School of Physiotherapy

SHORT TERM EFFECTS OF EXERCISE TRAINING ON EXERCISE CAPACITY AND QUALITY OF LIFE IN INDIVIDUALS WITH PULMONARY ARTERIAL HYPERTENSION

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This thesis is presented for the Degree of
Doctor of Philosophy
of
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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

This thesis contains no material that has been accepted for the award of any other degree or diploma in any University.

Signature:

Date:

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy at Curtin University, Western Australia. Studies were undertaken between May 2007 and October 2011, through the School of Physiotherapy at Curtin University, in association with the Advanced Lung Disease Unit, the Physiotherapy Department and the Respiratory Medicine Department at Royal Perth Hospital.

This research project was developed in association with my supervisors who have been involved in editing both this thesis and all associated publications.

All of the material presented in this thesis is original.

ABSTRACT

Background and research hypotheses

Pulmonary arterial hypertension (PAH) is characterised by pathological changes in the pulmonary vasculature that cause an increase in pulmonary vascular resistance and restrict blood flow through the pulmonary circulation. Disease progression leads to right ventricular dysfunction, right heart failure and premature death.

Exertional dyspnoea and fatigue are common symptoms for individuals with PAH despite the recent advances in pharmaceutical management of this condition. Consequently, individuals experience impairments in exercise capacity and health-related quality of life (HRQoL). The causes of exercise intolerance in PAH are complex and multifactorial. Factors contributing to exercise intolerance include: (i) right ventricular dysfunction, (ii) impaired gas exchange, (iii) an attenuated cardiac output response to exercise, and (iv) peripheral endothelial and skeletal muscle dysfunction.

The studies in this thesis focussed on the effects of exercise training on exercise capacity and HRQoL in PAH.

The following research questions were addressed:

i. Is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) a valid and reliable tool to measure HRQoL in the Australian and New Zealand PAH population?
ii. What are the effects of a supervised, outpatient, individually prescribed, whole-body exercise training program on exercise capacity and HRQoL in individuals with PAH?
iii. Can any benefits achieved from a supervised exercise training program be maintained with an unsupervised home exercise program?
iv. What are the differences in physiological and symptom outcomes between laboratory and field-based exercise tests used to assess exercise capacity in PAH?

Methods

This program of research involved two studies. The first study explored the validity and reliability of the CAMPHOR in an Australian and New Zealand PAH population. The CAMPHOR is the only available disease-specific HRQoL measure for PAH and required validation in the Australian and New Zealand PAH population prior to being used as an outcome measure for the second study that investigated the effects of exercise training on exercise capacity and HRQoL in PAH.

Study 1 (addressing the first research question)

The CAMPHOR study comprised two parts: Semi-structured interviews were initially conducted with a cohort of 15 PAH patients (11 females) to determine the relevance of the CAMPHOR and ensure the terminology and language used were understandable and appropriate for the Australian and New Zealand PAH population. Subsequently, the CAMPHOR postal validation study recruited 61 participants (48 females) from PAH Specialist Centres in Australia and New Zealand. Participants were required to complete the CAMPHOR and the Medical Outcomes Study Short Form 36 General Health

Survey Version 2 (SF-36) on two occasions, two weeks apart, in order to examine test-retest reliability, internal consistency and construct validity of the CAMPHOR.

Study 2 (addressing the final three (ii-iv) research questions)

This prospective, single blind, randomised controlled trial investigated the effects of exercise training on exercise capacity and HRQoL in a PAH population. Participants were recruited from the Western Australian State Pulmonary Hypertension Service, at Royal Perth Hospital, Western Australia.

The medical records of the 242 individuals registered with the Western Australian State Pulmonary Hypertension Service were reviewed, of whom 121 had a confirmed diagnosis of PAH. Detailed review of the medical records for these 121 individuals identified 42 who met study criteria. Of the 42 individuals who were invited to participate in the study, 28 individuals declined. Baseline assessments were conducted on the 14 individuals willing to participate in the study, following which, 10 participants (9 female) were appropriate for the study and were randomised to either the exercise group (n=5) or control group (n=5). Participants in both groups continued to receive usual medical care. Participants randomised to the exercise group underwent a 12-week, supervised, outpatient, individually prescribed, whole-body exercise training program at Royal Perth Hospital, followed by a 12-week unsupervised home exercise program. Both groups were reassessed at 12 weeks and 24 weeks.

At each assessment block, participants were required to attend three visits within a two-week period to complete the assessments of exercise capacity and HRQoL. Visit 1 comprised assessment of functional exercise capacity, using the six-minute walk test (6MWT), and assessment of HRQoL, using the CAMPHOR and the SF-36. During visit 2, maximal exercise capacity was assessed using an incremental cardiopulmonary exercise test (CPET) with a continuous ramp protocol on a cycle ergometer. On the third visit, endurance exercise capacity was assessed via a constant workload cycle ergometer test (CWLT) set at 75% of the maximum workload achieved on the CPET.

Measurements collected at each time point were analysed for differences within and between groups.

Secondary analyses of the baseline exercise tests were performed to compare the physiological and symptom responses across the CPET, CWLT and 6MWT and to describe the measurement properties of these tests in a PAH population.

Results

Study 1

Data from the patient interviews confirmed that the CAMPHOR is appropriate for use in an Australian and New Zealand population with PAH. The three CAMPHOR scales (Symptoms, Activities and Quality of Life) had excellent test-retest reliability (correlation coefficients [r_s] = 0.86 to 0.94, $p<0.01$) and internal consistency (Cronbach's alpha coefficients = 0.89 to 0.92). The CAMPHOR also demonstrated the ability to distinguish between individuals with different levels of functional impairment, as assessed using the World Health Organisation functional classification system.

Study 2

Five participants (5 females) were randomised to the exercise group, of whom four completed the 12-week reassessment, following the supervised exercise training period. Three of these exercise group participants went on to complete the 24-week reassessment, following the unsupervised home exercise program. All five participants (4 female) randomised to the control group completed the 12-week and 24-week reassessments. Due to the small sample size, data are reported as median and interquartile range (IQR).

Following the supervised exercise training program, the exercise group demonstrated significant improvements in exercise capacity. Peak oxygen uptake ($\dot{V}O_2$) improved significantly (baseline: 1125mL/min, IQR 1109-1296mL/min; "12 weeks": 1253mL/min, IQR 1227-1423mL/min; p=0.024), in

addition to an improvement in $V'O_2$ at the anaerobic threshold (AT) (baseline: 641mL/min, IQR 612-695mL/min; "12 weeks": 789mL/min, IQR 747-835mL/min; p=0.005). Further, endurance time on the CWLT improved significantly (baseline: 469 seconds, IQR 422-626 seconds; "12 weeks": 1280 seconds, IQR 1104-1386 seconds; p=0.024) and was associated with an improvement in minute ventilation (V'_E). The 6MWD increased by 33m (IQR 12-90m, p=0.276).

The improvements in exercise capacity achieved during the supervised exercise training program were maintained with no change, or non-significant decreases, in $V'O_2$ peak, $V'O_2$ at the AT, endurance time and 6MWD.

No significant changes were observed in any of the exercise capacity outcomes for the control group, throughout the 24-week study period.

The exercise group participants demonstrated some improvement in individual scales on the CAMPHOR and SF-36, however these changes did not reach statistical significance.

An adverse event was recorded in one participant during the supervised exercise training period. The participant experienced an isolated episode of dizziness during their third training session, which required them to cease the session. Review of the participant's exercise log identified an attenuated heart rate (HR) response whereby, with an increase in exercise intensity, the HR did not increase accordingly. The participant continued in the study with no further episodes.

Secondary analyses of the baseline exercise testing data demonstrated similar physiological and symptom responses on the CPET and CWLT. There were no significant differences in (i) peak HR (138±14bpm vs 138±16bpm), (ii) nadir oxygen saturation (SpO_2) levels (96±4% vs 96±3%) and (iii) symptom scores of dyspnoea (6±3 vs 6±3) and perceived exertion (6±2 vs 6±3) on the CPET and CWLT, respectively. Peak $V'O_2$ averaged 5±6% higher on the CWLT (p=0.034) compared to the CPET. Peak HR ($p \leq 0.014$) and symptom scores for leg fatigue ($p \leq 0.027$) and general fatigue

($p \leq 0.025$) were lower on the 6MWT, when compared to the CPET and CWLT. Nadir SpO_2 levels were lower on the 6MWT (94±2%), when compared to the CPET and CWLT, although this difference did not reach statistical significance.

Discussion and conclusions

The CAMPHOR has been shown to be valid and reliable in an Australian and New Zealand PAH population and its use, in clinical practice and research, is recommended.

The improvements in exercise capacity following supervised training, suggest improvements in aerobic capacity and peripheral muscle function have occurred. The improvements seen in endurance time appear to be related to the improvements in V'_E, which have translated into improvements in symptoms and a capacity to exercise for longer. This is likely to be due to a delay in the onset of acidosis and improvements in the oxidative capacity and efficiency of the peripheral muscles. Importantly, this is the first study to demonstrate that benefits associated with a supervised, outpatient exercise training program can be maintained with an unsupervised home exercise program. A major limitation to this study was the very small sample size, which has impacted on the ability to generalise findings and explore the mechanisms for the improvement in exercise capacity.

Secondary analyses of the exercise testing data has shown that, in the PAH population, the unencouraged 6MWT elicits submaximal responses compared to the CPET and the CWLT.

The results of this study concur with those that have previously been published in the literature, contributing to the evidence supporting the role of exercise training in this population. Further, this is the first study to demonstrate that the improvements achieved following a supervised exercise training program can be maintained with an unsupervised home exercise program.

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Ganderton L, Jenkins S, Gain K, Fowler R, Winship P, Lunt D, Gabbay E. Short term effects of exercise training on exercise capacity and quality of life in patients with pulmonary arterial hypertension: protocol for a randomised controlled trial. BMC Pulmonary Medicine. 2011;11(25).

Presentations and Abstracts

Invited speaker. Australian Physiotherapy Association National Conference, Brisbane, 30th October 2011 "Exercise training in pulmonary arterial hypertension".

Invited speaker. Australian and New Zealand Thoracic Society annual scientific meeting, Perth, 5th April 2011 "Pulmonary arterial hypertension case presentation: optimising medical management and exercise training".

American Thoracic Society International Conference, San Diego, 17th May 2009, poster presentation:

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Australian and New Zealand Thoracic Society Annual Scientific Meeting, Darwin, 5th April 2009, poster presentation:

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Australian and New Zealand Thoracic Society Annual Scientific Meeting, Darwin, 5th April 2009, poster presentation:

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LIST OF ABBREVIATIONS

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
aPAH	Pulmonary arterial hypertension associated with connective tissue disorders
AT	Anaerobic threshold
ATS	American Thoracic Society
BP	Blood pressure
bpm	Beats per minute
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CTEPH	Chronic thromboembolic pulmonary hypertension
CWLT	Constant workload cycle ergometry test
D_LCO	Diffusing capacity of the lung for carbon monoxide
ECG	Electrocardiography
ERS	European Respiratory Society
ERV	Expiratory reserve volume
$FEF_{(25-75\%)}$	Forced expiratory flow between 25% and 75% of vital capacity
FEF_{max}	Peak forced expiratory flow
FEV_1	Forced expired volume in one second
fPAH	Familial pulmonary arterial hypertension
FVC	Forced vital capacity
HR	Heart rate
HRmax	Maximum heart rate
HREC	Human Research Ethics Committee
HRQoL	Health-related quality of life
IC	Inspiratory capacity
ICC	Intraclass correlation coefficient
ILD	Interstitial lung disease
iPAH	Idiopathic pulmonary arterial hypertension
iPAQ	International Physical Activity Questionnaire
IQR	Interquartile range
kg	Kilogram

L	Litre
LLN	Lower limit of normal
m	Metre
MET	Metabolic equivalent
MID	Minimally important difference
min	Minute
mL	Millilitres
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of oxygen in arterial blood
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
$P_{ET}CO_2$	End tidal carbon dioxide
PVR	Pulmonary vascular resistance
QoL	Quality of life
RCT	Randomised controlled trial
RHC	Right heart catheterisation
RER	Respiratory exchange ratio
RPE	Rating of perceived exertion
RV	Right ventricle
sec	Seconds
SD	Standard deviation
SF-36	Medical Outcomes Study Short Form 36 General Health Survey Version 2
SpO_2	Oxygen saturation
SV	Stroke volume
SVC	Slow vital capacity
$V'CO_2$	Carbon dioxide production
V'_E	Minute ventilation
$V'_E V'CO_2$	Ventilatory equivalent for carbon dioxide
$V'_E V'O_2$	Ventilatory equivalent for oxygen
$V'O_2$	Oxygen uptake
$V'O_2$ peak	Peak oxygen uptake
$V_{A\ eff}$	Effective alveolar volume
W	Watts
WA	Western Australia
WHO	World Health Organisation

Chapter 1

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterised by vascular remodelling and extensive narrowing of the pulmonary arteries and arterioles which leads to a progressive rise in pulmonary vascular resistance (1). If left untreated, right ventricular dysfunction and right heart failure eventuate and, ultimately, premature death occurs (2-4).

Advances in the understanding and management of PAH have enabled earlier diagnosis and improved prognosis (5). However, despite best available therapy, symptoms of exertional dyspnoea and fatigue are commonly reported and result in a reduced capacity to perform daily activities and impairments in health-related quality of life (HRQoL) (6). Exercise training has demonstrated efficacy in individuals with other chronic respiratory and cardiovascular diseases (7-14). Historically, however, exercise training has not been utilised as a form of therapy in PAH due to the perceived risk of sudden cardiac death and the theoretical possibility that exercise would lead to worsening pulmonary vascular haemodynamics, acceleration of vascular remodelling and deterioration in right heart function (6). Now, with the advances in pharmaceutical management, determining the safety and benefits of exercise training in this population has become more relevant. This premise formed the basis for this thesis.

This program of research involved two studies. The primary objective of this program of research was to investigate the effects of exercise training on exercise capacity and HRQoL in individuals with PAH. Further, in order to assess HRQoL, validation of the only disease-specific HRQoL measure, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), was necessary to ensure it was appropriate for use in the Australian and New Zealand PAH population.

The studies were designed to address the following research questions.

1.1 Research questions

1.1.1 Primary research questions

- Is the CAMPHOR a valid and reliable tool to measure HRQoL in the Australian and New Zealand PAH population?
- What are the effects of a supervised, outpatient, individually prescribed, whole-body exercise training program on exercise capacity and HRQoL in individuals with PAH?
- Can any benefits achieved from a supervised exercise training program be maintained with an unsupervised home exercise program?

1.1.2 Secondary research questions

- What are the differences in physiological and symptom outcomes between laboratory and field-based exercise tests used to assess exercise capacity in PAH?

This Chapter presents an overview of the literature pertaining to the development of each research question. The hypotheses for each research question are described and the significance of the research program is discussed.

1.2 Question 1

Is the CAMPHOR a valid and reliable tool to measure HRQoL in the Australian and New Zealand PAH population?

1.2.1 Hypothesis

The CAMPHOR will be a valid and reliable tool in the Australian and New Zealand PAH population.

1.2.2 Background

The CAMPHOR was developed in the United Kingdom (UK) and is the only available disease-specific HRQoL measure for the PAH population. The CAMPHOR has been shown to be a valid and reliable tool for individuals with PAH in the UK (15), the United States of America (16), Canada (17) and Germany (18). Disease-specific HRQoL measures are potentially more responsive to change because they explore aspects of HRQoL associated with a specific condition (19). To assess whether the CAMPHOR would be an appropriate tool to use in the exercise training study, a validation study in the Australian and New Zealand PAH population was performed as part of this program of research.

1.3 Question 2

What are the effects of a supervised, outpatient, individually prescribed, whole-body exercise training program on exercise capacity and HRQoL in individuals with PAH?

1.3.1 Hypotheses

i. When compared to a control group that receive usual medical care, a 12-week, supervised, outpatient, individualised, whole-body exercise training program will improve:
   - Exercise capacity, as measured by: (i) peak oxygen uptake ($\dot{V}O_2$ peak) and $\dot{V}O_2$ at the anaerobic threshold (AT) on an incremental cardiopulmonary exercise test (CPET), (ii) endurance time

measured during a constant-workload cycle ergometry test (CWLT), and (iii) distance walked on the six-minute walk test (6MWT);

- HRQoL.

ii. Exercise training will be demonstrated to be safe and improvements in exercise capacity will be achieved without evidence of clinical worsening.

1.3.2 Background

Symptoms of exertional dyspnoea and fatigue are common in individuals with PAH, despite being on optimal pharmaceutical therapy. The causes of exercise limitation in this population are complex and multifactorial. An impairment in cardiac output to meet peripheral oxygen demands during exercise largely contributes to exercise limitation (20), however, right ventricular dysfunction, impaired gas exchange and peripheral endothelial and skeletal muscle dysfunction may also be implicated in the exercise limitation experienced by individuals with PAH (20-26). Exercise training has a role in potentially addressing some of these factors, however, the theoretical concerns regarding the detrimental effects of exercise have historically lead to individuals being discouraged from performing exercise (27). The benefits of exercise training in other cardiopulmonary populations are well recognised and include improvements in symptoms, exercise capacity, peripheral muscle function and HRQoL (7-14).

A small number of exercise training studies in the PAH population have been conducted (6, 23, 28-33), with results demonstrating improvements in exercise capacity, peripheral muscle function and HRQoL. These benefits have been achieved following supervised exercise training programs.

The historical concerns regarding the safety of exercise training in PAH have been addressed, to some degree, with studies suggesting that exercise training can be performed without serious adverse events nor detriment to cardiac function and pulmonary haemodynamics, both in the short-term (6, 23, 29, 32, 33) and long-term (29).

To date, only one randomised controlled trial (RCT) investigating the effect of exercise training in PAH has been conducted (6). In this study conducted by Mereles and colleagues (6), participants completed an intensive 3-week inpatient exercise training program prior to performing a 12-week home exercise program. This study is the first RCT to investigate the effects of exercise training in PAH performed in the outpatient setting, the most common format for exercise programs for individuals with cardiopulmonary disease within Australia. Three other PAH exercise training studies have conducted exercise training in the outpatient setting (23, 28, 31). A control group was used for comparison in only one of these studies (28), however, allocation to the control group in this study was non-random and based on the willingness of individuals to participate in the exercise training program. The exercise training protocols differed among these studies, as did the choice of outcome measures. As such, further research is required to investigate the effects of exercise training in the outpatient setting. Importantly, the previous studies did not measure the effects of exercise training on HRQoL, as measured using a disease-specific tool. In the study described in this thesis, HRQoL outcomes following exercise training were assessed for the first time in PAH using the CAMPHOR, a questionnaire specifically developed for the PAH population.

1.4 Question 3

Can any benefits achieved from a supervised exercise training program be maintained with an unsupervised home exercise program?

1.4.1 Hypothesis

An additional 12-week, unsupervised home exercise program will maintain and/or further improve the benefits gained during the 12-week, supervised, outpatient program.

1.4.2 Background

Some evidence is available in populations with chronic respiratory disease that suggests benefits following supervised exercise training programs can be maintained (34, 35), however, others report a decline in exercise capacity close to pre-training levels, over a period of 6 to 24 months (36-40). The studies in PAH have reported immediate benefits following exercise training programs of 7 to 15 weeks duration (6, 23, 28-33), however, whether these benefits can be maintained with a home exercise program remains unknown.

1.5 Question 4

What are the differences in physiological and symptom outcomes between laboratory and field-based exercise tests used to assess exercise capacity in PAH?

1.5.1 Hypothesis

Submaximal physiological and symptom outcomes will be achieved on both (i) the 6MWT, using an unencouraged protocol, and, (ii) the CWLT, when compared to the incremental CPET.

1.5.2 Background

Exercise testing provides essential information to determine the factors contributing to exercise impairment and evaluate an individual's exercise capacity (41), however, there is no consensus regarding which measure of exercise capacity should be used in the clinical evaluation of exercise performance in individuals with PAH. Commonly, the 6MWT is used as a primary endpoint in clinical trials of pharmaceutical therapy in this patient population (42). The 6MWT is a valid, repeatable measure to objectively assess functional exercise capacity (43). The CPET is, however, considered the gold standard for determination of exercise intolerance in cardiopulmonary populations (44). The CPET provides information to distinguish between cardiovascular and pulmonary causes of exercise intolerance, as well as identify normal and abnormal cardiopulmonary responses to exercise (41). The CWLT

is increasingly being utilised in research and clinical settings because of its better prognostic power, characterisation of exercise intolerance, and increased responsiveness to the effects of therapeutic interventions (44, 45).

One study in the PAH population (46) has shown the 6MWT to be a maximal test, when using an unencouraged protocol. This study recruited 20 PAH participants in World Health Organisation functional class I to III, demonstrating a similar peak oxygen uptake is achieved on the 6MWT, when compared to the CPET (46).

To the best of my knowledge, comparisons of physiological and symptom outcomes during these three tests have yet to be reported in individuals with PAH.

1.6 Novelty and significance of this research

The studies described in this thesis are the first, in the PAH population, to:

iii. *Examine the validity and reliability of the CAMPHOR in an Australian and New Zealand population.*
This will enable the CAMPHOR to be used in clinical practice and research in this patient population.

iv. *Conduct a RCT to examine effects of a 12-week supervised, outpatient, whole-body exercise training program.*
The variability in exercise training protocols and settings in which the exercise training has been conducted, make it difficult to generalise findings and formulate recommendations for this patient population (47). This is the first RCT in PAH to conduct exercise training in the outpatient setting. Further, this is the first study in PAH to utilise a disease-specific HRQoL measure, the CAMPHOR, to assess the effects of exercise training on HRQoL. The findings of this program of research are clinically relevant and provide further evidence to support the use of exercise training in the PAH population.

v. *Determine whether an unsupervised home exercise program can maintain any benefits achieved following a supervised exercise training program.*

   Whether an unsupervised home exercise program can maintain benefits has clinical implications regarding the provision of maintenance exercise programs.

vi. *Compare the physiological and symptom outcomes on the CPET, CWLT and 6MWT.*

   Comparing the physiological and symptom outcomes across these tests will assist in describing the measurement properties of the tests and the utility of these tests for clinical practice.

Chapter 2

LITERATURE REVIEW

2.1 Overview

Pulmonary arterial hypertension (PAH) is a pulmonary vascular disease with a historically poor prognosis (5). Advances in the pharmaceutical management of PAH have led to improved survival (5), however, despite best available therapy, individuals commonly present with exertional symptoms, exercise intolerance and impaired health-related quality of life (HRQoL) (6). Exercise training has a well established role in improving symptoms, exercise capacity and HRQoL in other chronic respiratory and cardiovascular diseases (7-14), and a small number of studies have demonstrated similar benefit in the PAH population (6, 23, 28-33).

This chapter comprises five main sections. The first section (2.2) provides an overview of the classification and pathophysiology of PAH. The second section (2.3) outlines the factors contributing to exercise intolerance in this patient population. The third section (2.4) describes the cardiopulmonary exercise tests used to quantify exercise intolerance in PAH. Section 2.5 provides an overview of the current literature pertaining to exercise training in PAH, including a detailed summary of the outcomes of exercise training on exercise capacity and HRQoL. The final section (2.6) provides an overview of

the important factors in the assessment of HRQoL and the measures commonly used in PAH.

2.2 Pulmonary arterial hypertension: clinical classification, diagnosis, pathophysiology and epidemiology

This section outlines the clinical and functional classification of PAH, the process of diagnosing PAH, the aetiology and pathophysiology of PAH and the incidence, prevalence and survival in this patient population.

2.2.1 Clinical classification of pulmonary arterial hypertension

The clinical classification of pulmonary hypertension was revised in 2009 to reflect advances in the understanding and management of the condition (48). Endorsed by the World Health Organisation (WHO), a clinical classification system has been developed that categorises the different forms of pulmonary hypertension based on shared pathology, clinical features and therapeutic options (48, 49). Pulmonary arterial hypertension forms Group 1 of this classification system.

By definition, individuals with PAH have a pulmonary vascular disease whereby the primary abnormality lies within the small pulmonary arteries and arterioles (4). Further, PAH occurs in the absence of significant left heart disease, pulmonary disease or chronic thromboembolic disease (3).

Pulmonary arterial hypertension can occur in either an idiopathic form, or in association with other diseases or environmental exposures that are believed to be linked with genetically determined susceptibilities (3, 50). Idiopathic PAH (iPAH) occurs without any identifiable risk factor or family history of PAH (48). Familial PAH (fPAH), also known as heritable PAH, is most commonly associated with mutations in the bone morphogenetic protein receptor type II gene and is inherited as an autosomal dominant disease (4, 48). Pulmonary arterial hypertension associated with connective tissue disorders (aPAH) is reported to be most prevalent in individuals with the limited cutaneous form of systemic sclerosis, however, cases have also been

reported in individuals with diffuse systemic sclerosis, systemic lupus erythematosis and mixed connective tissue disease (4, 48). Other subgroups of PAH include drug and toxin-induced PAH and conditions associated with human immunodeficiency virus infection, portal hypertension and congenital heart diseases (48). This research has focussed on the role of exercise training in individuals with iPAH, fPAh and aPAH.

2.2.2 Diagnosis and assessment

2.2.2.1 Clinical presentation

Individuals with PAH present with exertional symptoms that have progressively worsened over months to years (3). Diagnosis can be delayed due to the non-specific symptoms experienced and the subtle findings on physical examination (2, 3). In the early stages of the disease, physical examination is often normal (2). Changes on physical examination become apparent as the disease progresses and include evidence of right heart failure (peripheral oedema, increased jugular venous pressure) and cyanosis (2).

2.2.2.2 Diagnostic evaluation

A comprehensive evaluation is required to detect and characterise PAH (3, 51). The aim of diagnosis is to: (i) determine the aetiology of PAH, according to the WHO clinical classification system, (ii) identify underlying causes that may be associated with the condition, (iii) determine the most appropriate medical therapy for the individual, and (iv) establish the likely prognosis (2).

Transthoracic echocardiography

The first diagnostic test is commonly echocardiography, a non-invasive procedure that allows estimation of pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR) (51). Additionally, echocardiography provides essential information regarding cardiac function for differential diagnosis (51, 52). An elevated PASP is indicative of pulmonary hypertension of any aetiology and, as such, is not specific to the diagnosis of PAH (2).

Determination of underlying causes

Identification of conditions that may be associated with the underlying cause of PAH is essential to determine aetiology and the most appropriate treatment strategy (4).

Changes on chest radiography typically associated with PAH comprise enlargement of the pulmonary arteries and dilatation of the right ventricle (RV) (3). Additionally, a high-resolution computed tomography scan may be performed to exclude parenchymal lung disease (2).

Spirometric indices are typically normal or demonstrate only mild restriction in individuals with iPAH (53) and aPAH (54). The diffusing capacity of the lung for carbon monoxide (D_LCO) is often moderately reduced (53, 54). Pulmonary function tests are used to exclude the contribution of underlying airway or parenchymal disease (2) to symptoms such as dyspnoea.

Haematology results provide useful information such as antinuclear antibody concentrations, which are high in individuals with connective tissue disorders. Full blood counts also provide useful information to characterise the condition and determine aetiology (2, 51).

Ventilation-perfusion scintigraphy may be performed to exclude the presence of pulmonary emboli (51) and the possibility of chronic thromboembolic pulmonary hypertension (2, 3, 51). An abdominal ultrasound and liver function tests may also be performed to identify liver disease and portal hypertension (2).

Invasive haemodynamic assessment (right heart catheterisation)

The gold standard for the assessment of PAH is right heart catheterisation (RHC) (2), however, RHC will only typically be performed once the suspicion of PAH is established through non-invasive means (3). Right heart catheterisation confirms the presence and severity of PAH, as well as providing important information regarding cardiac valve, ventricular and aortic function (2, 3, 51). Right heart catheterisation will also identify the presence of left heart disease and pulmonary veno-occlusive disease (2, 51). Acute

vasodilator response may be measured during the RHC to inform initial medical management (2, 51).

2.2.3 Aetiology and pathophysiology

Pulmonary arterial hypertension is clinically defined as a sustained increase in mean pulmonary artery pressure (PAP) greater than 25mmHg with a pulmonary capillary wedge pressure or left ventricular end diastolic pressure less than or equal to 15mmHg and an increased PVR greater than 3 Wood units (4).

Numerous biochemical pathways and cell types are known to be responsible for the pathophysiology associated with PAH. Vasoconstriction, pulmonary vascular remodelling, inflammation and thrombosis cause an increase in PVR (4, 55). A variety of mediators in the pulmonary circulation influence vascular tone, cellular growth and coagulation (4, 55, 56). Concentrations of mediators such as endothelin-1 and serotonin, responsible for vasoconstriction and cell proliferation, are increased in individuals with PAH (55, 56). In healthy individuals, prostacyclin, vasoactive intestinal peptide and nitric oxide, responsible for vasodilation and inhibition of the proliferation of pulmonary artery smooth muscle cells, provide a counterbalancing effect to optimise homeostasis, however, in PAH circulating concentrations of these mediators are reduced (4, 55, 56).

Histologically, all layers of the vessel wall are involved in the vascular remodelling which is characterised by proliferative and obstructive changes comprising intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion and plexiform lesions (55).

In healthy individuals, the mean PAP at rest is between 12 – 16mmHg (55). This low pressure results from the large cross-sectional area of the pulmonary circulation which creates a low resistance to blood flow and allows for a high volume of blood through the system (55, 57). In PAH, the increase in PVR in the pulmonary arteries and arterioles leads to an increase in PAP and consequently an impairment in blood flow, if the RV cannot generate sufficient pressure to increase flow. The impairment in blood flow,

caused by the rise in PVR, increases the load on the RV to move blood through the pulmonary circulation (24) and, consequently, RV afterload increases. Due to this increase in myocardial work, RV hypertrophy and dilatation occur (4), and as the disease progresses, eventually right heart failure ensues (2).

2.2.4 World Health Organisation functional classification system

In 1998, the WHO endorsed a modification of the New York Heart Association (NYHA) Functional Classification system for pulmonary hypertension (58). This system reflects disease progression and the extent of functional limitation caused by symptoms (58), as outlined in Table 2.1. Class I describes individuals who experience no limitation in functional capacity, progressing to class IV in which individuals are unable to perform any physical activity (without symptoms) and have symptoms at rest (58). Individuals in class I are not eligible for subsidised PAH-specific pharmaceutical therapy. Individuals in class II and III often remain symptomatic on exertion despite optimal therapy, whilst individuals in functional class IV are considered to have advanced disease with extensive vascular changes and are generally treated aggressively with intravenous therapy and, if appropriate, are listed for lung transplantation.

2.2.5 Medical management of PAH

The goals of treatment in PAH are to improve the patient's symptoms, HRQoL and survival (4). Pharmaceutical therapies aim to address the abnormalities in the small arteries and arterioles present in PAH, improving pulmonary haemodynamics (4). Current evidence suggests that the use of a combination of medical therapies are beneficial given the multiple mechanisms of action for different medications (4). Surgical intervention, namely lung transplantation, is considered for individuals whose condition progresses despite optimal medical management (4).

Table 2.1. World Health Organisation functional classification for pulmonary hypertension

Class I:	Individuals with pulmonary hypertension who do not experience any limitation in physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class II:	Individuals with pulmonary hypertension who experience a slight limitation in physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class III:	Individuals with pulmonary hypertension with marked limitation in physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV:	Individuals with pulmonary hypertension who are unable to carry out any physical activity without symptoms. These individuals manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Adapted from Rubin et al, 2004 (58)

2.2.6 Epidemiology and survival

Although the prevalence of PAH is estimated to be 40 cases/million in Australia, the incidence and prevalence of iPAH remains unknown (2). An epidemiological study in Scotland reported the incidence of iPAH to be 2.5/million per year in men and 4/million per year in women (59). An Australian study published in 2009 reported the prevalence of PAH in a group of 184 patients with scleroderma to be 13% (54).

Long term survival in individuals with PAH remains poor, with the majority of individuals dying of right heart failure (60). Advances in medical management, however, have lead to improved survival rates (3). Estimated survival rates from the National Institute of Health registry of 187 PAH patients in the United States were reported in 1987 as 68% at one year, 48%

at 3 years and 34% at 5 years (61). This compares with an analysis in 2007 of survival in a cohort of 576 patients who were listed on a PAH register in the United States that demonstrated the following survival rates: 84% at one year, 67% at 3 years and 58% at 5 years (62). Further, median survival time from diagnosis has improved from 2.8 years (61) to 3.6 years (62). Survival in individuals with aPAH has been reported to be worse than those with iPAH, despite the use of pharmaceutical therapy (48).

2.3 Factors contributing to exercise intolerance in pulmonary arterial hypertension

Individuals with PAH report symptoms of dyspnoea and fatigue on exertion which give rise to difficulty in performing activities of daily living and may lead to the avoidance of physical activity (6). Inactivity, and subsequent physical deconditioning (20), are likely to compound the functional limitations associated with PAH (21). This section outlines the factors that contribute to dyspnoea and fatigue and ultimately cause an impairment in exercise capacity in individuals with PAH.

2.3.1 Abnormal cardiopulmonary responses

2.3.1.1 Cardiopulmonary haemodynamics

Physiologically, the response of the pulmonary vasculature to exercise in individuals with PAH is markedly different to normal. In healthy individuals, the pulmonary arteries and arterioles distend and recruit previously quiescent vascular units to accommodate the increase in oxygen uptake ($\dot{V}O_2$) required for exercise (63). As a result, PVR decreases, pulmonary blood flow increases and the rise in PAP is minimised (27). An increase in the output from the RV increases blood flow through the pulmonary circulation to the left side of the heart to achieve the rise in cardiac output (CO) required for adequate oxygen delivery to the peripheral musculature (63). The initial increase in CO during exercise is normally achieved through an increase in stroke volume (SV) (63). As the intensity of exercise increases, further

increases in CO, required to meet the metabolic demands of exercise, are subsequently augmented by an increase in heart rate (HR) (63).

Due to the pathological vascular changes that characterise PAH, the pulmonary arteries and arterioles have an impaired capacity to vasodilate and distend. Consequently, PVR and PAP rise further with exercise and RV afterload increases. Right ventricular contractility is subsequently reduced and a rise in RV filling pressure occurs. As a result, pulmonary blood flow and left ventricular diastolic filling are reduced (24). The exercise-induced increase in PVR and PAP, which causes deterioration in RV function and under-filling of the left ventricle, leads to an impaired ability to increase SV in response to exercise (25), negatively impacting on CO. Consequently, CO is largely achieved through an increase in HR (25, 64-66). Several studies have, however, identified the presence of chronotropic incompetence in PAH, that results in an attenuated HR response to exercise and limits the increase in CO (66-70). The combination of impaired SV response, and the possibility of chronotropic incompetence, leads to an overall reduction in the delivery of oxygen to the peripheral muscles (65) and contributes to the symptoms of muscle fatigue and dyspnoea in this patient population (24, 27, 65). Further, minute ventilation (V'_E) has been shown to correlate with RV pressure (71). A rise in RV pressure has been shown to stimulate stretch receptors in the ventricle which cause an increase in V'_E, via sympathetic and vagal pathways (71), contributing to the sensation of dyspnoea.

2.3.1.2 Gas exchange

Hypoxaemia, defined as reduced partial pressure of oxygen in arterial blood (PaO_2), has been reported in PAH, at rest and during exercise (26). In PAH, hypoxaemia is thought to be due to several factors:

i. Limitation in the D_LCO is a common clinical finding and has been shown to be related to an impairment in pulmonary membrane diffusion capacity and, to a lesser extent, reduction in pulmonary capillary blood volume (72).

ii. Shunting through a patent foramen ovale, observed as a step-wise fall in oxygen saturation, results in poorly oxygenated blood re-entering the systemic circulation (65).
iii. Diminished red cell transit time (65) reduces the oxygen saturation of haemoglobin.
iv. Diminished pulmonary perfusion may lead to ventilation-perfusion mismatching (24) through the increase in physiologic dead space, due to poor perfusion of well ventilated alveoli (65).

The reduction in oxygen uptake in the lung contributes to less oxygen being delivered to the exercising muscles. Further, hypoxic pulmonary vasoconstriction occurs when the PaO_2 falls below 60mmHg (58). The resultant elevation in PVR is likely to lead to further cardiac compromise, compounding the impairment in oxygen delivery. Consequently, early development of lactic acidosis impacts negatively on cardiac function and results in greater muscle fatigability (65).

2.3.1.3 Cardiopulmonary and metabolic coupling

During an incremental cardiopulmonary exercise test (CPET) in a healthy individual, CO and $\dot{V}O_2$ progressively increase as work rate increases to meet the metabolic demands of the exercising muscles (63). Oxygen uptake increases linearly with an increase in HR (63). Furthermore, the increase in metabolic activity of the muscles causes an increase in carbon dioxide production ($\dot{V}CO_2$). Initially, $\dot{V}_E$ increases linearly with $\dot{V}CO_2$, however, as work rate increases, $\dot{V}CO_2$ increases disproportionately to the increase in $\dot{V}O_2$ when the anaerobic threshold (AT) is exceeded (63). At levels of exercise above the AT, metabolic acidosis stimulates $\dot{V}_E$ to reduce circulating carbon dioxide levels, reflecting a ventilatory compensation to regulate pH (63).

In individuals with PAH, the rate of increase in $\dot{V}O_2$ relative to the rate of increase in workload slows, due to RV dysfunction, limitations in gas exchange and the impaired ability to increase CO to raise muscle blood flow sufficiently to meet the oxygen requirements of exercising muscles (65, 73).

This suggests a higher than normal dependency on anaerobic metabolism (65) and an abnormality in oxygen delivery (26, 41), which is evidenced by a lower AT, as well as a reduced peak $V'O_2$ (41). Heart rate continues to increase with increasing workloads, such that HR increases more steeply relative to $V'O_2$ (73). This results in a lower than normal peak oxygen pulse ($V'O_2$/HR).

An increase in the ventilatory equivalent for carbon dioxide ($V'_E V'CO_2$) is a characteristic feature of PAH (65, 74, 75), however, there is contention in the literature as to the causative mechanism. One proposed mechanism relates to ventilation-perfusion mismatch resulting from impaired pulmonary perfusion (41, 65, 74, 76). The partial pressure of carbon dioxide in arterial blood and end-tidal carbon dioxide ($P_{ET}CO_2$) have, however, been reported to be reduced in PAH at rest, and during exercise (26). This suggests that the factors driving V'_E upwards, such as RV dysfunction and impaired oxygen delivery, causing in a greater increase in V'_E relative to $V'CO_2$, may be a more plausible explanation for the increased $V'_E V'CO_2$ observed in this population (26).

2.3.2 Peripheral endothelial dysfunction

The endothelium lines the internal surface of blood vessels and responds to shear stress from changes in haemodynamic forces and blood flow (77, 78). In response to an increase in shear stress in the endothelial surface, the endothelium releases vasoactive substances that induce vasodilation (77, 78). In healthy individuals, this endothelial response during exercise causes progressive vasodilation to optimise peripheral perfusion and, therefore, oxygen delivery to exercising muscles (78).

In individuals with chronic left heart failure, an impairment in endothelial response has been shown to increase peripheral vasoconstriction and reduce peripheral blood flow (79, 80). The resultant decrease in oxygen delivery to exercising skeletal muscle (79, 80) contributes to premature lactic acidosis and an impairment in exercise capacity (81). Whilst the underlying mechanism of PAH involves pulmonary endothelial dysfunction (4),

peripheral endothelial dysfunction has been reported in iPAH and aPAH (scleroderma) (82). This would suggest similar impairments in peripheral blood flow and oxygen delivery occur in PAH, which may further explain the exercise limitation in this patient population.

2.3.3 Morphological and functional changes of the skeletal musculature

Skeletal muscle dysfunction may also be implicated in the exercise limitation experienced by individuals with iPAH (20-23). Several studies have demonstrated significant morphological and functional changes in skeletal musculature, namely the respiratory (21, 83, 84), forearm (21) and quadriceps (22, 23) muscles. Functionally, impairment in muscle strength (21, 22, 83, 84) and endurance (23) has been reported. The abnormalities reported include a decrease in oxidative enzymes (22, 23), decreased mitochondria (22) and a relative increase in the proportion of easily fatigable type IIx muscle fibres (22). Consequently, these abnormalities result in the early onset of lactic acidosis and a reduction in aerobic capacity (22). These changes may be related to the reduction in systemic oxygen transport (20, 21) due to the impaired CO response to peripheral oxygen requirements (20).

Additionally, a 'muscle hypothesis' has been proposed whereby the symptoms of dyspnoea and fatigue may be related to dysfunctional skeletal muscle metaboreceptor and/or ergoreceptor reflexes (20) and increased sympathetic nervous system activation (85). The release of metabolites during exercise stimulate metaboreceptors which lead to a reflex increase in blood pressure and V'_E (86). Muscle ergoreceptors modulate haemodynamic, ventilatory and autonomic responses during exercise to maintain a metabolic equilibrium between muscle work and energy supply (87). On activation, ergoreceptors respond by increasing blood pressure, HR and V'_E (87). Skeletal muscle dysfunction has been reported in heart failure and results in persistent activation of these metaboreceptors and ergoreceptors causing an increase in sympathetic nerve activity which in turn increases PVR and decreases muscle perfusion (88). These responses increase V'_E and

contribute to the symptoms of dyspnoea and fatigue in individuals with heart failure (20, 88) and are likely to be present in PAH populations (20).

2.4 Assessment of exercise impairment in pulmonary arterial hypertension

Laboratory and field-based exercise tests are widely used to assess exercise capacity in individuals with PAH. A laboratory-based CPET is considered the gold standard for assessment of exercise capacity in cardiopulmonary populations (44). The CPET allows for the determination of the causes of exercise impairment which cannot be confidently predicted from resting physiological measures (41). The CPET is useful to distinguish between cardiovascular and pulmonary causes of exercise intolerance, as well as to identify normal and abnormal cardiopulmonary responses to exercise (41).

The six-minute walk test (6MWT) is the most commonly used field-based test in PAH. The 6MWT is a repeatable measure that objectively assesses functional exercise capacity (43). Peak $\dot{V}O_2$, measured on a CPET, and six-minute walk distance (6MWD) have been shown to have a strong, independent association with mortality in the PAH population (75, 89).

The results of pulmonary and cardiac function tests performed at rest correlate poorly with exertional symptoms and do not reliably predict exercise capacity in individuals with cardiopulmonary conditions (41, 44, 45, 69). For this reason, exercise testing provides essential information to determine the factors contributing to exercise impairment and evaluate an individual's exercise capacity (41). This section provides an outline of the laboratory and field-based exercise tests routinely performed to assess the exercise capacity of individuals with cardiopulmonary conditions.

