poor. People with chronic heart failure suffer a variety of symptoms, most commonly shortness of breath, muscle weakness and fatigue, all of which impact their ability to exercise.

Eccentric exercise has been demonstrated to require less oxygen consumption while improving strength in healthy adults, but less is known about its safety or effectiveness in people with chronic cardiorespiratory disease. Eccentric exercise may be a potential strategy to decrease the burden of chronic heart failure both at the individual and health service levels. This thesis aims to determine whether eccentric exercise is safe and effective in people with chronic heart failure.

1.2 What is chronic heart failure?

Chronic heart failure is a clinical syndrome whereby people typically experience symptoms such as dyspnoea (shortness of breath), muscle weakness and fatigue (1). It is caused by damage to the heart, affecting its ability to fill with blood or contract and eject sufficient blood (1). Damage may arise from impaired function of any of the structures of the heart, including the valves and the great vessels, but most commonly damage to the myocardium, particularly the left ventricle (2). Heart failure was previously described as either systolic or diastolic failure. Systolic failure refers to a reduced ability of the heart to contract in its contraction phase; systole (1, 3). Diastolic heart failure refers to a

decreased ability of the ventricle to fill, either due to early relaxation or stiffening of the heart muscle (1, 3). With patients often having aspects of both systolic and diastolic dysfunction (2), there has been a shift in recent years to use echocardiogram results to classify the condition as either heart failure with reduced ejection fraction (HFrEF), or heart failure with preserved ejection fraction (HFpEF) (1). Ejection fraction is the percentage of blood ejected from the left ventricle with each heartbeat and is defined as preserved if the percentage is above 50% based on Australian and New Zealand guidelines (1), or above 40% in American guidelines with 41 to 49% considered 'borderline' (2). For those with HFpEF, in addition to an ejection fraction of 50 or greater, diagnosis is based on the presence of heart failure signs and symptoms plus evidence of structural heart disease and/or diastolic dysfunction (1). Previous research studies of different treatments for heart failure, including exercise, focused on those with systolic failure or reduced ejection fraction. With an increasing prevalence of people with HFpEF, likely due to an aging population, now representing more than half of those with heart failure (1, 4), research including this group of people is also important and increasingly more common.

1.3 Burden of chronic heart failure

Chronic heart failure is a significant public health burden with an estimated 38 million people affected worldwide (1, 5). In developed countries, more than one in 10 people over the age of 75 are affected by heart failure (1). In Australia, there were over 70,000 hospital admissions with a principal diagnosis of heart failure or cardiomyopathy during 2017 to 2018 and an even greater number where heart failure or cardiomyopathy was an additional diagnosis (6). In 2015 to 2016, the combined health care costs for all cardiovascular diseases in Australia was more than $10 billion (7).

Survival rates for chronic heart failure are approximately 52% at five years compared with 85% in the general population. Survival rates vary depending on the type of heart failure. People with preserved ejection fraction have an approximately seven to 10% better chance of survival at three years than those with reduced ejection fraction (1, 8, 9). These rates have seen limited improvements over the last 20 years despite improvements in options for pharmacological management of heart failure with reduced ejection fraction. Further research is required to understand this modest improvement (8, 10). A possible explanation is the increased number of people with preserved ejection fraction for which treatment does not yet improve survival, or the insufficient use of evidence-based treatments in those with reduced ejection fraction due to a lack of appropriate prescription (11). Given the considerable financial and physical burden of heart failure and the increasing future costs associated with an aging population, cost-effective treatment options such as group exercise programs are of interest.

1.4 Symptoms of chronic heart failure

Dyspnoea is one of the most common symptoms of chronic heart failure. It can occur when recumbent, at rest or on exertion. It generally occurs on exertion in milder cases and as the disease progresses it is experienced with less and less activity. Dyspnoea is the primary classification system used to categorise the severity of heart failure. People are classified into one of the four following categories according to the New York Heart Association classification: 1) no limitation of normal physical activity due to shortness of breath, 2) mild limitation, 3) marked limitation, and, 4) short of breath at rest (1, 2).

People with heart failure also commonly experience generalised fatigue and muscle weakness leading to a reduction in exercise tolerance (3). Fatigue is a subjective symptom which involves physical, cognitive and emotional aspects and is experienced

by 69% to 88% of people with heart failure (12). It is described as ‘an overwhelming sense of exhaustion and decreased capacity for physical and mental work’ (12, 13) and may be related to physical exertion, psychological symptoms, or both (14). The mechanisms behind the limitations of physical activity, which may be experienced as exertional fatigue in people with heart failure include inadequate blood flow to skeletal muscles, inability to increase cardiac output in response to activity (3), decreased muscle strength (15) and muscle atrophy (16). Exercise tolerance has been found to poorly correlate with resting ventricular function defined by ejection fraction (17), highlighting the impact of peripheral physiological factors and the importance of symptom assessment and management. With symptoms common to heart failure with both preserved and reduced ejection fraction, somewhat irrespective of structural abnormality, treatments that focus on improving symptoms, such as exercise, may also apply to both types of heart failure.

The idea of focusing on symptom management allows for the consideration of treatments that benefit other cardiorespiratory diseases as potential treatments for chronic heart failure. Chronic heart failure and chronic obstructive pulmonary disease (COPD), for example, differ in pathophysiology but cause similar symptoms. The typical symptoms of exertional dyspnoea, paroxysmal nocturnal dyspnoea and nocturnal cough are common to both conditions. They also often co-occur, with 10 to 50% of people with chronic heart failure having COPD (18). People with chronic heart failure and COPD show obstructive and restrictive deficits on respiratory function tests (18) and these ventilatory problems lead to decreased exercise tolerance and, with time, deconditioning and subsequently diminished general function.

Alternatively, cardiorespiratory diseases of cardiac origin, that is coronary heart disease and chronic heart failure, are related in both physiology and aetiology. Coronary heart disease is caused by atherosclerosis, which may cause blockage of the coronary arteries resulting in myocardial infarction. Such damage to the heart muscle is the leading cause of heart failure, with one study (19) reporting in the seven to eight years after myocardial infarction as many as 36% of patients developed heart failure. With coronary heart disease having a causal relationship to heart failure, treatments that benefit people with coronary heart disease, may also prevent the development of subsequent heart failure or at least improve health or functional outcomes for this group.

1.5 Management of chronic heart failure management using exercise

There is high-quality evidence for a number of treatments for chronic heart failure. These include pharmacological management (such as the prescription of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers and mineralocorticoid receptor antagonists (MRA) in people with reduced ejection fraction), surgical or invasive treatments in certain individuals, referral to a multidisciplinary disease management program and exercise (1, 2). Guidelines for the management of chronic heart failure recommend rehabilitation programs should include education and exercise. Education includes information about disease pathophysiology, medication management and other self-management strategies such as restricting fluids in select patients and weight monitoring (1). Exercise is recommended for those who are medically stable, and while supervised, centre-based rehabilitation programs including at least once weekly education and exercise sessions are the traditional approach, independent completion of an exercise program has also been found to be beneficial (1, 20).

Exercise aims to improve physical function and quality of life by addressing the symptoms of dyspnoea, muscle weakness and fatigue and also reducing hospitalisations (1, 20, 21). Historically, exercise studies were conducted in those with reduced ejection fraction, with results demonstrating an improvement in symptoms, which was attributed to improved ventricular function (22). However, more recent studies of exercise in those with preserved ejection fraction have demonstrated improvements in quality of life and physical function without changes in ventricular function (1, 23). In these patients, positive outcomes with exercise appear linked to improved cardiorespiratory function, and peripheral changes in skeletal muscle function (23). Exercise also demonstrates anti-inflammatory effects, improves endothelial function and decreases peripheral vasoconstriction (24, 25). Studies reviewing the safety of exercise in people with heart failure have demonstrated improvements in hospitalisation and quality of life (20, 26, 27). These studies focus predominately on aerobic exercise but studies involving resistance training specifically have also reported improvements without adverse events (24, 28, 29).

Based on high-quality evidence, current national and international guidelines recommend moderate intensity, continuous exercise for people with chronic heart failure (1, 2, 30). Strengthening exercises for large and small muscle groups are also recommended, particularly for people with heart failure with preserved ejection fraction or for people who are elderly, frail or at risk of muscle wasting (1, 24, 29, 30). The guidelines recommend resistance exercise be performed at low to moderate intensity, using dynamic contractions with advice to avoid Valsalva manoeuvres and to allow for adequate rest periods between sets (24, 29). These considerations mean supervision provided in rehabilitation classes is valuable when commencing new exercise regimens or for those who are either new to exercise or who have not exercised recently.

1.6 Barriers to exercise in people with chronic heart failure

Despite exercise having been shown to be beneficial in improving function and quality of life and decreasing hospitalisations for people with heart failure, a number of barriers to participation in exercise have been identified. Exercise adherence, which is defined as the extent to which a person's behaviour corresponds with that which is recommended by health care providers (31), is measured in different ways and is often not well reported in heart failure trials making reporting of adherence rates difficult. In a large trial involving 2331 people with heart failure, which made multiple attempts to encourage exercise adherence including telephone contact, activity logs, heart rate monitoring and regular clinic visits, only approximately 30% of people were found to be exercising as prescribed after 3 months (when participants were completing supervised sessions) and after 12 months (during home exercise) (24, 26). This is compared with average adherence rates to exercise interventions of approximately 50% for cardiac rehabilitation programs and 63 to 78% in healthy adults (32). Adherence also varies with treatment type. For example, in a survey of 501 people with heart failure, adherence with medication and appointment attendance was greater than 90%, while exercise and regular weight checks were much lower (39% and 35% respectively) (33). Barriers to exercise include patient-related factors (e.g. older age, lower education, lower socioeconomic status, work and time commitments), service-related factors (e.g. lack of expertise, referral or capacity) and condition-related factors (e.g. comorbidities, physical and mental health, hospitalisations and symptom severity) (32, 34). It is these condition-related barriers (i.e. feelings of fatigue or tiredness, as well as lack of motivation and lack of energy), that consideration of alternate modes of exercise such as eccentric exercise may help combat.

1.7 Why eccentric exercise might be helpful for people with chronic heart failure

Eccentric exercise involves isolated and repeating eccentric muscle contractions. There are three types of muscle contractions: isometric, concentric and eccentric contractions. During an isometric contraction, the muscle contracts but its length does not change. During a concentric contraction, the muscle contracts and the muscle fibres shorten, while during eccentric contractions the muscle fibres lengthen. During the lengthening of an eccentric contraction, the muscle stretches and, like a spring, it stores elastic recoil energy which can be used to produce high forces (35). Eccentric contractions generate more force than concentric contractions but result in significantly less oxygen consumption and less energy expenditure by muscles (36). For this reason, eccentric contractions can seem like they require less effort. Consider the difference felt in descending versus ascending stairs or lowering versus lifting a weight. Descending stairs and lowering a weight feels easier. The difference in oxygen cost of eccentric contractions compared with concentric contractions varies from 50% to 86% less in healthy adults (37, 38). Generally, when exercising, muscles complete both concentric and eccentric contractions. For example, to be able to complete repetitions in a traditional strengthening exercise, the weight must usually be lifted before being able to be lowered again. Eccentric biased exercise programs look to isolate the eccentric contractions and repeat them in order to benefit from its high force coupled with low energy cost mechanism. Commonly, specific exercise equipment is required such as eccentric steppers, eccentric cycles or treadmills designed to facilitate downhill walking.

Figure 1. Eccentron^{TM} negative resistance trainer.

Traditionally, eccentric exercise has been used in athlete strengthening programs and in the rehabilitation of soft tissues injuries, to use this high force production to increase a specific muscle's strength and size (36). Emerging literature suggests older people may also benefit from low energy cost exercise performed at an endurance (continuous and submaximal) dosage (39) and with no eccentric specific adverse outcomes arising these exercise programs have been trialled with older people who have chronic diseases such as Parkinson disease, diabetes, chronic obstructive pulmonary disease, coronary heart disease and chronic heart failure (40). Although eccentric contractions have been associated with exercise induced muscle damage, experienced as muscle stiffness or delayed onset muscle soreness (DOMS), in early trials with frail older people and those with chronic disease this was not experienced when exercise intensity was increased gradually (39-41). This suggests that with the right program set-up, eccentric exercise may be implemented successfully in people with chronic heart failure.

1.8 Thesis overview and aims

This thesis aimed to explore the safety and effectiveness of an energy efficient exercise program for people with a chronic cardiorespiratory condition that not only reduces their life expectancy and leads to increased health care costs, but also affects their quality of life and limits functional capacity. This thesis comprises three studies: a systematic

literature review (Chapter 2), a reliability study (Chapter 3), and a randomised controlled trial (Chapter 4). This is followed by a general discussion (Chapter 5).

Chapter 2 describes a systematic review to investigate the effects of eccentric exercise in people with chronic cardiorespiratory disease, with the idea that what may be beneficial for people with this group of conditions and similar symptoms may be transferable to those with chronic heart failure.

In Chapter 3, the reliability of an outcome measure to be used in a randomised controlled trial (a one-repetition maximum 1-RM test using a leg-press) was determined. An inter-rater and inter-rater reliability study was conducted to consider the appropriateness of this outcome measure for use in randomised controlled trials and clinical settings.

Chapter 4 reports the outcomes of a randomised controlled trial of the effects of an eccentric biased exercise program in people with chronic heart failure. The trial consisted of a wait-list control group, a traditional rehabilitation program and an eccentrically biased exercise program. Given the well-established guidelines recommending rehabilitation components such as education on self-management strategies and exercise comprising both strengthening and aerobic exercise, the eccentrically biased exercise group also received education and other exercises, with the exercise session including a significant portion of continuous eccentric exercise.

Chapter 5 is a discussion of the key findings of the thesis. The clinical implications of the systematic review, reliability study and randomised controlled trial findings are presented and how eccentric exercise may be used for people with chronic heart failure, and how

best to implement exercise programs to maximise its effectiveness in this population, are discussed.

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Chapter 2: Eccentric exercise in adults with cardiorespiratory disease: a systematic review

2.1 Introduction

This chapter presents a systematic review which investigated the available evidence for the effectiveness of eccentric exercise in people with chronic cardiorespiratory conditions. Eccentric exercise was considered as a potential exercise modality for these populations because of its demonstrated low energy cost in healthy adults. Given the limited evidence sourced in preliminary searches, chronic heart failure, chronic obstructive pulmonary disease and coronary artery disease, with commonality in pathology or symptoms, were combined in this review. Exclusion criteria were set to increase the yield while at the same time identifying worthwhile and applicable studies relevant to the research question. This review looked to explore both the efficacy and safety of eccentric exercise and its ability to be implemented in people with chronic heart failure.

2.2 Study One

This review is presented in its published form:

> Ellis R, Shields N, Lim K, Dodd KJ. Eccentric exercise in adults with cardiorespiratory disease: a systematic review. Clinical rehabilitation. 2015;29(12):1178-1197.

Article

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Eccentric exercise in adults with cardiorespiratory disease: A systematic review

Rachel Ellis[1], Nora Shields[2,3], Kwang Lim[4] and Karen J Dodd[2]

Abstract

Objective: To determine if eccentric exercise is effective, tolerable and safe for adults with chronic cardiorespiratory disease.

Data sources: We searched electronic databases from inception until January 2015 (Medline, CINAHL, Embase, SportDiscus, PEDro, Cochrane Central and AMED) supplemented by citation tracking and reference list scanning.

Review methods: Included articles had to report effects of eccentric exercise, alone or as a primary component of intervention, of any intensity and duration, on adults with chronic cardiorespiratory disease. Trials needed to be reported as full text in a peer-reviewed journal and include control data (randomised, quasi-randomised and single group cross-over design trials). Any outcomes or comparison interventions were accepted. Methodological rigor was assessed using the PEDro scale.

Results: Of 22 potentially relevant articles, 10 met inclusion criteria. They reported results from seven trials with a total of 112 participants across the diseases. PEDro scores were low (median 3). Eccentric exercise increased strength and mobility to comparable levels as concentric exercise, however, it did so with lower oxygen consumption (effect size as large as $d=-3.07$ (–4.12, –1.80)), and four-fold power output (effect size $d=-3.60$ (–5.03, –1.66)). There were no adverse events reported for eccentric exercise. Pain was avoided with familiarisation sessions and individual exercise prescription.

Conclusion: Eccentric exercise is beneficial and at least comparable with traditional exercise in improving walking and strength for people with chronic cardiorespiratory disease. It was well tolerated and we identified no safety concerns for the use of this intervention for this population.

Keywords

Eccentric exercise, coronary artery disease, chronic obstructive pulmonary disease (COPD), chronic heart failure, systematic review

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Introduction

Eccentric exercise may benefit adults with chronic cardiorespiratory diseases, such as coronary artery disease, chronic heart failure and chronic obstructive pulmonary disease.[1,2] During eccentric exercise, muscles lengthen and store elastic recoil energy which is used to create high forces.[3] In healthy adults, eccentric exercise can increase muscle strength while requiring less oxygen consumption than other forms of exercise.[4,5] Guidelines recommend regular aerobic and resistance exercise for all forms of cardiorespiratory disease.[6–9] However, the tolerability of exercise in these populations may be limited by symptoms such as respiratory deficits.[8] Therefore, there is interest in determining if global eccentric exercise can safely increase strength and function in these people.

Three previous reviews investigating the effects of eccentric exercise have included people with cardiorespiratory disease.[1,2,10] The reviews concluded that older people with chronic diseases had an increased work output for lower metabolic cost with global eccentric exercise. From the three trials in cardiorespiratory disease[11–13] it was suggested that eccentric exercise led to improvements in walking and strength equivalent to comparison groups. While these reviews provide preliminary evidence, limitations include inadequate reporting of the review processes and results,[1] and no quantitative analysis.[1,2,10] In addition, there has been limited analysis of the safety of eccentric exercise.

The aim of this review was to complete a qualitative and quantitative analysis of current literature to determine if eccentric exercise is effective, tolerated and safe for adults with chronic cardiorespiratory diseases.

Methods

This review was completed using a pre-specified (but unregistered) protocol and reported according to PRISMA guidelines.

Search strategy

The following databases were searched: Medline, CINAHL, Embase, SportDiscus, PEDro, Cochrane Central and AMED; from their inception to January 2015. The search was devised according to two key concepts: (1) eccentric exercise, and (2) cardiorespiratory disease. Keywords were identified using MeSH terms and related synonyms (Appendix A, available online). Citation tracking, using Google Scholar and Web of Science, and manual reference list scanning of the included articles was completed.

Inclusion and exclusion criteria

Trials were selected for review if they included control data (randomised, quasi-randomised trials and single group crossover designs), and recruited adults (>18 years) with chronic cardiorespiratory disease. Acute cardiorespiratory conditions, such as post-heart transplantation and pneumonia, were excluded because of their potential reversibility. Participants with cystic fibrosis were excluded because of their younger age[14] and the difference that may make in their ability to exercise compared with older people with chronic diseases. Trials that included participants with cardiorespiratory diseases and participants with other diagnoses were only included if separate data were provided for each group.

As the safety of eccentric exercise may be demonstrated in a single session, no exclusion criteria were set on exercise intensity and duration. No restrictions were made on the outcome measures investigated, and all forms of comparison interventions or control groups were included.

Only full text articles published in peer-reviewed journals were included.[15] Review articles were excluded if they did not provide any new information than that gained from primary trials.

Study selection

Following the initial search, duplicate references were removed and two reviewers (RE and NS or KD) independently applied the inclusion/exclusion criteria. For abstracts where the trial details were unclear, full text articles were retrieved. Disagreements between reviewers were resolved through discussion.

Quality assessment

The PEDro scale was used to determine trial quality.[16] Two reviewers (RE and NS) independently

assessed all trials for quality, with disagreements resolved by discussion. A Cohen kappa co-efficient was calculated using an online programme (http://graphpad.com/quickcalcs/kappa1.cfm) based on the results of each individual criterion to demonstrate the inter-rater agreement.[17]

Data extraction

Data extraction tables (Appendix B, available online) to summarise trial information were completed by one reviewer (RE) and checked by a second (NS).

Data analysis

Descriptive analyses identified major themes. A meta-analysis was not carried out owing to the heterogeneity of outcome measures and disease types. However, effect sizes with 95% confidence intervals were calculated to demonstrate trends in clinical importance.[18] Effect sizes were calculated (using an online programme http://www.cemcentre.org/renderpage.asp?linkid=30325017) by subtracting the control group post-intervention mean from the experimental group post-intervention mean, and dividing the result by the pooled standard deviation.[19] As recommended by Cochrane, effect sizes for trials using cross-over designs were calculated as though they used a parallel group design.[20]

For trials that did not provide numerical data, authors were contacted. If data were still unavailable, estimations were made based on graphical data.[18] Cohen's convention was used to determine the strength of effect sizes, with effect sizes of $d=0.20$ considered small, $d=0.50$ considered medium and $d=0.8$ considered large.[21]

Results

The database searches identified 1050 potentially relevant articles. After applying the inclusion/exclusion criteria, 22 articles remained. Of these, 10 articles were included (Figure 1).

Quality assessment

The PEDro scores for the included articles are presented in Table 1. The inter-rater agreement was moderate ($\kappa=0.6$).[17] The items where disagreement occurred (items 4, 8, 9, and 10) were largely owing to a lack of reporting in the involved articles (Appendix C, available online). The nature of the intervention made blinding of participants and therapists impossible, therefore no article received a PEDro score of 10. The two main sources of bias were a lack of blinding of assessors and a lack of allocation concealment. The median PEDro score was 3 (range 2–7), indicating poor methodological quality.

The 10 included articles reported data from seven trials; for further analysis, reference will be made to these seven trials. Four of the seven trials were randomised controlled trials. One trial[22] was quasi-randomised and allocated participants according to age, weight, body mass index and strength; one trial[23,24] used a single-group, cross-over design; and one trial[25] was a single group pre–post design with a single session comparison of eccentric and concentric exercise.

Study demographics

Tables 1 and 2 summarise details of the included trials and highlight their similarities in terms of the context, content and setting of the eccentric exercise programmes.

The intensity of exercise was variable across trials. All trials set the intensity for each participant individually, with only one trial[22] choosing a standard steps-per-minute on an eccentric stepper for participants. Five of the six trials using an eccentric cycle, set participant's revolutions per minute.[26] Three of these trials[11,23–25] set the revolutions per minute at 60; two[12,27] set it at 15 and 20, referencing studies in healthy subjects which found that slower velocity contractions resulted in decreased muscle damage.[28] With revolutions set, trials used participant's results from an initial concentric exercise test, that determined first ventilatory threshold,[12,27] peak oxygen uptake,[13,26,29] or maximum work rate[11,23–25] to set their target intensity. All trials increased exercise intensity during the programme but not in a standardised way.

