Optimising clinical and functional outcomes in older adults with CHF using the Peripheral Remodelling through Intermittent Muscular Exercise (PRIME) approach: A pilot study

Research Proposal V8
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1 Scientific Background

1.1 Chronic Heart Failure: a condition of the aged

An estimated 30,000 Australians are diagnosed with heart failure each year, with health care costs of chronic heart failure (CHF) in excess of 1 billion per year (Australian Institute of Health and Welfare, 2003).

Advances in the medical and surgical management of other cardiovascular conditions have seen survival rates from acute coronary events improve by 18% between the years of 1994 to 2009 (Australian Institute of Health and Welfare, 2014). As a consequence, CHF is becoming a condition of the aged, with rates of HF in those over 65 years rapidly increasing from 2-3% to 23% (Australian Bureau of Statistics, 2011). At Western Health (WH), patients over 65yrs account for 89% of all admissions with the primary diagnosis of acute decompensated heart failure (WH Performance Unit 2013). The advancing age of patients is recognised as a key strategic challenge for WH and, as part of the new Cardio-Geriatric Heart Failure Service, WH aims to ensure that future delivery of heart failure services meets the needs of the elderly patient. A new model of care founded on evidence based practice and multidisciplinary care has been implemented, that facilitates early access to cardiology intervention, comprehensive geriatric assessment and individualised navigation from acute care to community follow-up and specialised exercise rehabilitation.

In non-CHF subjects, many of the age-related declines in function are correlated with peripheral mechanisms, including (a) reduced vascular function and blood flow delivery, (b) reduced skeletal muscle mass, and (c) impaired muscle oxygen utilization. In CHF patients these peripheral declines maybe even more pronounced with rarefaction of skeletal muscle capillary density, loss in muscle cross sectional area and a relative loss of type 1 (oxidative) muscle fibres creating a more glycolytic response to exercise. This combination of age plus disease pathology presents a substantial challenge for clinicians to offer suitable and effective rehabilitative approaches to increase clinical function, functional independence and quality of life. Developing exercise rehabilitation programs that are inclusive of this patient group and duly considers their unique physical presentation, is an area of considerable interest to Western Health.

Noting the urgent "real world" need, this project is fully supported by the “Cardio-Geriatric Heart Failure Service” committee personnel, including the WH director of cardiology, critical care services manager, head of the unit in general medicine, the manager of physiotherapy, and supervisors for this project, Professor Jason Allen, Clinical exercise Science Research Program Leader in the Institute of Sport, Exercise and Active Living (ISEAL) and Director of the Clinical Exercise Science and Rehabilitation in the College of Sport and Exercise Science at Victoria University, A/Prof Chris Neil, Consultant Cardiologist, A/Prof Itamar Levigner senior researcher at Victoria University, and Dr Lizzie Skinner, Senior Research Physiotherapist.

1.2 Exercise is Medicine

Despite earlier beliefs that exercise training may adversely affect left ventricular remodeling, the importance of physical activity and exercise training in patients with CHF has been acknowledged in many studies as safe and effective and is now a vital component in the treatment paradigm for patients with CHF. The 2011 Heart Foundation Guidelines strongly recommend regular physical activity for patients with CHF, on the basis that regular participation can reduce physical deconditioning (Chati, et al., 1996), improve functional capacity (Meyer, et al., 1997), improve symptoms and quality of life (O'Connor et al., 2009), reduce total mortality (Piepoli et al., 2004) and re-hospitalization (Chung & Shulze, 2011).

Best practice guidelines for exercise training in heart failure are inclusive of older adults and of patients in NYHA III-IV (Selig, et al., 2010). In fact, in a meta-analysis of exercise training in CHF, Piepoli et. al (2004) found a greater mortality and morbidity benefit in subgroups of patients who were actually more frail, more symptomatic and who had a worse functional capacity (higher New York Heart Association class, or NYHA class), lower VO_2 peak (<15 ml/kg/min) and who were older than 60 years.