2.4.1 Laboratory-based exercise testing: cardiopulmonary exercise tests

The CPET is considered the gold standard for evaluating exercise impairment in pulmonary and cardiac conditions (44). The test is widely used

to evaluate exercise-related symptoms, identify the causes of exercise intolerance and objectively determine exercise capacity and degree of impairment (41, 45). Indices derived from a CPET have proven to be better predictors of prognosis, compared to resting spirometric measures for example, and can provide useful information regarding the effect of therapeutic interventions (44). Additionally, the CPET derived indices provide important information to inform exercise training parameters for clinical safety (45) and are often used as a primary end point for the evaluation of exercise training programs (45).

The CPET allows for the analysis of the ventilatory, cardiovascular and skeletal muscle systems at a known exercise workload (90, 91). Simultaneous electrocardiogram (ECG), blood pressure, oxygen saturation and breath–by-breath measurements of gas exchange, provide a dynamic physiological overview of the exercise response to both submaximal and peak exercise performances (45, 90). Characteristic physiological abnormalities during exercise are observed in individuals with pulmonary and cardiac disease (44). The increased requirement for oxygen and removal of metabolic carbon dioxide during exercise requires the coordinated response of the cardiovascular and ventilatory systems to meet this demand (91). The CPET provides the information required to grade the adequacy of this coupling mechanism and to distinguish between cardiovascular and pulmonary causes of exercise intolerance (41).

2.4.1.1 Incremental CPET

The incremental CPET involves a progressively increasing workload to the point of symptom limitation, whereby the individual reaches a point of volitional exhaustion, or alternatively, the test is terminated by the supervising medical team for clinical safety reasons (45, 92). Protocols used for the CPET typically involve a phase of data collection at rest and a period of unloaded exercise, followed by the commencement of an incremental workload to test termination (45). The workload increments can be increased at a constant rate, for example every minute, or alternatively can be increased continuously in a ramp-like fashion (ramp protocol). Calculations

are available to determine the rate of workload increase, based on the individual's gender, height, weight, D_LCO and predicted $\dot{V}O_2$ (92). Individuals receive standard instructions and encouragement before the test and encouragement during the test to achieve a maximal effort (45, 92). Optimal duration of the incremental phase of the test is 8 to 12 minutes (93), however, the ideal test duration required to provide useful diagnostic information has been shown to vary depending on the patient population (94). The American Thoracic Society have developed criteria for test termination before symptom limitation occurs, to ensure the clinical safety of the patient (45).

Despite being more expensive and technically more challenging than field-based exercise tests, such as the 6MWT, the CPET is highly reproducible in PAH populations (95) and provides physiological information regarding the determinants of exercise impairment that cannot be obtained from field-based tests (44), unless a portable metabolic system is used.

2.4.1.2 Constant-workload cycle ergometry test

The constant workload cycle ergometry test (CWLT) is performed at a constant workload, most commonly 75-80% of the peak workload achieved during the CPET (41, 44). A CWLT protocol typically involves a phase of data collection at rest and during a period of unloaded cycling, followed by the commencement of the constant workload to test termination (45). Individuals are instructed to exercise for as long as possible, to symptom limitation.

The endurance time to exercise limitation is a useful indicator to monitor responses before and after therapeutic intervention (44, 45), with a longer endurance time reflecting an improvement in exercise tolerance (44). The CWLT has been shown to be a valid, reliable and reproducible measure of exercise endurance, with minimal learning effect, in individuals with chronic obstructive pulmonary disease (COPD) (96, 97).

Whilst the incremental CPET is useful to provide accurate assessment of exercise capacity and causes of exercise intolerance, the test is relatively insensitive to improvements in function following rehabilitation (41, 98). The

CWLT is increasingly being utilised in research and clinical settings because of its increased responsiveness to the effects of therapeutic interventions, in addition to its better prognostic power and characterisation of exercise intolerance (44, 45). The CWLT has been shown to be more responsive than the 6MWT in detecting improvement in exercise tolerance following exercise training and has demonstrated a stronger association with improvements in health status in individuals with COPD (99). In PAH, endurance time on a CWLT has been identified as an important clinical endpoint for monitoring response to therapy (5, 100).

To date, two studies have measured endurance time on a CWLT in iPAH populations following exercise training (23, 31). The study conducted by de Man and colleagues (23) recruited 19 participants, whilst the study by Mainguy et al (31) recruited 5 individuals. These studies reported improvements in endurance time of 89% (23) and 53% (31), respectively.

2.4.2 Field-based exercise testing: the six-minute walk test

The 6MWT measures the maximum distance walked by an individual during a six-minute period (43). The test is commonly used to assess functional exercise capacity in individuals with cardiopulmonary conditions (43, 101-104) and is among the most frequently used field-based outcome measures for determining the effectiveness of exercise training programs in these populations (14, 39, 105-107). The popularity of the 6MWT stems from its simplicity, minimal resource requirement and low cost (101, 103). Additionally, the 6MWT closely reflects daily activity, given that walking is an essential component of day-to-day tasks for most individuals (103, 108).

The 6MWT integrates the responses of all systems involved during exercise. However, it does not have the capacity to provide information regarding individual cardiopulmonary system responses, nor the causes of exercise impairment (109). Guidelines suggest the 6WMT provides complementary information to that obtained on an incremental CPET and CWLT and should not be considered as a replacement for these tests (43).

Exercise capacity, as measured by 6MWD, has been widely used in PAH-specific pharmaceutical trials as a primary endpoint (42). In the clinical evaluation of PAH, the 6MWT is routinely performed to provide information regarding disease severity, response to therapy and disease progression (42, 69). In the PAH population, 6MWD has been shown to correlate with haemodynamic variables at baseline (89, 110) and following the initiation of PAH-specific medication (111). Furthermore, 6MWD has been shown to correlate with WHO functional classification and peak $\dot{V}O_2$, and has been found to be a good predictor of morbidity and mortality in PAH (89). The 6MWT has been the only field-based test used in PAH. The incremental shuttle walk test and endurance shuttle walk test are other field-based exercise tests commonly used in chronic respiratory disease (9, 112-114) and heart failure (115, 116) populations.

The 6MWT is a self-paced test (43). In the PAH population, one study has demonstrated the 6MWT to be a maximal test in 20 individuals in functional class I-III, as evidenced by individuals achieving a similar peak $\dot{V}O_2$ to that achieved on a cycle ergometry CPET (46). The 6MWT protocol requires an individual to walk as far as possible during the 6 minutes, however they are permitted to slow down or stop and rest if necessary (43). The 6MWT has been found to be reproducible, with or without encouragement, providing the tests are performed in a consistent manner (117). Encouragement has, however, been shown to increase the distance walked (117). Further, whilst considered a reliable test, several studies in chronic respiratory disease (117-119) and heart failure (117, 120) groups have reported an increase of between 3% to 22% in the 6MWD achieved on a second test, indicating the presence of a learning effect. For this reason, it is considered appropriate to conduct two 6MWT prior to the commencement of a rehabilitation program to familiarise the individual and obtain their best result (118). The course length and layout has also been shown to significantly impact on the distance walked (121). However, in COPD, one study has demonstrated greater variability in distance walked by individuals when the test is performed on different days when compared to the changes in 6MWD seen from a modification of track layout (122).

Regression equations have been generated from population-based studies of healthy participants aged 40 to 85, to predict 6MWD and assist in quantifying the magnitude of disability experienced by an individual (123-125). Currently, two studies have reported on a minimally important difference (MID) in 6MWD in PAH populations. Gilbert and colleagues (126), analysed data from 207 participants enrolled in a PAH pharmaceutical study, used distribution-based (statistical) methods to estimate a MID of 41 metres. Mathai and colleagues (127), analysed data from 405 participants enrolled into a large PAH clinical trial, utilised both distributional and anchor-based (patient-related) methods and derived a MID of approximately 33 metres. The methodology employed in the latter study is recommended (128) whereby concurrent use of distributional and anchor-based approaches are utilised to determine a final MID value.

Concern regarding the potential for a 'ceiling effect' has been reported in clinical trials in PAH participants walking greater than 450m (129), which has led to the exclusion of these participants in many clinical trials (130-133). Degano and colleagues (42) conducted a study investigating the responses to PAH-specific pharmaceutical treatment in individuals with PAH who walked greater than 450m at baseline on an unencouraged 6MWT. The mean(SD) 6MWD in this group of 49 individuals was (491±42m) (42). Each of the 49 individuals was matched for haemodynamic measures with two participants (n=98) who had a 6MWD of less than 450m at baseline (335±81m) (42). This study demonstrated that both groups improved in terms of haemodynamic measures, however, those who had a 6MWD greater than 450m at baseline demonstrated a smaller magnitude of change in distance walked compared to those with a lower baseline functional capacity (<450m) (42). Specifically, the non-significant increase in 6MWD in the participants who walked >450m at baseline was 500±90m (data derived from Figure 1B) as compared to a mean increase of 65m ($p<0.0001$) in the group who walked <450m at baseline (42). As such, the 6MWT may not be the most suitable test for individuals who walk over 450m to reflect the response to an intervention. For this reason, in this study, exercise capacity

was measured not only by assessing change in 6MWD but also investigating measures on the incremental CPET and the CWLT.

2.5 Exercise training in pulmonary arterial hypertension

Historically, exercise training has not been utilised as a form of therapy in PAH (134) due to the perceived risk of sudden cardiac death and the theoretical possibility that exercise would lead to worsening pulmonary vascular haemodynamics and deterioration in right heart function (6). Despite advances in pharmaceutical therapies, which have resulted in improvements in exercise capacity, pulmonary haemodynamics and survival in individuals with PAH (4), exertional dyspnoea and fatigue continue to result in difficulty performing activities of daily living, lead to the avoidance of physical activity and adversely impact on HRQoL (6). This inactivity and the resultant physical deconditioning are likely to worsen the functional limitations associated with PAH (21). This section provides a brief description of the benefits of exercise training in cardiopulmonary populations and a detailed overview of the current literature, up until November 2012, that pertains to exercise training in PAH.

2.5.1 Benefits of exercise training in cardiopulmonary populations

Whilst there is a paucity of literature in the PAH population, the benefits of exercise training in individuals with other cardiopulmonary conditions are well established. Specifically, improvements in symptoms, exercise capacity, peripheral muscle function and HRQoL are well documented following exercise training in left-sided heart failure (7, 10, 12, 135-137) and in chronic respiratory disease (9, 11, 13, 38, 138), populations that both report exertional symptoms similar to PAH. These benefits have been achieved following supervised endurance exercise training, 2 to 3 times per week for a period of 6 to 12 weeks, at a target intensity of between 40% and 80% of peak exercise capacity (peak $\dot{V}O_2$ or maximum HR) (7, 10, 11, 137, 138). In COPD, programs of 12 weeks duration have been shown to produce greater and more sustained improvements in exercise outcomes when compared to programs of shorter duration (11, 138, 139).

2.5.2 Current evidence for exercise training in PAH

To date, only seven prospective studies (6, 23, 28-31, 33) and one case series (32) of exercise training in PAH populations have been published. These studies recruited participants with iPAH (n=210), aPAH (n=64) and chronic thromboembolic pulmonary hypertension (n=45) who were stable on medical therapy for a period greater than 3 to 6 months. Participants in these studies were in WHO functional classes II to IV. Table 2.2 summarises the participant inclusion criteria, exercise training regimes, testing protocols and outcomes of the prospective studies.

The exercise training regimen varied in these studies in terms of the frequency of sessions each week (ranging from 2 to 7), duration (7 to 15 weeks) and the exercise modalities (6, 23, 28-33). The types of exercises performed included cycle ergometry (6, 23, 28-33), walking (6, 29, 30, 33), upper limb exercises (6, 29-31, 33), breathing exercises (6, 29, 30, 33), yoga (6, 29, 30) and mental conditioning (6, 29, 30). The studies demonstrated significant improvements in exercise capacity as measured by an increase in: (i) $V'O_2$ peak (6, 28-30), (ii) $V'O_2$ at the AT (6, 23, 29, 30), (iii) endurance time on a CWLT (23), or (iv) 6MWD (6, 28-31, 33). Several of these studies reported significant improvements in muscle strength (23) and endurance (23, 31). Significant improvements in HRQoL on the Medical Outcomes Study Short Form 36 General Health Survey (SF-36) were reported in three studies (6, 29, 30), all of which utilised the same exercise training protocol. No serious adverse events during the exercise training sessions were reported in any of the studies. Further, Grünig and colleagues (29) demonstrated good long-term safety following closely supervised exercise training with two year survival rates of 100% and 95% which is comparable to rates reported in patients receiving pharmaceutical therapy alone. The studies to date have demonstrated improvements in exercise capacity in PAH (6, 23, 28, 31-33), however, the variability in exercise training protocols make it difficult to formulate recommendations and guidelines for exercise training in this patient population (47).

Uchi and colleagues (33) published the first exercise training study in PAH. This study recruited 24 individuals with PAH in functional class III and IV. Limited information is available regarding the exercise training protocol for this study because the paper is published in Japanese and only the abstract has been translated into English. The participants in this had recently commenced intravenous PAH therapy and thus it is not possible to differentiate between the benefits of exercise training and those attributed to the initiation of medication.

The three largest exercise training studies to date have been conducted by Mereles et al (6) and Grünig et al (29, 30). These three studies utilised the same study design whereby participants were admitted for an intensive 3-week, 7 day per week, inpatient training program prior to performing a 12-week home exercise program. The study published by Grünig et al (30) in 2012 reports findings from a new cohort of participants, whose results have not been published previously. A response has not been received by the authors of the study by Grünig and colleagues to confirm whether their study published in 2011 (29) is reporting the same cohort of increasing size to that of Mereles et al (6). In total, these three studies recruited 271 participants, however, in the study conducted by Grünig and colleagues (30) 44% of participants (n=80) were not reassessed following the 15 week intervention, largely due to issues with transport. Whist the results from these studies have demonstrated improvements in both exercise capacity and quality of life (6, 29, 30) the training programs have included a variety of modalities such as mental training and yoga (6), interventions that do not form part of most cardiopulmonary rehabilitation programs. Within Australia, most rehabilitation programs designed for respiratory or cardiac populations consist of whole-body exercise training and take place in hospital outpatient departments or in community settings (140, 141). In Australia, the resources for providing inpatient exercise training to individuals who are stable on medical therapy are limited (142) and as such, outpatient-based studies are required to determine the efficacy of exercise training in such settings.

Three PAH exercise training studies have conducted exercise training in the outpatient setting (23, 28, 31). The sample sizes in these studies, however, are relatively small. Fox and colleagues (28) recruited 22 participants, de

Man et al (23) recruited 19 individuals and Mainguy et al (31) recruited 5 participants. These studies required participants to attend one hour sessions, two (28) or three (23, 31) times per week for a period of 12 weeks with sessions focussing on lower limb endurance training. All three studies demonstrated improvements in exercise capacity. Fox and colleagues (28) were the only group to conduct a controlled trial, however, allocation to the control group in this study was non-random and based on the willingness of individuals to participate in the exercise training program. The non-random allocation to groups may reflect a bias towards motivated individuals and hence better outcomes in the exercise group may have occurred as a result. The study by de Man et al (23) comprised cycling and quadriceps training. The specificity of lower limb exercise training in this study (23) is likely to account for the large increase in endurance cycle time and may explain the non-significant improvement in 6MWD.

To date, the exercise training studies in PAH have only reported the immediate effects of exercise training and thus it remains unknown whether the benefits of improved exercise capacity and HRQoL can be maintained with the continuation of a home exercise program.

Table 2.2. Summary of prospective exercise training studies in pulmonary arterial hypertension

	Subjects and study design			Training protocol				Outcomes	
Author	Number (Diagnosis)	Study design	Inclusion criteria	Location	Modality	Intensity	Frequency and duration	Significant changes	Non-significant changes
Uchi et al° 2005 (33)	24 (iPAH)	Interventional	Severe heart failure Medical management including intravenous prostacyclin NYHA functional class III/IV		Breathing exercises Upper limb training Gait training Cycling Treadmill walking		30 to 60 minute sessions 5 times/week Average 6.7 weeks	6MWD* Resting heart rate* NYHA functional class* Lower limb strength*	
Mereles et al 2006 (6)	30 Exercise=15 Control=15 (iPAH, CTEPH)	Randomised controlled trial	Stable on PAH specific medical therapy for > 3 months; 18-75 years of age; WHO class II – IV; No recent syncope	(i) Hospital inpatient (ii) Home	(i) Cycling (interval training) Walking Mental training Single muscle group resistance training Respiratory training (ii) Cycling Walking Single muscle group resistance training Respiratory training	(i) 60 – 80% HR max achieved during CPET (limited to peak HR of 120bpm) (ii) 60 – 80% HR max achieved during CPET (limited to peak HR of 120bpm)	(i) 7 days/week, 3 weeks (ii) 7 days/week 12 weeks	22% ↑ 6MWD*† 17% ↑ peak V'_{O_2}*† 29% ↑ peak workload*† 17% ↑ V'_{O_2} at AT *† 44% ↑ workload at AT *† 12% ↑ HRmax*† QoL† WHO class†	
de Man et al 2009 (23)	19 (iPAH)	Interventional	No change in (i) 6MWD ≥ 10% in ≥ 12 months, (ii) medical therapy ≥ 3 months; ≥ 18years of age; Reside within 5km of rehabilitation centre	Outpatient rehabilitation centre	(i) Cycling (ii) Quadriceps endurance training (iii) Quadriceps strength training	(i) 50 – 75% VO_2 max (ii) 30 – 40% ORM (iii) 50 – 75% ORM	3 times/week 12 weeks	89% ↑ endurance time* 44% ↑ workload at AT* Quadriceps endurance* Quadriceps muscle strength * Quadriceps capillarisation *	Peak V'_{O_2} 6MWD

Studies ordered by publication date; aPAH: pulmonary arterial hypertension associated with other conditions; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; CTEPH: chronic thromboembolic pulmonary hypertension; HRmax: maximum heart rate; iPAH: idiopathic pulmonary arterial hypertension; max: maximum; MVC: maximal voluntary contraction; NYHA: New York Heart Association; ORM: one repetition maximum; PH: pulmonary hypertension; QoL: quality of life; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; V'_{O_2}: oxygen uptake; WHO class: World Health Organisation functional class; V'_{O_2}: oxygen uptake; WHO: World Health Organisation; 6MWD: six minute walk distance; ↑: increase; *p<0.05 from baseline; †p<0.05 vs change in control group; °Abstract only published in English, limited information available.

Table 2.2. (continued) Summary of prospective exercise training studies in pulmonary arterial hypertension

Author	Subjects and study design			Training protocol				Outcomes	
	Number (Diagnosis)	Study design	Inclusion criteria	Location	Modality	Intensity	Frequency and duration	Significant changes	Non-significant changes
Mainguy et al 2010 (31)	5 (iPAH)	Interventional	WHO class II/III; No change in medical therapy ≥ 6 months	Hospital-based outpatient department	(i) Cycling (ii) Treadmill walking (iii) Single muscle group resistance training	(i) 60% max CPET workload (ii) 85% 6MWT speed (iii) 70% MVC	1 hour/session 3 times/week 12 weeks	13% ↑ 6MWD* Proportion type IIx muscle fibres (decreased)* 15% ↓ V'_E at isotime* 8% ↓ $V'_EV'CO_2$ at isotime*	53% ↑ endurance time
Fox et al 2011 (28)	22 Exercise=11 Control=11 (iPAH, aPAH, CTEPH)	Controlled trial	Stable on PAH-specific medication ≥ 3 months; NYHA class II/III; ≥18years of age	Outpatient rehabilitation centre	1st 6 weeks: Interval aerobic training 2nd 6 weeks: Continuous aerobic training and resistance training Aerobic home exercise program	60 – 80% HR max achieved during CPET	1 hour/session 2 times/week 12 weeks Home ex program daily	9% ↑ 6MWD*† 13% ↑ peak V'_{O_2}† 17% ↑ peak V'_E *	38% ↑ peak workload 21% ↑ oxygen pulse
Grünig et al 2011 (29)	58 (iPAH, aPAH, CTEPH, other forms of PH)	Interventional	Right heart failure; Stable on PAH specific medical therapy for > 3 months; > 18 years of age; WHO class II - IV	As described for Mereles, 2006	As described for Mereles, 2006	As described for Mereles, 2006)	As described for Mereles, 2006	20% ↑ 6MWD* 17% ↑ peak V'_{O_2}* 14% ↑ V'_{O_2} at AT * 19% ↑ peak V'_E * 8% ↑ HRmax* QoL* WHO class*	
Grünig et al 2012 (30)	183 (iPAH, aPAH, CTEPH, other forms of PH)	Interventional	Stable on optimal medical therapy for > 2 months; 18-80 years of age; WHO class II - IV	As described for Mereles, 2006	As described for Mereles, 2006	As described for Mereles, 2006	As described for Mereles, 2006	19% ↑ 6MWD* 11% ↑ peak V'_{O_2}* 14% ↑ V'_{O_2} at AT * 3% ↑ oxygen pulse* 9% ↑ HRmax* QoL* WHO class*	

Studies ordered by publication date; aPAH: pulmonary arterial hypertension associated with other conditions; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; CTEPH: chronic thromboembolic pulmonary hypertension; HRmax: maximum heart rate; iPAH: idiopathic pulmonary arterial hypertension; max: maximum; MVC: maximal voluntary contraction; NYHA: New York Heart Association; ORM: one repetition maximum; PH: pulmonary hypertension; QoL: quality of life; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; V'_{O_2}: oxygen uptake; WHO class: World Health Organisation functional class; 6MWD: six minute walk distance; ↑: increase; ↓: decrease; *p<0.05 from baseline; †p<0.05 vs change in control group; °Abstract only published in English, limited information available.

2.6 Assessment of health-related quality of life in pulmonary arterial hypertension

Health-related quality of life can be defined as an individual's perception and reaction to health related issues, such as physical, emotional and mental wellbeing, as well as non-medical aspects of life, such as relationships, occupation and social standing (143). Measuring HRQoL is important to provide an overall indication of an individual's wellbeing, combining the physical, psychological and social factors that influence one's general health status (144).

Individuals with the same clinical presentation commonly have very different responses to a disease process and its associated treatment (145). Moreover, resting physiological measures often correlate poorly with functional capacity and feelings of wellbeing (145, 146). Further, improvements following treatment that are statistically significant do not necessarily correspond with a clinical benefit for the individual (147). Consequently, measuring HRQoL is imperative to individualising patient presentations and, as such, provides an important clinical endpoint in the measurement of treatment effectiveness (145).

The importance of valid and responsive HRQoL measurement is increasingly being recognised due to: (i) a shift over time from infectious to chronic diseases, (ii) advances in medical management resulting in the prolonging of life despite significant illness, and (iii) increasing limitations on resources in the health sector (148).

This section details the measurement of HRQoL using both generic and disease-specific instruments, the important psychometric properties of assessment tools and the assessment of HRQoL in the PAH population.

2.6.1 Measurement of health-related quality of life

Quantifying HRQoL is a complex task that is best achieved through the use of various domains, such as symptoms, physical function and disability (149).

Health-related quality of life is typically evaluated according to the item-measurement theory whereby a series of questions, or items, can indirectly measure the same concept or construct (149). The responses to each item are then converted to numerical values to yield an overall score (149).

The evaluation of HRQoL has historically been approached in two ways, utilising generic or disease-specific instruments.

2.6.1.1 Generic assessment instruments

Generic instruments are utilised to summarise HRQoL and encompass a broad range of quality of life dimensions (150). These instruments are used widely to assess HRQoL for a variety of conditions and populations (145). Generic tools are useful to compare disease states and for conducting general health research through population studies (149).

Generic instruments attempt to evaluate all important aspects of HRQoL. As a result, generic health profiles are useful for population studies, whereby broad comparisons of the relative impact of various conditions and/or interventions can be made (145). These tools provide individual dimension scores and, when appropriate, can also be used to provide an aggregate score (150). Commonly used examples of generic instruments include the SF-36 and the Nottingham Health Profile.

2.6.1.2 Disease-specific assessment instruments

Disease-specific HRQoL instruments explore the problems associated with specific conditions or diseases such as symptoms and activity limitations (145, 148). These instruments are potentially more responsive to change because they include important aspects of HRQoL relevant to that population, such as physical, emotional and social function (19, 145, 151, 152). Additionally, disease-specific instruments have the benefit of relating closely to patient outcome measures commonly analysed by clinicians (145). Hence, to accurately reflect changes in HRQoL associated with therapeutic intervention, disease-specific measures are most appropriate (149).

2.6.2 Psychometric properties of HRQoL instruments

The assessment of the psychometric properties of a HRQoL instrument assist in determining whether the tool is useful for the intended purpose (150). These properties comprise:

2.6.2.1 Appropriateness/Coverage

Quality of life instruments need to be relevant to the patient population being studied. That is, the components of health that are likely to be affected, positively or negatively, by intervention or change over time (135, 149).

2.6.2.2 Reliability

A HRQoL instrument must yield consistent results under constant conditions with low associated random error measurements (149). This means that an instrument should produce the same results on repeated administrations under the same conditions (135).

Internal reliability is commonly used to establish reliability, whereby the degree of agreement of items measuring comparable concepts is examined (135). Additionally, test-retest reliability is often performed to ensure the instrument produces the same results with multiple administrations (135).

2.6.2.3 Validity

Validation refers to the ongoing examination of the instrument in different contexts to ensure that it measures what it is suggested to measure (148). Construct validity demonstrates the ability of the instrument to accurately represent the concept, or area, of interest (148). Content validity is associated with the ability of the items to reflect the extensive domain of HRQoL (148). Criterion validity includes convergent and discriminant validity. Convergent validity refers to the ability of an instrument to correlate with another measure purported to measure a similar factor or construct (153), for example symptoms. Discriminant validity demonstrates the ability of an instrument to discriminate between different groups (153) based on, for example, disease severity.

2.6.2.4 Responsiveness and sensitivity

Health-related quality of life instruments should be designed such that they are responsive, that is, that they have the ability to detect change (19, 149). Sensitivity refers to the ability of an instrument to accurately reflect the magnitude of change from baseline (149). A HRQoL instrument can be responsive to change, however, may not adequately reflect the magnitude of change due to issues such as inadequate response choices (149). Lack of sensitivity, therefore, can mask clinically meaningful changes in HRQoL (149).

Responsiveness and sensitivity may be reduced when items included in the HRQoL instrument are not relevant to a particular disease or population (135). Additionally, instruments will appear less responsive and sensitive when items are chosen that are not feasible outcomes of health care intervention, for example personal relationships (135). Finally, HRQoL instruments may be subject to floor and ceiling effects where, for example, a patient's reported HRQoL at baseline is maximal and as a result there may be no scope to exhibit any improvement (135).

2.6.3 Mode of administration

Health-related quality of life instruments can be administered in several ways. Interviewer-led tools can be delivered face-to-face or over the telephone. Questionnaires administered by an interviewer require resources and training (150). Increasingly, self-administered questionnaires are being utilised due to their economy of use (135).

Self-administered and interviewer-led questionnaires have demonstrated similar results in discriminating between an individual's HRQoL (154, 155). Interviewer-led administration has been shown to provide a more optimistic view of HRQoL when compared to the self-administered mode of delivery (156). Further, the responsiveness of self-administered questionnaires has been shown to be greater than interviewer-led versions (157). This increase in responsiveness following intervention may be attributed to a individual's willingness to declare severe limitation in the absence of an interviewer (157).

2.6.4 Quality of life assessment in PAH

In the PAH population, patient-reported outcomes have been measured using generic tools, commonly the SF-36 (158). The SF-36 is a 36 item, self-administered health survey that has demonstrated validity and internal consistency in healthy populations and those with specific conditions, including PAH (159, 160). The questionnaire has eight domains that assess components of physical and mental health and includes an additional health transition item that is not scored. Each domain is scored separately with a lower score indicating a greater level of impairment. However, as the SF-36 is a generic measure and was developed before modern psychometric techniques became available, it has poor scaling properties and limited reproducibility and responsiveness (161).

Cardiac and respiratory-specific patient-reported outcome measures have also been utilised in the PAH population as they explore similar constructs such as dyspnoea, fatigue and activity limitation (144, 160, 162-164). In PAH, the validity of using disease-specific measures developed for a different patient population remains questionable.

Disease-specific patient-reported outcome measures are more responsive to change given that they measure only the aspects that are relevant to the population (145). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a disease-specific HRQoL measure for PAH, developed in the United Kingdom (UK). The CAMPHOR is a 65-item, self-administered questionnaire with content derived from qualitative interviews with patients diagnosed with PAH and chronic thromboembolic pulmonary hypertension (15). The CAMPHOR has three scales that measure: (i) overall symptoms (such as fatigue and dyspnoea), (ii) activity limitations and (iii) quality of life. The Symptoms and Quality of life scales are answered using a dichotomous scale. The Activities scale has a three-point response format. The CAMPHOR scales are scored separately with a higher score indicating a greater level of impairment. These scales have been shown to be unidimensional and to have good reproducibility and construct validity (15). The CAMPHOR has been shown to be reliable and valid in the UK (15), the

United States of America (16) Canada (17) and Germany (18). Validation of the CAMPHOR for an Australian and New Zealand PAH population has been completed as part of this program of research (Chapter 3).

2.7 Conclusion

Exertional symptoms of dyspnoea and fatigue are common in individuals with PAH, despite advances in pharmaceutical management. The cause of these symptoms is multifactorial and includes right ventricular dysfunction, impaired gas exchange and an attenuated CO response to exercise, resulting in a limitation in the delivery of oxygen to exercising muscles. Peripheral endothelial and skeletal muscle dysfunction also contribute to exercise intolerance in PAH. Consequently, individuals with PAH experience difficulty performing activities of daily living, which leads to the avoidance of physical activity and adversely impacts on HRQoL.

The CAMPHOR is the only available disease-specific HRQoL measure for the PAH population. The CAMPHOR has been shown to be a valid and reliable tool for individuals with PAH in the UK, the United States of America, Canada and Germany. Validation of the CAMPHOR is necessary in the Australian and New Zealand PAH population to enable its use in clinical and research settings.

Exercise training is a well established intervention in other chronic respiratory and cardiac disease populations with demonstrable benefits in terms of improvements in symptoms, exercise capacity, peripheral endothelial and skeletal muscle function, and HRQoL. A small number of studies have investigated the benefits of supervised exercise training in individuals with stable PAH and reported improvements in exercise capacity, skeletal muscle function and HRQoL, in the absence of serious adverse events. The current studies have reported improved outcomes following exercise training, however, the training protocols have varied making it difficult to determine which training strategies are most appropriate in this patient population. As such, further research is required to investigate the effects of exercise training in the outpatient setting. Importantly, the previous studies have not

measured the effects of exercise training on HRQoL, as measured using a disease-specific tool.

Further, the benefits of exercise training have been shown to occur following short term, supervised exercise training programs. Further research is required to determine whether benefits achieved during a supervised period can be maintained with an unsupervised home exercise program.

Chapter 3

THE CAMBRIDGE PULMONARY HYPERTENSION OUTCOME REVIEW: VALIDATION FOR THE AUSTRALIAN AND NEW ZEALAND PULMONARY ARTERIAL HYPERTENSION POPULATION

3.1 Overview

The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is the only available disease-specific health-related quality of life (HRQoL) measure for the pulmonary arterial hypertension (PAH) population (15). The CAMPHOR was developed by Galen Research, in collaboration with the Papworth Hospital Pulmonary Vascular Disease Unit, in the United Kingdom (UK) and has subsequently been validated in the UK (15), the United States of America (16), Canada (17) and Germany (18). This Chapter outlines the methodology and results for the validation of the CAMPHOR for the Australian and New Zealand population and provides a discussion on the implications for its use in this population. The results of this study have been published in a peer-reviewed journal (165).

3.2 Methods

Data collection for this study was completed between March 2008 and February 2009. Participants were recruited from PAH-specialist centres in Australia and New Zealand.

3.2.1 Study Design

This study comprised two parts: (i) field interviews to assess the face and content validity of the CAMPHOR and (ii) a validation study, in which the CAMPHOR and the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF-36) were mailed to participants, in order to examine test-retest reliability, internal consistency and construct validity of the CAMPHOR.

The CAMPHOR has three scales, namely Symptoms, Activities and Quality of Life (QoL). The Symptoms and Quality of life scales have 25 items each, are answered using a dichotomous scale and have a total score of 25 per scale. The Activities scale has 15 items, a three-point response format and a total score of 30. The CAMPHOR scales are scored separately with a higher score indicating a greater level of impairment.

The SF-36 questionnaire has eight domains that assess components of physical and mental health. Each domain is calculated based on an aggregate percentage score, which ranges from 0% to 100%. A lower score on the SF-36, indicates a greater level of impairment.

3.2.2 Ethics approval and trial registration

The study was approved by the Human Research Ethics Committee (HREC) at Curtin University (approval number HR 143/2007) and the PAH-specialist centres involved in each part of the study, as outlined below. The study was registered with the Australian New Zealand Clinical Trials Registry on the 18th March 2008 (ACTRN12608000139370).

3.2.2.1 Face and content validity

Approval for investigating the face and content validity of the CAMPHOR was also obtained from the HREC at Royal Perth Hospital (approval number EC 2008/055).

3.2.2.2 Reliability, internal consistency and construct validity

Approval for postal validation study was also obtained from the HREC at the following six PAH-specialist centres:

Royal Perth Hospital (Western Australia): EC 2008/055

St Vincent's Hospital (New South Wales): SVH file number 08/046

The Prince Charles Hospital (Queensland): EC 2858

The Royal Adelaide Hospital (South Australia): RAH protocol number 080516

The Alfred Hospital (Victoria): Project number 146/08

Christchurch Hospital (New Zealand): URB/08/22/EXP

3.2.3 Inclusion criteria

Individuals were considered for inclusion in the study if they were over 18 years of age, had a confirmed diagnosis of PAH according to the World Health Organisation (WHO) Diagnostic Classification (Group 1), and were native English speaking (166). Only individuals in Group 1 were studied because this group shares the same pathology, clinical features and therapeutic options (48). The WHO diagnostic classification was determined by the patient's PAH physician at the time of diagnosis.

Individuals were excluded if they were unable to complete the questionnaires due to cognitive impairment or if they had clinically significant cardiovascular or pulmonary co-morbidities.

3.2.4 Face and content validity

3.2.4.1 Participant recruitment

Participants were recruited from the Western Australian (WA) State Pulmonary Hypertension Service, at Royal Perth Hospital, WA. Participants were randomly selected from among the PAH patients registered with the WA State Pulmonary Hypertension Service and contacted via telephone to invite them to participate in the study. Written, informed consent was obtained from the participants prior to data collection.

3.2.4.2 Interviews

Interviews were conducted at the participant's home (n=13) or at Royal Perth Hospital (n=2). Participants were required to complete the CAMPHOR in the presence of an interviewer (LG). This was followed by a semi-structured interview (Appendix 1) to determine whether the content of the CAMPHOR was relevant and whether the terminology and language used were appropriate and could be understood. Further questions were asked of the participants if difficulties had arisen during completion of the CAMPHOR, for example, a prolonged time to complete a specific item or perceived ambiguities in the language or phrasing of items.

3.2.4.3 Data management and analysis

The distributional properties of the CAMPHOR were examined using descriptive statistics. Individual responses to the interview questions were collated and a report generated for Galen Research, developer and copyright holder for the CAMPHOR (Appendix 2).

3.2.5 Reliability, internal consistency and construct validity

3.2.5.1 Participant recruitment

Participants were recruited from specialist PAH centres in WA, New South Wales, Queensland, South Australia, Victoria and New Zealand. Participants were required to complete the CAMPHOR and a generic HRQoL measure, the SF-36.

3.2.5.2 Questionnaire completion

The questionnaires were sent to participants with the instruction to refrain from completing them until they had been contacted by an investigator (LG) to discuss the study procedures. Participants completed the SF-36 immediately followed by the CAMPHOR, on two occasions, two weeks apart (Time 1 [T1] and Time 2 [T2]). Participants were instructed to place the completed questionnaires in a sealed envelope, following completion on the first occasion [T1], thereby concealing their responses for the second occasion [T2]. All participants were reminded, via telephone, to complete the second questionnaire, in an attempt to optimise completion and return rates.

3.2.5.3 Data management and statistical analyses

Sample size calculation

As PAH is a rare disease, the study aimed to recruit as many individuals with PAH as possible, within the study timeframe. A minimum sample size of 50 was chosen based on a study that sought to evaluate an adaptation of the CAMPHOR for a Canadian population with PAH [24]. Allowing for a response rate of 75% (15), at least 67 participants were required. Verbal agreement to be involved in the study was obtained from participants at each PAH centre prior to sending out the questionnaires. Formal consent was implied by the return of the questionnaires.

Data management

CAMPHOR data management

CAMPHOR data were entered into a spreadsheet created using Microsoft Office Excel (2003). The data were checked for missing items. Missing items were not replaced with estimation values. In the instance where the number of missing items exceeded 20% of the total number of items for a scale on the CAMPHOR, the scale score was rendered missing.

SF-36 data management

SF-36 data were entered into the QualityMetric Health Outcomes™ Scoring Software 4.0 (167). The data were checked for missing items. Missing items were not replaced with estimation values. In the instance where the number of missing items exceeded 50% of the total number of items for a domain on the SF-36, the scoring software rendered a domain score as missing. Data outputs were exported into Microsoft Office Excel (2003) spreadsheets.

Statistical analyses

Data were analysed using non-parametric statistical tests (SPSS® Version 17.0; SPSS Inc.; Chicago, USA).

Distributional properties

The distributional properties of the CAMPHOR were examined using descriptive statistics. Floor and ceiling effects were determined as the percentages of individuals scoring the minimum and maximum scores possible on each scale, respectively. Large floor or ceiling effects indicate the scale lacks sensitivity and/or relevance.

Reliability and internal consistency

Test-retest reliability of the CAMPHOR was examined using Spearman's rank correlation coefficients. A correlation coefficient of ≥0.85 is required for low random error (168). Internal consistency was assessed using Cronbach's alpha coefficients. For items within one scale to be sufficiently related, an alpha of greater than 0.70 is required (169).

To further assess test-retest reliability, an intraclass correlation coefficient (ICC) was used (170). The weighted kappa (171) was used to determine the concordance of the responses between T1 and T2 for the CAMPHOR scales and the individual items within each scale. The chance-corrected proportion of agreement varies between -1 and 1 with zero indicating chance agreement, a positive value indicating better than chance agreement and a negative value indicating worse than chance agreement (171). The reference values for the strength of agreement are described by Altman (172) as follows: poor

<0.20, fair 0.21 – 0.40, moderate 0.41 – 0.60, good 0.61 – 0.80, very good 0.81 – 1.00. Further, agreement between administrations for each CAMPHOR scale was examined visually and analysed according to the methods described by Bland and Altman (173).

Construct validity

Construct validity was analysed by examining convergent, divergent and known groups validity.

Associations between CAMPHOR scale scores and the SF-36 domains were examined using Spearman's rank correlation coefficients to examine convergent and divergent validity. Higher correlations were expected between CAMPHOR scales and SF-36 domains that measure similar constructs, for example, the Activities scale on the CAMPHOR and the Physical Functioning domain on the SF-36.

Known groups validity was assessed by investigating whether CAMPHOR scores were able to distinguish between participants based on their WHO functional classification using a Mann-Whitney U Test. An alpha (*p)* value of <0.05 was considered statistically significant.

3.3 Results: CAMPHOR

3.3.1 Face and content validity

Fifteen participants completed field interviews. The characteristics of these participants are summarised in Table 3.1 (part 1). The mean time taken to complete the CAMPHOR was 9.5 minutes (range 6 to 15 minutes). All participants found the CAMPHOR easy to understand and complete, thought it asked relevant questions and considered all items acceptable.

3.3.2 Reliability, internal consistency and construct validity

Seventy-six participants were recruited from the six PAH-specialist centres. Responses were received from 65 individuals (86% response rate from those who gave verbal consent) with 61 individuals meeting the inclusion criteria.

The characteristics of these 61 participants are shown in Table 3.1 (part 2). Of the individuals excluded from the study, two had a diagnosis of pulmonary hypertension secondary to lung disease and two individuals had a diagnosis of chronic thromboembolic pulmonary hypertension.

The mean time between completion of the questionnaires at T1 and T2 was 15.3 days (range 11 to 33 days).

Missing items only exceeded 20% once for the CAMPHOR Symptom scale at T1. Four SF-36 domains were affected by missing data at T1, resulting in a total of five missing domain scores (Physical Functioning [n=2], Role Physical [n=1], General Health [n=1] and Role Emotional [n=1]). Five SF-36 domains had missing data at T2, resulting in a total of 8 missing domain scores (Physical Functioning [n=2], Role Physical [n=1], Bodily Pain [n=1], General Health [n=3] and Social Functioning [n=1]).

Table 3.1. Characteristics of the study participants

	Part 1 Field interviews (n=15)	**Part 2 Postal validation (n=61)**
Female	11 (73)	48 (79)
Age, years	68.9±10.0	56.9±14.5
Idiopathic PAH	9 (60)	37 (60)
Familial PAH	1 (7)	1 (2)
Associated PAH		
Connective tissue disease	5 (33)	18 (30)
Congenital heart disease	0	3 (5)
Portal hypertension	0	2 (3)
WHO Functional Classification		
Class I	2 (13)	3 (5)
Class II	8 (54)	18 (29)
Class III	5 (33)	36 (59)
Class IV	0	4 (7)
Recruiting site		
Western Australia	15 (100)	9 (15)
New South Wales		7 (11)
Queensland		12 (20)
South Australia		9 (15)
Victoria		15 (24)
New Zealand		9 (15)

Data are presented as number of participants (n) with percentages given in parentheses or as mean±SD; PAH: pulmonary arterial hypertension; WHO: World Health Organisation.

Distributional properties

The descriptive statistics for the CAMPHOR scales at T1 and T2 are shown in Table 3.2. Minimal floor and ceiling effects were identified.

3.3.2.1 Test-retest reliability

The test-retest correlation coefficients for the CAMPHOR scales were: Symptoms 0.86, Activities 0.87 and QoL 0.94 (all $p<0.01$). The ICC for the three CAMPHOR scales indicated very good agreement in the responses between T1 and T2 (Table 3.3).