Outcome measures

All trials included impairment measures, such as heart rate, oxygen consumption, dyspnoea and

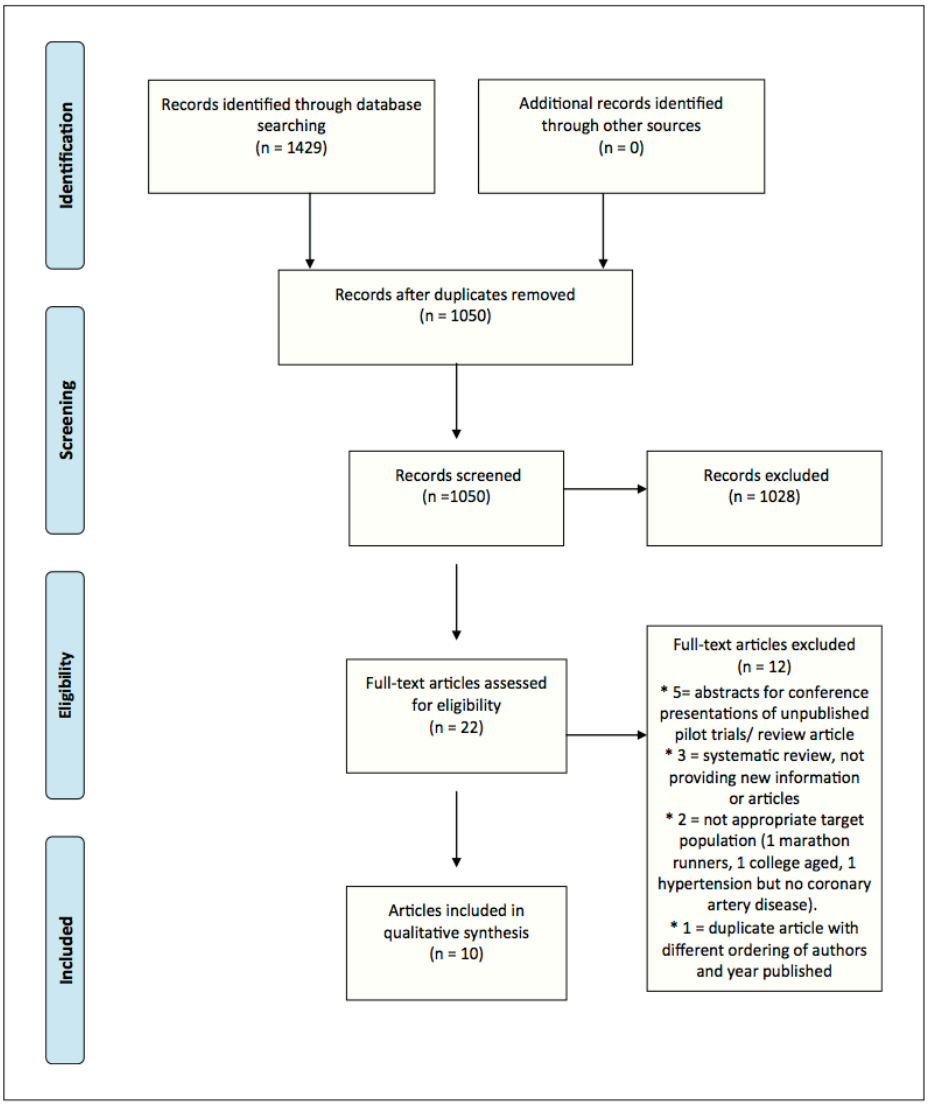

Figure 1. Flowchart detailing selection of articles included in the review.

rating of perceived exertion (Table 3). Only one trial[11] included a measure of participation (quality of life) and three trials[11,12,27] included a measure of activity (walk test).

Findings

Table 4 summarises the findings, while the effect sizes are presented in Figure 2.

Table 1. Characteristics of included studies.

Study	PEDro score	Disease	Study type	Sample size	Severity of diagnosis	Patient age (mean and range)	Patient sex
Gremeaux et al. (2010)[12]	7	CAD	RCT	*N* = 15 7 ECC 8 CON	Sub-acute: within 6 weeks of PTCA or stenting	ECC 53 (0.7) CON 45.3 (5.2)	15 M
Steiner et al. (2004)[13,a]	4	CAD	RCT	*N* = 12 6 ECC 6 CON	Stable CAD	CON 56 (3.5) ECC 55 (2.6)	12 M
Meyer et al. (2003)[26,a]	3	CAD	RCT	*N* = 13 7 ECC 6 CON	Stable CAD PTCA: ECC6/CON3 CABG: ECC1/CON2 Myocardial infarction: 1 CON	ECC = 56 (9) CON = 56 (8)	13 M
Zoll et al. (2006)[29,a]	2	CAD	RCT	*N* = 12 6 ECC 6 CON	Stable CAD	Not stated	12 M
Rooyackers, et al. (2003)[11]	4	COPD	RCT	*N* = 24 12 ECC 12 CON	Severe but stable COPD: SpO_2 <90% on max. exertion FEV1 % predicted: ECC 45 ±13, CON 38 ±11	ECC 59 (10) CON 59 (13)	ECC = CON 10 M 2 F
Rocha Vieira et al. (2011)[25]	3	COPD	Single group case series	*N* = 6	Severe but stable COPD: FEV1 35% (range 17–49) predicted	63 (range 54–71)	12 M
Rooyackers et al. (1997)[23,24,b]	3	COPD	Single group cross-over	*N* = 12	Mod-severe COPD: FEV1 46 (16 SD) % predicted	56 (12)	10 M 2 F
Besson et al. (2013)[27]	5	CHF	RCT	*N* = 30 15 ECC 15 CON	Mild CHF: LVEF <45% or plasma NT-proBNP 3 × superior to healthy participants but NYHA superior or equal to 2	ECC 63.3 (10.1) CON 60.7 (11.8)	ECC = CON 11 M 4 F
Theodorou et al. (2013)[22]	3	CHF	Quasi-RCT	*N* = 12 6 ECC 6 CON	Diagnosis and severity not reported	ECC 66.8 (1.7) CON 64.8 (2.3)	12 M

CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: chronic heart failure; CON: concentric; COPD: chronic obstructive pulmonary disease; ECC: eccentric; FEV1: forced expiratory volume in one second; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PTCA: percutaneous transluminal coronary angioplasty; RCT: randomised controlled trial; SpO_2: pulse oximetry oxygen saturation.

[a]Articles contained the same sample population

[b]Rooyackers et al.[23,24] combined as same trial.

Table 2. Characteristics of included studies – intervention.

Study	Intervention	Time	Intensity	Frequency	Duration	Preconditioning sessions	Follow-up	Exercise setting	Group or individual exercise	Exercise facilitator
Gremeaux et al. (2010)[12]	Standard programme for both groups plus ECC vs. CON cycling	90 min exercise session: 30 min ECC vs. CON cycling (warm-up, cool-down, 20 min circuit training and 2 × 30 min aerobic exercise – arm cycle and leg cycle)	HR that corresponded with 1st ventilatory threshold. CON = 50 r/min ECC = 20 r/min	3 × week	5 weeks	Nil	Nil	Hospital outpatient rehabilitation programme	Not stated	Not stated
Steiner et al. (2004)[13,a]	Standard rehab programme = light calisthenics, stretching and relaxation plus ECC vs. CON cycling on ergometer	30 min cycling	60% VO_2 peak. Aimed to have patients work at same metabolic intensity (85% peak HR on baseline test) r/min chosen individually	3 × week	8 weeks	Nil	Nil	Hospital outpatient rehabilitation programme	Not stated	Not stated
Meyer et al. (2003)[26,a]	ECC vs. CON cycling on ergometer	30 min cycling	60% VO_2 peak or 85% peak HR	3 × week	8 weeks	Nil	Nil	Hospital outpatient rehabilitation programme	Not stated	Not stated
Zoll et al. (2006)[29,a]	ECC vs. CON cycling on ergometer	30 min cycling	60% peak oxygen uptake	3 × week	8 weeks	Nil	Nil	Hospital outpatient rehabilitation programme	Not stated	Not stated
Rooyackers et al. (2003)[11]	General exercise vs. general exercise plus ECC cycling	General exercise programme = strength training and 20 min interval training ECC = general exercise plus 5–15 min of ECC	Work rate that could be maintained for 5–15 min without SpO_2 < 90%	5 days/week	10 weeks	Nil	Nil	Inpatient programme	Not stated	Not stated
Rocha Vieira et al. (2011)[25]	ECC cycling on ergometer	20 min cycling	60 r/min 4 × power output for 60% CON peak	3 × week	5 weeks	1st session for 'familiarisation'	Nil	Not stated	Not stated	Not stated
Rooyackers et al. (1997)[23,24,b]	ECC vs. CON cycling on ergometer	6 min cycling	60 r/min 50% maximum CON power	4 single-stage exercise test in random order (2 on each day)	2 consecutive days	Nil	Nil	Not stated	Not stated	Not stated

Table 2. (Continued)

Study	Intervention	Time	Intensity	Frequency	Duration	Preconditioning sessions	Follow-up	Exercise setting	Group or individual exercise	Exercise facilitator
Besson et al. (2013)[27]	ECC vs. CON cycling on ergometer	32 min cycling (5 min warm-up, 25 min then 2 min cool-down)	ECC = 15 r/min and RPE 9–11 CON = 60 r/min and 1st ventilatory threshold	3 × week	7 weeks	1 session	Nil	Not stated	Not stated	Unclear
Theodorou et al. (2013)[22]	Automatic escalator-ascending and descending	12 min stepping (4 sets × 3 min separated by 2 min rest break)	1st 2 weeks at 45 step/min → 2 weeks at 50 → 2 weeks at 55	3 × week	6 weeks	Nil	Nil	Not stated	Not stated	Physiotherapist

CON: concentric; ECC: eccentric; HR: heart rate; r/min: revolutions per minute; RPE: rating of perceived exertion; SpO_2: pulse oximetry oxygen saturation; VO_2: oxygen uptake.
[a]Studies contained the same sample population.
[b]Rooyackers et al.[22,23] combined as same trial.

Effectiveness

Fitness outcomes. Three trials[11,12,27] completed a training programme and then performed a post-training concentric exercise test to show the effect of training on exercise tolerance. Heart rate,[12] oxygen consumption (VO_2)[12] and power output[11,12] were significantly improved from baseline following eccentric exercise (Table 4). There were no significant differences in heart rate,[11] VO_2,[11,12,27] shortness of breath[11] and power output[11,12] between eccentric and concentric exercise.

Power output (W). As shown by the large effect size in Figure 2, participants were able to generate four times the power output during eccentric exercise than concentric exercise.[26] Significant improvements in power from baseline were seen in eccentric groups,[11,12,25] however, if measured in a post-programme concentric test there was no significant difference.[11,12]

Muscle strength. Three trials found eccentric exercise led to significant improvements in muscle strength compared with baseline and equivalent to concentric exercise. Two trials reported greater strength gains in the eccentric group when performing eccentric knee extension strength[22] and isometric ankle plantar flexion[12] compared with concentric exercise. One trial[13] measured muscle mass and found both groups significantly increased from baseline, but no group achieved superior results.

Six-minute walk test and quality of life. Despite their clinical importance, activity and participation measurements were limited. All three trials that completed post-training walk tests[11,12,27] reported significant improvements in both groups but no between-group differences, as did the only trial[11] that studied quality of life.

Tolerability

Muscle soreness. Eccentric exercise resulted in minimal pain that did not limit exercise participation.[22,25,27] To measure skeletal muscle damage that may be associated with delayed onset muscle soreness, one trial[22] measured creatine kinase. An

Table 3. Characteristics of included studies – outcome measures.

Study	Impairment				Activity	Participation
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate		
Gremeaux et al. (2010)[12]	–	Symptom limited VO_2	Maximum isometric knee extension and ankle plantar flexion strength	Power (W)	6MWT 200 m fast walk	–
Steiner et al. (2004)[13a]	–	–	Knee extensor strength Muscle biopsy (R VL at mid-thigh) BMI and body composition	RPE (BORG 6–20)	–	–
Meyer et al. (2003)[23a]	HR MAP PCP Vascular resistance Arteriovenous O_2 difference Cardiac index Blood lactate	Peak VO_2	–	RPE (BORG 6–20) Power (W)	–	–
Zoll et al. (2006)[29a]	–	–	Muscle biopsy Muscle morphology Histochemistry (muscle fibres processed for myofibrillar ATPase) Total RNA extraction Reverse transcription	–	–	–
Rooyackers et al. (2003)[11]	HR ABG	VE VO_2 Dyspnoea (BORG 0–10)	–	Power (W)	6MWT	QOL on Chronic Respiratory Disease Q
Rocha Vieira et al. (2011)[25]	CK	Breathing reserve Dyspnoea (BORG 0–10)	Body plethysmorgraphy Muscle soreness (VAS 0–10)	Power (W) RPE (BORG 0–10)	–	–
Rooyackers et al. (1997)[23b]	Potassium ABG HR via ECG	VE VO_2 CO_2 production	–	–	–	–

Table 3. (Continued)

Study	Impairment				Activity	Participation
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate		
Rooyackers et al. (1997)[24,b]	ABG HR via ECG	VE VO_2 CO_2 production Breathing reserve Dyspnoea (BORG 0–10)		RPE (BORG 0–10)	–	–
Besson et al. (2013)[27]	NT-pro-BNP HR during exercise	VO_2 during 6MWT	Muscle soreness on VAS	RPE (BORG 6–20)	6MWT	–
Theodorou et al. (2013)[22]	CK	–	Peak isometric CON and ECC knee extensor torque Muscle soreness (during squat 1–10)		–	–

6MWT: six minute walk test; ABG: arterial blood gas; BMI: body mass index; CK: creatine kinase; CO_2: carbon dioxide; CON: concentric; ECC: eccentric; ECG: electrocardiograph; HR: heart rate; MAP: mean arterial pressure; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; PCP: pulmonary capillary pressure; QOL: quality of life; R: right; RNA: Ribonucleic acid; RPE: rating of perceived exertion; VE: minute ventilation; VL: vastus lateralis; VAS: visual analogue scale; VO_2: oxygen uptake; BORG rating scale; ATPase: adenosine triphosphatase.

[a,b]Studies contained the same sample population.

Table 4. Characteristics of included studies – results.

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Gremeaux et al. (2010)[12]		Significant inc symptom limited VO_2 both groups	Significant inc maximum isometric knee extension and ankle plantar flexion strength both groups but ECC more than CON	Significant inc peak workload both groups	Significant inc 6MWT but not in 200 m fast walk both groups		None
Steiner et al. (2004)[13a]			Strength: no change CON, not significant ECC Mass: significant inc in both groups with no diff between groups Morphology: inc muscle fibre cross sectional area in CON Body comp: no change ECC, significant change in CON	RPE did not exceed 11 'fairly light'	Patients reported CON = cardiorespiratory effort greater, ECC = LL effort greater		None

Table 4. (Continued)

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Meyer et al. (2003)[26,a]	Significant difference in HR (higher in ECC), Ateriovenous O_2 difference and blood lactate between ECC and CON (0–5 min changes) Significant improvement in LVEF in ECC after 8 weeks	Significant difference in VO_2 between ECC and CON (0–5 min changes)		4 × greater power output at similar HR No difference in RPE (<11 for both groups)			None
Zoll et al. (2006)[29,a]			ECC = dec in expression of the mitochondrial respiratory chain component COX-4 and dec level of the factor of mitochondrial biogenesis, Tfam.				None

(Continued)

Table 4. (Continued)

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Rooyackers et al. (2003)[11]	No significant difference in ABG results in both ECC and CON groups	Max exercise limited by SOB for CON participants SpO_2 did not drop below 90% for ECC No significant difference between groups	Exercise limited by leg fatigue for ECC participants	BORG <3	Significant inc 6MWT for both groups. No between group difference	QOL improved for both groups but no between group difference	None
Rocha Vieira et al. (2011)[25]	No inc CK	VE, ventilatory reserve and RR did not differ between ECC and CON but work rate 5 × in ECC session	Patients complained of muscle soreness and fatigue but did not compromise progression	ECC power inc to 7-fold baseline All participants reached target intensity of 4 × 60% CON peak			None

Table 4. (Continued)

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Rooyackers et al. (1997)[23,b]	No significant diff in K+ between ECC and CON ABG: pH, BE, and PaO_2 similar in both types of exercise Inc in $PaCO_2$ was less during ECC than CON HR similar both groups For a given inc in K+ the inc in VE was significantly less in ECC therefore K+ deemed to not contribute to the difference in ventilatory response between ECC and CON	After ECC VE, VO_2, VCO_2 40% lower than during CON No correlations between change VE (CON-ECC) and change K+ (CON- ECC) Difference in change VE between CON and ECC closely correlated with change VCO_2					None

(Continued)

Table 4. (Continued)

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Rooyackers et al. (1997)[24,b]	ABG: no significant dec in BE, inc $PaCO_2$ significantly less in 50% ECC	VE, VO_2, VCO_2 30% lower for ECC and so participants had greater ventilatory reserve Highest VO_2 in 50% CON Ventilatory equivalents for O_2 and CO_2 did not differ between CON and ECC					None (CON = 3 participants experience short term hypoxia but exercise was not ceased)
Besson et al. (2013)[27]	NT-pro-BNP: significant change (direction not stated) after CON. No change with ECC. HR = significantly less in ECC	CON = significant inc VO_2 uptake.	ECC = 1 participant = knee pain, 1 = thigh pain CON = 1 × muscular pain. 48-hours post = 2 × CON, 1 × ECC complained of muscle or joint pain VAS >7	RPE: ECC told to work at 9–11. CON 10–12	Significant inc 6MWT for both groups. No between group difference		ECC = 1 participant developed arrhythmia, received medications and continued. CON = 1 participant withdrew due to acute decompensated heart failure, not related to training

Table 4. (Continued)

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/blood investigation	Respiratory	Musculoskeletal	Work rate			
Theodorou et al. (2013)[22]	Significant inc in CK in both ECC and CON groups after first session		Inc muscle strength for both ECC and CON but only isometric strength inc significantly in ECC group. Significant inc in VAS pain score after 1st bout of ECC ex but not after last				Nil reported

6MWT: six minute walk test; ABG: arterial blood gas; BE: base excess; CK: creatine kinase; CO_2: carbon dioxide; CON: concentric; ECC: eccentric; HR: heart rate; inc: increase; K+: potassium; LL: lower limb; LVEF: left ventricular ejection fraction; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; O_2: oxygen; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; QOL: quality of life; RPE: rating of perceived exertion; SOB: shortness of breath; SpO_2: pulse oximetry oxygen saturation; VAS: visual analogue scale; VCO_2: carbon dioxide elimination; VE: minute ventilation; VO_2: oxygen uptake. COX: Cytochrome c oxidase; Tfam: Mitochondrial transcription factor A; BORG: as above; inc: already listed after heart rate; dec: decrease.

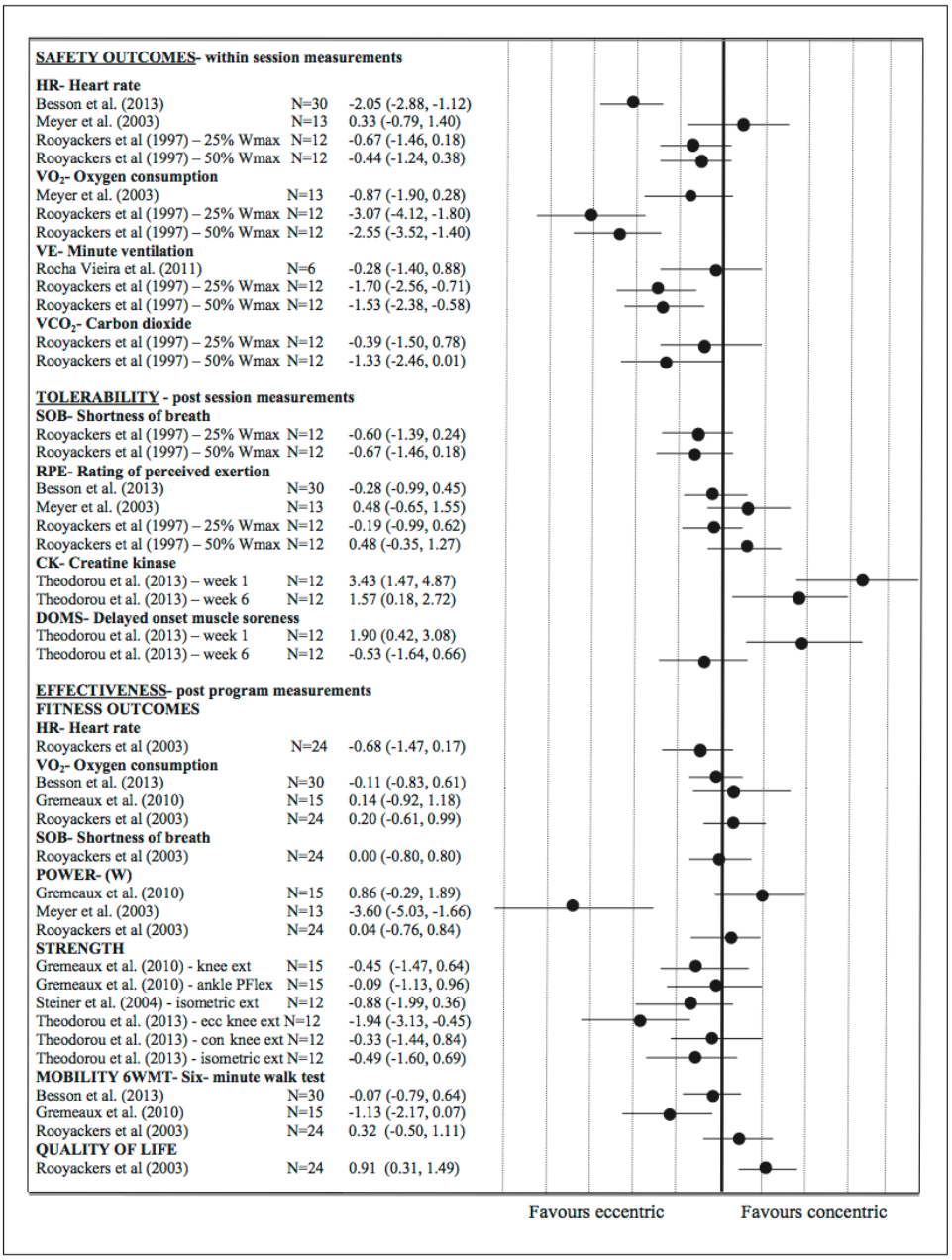

Figure 2. Effect sizes and 95% confidence intervals for differences between eccentric and concentric exercise. Strength: Gremeaux et al.[12] ankle plantar flexion strength effect size calculation does not highlight the statistical difference reported owing to baseline differences in groups.

increase was reported in both eccentric and concentric groups after the first and sixth week exercise sessions, significantly more for eccentric exercise. However this trial set a standard intensity for all participants regardless of individual fitness level, which may have been a large insult to some participant's muscles resulting in damage. Two trials[25,27] provided participants with a preconditioning session (exposure to eccentric exercise) prior to commencing the programme and increased intensity gradually, which allowed them to avoid significant pain.

Effort. The effort of completing eccentric exercise was measured using shortness of breath and rating of perceived exertion scales with no significant differences between exercise types.[11,24,26,27] Overall, measures of shortness of breath and rating of perceived exertion were low (less than 3/10 shortness of breath and 'somewhat hard' exertion).

Adherence. No participants withdrew from eccentric exercise. Adherence was reported as 100% for two trials.[12,25] One trial reported that participants completed 20 sessions, but the time frame was not stated.[27] Other trials reported that eccentric exercise was well tolerated and did not report any missed sessions.

Safety

Safety was primarily determined by assessing the impact on the respiratory and cardiovascular systems.

Respiratory measures. When measured during exercise and compared with the same intensity of concentric exercise, the results showed significantly less respiratory demand during eccentric exercise as measured by oxygen consumption (VO_2), minute ventilation and carbon dioxide (CO_2) production. Conversely, when eccentric exercise was completed at work rates four[26] or five[25] times that of concentric exercise, there were no significant differences in VO_2 or minute ventilation.

Cardiac measures. There were no cardiac complications reported. At the same intensity of exercise for both eccentric and concentric groups, there were no significant differences in heart rate. One study[27] reported significantly lower heart rates during eccentric exercise, however the intensity of eccentric exercise was low. Invasive measures of cardiac stress (mean atrial pressure, mean pulmonary capillary pressure systemic vascular resistance,[26] N-terminal pro-brain natriuretic peptide (NT pro-BNP)[27]) showed no significant differences between eccentric and concentric exercise. One trial[26] in coronary artery disease, however, found significant improvement (5%) in left ventricular ejection fraction in the eccentric group, suggesting better heart function following eccentric exercise.

Adverse events. Only one trial[27] reported an adverse event; a participant developed an arrhythmia, for which medications were prescribed. No participants withdrew from eccentric exercise in any programme.

