School of Physiotherapy

The impact of elevated pulmonary artery pressure on exercise responses

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

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

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 2006 and May 2012, through the School of Physiotherapy at Curtin University, in association with the Advanced Lung Disease Unit at Royal Perth Hospital and the Lung Institute of Western Australia.

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

ABSTRACT

Background and research questions

The four studies reported in this thesis investigated the implications of an elevated pulmonary artery pressure (PAP) on the response to an exertional challenge. The level of symptoms and exertion that healthcare professionals consider appropriate for patients with pulmonary arterial hypertension (PAH) was explored in the first study. In studies two, three, and four, exercise responses and exercise testing were evaluated in individuals with an elevated PAP on exercise, but a normal PAP at rest (exercise-induced pulmonary arterial hypertension, [EIPAH]). The following research questions were addressed:

1. Is there consistency in the advice given by healthcare professionals in Australia regarding physical exertion and symptoms, and in referral for exercise rehabilitation, for patients with PAH?

2. What are the clinical implications of an elevated PAP in symptomatic individuals with risk factors for PAH but who have a normal PAP at rest (EIPAH)?

3. Can the six-minute walk test (6MWT) identify reduced exercise capacity and accurately estimate aerobic capacity in individuals with EIPAH?

4. Are the haemodynamic and symptomatic responses to maximal and submaximal resistance exercise similar to the responses demonstrated during comparable intensities of aerobic exercise in individuals with EIPAH?

Abstracts for the reported studies

This PhD program formed the basis for four publications in peer reviewed, international, scientific journals. These four publications are summarised, in abstract form, below. The full manuscripts of these publications constitute Chapters 4-7 of this thesis.

Study 1: Australian perspective regarding recommendations for physical activity and exercise rehabilitation in pulmonary arterial hypertension.

Background: Limited data regarding the longer term consequences of physical activity and exercise rehabilitation, or the origin and importance of exertional symptoms associated with PAH, have made it difficult for clinicians to advise patients with PAH regarding physical activity, the appropriate level of symptoms, and exercise rehabilitation. The aim of this study was to determine the opinion of healthcare professionals, within Australia, regarding acceptable levels of exertion and symptoms, and referral for exercise rehabilitation in patients with PAH.

Methods: In 2010, 76 healthcare professionals at a specialist pulmonary hypertension meeting, in Australia, were surveyed using a self-administered questionnaire. The questionnaire included case studies of patients with PAH in World Health Organisation functional classes II-IV. For each case study, respondents were asked to report their opinion regarding the acceptable level of exertion and symptoms during daily activities, and whether they would refer the patient for exercise rehabilitation. Three additional questions asked about advice in relation to four specific physical activities.

Results: The response rate was 70% (n=53). Overall, 58% of respondents recommended patients undertake daily activities 'as tolerated'. The other 42% of respondents recommended either mild (14%) or moderate (17%) exertion, or did not answer this question (11%). There was no consensus regarding acceptable levels of breathlessness or fatigue, but the majority of respondents considered patients should have no chest pain (73%) and no more than mild light-headedness (92%) during daily activities. Overall, 63% of respondents would have referred patients for exercise rehabilitation. There was little difference in opinion regarding the acceptable level of exertion or symptoms, or referral for exercise rehabilitation, according to functional class. However, the patients' functional class did influence the advice given regarding the specific physical activities.

Conclusions: In 2010, there were inconsistencies, between individual healthcare professionals within Australia, regarding appropriate levels of physical exertion and acceptable symptoms during daily activities. Almost two thirds of the respondents reported they would refer patients for exercise rehabilitation.

Study 2: Implications of exercise-induced pulmonary arterial hypertension.

Background: Pulmonary arterial hypertension is associated with characteristic exercise abnormalities and reduced quality of life (QoL). However, the implications of an elevated PAP on exercise in individuals with a normal PAP at rest were uncertain. The aim of this study was to characterise the haemodynamic and ventilatory responses to exercise in a group of patients with unexplained dyspnoea, increased risk for PAH, a normal mean pulmonary artery pressure (mPAP) at rest and an elevated mPAP (>30mmHg) on exercise (exercise-induced pulmonary arterial hypertension [EIPAH]).

Methods: Thirty-seven symptomatic patients (34 females), with risk factors for PAH, and 20 healthy controls (19 females), underwent a symptom-limited cardiopulmonary exercise test (CPET) and were assessed for QoL. Patient subjects had a pulmonary artery catheter in situ during the exercise test.

Results: Seventeen subjects (15 females) had EIPAH, which we defined as mPAP ≤25mmHg at rest, and mPAP >30mmHg and pulmonary artery wedge pressure <20mmHg on exercise. These subjects had reduced peak exercise cardiac output (72±19% predicted). Further, compared with matched controls, subjects with EIPAH had reduced peak oxygen consumption (1.2±0.4 vs 1.7±0.5 L/min, $p<0.05$), an elevated ventilatory equivalent for carbon dioxide (41.0±7.3 vs 31.0±3.0, $p<0.05$) and reduced end tidal carbon dioxide tension (32.6±3.6 vs 39.4±2.7mmHg, $p<0.05$) at the anaerobic threshold. These exercise abnormalities were associated with impaired QoL ($p<0.05$).

Conclusion: Elevated PAP on exercise can be associated with haemodynamic and ventilatory abnormalities typical of PAH, along with impaired exercise capacity and reduced QoL.

Study 3: Measurement properties of the six-minute walk test in individuals with exercise-induced pulmonary arterial hypertension.

Background: Exercise-induced pulmonary arterial hypertension (EIPAH) is associated with reduced peak exercise cardiac output (CO) and aerobic capacity (peak $\dot{V}O_2$). The aim of this study was to investigate the validity of the encouraged six-minute walk test (6MWT) to identify exercise impairment and estimate aerobic capacity in subjects with EIPAH. Additionally, we examined the relationship between exercise capacity and peak CO.

Methods: Seventeen subjects with EIPAH (15 females) and 20 healthy controls (19 females) underwent two encouraged 6MWTs and a symptom-limited cardiopulmonary exercise test (CPET). The best six-minute walk distance (6MWD) was use***d*** in all analyses. To measure CO, subjects with EIPAH performed the CPET with a pulmonary artery catheter in situ.

Results: Compared with controls, subjects with EIPAH had reduced peak $\dot{V}O_2$ (1.2±0.4 vs 1.7±0.5, L/min, p<0.01), 6MWD (575±86 vs 665±77m, p<0.001), and six-minute walk work (6MWW) (39±11 vs 45±7 km.kg, p<0.01). In subjects with EIPAH, there was a moderate correlation between 6MWD and peak $\dot{V}O_2$ (r=0.72, p<0.01) and a strong correlation between 6MWW and peak $\dot{V}O_2$ (r=0.86, p<0.001). There were significant correlations between 6MWD and peak CO (r=0.59, p<0.05), and between peak $\dot{V}O_2$ and peak CO (r=0.55, p<0.05). Peak exercise CO accounted for 21% of the variance in 6MWW, 36% of the variance in 6MWD and 30% of the variance in peak $\dot{V}O_2$. Peak heart rate was similar in the CPET and 6MWT in subjects with EIPAH (132±15 vs 133±19 beats/minute, p=0.8).