Figure 3.1 outlines the mean difference in CAMPHOR scale scores between T1 and T2. Using the methods described by Bland and Altman (173), the mean difference in the Symptom scores was 0.7 with a limit of agreement (LOA) of 6.5. The upper and lower LOA for the Symptoms scale occurred at 7.2 (95% confidence interval (CI): 5.7 to 8.7) and -5.9 (95% CI: -7.4 to -4.4), respectively. The mean difference in the Activities scores was -1.0 with a LOA of 6.6. The upper and lower LOA for the Activities scale occurred at 5.7 (95% CI: 4.2 to 7.2) and -7.6 (95% CI: -9.1 to -6.1), respectively. The mean difference in the QoL scores was -0.4 with a LOA of 4.2. The upper and lower LOA for the QoL scale occurred at 3.8 (95% CI: 2.8 to 4.7) and -4.6 (95% CI: -5.5 to -3.7), respectively.

3.3.2.2 Internal consistency

The Cronbach's alpha coefficients for the three CAMPHOR scales at each time point are given in Table 3.3.

3.3.2.3 Construct validity

Convergent and divergent validity

Table 3.4 shows the correlation coefficients for the associations between scores obtained on the CAMPHOR and SF-36. The Symptom and QoL scales of the CAMPHOR had the strongest correlations ($r_s \geq 0.65$) with the Vitality, Mental Health and Social Functioning domains of the SF-36. The

Activities scale of the CAMPHOR had the strongest correlation with Physical Functioning domain of the SF-36 ($r_s \geq 0.75$).

Known Groups Validity

There were no significant differences in the mean CAMPHOR scale scores between participants grouped by gender or age (above and below the median). However, individuals with more severe disease, as indicated by a higher WHO functional classification (Class III and IV), had significantly higher CAMPHOR scores for all three scales at both time points ($p<0.05$) when compared to participants in WHO functional classes I and II. Figure 3.2 illustrates the mean CAMPHOR scores at T1 and T2, with participants stratified according to WHO functional classification.

Table 3.2. Descriptive statistics for CAMPHOR scale scores (n=61)

Scale	T1 Median (IQR)	T2 Median (IQR)	T1 Range	T2 Range	T1 Floor Effect (%)	T2 Floor Effect (%)	T1 Ceiling Effect (%)	T2 Ceiling Effect (%)
Symptoms	14 (8 –18.5)	13 (7 – 17)	2 – 23	1 – 25	0	0	0	1.6
Activities	9 (4 – 14.5)	10 (6 – 15)	0 – 24	0 – 23	3.3	4.9	0	0
QoL	11 (5 – 16)	12 (5 – 16)	0 – 23	0 – 23	4.9	1.6	0	0

T1: time point 1; T2: time point 2; IRQ: inter-quartile range; QoL: Quality of Life.

Table 3.3. Reliability and internal consistency for the CAMPHOR scale scores (n=61)

Scale	T1 Mean±SD	T2 Mean±SD	Mean difference between T1 & T2 (95% CI)	ICC (95% CI)	Test-retest correlation coefficient (r_s)	T1 Cronbach's alpha coefficient	T2 Cronbach's alpha coefficient
Symptoms	13.1±5.9	12.6±6.0	2.2 (1.6 – 2.8)	0.86 (0.79 – 0.93)	0.86*	0.89	0.90
Activities	9.9±5.9	10.9±6.2	2.4 (1.7 – 3.1)	0.83 (0.72 – 0.95)	0.87*	0.92	0.91
QoL	10.6±6.4	11.0±6.3	1.6 (1.3 – 2.0)	0.94 (0.92 – 0.97)	0.94*	0.91	0.90

T1: time point 1; T2: time point 2; SD: standard deviation; CI: confidence interval; ICC: intraclass correlation coefficient; r_s; Spearman's rank correlation coefficient inter-quartile range; QoL: Quality of Life; *p<0.01.

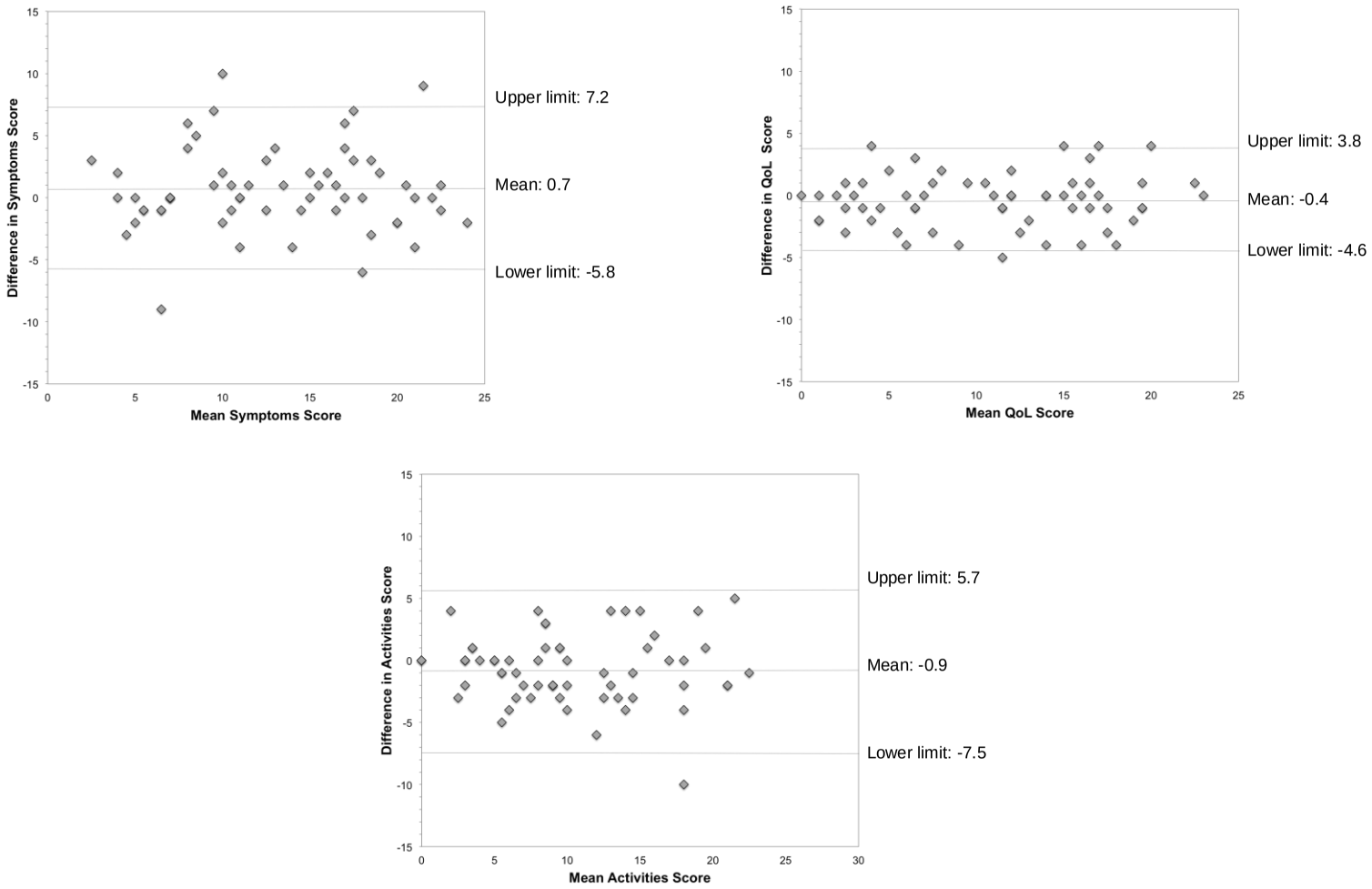

Figure 3.1. Bland-Altman plots for differences in mean scores between administrations for each CAMPHOR scale

QoL: Quality of Life; limits of agreement = mean difference ± 1.96 SD

Table 3.4. Correlations between CAMPHOR and SF-36 scores

	CAMPHOR					
	Symptoms		Activities		QoL	
	T1	**T2**	**T1**	**T2**	**T1**	**T2**
SF-36						
Physical Functioning	.60	.62	.75	.77	.58	.56
Role Physical	.52	.63	.59	.62	.45	.40
Bodily Pain	.47	.63	.45	.44	.38	.47
General Health	.52	.57	.46	.56	.49	.58
Vitality	.74	.80	.59	.57	.68	.67
Social Functioning	.66	.77	.59	.61	.65	.75
Role Emotional	.63	.64	.52	.42	.57	.47
Mental Health	.71	.74	.36	.33	.71	.66

T1: 1st occasion; T2: 2nd occasion; All correlations are significant at the 0.01 level and expressed as positive values; QoL: Quality of Life; n=61.

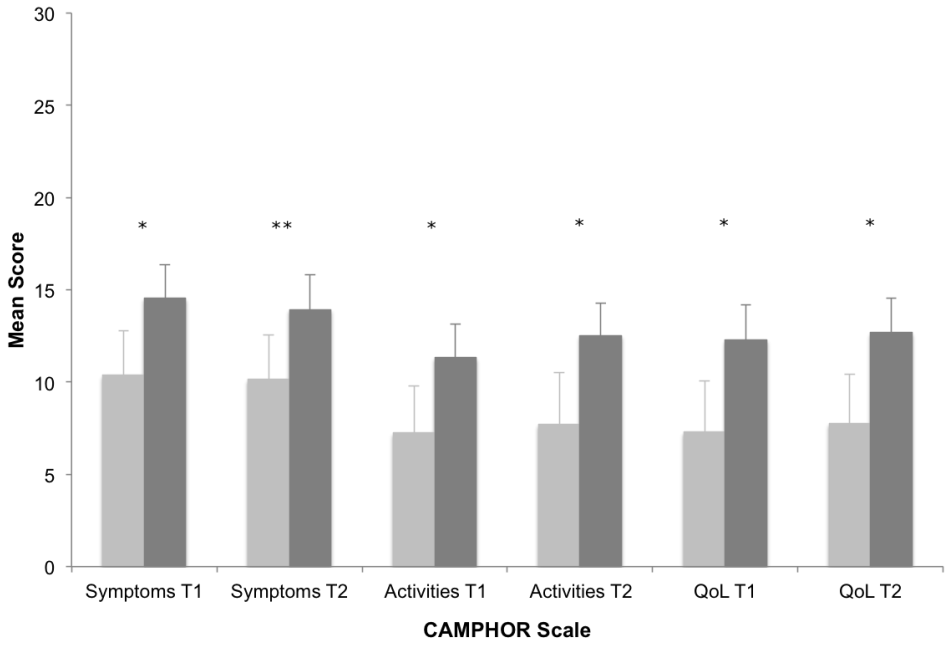

Figure 3.2. CAMPHOR scores by World Health Organisation functional classification

Data presented as mean (95% CI); T1: time point 1; T2: time point 2; ■ WHO class I/II (n=21); ■ WHO class III/IV (n=40); QoL: Quality of Life; * p<0.01; ** p<0.05.

3.4 Discussion

This study demonstrates that the CAMPHOR is a valid and reliable patient-reported outcome measure for the Australian and New Zealand PAH population. This study also shows that the CAMPHOR is applicable across a range of PAH severity, when classified according to WHO functional class. The field interviews confirmed the face and content validity of the CAMPHOR in individuals with PAH. As a result, it was not necessary to change the wording of any of the CAMPHOR items. The scores obtained on the CAMPHOR were reproducible with low random measurement error as indicated by test-retest correlation coefficients that ranged between 0.86 and 0.94. Further, the ICC indicated very good agreement between time points for the three CAMPHOR scales. Bland-Altman analyses demonstrate good agreement between administrations, with the mean differences in CAMPHOR scale scores ranging between -1.0 and 0.7. The LOA for the QoL scale were tighter, compared to the Symptoms and Activities scales. This is likely to reflect the daily variability in symptoms and, therefore, ability to perform activities that are characteristic of this population. The CAMPHOR also demonstrated excellent internal consistency with alpha coefficients ranging between 0.89 and 0.92. Additionally, minimal floor and ceiling effects were found, indicating that the CAMPHOR items were well matched to the severity level of the participants. Low floor and ceiling effects support the longitudinal use of the CAMPHOR to assess change following interventions (174).

This study demonstrates the ability of the CAMPHOR to distinguish between participants with PAH who differed according to WHO functional class when grouped into class I and II, or class III and IV. However, participant numbers were too low to demonstrate statistically significant differences across all four WHO functional classes. The validation studies performed in the United Kingdom (15), United States of America (16) Canada (17) and Germany (18) report comparable findings in relation to the ability to distinguish individuals according to WHO functional class. We found significant relationships between the CAMPHOR scales and the relevant domains of the SF-36,

confirming the construct validity of the CAMPHOR in this population, consistent with the findings of the US study (16).

A greater number of females were recruited for this study, which is consistent with the prevalence of disease in the WA State Pulmonary Hypertension Service. The predominance of females recruited for this study is consistent with the much higher percentage of females than males included in the US-based PAH registry (175).

There are some limitations to this study. Participants recruited for the field interviews came from a single State Pulmonary Hypertension Service, namely that in Western Australia. In both the field interviews and postal validation study, the ethnic background of participants, while mixed, was predominantly Caucasian. Finally, the number of participants included in the study was relatively small. Despite this the performance of the CAMPHOR was very good. Evidence of validity is cumulative rather than absolute and further investigations of the validity of the Australian CAMPHOR would be beneficial. It should also be noted that while the sample size was small, the sample was recruited from several clinical centres in Australia and New Zealand.

Given that the validation studies carried out in the UK (15) Canada (17) and Germany (18) demonstrated the validity and reliability of the CAMPHOR in individuals with chronic thromboembolic pulmonary hypertension (CTEPH), we would expect the CAMPHOR to be applicable in the Australian and New Zealand CTEPH population also. The ability of the CAMPHOR to reflect change associated with therapeutic interventions requires examination.

Generic HRQoL measures, such as the SF-36, have proven useful in quantifying the level of impairment experienced by individuals with PAH. However, performance in clinical trials has shown the SF-36 to be only moderately responsive to changes following intervention (176). We have shown the CAMPHOR to be valid and reliable in an Australian and New Zealand PAH population and recommend its use in clinical practice.

The validation of the CAMPHOR for the Australian and New Zealand populations has important implications for the assessment of individuals with this condition and for evaluating therapeutic interventions. Further studies are required to investigate the responsiveness of the CAMPHOR to a change in HRQoL. Recommendations for further research arising from this study are discussed in Chapter 6.

Chapter 4

EFFECTS OF EXERCISE TRAINING IN PULMONARY ARTERIAL HYPERTENSION: METHODS AND RESULTS

4.1 Overview

This Chapter outlines the methodology and results of the randomised controlled trial (RCT) that investigated the effects of exercise training on exercise capacity and health-related quality of life (HRQoL) in individuals with pulmonary arterial hypertension (PAH). The protocol for this study has been published in a peer-reviewed journal (177).

Further data analyses arising from this study are discussed in Chapter 5, “Results: Comparison of physiological and symptom outcomes during exercise testing in pulmonary arterial hypertension".

4.2 Methods

4.2.1 Overview

Section 4.2 of this Chapter describes the design and objectives of this RCT. Participant inclusion and exclusion criteria, recruitment strategies, data

management and statistical analyses are described, as well as the assessment and exercise training protocols and procedures.

4.2.2 Study Design

This study was a prospective, single blind, RCT. Data collection for the study occurred between October 2009 and August 2011. Participants were required to attend three visits within a two-week period to complete the baseline assessments of exercise capacity and HRQoL. Following baseline assessment, participants were randomised to either the exercise group or control group. Participants in both groups received usual medical care. Participants randomised to the exercise group underwent a 12-week, individually prescribed, supervised, outpatient, whole-body exercise training program, followed by a 12-week unsupervised home exercise program. Both groups were reassessed at 12 and 24 weeks. Figure 4.1 provides an overview of the study design and timeline.

4.2.2.1 Ethics approval and trial registration

This study was approved by the Human Research Ethics Committee (HREC) at Royal Perth Hospital (approval number EC 2009/012) and Curtin University (approval number HR 75/2009). The study protocol was registered with the Australian New Zealand Clinical Trials Registry on the 23rd June 2009 (ACTRN12609000502235).

4.2.2.2 Participants

Participant recruitment

Participants were recruited from the Western Australian (WA) State Pulmonary Hypertension Service, at Royal Perth Hospital, WA. The primary investigator (LG) reviewed the notes of all patients registered with the WA State Pulmonary Hypertension Service. A screening checklist was completed and potential patients discussed with the PAH Specialist Physician to confirm suitability.

Those willing to participate in the study attended an initial assessment where the study was explained in detail. Participants received written and verbal information regarding participation in the study. Written, informed consent was obtained from all participants prior to data collection.

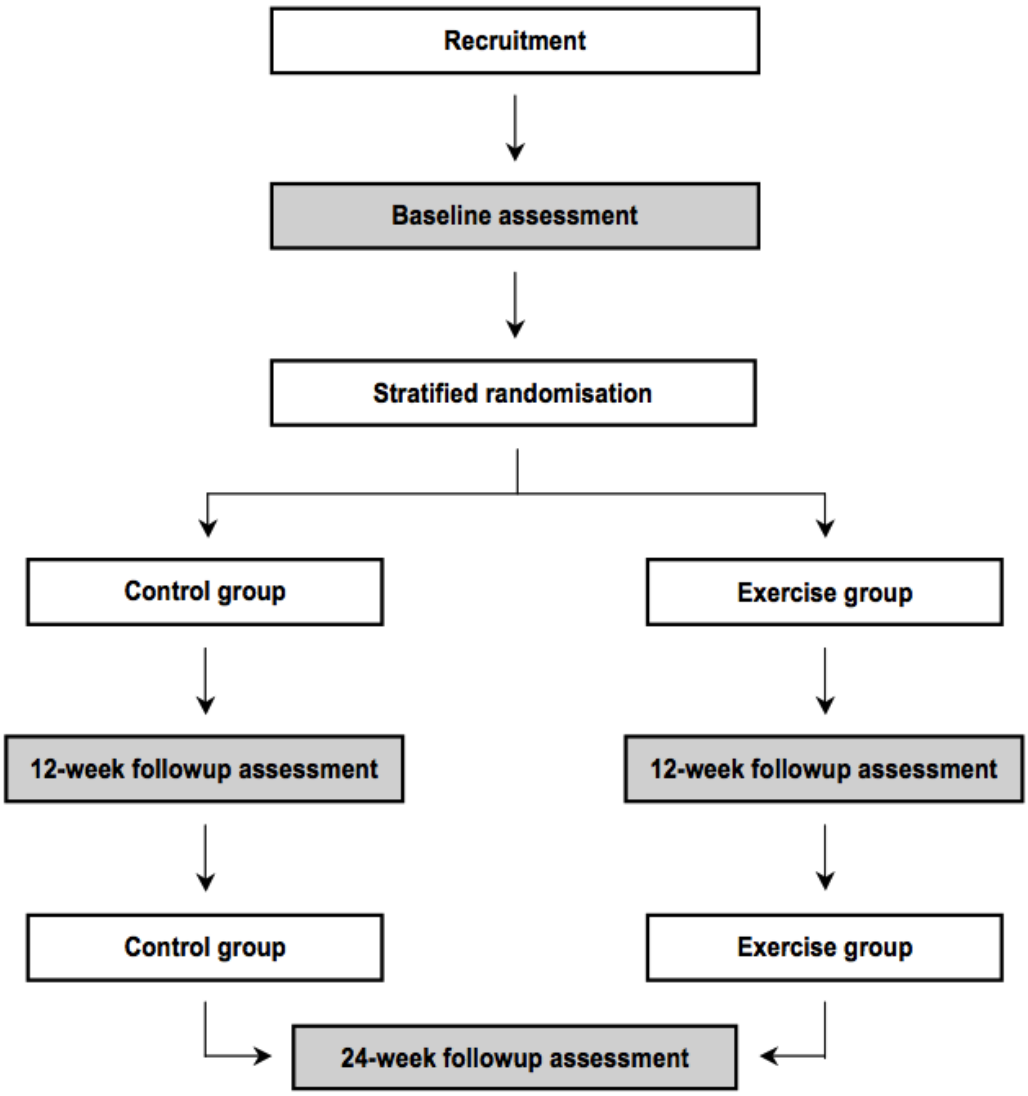

Figure 4.1. Study design and timeline

Inclusion criteria

Participants were included in the study if they:

vii. had a confirmed diagnosis of idiopathic PAH, familial PAH or PAH associated with connective tissue disorders, based on elevated pulmonary artery pressures (greater than 25mmHg at rest or greater than 30mmHg during exercise) measured by right heart catheterisation;
viii. were medically stable and had been on PAH-specific pharmaceutical therapy for 3 months prior to enrolment into the study;
ix. were in World Health Organisation (WHO) functional class II or III; and
x. were willing to complete the 12-week supervised and 12-week home exercise training programs.

Medical stability was defined as the absence of recent changes (3 months unless otherwise stated) in:

i. specific PAH therapy (no change in sildenafil citrate dose for 6 weeks, no change in endothelial antagonist receptors for 3 months);
ii. inotropes (including digoxin) and diuretics;
iii. symptoms (dyspnoea, fatigue and/or dizziness);
iv. body weight (a gain of ≥1.8kg over a period of 1-3 days indicating worsening right heart failure (178));
v. co-morbid conditions.

Exclusion criteria

Participants were excluded if they had:

i. resting hypoxaemia requiring supplemental oxygen therapy;
ii. significant musculoskeletal disease, claudication pain, neurological or cognitive impairment, psychiatric/psychological or mood disorders that may have affected their ability to undertake exercise testing or training;
iii. a history of moderate or severe chronic lung disease;

iv. cardiac disease associated with cardiac failure, poorly controlled angina, unstable cardiac rhythm;
v. participated in a supervised exercise training program within the last 12 months.

Withdrawal criteria

Participants were withdrawn from the study if they demonstrated deterioration in their clinical status, defined by the presence of two or more of the following (1, 179):

i. escalation of medical therapy (increased dose of medication or commencement of intravenous epoprostenol);
ii. deterioration in WHO functional classification (58);
iii. development of right heart failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites or peripheral oedema);
iv. resting echocardiogram changes (deterioration in right ventricular size and function, right atrial size, pulmonary arterial systolic pressure (PASP) and, where PASP could not be determined, pulmonary acceleration time);
v. peripheral oedema that did not respond to oral diuretics;
vi. hospitalisation for PAH;
vii. listed for lung or combined heart and lung transplantation;
viii. ≥ 20% deterioration in six-minute walk distance (6MWD);
ix. progressive worsening of dyspnoea at rest or on exertion over the previous 3-5 days (178);
x. deterioration in the ventilatory equivalent for carbon dioxide ($V'_E V'_{CO_2}$) reflecting worsening gas exchange.

Participants were also to be withdrawn from the study at their request or if they experienced a serious adverse event during or up to 24 hours following an exercise training session and ongoing participation was deemed unsafe by the treating medical officer from the Royal Perth Hospital Pulmonary Hypertension Service. Adverse events were defined as:

i. an incident requiring a medical emergency team call (according to Royal Perth Hospital criteria);
ii. exercise-related incident requiring presentation to the Emergency Department or General Practitioner;
iii. hospital admission due to PAH or worsening right heart failure;
iv. an incident resulting in the participant ceasing exercise during class (chest pain, syncope/pre-syncope, worsening dyspnoea despite rests, hypotension/hypertension, bradycardia/tachycardia (as measured by a Polar monitor and confirmed by palpation), nausea (associated with sweating, pallor and/or tremor), vagueness, vasovagal, arrhythmia;
v. death.

4.2.2.3 Randomisation

Following baseline assessment, participants were stratified into two groups based on the peak oxygen uptake ($V'O_2$); peak $V'O_2$ >70% or peak $V'O_2$ ≤70% of predicted values (180), in order to achieve groups balanced for exercise capacity. Stratification was based on one previous outpatient-based exercise training study in a PAH sample which demonstrated participants had a reduced aerobic capacity with a calculated mean predicted peak $V'O_2$ value of approximately 65% (23).

Permuted block randomisation with block sizes of four was used (181) to generate a randomisation chart. Fourteen blocks were created in total using a web-based research randomiser (182). Seven blocks were created for those stratified to ≤70% predicted peak $V'O_2$ and seven blocks for those stratified to >70% predicted peak $V'O_2$. One block was utilised for individuals stratified to ≤70% predicted peak $V'O_2$ and two blocks were utilised for those stratified to >70% predicted peak $V'O_2$.

4.2.2.4 Blinding

The primary investigator (LG) carried out all assessments at baseline, 12 weeks and 24 weeks and was blinded to the participant's group allocation.

Following baseline assessment, participant demographics and assessment data were given to the physiotherapists who conducted the exercise training sessions. These physiotherapists randomised the participants to the exercise or control group and recorded the allocation on the randomisation chart. The physiotherapist then contacted the participant to notify them of their group allocation, and in the case of the exercise group, to arrange commencement of the exercise training sessions. The physiotherapists responsible for conducting the exercise training sessions were not involved in any of the formal assessments.

4.2.3 Assessment blocks

All participants underwent a baseline assessment and reassessment at 12 and 24 weeks at Royal Perth Hospital. Researchers 'blinded' to the participant's group allocation performed all follow up assessments. For each assessment block, participants were required to attend three visits within a 2-week period, with each visit separated by at least 24 hours.

4.2.3.1 Visit 1

This assessment session lasted approximately 3 hours. Two six-minute walk tests (6MWT) were performed to measure functional exercise capacity, using an unencouraged protocol to reflect performance of daily activity (103). The 6MWT were separated by a rest period of at least 30 minutes. Participants completed three questionnaires during the rest period, in the following order: (i) the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF-36), (ii) the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and (iii) the International Physical Activity Questionnaire (iPAQ). The questionnaires were completed in the same order at each assessment block. During the baseline assessment visit, participants were also familiarised with the cycle ergometer and gas analysis equipment.

4.2.3.2 Visit 2

This session lasted approximately 1.5 hours. Participants performed spirometry and a maximal voluntary ventilation test followed by an incremental cardiopulmonary exercise test (CPET) on a cycle ergometer to measure maximum exercise capacity, as indicated by $V'O_2$ peak. At baseline, measures of diffusing capacity of the lung for carbon monoxide (D_LCO) were also taken to describe the study population.

4.2.3.3 Visit 3

This session lasted approximately one hour. Participants performed a constant workload cycle ergometer test (CWLT) to measure endurance.

4.2.4 Measurements

4.2.4.1 Exercise capacity

Exercise capacity was measured using laboratory-based and field-based tests.

Laboratory-based exercise tests

The incremental CPET and CWLT were performed on an electronically braked cycle ergometer with an optional motor to enable a true unloaded cycling phase for the tests (Lode Corival II cycle ergometer, Lode BV, Groningen, The Netherlands). The system met all American Thoracic Society (ATS) and European Respiratory Society (ERS) standards (45).

Breath-by-breath gas exchange analyses (Medical Graphics CPX-D system, Medical Graphics Corporation, St Paul, Minnesota, United States of America) were performed during all cycle ergometer tests. Direct measurements included air flow, respiratory rate, end tidal oxygen and end tidal carbon dioxide concentrations. Derived measures included $V'O_2$, carbon dioxide production ($V'CO_2$), minute ventilation (V'_E), duty cycle, and ventilatory equivalents for both oxygen ($V'_EV'O_2$) and carbon dioxide ($V'_EV'CO_2$). The preVent® flow sensor was connected to a flanged rubber mouthpiece, with saliva trap, and a nose clip was used to prevent air leaks.

Additional inputs included continuous recording of oxygen saturation (SpO_2) using a pulse oximeter and ear probe (Masimo Radical oximeter, running Masimo SET® software version 4.3.2.1, Masimo Australia Pty Ltd, Frenchs Forest, New South Wales, Australia). The oximeter was set to average over 8 seconds. Blood pressure was measured every 2 minutes by automated sphygmomanometry. Heart rate was continuously recorded from a 12-lead electrocardiogram (ECG) using the CardioPerfect^{TM} ST ECG system (Welch Allyn Cardio Control NV, Delft, The Netherlands). Borg category-ratio 10-point (CR10) scale scores for the sensation of dyspnoea and rating of perceived exertion (RPE) were collected at rest, during the last 15 seconds of every minute during exercise and on test completion.

Standardised instructions were given to the participants prior to each test, including standardised encouragement before and during the test. Standard criteria, based on the ATS CPET guidelines (45), were used to determine if test termination was required for safety reasons (Appendix 3).

Incremental cardiopulmonary exercise test

A continuous ramp protocol to volitional exhaustion was carried out. The test protocol comprised 3 minutes of upright rest on the bicycle, followed by 3 minutes of unloaded cycling (0 watts [W]). Subsequently, workloads were increased continuously by 5W/min, 10W/min or 15W/min. The workload increments were determined based on the participant's age, gender, weight, 6MWD and D_LCO (92). Participants were instructed to cycle at a cadence of 50 to 70 revolutions per minute. The aim of the test was to achieve a test duration of 8 to 12 minutes from commencement of the loaded cycling phase of the test to peak exercise. Test data were averaged over the last 20 seconds of the resting, unloaded and peak phases. Standard deviations were calculated for the breath-by-breath data. Data outside three standard deviations were removed and the 20 second mean recalculated. The anaerobic threshold (AT) was identified using the v-slope method (183). The test protocol is outlined in Appendix 4.

Constant workload cycle ergometer test

The CWLT protocol comprised 3 minutes of upright rest on the cycle ergometer, followed by 3 minutes of unloaded cycling (0W), followed by a step increase in workload to 75% of the peak workload achieved during the incremental CPET. Participants were instructed to cycle until exhaustion. The test was terminated after 20 minutes of loaded cycling if volitional exhaustion was not reached. The CWLT, at 12 and 24 weeks, were performed using the identical workload to that used at the baseline assessment. Test data were averaged over the last 20 seconds of the resting and unloaded phases. Data from the final minute of the test (defined as "peak responses"), as well as isotimes, were also averaged over 20 seconds. The isotimes were defined as equivalent time points within each test from the commencement of loaded cycling, namely 30, 60 and 90 seconds and 3 minutes, in addition to the shortest test time across the three assessment blocks. Standard deviations were calculated for the breath-by-breath data. Data outside three standard deviations were removed and the 20 second mean recalculated. The test protocol is outlined in Appendix 5.

Cycle ergometer equipment and calibration

The gas analysis system comprised a PreVent® pitot tube pneumotach oxygen analyser (fuel cell) and carbon dioxide analyser (infra-red). All gas measurements were made on dry gas. The analyser signals were processed by the Breeze Suite integrated pulmonary function software version 6.4.1 (Medical Graphics Corporation, St Paul, Minnesota, United States of America).

The equipment was calibrated prior to each test. Barometric pressure (mercury barometer), room temperature and relative humidity (wet and dry thermometer) were recorded in the system prior to calibration of the analysers. The gas analysers were calibrated using a two-point calibration immediately before each test. Calibration gases were ß-standard gas mixtures supplied by Medical Graphics (Mortara Instruments Australia Pty Ltd, Castle Hill, New South Wales, Australia). The reference gas used was

21% oxygen, 0% carbon dioxide, balance nitrogen, and the calibration gas contained 12% oxygen, 5% carbon dioxide, balance nitrogen. The flow sensor was calibrated using five inspiratory and expiratory strokes from a certified 3-litre syringe that covered the flow range 0 to 15 L/second. A timed and dated calibration report was generated detailing the amplifier settings and calibration factors for each analyser (Appendix 6). These reports were signed off by the primary investigator (LG) and filed with the instruments.

A full resuscitation cart, suction and defibrillator were available in the laboratory for all exercise tests. This equipment was monitored and checked daily by laboratory staff. A medical officer was also present during all tests.

Field-based exercise test

Six minute walk test

The 6MWT was performed using a standardised protocol, modified from the ATS guidelines (43) (Appendix 7). Participants were instructed to "walk at your own pace to cover as much distance as possible". The test was performed on a 45m track in a quiet, enclosed hospital corridor within an outpatient department. Cones were placed at the start, mid-point and end of the track to enable seated rests. Participants were notified of the elapsed time every 2 minutes, however, no encouragement was provided at that time. Continuous monitoring during the test comprised: (i) heart rate (HR) via telemetry (Polar FS3C heart rate monitor, Sportstek, Victoria, Australia) and, (ii) SpO_2 via finger probe (Respironics 512 pulse oximeter and finger sensor, Philips, Massachusetts, United States). The participant carried the oximeter, which weighed approximately 200g, whilst the primary investigator (LG) walked behind the participant to monitor clinical signs and symptoms and record HR and SpO_2 each minute. Borg scores for dyspnoea, RPE, general fatigue and leg fatigue were collected prior to commencing and at cessation of the test, using the Borg CR10 scale (184). Two tests were performed at each assessment block with a minimum of 30 minutes rest between tests. The greater of the two distances was recorded. Test termination criteria followed ATS guidelines, including the onset of chest pain, the development

of an abnormal HR response (eg. tachycardia, HR >220-age) and profound desaturation (SpO_2 <80%) (43).

4.2.4.2 Health-related quality of life

Health-related quality of life was assessed using the disease-specific CAMPHOR (15, 165), and the generic SF-36 (158). Both tools are self-administered questionnaires and were completed during the rest period between 6MWT. On completion of the questionnaires, the investigator reviewed the responses to ensure all items had been answered. In the event that an item on the questionnaire had been missed, the participant was asked to reread the item and provide a response.

A sample page of the CAMPHOR can be accessed via the following URL:
http://www.galen-research.com/content/measures/CAMPHOR%20UK%20-%20First%20page%20sample.pdf

A sample of the SF-36 Version 2 can be accessed via the following URL:
http://www.qualitymetric.com/demos/TP_launch.aspx?SID=100

4.2.4.3 Self-reported physical activity

The short form version of the iPAQ (185) was used to assess self-reported physical activity levels. The iPAQ is a 7 item, self-administered questionnaire that has demonstrated validity and reliability as a self-reported physical activity measure (186). The iPAQ explores the kinds of physical activity performed by an individual over the last 7 days, ranging from vigorous activity to the amount of time spent sitting. The iPAQ was completed during the rest period between 6MWT and was used to describe the study population and determine whether physical activity levels had changed following the intervention. The iPAQ score is expressed as MET-minutes/week. This cumulative score is derived from an individuals reported amount of (i) walking and (ii) moderate and vigorous intensity activities over the last week.

A copy of the iPAQ can be accessed via the following URL:
https://sites.google.com/site/theipaq/home

4.2.4.4 Baseline resting lung function testing

At baseline, participants underwent spirometry and measurement of D_LCO. All pulmonary function tests were conducted by an experienced respiratory scientist, according to ATS/ERS guidelines (187), using a Medical Graphics Elite DL plethysmograph system (Medical Graphics Corporation, St Paul, Minnesota, United States of America). The measurements were made using the same Breeze Suite software as per the laboratory-based exercise test measurements.

Spirometric indices recorded were: forced expired volume in one second (FEV_1); forced vital capacity (FVC); slow vital capacity (SVC); peak forced expiratory flow (FEF_{max}); and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$). The values reported for FEV_1, FVC and FEF_{max} were the highest from three acceptable and repeatable manoeuvres, by ATS/ERS criteria (188). The values for the $FEF_{25-75\%}$ were taken from the acceptable flow loop having the highest sum of FEV_1 and FVC (best loop by ATS/ERS criteria (187). All values reported were as per ATS/ERS guidelines (188) and referenced to predicted values (189). Derived spirometric measures comprised inspiratory capacity (IC) and expiratory reserve volume (ERV).

The single-breath method for D_LCO was used according to ATS/ERS guidelines (190). Standard settings were used for all participants *viz* washout volume of 750ml and sample volume of 500ml, with a nine second breath hold time. The breath hold time was computed by the Jones-Meade method (191). The inspired volume for the measurement was required to be greater than 85% of the vital capacity (190) and referenced to predicted values (192).

Calibration of the lung function testing equipment

Barometric pressure (mercury barometer), room temperature and relative humidity (wet and dry thermometer) were recorded in the system prior to the calibration of the analysers. The spirometer was calibrated daily and recalibrated if the flow sensor or patient circuit was changed during the day. Calibration required five strokes of a certified 3 litre syringe covering a range

of flows from 0 to 15 L/second. A calibration was performed for every D_LCO testing session using a ß-standard gas mixture (BOC Limited, North Ryde, New South Wales, Australia). The calibration was performed using the gas mixture inhaled during the test and comprised 0.50% neon, 0.30% carbon monoxide, 21% oxygen, balance nitrogen. Gas analysis was by gas chromatography.

4.2.5 Intervention: exercise group

An exercise training protocol was developed for this study, based on the principles of exercise training for stable left-sided heart failure (7, 10, 12, 137) and chronic obstructive pulmonary disease (COPD) (9, 11, 13, 138). Specifically, the training intensity, symptom limitation parameters, exercise modalities and duration of program were adapted from the evidence supporting exercise training in these populations.

4.2.5.1 Supervised exercise training program

Participants attended an individualised, supervised, outpatient, whole-body exercise training program involving one hour sessions, three times a week for 12 weeks. Sessions were supervised by one of three senior physiotherapists with experience in the exercise training of individuals with advanced lung disease. The physiotherapists were familiarised with the training protocol prior to the commencement of the study. The participants were enrolled into existing pulmonary rehabilitation classes for advanced lung disease patients. Class sizes ranged from 8 to 10 patients.

The sessions focused on lower limb endurance training. Lower limb functional strength training and endurance training of the upper limbs were also included with the aim of improving the participant's ability to undertake activities of daily living. During the sessions, HR was monitored continuously via telemetry (Polar FS3C heart rate monitor, Sportstek, Victoria, Australia) and SpO_2 levels (Respironics 512 pulse oximeter and finger sensor, Philips, Massachusetts, United States) were measured prior to and following each exercise. Participants were required to maintain SpO_2 ≥92% and symptom intensity scores for dyspnoea and RPE of ≤4 (rating of "somewhat severe")

on the Borg CR10 scale (184), for all exercises. Additionally, HR was not to exceed 70% of the age-predicted HR maximum (HRmax) on any exercise. Following the warm up, the order of the exercises was predominantly influenced by the availability of the equipment.

Warm up and cool down

Prior to commencing each training session, participants performed a 5 minute warm-up of either walking or cycling, at an intensity that did not elicit symptoms (193). Following the completion of each exercise session, participants performed a 5 minute cool-down at a similar intensity (193).

Lower limb endurance training exercises

International guidelines recommend that a minimum of 30 minutes of endurance training per session is required for optimal benefit (11). The intensity of lower limb endurance exercise was prescribed with the aim of achieving 60-70% age-predicted HRmax while maintaining SpO_2 ≥92% and symptom intensity for dyspnoea and RPE of ≤4 on the Borg CR10 scale (184). If SpO_2 levels were unable to be maintained ≥92%, interval training principles were to be adopted. Exercise intensity was progressed, based on the individual's response to training in order to maintain HR within the target HR range.

Maximum HR was calculated based on the age-predicted equation (220-age) (194), because it is not routine practice in Australia for patients to undergo a CPET prior to enrolling into an exercise training program. Several studies have identified chronotropic incompetence in PAH (66-70). For this reason, each participant's age-predicted HRmax was compared to the peak HR achieved on CPET. If the peak HR achieved on the CPET was between 80% to 100% of the age-predicted HRmax, the age-predicted HRmax was used to calculate the target HR range for exercise training. If the peak HR achieved on CPET was less than 80% (195, 196) of the predicted HRmax, the target HR range was calculated based on the CPET HR data.

Corridor walking

Participants were asked to walk at a speed that elicited a HR within the target HR range (60-70% age-predicted HRmax) for a period of 10 minutes. They were encouraged to change their walking speed during the 10 minutes according to their HR response.

Treadmill walking

The initial treadmill speed was prescribed at 80% of the average speed achieved during the baseline 6MWT and was subsequently adjusted according to the HR response. If the HR was below target, the speed was increased and if the HR was above target, the speed was reduced. The initial incline on the treadmill was set to 3%. Exercise intensity was progressed by increasing speed initially and then by increasing the incline. Participants were instructed to walk on the treadmill for 10 minutes.

Cycle ergometer training

The cycle training was performed on an Ergoline 100P cycle ergometer (Ergoline, Bitz, Germany). The Ergoline 100P has a computer-controlled eddy current braking system with a cadence-independent workload between 6 to 999 Watts. The physiotherapist responsible for supervising the class selected the workload and time for each training session manually. The initial workload was determined from the CWLT. Participants commenced 10 minutes of cycling at an intensity to achieve the target HR range, increasing or decreasing the workload based on HR and symptom responses.

Lower limb functional strength training exercises

The lower limb functional strength training exercises were performed at an intensity that elicited subjective reports of moderate muscle fatigue (RPE 3 to 4) following the completion of two sets of 10 repetitions. The lower limb exercises comprised ‘sit to stands’ and ‘step ups’. Exercises were progressed in increments of two, up to 20 repetitions. Subsequent progressions comprised adding hand weights for step ups and decreasing

the height of the chair for sit to stands with the aim of maintaining the target intensity at an RPE of 3 to 4.

Upper limb endurance training exercises

The upper limb endurance exercises were performed using free weights at an intensity that elicited subjective reports of moderate muscle fatigue (RPE 3 to 4) following the completion of two sets of 10 repetitions. Initially, dumbbells weighing between 1 and 2kg were used for females and between 1.5 and 3kg for males. Exercise progression occurred by increasing the dumbbell weight by 0.5 to 1kg to maintain the target intensity at an RPE of 3 to 4.

4.2.5.2 Unsupervised home exercise program

The participants randomised to the exercise group were instructed to commence one session per week of their home exercise program during the last 4 weeks of their supervised program. This was to ensure participants had the opportunity to discuss the home exercise program with the supervising physiotherapist who assisted in troubleshooting any problems that may have arisen. On completion of the supervised program, participants increased the frequency of their home program to three sessions per week for an additional 12 weeks.

The home program comprised: (i) 20 minutes of lower limb endurance training (walking) and (ii) lower limb functional strength exercises (sit to stands and step ups). The program was individually tailored based on the individual's performance during the supervised exercise sessions. To guide the home exercise training intensity, symptoms during the supervised period were correlated to an upper HR limit of 120bpm (6). Participants were instructed to achieve these symptom responses (Borg CR10 dyspnoea ≤4 and RPE ≤4) at home. Participants were instructed to progress the exercises to maintain the target symptom responses by (i) increasing the speed of walking and (ii) increasing the number of lower limb functional strength exercises (as previously described in section 4.4.1.3 and 4.4.1.6, respectively). Participants were also instructed to monitor their weight and

symptoms and notify the treating team should an increase in weight or worsening of symptoms occur. Participants were required to record each session on an exercise log.