Discussion

Our results suggest eccentric exercise is well tolerated and safe for adults with cardiorespiratory disease. Eccentric exercise resulted in up to four times greater force production than concentric exercise, with comparable heart rates and lower oxygen consumption and minute ventilation. Eccentric exercise also produced stable oxygen saturations and, at times, demonstrated lower levels of carbon dioxide production suggesting lower respiratory demand. For all major outcomes, eccentric exercise appeared to be equally effective in improving outcomes from baseline compared with concentric exercise. When aerobic fitness was assessed by taking cardiovascular measurements in a post-training, maximal exercise test (concentric cycling or walking), eccentric exercise achieved results equivalent to concentric exercise, despite not training in this format. Furthermore, strength, mobility and quality of life improved from baseline, although not statistically better than concentric exercise. The three trials that investigated mobility, reported improvements in the six-minute walk test for eccentric exercise of greater than 50 m. This is twice the minimal clinically important difference determined in previous studies for these populations.[30,31] Overall, this suggests eccentric exercise using an endurance dosage is

comparable with traditional exercise in improving functional outcomes for patients with cardiorespiratory diseases, but requires less oxygen and can create greater power output. Further questions remain as to what functional benefit being able to exercise at greater intensity or with significantly greater power output is.

Adverse events were rare, with no participants in any eccentric group unable to complete a programme. With the low number of studies, trends for individual diseases are unclear. However, favourable results for safety and tolerability are demonstrated in at least one study for each population. The disease states of the included populations were stable, but all of the chronic obstructive pulmonary disease populations had moderate-severe or severe disease, supporting the view that eccentric exercise can be safe, not only in the early stages of disease but also in end-stages where management becomes increasingly important as healthcare usage and disability rises. However, heart failure severity was mild in one study[27] and not clearly reported in the second[22] and so further research in more severe forms of this disease would add weight to claims of safety of eccentric exercise.

Eccentric exercise can cause muscle soreness when first commenced, even in healthy people.[32] Concerns for the tolerability of eccentric exercise with older or frail people, may not be warranted, as it did not limit participation even if creatine kinase levels rose. A preconditioning session aimed to increase adherence and safety, and provide muscles with exposure to eccentric exercise, which in combination with a gradual increase in exercise intensity may help avoid muscle soreness.[33]

Limitations of current literature and future research recommendations

Our results suggest eccentric exercise may be used as an option for exercising deconditioned patients. However, only a very limited body of evidence exists; 10 articles reporting seven clinical trials including 112 participants. When rated on the PEDro scale, these trials were of poor methodological quality, three of which were not randomised trials. In addition to the small sample sizes (6–30 participants), four of the seven trials only included men, and in the other three trials the percentage of women was small (16%–26%). Participants were aged 45–67 years, which may be typical for heart disease, but is not representative of the heart failure or chronic obstructive pulmonary disease population.

Cost-effectiveness of eccentric exercise was not addressed by any trial. Although the eccentric and concentric programmes were the same length and duration, with no differences in labour costs evident, the eccentric exercise programmes all required custom-made equipment; this start-up cost might decrease clinical feasibility. Such specific equipment also means participants were unable to exercise eccentrically at home. No follow-up was completed to measure the long-term effects of eccentric exercise. No trial reported whether the programmes were completed one-on-one or in a group environment. Cost effectiveness may be improved by using group programmes, however, if this were to occur, the programme would require multiple devices on which to complete eccentric exercise or would need to involve a circuit arrangement.

The reported outcomes were generally limited to impairment outcome measures. Three trials, in chronic obstructive pulmonary disease and heart failure populations, did include a walk test, but only one trial measured participation. While eccentric exercise appeared to require less oxygen for greater force output, the efficacy of this treatment in changing health outcomes, morbidity and mortality has not been demonstrated. Further, well designed, large randomised control trials with older populations of both men and women, looking at functional outcomes are required to really begin to confidently view the effects of eccentric exercise in these chronic disease populations.

Limitations of the current review must also be considered. In order to exert some control over methodological quality, only trials published in peer review journals were included, but this adds the risk of publication bias. The heterogeneity of the outcomes and disease populations did not allow pooling of data for analysis, however, effect sizes were calculated. In attempting to increase study yield, trials that included control data, even if they were non-randomised, were included. This contributed to the poor scoring of trials on the PEDro scale.

Subsequently, caution in interpreting results must be taken.

Clinical messages

- Improvements in fitness, strength and mobility for eccentric exercise appear comparable with concentric exercise.
- Eccentric exercise appears to be well tolerated with studies reporting good adherence.
- Preliminary evidence suggests eccentric exercise can be used safely in adults with moderate cardiorespiratory disease to exercise at high intensity with less oxygen consumption.

Conflict of interest

The authors declare that there is no conflict of interest.

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Appendix A: Search strategy example- Medline

1. “eccentric exercise”.mp. [mp = title, abstract, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. “eccentric contraction”.mp.
3. (eccentric adj3 training).mp.
4. (eccentric adj5 strength*).mp.
5. “eccentric therap*”.mp.
6. “eccentric rehabilitation”.mp.
7. “lengthening contract*”.mp.
8. “negative work”.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp heart disease/
11. exp coronary heart disease/
12. (heart or coron* or cardio*).mp
13. exp respiratory tract disease/
14. (COPD or COAD or “chronic obstructive pulmonary disease” or “chronic obstructive airway*”)
15. exp chronic obstructive lung disease/
16. exp lung disease/
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 9 and 17

Appendix B: Data extraction table

Reviewer: **Date of extraction:** **Included/ Excluded :**

Full reference details: .....

Study Objective:.....

Study design: .....

Subject details:
* Inclusion criteria:.....
* Exclusion criteria:.....
* Recruitment procedures used: .....
* Control Group: - Subject number:……..
- Sex:…….
- Age (mean & range):……
* Experimental Group: - Subject number:……
- Sex:…….
- Age (mean & range):……
* Group characteristics (e.g. pathology- disease type and severity, demographics)
* Experimental group:.....
* Control group:.....

Description of intervention (content e.g. intensity, equipment, total time of each session, number of sets and reps)
* Type of exercise:…….
* Frequency: .....
* Intensity: .....
* Duration of exercise session and treatment program:.…….
* Equipment required: .....
* Group or individual intervention:.....
* Setting for intervention .....
* Exercise facilitator: .....
* Pre-conditioning sessions: .....

Outcome measures used (at baseline and follow-up):
* Impairment: .....
* Activity: .....
* Participation: .....
* Were the tools used to measure the intervention valid and reliable? How was this demonstrated? .....

Results (statistical techniques used, statistical results, effect sizes, attrition rates): .....
Additional comments (especially adverse events/ tolerance of exercise): .....

Appendix C. Detailed description of PEDro scores.

Study (year)	2. Random allocation	3. Concealed allocation	4. Baseline comparability	5. Assessors blinded	6. Participants blinded	7. Therapists blinded	8. Follow-up	9. Intention-to-treat analysis	10. Between group analysis	11. Point estimated and variability	Total Score
Besson et al. (2013)	No	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Gremeaux et al. (2010)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Meyer et al. (2003)	Yes	No	No	No	No	No	No	No	Yes	Yes	3/10
Rocha Vieira et al. (2011)	No	No	No	No	No	No	Yes	Yes	No	Yes	3/10 Not RCT
Rooyackers et al. (1997a)	No	No	No	No	No	No	Yes	No	No	Yes	2/10 Not RCT
Rooyackers et al. (1997b)	No	No	No	No	No	No	Yes	Yes	No	Yes	3/10 Not RCT
Rooyackers et al. (2003)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Steiner et al. (2004)	Yes	No	No	No	No	No	Yes	No	Yes	Yes	4/10
Theodorou et al. (2013)	No	No	Yes	No	No	No	No	No	Yes	Yes	3/10 Not RCT
Zoll et al. (2006)	Yes	No	No	No	No	No	No	No	No	Yes	2/10

Chapter 3: Reliability of one-repetition maximum performance in people with chronic heart failure.

3.1 Introduction

This chapter presents a study that determined the reliability of one-repetition maximum (1-RM) assessment using a leg press in people with chronic heart failure. Both intra-rater and inter-rater reliability were investigated. This study was conducted as there have been limited studies investigating the reliability of muscle strength outcomes in patients with chronic heart failure, which was an outcome measure used in the randomised controlled trial reported in this thesis (Chapter 4). We hypothesised the use of 1-RM on a leg press in people with chronic heart failure would demonstrate good intra-rater and inter-rater reliability and provide justification for its use in the trial.

3.2 Study Two

This study is presented in its accepted format. This is the authors' accepted manuscript of an article published as the version of record in Disability and Rehabilitation, 24th February 2018.

http://www.tandfonline.com https://www.tandfonline.com/doi/full/10.1080/09638288.2018.1443160

> Ellis R, Holland AE, Dodd K, Shields N. Reliability of one-repetition maximum performance in people with chronic heart failure. Disability and Rehabilitation. 2019;41(14):1706-10.

Reliability of one-repetition maximum performance in people with chronic heart failure.

Abstract

***Purpose*:** Evaluate intra-rater and inter-rater reliability of the one-repetition maximum strength test in people with chronic heart failure.

***Design*:** Intra-rater and inter-rater reliability study.

***Setting*:** A public tertiary hospital in northern metropolitan Melbourne.

***Participants*:** Twenty-four participants (nine female, mean age 71.8 ±13.1 years) with mild to moderate heart failure of any aetiology.

***Methods*:** Lower limb strength was assessed by determining the maximum weight that could be lifted using a leg press. Intra-rater reliability was tested by one assessor on two separate occasions (two - five days apart). Inter-rater reliability was tested by two assessors in random order.

***Statistical analyses*:** Intra-class correlation coefficients and 95% confidence intervals were calculated. Bland and Altman analyses were also conducted, including calculation of mean differences between measures ($\bar{d}$) and limits of agreement.

***Results*:** Ten intra-rater and 21 inter-rater assessments were completed. Excellent intra-rater (intra-class correlation coefficient $_{2,1}$ 0.96) and inter-rater (intra-class correlation coefficient $_{2,1}$ 0.93) reliability was found. Intra-rater assessment showed less variability (mean difference 4.5 kg, limits of agreement -8.11 to 17.11 kg) than inter-rater agreement (mean difference -3.81 kg, limits of agreement -23.39 to 15.77 kg).

Conclusion: One-repetition maximum determined using a leg press is a reliable measure in people with heart failure. Given its smaller limits of agreement, intra-rater testing is recommended.

Implications for rehabilitation:

Using a leg press to determine a one-repetition maximum we were able to demonstrate excellent inter-rater and intra-rater reliability using an intra-class correlation coefficient. The Bland and Altman levels of agreement were wide for inter-rater reliability and so we recommend using one assessor if measuring change in strength within an individual over time.

Keywords

Chronic heart failure, strength, 1-RM, one-repetition maximum, reliability

Introduction

Chronic heart failure affects 26 million people worldwide (1) at an estimated annual cost of over $1 billion in Australia (2). People with heart failure experience exertional dyspnoea, fatigue and weakness (3) leading to reduced exercise tolerance. The mechanisms behind limitations in physical activity among people with heart failure include inadequate blood flow to skeletal muscles, inability to increase cardiac output in response to physical activity, (3) muscle weakness (4) and muscle atrophy (5). Reduction in muscle function contributes significantly to exercise intolerance in people with chronic heart failure and its cause is multifactorial (6). One study reported quadriceps strength was the most important individual correlate of exercise tolerance in people with chronic heart failure, (4) while another study found quadriceps weakness was predominately due to loss of muscle mass and suggested exercise tolerance was significantly affected by muscle atrophy (5).

To minimise the effect of muscle atrophy and increase muscle strength, exercise is a recommended component of heart failure rehabilitation (3). To ascertain if treatment is successful, therapists require reliable outcome measures that are easily used in the clinic.

To date, limited studies (7-9) have investigated the reliability of muscle strength outcomes in patients with chronic heart failure with complex dynamometry equipment primarily being used. This is consistent with the literature available for other chronic disease such as chronic obstructive pulmonary disease (10) and chronic stroke (11), where only the reliability of dynamometry has been investigated, with the exception of one study that explored the reliability of an estimated one-repetition maximum (1-RM) in people with Type 2 diabetes (12). Although isokinetic dynamometry is reliable and considered as the gold standard, with one study suggesting that compared to isokinetic dynamometry the use of the 1-RM technique overestimates strength gains over time, (7) this type of equipment is expensive and not commonly available in regular clinics.

In healthy adults 1-RM testing has also demonstrated good reliability (13) and completing a 1-RM measurement requires common gymnasium equipment, and so with no previous studies having assessed the reliability of the 1-RM strength measure in people with heart failure or in fact chronic disease, this study aimed to determine both the intra-rater and inter-rater reliability of 1-RM with a leg press in people with mild to moderate chronic heart failure.

We hypothesised the leg press 1-RM in people with chronic heart failure would demonstrate good intra-rater and inter-rater reliability.

Methods

Research design: This was an intra-rater and inter-rater (within-therapist and between-therapist) reliability study. For inter-rater reliability the order of testing by the two assessors was randomly generated using a random list generator (14). Ethics approval for

the study was obtained from the relevant hospital and university human ethics committees.

Participants: This study was conducted alongside a randomised controlled trial investigating the effects of eccentric exercise in people with chronic heart failure (ClinicalTrials.gov Identifier: NCT02223624). The eligibility criteria for this reliability study were the same as for the randomised controlled trial. Patients were included if they were: (1) aged 18 years or above; (2) had a clinical diagnosis of mild to moderate heart failure (any aetiology); (3) were medically stable; and (4) had been assessed by a physiotherapist as having no contraindications to exercise. Where there were concerns about an individual taking part, clearance was sought from the treating cardiologist.

The exclusion criteria were: (1) hospitalisation for an exacerbation of chronic heart failure within the previous month; (2) severe heart failure classified as level four on the New York Heart Association classification (i.e. short of breath at rest); (3) a concurrent unstable medical condition such as uncontrolled angina, diabetes or hypertension; (4) dementia or a psychological disorder that would interfere with participation in group exercise; (5) participation in a cardiac or heart failure rehabilitation program in the previous six months; (6) the presence of a contraindication to exercise or (7) the presence of any pre-existing neurological or musculoskeletal condition, for example stroke, that on assessment was deemed to interfere with exercise participation.

Participants were recruited following referral to heart failure rehabilitation either from local general practitioners, a heart failure clinic or referral from an acute hospital admission at a metropolitan health service located in the north of Melbourne.

1-RM leg press testing protocol: All assessments were completed in an air-conditioned gymnasium of a hospital. Assessments were conducted at the same time of day (between 10:00 a.m. and 1:00 pm). Intra-rater reliability was measured by one assessor completing testing on two separate occasions two - five days apart. Inter-rater reliability was completed by two assessors in random order with a short rest period (five -10 minutes) in between. Both inter-rater assessors were physiotherapists with multiple years of experience. Assessor one had 11 years of clinical experience, including experience completing heart failure assessments and rehabilitation. Assessor two had five years of clinical experience including experience working with people with heart failure during acute hospitalisation. Neither assessor had previously used the 1-RM assessment of leg strength as an outcome measure for heart failure rehabilitation. All intra-rater assessments were completed by the same physiotherapist (assessor two).

A multi-gym leg press apparatus (ACUFIT ENTERPRISE Co., LTD, Taiwan) was used to perform the testing. Participants were instructed on correct performance by the assessor. This involved sitting upright on the leg press apparatus with their back against the support. Feet were placed flat on the platform, shoulder width apart and with neutral rotation. The seat was moved forward or back to create 90 degrees knee flexion which was measured using a goniometer. Participants were prompted to place their hands on the hand grips at their side. Participants were instructed to straighten their knees, moving slowly through range until extended fully (but not hyperextended).

Once correct posture was obtained (using demonstration if necessary) participants warmed up by completing five -10 submaximal (~50% maximum) repetitions. Following this, the assessor estimated an initial near maximum load. Rest periods of three - five minutes between attempts were allowed. Assessors progressed resistance by 5 kg each attempt (1 plate) or 5% whichever was greater and aimed to determine 1-RM within four

attempts. The final weight successfully lifted through full range of motion was recorded as the 1-RM. This procedure was based on that described by the American College of Sports Medicine and National Strength and Conditioning Association (15, 16) . Participants were not informed of their results throughout the procedure.

Statistical Analyses: Based on a calculation by Walter, Eliasziw and Donner, (17) in order to achieve an Intra-Class Correlation (ICC) value of greater than 0.8, a sample size of n = 46 was required, assuming an alpha of 0.05 and power of 80%. Although some suggest a level of agreement of 0.7 is good (18) based on previous reliability studies in the heart failure population the minimum value of 0.8 was deemed clinically acceptable (8). During the completion of the study, assessor two moved overseas and so the decision was made to cease further assessments rather than recruiting a new assessor to avoid introducing a new source of variability. This meant that the estimated sample size was not reached.

Intra-class correlation coefficients ($ICC_{2,1}$) and the associated 95% confidence interval (CI) were calculated. Bland and Altman plots were used to assess agreement between testing occasions, which involved calculation of the mean difference between measures ($\bar{d}$) and the limits of agreement (1.96 x SD_{diff}).

Results

Participants: The sample consisted of 24 participants with chronic heart failure (nine female) and mean age 72 ± 13 years (table 1). Heart failure severity based on New York Heart Association classification was mild to moderate (n = 13 class II). Sixteen participants had systolic dysfunction on echocardiogram. Four participants had diastolic dysfunction, two had evidence of both, one had no reported dysfunction on

echocardiogram and the final participant was newly diagnosed and awaiting echocardiogram, thus diagnosis was based on clinical presentation. Ejection fraction (n=19) was reduced with a mean percentage of 37.0 ± 13.5. Four participants did not have a documented ejection fraction on transthoracic echocardiogram and one participant was awaiting echocardiogram. Cause of heart failure was classified as ischaemic in 10 participants and non-ischaemic (including valvular) in 13 participants. All participants were taking cardiac medications (table 1).

Exercise protocol: Fourteen participants could not achieve the starting position of 90 degrees of knee flexion, due to reduced range of motion or body stature. The actual starting position ranged from 45 to 90 degrees (mean assessor one 85±11 degrees, mean assessor two 82 ± 9 degrees).

Two participants were able to lift the maximum possible weight (120 kg). All participants could lift the minimum weight of 5 kg.

Reliability: The inter-rater ICC $_{(2,1)}$ was 0.93 (95% CI 0.83 – 0.97) (table 2) suggesting an excellent level of agreement. The intra-rater ICC $_{(2,1)}$ was also excellent at 0.96 (95% CI 0.81 – 1.00). The Bland and Altman method showed a mean difference between measures ($\bar{d}$) for inter-rater reliability (figure 1) of -3.81 kg with limits of agreement of -23.39 to 15.77 kg. For intra-rater reliability (figure 2) the mean difference between measures ($\bar{d}$) was 4.5 kg and limits of agreement were -8.11 to 17.11 kg.

Adverse events: One participant reported chest discomfort during testing that quickly resolved with rest. No other negative events were reported.

Discussion

Our results suggest assessment of lower limb strength using leg press 1-RM had excellent reliability in people with heart failure. The mean difference between testing occasions for both inter-rater reliability and intra-rater reliability was small, equivalent to less than one 5 kg plate on the leg press. However, the limits of agreement were wide, particularly for inter-rater assessments (-23.39 kg to 15.77 kg), with the range of inter-rater differences varying from no difference to 25 kg difference between testing occasions. As a result, the use of one outcome assessor is recommended to accurately measure strength changes using this method in people with heart failure. Increasing evidence suggests that not only is lack of muscle strength a significant result of chronic heart failure (4, 5) but that strengthening exercises can safely be included in rehabilitation programs to address this (3). The results of this study allow staff and patients with chronic heart failure completing strengthening exercise to assess baseline strength, which can then be used in exercise prescription and tracking of progress. Given the lack of studies demonstrating the reliability of this technique in other chronic diseases but its frequent use as an outcome to measure strength changes, this present study may have applications across a broader population. Further research in other chronic disease populations is recommended.

In previous reliability studies including people with heart failure and other cardiac conditions, familiarisation sessions were reported to improve reliability (9). In our study, for five of the 21 inter-rater assessments the participant had completed the procedure once before. The mean difference for these five assessments was -12 kg compared with the mean for all measurements of -3.81 kg suggesting that, familiarisation did not help in increasing agreement. When intra-rater reliability was investigated using the Bland and Altman plot it revealed that in nine out of 10 assessments the participant scored higher values than on the first. This suggests a learning effect, either on the part of the patient or on the part of the assessor, who may feel more confident when completing the procedure

with a participant for the second time in what has been generally considered a high-risk population. No consistent differences were observed between assessor one and assessor two, suggesting that level of experience did not affect results.

Limitations

The apparatus used in this study measured strength in 5 kg increments which limits sensitivity to change and affects the analysis of reliability. Contrary to expectations, two participants experienced a ceiling effect by being able to lift the maximum possible weight (120 kg). While one participant was young (49 years) with mild, poorly defined heart failure (New York Heart Association class 1) the other participant was assessed as New York Heart Association class 3 and had dilated cardiomyopathy with severe systolic dysfunction and an ejection fraction of 16%. This supports the finding that heart function particularly as measured by ejection fraction does not necessarily correlate with exercise tolerance (19) and perhaps participant age was a greater determinate of strength (40 year old male). One participant was only able to lift the minimum amount, however, a floor effect was not evident. The assessment procedure required both assessors aim for a set-up position of 90 degrees of knee flexion. This was not achievable for 14 (58%) of participants suggesting it may need to be revised.

The major limitation identified for this study is that the previously determined sample size was not reached due to the departure of assessor two from the country. Introducing a new assessor would have increased variability, rather than increasing the confidence in the results and as such was not carried out. Given the high $ICC_{(2,1)}$ achieved and the spread of values spans across the range of possible values on the Bland and Altman plot it is likely that the sample size was sufficient to demonstrate reliability however a further study with larger sample should be considered.

Conclusion

One-repetition maximum determined using a leg press is a reliable measure in people with heart failure. Given the larger limits of agreement for inter-rater reliability, assessment by the same rater on each testing occasion is recommended.

Declaration of interest

The authors report no conflicts of interest.

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Figure 1: Bland and Altman plot showing mean measurements against differences for inter-rater reliability, including levels of agreement (LOA).

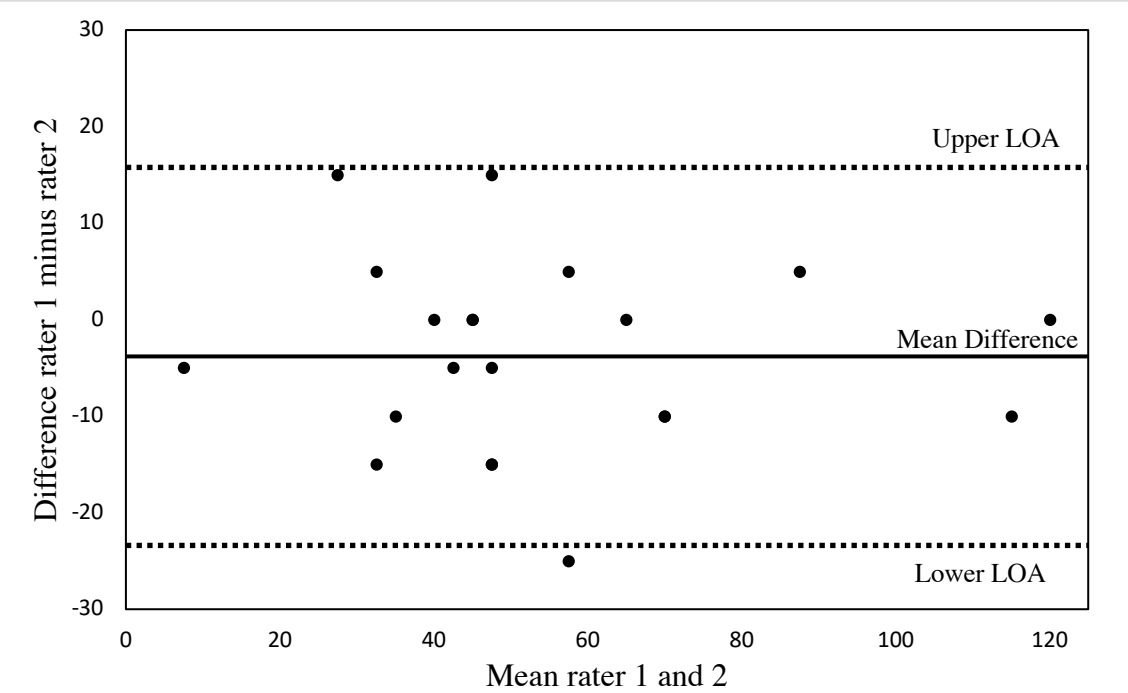

Figure 2: Bland and Altman plot showing mean measurements against differences for intra-rater reliability, including levels of agreement (LOA).