1.3 The Muscle Hypothesis and Related Failures

The clinical syndrome of CHF is complex, and many models have been defined to explain the mechanisms of disease progression, thus forming the basis for medical and pharmaceutical intervention. The Muscle Hypothesis is one model of particular interest to the design of exercise training for the treatment and management of CHF. This model describes the possibility that abnormalities in the peripheral muscle tissue beds initiate a deleterious feedback loop and become drivers for disease progression. Specifically, an over activity of muscle ergo receptors results in abnormal coupling of ventilation leading to breathlessness and reduced physical activity. In turn, this stimulates a sympathetic nervous system response, further increasing afterload, left ventricular strain and disease progression. Furthermore, vasoconstriction occurs in remote tissues in order to increase blood supply to the apparently stimulated muscle, which can result in permanent damage and endothelial dysfunction to organs experiencing chronically reduced blood supply (Piepoli, Dimopoulos, Concu, & Crisafulli, 2008). Improving peripheral skeletal muscle function through exercise training may reduce the overactivity of muscle ergo receptors, thereby interrupting these maladaptive feedback loops (Peipoli, Clark, Volterrani, Adamopoulos, Sleight, & Coats, 1996)

Energy substrate utilisation is also of particular relevance to the exercise physiology of CHF. One study investigating mitochondrial involvement in CHF demonstrated an approximate 75% reduction in the total area of skeletal and cardiac muscle occupied by mitochondria (Mentesana, et al., 2014).

Furthermore, older adults with CHF often present with cachexia or sarcopenia. Individuals with muscle atrophy have a reduced aerobic capacity, are less able to perform daily activities and, in the elderly population, sarcopenia is associated with increased falls, slow gait speed and reduced functional performance (Landi et al., 2012). Savage et al (2011) investigated the relationship between aerobic capacity and muscle strength on performance in activities of daily living (ADL's) in 10 patients with CHF and found that performance in ADLs was 30% poorer in patients with CHF compared to healthy controls, and that both reduced aerobic capacity and muscle weakness attributed to this impairment (Savage, et al., 2011).

In light of these compounding factors which ultimately lead to disability, loss of independence and disease progression in the elderly patient with CHF, exercise training, in particular resistance training, has been used to mitigate the effects of peripheral muscle dysfunction associated with CHF. Levinger et al. (2005) investigated the effects of a resistance only training program in patients with CHF on beta blocker medications compared to a non-training control group (Levinger, Bronks, Cody, Linton, & Davie, 2005). Following an 8 week resistance training program performed 3 times per week, the intervention group showed significant increases in VO_{2peak}, increased time to fatigue during a sub maximal walking test, increased maximal strength in trained muscle groups and an 87% improvement in quality of life scores. The study participants were compared to an inactive control group and were younger and more functional than the "Cardio-Geriatric" population, and those with severe locomotive disability were excluded.

1.4 Attendance to CHF Rehabilitation

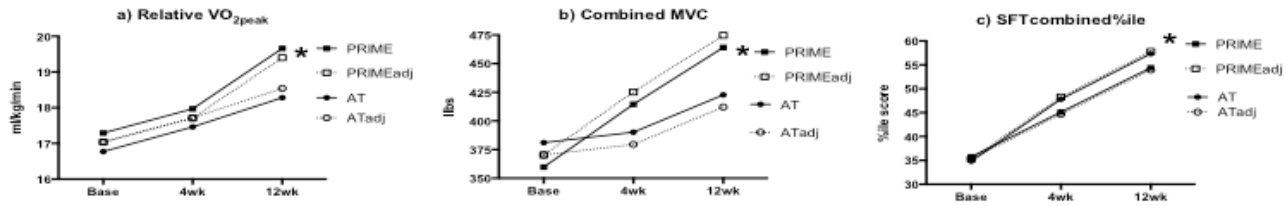
Despite profound evidence supporting exercise training for older adults with heart failure, attendance to CHF Rehabilitation in this patient group at Western Health's hospital network is very poor. To illustrate, experience over a 6-month period demonstrates that only 52 out of 174 patients (29.9%) admitted under the "Cardio-Geriatric Heart Failure Service" were referred to CHF rehabilitation following an acute inpatient admission with heart failure. Of this 52 of patients referred, 44 (85%) dropped out, or did not commence the program.