4.2.6 Outcome Measures

The primary outcomes of this study were:

(i) Exercise capacity, as measured by:

- Peak $V'O_2$;
- Anaerobic threshold;
- Endurance time measured from the constant workload cycle ergometry test;
- 6MWD (measured from the best of two 6MWTs at each assessment).

(ii) The number of reported acute adverse events (i) reported during exercise training and (ii) resulting in the withdrawal of a subject from the study.

(iii) HRQoL measured using the CAMPHOR and SF-36 Version 2;

The secondary outcomes of this study were:

(i) Ventilatory variables at isotime during the constant workload cycle ergometry test (including ventilatory equivalent for carbon dioxide [$V'_E V'CO_2$] and end tidal carbon dioxide [$P_{ET}CO_2$] to describe gas exchange);

(ii) Change in WHO functional class.

4.2.7 Data management and statistical analysis

4.2.7.1 Sample size calculation

The initial sample size calculations were based on data from one study of exercise training undertaken in a sample of 19 participants with iPAH (23). These authors (23) reported a mean increase in endurance time, as measured from a CWLT, of 270 seconds from 390±40 at baseline to 660±60 seconds post training. The CWLT were set at 75% of the peak workload

achieved during the incremental CPET, which is consistent with our study's protocol.

Conservative sample size calculations were performed using a two-sided Mann-Whitney U test, assuming that the actual distribution was a double exponential. Group sizes of 14 were required to achieve 91% power to detect a difference of 200 seconds between the null hypothesis that both group means are 600 seconds and the alternative hypothesis that the mean of the control group is 400 seconds with estimated group standard deviations of 180 and 120 and with a significance level (alpha) of 0.01.

A total of 34 participants (17 in the exercise group and 17 controls) were required to allow for 20% attrition of participants from the *per protocol* analyses.

4.2.7.2 Statistical analyses

Data were analysed using (i) *per protocol* analysis and (ii) *intention-to-treat* analyses. *Per protocol* analyses were restricted to the data from participants who completed all assessments and for those randomised to the exercise group who completed at least 75% of the exercise sessions (ie. 27 sessions). This number of sessions had to be completed within a period of 16 weeks for both the 12-week supervised and 12-week home exercise training programs, allowing for intercurrent illness and other factors that may have impacted on an individual's ability to participate, in order to satisfy the criteria for including the participant's data in the *per protocol* analysis.

Data from individuals who were withdrawn, or, who did not meet the criteria for *per protocol* analyses, were included in the *intention-to-treat* analyses. The last-observation-carried-forward method was used to impute missing data at 12 and 24 weeks for the *intention-to-treat* analyses (197).

Statistical analyses were performed using SPSS® software (Version 17.0; SPSS Inc.; Chicago, USA) and SigmaPlot (Version 12; Systat Software Inc). Non-parametric statistics were used to analyse differences between and within groups, due to the small sample sizes (198, 199). Between-group

comparisons were performed using Mann-Whitney U tests and within-group differences were compared using Wilcoxon signed-rank tests. Kruskal-Wallis tests were performed for HRQoL and symptom score analyses. For all analyses, an alpha (p) value of less than 0.05 was considered significant.

4.3 Results

4.3.1 Overview

Section 4.3 details the results of the RCT and discusses the outcomes following the supervised exercise training period and subsequent unsupervised home exercise program. These results are divided into four parts. Part One describes participant recruitment and the baseline data for the exercise and control groups. Part Two describes the data pertaining to adherence to training, training loads and exercise capacity outcomes following the supervised exercise training period and compares this to control group data at the "12 week" assessment. Part Three outlines the exercise capacity outcomes following the unsupervised home exercise program and compares this to the control group data at the "24 week" assessment. Part Four describes the effects of this study on HRQoL and WHO functional classification at the "12 week" and "24 week" assessment and compares the responses between the exercise group and control group.

PART ONE: BASELINE DATA

4.3.2 Participant Recruitment

The primary investigator (LG) reviewed the medical records of the 242 individuals registered with the Western Australian State Pulmonary Hypertension Service. Of those, 121 had a confirmed diagnosis of idiopathic PAH (iPAH), familial PAH (fPAH) or PAH associated with connective tissue disorders (aPAH). Detailed review of these records led to the exclusion of 79 individuals for the following reasons: (i) presence of comorbid conditions (n=39); (ii) lived outside the Perth metropolitan area (n=21); (iii) not prescribed PAH-specific pharmaceutical therapy (n=11); (iv) enrolled in an exercise training program in the last 12 months (n=3); (v) oxygen dependent

(n=2); (vi) unstable PAH requiring escalation of medical therapy (n=1); (vii) limited English language and requiring an interpreter (n=1); and (viii) less than 18 years of age (n=1).

The remaining 42 individuals were sent study information via mail and invited to participate in the study. Attempts were then made to contact these individuals by telephone to discuss participation, with the following results: (i) willing to participate (n=14); (ii) declined due to the time commitment required for the study (n=11); (iii) declined due to work/home commitments (n=9); (iv) declined for personal reasons (n=6); and (v) unable to be contacted (n=2).

Baseline assessments were conducted on the 14 individuals who were willing to participate. Of these, 10 were appropriate for the study, whilst four were withdrawn due to: (i) co-morbid musculoskeletal conditions limiting their ability to perform exercise (n=3) and (ii) request to be withdrawn due to the time commitment required for the study (n=1).

Following consent and baseline assessments, the 10 participants were randomised into either the exercise or control group. Two randomisation charts were generated to allow stratified randomisation, with the aim of achieving groups balanced for exercise capacity. Stratification was based on peak oxygen uptake ($\dot{V}O_2$ peak) measured on the baseline incremental cardiopulmonary exercise test (CPET), expressed as a percentage of the predicted normal value (>70% predicted or ≤ 70% predicted) (180). Participants were informed of their group allocation following baseline assessment.

Participants randomised to the exercise group attended the Physiotherapy Department, at Royal Perth Hospital. Participants attended supervised exercise training sessions for one hour, 3 times per week, for 12 weeks. Following this period, the exercise group continued with an unsupervised home exercise program for a further 12 weeks. Both groups were reassessed at 12 and 24 weeks.

The recruitment and flow of participants through the study (Figure 4.2) was consistent with recommendations from the Consolidated Standards of Reporting Trials (CONSORT) statement (200).

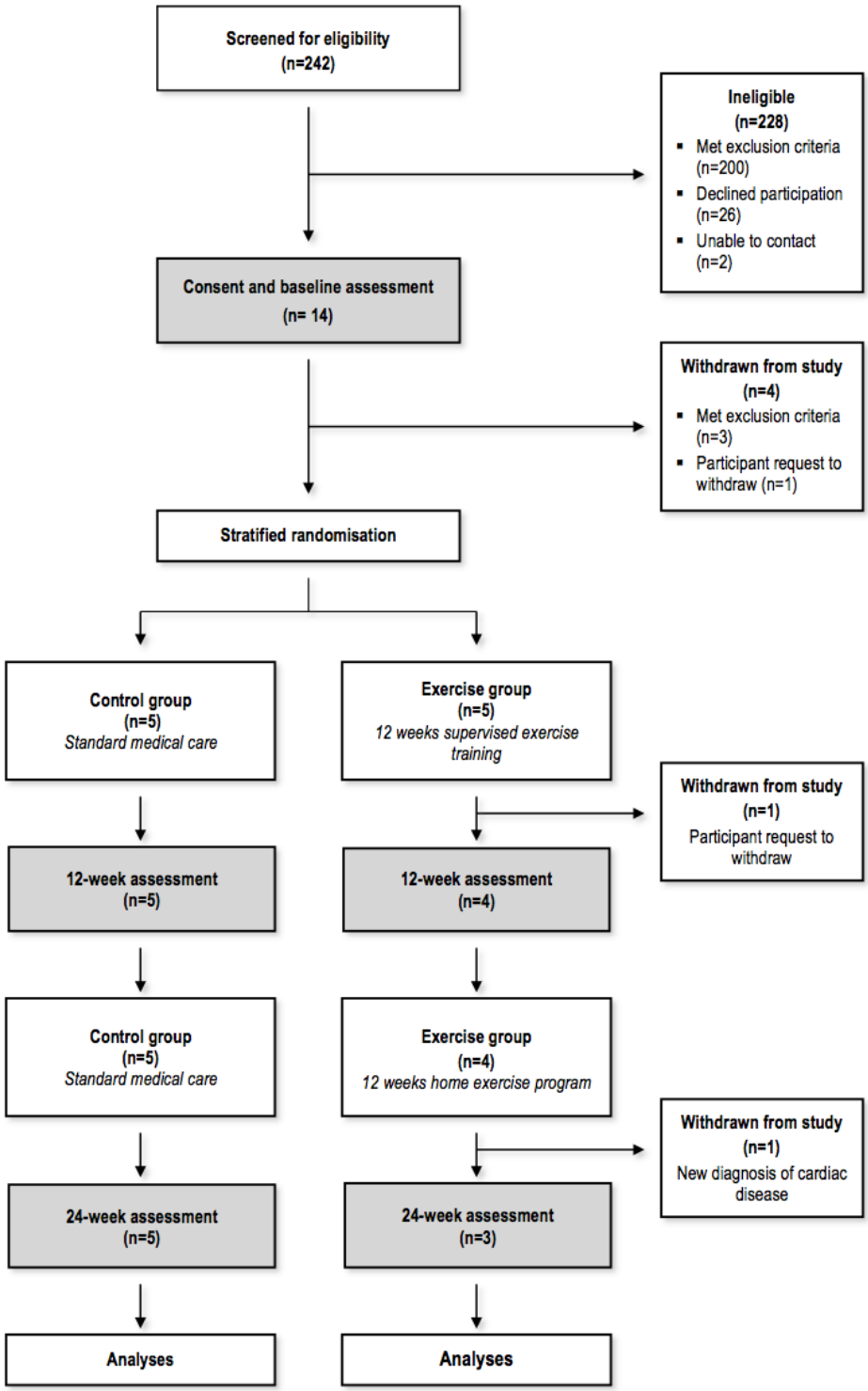

Figure 4.2. Recruitment and participant flow through the study

4.3.3 Participants

Ten participants met the inclusion criteria for the study and were randomised into the exercise (n= 5) or control (n=5) groups.

Two participants randomised to the exercise group were withdrawn during the study period. One participant was withdrawn prior to the 12-week reassessment, due to illness unrelated to PAH. Baseline data collected for this participant were not included in the *per protocol* analyses. The second participant was withdrawn prior to the 24-week reassessment, following a new diagnosis of cardiac disease. Data collected at baseline and 12 weeks for this participant were included in the *per protocol* analyses, however, data were unavailable for the 24-week reassessment. The last-observation-carried-forward method (197) was utilised for the *intention to treat* analyses.

Results are presented for the five control group participants who completed the 24-week study period. Results are presented for the four exercise group participants who completed the 12-week reassessment and for the three exercise group participants who completed the 24-week reassessment. Data are presented as median and interquartile range (IQR) using *per protocol* analysis, unless otherwise stated.

4.3.4 Baseline characteristics

There were no significant differences between the exercise and control group participants in anthropometrics, World Health Organisation (WHO) functional classification and mean pulmonary artery pressures (Table 4.1).

4.3.4.1 Resting lung function

At baseline, there were no significant differences in lung function (spirometry and diffusing capacity of the lung for carbon monoxide [D_LCO]) between groups (Table 4.1). Spirometric data for one exercise group participant demonstrated a mild obstructive defect (FEV_1/FVC 57%, FEV_1 76% predicted). The effective alveolar volume ($V_{A\ eff}$) for two control group participants was less than the lower limit of normal (LLN), indicating the presence of restriction. The $V_{A\ eff}$ for these two participants were 2.5L (LLN

4.3L) and 3.8 (LLN 4.5L). One of these control group participants had a diagnosis of aPAH, namely scleroderma.

4.3.4.2 PAH-specific pharmaceutical management

The participants' PAH-specific medication and dose remained unchanged during the study period (Table 4.1).

4.3.4.3 Heart rate response

In addition to the PAH-specific medication, the PAH pharmaceutical management of one of the exercise group participants also included a beta-1 selective adrenoreceptor blocking agent (Atenolol). As a result, the peak heart rate (HR) during exercise for this participant was attenuated. At baseline, however, there were no significant differences in peak HR measured on the incremental CPET between groups.

Chronotropic incompetence is broadly defined as an inadequate HR limiting exercise capacity, whereby the heart fails to appropriately increase rate for a given increase in workload (196). There is, however, a lack of clinical criteria for determining chronotropic incompetence (196). This study defined chronotropic incompetence as a peak HR <80% of the age-predicted maximum HR (HRmax) calculation (196), on documented maximal exertion (respiratory exchange ratio [RER] >1.15 (45)) on the incremental CPET. Based on this definition, chronotropic incompetence was identified in one control group participant.

4.3.4.4 Exercise capacity

At baseline, there were no significant differences between groups in exercise capacity (Table 4.2 and Appendices 9, 10, 11 & 17), as measured by: (i) peak $\dot{V}O_2$, (ii) $\dot{V}O_2$ at the anaerobic threshold (AT), (iii) endurance time on the constant workload cycle ergometer test (CWLT), and (iv) 6-minute walk distance (6MWD).

Table 4.1. Baseline characteristics of the study participants

	Exercise Group (n=5)	**Control Group (n=5)**
Anthropometrics		
Gender (female, %)	5 (100)	4 (80)
Age, years	51(40 – 53)	53 (42 – 57)
Height, cm	163 (161 – 164)	165 (165 – 168)
Weight, kg	63 (59 – 94)	71 (70 – 90)
BMI, kg/m^2	26 (23 – 41)	28 (26 – 31)
Diagnosis (n, %)		
iPAH	4 (80)	2 (40)
fPAH		1 (20)
aPAH	1 (20)	2 (40)
WHO functional class (n, %)		
II	3 (60)	3 (60)
III	2 (40)	2 (40)
Resting pulmonary artery pressures (mmHg)		
Mean	49 (20 – 65)	23 (19 – 29)
Systolic	78 (31 – 107)	34 (29 – 48)
Diastolic	28 (12 – 38)	14 (13 – 15)
Pulmonary function		
FEV_1, % pred	90 (83 – 90)	74 (66 – 100)
FVC, % pred	98 (92 – 102)	78 (72 – 110)
FEV_1/FVC, %	75 (74 – 77)	75 (74 - 77)
$V_{A\ eff}$, L	4.9 (4.8 – 4.9)	4.1 (3.8 – 5.1)
D_LCO uncorrected, % pred	84 (79 - 87)	63 (53 – 93)
PAH-specific medication (n, %)		
Endothelin receptor agonist	3 (60)	3 (60)
Endothelin receptor agonist and phosphodiesterase type-5 inhibitor	1 (25)	2 (40)
Endothelin receptor agonist and endothelin receptor antagonist	1 (25)	

Data presented as median (interquartile range) unless otherwise stated; iPAH: idiopathic pulmonary arterial hypertension; fPAH: familial pulmonary arterial hypertension; aPAH: pulmonary arterial hypertension associated with connective tissue disorders; WHO: World Health Organisation; FEV_1: forced expiratory volume in one second (189); FVC: forced vital capacity (189); $V_{A\ eff}$: effective alveolar volume (192); D_LCO: diffusing capacity of the lung for carbon monoxide (192); pred: predicted.

Table 4.2. Baseline measures of exercise capacity

	Exercise Group (n=5)	Control Group (n=5)
Incremental CPET		
Workload, W	102 (93 – 110)	96 (75 – 112)
$V'O_2$ peak, mL/min	1114 (1094 – 1137)	1165 (1152 – 1175)
$V'O_2$ peak, mL/kg/min	16.2 (14.2)	16.8 (12.1 – 17.3)
$V'O_2$ peak, % pred	71 (67 – 88)	64 (63 – 67)
$V'CO_2$, mL/min	1419 (1347 – 1516)	1361 (1327 – 1546)
V'_E, L/min	75 (56 – 78)	49 (45 – 62)
Heart rate, bpm	140 (139 – 150)	136 (128 – 139)
SpO_2, %	98 (91 – 99)	96 (95 – 98)
Workload @AT, W	45 (29 – 51)	28 (26 – 59)
$V'O_2$ @AT mL/min	633 (544 – 649)	636 (591 – 637)
$V'O_2$ @AT mL/kg/min	9.2 (6.7 – 9.3)	8.3 (8.2 – 9.1)
AT, % $V'O_2$ peak	58 (48 – 58)	55 (51 – 55)
$V'CO_2$ @AT, mL/min	512 (512 – 628)	571 (556 -592)
$V'_E V'CO_2$ @AT	42 (36 – 45)	40 (37 – 42)
Heart rate @AT, bpm	93 (83 - 94)	98 (95 – 103)
SpO_2 @AT, %	96 (92 – 99)	96 (96 – 98)
CWLT		
Endurance time, sec	436 (378 – 501)	441 (338 – 463)
Workload, W	75 (68 – 77)	72 (55 – 78)
$V'O_2$ peak, mL/min	1213 (1110 – 1256)	1209 (1162 – 1300)
$V'CO_2$, mL/min	1299 (1256 – 1339)	1470 (1280 – 1637)
V'_E, L/min	62 (54 – 68)	54 (44 – 61)
Heart rate, bpm	141 (129 – 142)	140 (136 – 154)
SpO_2, %	95 (95 – 96)	98 (96 – 99)
Six-minute walk test		
6MWD, m	560 (483 – 610)	575 (560 - 585)
6MWD, % pred	89 (85 – 93)	84 (83 – 90)
Heart rate, bpm	134 (99 – 137)	124 (112 – 128)
SpO_2, %	95 (93 – 96)	95 (94 – 95)

Data presented as median (interquartile range) at test end, unless otherwise stated; CPET: cardiopulmonary exercise test; $V'O_2$peak: peak oxygen uptake (163); $V'CO_2$: carbon dioxide production; V'_E: minute ventilation; bpm: beats per minute; SpO_2: oxygen saturation; AT: anaerobic threshold; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; CWLT: constant-workload test; 6MWD: six-minute walk distance (125); pred: predicted.

4.3.4.5 Ventilatory response

Compared to the control group, peak minute ventilation (V'_E) was higher in the exercise group on the incremental CPET (exercise: 75L/min, IQR 56-78L/min; control: 49L/min, IQR 45-62L/min; p=0.310; Table 4.2; Appendix 9). Further, the exercise group exhibited a higher peak respiratory rate (exercise: 43 breaths/min, IQR 42-43 breaths/min; control: 34 breaths/min, IQR 33-37 breaths/min; p=0.032) and higher peak tidal volume (exercise: 1.6L, IQR 1.5-1.8L; control: 1.4L, IQR 1.4-1.6L; p=0.690). The exercise group exhibited a lower peak breathing reserve of 20% (18L/min, IQR 13–48L/min) compared to 39% (28L/min, IQR 22-51L/min) in the control group (p=0.016). Ventilatory limitation has been reported to occur when the breathing reserve is less than 11L/min and the respiratory rate exceeds 50 breaths/min (180). Based on this, the exercise group participant who presented with mild obstruction on spirometry was limited by their ventilatory capacity, with a breathing reserve of 8.9L and a respiratory rate of 57 breaths/min at peak exercise on the incremental CPET.

4.3.4.6 Symptoms

On the incremental CPET, the exercise group reported a lower level of dyspnoea (exercise: 5, IQR 4-7; control: 9, IQR 5-9; p 0.413) and a lower level of general fatigue (exercise: 4, IQR 3-5; control: 7, IQR 6-8; p=0.016), compared to the control group on the Borg category-ratio 10-point (CR10) scale.

4.3.4.7 Health-related quality of life and self-reported physical activity levels

At baseline, there were no significant differences between groups in HRQoL on the three Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) scales (Table 4.3).

A difference in baseline scores was observed in the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF-36) domains of Role Emotional, Mental Health and the Mental Component Summary Score

($p<0.05$), with the exercise group reporting lower scores, indicating a greater level of impairment in HRQoL (Table 4.3).

At baseline, there were no significant differences in self-reported physical activity levels between groups using the International Physical Activity Questionnaire (iPAQ) (Table 4.3). Craig and colleagues (186) reported the median energy expenditure of a normal population to be 2,514 MET-minutes/week. This figure was based on a study of 1,974 individuals from a total of 12 countries and included 62 participants from Australia. Based on these results the exercise group reported substantially lower median activity levels, whilst the control group reported median activity levels comparable to the normal population.

Table 4.3. Baseline health-related quality of life and physical activity scores

	Exercise Group (n=5)	**Control Group (n=5)**
CAMPHOR Scales		
Symptoms	15 (3 – 16)	10 (3 – 11)
Activities	6 (5 – 8)	7 (5 – 7)
Quality of Life	14 (3 – 15)	4 (0 – 9)
SF-36 Domains		
Physical Functioning	40 (20 – 65)	45 (35 – 55)
Role Physical	44 (38 – 75)	100 (94 – 100)
Bodily Pain	100 (64 – 100)	74 (62 – 100)
General Health	65 (37 – 72)	37 (32 – 50)
Vitality	50 (38 – 63)	50 (38 – 63)
Social Functioning	75 (38 – 75)	88 (75 – 100)
Role Emotional	83 (75 - 84) *	100 (100 – 100)
Mental Health	70 (60 - 70) *	80 (80 – 90)
Physical component summary	37 (34 – 49)	38 (36 – 47)
Mental component summary	48 (46 – 51) *	56 (55 – 62)
International Physical Activity Questionnaire		
MET-minutes/week	594 (198 – 1272)	2856 (1188 – 9918)

Data presented as median (interquartile range); MET: metabolic equivalent; *$p<0.05$ between groups.

PART TWO: SUPERVISED EXERCISE TRAINING PERIOD

4.3.5 Supervised exercise training attendance

The median number of exercise training sessions attended by the exercise group participants was 31 of the 36 scheduled sessions (median 86%; range: 75% to 89%). Reasons for non-attendance included illness unrelated to PAH, for example gastrointestinal upset and flu-like symptoms. Further, over the Christmas period, there were no exercise sessions conducted at Royal Perth Hospital on the public holidays. This necessitated an increase in the number of weeks of attendance for two participants to ensure they completed the required number of exercise training sessions. All four participants attended more than 75% of the required number of sessions thus their data were included in the *per protocol* analyses.

4.3.6 Exercise progression during supervised training sessions

Exercise progression was examined by comparing the mean training load achieved during the first three and the final three supervised training sessions, for each exercise (Table 4.4).

The training load achieved during treadmill walking was calculated as (201):

> Treadmill work = weight (kg) x vertical displacement (m)
>
> Whereby, vertical displacement = treadmill speed (m/min) x time (min) x treadmill angle

Treadmill work increased by 100% (change: 4306kg.m, IQR 3471-5244kg.m; p=0.005), as illustrated in Table 4.4. The training load achieved during cycle ergometry training and the distance walked during corridor walking increased by 9% (change: 58W.min, IQR 38-75W.min; p=0.080) and 6% (change: 55m; IQR 14-96m; p=0.379), respectively (Table 4.4).

The number of repetitions achieved for the lower limb functional strength training exercises increased during the supervised exercise training period (Table 4.4). The number of step-ups performed increased by 68% (change:

15 repetitions, IQR 10-19 repetitions; p=0.034; Table 5.4) and the number of sit to stands increased by 57% (change: 13 repetitions, IQR 8-17 repetitions; p=0.040; Table 4.4).

Upper limb exercises were completed by three of the four exercise group participants. One participant was unable to complete the upper limb exercises due to hand and shoulder joint pain associated with scleroderma. The weights used during the upper limb endurance exercises increased by 65% (change: 0.8kg, IQR 0.4-1.3kg; p=0.081), whilst the number of repetitions remained the same (Table 4.4).

4.3.7 Cardiopulmonary and symptom responses during the supervised exercise training period

Heart rate, oxygen saturation (SpO_2) and Borg CR10 symptom scores for dyspnoea and perceived exertion were recorded at the beginning of each exercise session and immediately following each exercise. These variables were analysed to determine whether participants were able to achieve the prescribed intensity of exercise, as described in Section 4.2.5.1.

4.3.7.1 Lower limb exercise training

Participants exercised within the target HR range (60-70% age-predicted HRmax) 86%, 94% and 88% of the time for corridor walking, treadmill walking and cycle ergometry respectively (Table 4.5).

Participants were also instructed to avoid exceeding Borg CR10 dyspnoea and rating of perceived exertion (RPE) scores >4, during the lower limb exercise. Dyspnoea and RPE scores of ≤4 were reported during all exercises, 100% of the time. The participant, whose pharmaceutical management included a beta-blocker, was trained according to symptom responses only.

4.3.7.2 Upper limb endurance and lower limb functional strength training exercises

Participants achieved the target RPE intensity (3 to 4 on the Borg CR10 scale) 74%, 75% and 61% of the time for the step ups, sit to stands and upper limb exercises respectively (Table 4.6).

During the upper limb exercises, none of the participants exceeded the upper limit of the target HR range (70% HRmax). However, 70% HRmax was exceeded 12% (IQR 8–19%) and 2% (IQR 0–3%) of the time for the step ups and sit to stand exercises, respectively. Dyspnoea scores of ≤4 were reported during all exercises and at all sessions.

4.3.7.3 Oxygen saturation levels during exercise

The exercise training protocol required participants to maintain SpO_2 ≥92%. Table 5.7 outlines the proportion of sessions where SpO_2 was maintained ≥92%.

4.3.8 Adverse event

One adverse event was recorded during the supervised exercise training period. The participant experienced an episode of dizziness 40 minutes into their third exercise training session. This occurred during corridor walking and required the participant to cease the exercise. On resting, the dizziness resolved. The supervising physiotherapist discussed the event with the PAH Senior Medical Officer who gave approval for the participant to go home. Review of the participant's exercise log identified an attenuated HR response to exercise during this session, which was not identified during exercise testing, or during the two previous training sessions. Reported RPE scores were ≥4 for the lower limb endurance exercise during this session and were higher than the scores reported in previous and subsequent sessions.

Table 4.4. Training load at the first three and the final three supervised exercise training sessions

	First three sessions	Final three sessions
Treadmill walking		
Treadmill work, kg.m	4652 (3967 – 5112)	8750 (8399 – 9187) *
Cycle ergometry		
Training load, W.min	567 (525 – 625)	600 (600 – 638)
Corridor walking		
Distance, m	913 (867 – 946)	968 (898 – 1024)
Step ups		
Repetitions, n	20 (20 – 20)	35 (30 – 39) *
Sit to stands		
Repetitions, n	21 (20 – 23)	36 (30 – 40) *
Upper limb exercises		
Weight, kg	1.8 (1.6 – 1.9)	3 (2.8 – 3)

Data presented as median (interquartile range); *p<0.05 between first and final three sessions.

Table 4.5. Target intensity range (based on HRmax) during lower limb endurance exercises

	Within target (%)	Above target >70%HRmax (%)	Below target <70%HRmax (%)
Corridor walking	86 (72 – 86)	14 (7 - 25)	7 (3 – 7)
Treadmill walking	94 (91 – 97)	0 (0 – 6)	0 (0 – 3)
Cycle ergometry	88 (87 – 91)	9 (5 – 12)	3 (2 – 4)

Data presented as a percentage of the total number of sessions, expressed as median (interquartile range); HRmax: maximum heart rate.

Table 4.6. Target intensity range (based on Borg RPE) during lower limb functional strength training exercises and upper limb endurance exercises

	Within target (%)	**Above target RPE>4 (%)**	**Below target RPE<3 (%)**
Step ups	74 (41 – 96)	0 (0 – 1)	23 (0 – 47)
Sit to stands	75 (43 – 97)	0 (0 - 1)	25 (3 – 47)
Upper limb exercise	61 (51 – 71)	0 (0 - 0)	33 (21 – 39)

Data presented as a percentage of the total number of sessions, expressed as median (interquartile range); RPE: rating of perceived exertion.

Table 4.7. Proportion of sessions where oxygen saturation was maintained ≥92%

	Within target SpO_2 (%)
Corridor walking	98 (95 – 100)
Treadmill walking	98 (95 – 100)
Cycle ergometry	100 (100 – 100)
Step ups	96 (94 – 98)
Sit to stands	100 (96 – 100)
Upper limb exercise	100 (98 – 100)

Data presented as a percentage of the total number of sessions, expressed as median (interquartile range); SpO_2: oxygen saturation.

4.3.9 Exercise capacity outcomes at baseline and at "12 weeks", following supervised exercise training

Data collected at "12 weeks" were compared with baseline data to determine whether, in the exercise group, changes in exercise capacity and cardiopulmonary and symptom responses occurred following the supervised exercise training period. Four exercise group and five control group participants were assessed at "12 weeks". Summary data are presented in Table 4.8 for the exercise group and Table 4.10 for the control group. Complete data sets are provided in Appendices 8 to 16. There were no significant differences observed in exercise capacity outcomes and cardiopulmonary and symptom responses, in the control group, between assessments at baseline and "12 weeks" (Table 4.10, Appendices 8 - 16).

4.3.9.1 Incremental cardiopulmonary exercise test

Peak exercise

Individual plots of the $V'O_2$ peak data indicate all four participants in the exercise group demonstrated an improvement in aerobic capacity. Despite the small sample size, the exercise group demonstrated a significant improvement in $V'O_2$ peak from baseline to reassessment (baseline: 1125mL/min, IQR 1109-1296mL/min; "12 weeks": 1253mL/min, IQR 1227-1423mL/min; p=0.024), as illustrated in Table 4.8, Figure 4.3 and Appendix 8.

The median peak $V'O_2$ in the control group decreased at the "12 week" assessment due to the results of two individuals (Table 4.10, Figure 4.3). This was not a statistically significant finding. The results were largely affected by one control group participant whose foot came out of the pedal strap towards the end of the test. The participant recommenced cycling, however, was unable to maintain sufficient revolutions per minute to continue exercising (as per the protocol). At the "12 week" assessment, the peak workload and peak $V'O_2$ were 11% (11W) and 19% (225mL/min) lower respectively, compared to baseline results for this individual.

Oxygen pulse ($V'O_2$/HR) was examined at given levels of $V'O_2$, namely 500mL/min, 750mL/min and 1000mL/min. Compared to the control group, oxygen pulse at 500mL/min was higher in the exercise group on reassessment (exercise: 6mL/beat, IQR 6.0-6.2mL/beat; control: 5.4mL/beat, IQR 5.2-5.7mL/beat; p=0.016).

Intention to treat analyses identified a lower breathing reserve (exercise: 19%, IQR 19-30%; control: 49%, IQR 45-50%; p=0.032; Appendix 9) and a higher oxygen pulse at 500mL/min (exercise: 6.0mL/beat, IQR 5.9-6.0mL/beat; control: 5.4mL/beat, IQR 5.2-5.7mL/beat; p=0.016) in the exercise group on reassessment.

Anaerobic Threshold

Individual plots of the $V'O_2$ at AT data indicate all four participants in the exercise group demonstrated an improvement in aerobic capacity. Despite the small sample size, $V'O_2$ at the AT improved significantly in the exercise group following the supervised exercise training period (baseline: 641mL/min, IQR 612-695mL/min; “12 weeks”: 789mL/min, IQR 747-835mL/min; p=0.005; Table 4.8; Appendix 9). Compared to the control group, $V'O_2$ at the AT was significantly higher in the exercise group on reassessment (exercise: 789mL/min, IQR 747-835mL/min; control: 771mL/min, IQR 676-806mL/min; p=0.008; Table 4.8; Figure 4.3). Further, the carbon dioxide output ($V'CO_2$) (exercise: 715mL/min; IQR 681-756mL/min; control: 599mL/min, IQR 531-672mL/min; p=0.032) and the workload at AT (exercise: 64W, IQR 59-67W; control: 40W, IQR 25-53W; p=0.032) were significantly higher in the exercise group on reassessment, when compared to the control group (Table 4.8; Appendix 9). No significant differences between groups or within groups were observed in any of the other cardiopulmonary measures collected at the AT using both *per protocol* and *intention to treat* analyses.

Ventilatory response

In order to compare V'_E at identical exercise loads, V'_E at baseline and at “12 weeks” were compared at an identical workload, namely the peak workload achieved at baseline. Compared to the control group, V'_E, expressed as a

percentage of change from baseline, had reduced significantly in the exercise group at “12 weeks” by a median of 14% (IQR 9 – 23%; p=0.032).

4.3.9.2 Constant-workload cycle ergometry test

Peak exercise

Individual plots of the endurance time data indicate all four participants in the exercise group demonstrated an improvement in exercise capacity. Despite the small sample size, endurance time on the CWLT improved significantly in the exercise group following the supervised training period (baseline: 469 seconds, IQR 422-626 seconds; “12 weeks”: 1280 seconds, IQR 1104-1386 seconds; p=0.024; Table 4.8; Appendix 10). Further, compared to the control group, endurance time was significantly greater in the exercise group at reassessment (exercise: 1280 seconds, IQR 1104-1386 seconds; control: 460 seconds, IQR 393-508 seconds; p=0.016), as illustrated in Table 4.8, Figure 4.3 and Appendix 10.

Constant-workload isotimes

Isotimes for the CWLT were defined as the equivalent time points within each test from the commencement of loaded cycling, namely 30 seconds, 60 seconds, 90 seconds and 3 minutes, in addition to the shortest test time across the three assessment blocks. At 30-seconds, the exercise group demonstrated a lower $V'O_2$ (exercise: 521mL/min, IQR 484-569mL/min; control: 581mL/min, IRQ 546-647mL/min; p=0.036) and a lower HR (exercise: 80bpm, IQR 75-86bpm; control: 100bpm, IQR 95-101bpm; p=0.036) at “12 weeks”, when compared to the control group (Appendix 11).

Between group *intention to treat* analyses identified a lower HR (exercise: 84bpm, IQR 77-85bpm; control: 100bpm, IQR 95-101bpm; p=0.008) in the exercise group on reassessment, at 30-seconds isotime (Appendix 11).

Ventilatory and symptom responses

The pattern of V'_E and symptoms scores (dyspnoea and RPE) during the CWLT changed markedly in the exercise participants at “12 weeks”, following

the supervised exercise training period. At baseline, V'_E and symptoms progressively increased to the point of symptom limitation. At "12 weeks", V'_E and symptoms plateaued several minutes into the commencement of the constant workload. Figure 4.4 and Figure 4.5 illustrate V'_E and symptom responses, respectively, during the CWLT for a representative exercise and control group participant.

Associations between V'_E and symptom scores were explored using Pearson's correlation coefficients. Fair to moderate correlations were identified between (i) V'_E and Borg dyspnoea scores (r=0.50; p=0.008), and (ii) V'_E and Borg RPE scores (r=0.44; p=0.021).

Parameters for gas exchange

There were no significant changes within or between groups at "12 weeks" for the ventilatory variables at isotime during the constant workload cycle ergometry test, namely the $V'_E V'CO_2$ and $P_{ET}CO_2$.

4.3.9.3 Six-minute walk test

Individual plots of the 6MWD data indicate three of the four participants in the exercise group demonstrated an improvement in functional exercise capacity, whilst one individual demonstrated a decrease in 6MWD of 10m. This individual's 6MWD was 105% of predicted at baseline and 104% on reassessment at "12 weeks" following the supervised exercise training program.

The exercise group demonstrated a median increase in 6MWD of 33m (IQR 12 – 90m, p=0.276; Table 4.8; Figure 4.3; Appendix 17), however, this was not a statistically significant improvement within or between groups. Compared to the control group, the 6MWD, as a percentage of predicted (125), was higher in the exercise group on reassessment (exercise: 97% predicted, IQR 96–99% predicted; control 89% predicted, IQR 83–90% predicted; p=0.017; Table 4.8; Appendix 16). Leg fatigue, reported at test end on the Borg CR10 scale, was observed to be lower in the exercise group on reassessment (exercise: 2, IQR 1-2; control: 5, IQR 4-6; p=0.016).

Intention to treat analyses identified a similar difference in leg fatigue scores between groups at test end (exercise: 2, IQR 1-2; control: 5, IQR 4-6; p=0.008), as well as lower general fatigue scores in the exercise group (exercise: 1, IQR 0-2; control: 5, IQR 4-5; p=0.008).

No significant differences between groups or within groups were observed in any of the other cardiopulmonary measures or symptom responses collected on the 6MWT.

Table 4.8. Exercise group: Exercise outcomes at baseline and at "12 weeks"

	Exercise Group		
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*
n	5	4	5
Incremental CPET			
Workload, W	102 (93 – 110)	120 (115 – 128)	116 (113 – 124)
$V'O_2$, mL/min	1114 (1094 – 1137)	1253 (1227 - 1423) †	1245 (1175 – 1261)
$V'CO_2$, mL/min	1419 (1347 - 1516)	1607 (1531 - 1810)	1553 (1467 – 1662)
V'_E, L/min	75 (56 – 78)	70 (63 – 78)	64 (63 – 76)
Heart rate, bpm	140 (139 – 150)	147 (135 – 150)	144 (140 -150)
SpO_2, %	98 (91 – 99)	94 (90 – 97)	92 (89 – 97)
Workload @AT, W	45 (29 – 51)	64 (59 – 57)✶	61 (51 – 67)
$V'O_2$ @AT, mL/min	633 (544 – 649)	789 (747 – 835)✶†	771 (676 – 806)
$V'CO_2$ @AT, mL/min	512 (512 – 628)	715 (681 – 756)✶	699 (628 – 730)
$V'_EV'CO_2$ @AT	42 (36 – 45)	37 (31 – 43)	42 (31 – 44)
Heart rate @AT, bpm	93 (83 - 94)	95 (92 – 98)	93 (93 – 96)
SpO_2 @AT, %	96 (92 – 99)	98 (97 – 98)	97 (96 – 98)
CWLT			
Workload, W	75 (68 – 77)	76 (73 – 81)	75 (68 – 77)
Endurance time, sec	436 (378 – 501)	1280 (1104 – 1386)✶†	1197 (825 – 1362)
$V'O_2$, mL/min	1213 (1110 – 1256)	1284 (1213 – 1431)	1254 (1090 – 1315)
$V'CO_2$, mL/min	1299 (1256 – 1339)	1313 (1228 – 1465)	1272 (1095 – 1354)
V'_E, L/min	62 (54 – 68)	60 (55 – 64)	58 (54 – 63)
Heart rate, bpm	141 (129 – 142)	142 (134 – 143)	142 (129 – 143)
SpO_2, %	95 (95 – 96)	97 (96 – 98)	97 (95 – 97)
6MWT			
6MWD, m	560 (483 – 610)	650 (623 - 679)	629 (606 – 670)
6MWD, % predicted	89 (85 – 93)	97 (96 – 99)✶	96 (96 – 97)
Heart rate, bpm	134 (99 – 137)	124 (111 – 137)	134 (114 – 146)
SpO_2, %	95 (93 – 96)	93 (90 – 96)	93 (91 – 95)

Data presented as median (interquartile range) at test end, unless otherwise stated; CPET: cardiopulmonary exercise test; $V'O_2$peak: peak oxygen uptake; $V'CO_2$: carbon dioxide production; V'_E: minute ventilation; bpm: beats per minute; SpO_2: oxygen saturation; AT: anaerobic threshold; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; CWLT: constant-workload test; 6MWD: six-minute walk distance (125); pred: predicted ✶p<0.05 compared to control group; †p<0.05 compared with baseline measures (ie. within group).

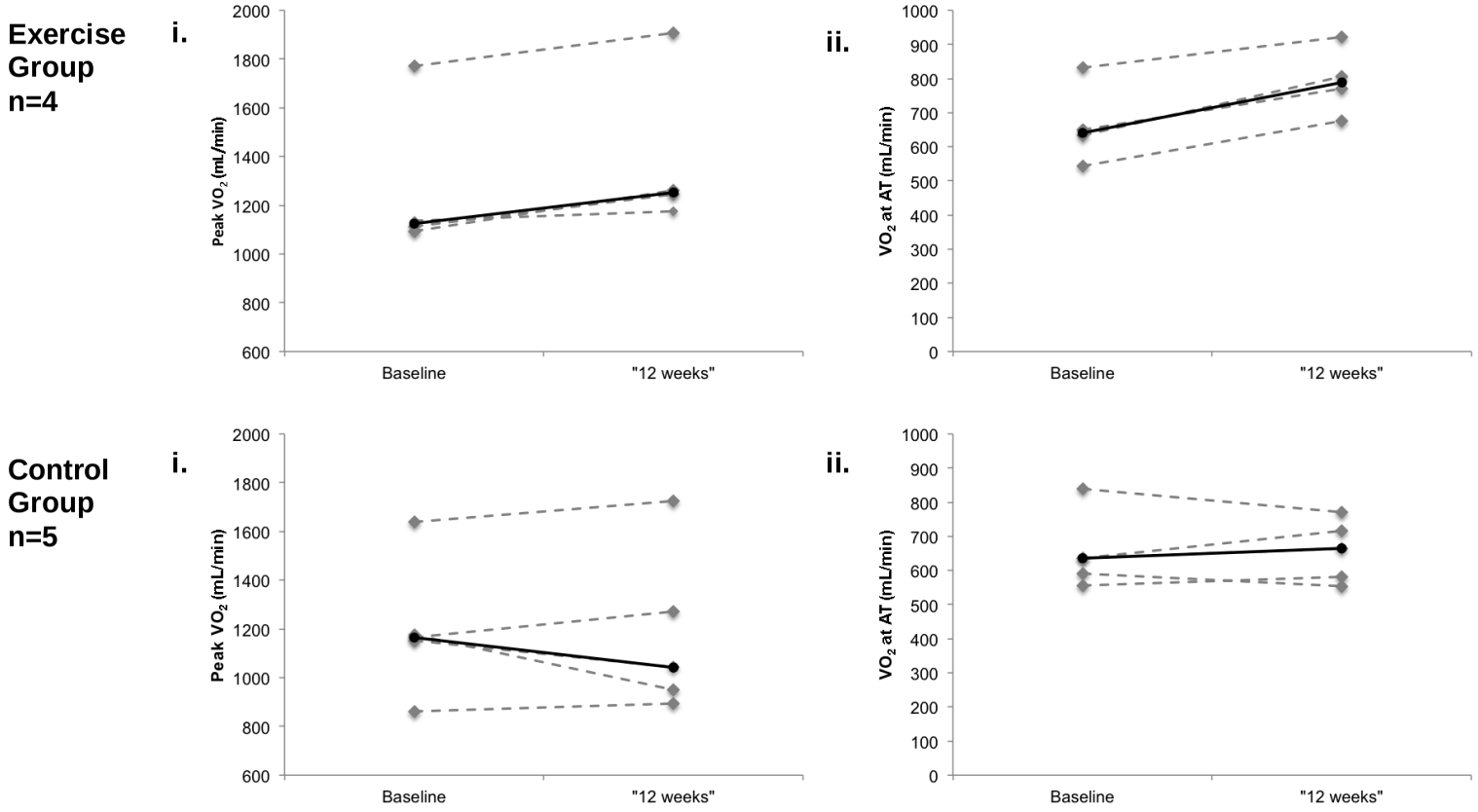

Figure 4.3. Individual plots for exercise capacity at baseline and "12 weeks"

Individual participant response (-◆-); median response for the group (-●-); (i) peak oxygen update ($V'O_2$); (ii) $V'O_2$ at the anaerobic threshold. Where the median response for the group is the same as an individual participant's response, data plots overlap.