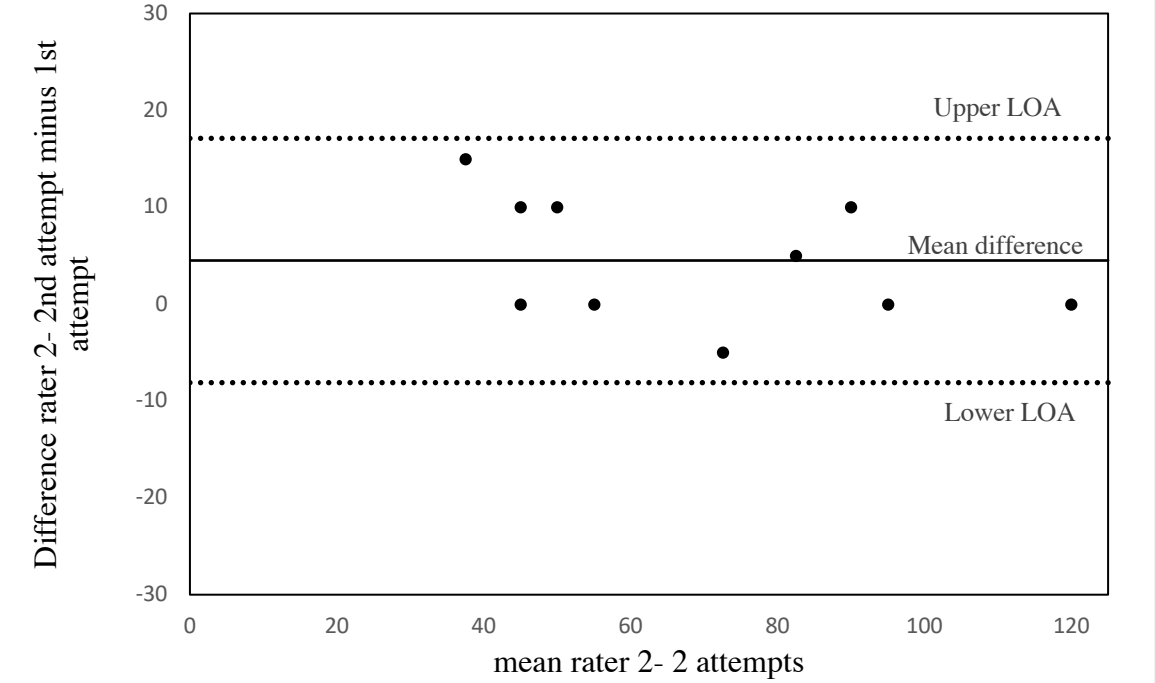

Table 1: Demographic Data for 1-RM participants

Characteristic	Inter-rater reliability (n=21)	Intra-rater reliability (n=10)
Sex (male/female)	13/8	8/2
Mean age (SD) (y)	71.9 (13.9)	71.3 (11.8)
Language (English/non-English speaking) (number)	15/6	7/3
Mean height (SD) (cm)	158.2 (39.1)	168.0 (11.6)
Mean weight (SD) (kg)	87.8 (23.2)	97.8 (21.8)
Mean BMI (SD) (kg/m2)*	32.1 (6.2)**	34.6 (7.0)**
NYHA Classification (Class 1-3) (number)	8/10/3	3/7/0
Diagnosis (Systolic/ Diastolic/ combined heart failure) (number)	14/4/2 (1 unreported)	8/1/0 (1 unreported)
Aetiology (Ischaemic/ Non-ischaemic heart failure) (number)	8/12 (1 awaiting investigation)	4/6
Mean EF (SD) (%)	36.0 (13.9)***	38.3 (13.9)***
Medications (number)		
Beta blocker	17	7
ACE inhibitor	14	7
Calcium channel blocker	5	3
Nitrate	4	2
Diuretic	15	5
Statin	14	8
Anticoagulant	18	10
ARA 2	5	2
Aldosterone antagonist	9	3
Amiodarone	4	1
Digoxin	1	0
Potassium	1	0
Anxiety/Depression medications	5	2
Respiratory medications	5	4

*Average BMI is 18.5–24.9kg/m2 , overweight is 25–29.9kg/m2 , obese is 30kg/m2 [20]
** Two participants had missing height data affecting two in the inter-rater and one in the intra-rater calculation
*** Five participants had nil EF documented on TTE in the inter-rater group and four in the intra-rater group.
Abbreviations: SD, standard deviation; BMI, body mass index; NYHA; New York Heart Association; EF, ejection fraction; TTE; transthoracic echocardiogram, ARA 2, angiotension II receptor agonists.

Table 2: Results for inter-rater and intra-rater reliability- ICC and Bland and Altman tests

	ICC		Bland and Altman	
	ICC co-efficient	95% CI	mean difference, $\bar{d}$ (kg)	limits of agreement (kg)
Inter-rater reliability	0.93	0.83 – 0.97	-3.81	-23.39 – 15.77
Intra-rater reliability	0.96	0.81 – 1.00	4.5	-8.11 – 17.11

Chapter 4: Effect of an eccentric exercise program on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial.

4.1 Introduction

A systematic review (Chapter 2) reported limited studies have investigated eccentric exercise in people with chronic cardiorespiratory disease, specifically chronic heart failure, and those that had been conducted largely evaluated physiological outcomes. Based on these gaps in the literature, a randomised controlled trial was devised to explore the effect of low energy cost (eccentric) exercise on quality of life and functional outcomes in people with chronic heart failure. A prospective, three-armed, parallel-design, assessor-blind trial was conducted using traditional rehabilitation and no treatment (waitlist control) as comparisons, given the established benefit of heart failure rehabilitation. Chapter 4 presents the results of this randomised controlled trial.

4.2 Study Three

The study in this chapter has been accepted for publication by Disability & Rehabilitation. It is presented in its accepted manuscript format:

> Ellis R, Dodd K, Holland AE, Lim, K, Tacey M, Shields N. Effect of eccentric exercise on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial. Disability and Rehabilitation. In press. Accepted 11th October 2020. https://doi.org/10.1080/09638288.2020.1836679

Effect of eccentric exercise on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial.

Abstract

Purpose*:* To determine if eccentric exercise was effective, safe and feasible in increasing function and quality of life in people with heart failure compared to usual care and a waitlist control group.

Methods**:** A prospective, three-armed, parallel-design, assessor-blind pilot randomised controlled trial with 1:1:1 allocation. Forty-seven participants (16 female; mean age 66 years) with mild to moderate heart failure were randomly allocated to either eccentric exercise, concentric exercise or a waitlist control group. Participants in the exercise groups completed twice-weekly exercise for eight weeks. Primary outcome was walking capacity. Secondary outcomes were quality of life, leg strength and fatigue. Outcomes were assessed at baseline, post intervention and three-month follow-up. Attendance, tolerability and adverse events were used to determine safety and feasibility.

Results: Intention-to-treat analysis showed no differences between eccentric exercise and either concentric exercise or waitlist for any outcome. Per-protocol analysis found improvements identified by the Minnesota living with heart failure questionnaire were significantly greater post-intervention for eccentric exercise compared to concentric exercise (-17.99 units, 95% confidence interval -35.96 to -0.01). No major adverse events were reported.

Conclusion: In this small trial, eccentric exercise did not demonstrate superior outcomes to concentric exercise or a waitlist control group.

Clinical trial registration: The protocol for this trial was registered at clinicaltrials.gov, registration number: NCT02223624, registration date: 22 August 2014.

Implications for rehabilitation:

Regular physical activity and referral to rehabilitation is recommended for people with chronic heart failure, however exercise can be challenging for this group.

Eccentric exercise was safe and tolerable for participants with heart failure.

Documentation of exercise progression is important to demonstrate a dose–response relationship.

In this study there were no differences between groups who received eccentric exercise, concentric exercise or no exercise.

Keywords

Chronic heart failure, heart failure, exercise, eccentric exercise, rehabilitation, quality of life, function.

Introduction

Current clinical guidelines recommend regular physical activity for people with chronic heart failure and referral to rehabilitation for patients who are medically stable (1). Rehabilitation programs primarily comprise moderate intensity, continuous, endurance exercise as well as weightlifting with the aim of improving physical function, quality of life and hospitalisation rates (1). Individuals with chronic heart failure show obstructive and restrictive deficits on respiratory function tests (2) as well as skeletal muscle dysfuction (3) which leads to exercise intolerance. For this reason, there is interest in determining if eccentric exercise with its low energy costs, may be used safely to achieve strength and functional gains in people with significant intolerance to exercise.

Eccentric exercise produces high forces but with low energy costs (4). During eccentric contractions, the muscle lengthens and stores elastic recoil energy which can then be used to create high forces with little metabolic demand (4). Eccentric contractions require

50% to 86% less oxygen than concentric contractions (5, 6). While eccentric exercise has traditionally been used in younger populations for its ability to increase muscle strength and size using high force production and to rehabilitate soft tissue injuries, (7) research trialing eccentric exercise with an endurance dosage suggests older people may also benefit from low energy-cost exercise (8).

Previous research of eccentric exercise in people with chronic diseases such as Parkinsons disease, diabetes, chronic obstructive pulmonary disease, and coronary heart disease have demonstrated comparable functional outcomes with low metabolic demand and no adverse outcomes (9-11). Specifically, in coronary heart disease, eccentric exercise was reported to be safe as it caused minimal cardiovascular or respiratory stress, was perceived by patients as "fairly light" exertion and when compared with concentric exercise resulted in comparable improvements in muscle strength and walking distance, often with reduced oxygen consumption (12, 13).

Four previous trials (14-18) investigated the effect of eccentric exercise on physiological and functional outcomes in people with heart failure. One trial showed a single bout of eccentric exercise was safe, with minimal impact on the cardiovascular and ventilatory systems when compared to concentric exercise (14, 15). Three trials implementing a rehabilitation dosage (three times weekly for 6-7 weeks), found eccentric exercise resulted in comparable walking and strength outcomes to concentric exercise but with lower levels of work (heart rate, ventilatory demand or ratings of percieved exertion) (16-18). Although these trials provide useful information, there were methodological limitations identified such as small sample sizes (11 to 50 participants), single group design (14, 15), limited information about randomisation and concealed allocation (17),

non-blinded assessment (17), no follow-up analysis (17) and no intention to treat analysis (16, 17).

The overall aim of this trial was to investigate the effect of eccentric exercise in people with mild to moderate heart failure, of any origin. The primary aim was to determine if eccentric exercise increases physical function in people with heart failure. The secondary aim was to investigate its effect on quality of life as well as the feasibility and safety of eccentric exercise.

Materials and methods

A prospective, three-armed, parallel-design, assessor-blind pilot randomised controlled trial with a 1:1:1 ratio for group allocation was completed. Participants were randomly allocated to one of three groups: (1) an eccentrically biased rehabilitation program (eccentric exercise); (2) a traditional rehabilitation program (concentric exercise); or (3) a waitlist control group. Allocation was achieved using an electronic block randomisation method (19). An assistant otherwise uninvolved in the trial generated the allocations and concealed them in numbered, opaque, sealed envelopes. Randomisation occurred after baseline assessment by opening the next envelope in the sequence. All participants gave informed written consent. Ethics approval was obtained from the relevant hospital and university human ethics committees (NH LR 49.2013).

Patients were included if they were: (1) aged 18 years or above; (2) had a clinical diagnosis of mild to moderate heart failure (systolic or diastolic, reduced or preserved ejection fraction); (3) were medically stable; and (4) had no contraindications to exercise. Where there were concerns about an individual taking part, medical clearance was sought from the treating cardiologist. Participants whose preferred language was not English

were not excluded from the trial. Interpreters were employed to facilitate these participants providing consent, completing assessments and outcome measures and for taking part in exercise sessions.

Patients were excluded if they were: (1) hospitalised for an exacerbation of chronic heart failure within the previous month; (2) had severe heart failure (New York Heart Association class IV, i.e. short of breath at rest); (3) had a concurrent unstable medical condition such as uncontrolled angina, diabetes or hypertension; (4) had dementia or a psychological disorder that would interfere with participation in group exercise; (5) had participated in a cardiac or heart failure rehabilitation program in the previous six months; (6) had a contraindication to exercise (i.e. aneurysm, valvular disease, severe aortic stenosis), or, (7) had any pre-existing neurological or musculoskeletal condition that on assessment was deemed to interfere with exercise participation.

All exercise was performed in a hospital outpatient gymnasium in a group setting. It was completed twice a week for eight weeks on regular days, at the same time each day. If participants missed an exercise session, they were given up to two extra weeks to make up that session. Program completion was defined as having attended 12 out of a possible 16 exercise sessions (75%). Each exercise group was supervised by two registered physiotherapists, or by one physiotherapist and one experienced allied health assistant. The group physiotherapist may have been a junior physiotherapist who completed an orientation to group supervision. All exercise sessions were individually tailored with ratings of perceived exertion on the BORG scale (6-20 scale), and shortness of breath on BORG scale (0-10) taken for each participant for each exercise. For both exercise groups, exercise intensity was progressed over the course of the program to maintain

symptom ratings of 11-13 (fairly light – somewhat hard) on the perceived exertion scale (20, 21).

***Eccentric exercise*:** Sessions typically included a 10-minute warm-up (whole body stretches and walking gentle laps of the gymnasium (1-2 minutes), 20 minutes on the eccentric stepper (Eccentron™ see figure 1), walking on a treadmill for 10 minutes at a moderate pace, and upper limb and lower limb free weights (1-3 sets, 8-10 repetitions) addressing all major upper and lower limb muscle groups (i.e. biceps curls, upward row, shoulder abduction and elevation, hip abduction and extension, hip and knee flexion, ankle plantarflexion, seated knee extension with cuff weights). On the Eccentron™, participants were provided with visual feedback via a television screen about their technique of resisting the pedals, which moved toward them (i.e. a negative resistance trainer). Where participants were unable to complete 20 minutes of continuous exercise on the Eccentron™, the aim was for them to complete two 10-minute bouts of eccentric exercise with rest as necessary within the 60-minute session.

Concentric exercise: Participants completed the same warm-up, walking and upper limb and lower limb weights. They also completed 20 minutes of concentric exercise comprising 10 minutes cycling on an exercise bike and climbing over and back on four steps (5-10 minutes, typically completed in sets of 10 repetitions). At the end of each exercise session each participant rested and their pulse rate and oxyhaemoglobin saturation was recorded.

Waitlist control: Participants completed two assessments, eight weeks apart, with no care provided during the wait period. After the wait period they were invited to participate in the usual care rehabilitation program but did not provide any further data to the study.

At baseline, all participants received advice about managing their condition. This included encouragement to maintain an active lifestyle and to walk regularly, and information on monitoring their fluid balance and weight as a means of monitoring their condition. Participants in the two exercise groups had access to once weekly, one-hour, multidisciplinary, group education sessions. The following topics were presented by health professionals: nutrition and healthy eating, stress management, energy conservation and relaxation, physical activity, socialising and self-management in chronic heart failure, medications, legal considerations (e.g. enduring power of attorney) and emotional reactions to heart failure.

Outcome measures were taken at baseline, immediately after the intervention period and three months after the intervention period. A physiotherapist, blinded to group allocation and not involved in delivering the intervention, conducted all assessments.

The primary outcome was:

Walking capacity- the 6-minute walk test was conducted along a 25 m corridor and participants were asked to walk as far as possible in six minutes during which they were allowed to take rests but encouraged to continue as soon as able. Standardised encouragement and information was provided each minute, in line with recommendations (22). This test has demonstrated high test-retest reliability (ICC 0.9) (23) and shown higher correlation with quality of life questionnaires than peak oxygen uptake in people with chronic heart and lung disease (22).

The secondary outcomes were:

Minnesota Living with Health Failure Questionnaire- is a 21-item questionnaire with a 0 to 5 rating scale of how much participants perceive their heart failure affects aspects of

their life. It provided a total score (range 0–105, from best to worst quality of life), as well as scores for two dimensions: physical (range 0–40) and emotional (range 0–25). Lower scores indicate better quality of life. It has evidence of validity and reliability with high test-retest reliability (r = 0.87) and internal consistency (Cronbach's alpha = 0.92) (24).

Assessment of Quality of Life- is a 15-item multiple-choice questionnaire with five domains: illness, independent living, social relationships, physical senses and psychological well-being. Each item has four response options scored from 0-3; higher scores (maximum 45) indicated lower quality of life. This outcome is sensitive to change in a variety of people- different sex, age, education level and health status- and has high internal consistency (alpha = 0.8) (25).

Lower limb strength- measured by one repetition maximum during a seated leg press. Participants completed a warm-up of 10 repetitions of a weight estimated to be approximately 50% of their maximum. The weight used for the warm-up was estimated using information from the baseline assessment (such as the 6-minute walk test and qualitative reports of physical activity levels and/or previous experience with weight training) as well as clinical experience. A near maximum weight was then estimated using the warm-up weight as a guide and lifted through range. Weight was progressively increased in increments of 5 kg or 5% (whichever was greater) until the weight was no longer able to be correctly lifted fully. Rests of at least three minutes were allowed between attempts and the one repetition maximum was aimed to be determined within five attempts (26, 27). This technique has excellent inter-rater reliability in people with heart failure (ICC 0.93) (28).

Fatigue- measured using the 9-item Dutch Exertion Fatigue Scale (DEFS). This measure rates the level of fatigue during everyday activities including walking for 10 minutes, walking for 30 minutes, standing in the shower, climbing stairs, vacuuming, cleaning up rubbish, visiting a friend and attending a birthday party. Higher scores indicate greater fatigue. This scale has high internal consistency (Cronbach's alpha 0.91) in people with heart failure (29).

The number of exercise sessions attended was documented for each participant. The tolerability of the program was measured using ratings of perceived exertion and shortness of breath. Pulse rate and oxyhaemoglobin saturation via pulse oximetry were monitored before, during and on completion of each exercise session with any within-session adverse events recorded by the treating physiotherapist. Participants were also asked to report any adverse events between sessions, as well as pain or muscle soreness, rated on a 0 -10 cm visual analogue scale (0= no pain to 10= worst pain imaginable) to the treating physiotherapist prior to starting each exercise session. Hospital admissions and deaths were monitored for all participants.

Assuming a between-group difference in the six-minute walk test of 60 m is clinically important (12) and the baseline standard deviation is 74.2 m (12) for a power of 0.8, with a two-tailed alpha of 0.5 a sample of 19 participants was required in each group. Based on historical completion rates for this heart failure rehabilitation program of approximately 75%, to allow for drop-outs we attempted to recruit a total of 25 participants to each group (75 participants total).

To determine whether the eccentric exercise group improved more than the concentric exercise group or waitlist control group immediately after the 8-week program, data were

analysed with analysis of covariance using the baseline measures as covariates. A deviation from protocol, was that multiple imputation was used to account for missing data instead of the carry forward technique, as it is a superior method (30). Categorical outcome variables (death or hospital admission) were analysed with relative risk ratios. Intention to treat analysis was used, with follow-up of withdrawals where possible. A per-protocol analysis was also completed including only those participants who completed the program (minimum 12 sessions over 10 weeks). Effect sizes were calculated using Cohen's d by subtracting the mean change over time for the control group (both concentric exercise and waitlist control) from the mean change for the eccentric exercise group, and dividing the result by the pooled standard deviation (31). Cohen's convention was used to determine the strength of effect sizes, with effect sizes of d= 0.20 considered small, d= 0.50 considered medium and d= 0.8 considered large (31).

Planned secondary analyses related to type of heart failure and correlations between primary and secondary outcomes were not conducted as the sample recruited was smaller than anticipated and insufficient for meaningful analysis.

Results

Recruitment occurred between July 2014 and August 2018. Three hundred and six people were assessed for eligibility and 47 were randomised (figure 2). Recruitment was much slower than expected due to large numbers of participants failing to attend hospital assessments, declining to participate or not meeting the eligibility criteria. Due to staffing changes, recruitment was ceased before the target sample size was achieved. The 47 participants were randomly assigned to the eccentric exercise group (n= 16), concentric exercise group (n= 16) and waitlist control group (n= 15). Participants were predominantly male and most were New York Heart Association (NYHA) class 2 (table

1). Exercise was delivered to all participants as planned except for one participant randomised to the eccentric exercise group (during a period of Eccentron^{TM} equipment repair) who received the concentric intervention.

There was no difference between the eccentric exercise group and concentric exercise group, or the eccentric exercise group and the waitlist control for any outcome in the intention to treat analysis (table 2). Effect sizes were small, ranging from 0 to -0.37 (6-minute walk test) for the eccentric exercise compared with the waitlist control and from 0 to -0.48 (Minnesota living with heart failure questionnaire) for the eccentric exercise compared with the concentric exercise groups, with a negative score indicating an improvement in quality of life.

The per-protocol analysis (table 3) included only participants that completed the program and accounted for the participant allocated to the eccentric group but who received concentric exercise due to equipment breakdown (figure 2). This analysis found no between group differences for the primary outcome of 6-minute walk test or secondary strength outcome. Significant between-group differences favouring the eccentric exercise group compared to concentric exercise group for quality of life at the post intervention assessment were found. The effect sizes for these two outcomes; Minnesota living with heart failure questionnaire- Total and Emotional, were -0.55 (-1.24 – 0.17) for both. These differences were not maintained at the three-month follow-up. Overall, effect sizes for the per-protocol analysis were largely similar to the intention to treat analysis.

Participants in the eccentric exercise and concentric exercise groups attended a mean of 12 exercise sessions (range 2 to 16). Twenty out of 32 participants completed the exercise program, with non-completers split equally between the eccentric exercise (n=

6) and concentric exercise (n= 6) groups. Exercise was well tolerated by participants in both groups. The protocol for the eccentric exercise group allowed participants to set their own work rate of 'somewhat hard' and their range of scores for rating of perceived exertion averaged 13 (range 7 to 17). The target time of 20 minutes spent on performing eccentric exercise was achieved for 11 of the 15 participants with the remaining four participants achieving 5, 10, 12 and 15 minute bouts of exercise. In the concentric exercise group, the average rating of perceived exertion was 12 (range 9 to 17). Shortness of breath averaged 2 on BORG scale (0-10) (slight to moderate) for the eccentric exercise group and 3 (moderate) for the concentric exercise group. Progression was comparable for the shared content (walking and free weights) of both groups. Exercise progression in the concentric exercise group was on average 173% in the levels of resistance for static bicycling. Exercise progression in the eccentric exercise group was an average change in force of 47%.

There were no major adverse events. Across the two exercise groups there were five unexpected hospital admissions, unrelated to the intervention. One participant in the eccentric exercise group was hospitalised for a urinary tract infection and sustained a fall between completing their program and the post-intervention assessment. Four participants in the concentric exercise required hospitalisation; one for delirium and a fall, one for postural hypotension, one for insertion of an Automatic Implantable Cardioverter Defibrillator and one for gastroenteritis and later for insertion of an Automatic Implantable Cardioverter Defibrillator. The latter participant withdrew from the trial, but all other participants who required hospitalisation continued with the intervention despite their medical conditions. The relative risk for hospital admission during rehabilitation tended to be higher in the concentric exercise group (RR 4, 95% CI: 0.50 to 31.98) when compared to the eccentric exercise group. Pain scores were

monitored for 23 participants (9 out of the 16 concentric exercise group participants and 14 of the 16 eccentric exercise group participants). The average VAS pain score was 1.4 cm (concentric exercise group mean 0.8cm vs eccentric exercise group mean 1.8 cm) suggesting only mild pain was experienced by participants in either group.