Among the possible barriers to attendance identified during routine patient-clinician discussion, was a focus on aerobic training based on a traditional cardiac rehabilitation model. **Drawing on the knowledge that fatigue, dyspnoea and exercise intolerance may be, in part, due to peripheral muscle abnormalities, it is conjectured that an exercise prescription with a defined focus on peripheral skeletal muscle and vasculature training may be more effective for counteracting peripheral tissue abnormalities that occur secondary to heart failure.**

1.5 Developing a new exercise model: addressing peripheral muscle pathology

In order to better address deficiencies in current training regimens for older and frail individuals, Professor Jason Allen (project supervisor) has developed, tested, and published a novel training regimen "Peripheral Remodelling via Intermitted Muscular Exercise" (PRIME). PRIME consists of a low mass, high repetition, localised stimulus to peripheral muscles, *without imposing central cardiorespiratory strain* (Allen, et al., 2013). The data generated from 76 completing subjects over 70yrs and at risk for losing functional independence can be seen in figure 1 (paper in preparation for publication). For Phase 1 of the study subjects were randomly assigned to either PRIME training (see below) or traditional aerobic exercise for 4 weeks. For Phase 2 all subject completed a combined aerobic and traditional resistance training program for 8 weeks. Subjects in both arms of the study showed significant increases in VO_{2peak}, Strength (MVC), and Function (using the Fullerton Senior Fitness test battery) in comparison to pre-training, however, the increases were statistically and clinically greater (group effect) for subjects randomized initially to the PRIME protocol than those in the aerobic program. This is despite no significant elevations in heart rates into a training zone during the initial 4 weeks of training for PRIME. This suggests, as hypothesized, that early improvements in the peripheral tissue resulting from the PRIME regimen allowed for greater potential functional gains once the individual is progressed into a well-rounded training program that also includes central (cardiac) stimulation. This makes the PRIME regimen ideal for subjects with central aerobic limitations and low levels of initial physical function, such as CHF.

Figure 1.



The intervention group experienced significantly greater gains to a) relative VO2peak, b) combined muscle voluntary contraction (MVC) and, c) performed better in the Seniors Fitness Test (SFT). *=P≤0.05.

1.6 Aims and Hypotheses

The primary hypothesis to be tested in this pilot study is that 4 weeks of PRIME exercise training prior to progressing to 4 weeks of ESSA recommended exercise training (4P+4E) will produce a greater clinical benefit (increases in strength, aerobic capacity, and quality of life) in older adults with CHF than 8 weeks of ESSA exercise training (8E).

In order to adequately develop power and inform a subsequent larger RCT, the following specific aims will be explored:

Aim 1: To determine group differences in the change in aerobic capacity, muscle strength, and Quality of Life following 4P+4E training versus 8E training

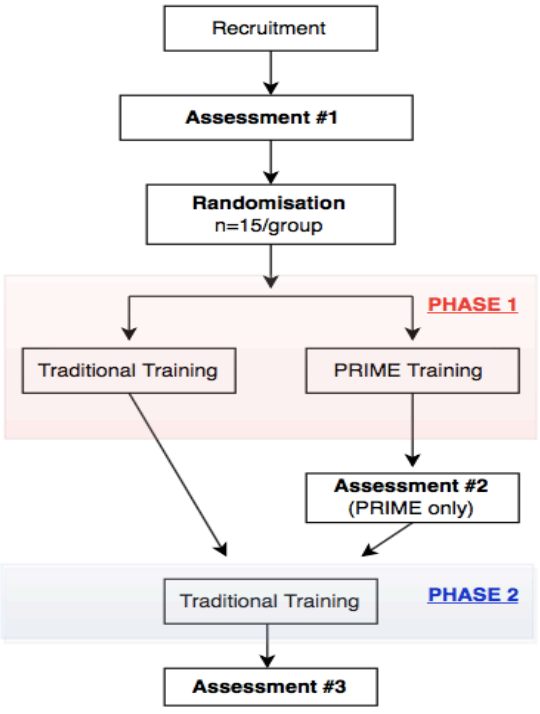
Aim 2: To determine compliance and adherence rates for the 4P+4E and the 8E training regimens.