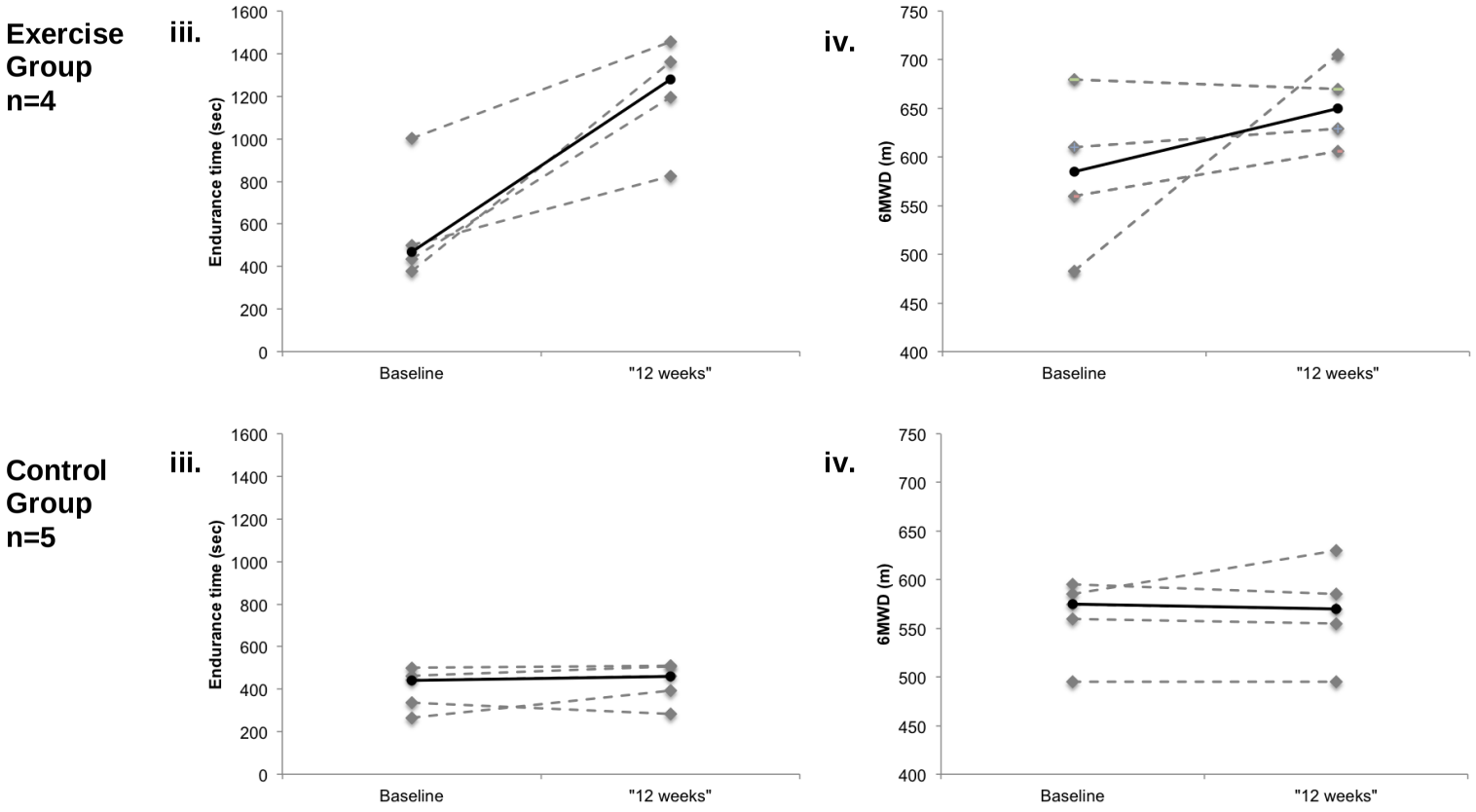

Figure 4.3. (continued) Individual plots for exercise capacity at baseline and "12 weeks"

Individual participant response (-◆-); median response for the group (-●-); (iii) endurance time; (iv) six minute walk distance (6MWD). Where the median response for the group is the same as an individual participant's response, data plots overlap.

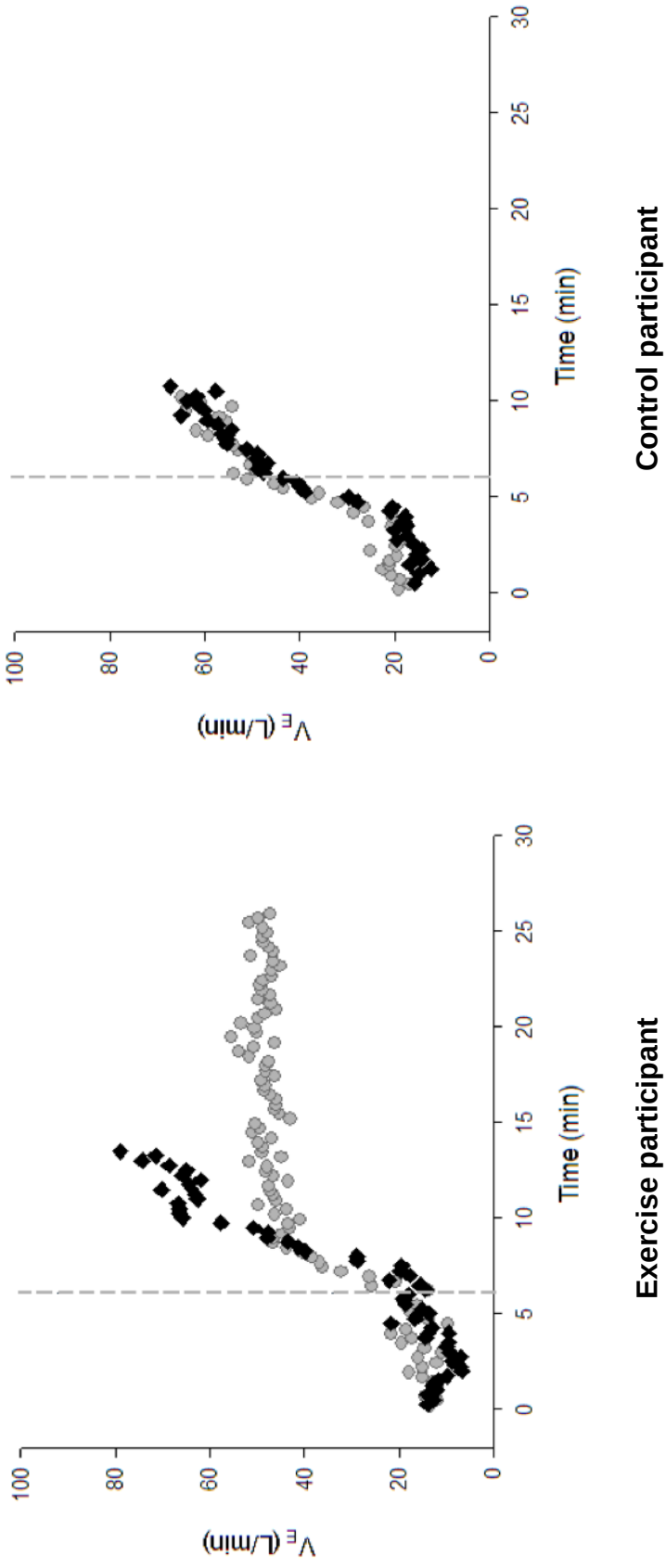

Figure 4.4. Minute ventilation (V_E) as a function of time on the constant workload test

Data are plotted at 15-second intervals at baseline (◆) and "12 weeks" (●) for a representative exercise and control group participant. Vertical grey line denotes commencement of constant workload at 6 minutes following 3 minutes of rest and 3 minutes of unloaded cycling.

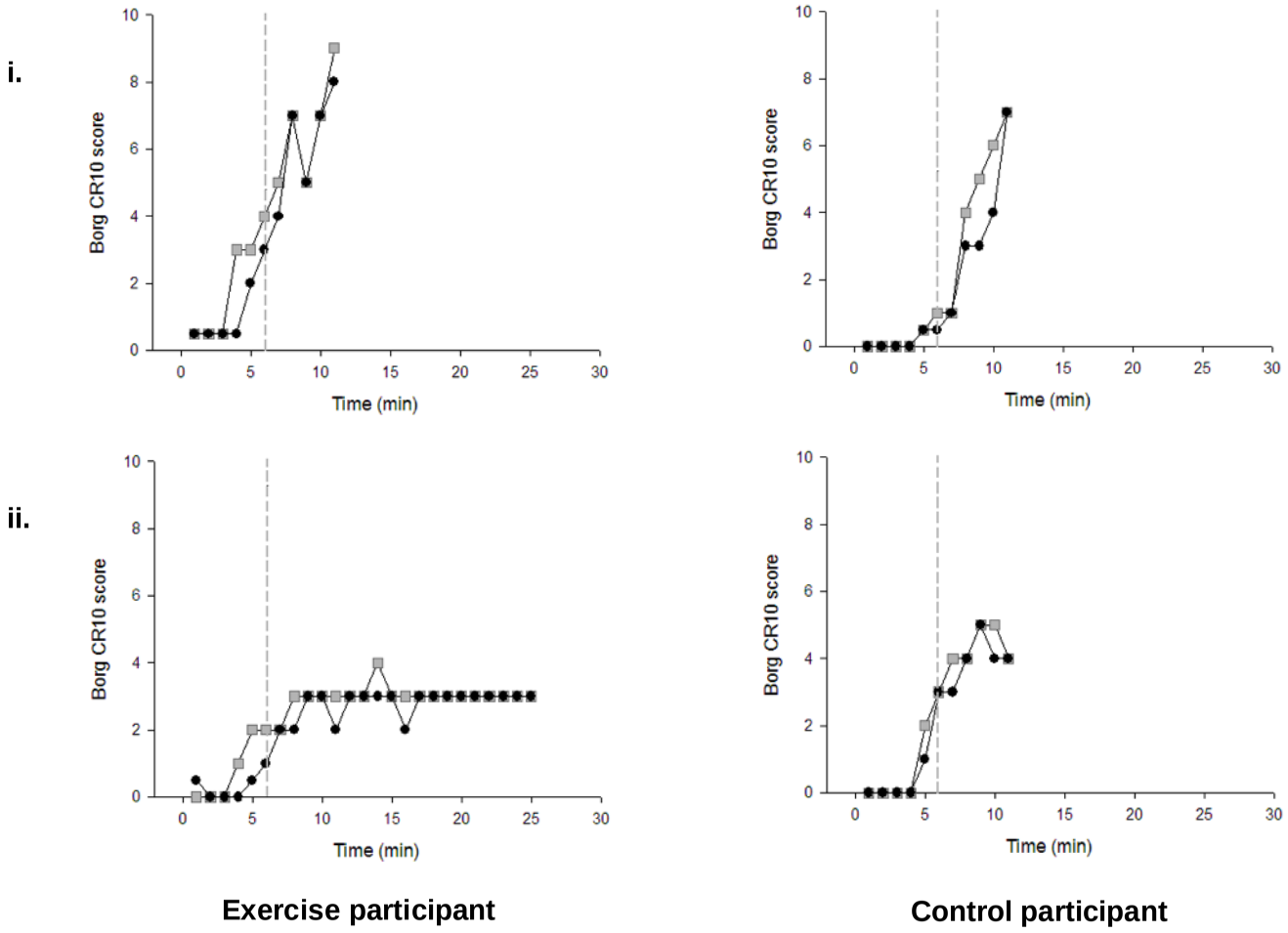

Figure 4.5. Symptom responses on the constant workload test

Borg CR10 symptom scores for (●) dyspnoea and (■) rating of perceived exertion at (i) baseline and (ii) "12 weeks" for a representative exercise and control group participant. Data are plotted at 1-minute intervals. Vertical grey line denotes commencement of constant workload at 6 minutes following 3 minutes of rest and 3 minutes of unloaded cycling.

PART THREE: UNSUPERVISED HOME EXERCISE TRAINING PERIOD

4.3.10 Exercise capacity outcomes at "12 weeks" and at "24 weeks", following an unsupervised home exercise program

Data collected at "24 weeks" were compared with data at "12 weeks" to determine whether, in the exercise group, improvements in exercise capacity had been maintained following the unsupervised home exercise program. Three exercise group and five control group participants were assessed at "24 weeks". Complete data sets are provided in Appendices 18 to 26. There were no significant differences observed in exercise capacity outcomes and cardiopulmonary and symptom responses, in the control group, between assessments at "12 weeks" and at "24 weeks" (Table 4.10, Appendices 17 - 25).

The key findings for the exercise group are outlined below and illustrated in Table 4.9.

4.3.10.1 Incremental CPET

On reassessment, individual plots of the $\dot{V}O_2$ peak data indicate individuals in the exercise group had maintained their improvement in aerobic capacity ("12 weeks": 1253mL/min, IQR 1227-1423mL/min; "24 weeks" 1286mL/min, IQR 1233-1631mL/min; p=0.593; Table 4.9; Figure 4.6; Appendix 17).

Individual plots of the $\dot{V}O_2$ at AT data indicate two of the three exercise group participants demonstrated a small decrease in $\dot{V}O_2$ on reassessment (Figure 4.6). Despite the small sample size, this decreased in $\dot{V}O_2$ at the AT was non-significant ("12 weeks": 806mL/min, IQR 789-864mL/min; "24 weeks": 718mL/min, IQR 688-882mL/min; p=1.000; Table 4.9; Appendix 18).

Compared to the control group, oxygen pulse at a $\dot{V}O_2$ of 500mL/min remained higher in the exercise group on reassessment at "24 weeks" (exercise: 6.6mL/beat, IQR 6.1-6.6mL/beat; control: 5.4mL/beat, IQR 5.3-5.4mL/beat; p=0.036). *Intention to treat* analyses also revealed a higher oxygen pulse at a $\dot{V}O_2$ of 500mL/min in the exercise group on reassessment (exercise: 6.0mL/beat, IQR 6.0-6.1mL/beat; control: 5.4 mL/beat, IQR 5.3-5.4 mL/beat; p=0.036).

4.3.10.2 Constant-workload cycle ergometry test

Individual plots indicate that endurance time for two of the three exercise group participants decreased on reassessment at “24 weeks” (Figure 4.6). Despite the small sample size, however, this decrease in endurance time was non-significant (“12 weeks”: 1197 seconds, IQR 1011-1328 seconds; “24 weeks” 1003 seconds, IQR 897 – 1257 seconds; p=0.593; Table 4.9; Appendix 19). Between groups, endurance time at “24 weeks” remained significantly higher in the exercise group (exercise: 1003 seconds, IQR 897–1257 seconds; control: 416 seconds, IQR 397–430 seconds; p=0.036; Table 4.9).

Intention-to-treat analyses revealed a significant difference between groups at “24 weeks” in HRR, 30 seconds into the commencement of loaded cycling (30-seconds isotime), with the exercise group demonstrating a higher HRR of 50% compared to 43% in the control group (exercise: 90bpm, IQR 84-90bpm; control: 73bpm, IQR 71-76bpm; p=0.016).

4.3.10.3 Six-minute walk test

Individual plots indicate that 6MWD for one of the three exercise group participants decreased on reassessment at “24 weeks” (Figure 4.6). The median 6MWD decreased from 629m (IQR 618–667m) at “12 weeks” to 615m (IQR 608–668m) at “24 weeks”, which despite the small sample size, was a non-significant finding (p=1.000; Table 4.9; Appendix 25).

PART FOUR: HEALTH-RELATED QUALITY OF LIFE AND WHO FUNCTIONAL CLASSIFICATION

4.3.11 Health-related quality of life outcomes and self-reported physical activity levels at "12 weeks" and "24 weeks"

There were no significant differences in responses observed in the CAMPHOR scale scores or SF-36 domain scores in the exercise group on reassessment at "12 weeks" (Table 4.11) and "24 weeks" (Table 4.12) using *per protocol* and *intention to treat* analyses. There were no differences in the responses observed in the control group across the three assessment blocks also (Table 4.13). Figure 4.7 illustrates individual participants scores on the three CAMPHOR scales at baseline and at "12 weeks".

There were no differences observed in reported physical activity levels, expressed as MET-minutes/week, assessed using the iPAQ within or between groups on reassessment at "12 weeks" and at "24 weeks" (Table 4.11 - 4.13).

4.3.12 World Health Organisation Functional Classification

There were no significant differences observed in WHO functional classification within or between groups on reassessment at "12 weeks" and "24 weeks" using *per protocol* and *intention to treat* analyses (Table 4.11-4.13).

Table 4.9. Exercise group: Exercise outcomes at “12 weeks” and at “24 weeks”

	Exercise Group			
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*
n	3	5	3	5
Incremental CPET				
Workload, W	124 (119 – 132)	116 (113 – 124)	117 (110 – 127)	116 (103 – 117)
$V'O_2$, mL/min	1262 (1253 – 1584)	1245 (1175 – 1261)	1286 (1233 – 1631)	1181 (1175 – 1286)
$V'CO_2$, mL/min	1553 (1510 – 1902)	1553 (1467 – 1662)	1665 (1590 – 2004)	1662 (1514 – 1665)
V'_E, L/min	70 (63 – 78)	64 (63 – 76)	83 (73 – 86)	64 (63 – 83)
Heart rate, bpm	150 (130 – 150)	144 (140 -150)	131 (120 – 142)	142 (132 – 147)
SpO_2, %	97 (94 - 98)	92 (89 – 97)	95 (91 – 97)	89 (88 – 95)
Workload @AT, W	67 (64 – 68)	61 (51 – 67)	50 (48 – 58)	50 (46 – 51)
$V'O_2$ @AT, mL/min	806 (789 – 864)	771 (676 – 806)	718 (688 – 882)	676 (657 – 718)
$V'CO_2$ @AT, mL/min	730 (715 – 782)	699 (628 – 730)	649 (614 - 757)	628 (579 – 649)
$V'_EV'CO_2$ @AT	37 (31 – 43)	42 (31 – 44)	41 (35 – 41)	41 (30 – 41)
Heart rate@AT, bpm	96 (93 – 99)	93 (93 – 96)	86 (84 – 88)	92 (88 – 93)
SpO_2 @AT, %	97 (97 – 98)	97 (96 – 98)	95 (94 – 97)	95 (93 – 98)
CWLT				
Workload, W	77 (83 – 86)	75 (68 – 77)	77 (73 – 86)	75 (68 – 77)
Endurance time, sec	1197 (1011 – 1328)	1197 (825 – 1362)	1003 (897 – 1257)✶	1003 (790 – 1362)
$V'O_2$, mL/min	1254 (1172 – 1515)	1254 (1090 – 1315)	1406 (1267 – 1729)	1315 (1128 – 1406)
$V'CO_2$, mL/min	1272 (1184 – 1535)	1272 (1095 – 1354)	1413 (1315 – 1716)	1354 (1217 – 1413)
V'_E, L/min	60 (55 – 64)	58 (54 – 63)	75 (70 – 76)	64 (58 – 75)
Heart rate, bpm	142 (125 - 144)	142 (129 – 143)	150 (129 – 154)	143 (129 – 150)
SpO_2, %	97 (95 – 98)	97 (95 – 97)	96 (94 – 97)	96 (95 – 97)
6MWT				
6MWD, m	629 (618 – 667)	629 (606 – 670)	615 (608 - 668)	615 (600 – 670)
6MWD, % predicted	96 (96 – 97)	96 (96 – 97)	98 (95 – 98)	98 (92 – 99)
Heart rate, bpm	134 (118 – 140)	136 (117 – 149)	146 (126 – 154)	146 (117 – 156)
SpO_2, %	91 (89 – 94)	93 (91 – 95)	94 (90 – 96)	94 (93 – 95)

Data presented as median (interquartile range) at test end, unless otherwise stated; CPET: cardiopulmonary exercise test; $V'O_2$peak: peak oxygen uptake; $V'CO_2$: carbon dioxide production; V'_E: minute ventilation; bpm: beats per minute; SpO_2: oxygen saturation; AT: anaerobic threshold; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; CWLT: constant-workload test; 6MWD: six-minute walk distance (125); pred: predicted; ✶$p<0.05$ compared to control group.

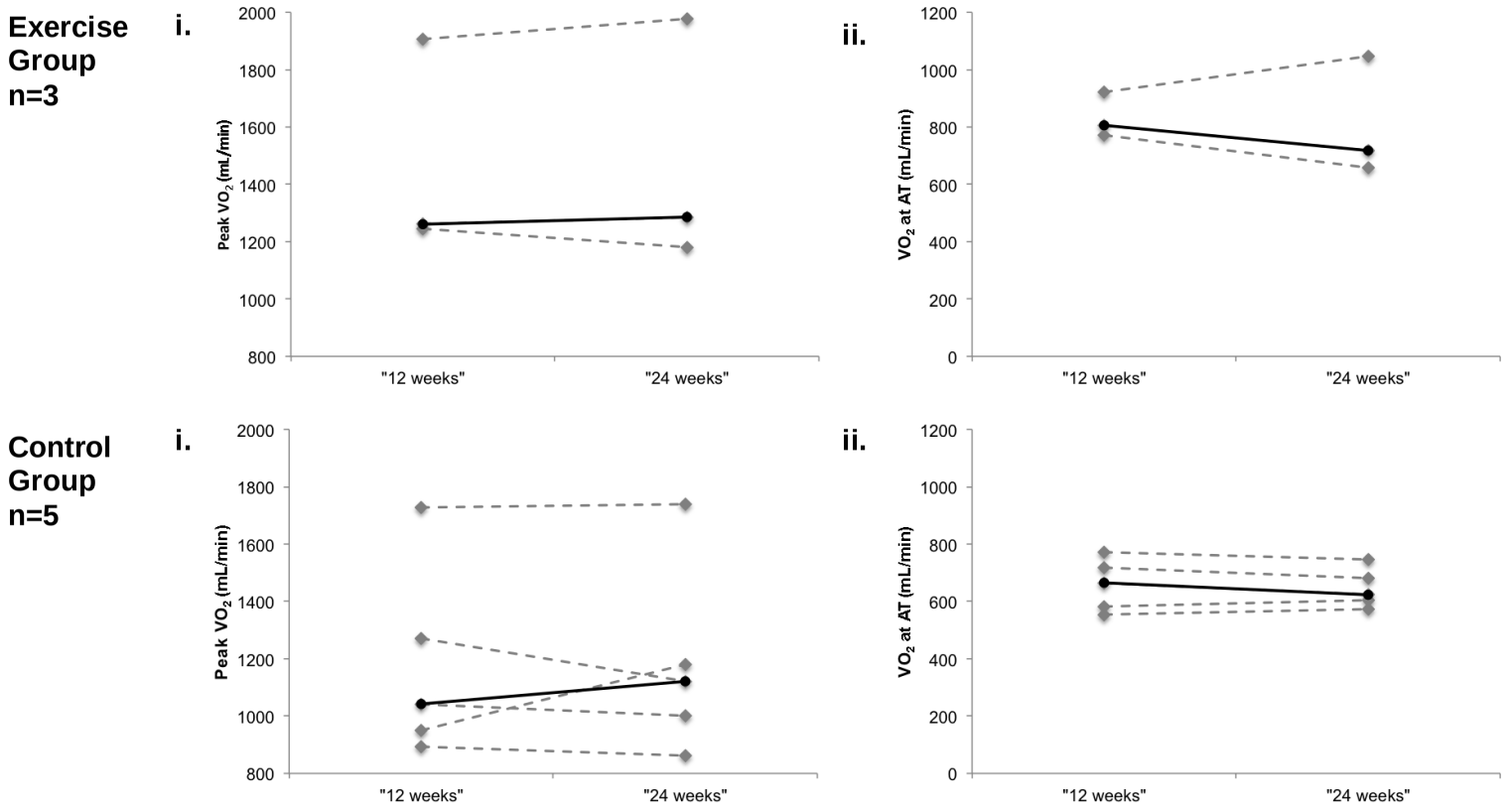

Figure 4.6. Individual plots for exercise capacity at "12 weeks" and "24 weeks"

Individual participant response (-◆-); median response for the group (-●-); (i) peak oxygen update ($V'O_2$); (ii) $V'O_2$ at the anaerobic threshold. Where the median response for the group is the same as an individual participant's response, data plots overlap.

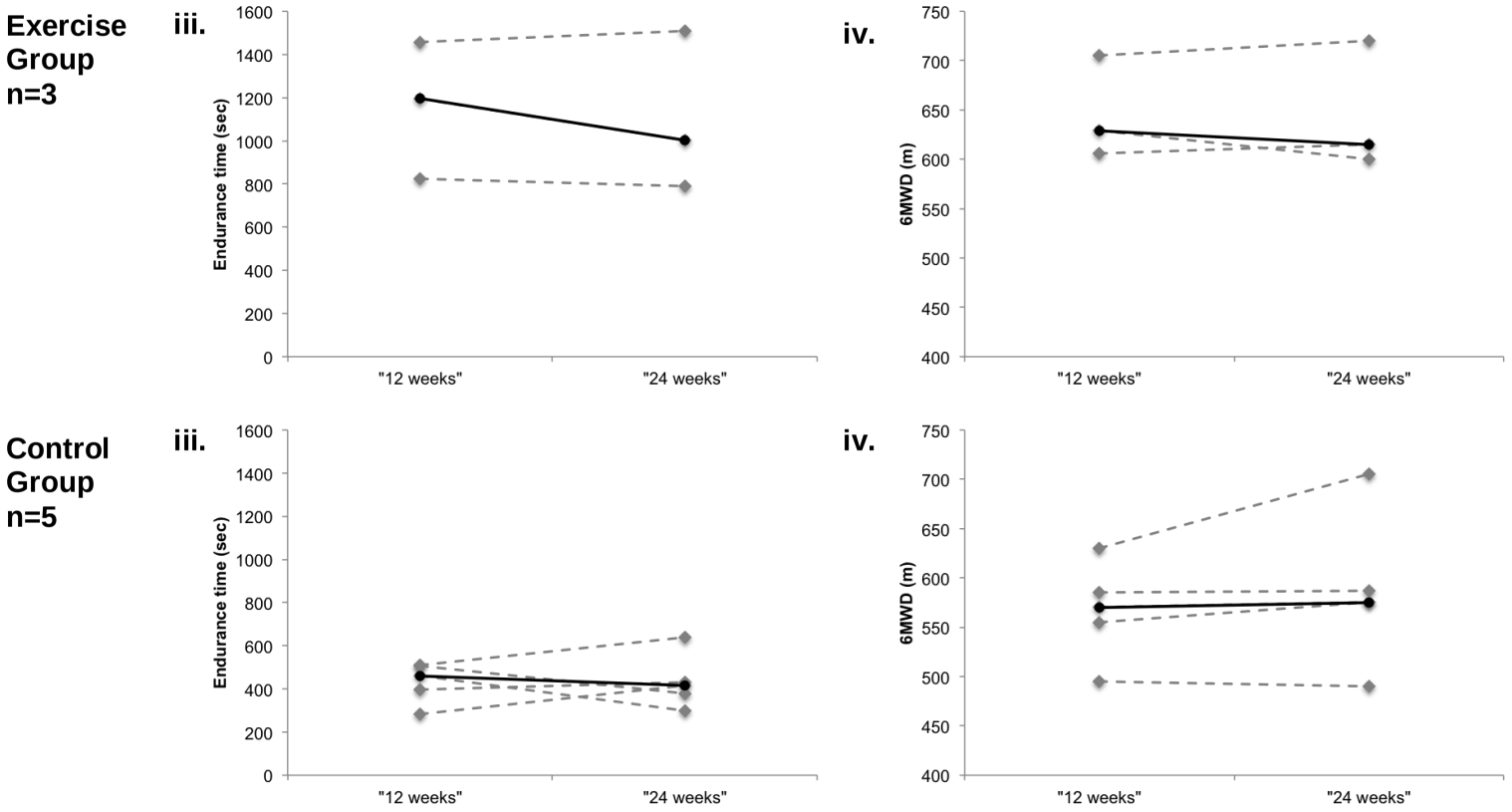

Figure 4.6. (continued) Individual plots for exercise capacity at "12 weeks" and "24 weeks"

Individual participant response (-◆-); median response for the group (-●-); (iii) endurance time; (iv) six minute walk distance (6MWD). Where the median response for the group is the same as an individual participant's response, data plots overlap.

Table 4.10. Control Group: Exercise outcomes at baseline, “12 weeks” and at “24 weeks”

	Control Group		
	Baseline	12 weeks	24 weeks
n	5	5	5
Incremental CPET			
Workload, W	96 (75 – 112)	85 (73 – 99)	101 (65 – 102)
$V'O_2$, mL/min	1165 (1152 – 1175)	1042 (949 – 1271)	1122 (1000 – 1181)
$V'CO_2$, mL/min	1361 (1327– 1546)	1161 (1109 – 1614)	1447 (1092 – 1512)
V'_E, L/min	49 (45 – 62)	46 (33 – 59)	49 (46 – 51)
Heart rate, bpm	136 (128 – 139)	134 (130 – 138)	130 (129 – 132)
SpO_2, %	96 (95 – 98)	97 (96 – 98)	97 (97 – 98)
Workload @AT, W	28 (26 – 59)	40 (37 – 48)	47 (31 – 49)
$V'O_2$ @AT, mL/min	636 (591 – 637)	665 (582 – 717)	623 (603 – 681)
$V'CO_2$ @AT, mL/min	571 (556 – 592)	599 (589 – 623)	589 (529 – 629)
$V'_EV'CO_2$ @AT	40 (37 – 42)	35 (33 – 40)	35 (34 – 39)
Heart rate @AT, bpm	98 (95 – 103)	105 (94 – 107)	99 (96 – 100)
SpO_2 @AT, %	96 (96 – 98)	97 (96 – 98)	97 (97 – 98)
CWLT			
Workload, W	72 (55 – 78)	72 (55 – 78)	72 (55 – 78)
Endurance time, sec	441 (338 – 463)	460 (395 – 508)	416 (379 – 430)
$V'O_2$, mL/min	1209 (1162 – 1300)	1267 (1063 – 1341)	1295 (1263 – 1304)
$V'CO_2$, mL/min	1470 (1280 – 1637)	1525 (1124 – 1665)	1584 (1357 – 1588)
V'_E, L/min	54 (44 – 61)	62 (47 – 69)	52 (52 – 56)
Heart rate, bpm	140 (136 – 154)	135 (132 – 152)	140 (135 – 147)
SpO_2, %	98 (96 – 99)	95 (94 – 98)	95 (88 – 96)
6MWT			
6MWD, m	575 (560 - 585)	570 (555 - 585)	575 (575 - 587)
6MWD, % predicted	84 (83 – 90)	89 (83 – 90)	89 (83 – 92)
Heart rate, bpm	125 (112 – 133)	135 (135 – 136)	128 (125 – 129)
SpO_2, %	95 (94 – 95)	94 (94 – 94)	94 (93 – 96)

Data presented as median (interquartile range) at test end, unless otherwise stated; CPET: cardiopulmonary exercise test; $V'O_2$peak: peak oxygen uptake; $V'CO_2$: carbon dioxide production; V'_E: minute ventilation; bpm: beats per minute; SpO_2: oxygen saturation; AT: anaerobic threshold; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; CWLT: constant-workload test; 6MWD: six-minute walk distance (125); pred: predicted.

Table 4.11. Exercise Group: Health-related quality of life, physical activity and World Health Organisation functional classification at baseline and at "12 weeks"

		Exercise Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*
n	5	4	5
CAMPHOR Scales			
Symptoms	15 (3 – 16)	9 (5 – 13)	13 (5 – 13)
Activities	6 (5 – 8)	7 (6 – 8)	7 (6 – 8)
Quality of Life	14 (3 – 15)	4 (0 – 9)	7 (0 – 13)
SF-36 Domains			
Physical Functioning	40 (20 – 65)	55 (44 -65)	45 (40 – 65)
Role Physical	44 (38 – 75)	47 (25 – 75)	38 (25 – 69)
Bodily Pain	100 (64 – 100)	68 (60 – 81)	64 (62 – 74)
General Health	65 (37 – 72)	65 (55 – 68)	62 (35 – 67)
Vitality	50 (38 – 63)	59 (55 - 63)	56 (50 – 63)
Social Functioning	75 (38 – 75)	81 (63 – 100)	63 (63 – 100)
Role Emotional	83 (75 - 84)✶	75 (50 - 94)	58 (42 – 92)
Mental Health	70 (60 - 70)✶	75 (71 – 76)	75 (60 – 75)
Physical component summary	37 (34 – 49)	42 (39 – 44)	40 (36 – 43)
Mental component summary	48 (46 – 51)✶	51 (46 – 55)	49 (37 – 53)
International Physical Activity Questionnaire			
MET-minutes/week	594 (198 – 1272)	2321 (1575 – 2838)	1851 (747 – 2790)
WHO Functional Classification			
Class II, n	3	4	4
Class III, n	2	0	1

Data presented as median (interquartile range) unless otherwise stated; MET: metabolic equivalent; WHO: World Health Organisation; ✶p<0.05 compared to control group.

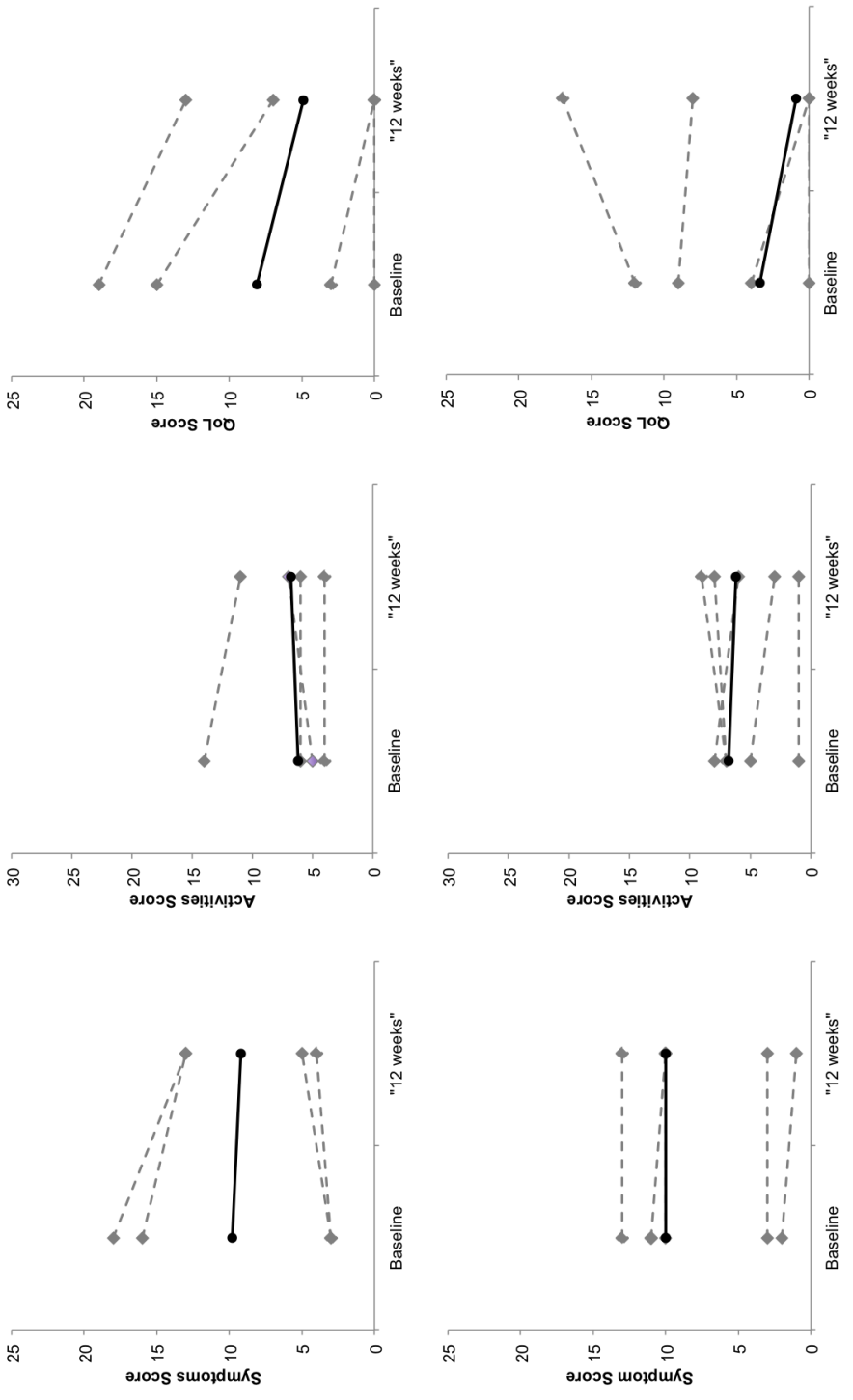

Figure 4.7. CAMPHOR scale scores at baseline and "12 weeks"
Individual participant responses (-◆-); median responses for the group (-●-).

Table 4.12. Exercise Group: Health-related quality of life, physical activity and World Health Organisation functional classification at “12 weeks” and at “24 weeks”

	Exercise Group			
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*
n	3	5	3	5
CAMPHOR Scales				
Symptoms	13 (9 – 13)	13 (5 – 13)	9 (7 – 12)	9 (5 – 15)
Activities	6 (5 – 9)	7 (6 – 8)	6 (6 – 8)	7 (6 – 8)
Quality of Life	7 (4 – 10)	7 (0 – 13)	10 (6 – 12)	10 (1 – 13)
SF-36 Domains				
Physical Functioning	45 (43 -55)	45 (40 – 65)	50 (45 – 55)	50 (40 – 60)
Role Physical	69 (47 – 81)	38 (25 – 69)	56 (50 – 72)	44 (38 – 56)
Bodily Pain	74 (68 – 87)	64 (62 – 74)	100 (81 – 100)	64 (61 – 100)
General Health	62 (49 – 66)	62 (35 – 67)	72 (51 -75)	67 (35 – 72)
Vitality	56 (53 – 59)	56 (50 – 63)	38 (38 – 50)	38 (38 – 63)
Social Functioning	100 (81 – 100)	63 (63 – 100)	75 (63 – 88)	63 (50 – 75)
Role Emotional	92 (75 – 96)	58 (42 – 92)	100 (88 – 100)	75 (42 – 100)
Mental Health	75 (75 – 78)	75 (60 – 75)	85 (83 – 90)	80 (60 – 85)
Physical component summary	40 (38 – 43)	40 (36 – 43)	42 (36 – 45)	42 (34 – 43)
Mental component summary	53 (51 – 56)	49 (37 – 53)	57 (54 – 58)	50 (37 – 57)
International Physical Activity Questionnaire				
MET-minutes/week	1851 (1299–2417)	1851 (747–2790)	2165 (1365-2709)	2165 (546-2790)
WHO Functional Classification				
Class II, n	3	4	3	4
Class III, n	0	1	0	1

Data presented as median (interquartile range) unless otherwise stated; MET: metabolic equivalent; WHO: World Health Organisation.

Table 4.13. Control group: Health-related quality of life, physical activity and World Health Organisation functional classification at baseline, “12 weeks” and “24 weeks”

	Control Group		
	Baseline	12 weeks	24 weeks
n	5	5	5
CAMPHOR Scales			
Symptoms	10 (3 – 11)	10 (3 – 10)	9 (7 – 13)
Activities	7 (5 – 7)	6 (3 – 8)	9 (5 – 10)
Quality of Life	4 (0 – 9)	0 (0 – 8)	5 (0 – 5)
SF-36 Domains			
Physical Functioning	45 (35 – 55)	55 (45 – 55)	50 (35 – 60)
Role Physical	100 (94 – 100)	63 (44 – 100)	88 (44 – 100)
Bodily Pain	74 (62 – 100)	51 (51 – 74)	62 (62 – 84)
General Health	37 (32 – 50)	45 (35 – 72)	42 (32 – 75)
Vitality	50 (38 – 63)	38 (31 – 75)	50 (25 – 56)
Social Functioning	88 (75 – 100)	75 (63 – 100)	100 (75 – 100)
Role Emotional	100 (100 – 100)	100 (83 – 100)	100 (75 – 100)
Mental Health	80 (80 – 90)	85 (75 – 85)	90 (85 – 95)
Physical component summary	38 (36 – 47)	36 (29 – 47)	38 (31 – 48)
Mental component summary	56 (55 – 62)	52 (52 – 59)	59 (48 – 60)
International Physical Activity Questionnaire			
MET-minutes/week	2856 (1188 – 9918)	1668 (891 – 2868)	4584 (1188 - 9918)
WHO Functional Classification			
Class II, n	3	3	3
Class III, n	2	2	2

Data presented as median (interquartile range) unless otherwise stated; MET: metabolic equivalent; WHO: World Health Organisation.

4.4 Discussion

This study has demonstrated that exercise training in individuals with PAH results in increased $V'O_2$ peak, $V'O_2$ at the AT and endurance time, indicating an improvement in exercise capacity. These findings support those previously published in the literature (6, 23, 28-31). Importantly, the improvements in exercise capacity in this study were achieved without serious adverse events. Further, this study is the first to demonstrate that improvements in exercise capacity, achieved through a supervised training program, can be maintained with an unsupervised home exercise program.

The control group remained stable throughout the study period, with no significant changes observed in exercise capacity, cardiopulmonary and symptom responses across the three assessment blocks. The stability of the control group suggests good repeatability of the exercise measurements over the 24-week study period and indicates that the changes observed in the exercise group are greater than those likely to occur by chance alone.

4.4.1 Participants, recruitment and study limitations

Recruitment of participants for this study was challenging. Many individuals with PAH, who met the inclusion criteria, had work and/or home commitments that precluded them from participating. Additionally, 11 individuals declined participation due to the time commitment required for the study. Consequently, of the 121 patients with PAH on the database, 14 met the inclusion criteria and agreed to participate in the study, of which 10 were confirmed suitable for the study following baseline assessment. Whilst two participants were withdrawn during the study period, neither was withdrawn due to deterioration in clinical status related to PAH.