Discussion

This trial demonstrated that eccentric exercise can be delivered in selected people with heart failure, however the results suggest eccentric exercise is not superior to traditional heart failure rehabilitation for outcomes of functional capacity or quality of life. Per protocol analysis found no difference for functional outcomes. A significant difference in quality of life favouring eccentric exercise was found when compared to concentric exercise, but not compared to no exercise. Eccentric exercise was tolerated equally well as concentric exercise in terms of program attendance and completion rates, participation during the exercise sessions, and reported symptoms of pain, exertion or shortness of breath during exercise.

The lack of difference between the groups may have been due to the rate at which exercise was progressed. While some recommend that exercise prescription in heart failure be determined using a symptom-limited cardiopulmonary exercise test and progressed according to this testing (32) others suggest exercise intensity be progressed gradually as fitness improves (33) or often have used patient reported ratings of perceived exertion to progress exercise (21). Based on these suggestions, we aimed to progress exercises based on a rating of perceived exertion of ‘somewhat hard’ or 11 -13 on the Borg scale (21). While this was achieved and appeared comparable between groups, it is a limitation of the study as progression as a percentage change in workload was varied and for some participants was low. For future trials, it is recommended that in

addition to rating of perceived exertion, all exercise components of the program be progressed according to a protocol, with regular percentage increases in exercise intensity or documented progressions, such as has been applied in pulmonary rehabilitation (34). The use of protocols for people with heart failure would assist researchers consider exercise intensity when developing trial protocols and/or clinicians to prescribe exercises which result in maximum change for the individual.

A further limitation of the study was that data were not collected that would allow for normalising the total amount of work completed by the two exercise groups. This would have aided in confirming if for the same intensity, eccentric participants were able to achieve a greater output. Although the duration of exercise was the same for each participant, and the intensity of exercise was measured on the BORG scale for all participants, due to varying information available from the equipment used, questions remain as to the dose-response relationship of the intervention and if this was the reason for the lack of difference found between both exercise groups and the waitlist control.

Physical activity completed by participants outside of rehabilitation may have also impacted the results. All participants were not asked how much exercise they completed prior to commencing the study or during the study, but they were encouraged during the initial assessment and education session lead by a physiotherapist to maintain an active lifestyle, to walk regularly or commence regular exercise at home. Although education can lead to increases in physical activity and studies show people with heart failure have low activity levels, there is also the potential for a ceiling effect if people were already active or rehabilitation simply substituted another activity.

In addition to considering if the intervention groups completed sufficient exercise to evoke meaningful changes, it must also be considered if the waitlist control group increased their physical activity levels while waiting for rehabilitation. Waitlist participants were not asked to report their physical activity levels during the waitlist period. At initial assessment, no education was provided on how to commence exercise at home during the wait period, but participants were encouraged to maintain an active lifestyle. In a large study of people with heart failure over a period of up to four years, only eight per cent of usual care participants reported exercising at every telephone check after the first three months despite being provided with self-management education and then regular (fortnightly for the first nine months and then decreasing frequency) telephone calls to check if they were exercising (35). Given participants were randomised, the limited education provided during the initial assessment and no further intervention during the wait period, the probability of improvement in the waitlist group due to increasing their levels of physical activity is considered to be low. Information regarding activity levels would have assisted in comparing the intervention group with this waitlist group, who may have commenced exercising in preparation for their rehabilitation program following their enrolment in the trial. Information regarding other lifestyle changes or medical input participants received during the waitlist period was also not collected.

In comparing the eccentric and concentric interventions the degree of overlap between the two groups needs to be considered. Due to the preliminary nature of the eccentric exercise intervention with this population, and well-established guidelines for aerobic exercise as part of heart failure rehabilitation, it was deemed important to keep some aspects of the rehabilitation program consistent. The exercise tolerance of the participants was also considered and therefore twenty minutes of continuous eccentric exercise was

deemed suitable. Given the results of this and other recent studies in this population which show equivalent results for eccentric and concentric exercise, future non-inferiority trials might consider if rehabilitation might comprise solely or of a greater proportion of eccentric exercise.

The primary limitation of this trial was the inability to reach the proposed sample size of 75 participants, leaving it underpowered. Recruitment took place over a four-year period and was slow. The main difficulty was that only 56% of people assessed were eligible to participate due to wanting to attend rehabilitation exercise programs just once weekly (n= 35/134), musculoskeletal limitations (n= 20), more appropriate for a different service e.g. Cardiac or Pulmonary rehabilitation (n= 18) and already completing rehabilitation or physiotherapy elsewhere (n= 16). Effect sizes were calculated in considering the effect of the sample size on the results. With the exception of the moderate effect size of 0.55 for quality of life for eccentric exercise compared with concentric exercise, all of the effect sizes were small.

For those excluded due to musculoskeletal limitation such as back and knee pain, it was felt these participants would not be capable of participating in either the exercise bike or Eccentron™ interventions. Whereas in usual practice, an alternative exercise program would be devised, with eccentric exercise requiring one specific piece of equipment, alternatives were limited. The cost of the Eccentron™ equipment may also limit widespread feasibility in real-world clinical environments. Due to cost, only one device was purchased which subsequently limited participant numbers and throughput, as well as hindering widespread roll-out across sites. It is recommended other cost-effective ways of facilitating eccentric contractions, such as downhill treadmill walking or eccentric cycling on an ergometer (upper limb or lower limb), could be considered.

Previous studies using eccentric exercise in people with heart failure have implemented eccentric exercise with either treadmill or ergometers rather than a recumbent stepper. While the stepper in some respects can mimic downhill walking, it differs from a treadmill in that users are prompted to resist the force plates as they move towards them. A dosing test is completed prior to its use, which measures the level of resistance provided by the participant. Then during the exercise session, visual feedback on the screen supports the participant to exert the correct force to remain in the target range based on the dosing test. As such, it was considered in this respect to be different to downhill walking on a treadmill however the complexity of movement may have prevented early uptake in an aging population with up to 40% requiring an interpreter or having a preferred language to English. In this population, downhill walking may be more intuitive.

To date, the evidence around eccentric exercise in heart failure is limited. The extension from those with chronic heart and respiratory disease to heart failure is a logical one but with only three other trials using this exercise modality in therapy (16-18) in this population, the field of knowledge is growing but remains small. These previous trials reported comparable outcomes with concentric exercise but with lower work levels. The consequence of this finding was not well explored. The results of our trial and the limitations involved, namely the inadequate sample size, means further research is required to determine if eccentric exercise can be used to improve functional and quality of life outcomes for people with heart failure greater than those achieved with traditional rehabilitation programs. At this stage, the seemingly equivalence of this intervention with concentric exercise means that it is unlikely to replace concentric exercise but may be considered as an adjunct or alternative exercise for select people who have difficulty participating in a traditional program. Lastly, the inability to easily complete eccentric

contractions without also completing concentric contractions means that specific exercise equipment is required and this limits feasibility. For eccentric exercise to truly be considered as an ongoing exercise modality for this population, a means of completion in the home environment is required.

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Figure 1. Eccentron™ negative resistance trainer.

Figure 2. Number of participants at each stage of the trial (enrolment, allocation, follow-up, analysis) based on Consolidated Standards of Reporting Trials (CONSORT).

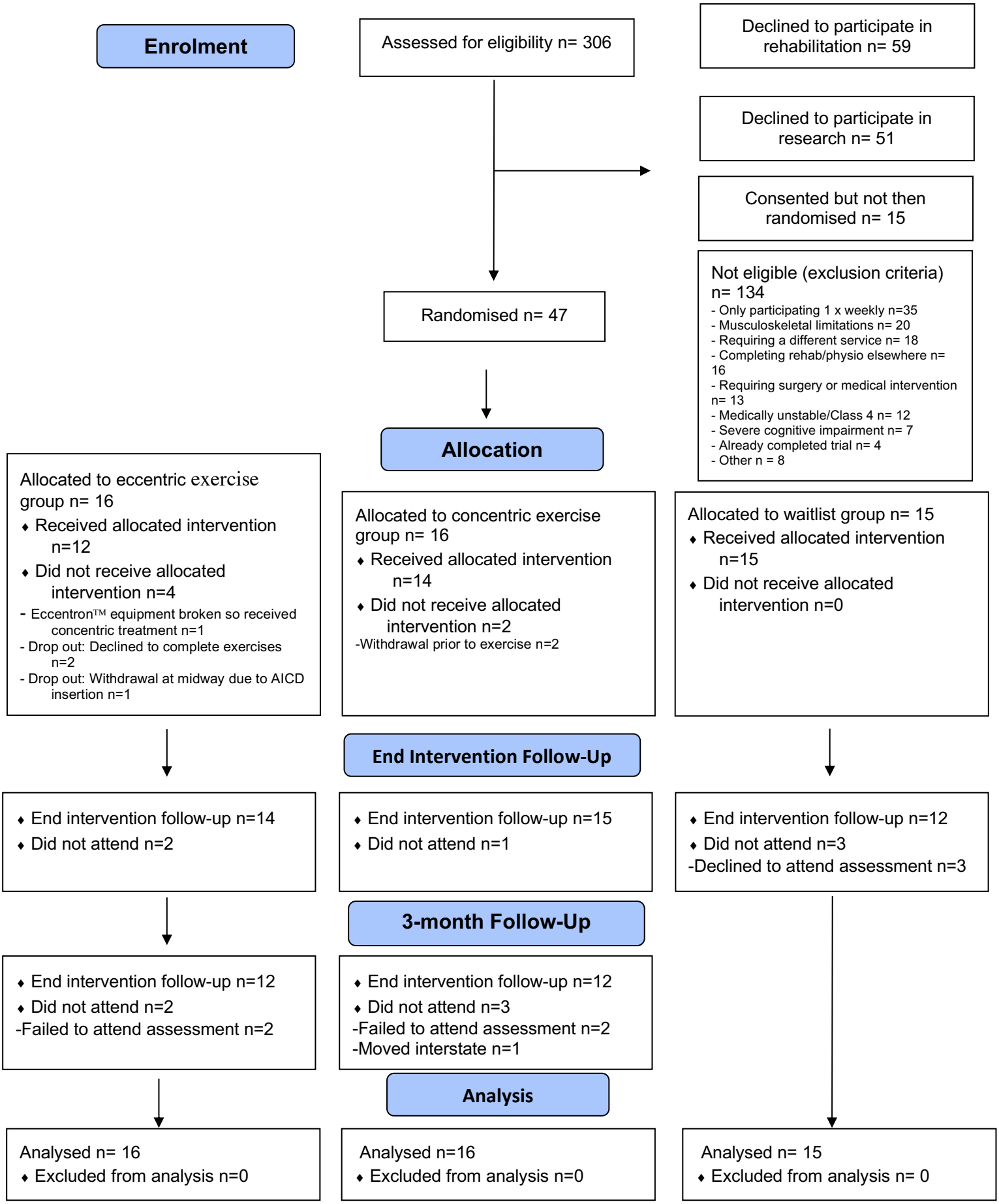

Table 1: Demographic Data for Intervention and Control Groups

Characteristic	Eccentric exercise group (n=16)	Concentric exercise group (n=16)	Waitlist group (n=15)
Sex (male/female)	10/6	13/3	8/7
Mean age (SD) (y)	66 (14)	68 (10)	65 (9)
Language (English/non-English speaking	13/3	15/1	9/6
Mean height (SD) (2)	168 (11)	169 (10)	165 (12)
Mean weight (SD) (kg)	92.8 (18.6)	97.2 (30.0)	84.7 (17.0)
Mean BMI (SD) (kg/m2)*	33 (8)	35 (11)	31 (6)
NYHA Classification (n) (Class 1-3)	4/11/1	1/13/2	3/9/3
Mean EF (%) (SD) (n)	34(12) (n= 13)	27 (18) (n= 10)	42 (18) (n= 15)
Medications (number)			
Beta blocker	15	15	13
ACE inhibitor	6	7	6
Calcium channel blocker	3	3	3
Nitrate	2	3	3
Diuretic	13	12	12
Statin	7	14	12
Anticoagulant	14	14	12
Digoxin	2	4	1
ARA 2	6	5	4
Aldosterone antagonist	6	8	6
Amiodarone	0	1	2
Potassium	1	2	1
Diabetes medications	4	6	5
Depression/ Anxiety medications	0	5	2
Respiratory medications	5	7	3
Reflux medications	4	6	8

Abbreviations: SD, standard deviation; BMI, body mass index; NYHA; New York Heart Association; EF, ejection fraction; ARA 2, angiotensin II receptor agonists.
*Average BMI is 18.5–24.9kg/m^2, overweight is 25–29.9kg/m^2, obese is 30kg/m^2 (36)

Table 2. Intention to treat analysis: Mean (SE) of groups at baseline, post intervention and 3 months, mean difference (95% CI) in change between groups and Cohen's d (95% CI) for difference between groups.

	Group Scores: Mean (SE)							
	Baseline			Post Intervention			Follow-Up	
Outcome (units)	Eccentric	Concentric	Waitlist	Eccentric	Concentric	Waitlist	Eccentric	Concentric
6MWT (m)	391.5 (30.8)	298.3 (30.8)	338.2 (31.8)	387.4 (33.3)	322.4 (31.5)	373.6 (33.5)	406.6 (33.2)	343.8 (32.0)
MLWHFQ Total	37.63 (5.57)	35.00 (5.57)	36.87 (5.75)	26.42 (5.94)	39.06 (5.68)	25.37 (6.00)	31.39 (6.46)	39.78 (6.22)
MLWHFQ Physical	16.88 (2.50)	16.56 (2.50)	18.07 (2.58)	12.82 (2.69)	18.61 (2.55)	12.74 (2.71)	14.35 (2.79)	17.16 (2.77)
MLWHFQ Emotional	8.25 (1.72)	7.13 (1.72)	6.80 (1.78)	5.90 (1.86)	8.93 (1.76)	4.57 (1.87)	6.36 (2.01)	8.25 (1.91)
AQOL	15.00 (1.43)	13.44 (1.43)	14.10 (1.52)	13.33 (1.55)	15.39 (1.46)	13.21 (1.56)	12.23 (1.82)	14.10 (1.66)
1-RM Leg strength (kg)	52.68 (6.83)	43.86 (6.67)	44.33 (6.73)	55.23 (6.98)	49.88 (6.71)	46.97 (6.89)	52.83 (7.08)	46.64 (6.91)
DEFS	13.63 (2.49)	15.63 (2.49)	15.73 (2.57)	11.32 (2.73)	17.64 (2.56)	10.97 (2.74)	11.71 (2.81)	15.18 (2.77)

	Difference between groups									
	Baseline to Post Intervention				Baseline to Follow-Up				Post Intervention to Follow-Up	
Outcome (units)	Concentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Concentric	d
6MWT (m)	-11.3 (-62.3 to 39.7)	-0.11 (-0.81 to 0.60	-28.1 (-81.2 to 24.9)	-0.26 (-0.95 to 0.44)	-39.5 (-93.4 to 14.5)	-0.37 (-1.07 to 0.35)	-30.3 (-87.3 to 26.7)	-0.26 (-0.95 to 0.44)	-2.2 (-40.0 to 35.6)	-0.03 (-0.72 to 0.67)
MLWHFQ Total	15.56 (-0.17 to 31.29)	0.50 (-0.23 to 1.20)	-15.27 (-31.00 to 0.46)	-0.48 (-1.17 to 0.24)	0.29 (-15.69 to 16.28)	0.01 (-0.70 to 0.71)	-11.02 (-28.92 to 6.88)	-0.30 (-0.99 to 0.40)	4.25 (-10.36 to 18.85)	0.14 (-0.55 to 0.83)
MLWHFQ Physical	7.38 (0.35 to 14.40) **	0.53 (-0.20 to 1.23)	-6.11 (-13.14 to 0.93)	-0.43 (-1.12 to 0.29)	1.27 (-5.88 to 8.42)	0.09 (-0.62 to 0.79)	-3.12 (-10.86 to 4.62)	-0.20 (-0.89 to 0.50)	2.99 (-2.48 to 8.45)	0.25 (-0.45 to 0.94)
MLWHFQ Emotional	4.03 (-1.15 to 9.22)	0.39 (-0.33 to 1.09)	-4.15 (-9.34 to 1.03)	-0.39 (-1.08 to 0.32)	-0.12 (-5.39 to 5.15)	-0.01 (-0.72 to 0.69)	-3.02 (-8.84 to 2.81)	-0.26 (-0.94 to 0.45)	1.14 (-3.66 to 5.94)	0.12 (-0.58 to 0.81)
AQOL	2.85 (-1.59 to 7.29)	0.32 (-0.39 to 1.03)	-3.62 (-8.00 to 0.76)	-0.41 (-1.09 to 0.30)	0.77 (-5.28 to 3.74)	0.09 (-0.62 to 0.79)	-3.43 (-8.64 to 1.79)	-0.33 (-1.01 to 0.38)	0.20 (-4.71 to 5.10)	0.02 (-0.67 to 0.71)
1-RM Leg strength (kg)	3.38 (-9.30 to 16.07)	0.13 (-0.57 to 0.84)	-3.48 (-16.58 to 9.62)	-0.13 (-0.82 to 0.57)	-0.10 (-13.11 to 12.92)	0.00 (-0.71 to 0.70)	-2.64 (-16.47 to 11.18)	-0.09 (-0.78 to 0.60)	2.85 (-3.28 to 8.97)	0.04 (-0.66 to 0.73)
DEFS	6.78 (1.14 to 12.43) **	0.61 (-0.13 to 1.31)	-4.32 (-10.08 to 1.45)	-0.37 (-1.06 to 0.34)	2.46 (-3.39 to 8.32)	0.21 (-0.50 to 0.91)	-1.47 (-8.02 to 5.08)	-0.11 (-0.80 to 0.59)	0.84 (-10.82 to 12.49)	0.23 (-0.47 to 0.92)

a Based on repeated measures mixed model, with multiple imputations for each outcome
** p-value, <0.05
Abbreviations: CI - confidence interval; MLWHFQ - Minnesota Living with heart failure questionnaire
AQOL - Assessment of Quality of Life; 6MWT - six-minute walk test, 1-RM - one-repetition maximum, DEFS - Dutch Exertion Fatigue Scale

Table 3. Per-Protocol Analysis: Mean (SE) of groups at baseline, post intervention and 3 months, mean difference (95% CI) in change between groups and Cohen's d (95% CI) for difference between groups.

	Group Scores: Mean (SE)							
	Baseline			Post Intervention			Follow-Up	
Outcome (units)	Eccentric	Concentric	Waitlist	Eccentric	Concentric	Waitlist	Eccentric	Concentric
6MWT (m)	413.6 (34.0)	307.7 (37.3)	338.2 (31.8)	414.8 (35.8)	337.4 (37.3)	373.6 (33.5)	434.9 (35.9)	343.8 (37.6)
MLWHFQ Total	40.92 (6.30)	34.20 (6.90)	36.87 (5.64)	26.13 (6.57)	37.4 (6.90)	25.37 (5.89)	31.38 (7.02)	38.06 (7.06)
MLWHFQ Physical	17.33 (2.81)	15.60 (3.08)	18.07 (3.08)	12.04 (2.95)	16.90 (3.08)	12.74 (2.64)	14.21 (3.04)	15.28 (3.14)
MLWHFQ Emotional	9.67 (1.94)	6.40 (2.13)	6.80 (1.74)	6.38 (2.04)	9.20 (2.13)	4.57 (1.83)	6.18 (2.17)	7.75 (2.18)
AQOL	14.83 (1.68)	13.00 (1.84)	14.10 (1.55)	13.00 (1.77)	14.80 (1.84)	13.21 (1.58)	11.76 (2.00)	13.42 (1.91)
1-RM Leg strength (kg)	59.17 (7.42)	46.61 (8.43)	44.33 (6.64)	63.21 (7.82)	52.65 (8.48)	46.97 (6.79)	59.60 (7.87)	51.44 (8.61)
DEFS	11.83 (2.66)	14.40 (2.92)	15.73 (2.38)	9.42 (2.85)	14.90 (2.92)	10.97 (2.56)	10.55 (2.93)	14.74 (2.98)

	Difference between groups									
	Baseline to Post Intervention						Baseline to Follow-Up		Post Intervention to Follow-Up	
Outcome (units)	Concentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Concentric	d
6MWT (m)	5.7 (-45.1 to 56.5)	0.06 (-0.64 to 0.75)	-28.5 (-82.1 to 25.1)	-0.27 (-0.96 to 0.43)	-34.2 (-88.0 to 19.6)	-0.32 (-1.04 to 0.41)	-14.8 (-69.3 to 39.6)	-0.14 (-0.83 to 0.56)	13.7 (-24.0 to 51.3)	0.19 (-0.52 to 0.88)
MLWHFQ Total	14.70 (-2.42 to 31.81)	0.43 (-0.28 to 1.13)	-17.99 (-35.96 to -0.01) **	-0.55 (-1.24 to 0.17)	-3.29 (-20.00 to 13.42)	-0.10 (-0.81 to 0.62)	-13.40 (-32.61 to 5.82)	-0.35 (-1.04 to 0.35)	4.59 (-9.84 to 19.02)	0.16 (-0.54 to 0.85)
MLWHFQ Physical	6.63 (-1.22 to 14.47)	0.43 (-0.28 to 1.12)	-6.59 (-14.83 to 1.65)	-0.40 (-1.10 to 0.31)	0.04 (-7.64 to 7.71)	0.00 (-0.71 to 0.72)	-2.81 (-11.37 to 5.76)	-0.17 (-0.86 to 0.53)	3.79 (-1.65 to 9.22)	0.36 (-0.35 to 1.05)
MLWHFQ Emotional	5.03 (-0.32 to 10.38)	0.48 (-0.24 to 1.17)	-6.09 (-11.71 to -0.47) **	-0.55 (-1.24 to 0.17)	-1.06 (-6.31 to 4.19)	-0.10 (-0.82 to 0.62)	-4.84 (-10.82 to 1.15)	-0.41 (-1.10 to 0.30)	1.25 (-3.15 to 5.65)	0.14 (-0.55 to 0.84)
AQOL	2.68 (-2.44 to 7.79)	0.27 (-0.44 to 0.96)	-3.63 (-8.94 to 1.69)	-0.35 (-1.04 to 0.36)	-0.95 (-5.94 to 4.03)	-0.10 (-0.81 to -0.62)	-3.49 (-9.32 to 2.34)	-0.30 (-0.99 to 0.40)	0.14 (-5.52 to 5.79)	0.01 (-0.68 to 0.71)
1-RM Leg strength (kg)	3.40 (-10.34 to 17.14)	0.13 (-0.57 to 0.82)	-2.00 (-16.99 to 12.99)	-0.07 (-0.76 to 0.63)	1.40 (-12.07 to 14.87)	0.05 (-0.66 to 0.77)	-4.41 (-20.19 to 11.38)	-0.14 (-0.83 to 0.56)	-2.41 (-14.45 to 9.63)	-0.10 (-0.79 to 0.60)
DEFS	5.27 (0.02 to 10.51) **	0.51 (-0.21 to 1.20)	-2.91 (-8.44 to 2.61)	-0.27 (-0.96 to 0.44)	2.35 (-3.07 to 7.77)	0.22 (-0.50 to 0.93)	-1.62 (-7.61 to 4.36)	-0.14 (-0.83 to 0.56)	1.29 (-4.29 to 6.87)	0.12 (-0.58 to 0.81)

a Based on repeated measures mixed model, with multiple imputations for each outcome
** p-value, <0.05
Abbreviations: CI - confidence interval; MLWHFQ - Minnesota Living with heart failure questionnaire
AQOL - Assessment of Quality of Life; 6MWT - six-minute walk test, 1-RM - one-repetition maximum, DEFS - Dutch Exertion Fatigue Scale

Chapter 5: General discussion

5.1 Summary of main findings

This thesis aimed to investigate the safety and effectiveness of eccentric exercise in people with chronic cardiorespiratory diseases, particularly heart failure. Three studies were completed:

- a systematic review of clinical trials investigating the effectiveness, tolerability and safety of eccentric exercise in people with cardiorespiratory disease including chronic heart failure
- a reliability study investigating the reliability of a one-repetition maximum strength test in people with chronic heart failure
- a randomised controlled trial comparing the effect of eccentric exercise with concentric exercise and no exercise on functional capacity and quality of life for people with chronic heart failure.