2 Methodology

2.1 Study Design:

This study is a randomised two-arm study as depicted in Figure 2 below. Assessment of outcome measures will occur at baseline (assessment 1), at week 5 (Assessment 2, PRIME group only) and at 10 weeks (Assessment 3).

Figure 2.



2.2 Sample Size

This study will identify and recruit 4 patients per month for 7-8 months, for a total of 30 patients with a diagnosis of CHF. A sample size of 30 patients would allow us to estimate with 95% confidence, successful adherence of 90% (see Aim 1) with a margin error of 10%.

2.3 Recruitment

Participants will be recruited from 4 referral sources: 1) Cardiac Care Unit (CCU), 2) WH heart failure clinic or 3) hospital admissions risk program (HARP) and 4) One Heart Cardiology Private Practice (all sites).

Specifically, subject recruitment will be guided by the following criteria:

2.3 Inclusion:

- Age ≥60
- Documented diagnosis of Heart Failure by a medical practitioner
- New York Heart Failure Class I-III

2.4 Exclusion:

-
- Progressive worsening of exercise tolerance, dyspnoea or other symptoms suggestive of deterioration of heart failure or acute illness
- Severe aortic stenosis or severe valvular disease
- Unstable Angina
- Resting systolic pressure ≥ 160 mmHg or diastolic BP ≥ 95mmHg
- Resting heart rate ≥100bpm
- Complex ventricular arrhythmia at rest or appearing with exertion
- Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise

For further details see Appendix A

3 Baseline assessment and outcome measures

Subsequent to informed consent at baseline, and at weeks 5 (PRIME group only) and 10, patients will undergo an assessment with an accredited exercise physiologist (Appendix B) at Western CHRE (Centre for Health, Research & Education) facility, Sunshine Hospital. Dependant variables measured will be peak oxygen consumption (VO_{2peak}) and muscle strength. VO_{2peak} will be measured by a symptom limited cardiopulmonary exercise test (CPEX) on a cycle ergometer including a 12-lead electrocardiogram (ECG), commencing at 10-20 watts and increasing by 10-20 watts in 2 minute stages. Standard measurements of haemodynamic and subjective data will be monitored throughout (HR, BP and RPE). This approach allows an objective baseline exercise performance to be documented in a heterogeneous sample, including frail/severely-deconditioned subjects. In this controlled environment, data from these tests will be

used to identify adverse responses (including a vasovagal reaction, consisting of transient bradycardia and hypotension) that would prevent safe exercise training and to determine appropriate exercise prescription.

During the CPEX test, we will also collect information related to cardiac function (such as systolic volume and cardiac output) via the PhysioFlow system (Manatec Biomedical Inc, France). This system is a **non-invasive** technique that, when used in conjunction with ECG monitoring and Cardio-pulmonary measures, will provide us with information related to peripheral adaptations in muscle tissue following the exercise training intervention.

Muscular strength will be assessed by a 1-3 repetition maximum (RM) test for chest press and leg press.

A number of secondary measures will also be collected to further assess efficacy and to further develop methodology for a larger trial, as follows:

1. Quality of Life Indices
    - The Kansas City Cardiomyopathy Questionnaire
    - Cardiac Depression Scale

2. Adverse Events
    - Number of falls
    - Number of hospitalisations
    - Decompensated HF events

3. Attendance

4. Functional Performance/ Balance
    - Timed up and go test (TUGT)
    - 10m walk test (walking speed)
    - 4 square step test
    - Clinical Test of Sensory Interaction and Balance (CTSIB)
    - 30 second sit to stand
    - 6MWT

4 Randomisation

Following initial assessment, participants will be randomised to the PRIME intervention group or the usual care group. On completion of this study, participants will be offered the opportunity to participate in the group that they were not randomised to.