Conclusions: The encouraged 6MWT identifies exercise impairment and is a valid test for the estimation of aerobic capacity in EIPAH. Peak exercise CO contributed a small proportion to the observed exercise impairment, suggesting that peripheral limitations are likely to also influence exercise capacity in EIPAH.

Study 4: A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with exercise-induced pulmonary arterial hypertension.

Background: Pulmonary arterial hypertension is associated with reduced muscle strength. Exercise-induced pulmonary arterial hypertension is associated with reduced exercise capacity and abnormal central haemodynamic responses to maximal aerobic exercise, however muscle strength has not been evaluated in this population. Aerobic and resistance exercise training are commonly employed to treat reduced exercise capacity. However, the haemodynamic response to aerobic and resistance exercise, at prescribed training intensities, in subjects with EIPAH are unknown. The aims of this study were to i) evaluate muscle strength, and, ii) the haemodynamic and symptomatic responses to maximal and submaximal and aerobic resistance exercise in individuals with EIPAH.

Methods: Fourteen subjects (11 with scleroderma, 12 females) with EIPAH and 15 healthy controls (14 females) underwent a cardiopulmonary exercise test on a cycle ergometer and a one repetition maximum (1RM) strength test on a bilateral leg press. The EIPAH group was also evaluated during resistance and aerobic exercise at 40% and 60% of maximum. The EIPAH subjects underwent all exercise tests with a pulmonary artery catheter in situ. Lower limb extensor muscle strength, determined by the 1RM weight, was compared between EIPAH and control groups. The haemodynamic and symptomatic responses to maximal (1RM and at peak $\dot{V}O_2$) and submaximal aerobic and resistance exercise were compared in the EIPAH group.

Results: 1RM was lower in the EIPAH group compared with the control group (75 versus 87 kg, $p<0.05$). In the EIPAH group, there were no differences in haemodynamic or symptomatic responses between the two modalities of submaximal exercise. At maximal exercise, all haemodynamic and symptomatic responses were lower during resistance compared with aerobic exercise ($p<0.05$).

Conclusions: The EIPAH group had reduced lower limb extensor muscle strength. At the intensities studied, lower limb resistance exercise was well tolerated and was mostly associated with similar or lower haemodynamic responses compared with aerobic exercise, in subjects with EIPAH.

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PUBLICATIONS ARISING FROM THIS THESIS

Peer reviewed journals

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Abstracts and presentations at scientific meetings related to this PhD program of research

ATS International Conference, Denver, May 2011 (Poster).
Fowler R, Jenkins S, Maiorana A, O'Driscoll G, Gabbay E.
The six-minute walk test identifies exercise impairment and provides a valid estimate of aerobic capacity in individuals with exercise-induced pulmonary arterial hypertension.

ATS International Conference, Denver, May 2011 (Poster).
Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.
Comparison of resistance and aerobic exercise in subjects with elevated pulmonary artery pressure.

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Maiorana A, **Fowler R,** Jenkins S, O'Driscoll G, Gabbay E.
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Characteristics of patients with unexplained dyspnoea and risk factors for pulmonary arterial hypertension.

Pulmonary Hypertension Perspectives meeting (Pfizer Australia). Sydney, June 2010 (Invited speaker).

Fowler R.

Non-pharmaceutical therapies in pulmonary hypertension. Mainstream and alternative options.

Annual Scientific Meeting of the American College of Sports Medicine. Seattle, USA, May 2009 (Oral).

Maiorana A, **Fowler R**, Jenkins S, O'Driscoll G, Gabbay E.

Exercise-induced pulmonary arterial hypertension is associated with an attenuated increase in cardiac output during exercise.

Young Investigator Awards, Royal Perth Hospital, July 2009 (Oral).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise induced pulmonary arterial hypertension is clinically important.

ATS International Conference, San Diego, May 2009 (Poster discussion).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise-induced pulmonary arterial hypertension is clinically important.

TSANZ Annual Scientific Meeting, Darwin, April 2009 (Oral).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise induced rises in pulmonary arterial pressure reflect the presence of a pulmonary vasculopathy and are clinically important.

Lung Institute of Western Australia 10th Anniversary Research Symposium, Perth, March 2009 (Invited speaker).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise induced pulmonary arterial hypertension is clinically important.

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Exercise induced pulmonary arterial hypertension is clinically important.

Annual conference of the Australian Cardiovascular Health and Rehabilitation Association and the Chronic Disease Network, Alice Springs, August, 2008 (Oral).

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Improving the diagnosis of pulmonary arterial hypertension using exercise testing; enhancing access to early interventions and disease management.

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Activity and exercise prescription for patients with pulmonary arterial hypertension.

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Activity and exercise prescription for patients with pulmonary arterial hypertension.

AWARDS

2011

Fowler R, Maiorana M, Jenkins S, Gain K, O'Driscoll G, Gabbay E. Implications of exercise-induced pulmonary arterial hypertension. *Med Sci Sports Exerc* 2011; 43:983-989.

Awarded Curtin University, School of Physiotherapy Elsevier Book Prize for best article in a scientific journal in 2011.

2009

Young Investigator Awards, Royal Perth Hospital, July 2009 (Oral).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise induced pulmonary arterial hypertension is clinically important.

Awarded the encouragement prize.

TSANZ Annual Scientific Meeting, Darwin, April 2009 (Oral).

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Exercise induced rises in pulmonary arterial pressure reflect the presence of a pulmonary vasculopathy and are clinically important.

Finalist in Ann Woolcock Young Investigator Session.

Awarded best physiotherapy research paper.

2008

TSANZ Annual Scientific Meeting, WA Branch, Mandurah, October 2008 (Oral).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Exercise induced pulmonary arterial hypertension is clinically important.

Awarded the Travel Prize

Annual conference of the Australian Cardiovascular Health and Rehabilitation Association and the Chronic Disease Network, Alice Springs, August, 2008 (Oral).

Fowler R, Maiorana A, Jenkins S, O'Driscoll G, Gabbay E.

Improving the diagnosis of pulmonary arterial hypertension using exercise testing; enhancing access to early interventions and disease management.

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TSANZ Annual Scientific Meeting, Melbourne , March 2008 (Oral).

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Awarded best presentation in the OLIV SIG.

Awarded best presentation in the physiotherapy SIG.

LIST OF ABBREVIATIONS

1RM	One repetition maximum
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
6MWW	Six-minute walk work
AE	Aerobic exercise
AF	Atrial fibrillation
AT	Anaerobic threshold
BMI	Body mass index
BMPR2	Bone morphogenetic protein receptor type II gene
bpm	Beats per minute
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCO	Continuous cardiac output
CI	Confidence Interval
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CWLT	Constant work load test
DLCO	Diffusing capacity for carbon monoxide
ECG	Electrocardiograph
EILVDD	Exercise-induced left ventricular diastolic dysfunction
EIPAH	Exercise-induced pulmonary arterial hypertension
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
HCO_3^-	Bicarbonate
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
HRQoL	Health related quality of life
IC	Inspiratory capacity
ILD	Interstitial lung disease
iPAH	Idiopathic pulmonary arterial hypertension
J receptors	Juxtapulmonary receptors
LHF	Left-sided heart failure
LV	Left ventricle
MET	Metabolic equivalent
MLHFQ	Minnesota Living with Heart Failure Questionnaire
mmHg	Millimetres of mercury
mPAP	Mean pulmonary artery pressure
MVC	Maximum voluntary contraction
MVV	Maximum voluntary ventilation
n	Number of subjects
NIH-PPH	National Institute of Health – Primary Pulmonary Hypertension
NO	Nitric oxide
noPAH	No pulmonary arterial hypertension
NT-proBNP	N - terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
O_2	Oxygen
O_2 pulse	Oxygen pulse