Each study is summarised below. The remainder of the chapter presents the most recent literature in the area (update of the systematic review), discusses key issues arising from this body of work, considers the strengths and limitations of the studies conducted, and proposes directions for future research.

A systematic review (Chapter 2) of eccentric exercise for people with cardiorespiratory disease (chronic obstructive pulmonary disease (COPD), chronic heart failure and coronary artery disease) included 10 articles reporting data from seven clinical trials. These populations were combined due to the limited studies in each population and the commonality in either pathology or symptoms. The methodological quality of the included studies was low; only four of the seven trials were randomised controlled trials. Results showed eccentric exercise increased strength and mobility to levels comparable

to concentric exercise, however, it did so with lower oxygen consumption (large effect size d = –3.07, 95% CI –4.12, –1.80), and four-fold power output (large effect size d = –3.60, 95% CI –5.03, –1.66). No adverse events were reported for eccentric exercise and pain was avoided by including familiarisation sessions and by using individual exercise prescription.

The reliability study (Chapter 3) found excellent inter-rater and intra-rater reliability of the one-repetition maximum test using a leg press for people with chronic heart failure. The Bland and Altman levels of agreement were large for inter-rater reliability and so having one assessor repeat the test is recommended if measuring change in strength within an individual over time. The procedure was well tolerated by participants with only one person reporting discomfort. The procedure was subsequently used as an outcome measure for the randomised controlled trial.

A randomised controlled trial (Chapter 4) determined the effect of eccentric exercise on quality of life, walking capacity and lower limb strength in people with chronic heart failure. There was no difference between eccentric exercise, concentric exercise or waitlist control for measures of quality of life and functional capacity. The per-protocol analysis showed a significant improvement in the quality of life measures in favour of eccentric exercise but given the inability to reach the proposed sample size, these data are considered to be hypothesis generating only. Eccentric exercise was tolerated and adhered to as prescribed.

These studies demonstrated that eccentric exercise delivers comparable outcomes to concentric exercise, however the requirement for specific equipment means it is unlikely

to replace traditional exercise programs. Eccentric exercise may be considered as an adjunct to therapy where alternatives to traditional exercise is sought.

5.2 Current literature in eccentric exercise in heart failure

An update of the systematic review search was completed (up to May 2020), to review all new clinical trials of eccentric exercise involving people with cardiorespiratory disease published since the original search was conducted in January 2015. The search was completed as per the original review (Chapter 2). The results of the updated search are presented in Appendix 1 Figure 1. The search identified 760 potentially relevant articles. After applying the inclusion and exclusion criteria, 38 articles remained. After review of the full text, a further 30 articles were excluded leaving eight articles reporting outcomes from six trials included in this update.

There has been a marginal improvement in the methodological quality of trials investigating eccentric exercise for people with cardiorespiratory conditions, with an increased reporting of assessor blinding and random allocation (see PEDro scores reported in Appendix 1 Table 1). In the 2015 review, the median PEDro score was three. For the recent articles, scores ranged from two to seven with a median score of 4.5. Similar to the 2015 review, not all trials were randomised controlled trials; there were three single group design trials in which the outcome of a single session of eccentric exercise was investigated.

The characteristics of the recent trials are presented in Appendix 1 Tables 2 to 5. There were no new trials including people with coronary artery disease. There were eight articles reporting data from six trials, of which two involved people with chronic heart failure and four involved people with COPD. One trial in people with chronic heart

failure (1, 2) was a single group trial that compared the effects of a single bout of short duration eccentric cycling with a single bout of equal duration concentric cycling with matched work rates, on cardiorespiratory, vascular and platelet function. In this trial there was no difference in heart rate, mean arterial blood pressure, blood lactate or platelet function outcomes between eccentric and concentric exercise but significantly lower cardiorespiratory demand in eccentric exercise for the same work rate. Eccentric exercise demonstrated a vasodilatory effect but given both vasodilation and platelet function have a role in acute coronary syndromes, the authors concluded that eccentric exercise could be conducted safely with this population.

A second trial involving people with chronic heart failure was a follow-up to a trial included in the initial systematic review which explored the feasibility, tolerability and functional effect (6-minute walk test) of eccentric exercise (3) compared to concentric exercise. This follow-up trial explored the effect of the same protocol on cardiopulmonary exercise testing and muscle strength with a larger group of participants (n = 42) (4). There were no between-group differences in 6-minute walk test distance and peak work rate. Eccentric exercise achieved these gains without a change in VO_2 peak and VO_2 at first ventilatory threshold and significantly less change in heart rate than concentric exercise.

These new trials confirm the safety of eccentric exercise in people with chronic heart failure as well as the decreased cardiorespiratory demand of this type of exercise compared to concentric exercise. However, questions remain about whether eccentric exercise should be used as an alternative to concentric exercise in rehabilitation programs due to the limited consideration of functional outcomes and comparable results when these outcomes have been included.

The updated search included four new trials involving people with COPD; three randomised controlled trials and one single group design trial. The differences in study design as well as intervention type make generalised conclusions difficult. The single group design studied the effects of a single session of downhill walking compared to downhill walking with load and level walking (5). They reported an increase in creatinine kinase (CK) levels 24 hours after downhill walking with and without load, but with low levels of pain and no difference in either dyspnoea or fatigue compared with level walking. Downhill walking and downhill walking with load also showed lower VO_2 and minute ventilation and a decrease in potentiated twitch force compared with level walking, suggesting greater fatigue of quadriceps muscle fibres. Generating this muscle fibre fatigue has been associated with increased improvements in exercise capacity and quality of life following an exercise program. The addition of load did not increase the effects of downhill walking.

Downhill walking was also used for a rehabilitation program (6) in another trial. This trial consisted of a structured 12-week intervention, in a supervised environment and compared it to a home-based walking program with an 'attendant' at their chosen speed and duration and progressed through telephone counselling, meaning that the two interventions varied in a number of ways. Significant improvements in the downhill walking group were reported in quality of life, 6-minute walk test, timed up and go, FEV_1 and FEV_1/FVC compared with level walking.

Resistance exercise was investigated in one trial, focusing on either the concentric or eccentric phase of weight-lifting using a therapist to assist (7). This trial was of short duration (six days out of one week) and the weight lifted for both the upper limb and

lower limb exercises was not stated. This limitation makes drawing conclusions difficult, but the authors reported a significant increase in FEV_1 and FEV_6 and decrease in dyspnoea compared with concentric exercise.

The final randomised controlled trial involved participants with COPD, with one paper (8) reporting data from 15 participants who agreed to muscle biopsy as part of a larger (n= 24) trial reported in a second paper (9). This trial found eccentric cycling, completed three times per week for 10 weeks led to significantly increased quadriceps strength and decreased dyspnoea and leg fatigue compared with concentric exercise. There were no between-group differences in peak power output and 6-minute walk test. Muscle biopsy found eccentric exercise did not change mean muscle fibre cross-sectional area or mitochondrial function while concentric exercises showed increases in both areas.

Overall, recent trials echo the findings of the previous systematic review (Chapter 2) None identified any safety issues. Cardiorespiratory demand for matched or similar work-rates was less in eccentric exercise with no significant changes in heart rate. The trials did not identify any tolerability issues for eccentric exercise with low levels of perceived exertion and muscle soreness rated from none to mild. Adherence and attendance levels were high, particularly in the trial with smaller samples and of short duration. Overall, there were few drop-outs; data from 90% of participants were included in the final analysis across the trials.

In regard to functional improvements, eccentric exercise was deemed comparable but not superior to concentric exercise in the initial review. Of the six new trials, only three trials included an activity-based outcome measure (4, 6, 9). Of these three, the two trials with a cycling intervention found no difference between eccentric and concentric exercise, with

only the downhill walking intervention resulting in greater improvements in walk tests than level walking. Only two trials considered quality of life (6, 7), with greater improvements demonstrated for downhill walking but not for eccentric resistance exercises. Outcome measures of activity and quality of life should be given greater focus in future trials to fully understand the potential impact of eccentric exercise on people with cardiorespiratory disease. Furthermore, with half of the recent trials being either single session or short duration (one week) and none of them including a follow-up assessment, the current literature does not yet answer if there are long term effects of eccentric exercise.

The updated search also found six published protocols for trials involving people with COPD (n= 4) (10-13) or chronic heart failure (n= 2) (14, 15) planned or currently under way, indicating an ongoing interest in the area. These trial protocols are summarised in Appendix 1 Table 6. In these ongoing trials, eccentric cycling is being compared to concentric cycling and in two cases, to resistance exercise, with doses ranging from a single session to 16 weeks. It appears the current goal is to establish eccentric exercise's usefulness in chronic disease rehabilitation with multiple sessions per week over the duration of a typical rehabilitation program being conducted. Despite this, none of the protocols referred to any follow-up assessment, meaning these trials will not be able to determine the long-term effect of this exercise for people with cardiorespiratory conditions such as chronic heart failure. There is a varied choice in outcome measures with impairment, activity and patient-reported measures such as quality of life all featuring. Although there seems to be an increased focus on activity measures, only two of the six protocols include a quality of life measure. Understanding what matters to people and how rehabilitation impacts their daily life are important if clinicians are going

to implement therapies that have good uptake and that result in lasting meaningful changes for individuals.

5.3 Key issues and clinical implications

5.3.1 Difficulties achieving the proposed sample size and barriers to heart failure rehabilitation

The power calculation for the randomised controlled trial (Chapter 4) was based on a clinically significant difference in the 6-minute walk test of 60 m. This resulted in a required sample size of 19 participants for each of the three groups, which was then increased to 25 to allow for drop-outs. Over the four-year duration of the trial, the achieved sample size was 47 with 12 participants remaining in each group at follow-up. Adherence to exercise in the trials included in the systematic review and the updated literature was not well reported. Where it was, attendance once enrolled was good. Although the loss of participants throughout the trial was as expected, the recruitment of participants to the trial was slower and more difficult than anticipated. A total of 306 participants were assessed for eligibility. Of the 259 participants not randomised, 134 were excluded based on eligibility, 59 declined to participate in rehabilitation, 51 declined to participate in research, and 15 consented but then did not return or respond to contact and so were not randomised. Overall, 36% of people asked to participate in our study declined. The main reported reason (n= 19) for declining to participate in research was stated as the person wanting to begin rehabilitation immediately and not wanting to risk being allocated to the control group. Another reason for declining was that people had previous experience with research or ideas about it, that made them not want to be involved (n= 5). Others did not explain why they wished to decline. For those that were excluded, the main reasons were only being able to attend rehabilitation once a week (n=

35) and musculoskeletal limitations such as severe back or knee pain requiring treatment or preventing the use of either an exercise bike or the Eccentron^{TM} (n= 20). Although only being able to attend rehabilitation once per week precluded people from being recruited to the research study, this proportion of the population was still offered rehabilitation. Working with people who are willing to engage in therapy but at a level that may be insufficient to illicit meaningful gains is another challenge health professionals face.

Ours is not the only trial to experience high rates of people declining to be involved, although this varies largely between trials. Information on reasons for declining to be involved in a trial of eccentric exercise was only provided in three of the 11 past trials in people with chronic heart failure or COPD and ranged from 0% declining (6) to 6% (4) and 25% (9). The intervention in these trials was provided three times weekly for seven to 12 weeks and so there was a similar time commitment to our trial, however none of the trials featured a control group, which was one of the reasons that people reported not wanting to participate in research. In people with chronic heart failure and other exercise interventions, the rate of declining to participate also varies. One trial with comparable flow of participants through their trial and rates of declining of 39% suggested that this was not unexpected given the population was elderly, had comorbidities, and were required to regularly attend the program held a considerable distance from their home (16). All of these factors were also relevant for our trial. These trials highlight that having large numbers of people decline our study is not unique.

While 36% of people declined to participate outright, if we assume that those people who were excluded for being able to attend rehabilitation only once per week is potentially modifiable, and those that consented but then did not return made the decision not to,

then the total number of people that chose not to receive the intervention could be as high as 160 out of the 259, or 60%. This leads us to the question of why people choose not to participate. Do they recognise the importance of rehabilitation or is there another barrier preventing exercise?

One barrier to attendance may be a lack of understanding of the importance of exercise. This may arise due to inadequate inter-disciplinary management and education by the referring clinician. There are studies which have highlighted a lack of prescription of heart failure medications by physicians, despite evidence of their benefit and findings to suggest prescription impacts on health service outcomes such as hospitalisations (17). Lack of referral to cardiac rehabilitation has also been demonstrated in Australia and internationally despite well-established benefits. These studies may include people with chronic heart failure as often both types of rehabilitation are referred to as 'cardiac rehabilitation'. A 2019 Australian study, reviewing almost 50,000 hospital separations between 2013 and 2015, found only 30% of eligible people were referred to cardiac rehabilitation and of these only 28% attended (18). These rates were lower in people with heart failure (18). This is compared with 46% referral rates for people with acute coronary syndrome in Australia and New Zealand (19). There is greater uptake of cardiac rehabilitation in the United Kingdom, where program attendance rates are around 50% for all cardiac patients, however only an estimated 7-20% of patients with heart failure are referred to cardiac rehabilitation from hospital wards (20). If health professionals don't follow evidence-based guidelines, people may not receive optimal education about the importance of participation in rehabilitation and exercise when they are referred. This issue needs to be addressed further in this population and begins with how exercise is introduced and prescribed at the outset both with hospital-based and primary health care providers.

Some people with chronic heart failure do not attend rehabilitation despite understanding the importance of exercise. Research has suggested that although there are barriers to adherence to a variety of clinical guidelines, exercise specifically is challenging i.e. adherence with medication and appointment keeping is much higher (>90%) than exercise (39%) (21). This lack of adherence was despite 80% of participants reporting exercise to be important (21). It was reported that difficulty exercising was due to physical symptoms (27%) and lack of energy (25%) (21). Barriers reported in other studies include lack of support (22), motivation, lack of time, difficulty with transport, presence of comorbidities and hospitalisations (23). There are mixed findings regarding the impact of depression and mental health, health literacy and educational level (21, 23). This suggests it is not a deficit in knowledge of the importance of exercise that prevents adherence but more likely a lack of knowledge of how to exercise effectively within physical limitations or overcome other personal barriers. The low energy costing nature of eccentric exercise aimed to combat these symptom limiting issues but is not helpful if people do not commence exercise in the first place.

Other attempts to address the barriers to heart failure rehabilitation have focused on home-based exercise programs and telehealth. Studies have demonstrated comparable improvements in quality of life and physical function following supervised, structured home-based exercise programs compared with centre-based programs (24, 25). Although eccentric exercise is likely to be difficult to complete independently at home or in settings such as community gymnasiums due to the specific equipment required, these other exercise formats are important options to consider for those who have difficulty or hesitancy to attend an outpatient rehabilitation program.

Regardless of the specific barrier to exercise affecting an individual, important adherence strategies include identifying the barrier early on, as well as goal setting, building self-efficacy and having the necessary social support to succeed (23). The initial assessments become vital to address these reservations, explore the individual's beliefs around exercise and their efficacy to succeed in attendance and also session completion. These staff members are pivotal to not only the success of research trials but in changing the perception of exercise in this population.

5.3.2 Importance of exercise progression

The results of the randomised controlled trial (Chapter 4) suggested there is no difference between eccentric exercise and both usual care (concentric) rehabilitation or a waitlist control group. One reason for the lack of difference between the exercise group participants is that the intervention dose may have been an insufficient stimulus to evoke meaningful change. There is a dose-response relationship to training and as such, to be effective exercise needs to be progressed. In order to progress exercise, duration, frequency or intensity of exercise needs to change. In our trial, both the duration and frequency were set, and thus to progress the exercises, intensity needed to change. By asking participants to continue to work at a rating of perceived exertion of 'fairly light' to 'somewhat hard' (BORG 11 - 13) each session it assumed that as strength and conditioning improved, the output for their 'somewhat hard' effort would increase. Although there was a degree of progression, only small average increases in each exercise were noted in the data across the period of the rehabilitation program. Progression of eccentric exercise could have been monitored using information that the equipment provided regarding their output (work completed, kilojoules expended, and average force achieved). Although this information was recorded, it should also have then been used to guide the intensity setting for each subsequent session.

Guidelines for exercise intensity in chronic heart failure are conservative. Intensity is recommended to be based on individual fitness and 'fairly light' to 'somewhat hard' exertion, (26) but increasingly intensity prescription based on cardiopulmonary or work rate testing have been suggested (27-30). Using changes in heart rates is problematic due to irregular heart rates and use of heart rate medications in this population (26) but in a controlled hospital environment symptom-limited graded exercise tests can be used safely to set initial exercise and then subsequent progression with the assistance of exertion ratings (28).

Only recently has intensity been set based on a percentage of maximum work or cardiorespiratory demand (1, 2, 14, 15). A third option, used in other chronic heart failure and eccentric exercise studies has been to utilise patient-perceived intensity and set one aspect of the exercise intensity such as steps or revolutions per minute (3, 4, 31). What is lacking from these trials, is guidance on how to appropriately progress the exercise intensity throughout the rehabilitation program once initial intensity is established.

Using the participant measure of perceived exertion has benefits as it means that the exercise is tailored to each individual. It is a safe means of progressing exercise in a population often thought of as high risk. However, issues can result due to its subjective nature as one person may deem themselves to be working 'somewhat hard' at quite different levels of intensity than another person. Previous experience with exercise, comorbidities, and willingness to feel uncomfortable within their symptoms of fatigue and breathlessness or an understanding that it is safe to exercise within parameters of these symptoms, will all affect the overall work completed throughout the rehabilitation program and ultimately the changes made.

If we look to other populations for further guidance, pulmonary rehabilitation with a population whose primary symptoms are also dyspnoea and fatigue, may assist. Pulmonary rehabilitation guidelines detail key aspects of exercise prescription; duration, frequency, intensity and progression. These guidelines make suggestions for different options for progression of exercise, with no consensus, including increasing duration and intensity based on symptoms, or as a percentage of peak work rate (32, 33). These guidelines suggest a baseline symptom limiting cardiopulmonary exercise test may be beneficial for exercise prescription but not a necessity (33, 34). Without resources for complex cardiopulmonary exercise testing, in this trial it would have been appropriate to use a rating of perceived exertion to progress exercise. With an understanding that each participant should progress throughout rehabilitation unless their exertion ratings are above the target range and appropriate documentation and monitoring of the work rate achieved for this exertion, symptom-based progression may have been successful. Had this monitoring occurred then if a participant failed to progress it would have been apparent during the trial and could have been addressed throughout their rehabilitation program.

There are reasons other than not identifying appropriate progression that may have limited progress through our trial. Throughout the trial there was numerous staff involved in the exercise sessions. Despite formal qualifications, orientation and guidance and in most cases, experience in supervising the exercise sessions, staff confidence may have varied. There is research that highlights the difference between decision making or clinical reasoning skills (35) and patient education abilities (36) between novice and expert clinicians. These differences may extend to exercise prescription and progression, with hesitancy to progress exercises or encourage what is perceived to be a high-risk

individual. It is for these staff that having well-defined exercise protocols become particularly helpful. Like the impact health care workers have on engaging people with exercise, they too may have a substantial impact on how effective exercise is, something that has not been previously explored in the literature.

5.3.3 Choosing outcomes that matter and long-term effects of the intervention

While exercise has well documented benefits for people with chronic heart failure, both at a functional and health status level, the lack of improvement among participants in this trial leads to a reflection on expectations. If we are to invest time and resources into rehabilitation, it needs to result in a positive impact on the individual. To do this it is important to measure the right outcome. Historically, the way we measure success is largely defined by the clinicians or researcher's choice of outcome measures and less by their importance to the person with the chronic disease. We commonly assume that if an individual can walk further or is stronger that they are better off. Patient-reported outcome measures such as quality of life questionnaires which rate the impact of people's conditions on everyday life or the perceived effect of an intervention are also important and should be considered for all exercise interventions to measure success. In our trial (Chapter 4), the choice of outcome measures centred on activity (mobility and strength) and patient- reported outcome measures (fatigue, disease-specific and general quality of life scales). With these chosen measures it was felt that had the intervention had a meaningful impact on a participant's life it would have been identified.

In a 2019 Cochrane review of exercise in people heart failure 29 out of 44 (66%) included studies featured a health-related quality of life outcome (37). Within the eccentric exercise literature for cardiorespiratory diseases, as included in the systematic review (Chapter 2) and literature update (Chapter 5), only three out of 14 trials (21%)

included a quality of life outcome. This has increased to two out of six clinical trial protocols (33%) but patient-reported measures still fail to be the focus of outcomes for this intervention. It may be that preliminary studies were focused on establishing the safety and physiological effect of eccentric exercise in this high-risk population, however with no adverse events eventuating, further outcomes should now be included. Given the proposed mechanism by which eccentric exercise might prove beneficial for this population, with their decreased exercise tolerance, dyspnoea and fatigue, it is important that its effect on quality of life and ability to perform activities of daily living be considered. This clinical trial may have been underpowered to demonstrate such an impact or suffered from limitations such as inadequate exercise progression and as such there is a requirement for further studies focusing on these outcomes.

5.4 Strengths and limitations

There are a number of strengths to this thesis. A variety of research methods were undertaken to investigate the effect of eccentric exercise in a higher risk population. A systematic review (Chapter 2) was completed using a pre-specified protocol and reported according to PRISMA guidelines (38). This review included a descriptive analysis as well as some quantitative analysis (effects sizes and confidence intervals) but no meta-analysis due to heterogeneity. A reliability study was also completed (Chapter 3) which included intra-class correlation coefficients and 95% confidence intervals and the use of Bland and Altman plots. The results of this study gave confidence to the choice of outcome measure used in the randomised controlled trial. Lastly, a prospective, three-armed, parallel-design, randomised controlled trial with a 1:1:1 ratio for group allocation was conducted (Chapter 4). The protocol for this trial was pre-registered on clinicaltrials.gov and its reporting was in line with the CONSORT (39) and TiDieR checklists (40). Due to the nature of the intervention only a single-blinded trial was

achievable, however randomising of participants and blinding of assessors minimised bias.

Another strength of the randomised controlled trial was that it included people with both types of heart failure- those with reduced and preserved ejection fraction. This is important given the increasing prevalence of heart failure with preserved ejection fraction, now estimated to represent more than half of those with heart failure (41, 42) and the historical focus of studies solely on those with reduced ejection fraction. This study also used broad inclusion criteria to increase generalisability and both males and females where some previous research have included solely males (although a majority of males did eventuate). The clinical trial also featured a 3-month follow-up period. Of all the studies investigating eccentric exercise in cardiorespiratory disease, no other studies have included a follow-up assessment. Due to the trial being underpowered, this assessment is unable to attest to the long-term effects of eccentric exercise in isolation and further research is required, but the inclusion of a follow-up assessment is an important aspect of the study design.

Limitations of this thesis are also recognised. As noted above, the heterogeneity of the outcomes and disease populations chosen for the systematic review did not allow any pooling of data for analysis and its pre-specified protocol was not registered. Both the reliability study (Chapter 3) and the randomised controlled trial (Chapter 4) had difficulty reaching the sample size estimated as required by power calculations. Attempts to consider the effect of the sample size were made for both studies. In the reliability study given the high ICC achieved and the spread of values spans across the range of possible values on the Bland and Altman plot, it was felt likely that the sample size was sufficient

to demonstrate reliability. In the randomised controlled trial, effect sizes were calculated and except for the moderate effect size of 0.55 for quality of life for eccentric exercise compared with concentric exercise, all of the effect sizes were small. Despite this, further studies with larger samples were recommended.