4.1 Phase 1 (Weeks 1-5)

Intervention Group (PRIME)

The PRIME intervention will utilise the exercise protocol developed by Allen et. al (2013) for training weeks 1-5, consisting of muscular contractions starting at approximately 50% of the 1 repetition maximal contraction (1RM) at a cadence of 1 every 4 seconds for a period of 3–5 minutes. Specific exercise selection will focus on large muscle groups involved in activities of daily living (table 1). Routine measurements of BP, HR and RPE will be taken before, during (if indicated) and after the training session. The routine is to be completed within 60 minutes including warm-up, rest periods and stretching between exercises, and cool down exercises. During each exercise subjects will be allowed to take rest breaks as needed but we have pre-specified that each break must be for a minimum of 30 seconds. Subject progression will initially occur by decreasing the number of required rest periods during each exercise. When the subject can complete the whole duration of the exercise without rest the load will be increased by 10%. The volume for each exercise will be calculated by multiplying the weight lifted by the number of repetitions completed and calculated as volume per exercise and total volume lifted per exercise session (sum of all exercises).

Table 1.

PRIME Phase 1 Exercise Protocol

Exercise	Days/week	Duration (min)	Starting intensity	Progression	Ideal cadence	Comments
Calf raises	3	5	Body weight	8–10% of body weight	1/4 s	Both legs
Handgrip	3	5	50% MVC	8–10% of previous load	1/4 s	Alternating hands
Leg press	3	6	40–50% MVC	8–10% of previous load	1/4 s	Both legs
Seated row	3	5	40–50% MVC	8–10% of previous load	1/4 s	Both arms
Chest press	3	5	40–50% MVC	8–10% of previous load	1/4 s	Both arms
Modified squats	3	5	Body weight	8–10% of body weight	1/4 s	Use of chair or exercise ball
Low back	3	3	As tolerated	8–10% of previous load	1/4 s	Crossed arms
Abdominal	3	3	As tolerated	8–10% of previous load	1/4 s	Pads on movement arm on chest

MVC — maximal voluntary contraction.

Traditional Training Group

Following assessment and randomisation, the traditional training group will complete a 10 week traditional exercise training regimen, established in Exercise and Sport Science Australia (ESSA) position statement on exercise training and chronic heart failure (Selig, et al., 2010). The program will include warm-up, aerobic and resistance training

components, finishing with a cool down activity. This training encompasses a more traditional approach involving an aerobic component commencing at 10–15 min at target exercise intensity of RPE 10-13 (Borg 6-20 scale) for NYHA I-II or RPE 11-14 for NYHA III-IV (table 2), progressing gradually according to patient's progress and tolerance to 45–60 min. Progression will be made when RPE or HR falls outside of the target zone at the same exercise intensity. Depending on individual responses, the exercise physiologist will adjust the exercise intensity so that the RPE and HR will remain in the target zones. Participants will then complete a resistance training component following ESSA guidelines consisting of resistance exercises that are individually selected, at an intensity of RPE 10-13 for NYHA I-II, or RPE 11-15 for NYHA III-IV (table 2). The load will be increased by 10% when the subject is able to complete 15 repetitions. Stretches targeting the involved muscle group are performed after each exercise. The volume for each exercise will be calculated by multiplying the weight lifted by the number of repetitions completed and calculated as volume per exercise and total volume lifted per exercise session (sum of all exercises).

4.2 Phase 2 (week 6-10)

Both groups will complete a further 5 weeks of Traditional training as outlined in the previous section.