$PaCO_2$	Arterial carbon dioxide tension
PAH	Pulmonary arterial hypertension
PaO_2	Arterial oxygen tension
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary artery wedge pressure
peak $\dot{V}\,O_2$	Peak oxygen consumption
$PetCO_2$	End tidal carbon dioxide tension
PPH	Primary pulmonary hypertension
PVR	Pulmonary vascular resistance
QoL	Quality of life
RCT	Randomised controlled trial
RE	Resistance exercise
RER	Respiratory exchange ratio
RHC	Right heart catheter
RHF	Right heart failure
RPE	Rate of perceived exertion
RV	Right ventricle
SBP	Systemic blood pressure
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SpO_2	Oxygen saturation
SV	Stroke volume
SvO_2	Mixed venous oxygen saturation
TPG	Transpulmonary gradient
USA	United States of America
$\dot{V}\,CO_2$	Carbon dioxide production
$\dot{V}\,E$	Minute ventilation
$\dot{V}\,E/\dot{V}\,CO_2$	Ventilatory equivalent for carbon dioxide
$\dot{V}$ Emax/MVV	Minute ventilation/maximal voluntary ventilation
$\dot{V}\,E_{peak}$	Peak minute ventilation
$\dot{V}$ Max	Maximum ventilation
$\dot{V}\,O_2$	Oxygen consumption
WHO	World Health Organization

CHAPTER 1
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy. Without treatment, and in a large proportion of individuals with PAH who receive pharmaceutical therapy, the condition is associated with progressive pulmonary vascular disease and right heart dysfunction, increasing exertional symptoms, and worsening functional capacity and quality of life (QoL) (1). Early diagnosis and treatment of PAH is associated with better outcomes following therapy with improved survival, functional capacity and QoL (2, 3). However, early diagnosis is difficult because of the non-specific nature of presentation (4) and diagnostic criteria that can only define the condition once the pulmonary vasculopathy is advanced (5). Delays in diagnosis have not reduced in over 20 years (4, 6).

Exertional symptoms, particularly dyspnoea and fatigue, are the presenting complaint in up to 90% of individuals with PAH (7). Progression of the condition is associated with worsening exercise tolerance and functional capacity. In individuals with PAH, haemodynamic responses, measured during exercise, better reflect functional capacity than haemodynamics measured at rest (8). Furthermore, gas exchange and ventilatory responses measured during exercise reflect disease severity and prognosis (9, 10), and are well described in PAH (11, 12). An incremental cardiopulmonary exercise test (CPET), with continuous gas exchange analysis, is well established as a non-invasive tool to aid differential diagnosis in individuals with dyspnoea of unknown aetiology (13).

Despite improvements in haemodynamics and survival following the development of pharmaceutical therapies that specifically address the pulmonary vascular abnormalities associated with PAH, a large proportion of individuals with PAH report persistent functional impairments (1). Historically, prior to the development of effective therapies, individuals with PAH were encouraged not to undertake an exercise program (14). However, interest has recently developed in the role of exercise rehabilitation for individuals with PAH who have persistent functional limitation. Prior to 2010, three studies had demonstrated that exercise rehabilitation could be achieved without adverse events and resulted in improvements in exercise capacity in individuals with PAH (15-17). However, there are few studies that report

the haemodynamic burden, in terms of the degree of elevation in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR) and right ventricular workload, associated with exercise in individuals with PAH. Furthermore, the attitudes of healthcare professionals regarding the implications of exertional symptoms, physical exertion and exercise rehabilitation were unknown.

This program of research involved four projects. The research was designed to evaluate the consistency, amongst healthcare professionals within Australia, regarding recommendations for patients with PAH pertaining to physical exertion, symptoms and exercise rehabilitation. Further, the research explored the potential of exercise testing to facilitate the early diagnosis of PAH, and evaluated the implications of an elevated PAP, during exercise, in terms of the haemodynamic *response* and clinical consequences, for symptomatic individuals with risk factors for PAH.

The studies were designed to address the following research questions.

1.1 Research questions

1. Is there consistency in the advice given by healthcare professionals regarding physical exertion and symptoms, and in referral for exercise rehabilitation, for patients with PAH within Australia?

2. What are the clinical implications of an elevated PAP in symptomatic individuals with risk factors for PAH but who have a normal PAP at rest (i.e. exercise-induced pulmonary arterial hypertension, [EIPAH])?

3. Can the six-minute walk test (6MWT) identify reduced exercise capacity and accurately estimate aerobic capacity in individuals with EIPAH?

4. Are the haemodynamic and symptomatic responses to maximal and submaximal resistance exercise similar to the responses demonstrated during comparable intensities of aerobic exercise in individuals with EIPAH?

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

1.2 Question 1

Is there consistency in the advice given by healthcare professionals regarding physical exertion and symptoms, and in referral for exercise rehabilitation, for patients with PAH within Australia?

1.2.1 Hypothesis

There will be no consistency in the advice given by healthcare professionals regarding physical exertion and symptoms, or in referral for exercise rehabilitation, for patients with PAH within Australia.

1.2.1.1 Background

Historical concerns regarding the response to physical exertion in individuals with PAH, and reports of exertional syncope and sudden death (18-20), resulted in a conservative approach to physical activity with recommendations for patients to avoid exercise training and physical exertion beyond the performance of daily activities (14). There has been limited discussion in the literature regarding the origins and significance of the symptoms associated with PAH, specifically symptoms of dyspnoea, fatigue and light-headedness. Furthermore, the first report of exercise rehabilitation in PAH was published in 2005, in Japanese (17), and was not accessible to most English speaking healthcare professionals. The first study of exercise training in PAH, written in English, was published in 2006 and before 2010 only three reports in English (15, 16, 21), with a total of 51 subjects with PAH who had undergone exercise rehabilitation, were published. In 2010 there were no longer term data on patients with PAH who had undergone exercise training. Therefore, at that time, there was very limited evidence to guide clinicians working within Australia and managing patients with PAH, regarding acceptable levels of exertion and symptoms, and the safety and efficacy of exercise rehabilitation for this population. It was uncertain if there was any consistency in the advice clinicians were providing for patients with PAH regarding physical activity and symptoms, and if patients were being referred for exercise rehabilitation.

1.3 Question 2

What are the clinical implications of an elevated PAP in symptomatic individuals with risk factors for PAH but who have a normal PAP at rest (i.e. EIPAH)?

1.3.1 Hypothesis

Symptomatic individuals with risk factors for PAH and a normal PAP at rest, but an elevated PAP on exercise (i.e. EIPAH), will demonstrate reduced exercise capacity and ventilatory abnormalities that are characteristic of PAH.