The cessation of both the studies was brought about by staffing changes; in the reliability study due to a sudden departure of an assessor and in the randomised controlled trial by slow and difficult recruitment and staff turnover. Although staff changes may at times be inevitable, its impact may be a consideration when involving staff in clinical research.

The studies were also limited by the equipment available as the exercise sessions were conducted in hospital gymnasium rather than a laboratory. This adds to the feasibility for use by others. In the reliability study, the apparatus used measured strength in 5 kg increments limiting sensitivity to change. Contrary to expectations, two participants experienced a ceiling effect by being able to lift the maximum possible weight (120 kg). In the randomised controlled trial, the lack of baseline cardiorespiratory testing equipment limited its use for prescription and progression of exercise, however this is typical of most rehabilitation programs and there are others potential methods of exercise prescription as discussed. The cost of the Eccentron™ equipment also limited the randomised controlled trial to a single-site study, which subsequently limited participant numbers and throughput.

Lastly, there were deviations to the protocol in the statistical analysis of the randomised controlled trial. Planned secondary analyses related to the type of heart failure and correlations between primary and secondary outcomes were not conducted as the sample recruited was smaller than anticipated and insufficient for meaningful analysis. Finally,

we proposed to undertake a separate randomisation procedure for each of the New York Heart Association classes so that disease severity did not affect the results. However, when the patient demographics were reviewed, we found most were in class II (70%), and the remainder split between class I and III, with IV excluded from the trial as their heart failure was too severe and thus this separate randomisation process was deemed unnecessary.

5.5 Directions for future research

Eccentric exercise in cardiorespiratory disease and other chronic disease populations continues to be an emerging field. The conclusions of this thesis suggest further research is required to determine with confidence its potential use as an adjunct or sole mode of rehabilitation exercise. If further trials were to be conducted key limitations would need to be addressed and the knowledge gained from the current trial considered, including:

Population:

- Achieving the proposed sample size to ensure the trial is well powered. Use of the 6-minute walk test to guide sample size calculation is appropriate
- Continuing to include people with heart failure with both preserved and reduced ejection fraction and broad exclusion criteria to reflect clinical practice
- It is not suggested that restrictions be made based on current activity levels or that measurement of physical levels is required if random allocation of the sample occurs.

Intervention:

- Development of progression protocols and monitoring of adherence to these progressions to guarantee an adequate training stimulus to result in meaningful change

- An increased proportion of eccentric exercise as part of the total exercise session. The warm-up and cool-down remain important aspects of the session and upper limb resistance exercise may be included to ensure full body exercise is occurring
- There have been a number of different eccentric exercise modalities reported in this thesis; cycle ergometry, downhill walking, eccentric resistance exercise with therapist assistance and use of the Eccentron^{TM}. For future research, these modalities can continue to be utilised and the potential exists for a study comprised of a session of both eccentric cycle and downhill walking compared with concentric cycle and level walking. This would allow a longer duration of eccentric exercise to be carried out than what would be possible in one form of exercise, in an easily fatigued population. There are, however, start-up equipment costs associated with ergometry and Eccentron^{TM} and this limits translation to the home environment.

Comparison:

- Consideration needs to be given to a two group versus three group study design. The inclusion of a waitlist control has not occurred in other trials investigating eccentric exercise in people with cardiorespiratory disease. This is likely due to the established benefit of exercise in managing these conditions. In the randomised controlled trial in Chapter 4, the no-exercise period reflected a typical wait period for the service. It is not recommended that people with heart failure be restricted to access of evidence-based care. The inclusion of the waitlist control in this trial raised interesting questions as to the prescription of exercises within our rehabilitation program, given neither intervention group improved significantly compared with the control. It did prove problematic during recruitment with 51/306 people offered inclusion to the trial declining as they did not want to be involved in research (but were happy to participate in

rehabilitation). Of these 51, 21 people explicitly said they did not want to risk being assigned to the waitlist group

- If a control group is included then continuing to provide as little intervention as possible is recommended. Initial assessments could be scripted and advice for exercising at home not included. This education would need to be provided to all participants when they later commenced rehabilitation. Any involvement during the waiting period may provide a form of feedback to the participant which may result in the completion of exercise so this is not recommended. The addition of activity monitoring such as home visits, telephone consults, heart rate monitors and pedometers may lead to an increase in activity in the control group (23, 43, 44). Even though there is the potential for a reporting bias it would be suggested that control group participants are asked to report their activity levels from throughout the waiting period at follow-up assessment as this may assist when analysing the results.

Outcomes:

- Maintaining the focus on activity and meaningful outcomes for participants such as quality of life, to ensure we are measuring what matters to people with chronic heart failure. The outcomes in the randomised controlled trial were well tolerated and suitable for this purpose
- Retaining the follow-up assessment and the potential for a further follow-up at 12 months to ascertain the long-term effects of this intervention, given that our randomised controlled trial is the only study in people with cardiorespiratory disease to include a follow-up assessment.

Another pertinent focus for future research may be an exploration of the barriers to exercise for this specific population and ways to improve adherence. International

research exists investigating barriers and adherence (23, 45-47), however more local research may assist in identifying strategies more applicable to our population. A protocol for a study has been developed to identify barriers for attendance at heart failure rehabilitation assessments and clarify reasons for failure to attend, as well as identify strategies to improve attendance in consultation with the patient, specifically whether an SMS reminder would be of benefit.

Two key questions would be asked:

- The primary research question: 'What are the reasons that patients fail to attend heart failure rehabilitation assessments?'
- The secondary research question: 'Are there any strategies that the patients identify that would increase attendance?'

A qualitative study, using semi-structured patient interviews is proposed. Demographic information would be collected as well as information regarding previous referral and attendance in heart failure rehabilitation. Patient interviews would be conducted with data analysed thematically. It is suggested that by interviewing patients and discussing with them the barriers to the attendance of rehabilitation, themes would be identified that may be used to predict the types of patients who may fail to attend appointments and also barriers that we can attempt to help the patient overcome.

Another focus of qualitative research may be to gather participants' perspectives of eccentric exercise. This could occur through simple questions for those completing the intervention and provide valuable information to be used when considering this mode of therapy in the future. Although the cost of the eccentric equipment means that it is unlikely to be considered as a cost-saving measure, this could also be included in an analysis of the benefits and challenges of this form of exercise, separate to participant outcome measures.

Future studies should also investigate clinician knowledge of exercise prescription to better understand the lack of progression in rehabilitation programs. One of the potential reasons for a lack of progression proposed above was deficient staff confidence. As discussed, there is research highlighting the difference that level of expertise may have when diagnosing, educating people and making clinical treatment decisions, but not specifically in the factors affecting exercise progression. Qualitative research methods could be used to explore clinician understanding and confidence in exercise prescription and what factors they use to determine when someone with a chronic condition such as heart failure is appropriate to progress. This may be a way of identifying knowledge gaps and sharing the knowledge of experienced clinicians.

Lastly, there is a need to continue to review how we refer patients and educate them about the importance of rehabilitation for people with chronic heart failure. Referral rates for this evidence-based intervention continue to be low and once referred, there are further issues with the uptake of programs. Research into barriers to exercise from the patient perspective is helpful for clinicians working in the field to understand why uptake is suboptimal. However, alongside this, quantitative data monitoring of referral rates and uptake through national databases and qualitatively understanding referral processes allows us to fully address the problem. Healthcare workers have a duty of care to educate patients about the importance of both exercise and rehabilitation, and work with people with heart failure to help them make informed decisions regarding their current management and ultimately future health.

5.6 Conclusion

There is growing evidence to suggest that eccentric exercise can be used safely in people with chronic cardiorespiratory disease, specifically chronic heart failure. This thesis demonstrated the inter-rater and intra-rater reliability of one-repetition maximum (1-RM) assessment using a leg press in people with chronic heart failure. It also showed that eccentric exercise delivers comparable outcomes to concentric exercise, however the requirement for specific equipment may limit uptake. This thesis also identified issues involving people with chronic heart failure in exercise and once participating, with exercise progression. In rehabilitation settings, eccentric exercise may be considered as an adjunct to therapy where specific limitations to exercise such as dyspnoea are preventing traditional exercise or an alternative exercise regimen is sought.

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Appendix 1: Data from update to systematic review

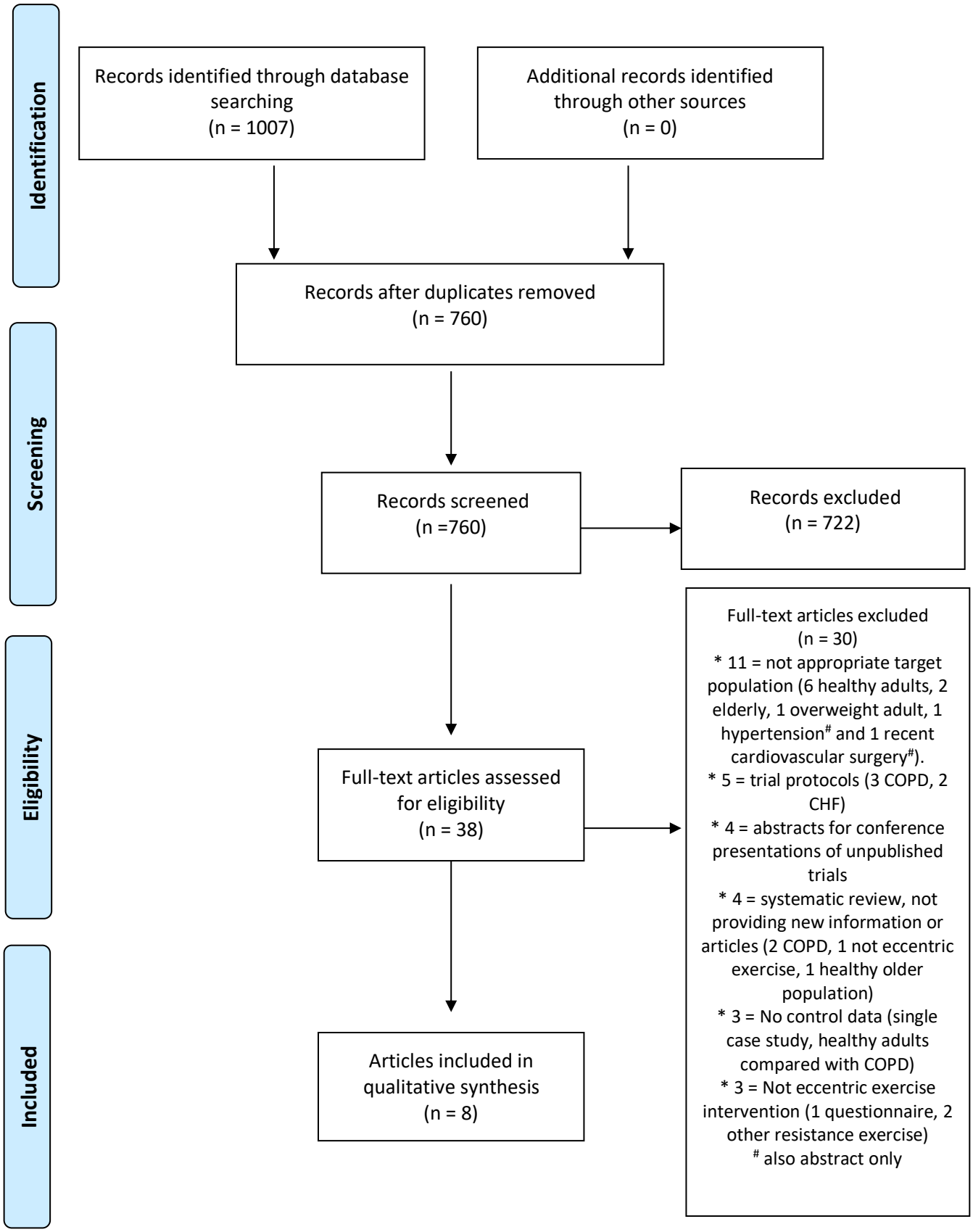

Figure 1. Flowchart detailing selection of articles from updated search- January 2015- May 2020

Table 1. Detailed description of PEDro scores for recent articles- January 2015 - May 2020.

Study (year)	2. Random allocation	3. Concealed allocation	4. Baseline comparab-ility	5. Assessors blinded	6. Participants blinded	7. Therapis-ts blinded	8. Follow-up	9. Intention-to-treat analysis	10. Between-group analysis	11. Point estimated and variability	Total Score
Bourbeau et al. (2020)	✓ Yes	✗ No	✓ Yes	✓ Yes	✗ No	✗ No	✓ Yes	✓ Yes	✓ Yes	✓ Yes	7/10
Camillo et al. (2015)	✓ Yes	✗ No	✗ No	✗ No	✗ No	✗ No	✓ Yes	✗ No	✗ No	✓ Yes	3/10 Not RCT
Macmillan et al. (2017)	✓ Yes	✗ No	✗ No	✓ Yes	✗ No	✗ No	✗ No	✗ No	✓ Yes	✓ Yes	4/10
Moezy et al. (2018)	✓ Yes	✗ No	✓ Yes	✓ Yes	✗ No	✗ No	✓ Yes	✗ No	✓ Yes	✓ Yes	6/10
Qadar et al. (2016)	✓ Yes	✗ No	✗ No	✗ No	✗ No	✗ No	✓ Yes	✓ Yes	✓ Yes	✓ Yes	5/10
Casillas et al. (2016)	✓ Yes	✗ No	✓ Yes	✓ Yes	✗ No	✗ No	✗ No	✓ Yes	✓ Yes	✓ Yes	6/10
Chasland et al. (2017	✗ No	✗ No	✗ No	✗ No	✗ No	✗ No	✓ Yes	✗ No	✗ No	✓ Yes	2/10 Not RCT
Haynes et al. (2017)	✗ No	✗ No	✗ No	✗ No	✗ No	✗ No	✓ Yes	✗ No	✗ No	✓ Yes	2/10 Not RCT

Table 2. Characteristics of recent articles- January 2015 - May 2020

Study	PEDro score	Disease	Study type	Sample size	Severity of diagnosis	Patient age (mean, range)	Patient sex
Bourbeau et al. (2020)*	7/10	COPD	RCT	N = 24 11 ECC 13 CON	Advanced COPD: post- bronchodilator FEV1 ≤ 50 % predicted	ECC 68.5(5.6) CON 62.5 (5.0)	24 M
Macmillan et al. (2017)*	4/10	COPD	RCT	N = 15 8 ECC 7 CON (15 participants of larger RCT)	Moderate to severe COPD: FEV1 % predicted: ECC 36.2 +/- 3.7, CON 45.8 +/- 5	ECC = 68 (2) CON = 63 (2)	15 M
Camillo et al. (2015)	3/10	COPD	Single group- random allocation of treatment order	N = 10	COPD: FEV1 % predicted: 51 +/- 15 Able to walk 15 minutes and familiar with treadmill walking (Also BMI < 30kg/m^2)	67 (7)	7 M 3 F
Moezy et al. (2018)	6/10	COPD	RCT	N = 32 14 ECC (16 recruited but excluded from results 16 CON	COPD: post-bronchodilator FEV1< 80% predicted together with an FEV1/FVC < 0.70 and FEV1 ≥ 30% of predicted (Also BMI < 30kg/m^2)	ECC = 64.7 (7.52) CON = 66.3 (8.20)	ECC 10 M 4 F CON 14 M 2 F
Qadar et al. (2016)	5/10	COPD	RCT	N = 40 20 ECC 20 CON	Moderate COPD (not defined further)	ECC 55.3 (6.82) CON 53.4 (6.36)	Not stated
Casillas et al. (2016) [#]	6/10	CHF	RCT	N = 50 24 ECC 26 CON	Stable but symptomatic mild to moderate systolic CHF: LVEF <45%, reduced LV function due to ischaemia on angiogram, NYHA II or III	ECC 63.6 (10.09) CON 61.8 (8.47)	ECC 18 M 3F CON 17M 4 F
Chasland et al. (2017)^	2/10	CHF	Single group	N = 11	CHF NHYA I to III Ischaemic and non-ischaemic cardiomyopathy Reduced systolic function LVEF < 45% (actual 31% +/- 12)	50.5 (9.9)	10 M 1 F
Haynes et al. (2017)^	2/10	CHF	Single group	N = 11	CHF NYHA I to III Ischaemic and non-ischaemic cardiomyopathy Reduced systolic function LVEF < 45%	52.0 (9.3)	9 M 2 F

Note. COPD= Chronic obstructive pulmonary disease, CHF= Chronic heart failure, RCT= randomised controlled trial, ECC= eccentric, CON= concentric, N= number, M= male, F= female, FEV1= forced expiratory volume in one second, BMI= body mass index, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association

* articles contained the same sample- Macmillan includes 15 of Bourbeau's participants # Chasland is a follow-up study to Besson (included in original R/V) ^ 12 participants recruited, 1 excluded from either study so 10 are the same participants.

Table 3. Characteristics of recent articles- January 2015 - May 2020 – Intervention

Study	Intervention	Time	Intensity	Frequency	Duration	Pre-conditioning sessions	Follow-up	Exercise setting	Group or individual exercise	Exercise facilitator
Bourbeau et al. (2020)*	ECC vs. CON cycling on semi-recumbent ergometer	30 min cycling	CON = 60-80% peak power output during pre CON cardiopulmonary testing ECC = 4 x 60-80% peak power during pre CON cardiopulmonary testing	3 x week	10 weeks	2 weeks familiarisation	Nil	Exercise physiology laboratory	Not stated	'Exercise trainer' and research assistant
Macmillan et al. (2017)*	ECC vs. CON cycling on semi-recumbent ergometer	5 min unloaded warm-up and then 30 min cycling	CON = 60-80% peak power output during pre CON cardiopulmonary testing ECC = 4 x 60-80% peak power during pre CON cardiopulmonary testing	3 x week	10 weeks	2 weeks familiarisation sessions: intensity 20-40% target	Nil	Exercise physiology laboratory	Not stated	kinesiologist and research assistant
Camillo et al. (2015)	One session each of DW and DWL (-10%), and LW in random order.	Each session was 15-20 min	75% of mean walking velocity in initial 6MWT	1 x week	3 weeks	1 familiarisation session	Nil	Hospital outpatient clinic	Not stated	Not stated
Moezy et al. (2018)	ECC: DW on treadmill CON: 'free walk with an attendant' on a flat surface and avoid vigorous exercise	ECC: warm up of 10 min slow walking and static LL stretches then DW. Starting at 15-30 min and increasing to 60 min in final session First 3 weeks- 3 sets with 90-120 sec rest	ECC: Starting speed 3-4 on MBD scale Increased while maintaining $SpO_2 > 90\%$ Negative slope -5° to -7.5° CON: speed set by participant according to fatigue and SOB of 3-4 MBD scale Progressively increased through telephone counselling and while maintaining $SpO_2 > 90\%$	3 x week	12 weeks	Two familiarisation sessions- learn dyspnoea scales and ECC trained for DW on treadmill	Nil	University hospital 'training room'	ECC not stated CON at home with attendant	Sports medicine assistant

Study	Intervention	Time	Intensity	Frequency	Duration	Pre-conditioning sessions	Follow-up	Exercise setting	Group or individual exercise	Exercise facilitator
		CON: similar warm-up and then walking Duration set by participant								
Qadar et al. (2016)	UL (Bicep curls, triceps with dumbbells and bench press) and LL (seated knee extension, calf raises/dips with cuff weights and squats with rod) ECC and CON therapist assisted resistance exercise	3 sets of 10 repetitions daily 2 min rest between sets	Weight not stated	6 days/week	1 week	Nil	Nil	Hospital	Not stated	Therapist
Casillas et al. (2016) [#]	ECC vs. CON cycling on ergometer	32 min cycling (5 min warm-up, 25 min then 2 min cool-down).	ECC= 15 RPM and RPE 9-11 CON= 60 RPM and 1st ventilatory threshold	3 x week	7 weeks	Nil	Nil	Not stated	Not stated	Not stated
Chasland et al. (2017)^	ECC vs. CON cycling on ergometer	3 min warm-up then 5 min cycling	ECC: 3 min warm up @ 30% W_{max} → 5 min @ 70% W_{max} CON: workload altered each 30 sec to match ECC power output	2 single-stage exercise test (ECC always first)	Each session a week apart	3 min familiarisation session with no →increasing load	Nil	Laboratory	Not stated	Not stated
Haynes et al. (2017)^	ECC vs. CON cycling on ergometer	11 min (3 min warm-up then 5 min cycling and 3	ECC= 40 RPM Warm-up 30% W_{max}, 5 min 70% W_{max}, recovery no resistance	2 single-stage exercise test (ECC	Each session a week apart	No familiarisation but maximal grade exercise test was on the	Nil	Laboratory	Not stated	Not stated

Study	Intervention	Time	Intensity	Frequency	Duration	Pre-conditioning sessions	Follow-up	Exercise setting	Group or individual exercise	Exercise facilitator
		min recovery)	CON: workload altered each 30 sec to match ECC power output	always first)		same ergometer				

Note: ECC= eccentric, CON= concentric, vs. = versus, min= minutes, DW= downhill walk, DWL= downhill walk with load, LW= level walk, 6MWT= six minute walk test, LL= lower limb, MBD= modified BORG dyspnoea, SpO_2= pulse oximetry oxygen saturation, sec= seconds, SOB= shortness of breath, UL= upper limb, RPM = revolutions per minute, RPE= rating of perceived exertion, W_{max}= maximum work rate

* articles contained the same sample- Macmillan included 15 of Bourbeau's participants # Chasland is a follow-up study to Besson (included in original R/V) ^ 12 participants recruited, 1 excluded from either study so 10 are the same participants.