The very small sample size is a major limitation in this study. However, despite the small sample size, improvements in exercise capacity and a reduction in symptoms were demonstrated following exercise training. The small sample size has limited the ability to explore the physiological mechanisms related to improvements in exercise capacity. Further, the small

sample size limits the generalisability of these findings. The results of this study should be considered as exploratory and not necessarily representative of the wider PAH population. Further out-patient based studies are required to investigate the effects of exercise training in this population.

4.4.2 Baseline characteristics

The groups were well matched for diagnosis, pharmaceutical therapy and WHO functional classification. There were no significant differences at baseline between groups in exercise capacity, as measured by $V'O_2$ peak, $V'O_2$ at the AT, endurance time and 6MWD. At baseline, eight participants (80%) demonstrated a 6MWD greater than 80% of predicted (125). Despite the high 6MWD achieved (range 450m to 680m; 67% to 105% of predicted), these individuals demonstrated characteristic physiological abnormalities associated with PAH (65, 70, 74, 75), namely, low $V'O_2$ peak, low $V'O_2$ at the AT, high $V'_E V'CO_2$, and low $P_{ET}CO_2$.

The study sample was predominantly female. This is reflective of the PAH population registered with the Western Australian Pulmonary Hypertension Service. The high proportion of females recruited is also consistent with the United States-based PAH registry (175) and the predominance of females with PAH associated with connective tissue disorders (54).

One of the exercise participants demonstrated mild obstruction on spirometry and developed a ventilatory limitation to exercise on the incremental CPET, evidenced by a high respiratory rate, low breathing reserve and reported symptom limitation of breathlessness. The primary reason for test cessation on the incremental CPET in the three control group participants who presented with restrictive deficits, however, was peripheral symptom limitation, namely leg fatigue.

There were no significant differences between groups in resting pulmonary arterial pressure. The exercise group presented with higher pulmonary artery pressures and less impairment in D_LCO, compared to the control group. This is consistent with the literature which suggests D_LCO does not correlate well with the severity of PAH, based on mean pulmonary artery pressures (202).

The D_LCO for all participants in the exercise group was above the lower limit of normal. In contrast, the three control group participants who presented with restrictive deficits, had diffusion capacities below the lower limit of normal. Despite this, participants in both groups demonstrated minimal oxygen desaturation during exercise testing.

At baseline, the exercise group demonstrated a significantly higher ventilatory response on the incremental CPET, with a higher peak respiratory rate and lower breathing reserve. This, however, did not translate into higher symptom scores. The exercise group reported lower levels of dyspnoea and significantly lower levels of general fatigue on the Borg CR10 scale.

4.4.3 Efficacy of the PAH training protocol

To the best of my knowledge, the training protocol developed for this study was the first to use target HR ranges based on a calculated age-predicted HRmax in the PAH population. Participants were instructed to perform lower limb endurance exercises at an intensity that elicited a HR within 60-70% of the predicted HRmax and avoid exceeding their 70% target for the lower limb functional strength training and upper limb endurance exercises. For all exercises, participants were required to exercise within symptom limitation parameters of Borg CR10 dyspnoea and RPE scores $\leq$4 and SpO_2 $\geq$92%.

The exercise group achieved the required training intensities for the majority of the sessions. Further, these training intensities were sufficient to produce significant improvements in exercise capacity. Participants performed treadmill walking within the target HR intensity 94% of the time, compared to 86% of the time for corridor walking. The difference between treadmill and corridor walking, in part, lies in the external pacing that is afforded by the treadmill settings. Additionally, participants exceeded their prescribed walking goal at baseline, which was calculated based on 80% of the 6MWD speed. As such, participants exceeded both target HR range and prescribed walking distance at baseline, which may account for the small change in corridor distance observed during the training period. Participants exceeded

the upper limit of their target HR range 12% of the time during step ups presumably due to difficulties pacing the exercise.

Scores for perceived exertion (RPE) were maintained within or below target ranges (≤4). Dyspnoea scores were ≤4 for all exercises also. Symptom scores for dyspnoea and RPE were lowest during the upper limb exercises, compared to all the lower limb exercises, most likely due to less cardiopulmonary stress and ventilatory requirements as a result of the smaller muscle mass involved in upper limb exercises (203). Oxygen saturation levels were maintained above 92% for the majority of exercises. A decrease in SpO_2 was occasionally observed during lower limb exercises, with step ups inducing the greatest decrease in SpO_2, with levels below 92% during 5 sessions (5%). This is most likely due to the greater muscle mass involved in lower limb exercise and the higher oxygen requirements of these muscle groups (204).

4.4.3.1 Use of target heart rate and symptom ranges for prescribing exercise intensity

The decision to use an age-predicted HRmax calculation was made because it is not routine practice in Australia for patients with cardiopulmonary conditions to undergo a CPET prior to enrolment into an exercise training program (113). This approach to exercise training was suitable for four of the five individuals randomised to the exercise group, however, symptom responses were used to guide exercise intensity in one participant in the exercise group who was prescribed a beta-blocker. The exercise training outcomes for this participant, however, were no different to the outcomes of those participants who were trained using a combination of target HR range and symptom limitation parameters. Further, chronotropic incompetence was identified in one control group participant, suggesting the use of target HR ranges in this participant would have been inappropriate. As such, exercise training based on target HR range in two of the 10 participants (i.e. 20%) recruited to this study would not have been suitable.

An adverse event was recorded in one participant during the supervised exercise training sessions whereby, with an increase in exercise intensity, the HR did not increase accordingly. Failure of the HR to increase with an increase in intensity was not identified on any of the three exercise tests prior to commencing exercise training. The participant reported an increase in the level of fatigue prior to the commencement of the exercise training session and reported increasing symptoms scores during this session. The participant continued in the study without any further episodes.

Target symptom ratings of dyspnoea and RPE are commonly used to guide exercise intensity in other cardiopulmonary populations. In the COPD population, a score of 3 (moderate) for dyspnoea on the Borg CR10 scale has been shown to correlate to approximately 75% $V'O_2$ peak (205) and is recommended to guide intensity of training during supervised sessions, as well as inform individuals on the required target to maintain when performing home exercise programs (140). Perceived exertion scores of 12-14 on the traditional 15-point RPE scale (206), indicating a moderate intensity of exercise, have been reported to be well tolerated in the heart failure population (207) and recommended for use to guide exercise intensity in this population (12, 178). Further, RPE scores have been shown to have a strong correlation with HR (208) and some evidence exists to support the use of RPE to regulate exercise response in patients using beta-blockers (209).

In summary, symptom limitation parameters appear suitable for use in this patient population, consistent with that recommended in other cardiopulmonary populations. Monitoring of HR, via a Polar monitor, is recommended, particularly in the situation where an individual has difficulty quantifying their symptoms, to ensure HR is appropriately responding to a given level of exercise intensity.

4.4.4 Exercise capacity

This study assessed exercise capacity using a CPET, CWLT and 6MWT at each assessment block to determine the effectiveness of exercise training. The incremental CPET was chosen because it is considered the gold

standard for the assessment of exercise capacity and provides information to determine the causes of exercise intolerance in patients with cardiopulmonary conditions (41, 44). The CWLT has been reported to be more responsive than the CPET and 6MWT in detecting improvement in exercise tolerance following exercise training in other studies in the PAH population (23, 31), as well as in the COPD population (99, 210). Further, endurance time on the CWLT has been identified as an important clinical endpoint for monitoring response to therapy in PAH (5, 100). The 6MWT is one of the most commonly used outcome measures for determining the effectiveness of exercise training programs in cardiopulmonary populations (101) and has been widely used in PAH-specific pharmaceutical trials as a primary endpoint (42).

The time between the baseline and “12 weeks” assessment was significantly different between groups. Reassessments were not delayed for medical reasons, however, reassessments for two of the exercise group participants were delayed due to the timing of recruitment, which resulted in two participants commencing their supervised training period several weeks prior to Christmas. Over the Christmas period, there were no exercise sessions conducted at Royal Perth Hospital on the public holidays, which necessitated an increase in the number of weeks of attendance to ensure participants completed the required number of exercise training sessions.

4.4.4.1 Improvements in exercise capacity at “12 weeks”, following supervised exercise training

Following the 12-week supervised training period, the exercise group demonstrated statistically significant improvements in exercise capacity on both the incremental CPET and the CWLT.

Three previous studies in the PAH population have reported significant improvements in $\dot{V}O_2$ peak following exercise training (6, 28, 29). The improvement of 10% in $\dot{V}O_2$ peak in the exercise group at “12 weeks” is of a similar magnitude to that reported by Mereles et al (17%) (6), Fox et al (9%) (28) and Grünig et al (17%) (29, 30). Further, there were no significant

changes in RER and Borg CR10 dyspnoea and RPE scores, suggesting the improvements in $V'O_2$ peak were not related to motivation levels.

Two previous studies in PAH have reported significant improvements in $V'O_2$ at the AT following exercise training (6, 29). Following supervised training, the exercise group demonstrated an improvement of 22% in $V'O_2$ at the AT which is similar to that reported by Mereles et al (17%) (6) and Grünig et al (14%) (29). Further, in the exercise group, workload at the AT was higher at "12 weeks" which is consistent with three other exercise training studies in the PAH population (6, 23, 29).

Endurance time on the CWLT improved in the exercise group by over 170% following supervised training. Only two previous studies have measured endurance time on a CWLT in PAH populations following exercise training and reported improvements of 89% (23) and 53% (31). A minimal important difference (MID) in endurance time following exercise training is yet to be determined for the PAH population. In the COPD population, a change in endurance time on a CWLT of 100 to 200 seconds has been identified as clinically important (99). Without an MID for the PAH population, it is difficult to interpret the observed changes and determine the magnitude of change considered meaningful for an individual, however, an improvement of over 170% would be expected to be clinically important in this population.

The four participants in the exercise group who were reassessed at "12 weeks" demonstrated a median increase of 33m in the 6MWD. Whilst the change in 6MWD was not statistically significant, this magnitude of change is equivalent to the reported MID of 33m (95% confidence interval 15 – 50m) described in a PAH-specific pharmaceutical trial (127), and as such, is likely to represent a meaningful change for the individual. The baseline 6MWD for the exercise group was 560m, which equates to 89% of the predicted 6MWD based on a regression equation derived in healthy West Australians (125). This suggests that the exercise group had a high 6MWD at baseline and as such, may have had limited potential to increase 6MWD on reassessment at "12 weeks". Consequently, the high baseline 6MWD in the exercise group is likely to have affected the responsiveness of the 6MWT and, together with the

small sample size, is likely to have reduced the possibility of detecting a statistically significant change in functional exercise capacity. De Man and colleagues (23) reported a similar finding, in that their PAH participants had a high baseline 6MWD (496±108m) and subsequently demonstrated a non-significant change in 6MWD of approximately 7m to 505±108m (6MWD calculated based on Figure 1 in publication) following exercise training. De Man et al (23) also reported significant improvements in endurance time on a CWLT. The findings from both the study described in this thesis and that conducted by De Man et al (23), supports the contention raised by Degano and colleagues (42) that for individuals who walk greater than 450m, the 6MWT may not be the most responsive test to detect change following an intervention.

The physiological mechanisms underlying the improvements in exercise capacity in PAH remain largely unknown, primarily due to the paucity of literature in this area and the small subject numbers in the majority of studies. Benefits from exercise training in PAH have been attributed to peripheral muscle change rather than alterations in pulmonary haemodynamics and gas exchange (6, 23, 28, 31). In this study, supervised exercise training led to no change in measures of gas exchange, including $V'_E V'CO_2$ and $P_{ET}CO_2$ in the exercise group. This suggests the changes in the pulmonary vasculature related to PAH remain unaffected by exercise training, a finding which is consistent with that reported by Fox et al (28). The improvements in exercise capacity observed in the exercise group following training, suggest the exercising muscles are utilising oxygen more efficiently and reflects an improvement in the aerobic capacity of these muscles (6, 41). Additionally, between groups, the exercise group demonstrated significant reductions in HR as well as oxygen pulse at a specified $V'O_2$ (500mL/min) on the incremental CPET. This may suggest there has been some improvement in cardiac performance, or, alternatively, may indicate improved extraction of oxygen by the exercising muscles (211). The small sample size in this study limits the ability to explore these mechanisms and the study lacks statistical power to confirm these findings.

4.4.4.2 Association between ventilation and symptoms

At an identical workload, namely the peak workload achieved on the baseline incremental CPET, the exercise group demonstrated a median decrease of 14% in V'_E, on reassessment at "12 weeks". Further, an improvement in the pattern of V'_E on the CWLT following the supervised exercise training period occurred. This reflects a training effect which is likely to be due to a delay in the onset of acidosis and improvements in the oxidative capacity and efficiency of the peripheral muscles (211). Whilst two other studies in PAH have reported improvements in V'_E following exercise training (28, 31), this study has been the first to report significant associations between V'_E and Borg CR10 symptom scores of dyspnoea and perceived exertion. The increase seen in endurance time appears to be related to the improvements in V'_E and symptoms, which has translated into a capacity to exercise for longer.

4.4.4.3 Maintenance of exercise capacity at "24 weeks", following an unsupervised home exercise program

The present study is the first to evaluate whether benefits achieved during a period of supervised exercise training can be maintained with an unsupervised home exercise program.

The improvements in exercise capacity achieved in the exercise group at "12 weeks" were maintained at "24 weeks" following the home exercise program, as evidenced by no significant change in $V'O_2$ peak, $V'O_2$ at AT and endurance time at these two assessments. Further, oxygen pulse and HRR were higher on reassessment at "24 weeks". Whilst the results indicate exercise capacity has been maintained following the unsupervised home exercise program, the very small sample size limits the generalisability of these findings.

These results suggest that aerobic capacity has been maintained, presumably due to the more efficient utilisation of oxygen by the exercising muscles (6, 41). Whilst this is the first study in the PAH population to examine maintenance of benefits achieved in exercise capacity following a

home exercise program, the literature in populations with chronic respiratory disease reports that following a period of 6 to 24 months, exercise capacity has decreased close to pre-training levels (36, 37, 39, 40). One RCT investigating the effects of exercise training in individuals with interstitial lung disease (ILD) (38) reported significant improvements in exercise capacity immediately following an 8-week supervised exercise training program, however, at 6 months, the benefits from training had not been sustained. The study in the ILD population was similar in design to this study in PAH, in terms of provision of a supervised exercise training program, followed by an unsupervised home exercise program. The type of ILD, in particular the rapidly progressive nature of idiopathic pulmonary fibrosis, and limited pharmaceutical management for this population (38), may have impacted on the results of the study.

4.4.4.4 Health-related quality of life, self-reported physical activity and WHO functional classification

The exercise group displayed greater variability at baseline across all three scales on the CAMPHOR, when compared to the control group. Where an individual in the exercise group reported a higher score, indicating a greater level of impairment, a lower score was reported at “12 weeks”, following the supervised exercise training period. However, those in the exercise group who reported a good level of HRQoL at baseline showed little improvement, indicating that there may be a ceiling effect on the questionnaire. Whilst the Australian and New Zealand CAMPHOR validation study (165) reported minimal floor and ceiling effects, that study was not designed to explore the ability of the CAMPHOR to detect change following an intervention. The small sample size in this study is likely to have limited the ability to detect change in this measure and to assess whether the CAMPHOR is responsive to changes following exercise training.

At baseline, there was a significant difference between groups observed in the Role Emotional, Mental Health and the Mental Component summary scores on the SF-36, with the exercise group demonstrating a greater level of impairment in HRQoL. On reassessment at “12 weeks” and “24 weeks”, *per*

protocol analyses indicates that scores for these domains improved such that the difference between groups was no longer significant. This suggests there has been some improvement in HRQoL in the exercise group following exercise training, despite the fact that no significant within group differences were identified.

Three other studies (6, 29, 30) have assessed HRQoL as an outcome measure following exercise training. These authors reported significant improvements in the Physical and Mental Component summary scores (6), as well as the Physical Functioning (6, 29, 30), Role Physical (6, 29, 30), Vitality (6, 29, 30), Social Functioning (6, 29, 30), Mental Health (6, 29, 30), Role Emotional (29, 30) and General Health (29) domains on the SF-36 . These three studies utilised the same exercise training protocol comprising a 3-week inpatient exercise training program, followed by a 12-week home exercise program. Improvements reported in HRQoL may, in part, be due to the intensive 3-week inpatient training period, which involved daily contact with health professionals, in addition to fortnightly telephone calls during the subsequent 12-week home exercise program period (6). In other cardiopulmonary populations, exercise training is commonly associated with improvements in HRQoL that persist beyond program completion (14, 37, 135).

There were no significant changes identified in self-reported physical activity on the iPAQ in either group, across the three assessment blocks. There was large variability in energy expenditure, expressed as MET-minutes/week, using the iPAQ within and between groups at all three assessments. This is likely to be due to the subjective nature of the questionnaire and the fact that physical activity questionnaires are more appropriately used for large population studies rather than small scale interventional studies (212). Objective measures of physical activity using activity monitors provide more accurate information regarding energy expenditure (213) and should be considered as an outcome measure in future exercise training studies in the PAH population.

Two exercise group participants were in WHO functional class III at baseline. One of these participants withdrew from the study prior to the 12-week reassessment due to illness unrelated to PAH. The other participant improved from class III to class II at “12 weeks”, a finding consistent with that reported by Mereles et al (6) and Grünig et al (29, 30) following supervised exercise training in a PAH population. The improvement in functional class for the study participant was sustained on reassessment at “24 weeks” following the unsupervised home exercise program.

4.4.5 Clinical implications and conclusions

The study findings support the hypotheses that exercise training results in significant improvements in $\dot{V}O_2$ peak, $\dot{V}O_2$ at the AT, endurance time and substantial improvements in symptom responses. Moreover, these results were maintained following an unsupervised home exercise program. A major limitation to this study was the very small sample size, which prohibits any generalisation of the findings to the wider PAH population and limits the ability to explore the mechanisms for the improvement in exercise capacity.

The training protocol developed for this study has been shown to be achievable by participants. A target HR range of 60-70% age-predicted HRmax with symptom limitation parameters of Borg dyspnoea and RPE scores of ≤ 4 resulted in demonstrable improvements in exercise capacity. Close monitoring of HR and symptom responses is recommended during exercise training in PAH due to the complexity of exercise limitation in this population.

Endurance time on the CWLT has proven a more responsive measure in this study, when compared to the 6MWT. This may, in part, be attributed to the high baseline 6MWD in the exercise group.

Whilst the small sample size in this study has had an impact on the ability to demonstrate change in HRQoL, the exercise outcomes suggest that improvements in aerobic capacity and the peripheral muscles have occurred.

The results of this study concur with those that have previously been published in the literature, adding to the evidence supporting the role of exercise training in this population. Whilst significant improvements in exercise capacity occurred in the exercise group, these findings should not be generalised to all patients with PAH due to the small sample size in this study. Recommendations for further research arising from this study are discussed in Chapter 7.

Chapter 5

COMPARISON OF PHYSIOLOGICAL AND SYMPTOM OUTCOMES DURING EXERCISE TESTING IN PULMONARY ARTERIAL HYPERTENSION

5.1 Overview

Physiological responses during the incremental cycle ergometry cardiopulmonary exercise test (CPET) and six minute walk test (6MWT) have previously been reported and compared, in one study, in the pulmonary arterial hypertension (PAH) population (46). The investigators (46) recruited six participants with idiopathic PAH (iPAH) and 14 participants with PAH associated with other conditions (aPAH). The participants were in New York Heart Association functional class I-III. The 6MWT elicited a greater aerobic capacity when compared to a CPET performed on a cycle ergometer, as indicated by higher peak oxygen uptake ($V'O_2$ peak) (46). The unencouraged 6MWT is a commonly used measure of exercise capacity in PAH to determine eligibility for pharmaceutical therapy and is frequently used as an outcome measure in clinical trials (42, 69). However, endurance time on a constant workload cycle ergometer test (CWLT) has also been identified as an important clinical endpoint for monitoring response to therapy (5, 100) and has been shown to be a more responsive measure to demonstrate change

following exercise training, compared to peak $V'O_2$ and 6MWD (23), in the PAH population. To the best of my knowledge, comparisons of physiological and symptom outcomes during the CPET, CWLT and 6MWT have yet to be reported in individuals with PAH.

This Chapter explores the physiological and symptom outcomes obtained during the CPET, CWLT and 6MWT in a PAH cohort and describes the measurement properties of these tests in this population.

5.2 Methods

5.2.1 Overview

Data for this study were obtained from the baseline exercise tests performed by the 10 participants enrolled in the randomised control trial (RCT) investigating the effects of exercise training in PAH. Criteria for enrolment into this study have been described in Chapter 4, Section 4.2.2. In brief, participants were included in the study if they: (i) had a confirmed diagnosis of iPAH, familial PAH or aPAH, and (ii) were stable on PAH-specific pharmaceutical therapy, in World Health Organisation (WHO) functional class II or III. The results of the RCT have been reported in Chapter 4, Section 4.3.

5.2.2 Exercise testing

Specific details regarding the exercise tests have previously been described in Chapter 4, Section 4.2.4.1. In brief, participants performed the following:

i. Two unencouraged 6MWT, separated by a rest period of at least 30 minutes. Heart rate (HR) and oxygen saturations (SpO_2) were monitored continuously via a Polar FS3C heart rate monitor (Sportstek, Victoria, Australia) and using a Respironics 512 hand-held pulse oximeter and finger probe (Philips, Massachusetts, United States), respectively, and recorded at the end of each minute. Dyspnoea and rating of perceived exertion (RPE) scores on the Borg category-ratio 10-point (CR10) scale (184) were recorded immediately

prior to and following completion of the test. The best test was defined as the test that achieved the highest six-minute walk distance (6MWD).

ii. An incremental CPET, using a continuous ramp protocol (Lode Corival cycle ergometer, Lode, Groningen, Netherlands), was performed to volitional exhaustion with breath-by-breath gas exchange analysis (Medical Graphics CPX-D, Medgraphics, Minnesota, United States). The test protocol comprised 3 minutes of upright rest on the bicycle, followed by 3 minutes of unloaded cycling (0 watts [W]). Subsequent workloads were increased by 5 W/min, 10 W/min or 15 W/min increments depending on the participant's age, gender, weight, 6MWD and diffusing capacity of the lung for carbon monoxide (D_LCO) (92).

iii. A CWLT was performed using the same equipment used for the incremental CPET. The test protocol comprised 3 minutes of upright rest on the bicycle, followed by 3 minutes of unloaded cycling (0 W), followed by an increase in workload to 75% of the peak workload achieved during the incremental CPET.

Heart rate and SpO_2 were monitored continuously on the CPET and CWLT via electrocardiography (CardioPerfect^{TM} ST system, Welch Allyn Cardio Control NV, Delft, The Netherlands) and the Masimo Radical pulse oximeter and ear probe (Masimo Australia Pty Ltd, Frenchs Forest, New South Wales, Australia), respectively. Dyspnoea and RPE scores on the Borg CR10 scale were recorded at rest, during the last 15 seconds of every minute during exercise and on test completion for the CPET and CWLT.

The three exercise tests were performed over three visits within a 2-week period, in the following order: (i) 6MWT, (ii) CPET and (iii) CWLT. Visits were separated by a minimum of 24 hours. The results from the best 6MWT were used for comparisons with the CPET and CWLT.

The physiological measures used for comparison across the three tests were (i) HR, (ii) heart rate reserve (HRR), and (iii) SpO_2. Reported symptoms of dyspnoea, RPE, leg fatigue and general fatigue on the Borg CR10 scale were compared across the three tests. Additional physiological measures

obtained from breath-by-breath gas analysis during the CPET and CWLT were used for comparisons between the two cycle ergometer tests. Data obtained at test end were analysed for all tests, unless otherwise stated.

5.2.3 Statistical analyses

Breath-by–breath data from the CPET and CWLT were grouped into increments as a proportion of total test duration using a two-dimensional data transformation in Sigmaplot (Version 12.0, Systat Software Inc). Data collected during the 3 minute resting phase and the 3 minutes of unloaded cycling that preceded the CPET and CWLT were excluded from the analyses. Statistical analyses were performed using SPSS® software (Version 17.0; SPSS Inc.; Chicago, USA). Peak physiological outcomes and peak Borg CR10 scale symptom scores on the CPET, CWLT and 6MWT were compared using one-way repeated measures analysis of variance and Kruskal Wallis tests, respectively. Paired t-tests were used to compare additional physiological measures obtained on the CPET and CWLT. Data that were not normally distributed were transformed and if transformation failed to satisfy normality, non-parametric tests were used. An alpha (p) value of less than 0.05 was considered significant. Results are expressed as mean ± standard deviation (SD) in text and tables and mean ± standard error of the mean (SEM) in figures.

5.3 Results

The characteristics of the 10 participants are illustrated in Table 5.1. The study sample was predominantly female (n=9, 90%) with idiopathic PAH (n=6, 60%), in WHO functional class II (n=6, 60%).

There were no adverse events associated with any of the exercise tests. The symptoms limiting each test are given in Table 5.2. Dyspnoea was the most common reason for test cessation on the CPET and CWLT. Five participants reported symptoms of dyspnoea or fatigue as the primary limitation to the 6MWT. Two of the participants reported pacing themselves

to avoid being limited by symptoms during the 6MWT. Rests were not required by any of the participants during the 6MWT.

Table 5.1. Participant characteristics

Anthropometrics	
Gender, female, n (%)	9 (90)
Age, years	50±11
Height, cm	164±7
Weight, kg	78±21
Diagnosis (n, %)	
iPAH	6 (60)
fPAH	1 (10)
aPAH	3 (30)
WHO functional class (n, %)	
II	6 (60)
III	4 (40)
Resting pulmonary artery pressures (mmHg)	
Mean	34±19
Systolic	55±33
Diastolic	20±12
Pulmonary function	
FEV_1, % predicted	83±17
FVC, % predicted	93±19
FEV_1/FVC, %	75±7
$V_{A\ eff}$, % predicted	89±18
D_LCO uncorrected, % predicted	82±25

Data presented as mean±SD unless otherwise stated; iPAH: idiopathic pulmonary arterial hypertension; fPAH: familial pulmonary arterial hypertension; aPAH: pulmonary arterial hypertension associated with connective tissue disorders; FEV_1: forced expiratory volume in one second (189); FVC: forced vital capacity (189); $V_{A\ eff}$: effective alveolar volume (192); D_LCO: diffusing capacity of the lung for carbon monoxide (192).

Table 5.2. Participant-reported symptom limitation

	CPET	**CWLT**	**6MWT**
Dyspnoea	6	5	2
Leg fatigue	3	1	1
General fatigue	1	2	2
Mouth dryness		2	
Couldn't walk any faster			3
Not limited by symptoms			2

Data presented as n, number. CPET: cardiopulmonary exercise test; CWLT: constant workload cycle ergometry test; 6MWT: six-minute walk test.

5.3.1 Exercise capacity

Exercise capacity was reduced in the participants, as indicated by reduced $V'O_2$ peak, $V'O_2$ at the anaerobic threshold (AT) and 6MWD (Table 5.3).

5.3.2 Effect of test repetition on six-minute walk distance

The magnitude of change between the two 6MWD averaged 7m (range 0 – 20m; p=0.058), equating to a 1% (range 0 – 3%) difference between tests.

5.3.3 Comparisons of peak outcomes on the three exercise tests

There were no significant differences in HR and SpO_2 recorded at rest among the three tests (Table 5.4). Table 5.5 illustrates the peak physiological and symptom outcomes for the three exercise tests. There were no significant differences observed in the peak HR and nadir SpO_2 on the CPET and CWLT. Further, there were no differences in peak symptom scores between the CPET and CWLT.

Peak HR ($p \leq 0.014$) and symptoms scores for leg fatigue ($p \leq 0.027$) and general fatigue ($p \leq 0.025$) were lower on the 6MWT, when compared to the CPET and the CWLT. In comparison to the CPET and CWLT, the nadir SpO_2 on the 6MWT was lower, although this difference was not significant ($p \geq 0.23$). Peak Borg dyspnoea and RPE scores were also lower on the 6MWT when compared to the CPET and CWLT, however, these scores did not reach statistical significance ($p \geq 0.05$).

Figure 5.1 illustrates the pattern of change in HR and SpO_2 during the three exercise tests. A curvilinear pattern was observed for HR on the CWLT and 6MWT compared to a more linear change in HR on the CPET. Oxygen saturations decreased most rapidly on the 6MWT, and then remained relatively stable.

There were no significant associations identified between (i) 6MWD and (ii) six-minute walk work (6MWW, the product of 6MWD and body weight) with the peak workload (r=0.47 and r=0.06, respectively, p>0.1 for both) and $V'O_2$ peak (r=0.44 and r=0.05, p>0.1 for both) achieved on the CPET

Table 5.3. Exercise capacity, as measured on the incremental cardiopulmonary exercise test, constant workload test and six-minute walk test

	CPET	CWLT	6MWT
Work rate, W	98±29	72±19	
Work rate, % predicted	94±21	68±15	
$V'O_2$ peak, mL/min	1188±305	1246±335✶	
$V'O_2$ peak, % predicted	72±18	75±19✶	
Work rate at AT, W	40±17		
$V'O_2$ at AT, mL/min	645±109		
$V'O_2$ at AT, % predicted $V'O_2$ peak	40±7		
Endurance time, seconds		459±210	
6MWD, m			568±68
6MWD, % predicted			86±11

Data presented as mean±SD at test end; CPET: incremental cardiopulmonary exercise test; CWLT: constant workload cycle ergometry test; 6MWT: six-minute walk test; W: watts; $V'O_2$: oxygen uptake (180); AT: anaerobic threshold; 6MWD: six minute walk distance (125); ✶p<0.05 between tests.

Table 5.4. Resting physiological outcomes on the incremental cardiopulmonary exercise test, constant workload test and six-minute walk test

	CPET	CWLT	6MWT
HR, bpm			
mean±SD	70±6	76±8	76±10
range	63 - 83	66 - 89	62 - 88
SpO_2, %			
mean±SD	97±2	97±1	97±1
range	93 - 100	96 - 99	95 - 97

Data presented as mean±SD at test end; CPET: incremental cardiopulmonary exercise test; CWLT: constant workload cycle ergometry test; 6MWT: six-minute walk test; HR: heart rate; bpm: beats per minute; SpO_2: oxygen saturation; SpO_2 data for one subject was removed from the constant-workload test analyses due to difficulties obtaining SpO_2 output on the pulse oximeter.

Table 5.5. Peak physiological and symptom outcomes on the incremental cardiopulmonary exercise test, constant workload test and six-minute walk test

	CPET	CWLT	6MWT
HR, bpm			
mean±SD	138±14	138±16	121±21✶†
range	112 - 155	103 - 158	86 - 156
HRR, bpm			
mean±SD	32±17	32±20	47±28✶†
range	14 - 68	13 - 77	13 - 94
HRR, %			
mean±SD	19±9	18±11	27±15✶†
range	9 - 38	8 - 43	8 - 52
SpO_2, %			
mean±SD	96±4	96±3	94±2
range	89 - 100	90 - 99	89 - 98
Borg CR10 dyspnoea			
mean±SD	6±3	6±3	4±2
range	1 - 9	1 - 9	0.5 - 7
Borg CR10 RPE			
mean±SD	6±2	6±3	5±3
range	3 - 9	0.5 - 9	0.5 - 9
Borg CR10 leg fatigue			
mean±SD	5±2	4±2	3±2✶†
range	3 - 9	1 - 8	0 - 5
Borg CR10 general fatigue			
mean±SD	5±2	5±2	2±2✶†
range	0.5 - 8	1 - 8	0 - 5

Data presented as mean±SD at test end; CPET: incremental cardiopulmonary exercise test; CWLT: constant workload cycle ergometry test; 6MWT: six-minute walk test; HR: heart rate; bpm: beats per minute; HRR: heart rate reserve; SpO_2: oxygen saturation; SpO_2 data for one subject was removed from the constant-workload test analyses due to difficulties obtaining SpO_2 output on the pulse oximeter. ✶$p<0.05$ compared to CPET; †$p<0.05$ compared to CWLT.

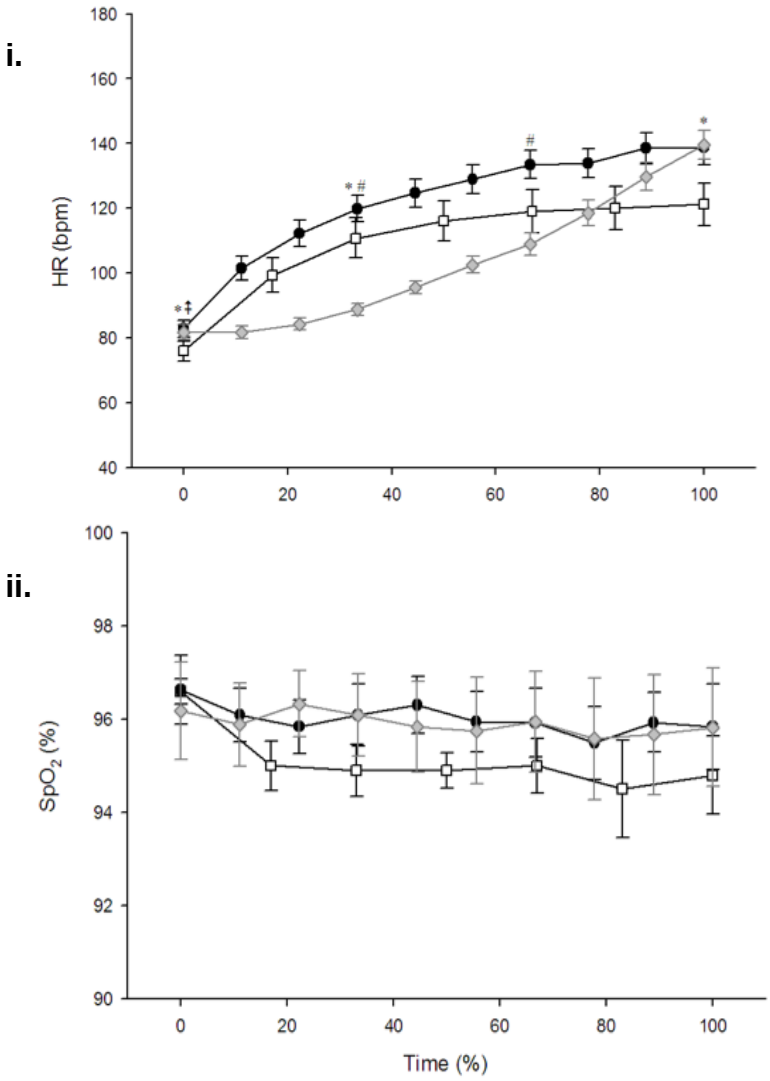

Figure 5.1. Comparison of (i) heart rate (HR) and (ii) oxygen saturation (SpO_2) on the incremental cardiopulmonary exercise test, constant workload test and six-minute walk test

Data grouped into epochs as a percentage of total test duration for the incremental cardiopulmonary exercise test **(**CPET, ◆**)**, constant workload test **(**CWLT, ●**)** and six-minute walk test **(**6MWT, □**)**. 0% time on the CEPT and CWLT data represents commencement of loaded cycling. SpO_2 data for one subject was removed from the constant-workload test analyses due to difficulties obtaining SpO_2 output on the pulse oximeter. *p<0.05 between CPET and 6MWT; # p<0.05 between CPET and CWLT; ‡ p<0.05 between CWLT and 6MWT.

5.3.5 Comparison of physiological outcomes between the CPET and CWLT

There were no significant differences in physiological data recorded at rest between the two tests (Table 5.6). Table 5.7 illustrates peak ventilatory and cardiovascular variables on the CPET and CWLT. The tests yielded similar outcomes for carbon dioxide output ($V'CO_2$), respiratory rate, minute ventilation (V'_E), ventilatory equivalent for oxygen ($V'_E V'O_2$), ventilatory equivalent for carbon dioxide ($V'_E V'CO_2$), end-tidal carbon dioxide ($P_{ET}CO_2$), rate of increase in V'_E over $V'CO_2$ ($\Delta V'_E/\Delta V'CO_2$), blood pressure and oxygen pulse. Peak $V'O_2$ averaged 5% higher on the CWLT (p=0.034) and was higher when expressed as a percentage of predicted (p=0.029, Table 5.3). Breathing reserve was also higher on the CWLT (p=0.004). The respiratory exchange ratio (RER) was higher on the CPET (p=0.009).

The pattern of response for (i) V'_E, expressed as a function of $V'CO_2$, and (ii) V'_E, $V'_E V'CO_2$, $V'_E V'O_2$, $P_{ET}CO_2$ and $P_{ET}O_2$, expressed as a function of $V'O_2$, was similar between tests (Figure 5.2).

Table 5.6. Resting physiological outcomes on the incremental cardiopulmonary exercise test and constant workload test

	CPET	CWLT
$V'O_2$, mL/min	223±62	227±49
$V'CO_2$, mL/min	211±62	205±42
RER	0.9±0.1	0.9±0.1
Respiratory rate, breaths/min	19±6	18±5
V'_E, L	11±4	10±2
$V'_E V'O_2$	51±11	44±9
$V'_E V'CO_2$	53±7	48±7
$P_{ET}CO_2$, mmHg	28±5	30±4
Breathing reserve, %	87±4	91±2
Systolic blood pressure, mmHg	133±22	128±18
Diastolic blood pressure, mmHg	79±9	78±12
Oxygen pulse, mL/beat	3.3±0.9	3.0±1.0

Data presented as mean±SD at test end; CPET: cardiopulmonary exercise test; CWLT: constant workload test; $V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide output; RER: respiratory exchange ratio; V'_E: minute ventilation; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide.

Table 5.7. Peak physiological outcomes on the incremental cardiopulmonary exercise test and constant workload test

	CPET	CWLT
$V'O_2$, mL/min	1188±305	1246±335✶
$V'CO_2$, mL/min	1498±379	1436±342
RER	1.3±0.1	1.2±0.1✶
Respiratory rate, breaths/min	40±8	38±6
V'_E, L	64±18	61±18
$V'_E V'O_2$	55±13	50±12
$V'_E V'CO_2$	43±9	43±9
$P_{ET}CO_2$, mmHg	28±7	28±6
$\Delta V'_E/\Delta V'CO_2$	41±10	42±10
Breathing reserve, %	30±11	46±11✶
Systolic blood pressure, mmHg	190±30	191±35
Diastolic blood pressure, mmHg	97±14	88±23
Oxygen pulse, mL/beat	8.8±2.9	9.2±3.3

Data presented as mean±SD at test end; CPET: cardiopulmonary exercise test; CWLT: constant workload test; $V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide output; RER: respiratory exchange ratio; V'_E: minute ventilation; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$: end-tidal carbon dioxide; $\Delta V'_E/\Delta V'CO_2$: rate of increase of V'_E over $V'CO_2$; ✶$p<0.05$ between tests.

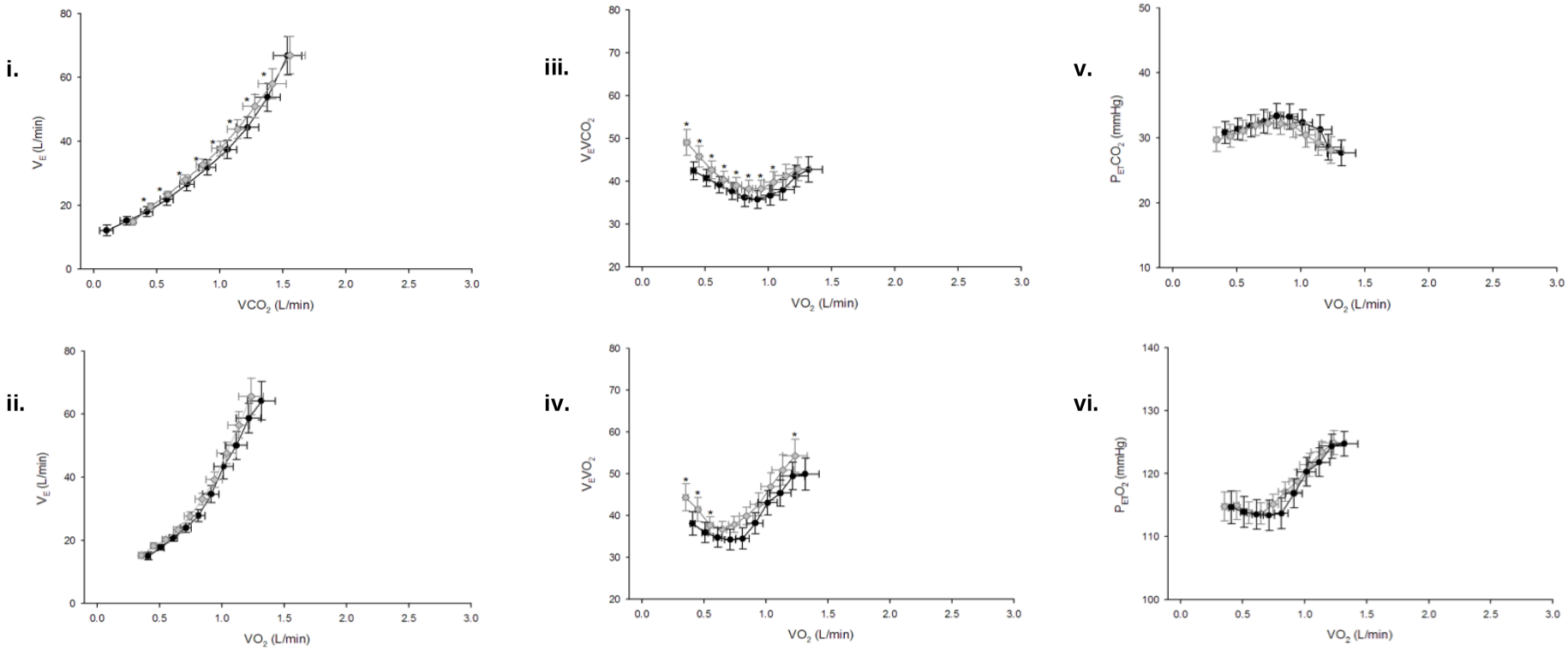

Figure 5.2. Pattern of ventilatory response on the incremental cardiopulmonary exercise test and constant workload test

(i-ii) Minute ventilation (V'_E), (iii) ventilatory equivalent for carbon dioxide ($V'_E V'_{CO_2}$), (iv) ventilatory equivalent for oxygen ($V'_E V'_{O_2}$), (v) End-tidal carbon dioxide ($P_{ET}CO_2$) (vi) End-tidal oxygen ($P_{ET}O_2$) on the incremental cardiopulmonary exercise test (◆) and constant-workload cycle ergometer test (●). Data grouped into epochs as a function of (i) carbon dioxide output (V'_{CO_2}) and (ii-vi) oxygen uptake (V'_{O_2}). *p<0.05 at equivalent epochs between tests.