1.3.1.1 Background

Pulmonary arterial hypertension is a progressive condition with poor prognosis if untreated (6). Pharmaceutical therapy improves survival, functional capacity and quality of life (22-24) and is most effective if commenced before the development of marked functional limitation (2, 3). Therefore early diagnosis of PAH is considered important. However, despite the recent development of effective pharmaceutical therapies, the timeliness in diagnosis of PAH has not improved in more than 20 years (4, 6, 25). The difficulties associated with early diagnosis of PAH include the non-specific nature of symptoms and the lack of abnormalities on standard assessment, until right heart failure (RHF) is present (4). A further, and important, barrier to early diagnosis lies in the current diagnostic recommendations which only support a diagnosis of PAH made on assessment of central haemodynamics performed at rest (1). By the time diagnosis can be made at rest, up to 70% of the small pulmonary arteries are diseased and the condition is advanced (5).

Pulmonary arterial hypertension is consistently associated with an elevated PAP and PVR and reduced cardiac output (CO) at peak exercise (8, 26-28). Exertional symptoms of dyspnoea and fatigue limit functional capacity. Aerobic capacity is reduced, and characteristic ventilatory and gas exchange abnormalities are well described (29). Exercise testing is well accepted as a non-invasive method for identifying the physiological cause of exertional dyspnoea and a system for identifying likely PAH based upon exercise responses is well established (13). However, diagnosis of PAH cannot be made without accurate measurement of central haemodynamics via right heart catheter (RHC) (1).

It is possible that measuring central haemodynamics during exercise could identify individuals with elevated PAP and early PAH. However, a wide range of PAP is demonstrated in healthy individuals during exercise (30) and therefore PAP during exercise is difficult to interpret, in isolation. The identification of characteristic gas exchange and ventilatory abnormalities in individuals with PAH (29) suggests that simultaneous evaluation of central haemodynamic, gas exchange and ventilatory responses during exercise has the potential to facilitate the early diagnosis of PAH in symptomatic individuals with risk factors for PAH. This possibility formed the basis for this research.

1.4 Question 3

Can the 6MWT identify reduced exercise capacity and accurately estimate aerobic capacity in individuals with EIPAH?

1.4.1 Hypothesis

The 6MWT will identify reduced exercise capacity and will accurately estimate peak oxygen consumption ($\dot{V}O_2$) in individuals with EIPAH.

1.4.1.1 Background

Quantifying functional exercise capacity provides a means for identifying the functional limitations associated with a condition, and can be used to objectively measure deterioration related to disease progression or improvement with therapy. The 6MWT is an extensively studied exercise test that is inexpensive, easy to administer, and is widely used in clinical practice to measure exercise capacity (31). Furthermore, the 6MWT is a valid test for quantifying functional exercise capacity and accurately estimating peak $\dot{V}O_2$ in individuals with chronic obstructive pulmonary disease (COPD) (31, 32) and PAH (33-35). Indeed, the main outcome of the 6MWT, i.e. the six-minute walk distance (6MWD), has been the primary outcome measure in the majority of clinical trials in PAH. However, the utility of the 6MWD in accurately reflecting functional exercise capacity in individuals with well preserved functional capacity has been challenged (36, 37). Individuals with EIPAH have a mild to moderate reduction in functional capacity (27) and the capacity for the 6MWT to identify impairments in exercise capacity and to estimate aerobic capacity in this

population has not previously been described. This study investigated the measurement properties of the 6MWT in individuals with EIPAH.

1.5 Question 4

In individuals with EIPAH, are the haemodynamic and symptomatic responses to maximal and submaximal resistance exercise similar to the responses demonstrated during comparable intensities of aerobic exercise?

1.5.1 Hypothesis

There will be no difference in haemodynamic or symptomatic responses to comparable intensities of lower limb aerobic and resistance exercise in individuals with EIPAH.

1.5.1.1 Background

Pulmonary arterial hypertension is associated with skeletal muscle weakness (38, 39). Skeletal muscle strength is important in the performance of activities of daily living and greater muscle strength and power are associated with reduced haemodynamic stress at a given absolute muscle force (40). Resistance exercise training is associated with improved muscle strength and is increasingly included in exercise training programs for healthy individuals and patients with left-sided heart failure (LHF) (40).

Historically, resistance exercise has been discouraged in individuals with PAH because of concerns regarding the safety of this modality of exercise in this population (41). Recent studies, involving small sample sizes, suggest that resistance training can be achieved without adverse events and results in improvements in muscle strength in PAH (16, 42). However, there are no data describing the haemodynamic burden of resistance exercise, and few that quantify the response to submaximal aerobic exercise in PAH (8, 28, 43). Evaluation of the haemodynamic response *to* exercise assists in predicting the likely safety and longer term consequences of exercise training in individuals with cardiovascular conditions.

Individuals with EIPAH have haemodynamic abnormalities, at peak aerobic exercise, similar to those identified in individuals with PAH (27). However, muscle

strength had not been evaluated, and the haemodynamic and symptomatic responses to maximal and submaximal resistance and aerobic exercise, in individuals with EIPAH, had not been determined. With increasing interest in aerobic and resistance training in many clinical populations (44), including PAH (16, 42), the need for and likely safety issues associated with resistance exercise training in individuals with EIPAH warranted evaluation. This study quantified the haemodynamic and symptomatic responses during an acute bout of maximal and submaximal aerobic and resistance exercise in individuals with EIPAH.

1.6 Novelty and significance of the research

Novelty

The studies described in this thesis are the first to explore

1. the consistency in advice given to patients with PAH regarding appropriate levels of physical exertion and acceptable symptoms during daily activities and referral of patients with PAH for exercise rehabilitation, in Australia
2. the clinical implications of EIPAH in relation to exercise capacity and QoL
3. the measurement properties of the 6MWT in individuals with EIPAH
4. muscle strength, and the haemodynamic and symptomatic responses to maximal and submaximal resistance exercise in individuals with EIPAH

Significance

1. Consistency in advice and referral for exercise rehabilitation is important in promoting adherence, by patients with PAH, to recommendations provided by healthcare professionals. The first study described in this thesis provides information regarding the consistency of advice given by healthcare professionals, within Australia in 2010, pertaining to physical activity and acceptable symptoms during activity, and referral for exercise rehabilitation.
2. There is an increasing awareness of the difficulties in early diagnosis, but also the need for early treatment, of PAH. Comprehensively exploring and describing the exercise responses and the clinical implications of EIPAH provides important baseline information regarding this condition. Should EIPAH be found to progress to PAH, this study describes the role of exercise testing in the early diagnosis of PAH. Also, regardless of possible disease

progression in EIPAH, the clinical consequences of EIPAH and a rationale for treatment of this condition have been explored.

3. The 6MWT is an inexpensive, reliable, easy to administer test for clinical practice, and for research. However, its validity for quantifying exercise limitation in individuals with EIPAH, with well preserved functional capacity, had not been determined. This study describes the measurement properties of the 6MWT and describes its utility in EIPAH.
4. Reduced muscle strength impacts negatively on the performance of physical activities, has been described in individuals with PAH. Prior to this research, muscle strength in individuals with EIPAH had not been evaluated. Increasing interest in aerobic and resistance exercise training in individuals with PAH identifies a need to determine the haemodynamic burden and likely safety of these therapies. Evaluating the response to intensities of submaximal and maximal resistance and aerobic exercise that are used in clinical practice in individuals with elevated PAP informs clinical practice, and further research.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter reviews the literature relating to the presentation of PAH, the likely causes of functional abnormalities, and the role of exercise testing in this condition. The chapter comprises four main sections. The first section (2.2) reviews the pathophysiology, diagnosis and management of PAH. The second section (2.3) discusses the factors that contribute to the exercise abnormalities, symptoms associated with exercise, and exercise limitation in PAH. The third section (2.4) reviews the literature relating to studies of exercise testing in individuals with PAH and the fourth section (2.5) reviews the literature on EIPAH and exercise testing as a potential means to facilitate the early diagnosis of PAH. Section 2.6 provides a final summary of the literature review and identifies the gaps in the literature.