Table 4. Characteristics of recent articles- January 2015 - May 2020 – Outcome measures

Study	Impairment				Activity	Participation
	Cardiac/ Blood Investigations	Respiratory	Musculoskeletal	Work rate		
Bourbeau et al. (2020)*	CK	Pulmonary function testing- VE/ maximal voluntary ventilation ratio Dyspnoea	Isometric and isokinetic quadriceps strength Muscle pain (VAS 0-10)	Symptom-limited peak incremental concentric cycling power (W) Leg fatigue RPE	6MWT Stair climbing Physical activity through armband	-
Macmillan et al. (2017)*	HR Blood pressure CK	Pre-post VO_2 and ventilation During ex: Dyspnoea (BORG), oxyhaemoglobin	Body composition Isometric quadriceps strength Muscle biopsy left VL Mitochondrial biogenesis transcript analysis Assessment of muscle damage through staining	RPE (BORG CR10)	-	-
Camillo et al. (2015)	HR CK Blood levels of lactate before and after session	Pre-post spirometry Dyspnoea (modified medical research council scale) During exercise: gas exchange, O_2 saturation, VE	Leg discomfort (modified BORG) during ex Muscle soreness (VAS 15cm) over the 7 days post session	-	-	-
Moezy et al. (2018)	HR	PFT: FEV1 and FEV1/FVC ratio O_2 saturation	-	-	6MWT TUG Stair climbing test	St. George respiratory QOL questionnaire
Qadar et al. (2016)	-	FEV1 FEV6 FEV1 / FEV 6 Dyspnoea (BORG scale)	-	-	-	Health status (BODE index)
Casillas et al. (2016) #	HR via ECG Blood pressure NT-proBNP	Incremental CPET- VO_2 peak	Maximal strength test- isokinetic dynamometry quadriceps and triceps surae Muscle soreness on VAS 0-10	RPE (BORG 6-20)	6MWT	-
Chasland et al. (2017)^	HR via ECG MAP Blood lactate	VE VO_2 RER	Muscle soreness (VAS 0-10)	-	-	-
Haynes et al. (2017)^	Vascular function tests- brachial artery diameter and FMD Platelet function test	-	-	-	-	-

***Note*.** CK= creatinine kinase, VE= minute ventilation, VAS= visual analogue scale, RPE= rating of perceived exertion, 6MWT= six minute walk test, HR= heart rate, O_2= oxygen, VO_2= oxygen uptake, VL= vastus lateralis, PFT= pulmonary function test, FEV1= forced expiratory volume in one second, FVC= forced vital capacity, TUG= timed up and go, QOL= quality of life, FEV6= forced expiratory volume in six seconds, ECG= electrocardiogram, NT- pro-BNP: N-terminal pro-brain natriuretic peptide, MAP= mean arterial pressure, FMD= flow mediated dilation, RER= respiratory exchange ratio

* articles contained the same sample- Macmillan included 15 of Bourbeau's participants # Chasland is a follow-up study to Besson (included in original R/V) ^ 12 participants recruited, 1 excluded from either study so 10 are the same participants

Table 5. Characteristics of recent articles- January 2015 - May 2020 – Results

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/ Blood Investigation	**Respiratory**	**Musculoskeletal**	**Work rate**			
Bourbeau et al. (2020)*	CK fluctuated in normal range both groups	Sig dec dyspnoea post ECC c.f. CON VE unchanged both groups	Sig inc isometric quadriceps strength ECC more than CON. Significant inc from baseline isokinetic strength ECC but not c.f. CON	Sig inc peak power output both groups with no diff between groups Sig less leg fatigue in ECC c.f. CON	Sig inc 6MWT ECC group but no diff between groups Total stair climb unchanged both groups and steps improved for ECC but not significantly more than CON		One CON participant developed back pain and required 3 sessions break
Macmillan et al. (2017)*	No significant difference in HR CK normal range both groups	Sig less dyspnoea in ECC c.f. CON	Sig less leg fatigue in ECC c.f. CON Body composition: No change weight or BMI ECC: sig dec body fat % Strength: ECC sig inc isometric quad strength Mean muscle fibre CSA inc in CON, unchanged in ECC Mitochondrial analysis: no change ECC, CON sig improved biogenesis, content and function	3 x greater training load in ECC than CON Sig less leg fatigue in ECC c.f. CON Sig inc peak work rate in cardiopulmonary testing for CON but not ECC			CON: one participant developed back pain and required 9 days break One had hip pain not limiting treatment ECC: two participants had knee pain not limiting treatment
Camillo et al. (2015)	CK levels sig inc 24hrs after DW and DWL but not LW No sig diff in HR during steady state for 3 modalities and no change in lactate levels from resting	DW and DWL associated with sig lower VO_2 and VE during "steady state" in final 5 mins of measurement % of VO_2 peak and VE peak sig lower in DWL and DW than LW	Sig dec in TWqpot, TWqunpot and MVC in DW and DWL Incidence LFF (defined as dec TWqpot > 15%) sig greater in DW and DWL than LW. No diff between DW and DWL				Nil serious adverse events DWL: tolerable discomfort hip (n = 1

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/ Blood Investigation	Respiratory	Musculoskeletal	Work rate			
		No sig diff in perceived dyspnoea between 3 modalities but small sig in from baseline for all 3	VAS scores low (median 1/15) for muscle soreness for all modalities. Small sig dec VAS score from day 1-7 post DWL No sig diff in perceived fatigue between 3 modalities but small sig in from baseline for all 3				and knee (n = 2) LW: one participant excluded due to dyspnoea and O_2 desaturation
Moezy et al. (2018)	No change in HR	ECC: sig improvement in FEV1, FEV/FVC and Spo2 c.f. baseline and in FEV1/FVC and FEV1 c.f. with CON CON: no change			ECC: sig improvement in 6MWT and stair climbing c.f. baseline and with 6MWT and TUG c.f. CON CON: no change	ECC: sig improvement in QOL c.f. baseline and CON CON: no change	None
Qadar et al. (2016)		CON: sig inc FEV1 and FEV6 post intervention FEV1 / FEV6 did not change Sig dec BORG dyspnoea ECC: sig inc FEV1 and FEV6 post intervention FEV1 / FEV6 did not change Sig dec BORG dyspnoea Also sig diff for these 3 measures between ECC and CON in favour of ECC				Health status on BODE index showed no significant difference	None
Casillas et al. (2016) #	No change HR max in pre-post CPET	ECC: No change VO2 peak and VO_2 at first ventilatory threshold	ECC: sig inc maximal triceps surae strength but not for quadriceps	Sig inc peak work rate post ECC and CON-	Sig inc both groups 6MWT with no		None

Study	Impairment				Activity	Participation	Adverse events
	Cardiac/ Blood Investigation	**Respiratory**	**Musculoskeletal**	**Work rate**			
	Difference between resting and end training HR sig greater for CON than ECC No change BP or NT-proBNP	CON: sig inc VO2 peak and VO_2 at first ventilatory threshold	CON: no change	no difference between groups No change RPE either group	difference between groups		
Chasland et al. (2017)^	No significant diff in HR, MAP or blood lactate between ECC and CON	VO_2, VE and RER lower during ECC than CON	No sig diff in muscle soreness between ECC and CON before and immediately after but was sig higher in ECC 24h and 48h post but diminished by 74h				None
Haynes et al. (2017)^	ECC: sig inc baseline artery diameter pre-post ex. CON no change No change peak artery diameter pre-post both groups ECC sig dec FMD% pre-post ex (only when changes in baseline diameter not accounted for). CON no change No change platelet function in either group						None

Note. CK= creatine kinase, ECC= eccentric, CON= concentric, c.f.= compared with, VE= minute ventilation, dec= decrease, inc= increase, sig= significant, diff= difference, RPE= rating of perceived exertion, 6MWT= six minute walk test, DW= downhill walk, DWL= downhill walk with load, LW= level walk, VO_2= oxygen uptake, VE= minute ventilation, TWqunpot= Unpotentiated quadriceps twitch contraction, TWqpot= potentiated quadriceps twitch contraction, MVC= maximal voluntary contraction, LFF= low-frequency fatigue, VAS= visual analogue scale, HR= heart rate, BMI= body mass index, CSA= cross sectional area, FEV1= forced expiratory volume in one second, FVC= forced vital capacity, SpO_2= pulse oximetry oxygen saturation, TUG= timed up and go, QOL= quality of life, FEV6= forced expiratory volume in six seconds, NT- pro-BNP: N-terminal pro-brain natriuretic peptide, RER= respiratory exchange ratio, FMD= flow mediated dilation

* articles contained the same sample- Macmillan included 15 of Bourbeau's participants # Chasland is a follow-up study to Besson (included in original R/V) ^ 12 participants recruited, 1 excluded from either study so 10 are the same participants.

Table 6. Clinical trial protocols- future or in progress

Author	Date submitted	Status	Condition	Intervention	Duration	Intensity	Outcomes		
							Impairment	Activity	Participation
Aranguiz, S	March 2016	Not yet recruiting	COPD c.f. healthy	ECC AND CON cycling	Acute effects- 2 bouts ecc and 1 bout con 30 min each	50% V VO_2 max	Oxidative stress Inflammatory markers Acute metabolic stress (O2 consumption and saturation) during cycling CK and muscle strength before and 24, 48, 72 and 96 hours after		
Aranguiz, S	March 2016	Not yet recruiting	COPD	ECC vs. CON cycling vs. lower body resistance ex	3 x weekly 16 weeks 5 min progressed up to 30 min cycling	Increased from 30% to 50% VO_2 max	As above – 72 hours after the 16 weeks		
Centre Hospitalier Universitair-e de Besancon	April 2019	Not yet recruiting	Severe COPD	ECC vs. CON cycling	Not stated	Not stated	Ventilatory adaptation (VE, RR/TV) Dynamic hyperinflation Brachial and quadriceps muscle enrolment (EMG) Ventilatory efficiency (dead vol/TV ratio, VE/CO2 production) Dyspnoea		
Green, D	February 2019	Not yet recruiting	CHF	ECC vs. CON cycling	2x weekly 12 weeks 10 min warm-up, 5 min cool down 40 min cycle	Matched cardiorespiratory demand- 70% HRR for both groups	Change aerobic capacity (VO2 peak, BP, BORG, SOB) Muscle size and strength Body composition Cardiac ECG and US	Activity level 6MWT TUG	MLFHQ
Laclautre, L	October 2018	Recruiting	CHF	ECC vs. CON cycling	5 x weekly 5 weeks	Same for both	Quads isometric strength Peak VO2	6MWT TUG	

Author	Date submitted	Status	Conditi-on	Intervention	Duration	Intensity	Outcomes		
							Impairment	Activity	Participation
				as part of cardiac rehabilitation	Ecc group will do 3 sessions ECC and 2 sessions CON 30 min sessions	groups based on initial cycling and associated VO2	Body fat mass Blood and muscle biomarkers	Gait speed test	
Ward, T	January 2019	Recruiting	COPD	Conventional cycling vs. ECC cycling vs. one-legged cycling vs. resistance training	3 weeks of exercise training in one of four modalities Nil further information	% change power output of ergometer, and kg weights	Develop idea of which group of patients benefit from each exercise not establish effectiveness- Training progression- % change Training adherence- % attended VO2 peak, change inspiratory capacity Breathlessness questionnaire Change work rate Quadriceps muscle ecc and con strength as well as 10 RM leg extension Muscle architecture on biopsy Balance Body composition	TUG 7 day activity monitor Qualitative experience questionnaire	StGRQ Frailty index

Note. COPD= Chronic obstructive pulmonary disease, CHF= Chronic heart failure, c.f.= compared with, ECC= eccentric, CON= concentric, min= minutes, VO_2= oxygen uptake, max=maximum, O_2= oxygen, CK= creatine kinase, vs.= versus, ex= exercise, VE= minute ventilation, RR= respiratory rate, TV= tidal volume, EMG= electromyogram, CO2= carbon dioxide, HRR= heart rate reserve, 6MWT= six minute walk test, TUG= timed up and go, MLFHQ= Minnesota living with heart failure questionnaire, kg= kilogram, RM= repetition maximum, StGRQ= St. George Respiratory questionnaire

Appendix 2: Ethics approvals statements

Chapter 3 (Reliability of one-repetition maximum performance in people with chronic heart failure) and Chapter 4 (Effect of eccentric exercise on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial) combined application:

Northern Health: LNR/17/NH/30 / LR 49.2013

La Trobe University: FHEC13/260

Austin Health: HREC/17/Austin/45

Northern Health

4th December 2013

Rachel Ellis
The Physiotherapy Department
Allied Health
Northern Health

Dear Rachel,

RE: LR 49.2013 Eccentric exercise in patients with chronic heart failure

The above project was reviewed and approved by the NH Low Risk Ethics committee in December 2013.

The following trial related documents were approved:

Patient Information and Consent Form Version 1.1 dated 04.12.2013

This project is approved until 31st December 2015. Researchers should note that an annual progress report is required annually in July each year until study completion.

Yours sincerely,

Anastasia Hutchinson

Chair of the Low Risk Ethics Committee
NORTHERN HEALTH
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LA TROBE UNIVERSITY

FACULTY OF HEALTH SCIENCES

MEMORANDUM

To: **Dr Nora Shields – Department of Physiotherapy**

Student: **Rachel Ellis**

From: **Chair, La Trobe University Faculty Human Ethics Committee**

Subject: **FHEC acceptance of Northern Health HREC approved project – LR49.2013. FHEC13/260**

Title: **Effect of an eccentrically biased aerobic exercise program on quality of life and functional capacity in people with chronic heart failure: A randomised controlled trial.**

Date: **11 December, 2013**

Thank you for submitting the above protocol to the Faculty Human Ethics Committee (FHEC). Your material was forwarded to the FHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Northern Health HREC**, the FHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by The Northern Health HREC.

Limit of Approval. La Trobe FHEC endorsement is limited strictly to the research protocol as approved by The Northern Health HREC.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by The Northern Health HREC for the project should be notified formally to the FHEC.

Annual Progress Reports. Copies of all progress reports submitted to The Northern Health HREC are to be forwarded to the FHEC. Failure to submit a progress report will mean that endorsement for your involvement in this project will be rescinded. An audit related of your involvement in the study may be conducted by the FHEC at any time.

Final Report. A copy of the final report is to be forwarded to the FHEC within one month of it being submitted by The Northern Health HREC.

If you have any queries related to the information above or require further clarifications, please fhechealth@latrobe.edu.au. Please quote FHEC application reference number FHEC13/260.

Northern Health

26th February 2015

A/Prof Kwang Lim & Rachel Ellis
Northern Health
185 Cooper Street
Epping VIC 3076

Dear Kwang & Rachel,

RE: LR 49.2013
Title: 'Effect of eccentrically based aerobic exercise on quality of life and functional capacity in people with chronic heart failure: a randomised controlled trial.

We have received and acknowledged your Annual Progress report and Amendment report for the study listed above and thank you for your submission. Your requested amendments (listed below) have been ratified by the Northern Health Low and Negligible Risk Ethics Committee.

- Allow patients who decline participation in the full trial but agree to participate in the heart failure rehabilitation program to consent to have their data of the 1 repetition maximum leg press outcome measure recorded for a separate reliability study.
- Associate Professor Anne Holland has been added to this study as an associate investigator.

Extension of ethical approval has been granted to 31st December 2016.

For future enquiries relating to Low Risk Research at Northern Health please email lowriskresearch@nh.org.au

Yours sincerely,

Chelsea Webster
Co - Chair of the Low Risk Ethics Committee
NORTHERN HEALTH
Ph. 03 8405 8480
Email: Chelsea.webster@nh.org.au

LA TROBE UNIVERSITY

COLLEGE OF SCIENCE, HEALTH & ENGINEERING

MEMORANDUM

To: **Nora Shields – Department of Community and Clinical Allied Health**

Student: **Rachel Ellis**

From: **Secretariat, La Trobe University Human Ethics Sub-committee**

Subject: **HESC acceptance of Northern Health HREC modification to approved project – LR 49.2013. FHEC13/260.**

Title: **Effect of an eccentrically biased aerobic exercise program on quality of life and functional capacity in people with chronic heart failure: A randomised controlled trial.**

Date: **2 March, 2015**

Thank you for submitting your modification to Human Ethics Sub-committee (HESC). Your material was forwarded to the HESC Chair for consideration. Following evidence of review and subsequent approval of the modification by the **The Northern Health HREC**, the HESC Chair agrees that the modified protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of modification approval outlined by The Northern Health HREC.

Limit of Approval. La Trobe HESC endorsement is limited strictly to the research protocol as approved by The Northern Health HREC.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by The Northern Health HREC for the project should be notified formally to the HESC.

Annual Progress Reports. Copies of all progress reports submitted to The Northern Health HREC are to be forwarded to the HESC. Failure to submit a progress report will mean that endorsement for your involvement in this project will be rescinded. An audit related of your involvement in the study may be conducted by the HESC at any time.

Final Report. A copy of the final report is to be forwarded to the HESC within one month of it being submitted by The Northern Health HREC.

If you have any queries related to the information above or require further clarifications, please hesc.she@latrobe.edu.au. Please quote FHEC application reference number FHEC13/260.

Northern Health

06 August 2015

A/Prof Kwang Lim & Rachel Ellis
Northern Health
185 Cooper Street
Epping VIC 3076

Dear Kwang & Rachel,

RE: **LR 49.2013**
Title: *'Effect of eccentrically based aerobic exercise on quality of life and functional capacity in people with chronic heart failure: a randomised controlled trial.*

The Northern Health Low and Negligible Risk Ethics Committee ratify your amendment request to increase the sample size to n=46 based on the advice of Biostatistician Mark Tacey.

Please Note: Template forms for reporting Amendments, Adverse Events, Annual Report/Final Reports, etc. can be accessed from: www.health.vic.gov.au/cchre.

Researchers should note that a progress report is required annually on the anniversary of your approval date each year until study completion. Please email this report to lowriskresearch@nh.org.au

The researchers should inform the Northern Health Low and Negligible Risk Ethics Committee if there are any changes to the study procedures or study personnel during the conduct of the study.

Yours sincerely,

David Price

Chair of the Low & Negligible Risk Ethics Committee
NORTHERN HEALTH
Ph. 03 9495 3472
Mobile 0424 757 331
Email: david.price@nh.org.au

LA TROBE UNIVERSITY

COLLEGE OF SCIENCE, HEALTH & ENGINEERING

MEMORANDUM

To: **Dr Nora Shields**

Student: **Rachel Ellis**

From: **Secretariat, SHE College Human Ethics Sub-committee (SHE CHESC)**

Reference: **SHE CHESC acceptance of Northern Health HREC modification to approved project – LR 49.2013. FHEC13/260**

Title: **Effect of an eccentrically biased aerobic exercise program on quality of life and functional capacity in people with chronic heart failure: A randomised controlled trial.**

Date: **8 September 2015**

Thank you for submitting your modification to Human Ethics Sub-committee (CHESC). Your material was forwarded to the SHE CHESC Chair for consideration. Following evidence of review and subsequent approval of the modification by the **Northern Health HREC**, the SHE CHESC Chair agrees that the modified protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of modification approval outlined by The Northern Health HREC.

Limit of Approval. La Trobe SHE CHESC endorsement is limited strictly to the research protocol as approved by The Northern Health HREC.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by The Northern Health HREC for the project should be notified formally to the SHE CHESC.

Annual Progress Reports. Copies of all progress reports submitted to The Northern Health HREC are to be forwarded to the SHE CHESC. Failure to submit a progress report will mean that endorsement for your involvement in this project will be rescinded. An audit related of your involvement in the study may be conducted by the SHE CHESC at any time.

Final Report. A copy of the final report is to be forwarded to the CHESC within one month of it being submitted by The Northern Health HREC.

If you have any queries related to the information above or require further clarifications, please contact chesc.she@latrobe.edu.au. Please quote SHE CHESC application reference number FHEC13/260.

Northern Health

12 January 2017

A/Prof Kwang Lim
Northern Health
185 Cooper Street
Epping VIC 3076

Dear Kwang,

RE: Transition from Northern Health Low & Negligible Risk Ethics Committee (LNREC) to Austin Health Clinical Research Review Committee (CRRC)

As of 22 Nov 16, Northern Heath Human Research Ethics Committee and LNREC closed and as a result your project has been transfer from Northern Health to Austin Health Office For Research which manages ethics approvals; this has been done electronically however some further changes need to be made by you.

The new approval number for your project is listed below.

Old Northern Health LNR No:	LNR/17/NH/30 / LR 49.13
New Austin Health LNR No:	HREC/17/Austin/45
Site Specific Application No. (unchanged):	LNRSSA/17/NH/32
Study Title:	Effect of eccentrically biased aerobic exercise on quality of life and functional capacity in people with chronic heart failure: a randomised controlled trial.
Next Annual Report Due:	01 April 2017
Ethical Approval:	Ongoing

Please ensure that you use the new Austin LNR No. when communicating with both the Northern Health Office of Research & Ethics (NHORE) & Austin Health Office For Research (AH-OFR).

Changes required:

1. Participant information consent form (PICF), delete the current text in reference to the Northern Health HREC as the reviewing HREC and replace with:

   'The Northern Health Human Research & Ethics Committee provided ethical approval and oversight of this research project until 22 November 2016, ethical oversight was then transferred to Austin Health Human Research & Ethics Committee.'

The Northern Hospital
Panch Health Service
Craigieburn Health Service
Broadmeadows Health Service
Bundoora Extended Care Centre

Northern Health
The Northern Hospital
185 Cooper Street
Epping Victoria 3076
Ph: 8405 2918

www.nh.org.au

Appendix 3: Copyright permissions

Ellis, Rachel (TNH - physio)

From: Mary Ann Price <permissions@sagepub.com>
Sent: Wednesday, 26 August 2020 6:44 AM
To: Ellis, Rachel (TNH - physio)
Subject: RP-2451 Inclusion in thesis which will be available in library repostitory

_____
Reply above this line.

Mary Ann Price commented:

Dear Rachel,

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Kind regards,

Mary Ann Price
Rights Coordinator

SAGE Publishing

2600 Virginia Ave NW, Suite 600

Washington, DC 20037

USA

T: 202-729-1403

www.sagepublishing.com

Mary Ann Price resolved this as Done.

1

Ellis, Rachel (TNH - physio)

From: Academic UK Non Rightslink <permissionrequest@tandf.co.uk>
Sent: Tuesday, 8 September 2020 5:42 PM
To: Ellis, Rachel (TNH - physio)
Subject: RE: Reusing part or all of my article somewhere else (UK)

Dear Rachel Ellis

Rachel Ellis, Anne E. Holland, Karen Dodd & Nora Shields (2019) Reliability of one-repetition maximum performance in people with chronic heart failure, Disability and Rehabilitation, 41:14, 1706-1710, DOI: 10.1080/09638288.2018.1443160

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Thank you for your interest in our Journal.

Yours sincerely

Karin Beesley - Permissions Administrator, Journals
Taylor & Francis Group
3 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
permissionrequest@tandf.co.uk
Tel: +44 (0)20 337 73116

From: Rachel Ellis <rachel.ellis2@nh.org.au>
Sent: 08 September 2020 02:05
To: Academic UK Non Rightslink <permissionrequest@tandf.co.uk>
Subject: Reusing part or all of my article somewhere else (UK)

I have a question about:

Ellis, Rachel (TNH - Physio)

From: IDRE-production@journals.tandf.co.uk
Sent: Tuesday, 13 October 2020 6:48 PM
To: Ellis, Rachel (TNH - physio)
Subject: Re: Re: Welcome to Taylor & Francis Production: Disability and Rehabilitation 1836679 #TrackingId:7457398
Attachments: Capture.PNG

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Rachel Ellis

Greetings from Rili!

Kindly note that the attached option would be the one that would best describe your requirement with the manuscript.

Thanking you.

Best Wishes & Warm Regards

Rili Muralidharan (Ms.)

Work Timings: Monday to Friday 5:30 AM - 2:30 PM (GMT)

Disability and Rehabilitation

From: Rachel.Ellis2@nh.org.au
Sent:13-10-2020 08.50 AM
To:IDRE-production@journals.tandf.co.uk
Cc:
Subject: Re: Re: Welcome to Taylor & Francis Production: Disability and Rehabilitation 1836679

Hi Rili,

Use my article internally within my institution or company	Yes (if it is the author[s]' institution or company)	Include a link to the Version of Record, using *"This is an Accepted Manuscript of an article published by Taylor & Francis in [JOURNAL TITLE] on [date of publication], available online: http://wwww.tandfonline.com/[Article DOI]."*

Appendix 4: Publication statements

Chapter 2

Statement from authors confirming the authorship contribution of the Doctoral candidate: "As an author of the paper 'Ellis R, Shields N, Lim K, Dodd KJ. Eccentric exercise in adults with cardiorespiratory disease: a systematic review. Clinical rehabilitation. 2015;29(12):1178-97.' I confirm that Rachel Ellis made the following contributions:"

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the data
- Writing the paper
- Critical appraisal of the content
- Response to reviewers

Professor Nora Shields	Nora Shields	Date: 9th October 2020
Professor Karen Dodd	Karen Dodd	Date: 16th October 2020
Professor Kwang Lim		Date: 6th November 2020

Chapter 3

Statement from authors confirming the authorship contribution of the Doctoral candidate: "As an author of the paper 'Ellis R, Holland AE, Dodd K, Shields N. Reliability of one-repetition maximum performance in people with chronic heart failure. Disability and Rehabilitation. 2019;41(14):1706-10.' I confirm that Rachel Ellis made the following contributions:"

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the data
- Writing the paper
- Critical appraisal of the content
- Response to reviewers

Professor Nora Shields	Nora Shields	Date: 9th October 2020
Professor Karen Dodd	Karen Dodd	Date: 16th October 2020
Professor Anne Holland		Date: 16th October 2020

Chapter 4

Statement from authors confirming the authorship contribution of the Doctoral candidate: "As an author of the paper 'Effect of eccentric exercise on quality of life and function in people with chronic heart failure: A pilot randomised controlled trial. Disability and Rehabilitation. In press.' I confirm that Rachel Ellis made the following contributions:"

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the data
- Writing the paper
- Critical appraisal of the content
- Response to reviewers

Professor Nora Shields		Date: 9th October 2020
Professor Karen Dodd		Date: 16th October 2020
Professor Anne Holland		Date: 16th October 2020
Professor Kwang Lim		Date: 6th November 2020
Mr. Mark Tacey		Date: 21st October 2020