5.4 Discussion

The primary objective of this study was to compare the physiological and symptom outcomes between the CPET, CWLT and 6MWT, to assist in describing the measurement properties and utility of these tests for clinical practice in the PAH population.

Characteristic physiological abnormalities associated with PAH (65, 70, 74, 75) were observed in the participants, namely, low V'_{O_2} peak, low V'_{O_2} at the AT, high $V'_E V'_{CO_2}$, and low $P_{ET}CO_2$. Further, the steep increase in V'_E relative to V'_{CO_2} indicates a higher than normal dependency on anaerobic metabolism (65).

All three tests utilised in this study have been shown to be valid, reliable and reproducible in cardiopulmonary populations. The CPET has been shown to be reproducible in one study in a PAH population (95), as well as in other cardiopulmonary populations (214-216). Further, the CWLT has been shown to be highly reproducible, with minimal learning effect, in individuals with chronic obstructive pulmonary disease (COPD) (96, 97). For these reasons, one CPET and one CWLT were performed in this study. A learning effect has been documented on the 6MWT, in chronic respiratory disease (118, 119, 121, 217, 218) and heart failure (120, 219) populations, with individuals frequently demonstrating an increase in 6MWD between the first and second test. Minimal increases in 6MWD have been observed with further test repetition, suggesting the 6MWT is reproducible following a familiarisation test. Due to the learning effect observed on the 6MWT, two tests were performed in this study to familiarise the individual and obtain their best result. The best result, defined as the test that achieved the highest 6MWD, was used for the comparison with outcomes from the CPET and CWLT.

5.4.1 Comparison of CPET and CWLT

One of the main findings from this study was that the CWLT elicited similar physiological and symptoms responses to those achieved on the CPET. These findings are consistent with data reported in individuals with moderate

to severe COPD (98). Further, in healthy individuals, Zeballos et al (220) reported a similar peak $V'O_2$ on a CPET and CWLT. These findings are in contrast to a study conducted by Riley and colleagues (221) in individuals with heart failure, where a lower peak $V'O_2$ was achieved on the CWLT when compared to that achieved on a CPET. Compared with the data from Riley et al (221) where participants were stopped at 10 minutes of loaded exercise, symptom limitation was the reason for test cessation on both the CWLT and CPET in our participants, and in the study by Oga et al (98) in COPD. Despite the difference in the exercise challenge between the CPET and CWLT, the similarities in the physiological responses observed on the tests supports the robust nature of these measurements in this study.

In this study, the workload set for the CWLT was 75% of the peak workload achieved on the incremental CPET. For all individuals, this workload was higher than the workload achieved at the AT on the CPET, indicating that participants were exercising above their AT during the CWLT. The higher $V'O_2$ peak achieved on the CWLT indicates individuals achieved a higher aerobic capacity. This is likely to have occurred because $V'O_2$ and blood lactate continue to increase, rather than stabilise, at this level of exercise intensity and progressively increase to the point of symptom limitation and test cessation (222). Further, this was achieved with lower metabolic stress, as evidenced by a lower RER and breathing reserve. Similar findings have been reported in a COPD population (98).

5.4.2 Comparison of all three tests

The 6MWT yielded a significantly lower peak HR, when compared to the CPET and CWLT. This finding is consistent with data reported by Deboeck and colleagues (46) in individuals with PAH who demonstrated a significantly lower HR on an unencouraged 6MWT when compared to the CPET. Overall, symptoms scores were lower on the 6MWT also. The lower HR and lower symptom scores on the 6MWT may be due to the unencouraged nature of the test, or alternatively, may reflect the self-paced nature of the test. In studies of individuals with exercise-induced PAH (223) and COPD (224-227), encouragement has been shown to result in peak HR (223-227) and peak

$V'O_2$ (224, 226, 227) that are similar to those achieved on an incremental CPET. Exercise intensity is commonly expressed relative to $V'O_2$ or HR (226) and, as such, the findings in these studies suggest that an encouraged 6MWT elicits a maximal response, compared to the submaximal response obtained from the unencouraged protocol in this study. In healthy subjects, Kervio et al (228) reported submaximal responses in HR and $V'O_2$ on the encouraged 6MWT when compared to that achieved on a CPET performed on a treadmill.

Oxygen saturation, measured by a pulse oximeter, was also shown to be lower on the 6MWT, when compared to the CPET and CWLT, despite the unencouraged protocol. Deboeck and colleagues (46) reported a similar, statistically significant, finding when comparing SpO_2 on the unencouraged 6MWT with that on a CPET performed on a cycle ergometer. The participants recruited to the Deboeck et al (46) study desaturated to 76±4% on the 6MWT compared to 86±3% on the CPET. These participants had more advanced disease with a mean pulmonary artery pressure of 57±8mmHg, which is likely to have accounted for the greater level of desaturation seen in this group (46). As in other populations with chronic respiratory disease (204, 218, 225-227), walking tests have shown to induce greater levels of desaturation than cycle-based tests, most likely due to the greater muscle mass involved and the higher oxygen requirements of these muscle groups (204).

A learning effect, as demonstrated by an increase of between 3% to 22% in 6MWD with a repeat test has been reported in chronic respiratory disease (118, 119, 218) and heart failure (106, 120, 219) populations. In healthy populations, a learning effect of approximately 5% has been reported (228-230). This study has identified a small, non-significant increase in 6MWD between the two tests, suggesting a minimal learning effect in this PAH cohort. This is likely to be due to participants being familiar with the test, given that the 6MWT is routinely performed to monitor response to pharmaceutical therapy and, in Australia, is a requirement for the ongoing supply of medication via the pharmaceutical benefit scheme (2). Further, the small

magnitude of difference between tests may relate to the unencouraged nature of the 6MWT.

In contrast to this study, several PAH studies have reported a strong correlation between peak $V'O_2$, achieved on a cycle ergometer with 6MWD (67, 89, 231) and 6MWW (231). In healthy individuals, (228, 229) and other cardiopulmonary populations, including heart failure (106, 232-234) and chronic respiratory disease (217, 218, 225-227), strong associations have also been reported between peak $V'O_2$ and peak workload with 6MWD and 6MWW. The majority of these studies have performed an encouraged 6MWT (217, 218, 225-229, 234), however, several studies in heart failure have reported strong associations using unencouraged protocols (106, 232). In contrast, many of the PAH participants in this study were experienced in performing the 6MWT, a factor that not only is likely to account for the modest change in distance between the two tests, but may have contributed to the high distances achieved on the test. Further, the relatively small sample size may have had an impact on the ability to demonstrate such relationships.

5.4.3 Study limitations

Measurement of gas exchange during the 6MWT would have strengthened this study. Further, whilst the findings of this study concur with those reported previously (46), the sample size of this study was relatively small and further studies are recommended to confirm these findings.

5.4.4 Conclusions and clinical implications

The assessment of exercise capacity is important for a number of reasons, including to: (i) determine the causes of exercise intolerance, (ii) provide the information necessary to establish safe exercise training intensities capable of inducing physiological adaptation, and (iii) to evaluate therapeutic intervention and monitor response to therapy over time.

The CPET is necessary for identifying physiological abnormalities in response to an exercise challenge and the determination of factors contributing to exercise intolerance (44). In the case of exercise training, the CPET should

be performed prior to the commencement of an exercise training program to provide important information regarding exercise safety and can assist in the prescription for exercise training. Further, a CPET needs to be performed in order to determine the workload at which to set a CWLT.

The benefit of the CWLT lies in its ability to provide information on endurance, a primary outcome for many exercise training programs. Endurance time has been shown to be more responsive to change following exercise training, when compared to peak $\dot{V}O_2$, as demonstrated in this program of research (Chapter 4) and reports from other studies in PAH (23, 31) and in COPD (39, 210). Further, endurance time is likely to be a more clinically meaningful outcome, when compared to peak aerobic capacity (peak $\dot{V}O_2$), because improvement in endurance should translate into a greater ability to perform daily activities (98). Therefore, a CWLT should be performed on reassessment, in preference to a CPET, when an improvement in endurance is the primary objective of an exercise training program.

In the PAH population, the unencouraged 6MWT elicits submaximal responses compared to the CPET and CWLT. The utility of the 6MWT appears to lie in its ability to detect exercise-induced hypoxaemia and hence, is useful in assessing the requirements for supplemental oxygen in individuals with PAH. Utilising an unencouraged protocol has been shown to produce submaximal physiological responses in this patient population. In settings where medical supervision and comprehensive monitoring via ECG and continuous blood pressure measures are unavailable, an unencouraged 6MWT may optimise the clinical safety of the test whilst providing useful information regarding functional capacity.

In the clinical setting, however, there are challenges to performing a CPET and CWLT. A CPET is required to be performed prior to conducting a CWLT. These laboratory-based tests are expensive and resource intensive. Clinically, the 6MWT is more commonly used to assess exercise capacity, compared to the CPET and CWLT, due to its simplicity, minimal resource requirement and low cost. However, compared to endurance time on a CWLT, 6MWD has been shown to be less responsive to change following

intervention, as demonstrated in this program of research (Chapter 4) and in other studies in PAH (23) and in COPD (39). For this reason, future studies investigating the utility of alternative measures of endurance, such as the endurance shuttle walk test, are necessary to determine the most suitable measures for use in the PAH population in the clinical setting.

Chapter 6

SUMMARY AND CONCLUSIONS

The primary focus of this program of research was to investigate the benefits of exercise training on exercise capacity and health-related quality of life (HRQoL) in individuals with pulmonary arterial hypertension (PAH). Further, in order to assess HRQoL using a disease-specific measure, validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) was necessary for the Australian and New Zealand PAH population. This Chapter summarises the findings presented in this thesis and discusses the implications of these findings for clinical practice and future research.

6.1 Validity and reliability of the Cambridge Pulmonary Hypertension Outcome Review

This was the first study to validate the CAMPHOR for use in the Australian and New Zealand PAH population. The CAMPHOR has demonstrated excellent internal consistency and has been shown to be reproducible with low random measurement error. Further, the CAMPHOR has the ability to distinguish between individuals across the World Health Organisation (WHO) functional classification. Based on these findings, the CAMPHOR is a valid

and reliable HRQoL measure and is recommended for use in clinical practice and research.

Future research is required to determine: (i) the responsiveness of the CAMPHOR to therapeutic interventions in the PAH population, (ii) the ability of the CAMPHOR to identify change in symptoms, activity limitations and quality of life within an individual over time, and (iii) the magnitude of change in CAMPHOR scores that represents the minimal important difference following different interventions.

6.2 The effects of exercise training in individuals with pulmonary arterial hypertension

This was the first randomised controlled trial in the outpatient setting to demonstrate that a 12-week supervised, whole-body exercise training program results in improvements in exercise capacity and substantial improvements in symptom responses. All four individuals randomised to the exercise group demonstrated improvements in oxygen uptake and endurance time. Additionally, three of the four individuals demonstrated an increase in six-minute walk distance (6MWD). The exercise outcomes suggest that improvements in aerobic capacity and peripheral muscle function have occurred. These findings concur with those previously reported in the PAH population (6, 23, 29-33). However, this is the first study, in a PAH population, to demonstrate that benefits achieved from a supervised program can be maintained with an unsupervised home exercise program. The findings of this study need to be viewed with caution due to the very small sample size, which constitutes a major limitation to this study. The findings of this study should not be generalised to the PAH population and future studies are required to further investigate the effects of exercise training in this population.

This was the first study to utilise a disease-specific HRQoL tool, the CAMPHOR, as an outcome measure following exercise training in the PAH population. The small sample size in this study had an impact on the ability

to detect change in HRQoL. However, the individuals who reported a greater magnitude of impairment in HRQoL at the baseline assessment demonstrated an improvement in HRQoL following exercise training. These findings are consistent with other PAH studies which have demonstrated improvements in HRQoL, utilising generic HRQoL measures, following exercise training (6, 29, 30)

Adverse events, while not serious, occurred during the early stages of exercise training, in this study, and have been reported in other studies (30, 31). For this reason, individuals with PAH should undertake a supervised exercise training program prior to the implementation of a home exercise program. Supervision during training enables close monitoring of heart rate and symptom responses and ensures individuals are appropriately educated on exercise training principles including intensity, modification and progression prior to performing exercise in an unsupervised environment at home.

A future study is required enhance the numbers of the current data set to further investigate whether the findings reported in this program of research can be replicated in a larger sample. Further research in this area is warranted to investigate the optimal exercise training protocol in this population, including intensity and program duration, in addition to determining the mechanisms associated with improvements in exercise capacity. Determining the minimal important difference in endurance time and 6MWD following exercise training would be useful in assessing meaningful change for an individual and to inform sample size calculations for future studies.

Physical activity, measured using activity monitors, is reduced in the PAH population and, in one study, has demonstrated a strong correlation with 6MWD (235). The impact of exercise training on physical activity levels is an important area for future research.

6.3 Comparison of physiological and symptom responses during exercise testing and implications for exercise testing in the PAH population

Due to the complexity of exercise limitation in the PAH population, comprehensive assessment of exercise capacity is indicated prior to the commencement of an exercise training program.

This study has shown that the physiological responses to the cardiopulmonary exercise test (CPET) and the constant workload test (CWLT) are similar and that the two tests elicit similar peak physiological and symptom outcomes. The CPET provides important information to objectively describe the physiological aspects that limit an individuals' exercise performance and is a necessary prerequisite to determine the maximum workload that an individual can achieve on a CWLT (236). Comparatively, the CWLT provides evidence of improvements in exercise capacity, namely endurance time, which is a more responsive measure to change following exercise training, when compared to peak oxygen uptake achieved on a CPET. The CWLT should be utilised as a reassessment tool, in preference to the CPET, to evaluate the effectiveness of exercise training programs when improvement in endurance is the primary objective.

The 6MWT performed according to an unencouraged protocol induces submaximal physiological and symptom responses, when compared to the CPET and CWLT. The 6MWT appears to be more sensitive in the detection of exercise-induced oxygen desaturation, in this study and in other studies both in the PAH population (46) and in individuals with chronic respiratory disease (204, 218, 225-227). Therefore, it is recommended that the 6MWT is used to identify exercise-induced oxygen desaturation and, where necessary, the response to supplemental oxygen. Further, in settings where medical supervision and comprehensive monitoring are not available, an unencouraged 6MWT may optimise clinical safety due to the submaximal nature of the test.

Further research investigating changes in pertinent CPET indices such as oxygen uptake, minute ventilation and ventilatory equivalent of carbon dioxide, at specific time points (isotimes) on the CWLT, will assist with elucidating the mechanisms responsible for improvement following exercise training. Additionally, the utility of exercise tests such as the incremental and endurance shuttle walk test should be investigated to determine their usefulness in evaluating the effects of exercise training in the PAH population (237, 238). A comparison of responses to the incremental and endurance shuttle walk tests to those tests currently used in the PAH, namely the 6MWT, CPET and CWLT, would help further describe the measurement properties of the exercise tests for this patient population.

6.4 Conclusion

In conclusion, the findings of this program of research contribute to the growing evidence supporting exercise training in the PAH population. This study is limited by the very small sample size, which prohibits any generalisation of the findings to the wider PAH population. This is, however, the first study to demonstrate that improvements in exercise capacity, achieved following a period of supervised, outpatient exercise training, can be maintained with an unsupervised home exercise program.

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Appendix 1. CAMPHOR Participant interview sheet

Participant Name:

Date of interview:

Start time: **Finish time:**

			Comments
Looks at instructions:	Initially	❑ Y ❑ N	
	Refers back to them	❑ Y ❑ N	
Items:	Needing clarification from interviewer	Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
	Delayed response time/left to be answered at end	Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
		Qu. #	
Were items:	Easy to understand	❑ Y ❑ N	
	Appropriate	❑ Y ❑ N	
	Including all important aspects of life	❑ Y ❑ N	
	Do you understand “overall wash”? Can you suggest a better word?	❑ Y ❑ N	
Any other comments:			

Appendix 2. Report to Galen Research following participant interviews

Cambridge Pulmonary Hypertension Outcome Review

Australian Field Test Report

General Information

Recruitment information:

Subjects were recruited by Louise Ganderton (co-investigator) via telephone from the State Pulmonary Hypertension Service database at Royal Perth Hospital, Perth, Western Australia.

Total number of interviews conducted: 15

Interviews conducted between: 05/03/2008 and 15/03/2008

Location of interviews: 13 participants were visited at home. All subjects resided in the metropolitan area of Perth, Western Australia. 2 participants were interviewed at Royal Perth Hospital as they were attending exercise rehabilitation classes at the hospital.

World Health Organisation functional assessment classification for pulmonary arterial hypertension: Class I – 2 participants; Class II – 8 participants; Class III – 5 participants.

Results

General:

Did any patients fail to understand instructions once they were read to them? No

Were all patients clear about the purpose of the interview? Yes

Mean number of minutes to complete the interview = 9.5 (range 6 to 15)

Skipped or Missing Items:

Were there any items that patients could not answer? No

6 participants initially missed boxes in the activities subscale. All 6 participants stated that they found the formatting of the boxes visually confusing.

Clarity and Relevance:

Generally, participants found the CAMPHOR easy to understand and complete. All participants suggested that the CAMPHOR asked questions relevant to their disease. Several participants stated that their responses would have been different prior to commencing PAH medication. Participants thought that all items were appropriate and acceptable.

Response Scales:

Were there any problems found using the response scales? 7 participants suggested that they would like a "sometimes" option for the symptoms and quality of life subscales, stating that there experiences "aren't always so black and white".

Problematic Items

Symptoms subscale:

Item #21: "I seldom feel happy"

Four participants found this wording to be slightly confusing, with a delay in response time noted. One participant suggested the phrase "I frequently feel unhappy" as a better way to ask the question.

Activities subscale:

Item #2: "Have an all over wash"

Whilst all participants understood the term "all over wash", they all suggested that the term "shower" would be better to use for the Australian and New Zealand population.

Item #12: "Lift heavy items"

One participant asked "how heavy is heavy?".

Quality of Life subscale:

Item # 12: "I feel dependent on other people"

One participant was unsure as to whether "other people" included hospital staff.

Item # 15: "Travelling distances is a problem"

Two participants needed clarification for this item. They were unsure whether travelling distances meant walking, going by car to the supermarket, driving to another town or travelling by aeroplane.

Appendix 3. Cardiopulmonary exercise test termination criteria

Based on the American Thoracic Society CPET guidelines (45), the test will be terminated in the event of any of the following:

- Chest pain suggestive of ischemia
- Ischaemic ECG changes
- Complex ectopy
- Second or third degree heart block
- Fall in systolic pressure 20 mmHg
- Hypertension (250 mmHg systolic blood pressure; 120 mmHg diastolic blood pressure)
- Severe desaturation (SpO_2 <80%)
- Sudden pallor
- Loss of coordination
- Mental confusion
- Dizziness or faintness

Appendix 4. Incremental cardiopulmonary exercise test (CPET) protocol

CPET familiarisation

Subjects will be familiarised with the CPET instructions and equipment during the first assessment visit. This will include sitting on the test bike, pedalling at 60rpm and breathing through the mouthpiece with a nose clip in situ. Subjects will practise scoring breathlessness, RPE and leg fatigue by pointing to the scale, as well as practising hand signals for communication.

Calibration

The flow sensor will be calibrated within 1 hour of the test beginning. Gas analysers will be calibrated immediately prior to test commencement.

Test protocol

- 3 minutes baseline measurement, at rest
- 3 minutes unloaded pedalling
- Ideally, 8 to 12 minutes from commencement of the incremental portion of the test to peak exercise (volitional task cessation or symptom limitation)
- Increase workload according to individual prescription, using a ramp protocol (5, 10 or 15 W/min)
    - based on age, gender, weight, 6MWD and DLCO @ 60 ± 10 rpm

Instructions to the subject

"You are about to complete a cycle test that gradually gets harder. This is a maximal test that requires you to exercise for as long as you can. You will be asked to rest on the bike for three minutes whilst we take some measurements. You will then cycle without any resistance for three minutes. After this time, the resistance on the bike will progressively increase until you are no longer able to continue. You will be asked to cycle at about 60rpm and if you are unable to cycle more than 40rpm for longer than 10 seconds the test will be terminated. This is a maximal test so we need you to work as hard as you possibly can for as long as possible. You must however let us know if you feel you need to stop or if you experience chest pain or increasing dizziness/lightheadedness. The doctor will be monitoring you closely and will stop the test if he is worried about any of these.

To communicate with us during the test, please use the following hand signs:

Thumbs up – good

Thumbs down – bad

Wavering hand – not sure

Hand on sternum – chest pain

After every minute of the test, we will ask you to point to the number that reflects your level of breathlessness and your level of exertion. I will say out loud the number you have pointed to – please give me a thumbs up if I have said the correct number."

Variables recorded throughout test (from resting prior to test commencement to recovery)

- *Cardiac:* 12 lead ECG, HR, BP (with an automated sphygmomanometer)
- *Respiratory/gas exchange:* breathing frequency, V_E, VO_2, VCO_2, $PetO_2$, $PetCO_2$, SpO_2 (with oximeter and ear probe), RER
    - Performed breath by breath

Prior to test commencement

- DLCO
- Flow-volume loop
- Borg Scale for breathlessness and RPE (CR10 scale)

Rest period

- 3 min sitting on cycle ergometer to record baseline measurements (encourage quiet breathing)
- Borg Scale for breathlessness and RPE (at commencement of 3 minutes)

Unloaded cycling

- 3 minutes @ 0 W/min
- Borg Scale for breathlessness and RPE (every minute)

Increments

- Standardised encouragement will be provided at every minute "You are doing well, keep going for as long as you can".
- Additional variables recorded during test
    - Inspiratory capacity measure every 2 minutes
    - Borg Scale for breathlessness and RPE (every minute)
- Additional variables recorded at test end
    - Borg Scale for breathlessness, RPE and leg fatigue

Recovery

- 2 min unloaded pedalling at a comfortable cadence to limit post exercise dizziness
- Additional variables recorded:
    - Borg Scale for breathlessness, RPE and leg fatigue
    - Subjective report for reason for ceasing exercise ie limiting symptoms (primary and secondary)

Appendix 5. Constant workload cycle ergometry test (CWLT) protocol

Calibration

The flow sensor will be calibrated within 1 hour of the test beginning. Gas analysers will be calibrated immediately prior to test commencement.

Test protocol

- 3 minutes baseline measurement, at rest
- 3 minutes unloaded pedalling
- Ideally, 6 to 8 minutes from commencement of the constant workload portion of the test to volitional task cessation or symptom limitation
- Increase workload according to 75% of peak workload achieved during the incremental CPET @ 60 ± 10 rpm. Workload will be increased to a maximum within 30 seconds of commencement of this phase.

Instructions to the subject

"You are about to complete another cycle test. This time you will be cycling against a constant resistance for as long as you possibly can. The resistance has been determined based on your test the other day. You will be asked to rest on the bike for three minutes whilst we take some measurements. You will then cycle without any resistance for another three minutes. After this time, the resistance will increase quickly to the level you will cycle at until you are no longer able to continue. You will be asked to cycle at about 60rpm and if you are unable to cycle more than 40rpm for longer than 10 seconds the test will be terminated. We need you to cycle for as long as you possibly can. You must however let us know if you feel you need to stop or if experience chest pain or increasing dizziness. The doctor will be monitoring you closely and will stop the test if he is worried about any of these.

To communicate with us during the test, please use the following hand signs:

Thumbs up – good

Thumbs down – bad

Wavering hand – not sure

Hand on sternum – chest pain

After every minute of the test, we will ask you to point to the number that reflects your level of breathlessness and your level of exertion. I will say out loud the number you have pointed to – please give me the thumbs up if I have said the correct number".

Variables recorded throughout test (from resting prior to test commencement to recovery)

- *Cardiac:* 12 lead ECG, HR, BP (with an automated sphygmomanometer)
- *Respiratory/gas exchange:* breathing frequency, V_E, VO_2, VCO_2, $PetO_2$, $PetCO_2$, SpO_2 (with oximeter and ear probe), RER
    - Performed breath by breath

Prior to test commencement

- Borg Scale for breathlessness and RPE (CR10 scale)

Rest period

- 3 min sitting on cycle ergometer to record baseline measurements (encourage quiet breathing)
- Borg Scale for breathlessness and RPE (at commencement of minute 3)

Unloaded cycling

- 3 minutes @ 0 W/min
- Borg Scale for breathlessness and RPE (every minute)

Constant workload

- Standardised encouragement will be provided at every minute “You are doing well, keep going for as long as you can”.
- Additional variables recorded during test
    - Borg Scale for breathlessness and RPE (every minute)
- Additional variables recorded at test end
    - Borg Scale for breathlessness, RPE and leg fatigue

Recovery

- 2 min unloaded pedalling at a comfortable cadence to limit post exercise dizziness
- Additional variables recorded:
    - Borg Scale for breathlessness, RPE and leg fatigue
    - Subjective report for reason for ceasing exercise ie limiting symptoms (primary and secondary)

Appendix 6. Example cycle ergometry test calibration printout

Calibration Log - Respiratory Physiology Laboratory

Workstation: D9WH981S CPX/D 18/11/2009 3:34:29 p.m.

	Value	Min	Max
Environment 18/11/2009 10:47:54 a.m.			
Room Temperature (C)	23.0	15.0	35.0
Barometric Pressure (mmHg)	753.0	500.0	800.0
Relative Humidity (%)	67.0	0.0	100.0
Pneumotach 18/11/2009 3:34:29 p.m.			
Syringe Volume (L)	3.00		
Expiratory			
Gain (L/Sec/V)	1.808	0.300	2.200
Mean Volume (L)	2.992	2.940	3.060
Volume Range (L)	0.047	-0.090	0.090
Error (%)	-0.280	-2.010	2.010
Inspiratory			
Gain (L/Sec/V)	1.833	0.300	2.200
Mean Volume (L)	3.001	2.940	3.060
Volume Range (L)	0.023	-0.090	0.090
Error (%)	0.040	-2.010	2.010
O2 & CO2 Analyzers 18/11/2009 3:34:29 p.m.			
O2			
Reference Gas (%)	21.00		
Calibration Gas (%)	12.00		
Phase Delay (Sec)	0.430	0.100	0.600
2-90% Response (Sec)	0.060	0.020	0.100
Gain (%/V)	10.02	8.00	12.00
Offset (V)	0.003	-0.100	0.050
CO2			
Reference Gas (%)	0.00		
Calibration Gas (%)	5.00		
Phase Delay (Sec)	0.460	0.100	0.600
90% Response (Sec)	0.100	0.020	0.160
Gain (%/V)	1.01	0.80	1.20
Offset (V)	0.025	-0.150	0.250

Appendix 7. Unencouraged six-minute walk test protocol

Introduction

The 6MWT is a simple, valid and reliable field measure of functional capacity. It can be utilised in the inpatient or outpatient setting although standard protocol needs to be followed to ensure intra and inter rater reliability. This protocol has been modified from the American Thoracic Society guidelines and PAH clinical trials.

Safety Considerations

Contra-indications Any medical condition that makes exercise testing unsafe that includes, but isn't limited to:	**Relative Contraindications** May be superseded if benefits outweigh risks
• Unstable cardiac rhythm, including heart block, causing symptoms or haemodynamic compromise	• A resting tachycardia > 120 beats per minute
• Acute myocardial infarction or acute coronary syndrome within the last month	• Systolic blood pressure > 180mmHg • Diastolic blood pressure > 100mgHg
• Acute febrile disorders eg influenza	• Significant ischaemic heart disease e.g. left main coronary artery disease
• Acute neurological disorder, eg CVA, within last month	• Severe pulmonary hypertension
• Severe cardiac valve disease	• Ventricular aneurysm
• Hypertrophic cardiomyopathy and other forms of outflow tract obstruction	• Hypo or hyperkalaemia or magnesaemia
• Acute myocarditis or pericarditis	• Neuromuscular, musculoskeletal, or rheumatoid disorders that are significantly exacerbated by exercise
• Unstable heart failure	• Uncontrolled metabolic disease (eg diabetes)
• Uncontrolled metabolic disease e.g. diabetes	• Resting SpO_2 < 90% (check accuracy of reading and consider trying ear sensor if available)
• Suspected or known dissecting aneurysm	
• Acute pulmonary embolus or infarction	*(American Thoracic Society Guidelines 2002, ACSM Guidelines 2000)*

Procedure

Advice for the patient on making the appointment:
1. Have a light meal or snack at least 2 hours prior to the test. Insulin dependent diabetics should carry whatever they use for hypoglycaemic events and may need a light snack within an hour prior to the test. 2. Wear appropriate footwear and loose fitting comfortable clothes. 3. Bring reliever MDIs and/or anti-anginal medications.
Equipment:
1. Unobstructed walking track with 2 cones or some system to mark ends of track 2. Hand held, battery driven pulse oximeter, sphygmomanometer and stethoscope 3. Stop watch 4. Borg dyspnoea and/or RPE scale 5. 6MWT form, Clipboard and pen 6. Portable oxygen in a trolley to be available and easily accessible 7. Easy access to patient's ventolin MDI and anginine
Preparation:
1. If the patient usually uses a short acting ß2 agonist or anti-anginal medication before exercise, this should be taken prior to the test, and recorded. 2. The patient should use their usual walking aid during the test and this should be recorded. 3. There should have been no vigorous exercise within 2 hours of beginning the test. 4. There should be no warm up prior to the test. 5. A short rest period, in sitting, while instructions are given should precede the test. The chair should be close to the start of the test track and the patient should be able to see the walk test track while the preliminary instructions are being given. 6. The patient should be made familiar with the Borg breathlessness and RPE scales. They should be told that they will be asked to rate their maximum breathlessness, leg fatigue or pain, and/or exertion using these scales at the beginning and end of the test, and if they stop to rest. 7. Once the patient has been informed of the above information, they should walk to the beginning of the walk track. While standing, the baseline figures should be recorded. Once this has been done and the patient feels ready, the test can begin. 8. Standardised instructions should be read from the instruction sheet throughout the test. 9. Standardised instructions should also be read from the instruction sheet for any rest period. 10. If it is necessary to walk with the patient, the physiotherapist must walk slightly behind and attempt not to influence the walking pace.

Supplemental oxygen:

If the patient uses ambulatory oxygen:

- The walk test should be performed using oxygen at the flow rate prescribed or the flow rate requested on the referral form.
- The patient should push or pull the oxygen cylinder, and should manoeuvre it inside the cone, while walking around the back of the cone. This should be practiced at the beginning of the track until the physiotherapist is happy that the patient will not be slowed unduly during the turn by the oxygen cylinder.
- If the patient is unable to manage this, the physiotherapist may need to pull, or carry, the oxygen cylinder. If this is the case, it must be recorded so that in future tests the same strategy will be used.
- If the physiotherapist pulls (or carries) the oxygen, they must walk behind the patient, so as not to set the patient's pace.

Monitoring:

The patient should be monitored continuously. The physiotherapist may walk behind the patient or, provided adequate monitoring of SpO_2 and HR and patient response are possible, can stand somewhere alongside the walk track.

Baseline	SpO_2, HR (polar monitor and palpate PR, rhythm and volume), BP (if indicated), SOB and RPE (Borg Scale)
Every Minute	SpO_2, HR (polar monitor)
Six Minutes	SpO_2, HR (polar monitor), BP (if indicated), SOB and RPE (Borg Scale), limiting factor The SpO_2 may continue to fall following the completion of the test. Record the lowest value
Rests	Note number of rests, resting position and time taken

Recovery: Wait with the patient (with minimal conversation so as not to interfere with recovery) and record recovery time to SpO_2 or HR at the pre values, or for other symptoms eg. leg pain to ease.

Criteria for test termination:

- Patients requests to terminate test
- Onset of chest pain/angina or angina-like symptoms
- Signs of poor perfusion (eg lightheadedness, confusion, ataxia, pallor, central cyanosis, nausea, cold clammy skin, diaphoresis)
- Physical or verbal manifestations of severe fatigue
- Excessive sweating
- Development of an abnormal gait (eg leg cramps, staggering)
- SpO_2 < 80% and falling - *suggest rest, recommence when/if SpO_2 increases to 90%* (NB pulse oximeters are very accurate above 90% but are much less accurate below 80%, therefore must also look at patient signs and symptoms).
- If patient has diabetes - shakiness, tingling lips, hunger, weakness, palpitations
- Abnormal HR response - tachycardia (HR >220-age) or failure of HR to increase with exercise (unless fixed rate pacemaker)

If the physiotherapist stops the patient for any reason, this must be clearly documented, and the reason for the stop described.

(American Thoracic Society Guidelines 2002, ACSM Guidelines 2000)

References:

American College of Sports Medicine. Guidelines for Graded Exercise Testing and Exercise Prescription. Sixth ed. Philadelphia: Lea & Febiger; 2000. p 351.

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Instructions to participant

Prior to testing:
• This is an exercise test. You have 6 minutes to walk at your own pace to cover as much distance as possible. You must walk around the back of the cones that mark the ends of the track. I will be walking slightly behind you at the pace that you set. • You can vary the speed at which you walk and if necessary you can stop. The timer will keep running while you are resting. You can sit, lean against the wall or stand unsupported during the time you are resting. If you do stop, you should begin to walk again when you are able. • If you feel unwell, develop any nausea, dizziness, chest pain, excessive shortness of breath, or any other symptoms that are bothering you, you must tell me but otherwise please refrain from talking during the test. • Every two minutes, I will tell you how much time you have left. • Once the 6 minutes are up, I will ask you to stop. I will then monitor you until you have recovered. I will measure the time this takes. • I will ask you what limited your ability to walk further.
During testing:
• Are you ready to begin? • *At 2 minutes*: You have four minutes to go • *At 4 minutes*: You have two minutes left • *At 6 minute*s: Stop. Well done. The 6 minutes are up.
If the patient stops during the test, repeat the following phrase once:
• Remember that you should start walking again when you are able. You can adjust the pace to suit you and you can stop again whenever you feel you have to.
At completion of testing:
• What symptoms did you experience during the test? • Do you think that was a good test of your walking ability?

Appendix 8. Incremental cardiopulmonary exercise test: peak exercise outcomes at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
Workload, W	102 (93 – 110)	120 (115 – 128)	116 (113 – 124)	96 (75 – 112)	85 (73 – 99)
$V'O_2$ peak, mL/min	1114 (1094 – 1137)	1253 (1227 - 1423)✝	1245 (1175 – 1261)	1165 (1152 – 1175)	1042 (949 – 1271)
$V'CO_2$ peak, mL/min	1419 (1347 - 1516)	1607 (1531 - 1810)	1553 (1467 – 1662)	1361 (1327– 1546)	1161 (1109 – 1614)
Respiratory exchange ratio	1.3 (1.2 – 1.3)	1.2 (1.2 – 1.3)	1.2 (1.2 – 1.4)	1.2 (1.2 – 1.3)	1.2 (1.1 – 1.2)
Respiratory rate, breaths/min	43 (42 - 43)✶	41 (37 – 45)	43 (40 – 43)	34 (33 – 37)	31 (30 – 31)
V'_T, mL	1557 (1503 – 1761)	1751 (1576 – 1961)	1596 (1518 – 1906)	1447 (1358 – 1562)	1489 (1054 – 2152)
V'_E peak, L/min	75 (56 – 78)	70 (63 – 78)	64 (63 – 76)	49 (45 – 62)	46 (33 – 59)
$V'_EV'CO_2$	52 (39 – 53)	41 (40 – 45)	43 (40 – 52)	40 (36 – 42)	37 (33 – 41)
$V'_EV'O_2$	68 (50 – 71)	52 (46 – 57)	54 (50 – 65)	52 (42 – 53)	46 (35 – 51)
$P_{ET}CO_2$, mmHg	23 (21 – 29)	28 (25 – 31)	25 (23 – 31)	29 (27 – 34)	30 (28 – 38)
Breathing reserve, %	20 (19 – 21)✶	24 (19 – 34)	19 (19 – 30)✶	39 (36 – 40)	49 (45 – 50)
SpO_2, %	98 (91 – 99)	94 (90 – 97)	92 (89 – 97)	96 (95 – 98)	97 (96 – 98)
Heart rate peak, bpm	140 (139 – 150)	147 (135 – 150)	144 (140 -150)	136 (128 – 139)	134 (130 – 138)
Heart rate reserve, bpm	26 (21 – 30)	24 (17 – 40)	30 (17 – 30)	28 (28 – 35)	29 (22 – 45)
Heart rate reserve, %	14 (13 – 17)	14 (10 – 22)	17 (11 – 17)	17 (15 – 21)	18 (13 – 25)
Systolic blood pressure, mmHg	191 (171 – 198)	190 (176 – 205)	180 (171 – 200)	188 (171 – 220)	181 (174 – 185)
Diastolic blood pressure, mmHg	107 (100 – 108)	119 (114 – 121)✶	118 (101 – 119)✶	87 (80 – 90)	89 (85 – 94)
Peak oxygen pulse, mL/beat	7.0 (7.0 – 8.0)	8.0 (8.0 – 10.4)	8.0 (8.0 – 8.0)	8.5 (7.6 – 9.5)	8.8 (8.0 – 9.3)
Borg CR10 dyspnoea score	5 (4 – 7)	5 (5 - 5)	5 (4 – 5)	9 (5 – 9)	4 (3 – 7)
Borg CR10 RPE score	5 (5 – 5)	4 (4 – 4)	5 (4 – 5)	9 (6 – 9)	5 (4 – 6)
Borg CR10 leg fatigue score	4 (4 – 5)	4 (4 – 4)	4 (4 – 5)	6 (5 – 7)	5 (3 – 6)
Borg CR10 general fatigue score	4 (3 - 5)✶	4 (3 – 4)	4 (4 – 5)	7 (6 – 8)	4 (4 – 5)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶p<0.05 compared to control group; ✝p<0.05 compared with baseline measures (ie. within group).

Appendix 9. Incremental cardiopulmonary exercise test: exercise outcomes at anaerobic threshold at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
Workload, W	45 (29 – 51)	64 (59 – 57)✶	61 (51 – 67)	28 (26 – 59)	40 (37 – 48)
$V'O_2$, mL/min	633 (544 – 649)	789 (747 – 835)✶✝	771 (676 – 806)	636 (591 – 637)	665 (582 – 717)
$V'CO_2$, mL/min	512 (512 – 628)	715 (681 – 756)✶	699 (628 – 730)	571 (556 – 592)	599 (589 – 623)
Respiratory rate, breaths/min	25 (19 – 27)	21 (18 – 25)	22 (19 – 27)	22 (22 - 30)	22 (17 – 24)
V'_T, mL	964 (862 – 1067)	1367 (1188 – 1465)	1306 (862 – 1427)	819 (804 – 821)	867 (847 – 1308)
V'_E, L/min	24 (23 – 24)	29 (26 – 30)	28 (23 – 30)	23 (18 – 26)	22 (21 – 22)
$V'_EV'CO_2$	42 (36 – 45)	37 (31 – 43)	42 (31 – 44)	40 (37 – 42)	35 (33 – 40)
$V'_EV'O_2$	38 (28 – 40)	36 (33 – 38)	38 (34 – 39)	36 (32 – 38)	33 (31 – 36)
$P_{ET}CO_2$, mmHg	29 (28 – 35)	33 (28 – 38)	29 (29 – 32)	35 (29 – 36)	35 (31 – 38)
Breathing reserve, %	76 (73 – 77)	72 (68 – 77)	68 (67 – 76)	73 (71 – 79)	79 (76 – 82)
SpO_2, %	96 (92 – 99)	98 (97 – 98)	97 (96 – 98)	96 (96 – 98)	97 (96 – 98)
Heart rate, bpm	93 (83 – 94)	95 (92 – 98)	93 (93 – 96)	98 (95 – 103)	105 (94 – 107)
Heart rate reserve, bpm	77 (76 – 80)	75 (66 – 86)	76 (67 - 84)	68 (65 – 72)	71 (65 – 71)
Heart rate reserve, %	45 (44 – 48)	44 (41 – 48)	45 (42 – 47)	40 (37 – 43)	40 (36 – 44)
Systolic blood pressure, mmHg	145 (136 – 178)	142 (135 – 151)	148 (136 – 159)	152 (132 – 173)	149 (134 – 151)
Diastolic blood pressure, mmHg	81 (76 – 96)	89 (81 – 93)	92 (86 – 97)	78 (71 – 84)	83 (72 – 84)
Oxygen pulse, mL/beat	7.0 (6.0 – 7.0)	8.0 (7.8 – 8.5)	8.0 (7.0 – 8.0)	6.0 (6.0 – 6.0)	6.0 (5.8 – 6.0)
Borg CR10 dyspnoea score	1 (1 – 2)	2 (2 – 2)	2 (1 – 2)	2 (1 – 4)	2 (1 – 3)
Borg CR10 RPE score	1 (1 – 3)	3 (2 - 3)	2 (1 – 3)	2 (1 – 4)	1 (1 – 2)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶$p<0.05$ compared to control group; ✝$p<0.05$ compared with baseline measures (ie. within group).