2.2 Pulmonary arterial hypertension

The following section defines and describes PAH and discusses diagnosis, screening and treatment.

Pulmonary arterial hypertension is a condition defined by primary abnormalities in the precapillary pulmonary arteries and arterioles. It forms Group 1 in the World Health Organisation (WHO) classification of pulmonary hypertension (1). This classification system identifies PAH as a unique entity, with a characteristic pathophysiology, clinical presentation and response to therapy that separates it from other forms of pulmonary hypertension.

Before a classification system for pulmonary hypertension was established, idiopathic PAH (iPAH) was known as primary pulmonary hypertension (PPH) (6). In this review, the terms iPAH and PPH will be used interchangeably, in accordance with the terminology used in the original papers that have been cited.

2.2.1 Pathogenesis

A fundamental endothelial abnormality is thought to play a key role in the pathogenesis of PAH (45-47). The endothelium lines the blood vessels of the pulmonary and peripheral circulations and produces a number of compounds that influence vascular tone, vessel wall structure, blood viscosity, blood and cell wall interactions and thrombosis and fibrinolysis (48).

In the normal pulmonary circulation, the endothelium maintains vascular health and facilitates appropriate adaptive responses to external stimuli, such as hypoxia or acute changes in pulmonary blood flow (48). This is achieved through balance in a number of opposing systems including the endothelin and angiotensin II systems that promote vasoconstriction and proliferation of vascular wall cells, and the nitric oxide (NO) and prostaglandin systems, that promote vasodilatation, apoptosis and antithrombotic activity (48). When in balance, regeneration of cells is balanced by cell apoptosis, regulation of vascular tone and blood flow is adapted to optimise gas exchange, and vessels are maintained free of thrombus (48).

Current hypotheses regarding the pathogenesis of PAH include the proposal that the abnormalities in the pulmonary vasculature develop through a two stage process (49). Initially, following exposure to an exogenous stimulus such as a viral or bacterial infection or toxin, transition of pulmonary artery smooth muscle cells and pulmonary artery endothelial cells from a normal to abnormal phenotype occurs. This is considered most likely due to multiple mutations of the bone morphogenetic protein (BMP) receptor type II (BMPR2) and others genes such as serotonin receptor and transporter, potassium and calcium channels and angiopoietin1 genes (49). Disease progression is then thought to be sustained by cellular factors that create a proliferative, anti-apoptotic, and vasoconstrictive state. In pulmonary artery smooth muscle cells, in individuals with PAH, the anti-proliferative effect of BMP is reversed and becomes proliferative and the pro-apoptotic effect of BMP is attenuated. In pulmonary artery endothelial cells the anti-apoptotic or survival effect of BMP changes and the system becomes pro-apoptotic (49). Elevated sensitivity of contractile proteins to calcium, smooth muscle cell proliferation and endothelial injury results in vasoconstriction and pulmonary vascular wall hypertrophy (49). The subsequent pulmonary vascular endothelial dysfunction results in up-regulation of the endothelin system, increased pulmonary vasoconstriction and cell proliferation. In addition, the NO and prostaglandin systems are down-regulated, limiting

pulmonary vasodilatation and reducing the anti-proliferative and anti-thrombotic effects of these compounds (47). Imbalance in the endothelin and NO/prostaglandin systems is believed to be of primary importance in PAH (1), although this does not occur in isolation. Recent studies have also identified a platelet derived increase in serotonin and loss of voltage-gated potassium channels, both of which contribute to smooth muscle vasoconstriction and cell proliferation. There is also evidence for up-regulation in a number of growth factors such as vascular endothelial growth factor (1).

Under normal circumstances, the pulmonary vasculature is in a state of active dilatation (50) but imbalance in the production of vasodilators and vasoconstrictors in PAH results in elevated pulmonary vascular tone. In addition, a state of pro-proliferation results in smooth muscle hypertrophy and extension of smooth muscle into the vessel walls in the periphery of the lung, and adventitial and intimal proliferation. Reduced endothelial cell production of antithrombotic agents results in intra-lumen thrombus and vessel obstruction. The ultimate outcome is a marked reduction in the vasodilatory capacity, distensibility and patency of the pulmonary circulation (1).

2.2.2 Diagnosis

Diagnosis of PAH requires exclusion of other conditions that may cause pulmonary hypertension, including left-sided heart disease, pulmonary parenchymal or airway disease, or pulmonary thromboembolic disease (1). Following exclusion of other conditions, diagnosis is made by RHC assessment of PAP, pulmonary artery wedge pressure (PAWP), CO and PVR. A resting mean PAP (mPAP) of >25mmHg, a PAWP <15mmHg (which excludes pulmonary venous hypertension caused by left heart disease) and a PVR of > 3 Woods units, are the criteria for diagnosis (1). Right heart catheter evaluation is the ‘gold standard’ and a diagnosis of PAH cannot be confirmed until RHC assessment has established that diagnostic criteria are met. However, by the time PAP and PVR are elevated sufficiently to meet diagnostic criteria up to 70% of the small pulmonary vessels are diseased (5). Before 2009, guidelines for diagnosis of PAH included criteria at rest or on exercise (51). However, due to a wide range of normal central haemodynamic responses during exercise (30), the current diagnostic guidelines for PAH recommend that diagnosis of PAH is based only on a RHC assessment performed at rest (1).

2.2.3 Haemodynamics

In PAH, the functional changes associated with a loss of vessel calibre and intra-lumen obstruction, include a reduction in the size of the pulmonary vascular bed (1), and a rise in PVR, PAP (43) and right ventricular afterload. The right ventricle (RV) is a thin walled chamber, built for a low pressure circulation and, under normal conditions, right ventricular afterload equates to 25% of left ventricular afterload (52, 53). In the presence of a sustained increase in right ventricular afterload a normal heart undergoes adaptive hypertrophy of the myocardium. However, the capacity for hypertrophic adaptation, and, in PAH, the development and progression of right ventricular dysfunction varies among individuals (53). It has been proposed that the development of RHF in PAH is related not only to elevated right ventricular afterload, but also to intrinsic abnormalities in the wall of the RV (54). Although it has not been a consistent finding (55), some individuals with PAH demonstrate an insertion allele polymorphism in the angiotension-converting enzyme gene. This insertion polymorphism is associated with a lower CO for the same PAP, compared with individuals who have a deletion allele polymorphism in the same gene (56). Having this insertion allele polymorphism is thought to contribute to the development of right ventricular dysfunction in some individuals with PAH (57). Myocardial fibrosis and reduced capillary density in the wall of the RV have been described in an animal model of progressive PAH (54). It is proposed that ischaemia of the RV, due to an imbalance between oxygen supply and demand, contributes to the development RHF in PAH (54, 58-60), in the presence of elevated right ventricular afterload and intrinsic abnormalities of the wall of the RV (54). In conditions such as scleroderma, RV function can be further compromised by inflammatory changes related to connective tissue disease (61). With an unrelenting increase in PVR associated with disease progression in PAH, increasing contractile dysfunction occurs (52).