Table 2. Phase 2 Target Intensities

Type	Class	Intensity	Volume/duration
Resistance Training	NYHA I–II	RPE 11–15/20	6–15 reps, 1-3 Sets
	NYHA III–IV	RPE 10–13/20	4–10 reps, 1-2 Sets
Aerobic Training	NYHA I–II	RPE 11–14/20	10-60 minutes
	NYHA III–IV	RPE ≤ 13/20	10-60 minutes

Cited from Exercise and Sport Science Australia Position Statement on exercise training for CHF (Selig, et al., 2010)

5 Facilities and equipment

Professor Allen will make facilities at Victoria University's Clinical Exercise Science and Rehabilitation Program, The Institute of Sport Exercise and Active Living (ISEAL) and Western Hospital's Centre for Health, Research and Education building (WCHRE) available as needed for this project. This includes numerous exercise training and testing facilities, all required testing equipment and laboratories and students from the Masters of Clinical Exercise Science and Rehabilitation degree program at VU will assist in the delivery of both intervention arms of the study.

Initial and follow-up assessments will be conducted in the CHRE metabolic laboratories by two accredited exercise physiologists. PRIME training will be take place at the CHRE Level 4 gymnasium.

5.1 Timeline

Ethics approval has been sought for this study in April 2015, with expected date of approval in June 2015. This study will commence recruitment in January 2016 with expected completion in December 2016. Participant enrolment will begin in February 2016 and will continue until recruitment goals are achieved. Approximately 7-12 months will be allocated to providing the intervention, depending on rate of recruitment.

5.2 Data Management

Once participants are enrolled in this study they will be allocated a study participant number. Paper databases will be de-identified and data coded with participant numbers in the electronic database. Paper data collection forms will be stored for the period of five years after the final publication or presentation associated with the study, in a locked cupboard in the Physiotherapy Department, Electronic data will be stored in a password-protected computer file accessible only to the investigators.

5.3 Statistical Analysis

To assess aims 1-4 of the primary hypothesis (Section 1.6) we will use descriptive statistics to summarise the data at each wave of data collection. Numbers and proportions will be calculated for categorical variables, and mean (standard deviation) or median (inter-quartile range) for normally distributed and skewed variables, respectively.

To assess the secondary hypothesis (see page 7), we will use a repeated measures mixed model for between group comparisons, which adjusts for the baseline measure of the outcome of interest (e.g. VO2 max).

Statistical analyses will be carried out in Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). Statistical analysis will be lead by Western Health Biostatistician and associate researcher for this study, Emily Karahalios.

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7 Appendix A

Absolute and relative contraindications for exercise training in patients with CHF

Absolute contraindications

1. Progressive worsening of exercise tolerance or dyspnoea at rest or on exertion over previous 3–5 days
2. Significant ischaemia at low exercise intensities (<2 METS, or ~50 W)
3. Uncontrolled diabetes
4. Acute systemic illness or fever
5. Recent embolism
6. Thrombophlebitis
7. Active pericarditis or myocarditis
8. Severe aortic stenosis
9. Regurgitant valvular heart disease requiring surgery
10. Myocardial infarction within previous 3 weeks
11. New onset atrial fibrillation
12. Resting heart rate >120 bpm

Relative contraindications

1. ≥2 kg increase in body mass over previous 1–3 days
2. Concurrent continuous or intermittent dobutamine therapy
3. Decrease in systolic blood pressure with exercise
4. New York Heart Association Functional Class IV
5. Complex ventricular arrhythmia at rest or appearing with exertion
6. Supine resting heart rate ≥100 bpm
7. Pre-existing co-morbidities
8. Moderate aortic stenosis
9. BP > 180/110mmHg (evaluated on a case by case basis)

Adapted from: Recommendations for exercise training in chronic heart failure patients. Working Group on Cardiac rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Eur Heart J 2001;22:125–35.

Appendix B

Table 1. Schedule for assessments

	Baseline		5 weeks (PRIME only)		10 -weeks	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Medical history	x					
Demographics	x					
Functional Performance / Balance (TUGT, 10MWT, Step test, DEMMI)	x		x		x	
1-3 repetition maximum test	x		x		x	
CPEX		x		x		x
MLwHFQ		x		x		x
CDS		x		x		x
Adverse events		x		x		x

Appendix C

Timeline per Patient

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Recruitment	x													
Assess 1		x x												
Phase 1			x	x	x	x	x							
Phase 2								x	x	x	x	x		
Assess 2													xx	
3 Month Follow-up														x