Appendix 10. Constant workload cycle ergometer test: peak exercise outcomes at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
Workload, W	75 (68 – 77)	76 (73 – 81)	75 (68 – 77)	72 (55 – 78)	72 (55 – 78)
Endurance time, sec	436 (378 – 501)	1280 (1104 – 1386)✶†	1197 (825 – 1362)	441 (338 – 463)	460 (395 – 508)
$V'O_2$ peak, mL/min	1213 (1110 – 1256)	1284 (1213 – 1431)	1254 (1090 – 1315)	1209 (1162 – 1300)	1267 (1063 – 1341)
$V'CO_2$ peak, mL/min	1299 (1256 – 1339)	1313 (1228 – 1465)	1272 (1095 – 1354)	1470 (1280 – 1637)	1525 (1124 – 1665)
Respiratory exchange ratio	1.1 (1.1 – 1.2)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	1.2 (1.1 – 1.2)	1.2 (1.2 – 1.2)
Respiratory rate, breaths/min	41 (38 – 45)	45 (38 – 48)	42 (38 – 48)	34 (32 – 38)	34 (33 – 37)
V'_T, mL	1404 (1368 – 1518)	1397 (1357 – 1497)	1404 (1380 – 1413)	1393 (1374 – 2254)	1420 (1274 – 1881)
V'_E peak, L/min	62 (54 – 68)	60 (55 – 64)	58 (54 – 63)	54 (44 – 61)	62 (47 – 69)
$V'_EV'CO_2$	49 (37 – 51)	43 (41 – 47)	44 (43 – 51)	37 (37 – 42)	41 (41 – 41)
$V'_EV'O_2$	49 (40 – 69)	44 (41 – 47)	44 (44 – 54)	47 (45 – 52)	50 (49 – 51)
$P_{ET}CO_2$, mmHg	24 (24 – 31)	26 (24 – 28)	25 (24 – 27)	30 (27 – 32)	27 (26 – 29)
Breathing reserve, %	41 (39 – 51)	49 (40 – 56)	42 (39 – 55)	56 (48 – 57)	51 (42 – 54)
SpO_2, %	95 (95 – 96)	97 (96 – 98)	97 (95 – 97)	98 (96 – 99)	95 (94 – 98)
Heart rate peak, bpm	141 (129 – 142)	142 (134 – 143)	142 (129 – 143)	140 (136 – 154)	135 (132 – 152)
Heart rate reserve, bpm	34 (24 – 50)	38 (28 – 55)	39 (33 – 49)	23 (14 – 25)	27 (23 – 32)
Heart rate reserve, %	16 (15 – 24)	17 (13 – 26)	21 (14 – 24)	14 (9 – 14)	17 (16 – 17)
Systolic blood pressure, mmHg	185 (185 – 223)	186 (169 – 206)	181 (172 – 200)	196 (165 – 212)	207 (177 – 222)
Diastolic blood pressure, mmHg	101 (86 – 104)	96 (82 – 109)	103 (89 – 104)	82 (77 – 83)	93 (73 – 100)
Peak oxygen pulse, mL/beat	8.6 (7.1 – 9.0)	8.8 (8.4 – 11.0)	8.6 (8.0 – 9.0)	8.6 (8.2 – 9.7)	8.9 (8.3 – 9.6)
Borg CR10 dyspnoea score	7 (3 – 7)	6 (4 – 8)	4 (3 – 7)	7 (5 – 9)	6 (4 – 9)
Borg CR10 RPE score	7 (3 - 7)	7 (5 – 8)	6 (3 – 7)	7 (6 – 8)	6 (5 – 8)
Borg CR10 leg fatigue score	3 (3 – 5)	3 (3 – 4)	3 (2 – 3)	5 (3 – 5)	5 (4 – 6)
Borg CR10 general fatigue score	5 (3 – 6)	3 (3 – 4)	3 (3 – 3)	5 (5 – 8)	4 (4 – 7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶p<0.05 compared to control group; †p<0.05 compared with baseline measures (ie. within group).

Appendix 11. Constant workload cycle ergometer test: exercise outcomes at 30-seconds isotime, at baseline and at"12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
$V'O_2$, mL/min	500 (423 – 545)	521 (484 – 569)✶	519 (423 – 523)	510 (510 – 525)	581 (546 – 647)
$V'CO_2$, mL/min	419 (411 – 497)	445 (382 – 524)	419 (404 – 486)	462 (426 – 471)	528 (489 – 617)
Respiratory rate, breaths/min	26 (22 – 28)	23 (18 – 30)	26 (19 – 28)	28 (25 – 29)	25 (24 – 30)
V'_T, mL	793 (761 – 824)	800 (729 – 875)	762 (749 – 850)	718 (563 – 746)	883 (710 – 897)
V'_E, L/min	20 (17 – 23)	21 (16 – 24)	20 (18 – 23)	18 (16 – 20)	19 (18 – 27)
$V'_EV'CO_2$	46 (38 – 48)	41 (37 – 46)	45 (38 – 48)	40 (39 – 41)	37 (36 – 40)
$V'_EV'O_2$	42 (34 – 47)	34 (33 – 37)	35 (34 – 45)	35 (32 – 38)	36 (33 – 42)
$P_{ET}CO_2$, mmHg	28 (27 – 32)	30 (27 – 33)	28 (27 – 32)	32 (30 – 35)	30 (29 – 35)
SpO_2, %	97 (95 – 97)	96 (94 – 98)	97 (95 – 98)	98 (98 – 98)	97 (96 – 97)
Heart rate, bpm	88 (85 – 91)	80 (75 – 86)✶	84 (77 – 85)✶	97 (92 – 99)	100 (95 – 101)
Oxygen pulse, mL/beat	5.8 (5.0 – 6.0)	5.9 (5.5 – 6.9)	5.6 (5.2 – 6.2)	5.2 (5.1 – 5.5)	5.8 (5.7 – 6.4)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; ✶$p<0.05$ compared to control group.

Appendix 12. Constant workload cycle ergometer: exercise outcomes at 60-seconds isotime, at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
$V'O_2$, mL/min	619 (488 – 756)	722 (604 – 810)	685 (462 – 758)	691 (658 – 827)	736 (714 – 745)
$V'CO_2$, mL/min	523 (461 – 721)	637 (496 – 738)	560 (461 – 714)	616 (608 – 648)	659 (581 – 805)
Respiratory rate, breaths/min	27 (20 – 28)	26 (20 – 30)	27 (22 – 29)	27 (23 – 28)	24 (19 – 28)
V'_T, mL	964 (799 – 1205)	984 (819 – 1144)	827 (799 – 1141)	833 (818 – 945)	977 (816 – 1081)
V'_E, L/min	22 (19 – 28)	27 (21 – 29)	25 (22 – 28)	22 (21 – 25)	23 (18 – 30)
$V'_EV'CO_2$	46 (35 – 47)	40 (35 – 45)	45 (35 – 47)	35 (35 – 38)	34 (33 – 37)
$V'_EV'O_2$	39 (29 – 44)	33 (29 – 39)	37 (29 – 44)	30 (29 – 31)	32 (29 – 32)
$P_{ET}CO_2$, mmHg	28 (26 – 34)	30 (26 – 35)	28 (27 – 34)	33 (29 – 36)	35 (30 – 36)
SpO_2, %	97 (96 – 97)	96 (96 – 97)	96 (96 – 97)	98 (96 – 99)	96 (95 – 98)
Heart rate, bpm	97 (96 – 104)	89 (80 – 97)	94 (84 – 96)	109 (105 – 109)	106 (104 – 110)
Oxygen pulse, mL/beat	6.0 (5.0 – 7.0)	7.2 (6.5 – 8.5)	7.0 (5.0 – 7.4)	6.3 (6.3 – 7.6)	7.1 (7.0 – 7.2)
Borg CR10 dyspnoea score	1 (1 – 2)	1 (0 – 1)	1 (0 – 1)	1 (0 – 2)	1 (0 – 1)
Borg CR10 RPE score	2 (1 – 2)	2 (1 – 2)	1 (1 – 2)	1 (1 - 2)	1 (0 – 2)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 13. Constant workload cycle ergometer: exercise outcomes at 90-seconds isotime, at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
$V'O_2$, mL/min	809 (653 – 937)	905 (778 – 969)	894 (627 – 917)	912 (835 – 987)	861 (851 – 866)
$V'CO_2$, mL/min	759 (688 – 1015)	894 (708 – 1000)	824 (688 – 964)	859 (743 – 936)	882 (784 – 932)
Respiratory rate, breaths/min	27 (15 – 32)	32 (27 – 33)	31 (27 – 32)	26 (23 – 26)	24 (23 – 28)
V'_T, mL	1462 (1100 – 1538)	1068 (952 – 1211)	1100 (988 – 1149)	1035 (981 – 1145)	1025 (1014 – 1169)
V'_E, L/min	30 (22 – 36)	36 (30 – 38)	36 (30 – 36)	29 (25 – 29)	28 (23 – 36)
$V'_EV'CO_2$	40 (32 – 43)	39 (34 – 44)	43 (34 – 43)	31 (31 – 34)	32 (30 – 33)
$V'_EV'O_2$	33 (32 – 47)	36 (31 – 42)	40 (32 – 47)	30 (27 – 31)	33 (27 – 34)
$P_{ET}CO_2$, mmHg	29 (27 – 36)	31 (26 – 36)	29 (26 – 36)	38 (32 – 38)	37 (33 – 39)
SpO_2, %	96 (95 – 97)	96 (95 – 97)	96 (96 – 97)	96 (96 – 96)	96 (95 – 97)
Heart rate, bpm	109 (104 – 111)	94 (86 – 105)	100 (88 – 109)	112 (110 – 114)	110 (110 – 116)
Oxygen pulse, mL/beat	7.4 (6.2 – 8.0)	8.4 (7.2 – 9.9)	7.7 (5.9 – 9.0)	8.0 (6.8 – 8.7)	7.9 (7.0 – 8.0)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute.

Appendix 14. Constant workload cycle ergometer test: exercise outcomes at 3-minutes isotime, at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
$V'O_2$, mL/min	954 (949 – 1075)	1062 (1009 – 1209)	1012 (998 – 1111)	1077 (1059 – 1160)	1107 (1015 – 1127)
$V'CO_2$, mL/min	1150 (1121 – 1244)	1217 (1081 – 1416)	1095 (1040 – 1339)	1455 (1144 – 1468)	1371 (1125 – 1438)
Respiratory rate, breaths/min	33 (25 – 38)	33 (25 – 39)	33 (27 – 39)	31 (25 – 33)	28 (24 – 32)
V'_T, mL	1654 (1404 – 1669)	1663 (1532 – 1707)	1636 (1404 – 1689)	1574 (1182 – 1734)	1416 (1370 – 1852)
V'_E, L/min	49 (46 – 55)	48 (43 – 54)	47 (46 – 50)	44 (40 – 52)	45 (44 – 47)
$V'_E V'CO_2$	44 (32 – 46)	38 (32 – 44)	43 (33 – 46)	36 (30 – 36)	33 (31 – 34)
$V'_E V'O_2$	51 (39 – 58)	38 (30 – 50)	47 (30 – 59)	43 (41 – 45)	41 (40 – 42)
$P_{ET}CO_2$, mmHg	27 (24 – 34)	31 (25 – 38)	27 (25 – 37)	32 (31 – 37)	34 (33 – 35)
SpO_2, %	96 (94 – 97)	98 (96 – 99)	97 (94 – 99)	96 (95 – 98)	96 (95 – 98)
Heart rate, bpm	127 (127 – 132)	114 (108 – 123)	117 (111 – 127)	123 (122 – 123)	126 (122 – 130)
Oxygen pulse, mL/beat	7.6 (7.4 – 8.0)	9.0 (8.6 – 10.7)	8.8 (8.0 – 9.1)	9.0 (8.0 – 9.3)	8.6 (7.3 – 9.0)
Borg CR10 dyspnoea score	3 (3 – 4)	3 (3 – 3)	3 (1 – 3)	3 (3 – 3)	3 (3 – 4)
Borg CR10 RPE score	4 (3 – 4)	3 (2 – 3)	2 (2 – 3)	3 (3 – 4)	3 (3 – 4)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; $V'_E V'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 15. Constant workload cycle ergometer test: exercise outcomes at the shortest test isotime, at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
Isotime, seconds	436 (378 – 501)			299 (282 – 397)	
Workload, W	75 (68 – 77)			72 (55 – 78)	
$V'O_2$, mL/min	1213 (1110 – 1256)	1211 (1131 – 1387)	1154 (1063 – 1268)	1168 (1152 – 1209)	1182 (1061 – 1216)
$V'CO_2$, mL/min	1299 (1256 – 1339)	1339 (1259 – 1477)	1311 (1101 – 1366)	1470 (1295 – 1548)	1509 (1124 – 1533)
Respiratory rate, breaths/min	41 (38 – 45)	37 (27 - 46)	38 (28 – 46)	34 (33 – 37)	33 (31 – 33)
V'_T, mL	1404 (1368 – 1518)	1617 (1463 – 1731)	1512 (1404 – 1722)	1374 (1325 – 2058)	1420 (1387 – 1765)
V'_E, L/min	62 (54 – 68)	55 (47 – 64)	54 (47 – 63)	53 (44 – 54)	54 (47 – 55)
$V'_E V'CO_2$	49 (38 – 51)	39 (35 – 45)	43 (36 – 51)	37 (34 – 42)	36 (36 – 41)
$V'_E V'O_2$	49 (40 – 69)	42 (39 – 47)	44 (40 – 54)	46 (45 – 52)	46 (45 – 50)
$P_{ET}CO_2$, mmHg	24 (24 – 31)	29 (24 – 33)	25 (24 – 32)	32 (27 – 33)	31 (26 – 33)
SpO_2, %	95 (95 – 96)	98 (96 – 99)	97 (95 – 99)	97 (96 – 98)	96 (95 – 97)
Heart rate, bpm	141 (129 – 142)	130 (121 – 138)	129 (125 – 136)	135 (133 – 150)	135 (133 – 152)
Oxygen pulse, mL/beat	8.6 (7.1 – 9.0)	8.8 (8.6 – 10.8)	8.6 (8.4 – 9.0)	8.7 (8.0 – 9.7)	8.5 (7.8 – 9.0)
Borg CR10 dyspnoea score	7 (3 – 7)	4 (3 – 4)	3 (2 – 4)	5 (4 – 8)	6 (5 – 7)
Borg CR10 RPE score	7 (3 – 7)	4 (3 – 4)	3 (3 – 4)	5 (5 – 8)	6 (5 – 7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; $V'_E V'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 16. Functional exercise capacity (six-minute walk test): exercise outcomes at baseline and at "12 weeks"

	Exercise Group			Control Group	
	Baseline	12 weeks *Per protocol*	12 weeks *Intention to treat*	Baseline	12 weeks
n	5	4	5	5	5
6MWD, m	560 (483 – 610)	650 (623 - 679)	629 (606 – 670)	575 (560 - 585)	570 (555 - 585)
6MWD, % predicted		97 (96 – 99)✶	96 (96 – 97)	84 (83 – 90)	89 (83 – 90)
Heart rate, bpm	134 (99 – 137)	124 (111 – 137)	134 (114 – 146)	124 (112 – 128)	135 (130 – 136)
Heart rate reserve, bpm	34 (23 – 81)	37 (32 – 52)	32 (31 – 43)	32 (30 – 66)	31 (28 – 43)
Heart rate reserve, %	20 (14 – 45)	23 (19 – 31)	19 (17 – 27)	32 (17 – 37)	24 (17 – 24)
SpO_2, %	95 (93 – 96)	93 (90 – 96)	93 (91 – 95)	95 (94 – 95)	94 (94 – 94)
Nadir SpO_2, %	94 (93 – 95)	93 (90 – 95)	93 (91 – 95)	93 (92 – 95)	94 (93 – 94)
Borg CR10 dyspnoea score	4 (4 – 5)	4 (3 – 4)	4 (3 – 4)	3 (2 – 4)	4 (4 – 5)
Borg CR10 RPE score	4 (4 – 7)	4 (3– 4)	4 (4 – 4)	5 (3 – 5)	5 (3 – 5)
Borg CR10 leg fatigue score	3 (1 – 3)	2 (1 – 2)✶	1 (1 – 2)✶	3 (3 – 3)	5 (4 – 6)
Borg CR10 general fatigue score	3 (1 – 3)	2 (1 – 2)	1 (0 - 2)✶	3 (1 – 4)	5 (4 - 5)

Data presented as median (interquartile range); measures taken at the end of the test unless otherwise stated; 6MWD: six-minute walk distance (125); SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶$p<0.05$ compared to control group.

Appendix 17. Incremental cardiopulmonary exercise test: peak exercise outcomes at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
Workload, W	124 (119 – 132)	116 (113 – 124)	117 (110 – 127)	116 (103 – 117)	85 (73 – 99)	101 (65 – 102)
$V'O_2$ peak, mL/min	1262 (1253 – 1584)	1245 (1175 – 1261)	1286 (1233 –1631)✶	1181 (1175 – 1286)	1042 (949 – 1271)	1122 (1000 – 1181)
$V'CO_2$ peak, mL/min	1553 (1510 – 1902)	1553 (1467 – 1662)	1665 (1590 – 2004)	1662 (1514 – 1665)	1161 (1109 – 1614)	1447 (1092 – 1512)
Respiratory exchange ratio	1.2 (1.2 – 1.2)	1.2 (1.2 – 1.4)	1.3 (1.2 – 1.3)	1.3 (1.3 – 1.4)	1.2 (1.1 – 1.2)	1.3 (1.2 – 1.3)
Respiratory rate, breaths/min	43 (36 – 47)	43 (40 – 43)	46 (39 - 48)	43 (40 – 46)	31 (30 – 31)	33 (30 – 36)
V'_T, mL	1906 (1712 – 2015)	1596 (1518 – 1906)	1799 (1776 – 1882)	1753 (1596 – 1799)	1489 (1054 – 2152)	1381 (1278 – 1691)
V'_E peak, L/min	76 (70 – 79)	64 (63 – 76)	83 (73 – 86)	64 (63 – 83)	46 (33 – 59)	49 (46 – 51)
$V'_EV'CO_2$	41 (40 – 45)	43 (40 – 52)	45 (43 – 47)	45 (42 – 50)	37 (33 – 41)	34 (34 – 42)
$V'_EV'O_2$	52 (46 – 57)	54 (50 – 65)	54 (46 – 59)	54 (54 – 65)	46 (35 – 51)	45 (42 – 53)
$P_{ET}CO_2$, mmHg	28 (25 – 31)	25 (23 – 31)	26 (24 – 28)	26 (23 – 30)	30 (28 – 38)	33 (28 – 35)
Breathing reserve, %	30 (24 – 38)	19 (19 – 30)	36 (34 – 37)	32 (19 – 36)	49 (45 – 50)	49 (44 – 50)
SpO_2, %	97 (94 – 98)	92 (89 – 97)	95 (91 – 97)	89 (88 – 95)	97 (96 – 98)	97 (97 – 98)
Heart rate peak, bpm	150 (130 – 150)	144 (140 -150)	131 (120 – 142)	142 (132 – 147)	134 (130 – 138)	130 (129 – 132)
Heart rate reserve, bpm	30 (24 – 51)	30 (17 – 30)	50 (38 – 60)	28 (24 – 40)	29 (22 – 45)	34 (32 – 47)
Heart rate reserve, %	17 (14 – 28)	17 (11 – 17)	27 (21 – 33)	16 (14 – 23)	18 (13 – 25)	22 (21 – 27)
Systolic blood pressure, mmHg	180 (172 – 190)	180 (171 – 200)	177 (170 – 184)	181 (169 – 198)	181 (174 – 185)	149 (147 – 183)
Diastolic blood pressure, mmHg	119 (110 – 122)	118 (101 – 119)	96 (89 – 104)	105 (96 – 113)	89 (85 – 94)	84 (84 – 87)
Peak oxygen pulse, mL/beat	8.0 (8.0 – 12.9)	8.0 (8.0 – 8.0)	13.5 (10.5 – 15.5)	8.0 (7.4 – 10.5)	8.8 (8.0 – 9.3)	8.7 (8.7 – 9.1)
Borg CR10 dyspnoea score	5 (5 – 5)	5 (4 – 5)	6 (5 – 7)	5 (4 – 6)	4 (3 – 7)	5 (3 – 6)
Borg CR10 RPE score	5 (5 – 5)	5 (4 – 5)	6 (5 – 7)	5 (4 – 6)	5 (4 – 6)	6 (5 – 6)
Borg CR10 leg fatigue score	4 (4 – 5)	4 (4 – 5)	5 (5 – 5)	5 (5 – 5)	5 (3 – 6)	3 (3 – 5)
Borg CR10 general fatigue score	4 (3 – 5)	4 (4 – 5)	4 (3 – 5)	4 (4 – 5)	4 (4 – 5)	6 (3 – 7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶p<0.05 compared to control group.

Appendix 18. Incremental cardiopulmonary exercise test: exercise outcomes at anaerobic threshold at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
Workload, W	67 (64 – 68)	61 (51 – 67)	50 (48 – 58)	50 (46 – 51)	40 (37 – 48)	47 (31 – 49)
$V'O_2$, mL/min	806 (789 – 864)	771 (676 – 806)	718 (688 – 882)	676 (657 – 718)	665 (582 – 717)	623 (603 – 681)
$V'CO_2$, mL/min	730 (715 – 782)	699 (628 – 730)	649 (614 - 757)	628 (579 – 649)	599 (589 – 623)	589 (529 – 629)
Respiratory rate, breaths/min	22 (21 – 28)	22 (19 – 27)	26 (24 – 31)	26 (21 – 27)	22 (17 – 24)	25 (21 – 26)
V'_T, mL	1427 (1130 – 1504)	1306 (862 – 1427)	1000 (928 – 1073)	1000 (862 – 1146)	867 (847 – 1308)	799 (714 – 1017)
V'_E, L/min	30 (29 – 31)	28 (23 – 30)	26 (25 – 28)	24 (23 – 26)	22 (21 – 22)	21 (21 – 21)
$V'_E V'CO_2$	37 (31 – 43)	42 (31 – 44)	41 (35 – 41)	41 (30 – 41)	35 (33 – 40)	35 (34 – 39)
$V'_E V'O_2$	38 (36 – 39)	38 (34 – 39)	36 (36 – 37)	36 (35 – 37)	33 (31 – 36)	35 (31 – 35)
$P_{ET}CO_2$, mmHg	28 (28 – 33)	29 (29 – 32)	29 (29 – 32)	29 (29 – 35)	35 (31 – 38)	36 (32 – 38)
Breathing reserve, %	68 (68 – 74)	68 (67 – 76)	79 (77 – 79)	76 (74 – 79)	79 (76 – 82)	77 (76 – 79)
SpO_2, %	97 (97 – 98)	97 (96 – 98)	95 (94 – 97)	95 (93 – 98)	97 (96 – 98)	97 (97 – 98)
Heart rate, bpm	96 (93 – 99)	93 (93 – 96)	86 (84 – 88)	92 (88 – 93)	105 (94 – 107)	99 (96 – 100)
Heart rate reserve, bpm	84 (75 – 87)	76 (67 – 84)	94 (92 – 96)	83 (74 – 92)	71 (65 – 71)	74 (67 – 79)
Heart rate reserve, %	48 (43 – 48)	45 (42 – 47)	52 (51 – 53)	48 (44 – 51)	40 (36 – 44)	44 (41 – 44)
Systolic blood pressure, mmHg	136 (135 – 142)	148 (136 – 159)	142 (132 – 151)	160 (150 – 167)	149 (134 – 151)	137 (133 – 160)
Diastolic blood pressure, mmHg	92 (79 – 95)	92 (86 – 97)	75 (72 – 79)	84 (79 – 90)	83 (72 – 84)	74 (71 – 84)
Oxygen pulse, mL/beat	8.0 (8.0 – 9.0)	8.0 (7.0 – 8.0)	10.0 (8.5 – 11.5)	7.0 (6.8 – 8.5)	6.0 (5.8 – 6.0)	6.0 (6.0 – 6.3)
Borg CR10 dyspnoea score	2 (2 – 3)	2 (1 – 2)	1 (1 – 2)	1 (1 – 2)	2 (1 – 3)	1 (1 – 2)
Borg CR10 RPE score	3 (2 – 3)	2 (1 – 3)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	1 (1 – 3)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_E V'CO_2$: ventilatory equivalent for carbon dioxide; $V'_E V'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 19. Constant workload cycle ergometer test: peak exercise outcomes at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
Workload, W	77 (73 – 86)	75 (68 – 77)	77 (73 – 86)	75 (68 – 77)	72 (55 – 78)	72 (55 – 78)
Endurance time, sec	1197 (1011 – 1328)	1197 (825 – 1362)	1003 (897 – 1257)✶	1003 (790 – 1362)	460 (395 – 508)	416 (379 – 430)
VO_2 peak, mL/min	1254 (1172 – 1515)	1254 (1090 – 1315)	1406 (1267 – 1729)	1315 (1128 – 1406)	1267 (1063 – 1341)	1295 (1263 – 1304)
VCO_2 peak, mL/min	1272 (1184 – 1535)	1272 (1095 – 1354)	1413 (1315 – 1716)	1354 (1217 – 1413)	1525 (1124 – 1665)	1584 (1357 – 1588)
Respiratory exchange ratio	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.1)	1.2 (1.2 – 1.2)	1.2 (1.1 – 1.2)
Respiratory rate, breaths/min	48 (38 – 49)	42 (38 – 48)	48 (42 – 48)	42 (38 – 48)	34 (33 – 37)	36 (36 – 38)
V_T, mL	1413 (1351 – 1581)	1404 (1380 – 1413)	1598 (1573 – 1673)	1549 (1404 – 1598)	1420 (1274 – 1881)	1358 (1314 – 1663)
V_E peak, L/min	63 (55 – 65)	58 (54 – 63)	75 (70 – 76)	64 (58 – 75)	62 (47 – 69)	52 (52 – 56)
V_EVCO_2	44 (40 - 49)	44 (43 – 51)	52 (45 – 53)	51 (43 – 52)	41 (41 – 41)	35 (33 – 46)
V_EVO_2	44 (40 – 49)	44 (44 – 54)	55 (46 – 56)	55 (44 – 57)	50 (49 – 51)	43 (40 – 56)
$P_{ET}CO_2$, mmHg	25 (24 – 29)	25 (24 – 27)	22 (21 – 26)	24 (22 – 27)	27 (26 – 29)	33 (25 – 34)
Breathing reserve, %	55 (45 – 57)	42 (39 – 55)	44 (35 – 45)	42 (39 – 44)	51 (42 – 54)	56 (48 – 59)
SpO_2, %	97 (95 – 98)	97 (95 – 97)	96 (94 – 97)	96 (95 – 97)	95 (94 – 98)	95 (88 – 96)
Heart rate peak, bpm	142 (125 – 144)	142 (129 – 143)	150 (129 – 154)	143 (129 – 150)	135 (132 – 152)	140 (135 – 147)
Heart rate reserve, bpm	55 (47 – 64)	39 (33 – 49)	22 (20 – 47)	22 (18 – 41)	27 (23 – 32)	28 (17 – 37)
Heart rate reserve, %	21 (17 – 31)	21 (14 – 24)	12 (11 – 26)	12 (11 – 24)✶	17 (16 – 17)	17 (11 – 20)
Systolic blood pressure, mmHg	172 (167 – 186)	181 (172 – 200)	195 (183 – 197)	195 (181 – 199)	207 (177 – 222)	199 (179 – 207)
Diastolic blood pressure, mmHg	89 (75 – 107)	103 (89 – 104)	97 (95 – 107)	103 (97 – 104)	93 (73 – 100)	85 (85 – 86)
Peak oxygen pulse, mL/beat	8.6 (8.3 – 12.5)	8.6 (8.0 – 9.0)	9.4 (8.2 – 14.2)	9.1 (7.0 – 9.4)	8.9 (8.3 – 9.6)	9.1 (8.8 – 9.5)
Borg CR10 dyspnoea score	4 (4 – 6)	4 (3 – 7)	5 (5 – 7)	5 (4 – 9)	6 (4 – 9)	8 (4 – 9)
Borg CR10 RPE score	6 (5 – 7)	6 (3 – 7)	6 (6 – 8)	6 (5 – 9)	6 (5 – 8)	8 (5 – 9)
Borg CR10 leg fatigue score	3 (3 – 5)	3 (2 – 3)	4 (3 – 6)	3 (2 – 4)	5 (4 – 6)	5 (3 – 7)
Borg CR10 general fatigue score	3 (3 – 4)	3 (3 – 3)	7 (5 – 8)	3 (3 – 7)	4 (4 – 7)	5 (5 – 7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶p<0.05 compared to control group.

Appendix 20. Constant workload cycle ergometer test: exercise outcomes at 30-seconds isotime, at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
$V'O_2$, mL/min	519 (448 – 521)	519 (423 – 523)	532 (486 – 677)	441 (423 – 532)	581 (546 – 647)	575 (516 – 587)
$V'CO_2$, mL/min	404 (360 – 445)	419 (404 – 486)	482 (429 – 569)	419 (377 – 482)	528 (489 – 617)	509 (480 – 548)
Respiratory rate, breaths/min	19 (17 – 23)	26 (19 – 28)	31 (25 – 32)	26 (18 – 31)	25 (24 – 30)	25 (24 – 25)
V'_T, mL	850 (800 – 900)	762 (749 – 850)	779 (758 – 929)	762 (749 – 779)	883 (710 – 897)	728 (710 – 743)
V'_E, L/min	18 (15 – 21)	20 (18 – 23)	23 (21 – 24)	20 (19 – 23)	19 (18 – 27)	18 (18 – 23)
$V'_EV'CO_2$	45 (40 – 47)	45 (38 – 48)	51 (43 – 52)	48 (35 – 51)	37 (36 – 40)	37 (34 – 42)
$V'_EV'O_2$	35 (32 – 40)	35 (34 – 45)	44 (36 – 46)	44 (29 – 47)	36 (33 – 42)	35 (30 – 40)
$P_{ET}CO_2$, mmHg	30 (27 – 33)	28 (27 – 32)	25 (24 – 30)	28 (25 – 34)	30 (29 – 35)	32 (31 – 38)
SpO_2, %	98 (96 – 98)	97 (95 – 98)	95 (94 – 97)	97 (95 – 98)	97 (96 – 97)	97 (94 – 97)
Heart rate, bpm	84 (77 – 88)	84 (77 – 85)	91 (85 – 91)	85 (79 – 91)	100 (95 – 101)	96 (90 – 105)
Oxygen pulse, mL/beat	5.6 (5.4 – 5.9)	5.6 (5.2 – 6.2)	6.0 (5.5 – 8.2)	5.2 (5.0 – 6.0)	5.8 (5.7 – 6.4)	6.1 (5.6 – 6.1)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute.

Appendix 21. Constant workload cycle ergometer: exercise outcomes at 60-seconds isotime, at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
$V'O_2$, mL/min	685 (522 – 722)	685 (462 – 758)	821 (720 – 950)	618 (462 – 821)	736 (714 – 745)	685 (680 – 858)
$V'CO_2$, mL/min	560 (431 – 637)	560 (461 – 714)	766 (624 – 795)	483 (461 – 766)	659 (581 – 805)	717 (611 – 750)
Respiratory rate, breaths/min	22 (17 – 26)	27 (22 – 29)	33 (24 – 34)	27 (15 – 33)	24 (19 – 28)	25 (23 – 26)
V'_T, mL	1141 (984 – 1148)	827 (799 – 1141)	1126 (963 – 1276)	827 (800 – 1126)	977 (816 – 1081)	866 (841 – 869)
V'_E, L/min	25 (18 – 29)	25 (22 – 28)	28 (25 – 33)	22 (21 – 28)	23 (18 – 30)	22 (20 – 30)
$V'_EV'CO_2$	45 (40 – 46)	45 (35 – 47)	44 (39 – 46)	44 (34 – 47)	34 (33 – 37)	33 (33 – 40)
$V'_EV'O_2$	37 (33 – 40)	37 (29 – 44)	35 (30 – 40)	35 (29 – 45)	32 (29 – 32)	29 (29 – 34)
$P_{ET}CO_2$, mmHg	30 (26 – 35)	28 (27 – 34)	26 (25 – 30)	28 (26 – 35)	35 (30 – 36)	35 (29 – 38)
SpO_2, %	96 (96 – 97)	96 (96 – 97)	95 (93 – 97)	96 (95 – 98)	96 (95 – 98)	96 (94 – 97)
Heart rate, bpm	94 (81 – 101)	94 (84 – 96)	96 (90 – 101)	96 (84 – 96)	106 (104 – 110)	105 (103 – 112)
Oxygen pulse, mL/beat	7.0 (6.0 – 7.2)	7.0 (5.0 – 7.4)	8.0 (7.3 – 10.5)	6.5 (5.0 – 8.0)	7.1 (7.0 – 7.2)	6.8 (6.6 – 7.8)
Borg CR10 dyspnoea score	1 (1 – 2)	1 (0 – 1)	2 (1 – 3)	1 (1 – 2)	1 (0 – 1)	1 (0 – 2)
Borg CR10 RPE score	2 (2 – 3)	1 (1 – 2)	2 (2 – 3)	2 (1 – 2)	1 (0 – 2)	1 (0 – 2)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 22. Constant workload cycle ergometer: exercise outcomes at 90-seconds isotime, at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
$V'O_2$, mL/min	894 (662 – 905)	894 (627 – 917)	935 (861 – 1147)	786 (627 – 935)	861 (851 – 866)	938 (879 – 987)
$V'CO_2$, mL/min	824 (592 – 894)	824 (688 – 964)	969 (813 – 1064)	688 (657 – 969)	882 (784 – 932)	882 (833 – 926)
Respiratory rate, breaths/min	31 (23 – 32)	31 (27 – 32)	33 (25 – 33)	27 (17 – 33)	24 (23 – 28)	25 (22 – 28)
V'_T, mL	1149 (997 – 1273)	1100 (988 – 1149)	1401 (1227 – 1467)	1100 (1053 – 1401)	1025 (1014 – 1169)	1047 (1032 – 1126)
V'_E, L/min	36 (24 – 40)	36 (30 – 36)	36 (31 – 41)	30 (26 – 36)	28 (23 – 36)	27 (25 – 33)
$V'_EV'CO_2$	43 (39 – 45)	43 (34 – 43)	40 (36 – 44)	40 (34 – 43)	32 (30 – 33)	31 (29 – 36)
$V'_EV'O_2$	40 (34 – 44)	40 (32 – 47)	34 (30 – 41)	34 (29 – 47)	33 (27 – 34)	29 (26 – 35)
$P_{ET}CO_2$, mmHg	31 (26 – 36)	29 (26 – 36)	28 (26 – 32)	29 (28 – 36)	37 (33 – 39)	39 (31 – 39)
SpO_2, %	96 (95 – 97)	96 (96 – 97)	95 (93 – 97)	96 (95 – 99)	96 (95 – 97)	96 (92 – 97)
Heart rate, bpm	100 (89 – 110)	100 (88 – 109)	103 (95 – 110)	103 (87 – 109)	110 (110 – 116)	110 (109 – 117)
Oxygen pulse, mL/beat	7.7 (6.6 – 8.4)	7.7 (5.9 – 9.0)	8.0 (7.7 – 11.8)	7.4 (5.9 – 8.0)	7.9 (7.0 – 8.0)	8.3 (7.2 – 8.7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute.

Appendix 23. Constant workload cycle ergometer test: exercise outcomes at 3-minutes isotime, at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
$V'O_2$, mL/min	1111 (1055 – 1308)	1012 (998 – 1111)	1091 (1009 – 1366)	1012 (926 – 1091)	1107 (1015 – 1127)	1136 (1063 – 1152)
$V'CO_2$, mL/min	1339 (1217 – 1493)	1095 (1040 – 1339)	1357 (1204 – 1558)	1051 (1040 – 1357)	1371 (1125 – 1438)	1285 (1207 – 1327)
Respiratory rate, breaths/min	39 (33 – 40)	33 (27 – 39)	41 (32 – 42)	33 (23 – 41)	28 (24 – 32)	29 (28 – 32)
V'_T, mL	1689 (1456 – 1725)	1636 (1404 – 1689)	1762 (1578 – 1826)	1636 (1404 – 1762)	1416 (1370 – 1852)	1303 (1218 – 1368)
V'_E, L/min	50 (48 – 58)	47 (46 – 50)	56 (50 – 66)	46 (43 – 56)	45 (44 – 47)	40 (39 – 42)
$V'_EV'CO_2$	43 (38 – 46)	43 (33 – 46)	41 (36 – 48)	41 (32 – 46)	33 (31 – 34)	30 (30 – 35)
$V'_EV'O_2$	47 (38 – 53)	47 (30 – 59)	46 (41 – 58)	46 (35 – 64)	41 (40 – 42)	37 (34 – 41)
$P_{ET}CO_2$, mmHg	31 (25 – 38)	27 (25 – 37)	27 (23 – 30)	27 (27 – 34)	34 (33 – 35)	37 (31 – 38)
SpO_2, %	97 (94 – 98)	97 (94 – 99)	95 (91 – 97)	95 (94 – 99)	96 (95 – 98)	95 (92 – 98)
Heart rate, bpm	117 (107 – 129)	117 (111 – 127)	120 (109 – 130)	120 (111 – 127)	126 (122 – 130)	121 (120 – 125)
Oxygen pulse, mL/beat	8.8 (8.4 – 12.1)	8.8 (8.0 – 9.1)	8.0 (7.9 - 12.5)	8.0 (7.9 – 9.1)	8.6 (7.3 – 9.0)	9.0 (7.2 – 9.5)
Borg CR10 dyspnoea score	3 (2 – 4)	1 (0 – 1)	2 (1 – 3)	1 (1 – 2)	1 (0 – 1)	1 (0 – 2)
Borg CR10 RPE score	3 (3 – 4)	2 (1 – 2)	2 (2 – 3)	2 (1 – 2)	1 (0 – 2)	1 (0 – 2)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 24. Constant workload cycle ergometer test: exercise outcomes at the shortest test isotime, at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
Isotime, seconds	501 (469 – 752)	436 (378 – 501)			299 (282 – 397)	
Workload, W	77 (73 – 86)	75 (68 – 77)			72 (55 – 78)	
$V'O_2$, mL/min	1268 (1166 – 1506)	1154 (1063 – 1268)	1306 (1183 – 1635)	1154 (1061 – 1306)	1182 (1061 – 1216)	1263 (1250 – 1295)
$V'CO_2$, mL/min	1311 (1206 – 1561)	1311 (1101 – 1366)	1364 (1262 – 1685)	1364 (1159 – 1366)	1509 (1124 – 1533)	1483 (1357 – 1588)
Respiratory rate, breaths/min	46 (37 – 47)	38 (28 – 46)	47 (37 – 48)	38 (28 – 47)	33 (31 – 33)	32 (31 – 35)
V'_T, mL	1512 (1414 – 1617)	1512 (1404 – 1722)	1563 (1524 – 1703)	1563 (1524 – 1703)	1420 (1387 – 1765)	1478 (1341 – 1663)
V'_E, L/min	63 (55 – 66)	54 (47 – 63)	71 (61 – 73)	54 (51 – 71)	54 (47 – 55)	46 (46 – 52)
$V'_EV'CO_2$	43 (39 – 48)	43 (36 – 51)	44 (40 – 49)	44 (36 – 51)	36 (36 – 41)	33 (31 – 43)
$V'_EV'O_2$	44 (40 – 49)	44 (40 – 54)	48 (42 – 52)	48 (40 – 57)	46 (45 – 50)	40 (37 – 50)
$P_{ET}CO_2$, mmHg	29 (24 – 33)	25 (24 – 32)	25 (23 – 28)	25 (24 – 31)	31 (26 – 33)	34 (27 – 37)
SpO_2, %	97 (95 – 98)	97 (95 – 99)	94 (93 – 97)	95 (95 – 99)	96 (95 – 97)	95 (89 – 95)
Heart rate, bpm	125 (117 – 135)	129 (125 – 136)	143 (123 – 145)	136 (129 – 143)	135 (133 – 152)	135 (133 – 147)
Oxygen pulse, mL/beat	9.0 (8.8 – 12.6)	8.6 (8.4 – 9.0)	9.0 (8.0 – 14.0)	8.4 (7.0 – 9.0)	8.5 (7.8 – 9.0)	9.0 (8.8 – 9.5)
Borg CR10 dyspnoea score	4 (3 – 5)	3 (2 – 4)	5 (5 – 5)	4 (3 – 5)	6 (5 – 7)	5 (4 – 6)
Borg CR10 RPE score	4 (4 – 5)	3 (3 – 4)	5 (5 – 6)	4 (3 – 5)	6 (5 – 7)	6 (5 – 7)

Data presented as median (interquartile range); $V'O_2$ peak: peak oxygen uptake; $V'CO_2$ peak: peak carbon dioxide output; V'_T: tidal volume; V'_E: minute ventilation; $V'_EV'CO_2$: ventilatory equivalent for carbon dioxide; $V'_EV'O_2$: ventilatory equivalent for oxygen; $P_{ET}CO_2$: end tidal carbon dioxide; SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion.

Appendix 25. Functional exercise capacity (six-minute walk test): exercise outcomes at "12 weeks" and at "24 weeks"

	Exercise Group				Control Group	
	12 weeks *Per protocol*	12 weeks *Intention to treat*	24 weeks *Per protocol*	24 weeks *Intention to treat*	12 weeks	24 weeks
n	3	5	3	5	5	5
6MWD, m	629 (618 – 667)	629 (606 – 670)	615 (608 - 668)	615 (600 – 670)	570 (555 - 585)	575 (575 - 587)
6MWD, % predicted	96 (96 – 97)	96 (96 – 97)	98 (95 – 98)	98 (92 – 99)	89 (83 – 90)	89 (83 – 92)
Heart rate, bpm	134 (118 – 140)	134 (114 – 146)	146 (126 – 154)	146 (114 – 156)	135 (130 – 136)	126 (121 – 127)
Heart rate reserve, bpm	32 (31 – 55)	32 (31 – 43)	22 (20 – 48)	22 (18 – 43)	31 (28 – 43)	34 (30 – 56)
Heart rate reserve, %	19 (18 – 31)	19 (17 – 27)	13 (12 – 27)	13 (10 – 27)	24 (17 – 24)	25 (16 – 30)
SpO_2, %	91 (89 – 94)	93 (91 – 95)	94 (90 – 96)	94 (93 – 95)	94 (94 – 94)	94 (94 – 97)
Nadir SpO_2, %	91 (88 – 94)	93 (91 – 95)	94 (90 – 95)	94 (93 – 95)	94 (93 – 94)	94 (93 – 96)
Borg CR10 dyspnoea score	3 (3 – 4)	4 (3 – 4)	4 (4 – 5)	4 (4 – 5)	4 (4 – 5)	3 (1 – 4)
Borg CR10 RPE score	4 (3 – 5)	4 (4 – 4)	4 (4 – 5)	4 (4 – 5)	5 (3 – 5)	3 (3 – 4)
Borg CR10 leg fatigue score	1 (1 – 2)	1 (1 – 2)✶	3 (2 – 4)	3 (1 – 3)	5 (4 – 6)	3 (2 – 4)
Borg CR10 general fatigue score	1 (1 – 2)	1 (0 - 2)✶	1 (1 – 3)	1 (1 – 3)	5 (4 - 5)	3 (3 – 4)

Data presented as median (interquartile range); measures taken at the end of the test unless otherwise stated; 6MWD: six-minute walk distance (125); SpO_2: oxygen saturation; bpm: beats per minute; RPE: rating of perceived exertion; ✶$p<0.05$ compared to control group.