In PAH, increased right ventricular pressure results in flattening and leftward movement of the interventricular septum during systole (62). Over time, the interventricular septum becomes thickened and an abnormal interventricular septal/posterior left ventricular wall ratio of >1 develops (63). At rest, left ventricular ejection fraction has been shown to be normal in individuals with PAH (62, 64), although left ventricular end-systolic and end-diastolic volume, and left ventricular SV are reduced (64). This reduction in left ventricular volume and SV is thought to be related to both reduced preload and altered septal geometry with subsequent diastolic dysfunction (64). Reduced LV compliance has been demonstrated in PAH,

although the extent of this is limited and LV filling pressures are generally not significantly elevated (64).

Initially, dilatation of the right atrium and RV results in a compensatory increase in preload and maintenance of stroke volume (SV) (52), but as contractile dysfunction worsens diastolic dysfunction develops, filling pressures rise and CO falls (52). Cardiac output is determined by heart rate (HR) and SV. Right ventricular SV is determined by contractility, end-diastolic volume and afterload. In healthy individuals, contractility of the RV increases with exercise, resulting in a decrease in right and left ventricular end-systolic volumes, stable right and left ventricular end-diastolic volumes and an increase in SV (65). In contrast, in individuals with PAH, right ventricular end-diastolic volume increases, left ventricular end-diastolic volume decreases and SV does not change, consistent with an impaired capacity to increase right ventricular contractility (65). In addition to reduced SV, PAH is associated with chronotropic impairment, demonstrated by a failure to achieve a normal HR response to exercise (26, 33, 66). Chronotropic impairment in PAH is related to down-regulation of right ventricular myocardial beta-adrenoreceptor activity (67), and reflects disease severity. The combined failure of SV and HR to increase normally during exercise results in an attenuated rise in CO and systemic blood pressure. Due to disease progression, in end stage PAH the RV fails to maintain adequate CO at rest, and, in the majority of cases, death occurs from RHF (5, 57).

2.2.4 Pharmacologic therapy

Until the advent of PAH specific pharmaceutical therapies that address the pulmonary vascular abnormalities associated with PAH, management was supportive and mostly comprised treatment for RHF, and anticoagulation. This treatment included vasodilators, oxygen therapy, warfarin and digitalis (68). The development of PAH specific therapies is relatively recent and the first Pharmaceutical Benefit Scheme listed medication became available in Australia in 2004 (69). The availability of PAH specific therapies has seen an improvement in haemodynamics and prognosis for individuals with PAH (1, 22). These PAH specific therapies include prostacylin analogues, endothelin antagonists and phosphodiesterase 5 inhibitors. Recent meta-analyses have shown a reduction in all cause mortality following treatment with PAH specific pharmaceutical therapy, compared with placebo, by 39% (23) and 43% (22) when data for all classes of PAH

specific medications were combined, and 51% for prostacyclin analogues alone (24). Other important outcomes following PAH specific pharmaceutical therapy include improvements in exercise capacity (22-24), dyspnoea scores (24), haemodynamic status (22-24) and hospitalisation (22).

The functional consequences of PAH are commonly reported in terms of the patients' WHO functional class. This system for determining the functional capacity of individuals with PAH was modified from the New York Heart Association (NYHA) functional classification system and adopted by the WHO in 1998 (70). These classification systems are often used interchangeably and both systems describe four categories of physical function. Functional class I describes minimal limitation in physical activity, functional class II describes mild limitation, functional class III describes moderate limitation and functional class IV describes severe physical limitation and symptoms at rest (71).

Commencement of PAH specific therapy prior to the development of marked physical dysfunction (while patients are in WHO functional class I or II) is associated with better outcomes than treatment once significant functional impairment (i.e. WHO functional class III or IV) is evident (2, 3). Functional class, at diagnosis, has been shown to be predictive of mortality (2, 51, 72) with patients in NYHA functional class II at diagnosis having a markedly better survival than those in classes III and IV (3).

2.2.5 Persistent abnormalities despite therapy

Evidence of better outcome if treatment is commenced earlier rather than later (2, 3, 24, 73, 74) suggests that PAH specific therapies delay disease progression (75). However, while effective in slowing disease progression and improving haemodynamics and function, current pharmaceutical therapy does not offer a cure for the disease. Despite therapy, most patients with PAH have persistent vascular and haemodynamic abnormalities, including an elevated PAP and PVR, and reduced CO on exercise (1). While therapy improves outcome, these persistent abnormalities contribute to an ongoing reduction in exercise capacity and impairment in QoL. Furthermore, in the majority of individuals, progression of the condition occurs despite therapy and life expectancy is reduced (1). Progression of PAH is associated with worsening haemodynamics and deterioration in symptoms and functional capacity (6).

2.2.6 Delays in diagnosis

The evidence for better outcomes with early treatment creates an imperative for early diagnosis. However, there has been no improvement in the time from initial symptom to diagnosis since a report was published, in 1987, from the National Institutes of Health-Sponsored Patient Registry for the Characterisation of Primary Pulmonary Hypertension in the United States of America (USA) (6). In this report the mean time from onset of symptoms to diagnosis was 2.0 ± 4.9 years. Reports from France in 2006 (25) and the USA in 2011 (4) describe mean delays in the diagnosis of PAH of 2.2 years and 2.8 years, respectively. Furthermore, there has been no improvement in NYHA functional class at presentation or diagnosis with approximately three quarters of the patients in each of these three reports (4, 6, 25) in NYHA functional class III or IV at presentation, or at the time of the diagnostic RHC. That is, there has been no improvement in the timeliness of diagnosis over a period of more than 20 years.

Delays in diagnosis are related to the non-specific nature of early symptoms, a delay in presentation, and a failure to recognise the relevance of symptoms in younger individuals, or in those with co-morbid conditions (4). Furthermore, early diagnosis is not supported by the current guidelines which recommend that diagnosis is made at rest (1), despite the knowledge that by the time mPAP is elevated to the diagnostic threshold (>25mmHg at rest) the disease is already advanced (5).

2.2.7 At risk populations

Pulmonary arterial hypertension may be idiopathic, however certain individuals are known to carry a greater risk for the development of PAH than the general population. Those at greater risk include individuals with: a specific genetic abnormality (BMPR2 mutation); connective tissue disease; human immunodeficiency virus; exposure to certain medications and toxins including some anorexigens, methamphetamine and cocaine; a congenital systemic to pulmonary shunt; Eisenmenger's syndrome; portal hypertension; some blood disorders including sickle cell disease; or disease of the thyroid or spleen (1).

2.2.7.1 Screening programs

Because of the morbidity and mortality associated with untreated PAH, and the improved outcomes associated with early therapy, screening programs for populations at risk of PAH are recommended (1). The recommendations for screening include yearly echocardiograms for individuals with the BMPR2 mutation, scleroderma or sickle cell disease. For other at risk populations, echocardiogram is recommended for individuals who report symptoms or have signs suggestive of PAH. In individuals found to have a high pulmonary artery systolic pressure (PASP) or right heart chamber enlargement on the screening echocardiogram, a RHC is recommended (1).

Exercise tests for screening

Although diagnosis of PAH based upon elevated mPAP during exercise has been removed from current diagnostic guidelines (1), there has been considerable recent interest in the role of exercise testing in screening individuals with risk factors and symptoms suggestive of PAH (2, 27, 76, 77). The research in this field is reported in Section 2.4 and in Section 2.5. In particular, the research and literature around invasive exercise haemodynamic and/or continuous gas exchange analysis in the assessment of individuals with exertional dyspnoea and fatigue, risk factors for PAH and an elevated mPAP (>30mmHg) during exercise but a mPAP ≤25mmHg at rest, is described in Section 2.5 describing exercise-induced pulmonary arterial hypertension (EIPAH) (27, 76, 77). This research identifies EIPAH as a clinical condition associated with functional impairment and reduced QoL. It is considered part of the spectrum of pulmonary vascular diseases (78) and has features that are characteristic of PAH. However, it is not known whether EIPAH is an early or mild form of PAH, or whether it is a different clinical condition. Longitudinal assessment of individuals with EIPAH is required to determine the nature of this condition, over time.

2.2.8 Clinical presentation

Pulmonary arterial hypertension is a progressive condition with poor prognosis (7). Prior to the development of PAH specific pharmaceutical therapy, between 45 and 60% of patients died within 2 years of diagnosis (79). Despite advances in therapy, current median survival remains poor at 5-6 years (80). Pulmonary arterial

hypertension is a relatively silent disease until the vascular pathology is extensive and even in advanced disease the symptoms are often vague and non-specific. Approximately 90% of individuals with PAH present with exercise intolerance as a result of exertional dyspnoea (7). Other presenting symptoms include fatigue, light-headedness, pre-syncope or syncope, chest pain and palpitations (7). On initial investigation physical examination may be normal. However, in more advanced disease, signs of RHF become evident with elevated jugular venous pressure, ankle oedema, auscultatory and electrocardiographic signs of right ventricular dilatation and hypertrophy. Enlargement of the main pulmonary arteries and paucity of peripheral vessels may be seen on chest x-ray (81).

Even without treatment, there is a variable rate of pulmonary vascular disease progression in PAH (7, 82). However, progression can be rapid (73) and there is considerable mortality in patients who are in functional class II on presentation. In a study of individuals in functional class II, with PAH associated with connective tissue disease, 39% demonstrated disease progression over a mean period of 3.3 years (2). Disease progression was defined as both a fall in 6MWD of 20% and an increase in WHO functional class, or, a 20% increase in both mPAP and PVR on follow-up RHC. Mortality in this study was 19.5% (2). Another study of 92 individuals with PAH, in functional class II at baseline assessment, demonstrated symptomatic progression of PAH, hospitalisation for PAH, or death, over a 6 month period, in 14% of subjects in the placebo arm of a clinical trial (73). These findings suggest that diagnosis when a patient is in functional class II can be associated with significant pulmonary vascular abnormalities and rapid disease progression.

2.2.8.1 Quality of life

Prior to 2004, little attention was paid to the assessment of QoL in individuals with PAH (83). However, the availability of therapies that improve survival, haemodynamics and functional capacity, and the difficulty in using survival as an endpoint in clinical trials (1), has resulted in expansion of trial endpoints to include measures of health-related QoL (HRQoL). It is also recognised that changes in physiological measures may not always translate into a benefit, as perceived by the patient (84). Since 2004 interest in the extent and nature of HRQoL impairments in individuals with PAH, and in the change in HRQoL following treatment, has been explored in a number of studies. A recent review by Chen et al (83) describes these studies and their findings. These studies describe moderate to severe impairments

in all QoL domains, including physical, emotional and social functioning (85-88). These impairments, in individuals with PAH, are similar in magnitude to those reported by individuals with spinal cord injury (89), interstitial lung disease (90), metastatic cancer (91), LHF with a reduced ejection fraction (HFrEF) (85, 92), COPD (93), or end-stage renal failure (94). Studies that have evaluated HRQoL prior to, and following, therapy have identified that, along with improvements in functional capacity and haemodynamics, PAH specific pharmaceutical therapies (85, 95-102), and exercise training (15), are associated with improvements in HRQoL for individuals with PAH (103). However, despite these improvements following therapy, many individuals report a persistent reduction in HRQoL (1).

2.2.8.2 Impaired exercise capacity

Exercise intolerance is a hallmark of PAH and exercise capacity is limited by symptoms. Formal evaluation of exercise capacity in individuals with PAH uniformly identifies reduced submaximal and maximal exercise capacity. Six minute walk distance and peak $\dot{V}O_2$ are reduced (1, 9, 15, 29, 33-35, 41, 85, 104-109) and impairments in exercise capacity correlate with prognosis (9, 110). A detailed discussion of exercise testing and exercise capacity in individuals with PAH is presented in Section 2.4 of this review.

2.2.8.3 Symptoms

In 1987, Rich and colleagues published prospective data from a USA National Registry of PAH, detailing the clinical features of PAH (6). In this comprehensive report, the mean time from onset of symptoms to diagnosis and Registry entry was 2 years. Dyspnoea was present in 60% of patients on initial presentation and 90% of patients by the time of diagnosis and entry into the National Registry. Other symptoms on presentation and Registry entry were; fatigue 19% and 47% respectively, chest pain 7% and 47%, near syncope 5% and 41%, syncope 8% and 36%, leg oedema 3% and 37% and palpitations 5% and 33%.

A recent study confirmed the prevalence of these symptoms in individuals with PAH (111). This study also reported the impact of symptoms on the pursuit of daily activities, which was quantified as the level of interference. The highest level of symptoms and symptoms that caused greatest interference in daily activities were dyspnoea, symptoms associated with Raynaud's Syndrome and fatigue (111).

Symptoms associated with PAH have a significant and detrimental influence on functional capacity and QoL (111).

2.2.9 Summary

Pulmonary arterial hypertension is disease of the small pulmonary arteries and arterioles that is associated with progressive central haemodynamic abnormalities, right ventricular dysfunction and impairments in functional capacity and QoL. Pharmaceutical therapy is effective in slowing progression of the disease, and in improving prognosis, functional capacity and QoL, but does not offer a cure. In many cases progression of the condition occurs and results in increasing symptoms, functional impairment and premature mortality. Treatment before symptoms become advanced is associated with better outcomes than treatment once the patient has marked physical impairment, however, there has been no improvement in the timeliness of diagnosis in more than 20 years.

2.3 Exercise abnormalities, exercise limitation and symptoms in PAH

Before the development of RHF, the symptoms associated with PAH are only evident on physical exertion. The following section reviews current literature relating to exercise abnormalities associated with PAH, compared with responses in healthy individuals, and discusses factors that contribute to exertional symptoms and exercise limitation in PAH.

2.3.1 Haemodynamic responses during exercise in healthy individuals

At rest, in the upright position, a pressure gradient results in a gravity dependent distribution of blood flow away from the apices, minimal vessel calibre and even collapse of some of the small apical pulmonary vessels (112). The functional result is a reservoir of quiescent vessels in the apices of the upright lung. At the onset of exercise, increasing CO, pulmonary blood flow, PAP and a rise in left ventricular filling pressure (reflected by an increase in PAWP) result in recruitment of the quiescent pulmonary microcirculation (113). As exercise intensity increases, blood flow and left ventricular end diastolic pressure continue to rise resulting in maximum distension of the pulmonary vascular bed (114). Vascular recruitment and distension

enable large changes in blood volume to be accommodated with relatively small increases in pressure (115). Pulmonary vascular resistance remains low (116, 117) and commonly falls during exercise (118). Along with recruitment and passive distension, there is evidence for active vasodilatation during exercise in the healthy pulmonary circulation. Nitric oxide contributes to maintaining a low pulmonary vascular tone at rest, blunts the vasoconstrictor influence of endothelin and actively contributes to pulmonary vasodilatation during exercise (119). This response is supported by parasympathetic mediated vasodilatation, which also contributes to a reduction in pulmonary vascular tone in the normal pulmonary circulation during exercise (119, 120).

In healthy, non-athletic adults, CO during maximal upright exercise increases 4 to 6 fold from the resting level. This is achieved by a 2 to 4 fold increase in HR and a 20-50% increase in SV (121). In younger adults, the increase in SV is achieved through greater left ventricular contractility and by peripheral vasodilation, and results in reduced left ventricular end systolic volume (121). In some older individuals, increases in left ventricular afterload due to arterial stiffening, increased aortic impedance, impaired left ventricular diastolic function, and reduced contractility have been reported to influence SV at peak exercise (122). However, a number of studies demonstrate that age has little influence on maximum exercise SV response, although the increase in SV in older individuals is generated by a greater augmentation of preload, rather than by increased emptying of the left ventricle and reduction of left ventricular end-systolic volume (121, 123, 124). Maximum HR declines by approximately one beat per minute per year resulting in a fall in maximum exercise CO (125).

Along with normal left ventricular and systemic vascular responses, increased CO during exercise depends on a healthy pulmonary vasculature and RV. In the normal pulmonary circulation the pulmonary capillary volume can double during exercise (13). Through recruitment of the apical reservoir, distension of the small pulmonary vessels and vasodilatation, the rise in PAP during exercise is, generally, less than 12mmHg (30) and the PVR remains low. As a consequence, even with exercise-induced circulating blood volumes of 20 L/min, mPAP is normally lower than 30mmHg in non-athletic young subjects (116). The mPAP during exercise for middle aged subjects (less than 50 years of age) is similar to the mPAP in young subjects (126). However, some healthy individuals less than 50 years of age, and a significant proportion of healthy individuals over 50 years of age, demonstrate

mPAP > 30mmHg during exercise. In a review of studies describing exercise haemodynamics in healthy individuals (30), Kovacs et al reported that 21% of individuals aged over 50 years demonstrate mPAP > 30mmHg during maximal exercise. Furthermore, approximately 47% of individuals aged over 50 years demonstrated mPAP > 30mmHg during 'slight' exercise. In this review by Kovacs, limited data precluded statistical analysis of mPAP in individuals aged over 50 years at maximal exercise. However previous reports have suggested that the values are higher for healthy individuals aged over 60 years, with exercise mPAP reported to be as high as 50mmHg (127).

As previously described, in older individuals, an increase in CO during exercise is supported more by an increase in preload (123) and PAWP (30) than an increase in cardiac contractility, compared with younger individuals. Other age-related changes include reduced pulmonary vascular distensibility and higher PVR with increasing age (114, 120, 128, 129). Furthermore, PVR falls during exercise in individuals less than 50 years of age but remains unchanged in individuals older than 50 years of age (128). However, despite a decrease in pulmonary vascular distensibility with increasing age, the overall resistance to pulmonary blood flow remains low (123) and most studies do not demonstrate a reduction in SV with increasing age (123, 124).

2.3.2 Haemodynamic responses during exercise in PAH

In PAH, elevated PAP overcomes the gravity driven pressure gradient in the lung, and the reservoir of quiescent vessels in the apices is recruited at rest. This limits the extent that the low pressure rise in PAWP, associated with the onset of exercise (113), can increase the size of the pulmonary vascular bed. Furthermore, due to impairment in the distensibility and vasodilatory capacity (119), and obstruction of pulmonary vessels by thrombus, PVR is high during exercise (130) and the increase in pulmonary blood flow during exercise is driven by a marked rise in PAP (43) and right ventricular work.

When the vascular abnormalities associated with PAH become extensive and PVR is very high, a limited capacity for the RV myocardium to generate sufficient force to overcome the increased afterload results in reduced right ventricular output. The resultant decrease in blood flow into the left atrium, in combination with left ventricular compression from volume and pressure generated movement of the

interventricular septum towards the left (131), results in reduced left ventricular preload (64) and a limited increase in SV (130, 132). This reduction in SV contributes to an attenuated increase in left ventricular output and systemic oxygen delivery. However, reduced CO during exercise in PAH is also related to a reduced capacity to increase HR to maximum at peak exercise and this is considered to represent chronotropic impairment (11, 26, 33, 133, 134). In advanced disease, the attenuated CO response during exercise results in a failure of systemic blood pressure to increase normally with exercise (9). Prognosis in PAH is known to be closely associated with right ventricular function (52) and the systemic blood pressure response during exercise (9).

2.3.2.1 Right ventricle/pulmonary haemodynamics and symptoms

There is increasing recognition that right ventricular dysfunction is the primary cause of symptoms (135), functional impairment and mortality in PAH (58). Mechanoreceptors and afferent sympathetic pathways situated in the right atrium and RV relay details of right atrial and right ventricular pressure and volume and the amount of work performed by the RV (136, 137) to the central nervous system, via afferent sympathetic pathways. In PAH an increase in sympathetic activity (138) occurs as a result of increased right atrial (139) or right ventricular systolic pressure (140). In animal models of PAH, sympathetic pathways have been implicated in mediating the association between right ventricular workload and ventilatory response (141), with increased right ventricular pressure and stimulation of mechanoreceptors in the right atrium, resulting in increased ventilation (141, 142).

A direct association exists between right ventricular function and exercise capacity in PAH. Mean right atrial pressure has been demonstrated as the haemodynamic variable which best correlates with exercise capacity (143), and SV and chronotropic response have been shown to independently predict 6MWD in individuals with PAH (133). Improvements in 6MWD, following pharmaceutical therapy, are positively related to changes in SV, chronotropic response (133) and cardiac index (8), and negatively related to changes in PVR and dyspnoea (133). Treatments that improve haemodynamics by unloading the RV, and/or improving right ventricular contractility, have also been shown to improve NYHA functional class (8).

Further insights into the role of the RV in the generation of symptoms and reduction in exercise capacity can be drawn from studies in patients with LHF. Pulmonary

hypertension, due to elevated pulmonary venous pressure, is commonly associated with LHF caused by HFrEF (due to ischaemia, cardiomyopathy or valve disease) (144, 145), heart failure with preserved ejection fraction (HFpEF) (due to cardiomyopathy or hypertension) (146), or heart failure due to reduced left atrial compliance (144). While there is a poor correlation between exercise capacity and left ventricular function in HFrEF, right ventricular function influences exercise capacity, ventilatory response and prognosis in this condition (145, 147-152).

A high prevalence of pulmonary hypertension has also been reported in COPD (153, 154) and severe pulmonary fibrosis (155). Pulmonary hypertension in these conditions is related to a combination of factors including hypoxic pulmonary vasoconstriction, increased intra-thoracic pressure due to airflow obstruction, left ventricular dysfunction and vascular remodelling (154, 155). In these pulmonary conditions (154, 156, 157), and in HFrEF (150) and HFpEF (158), the ventilatory response during exercise is more abnormal, exercise capacity is worse and levels of dyspnoea and fatigue are greater in individuals with pulmonary hypertension than those without. Furthermore, the increase in ventilatory response reflects the degree of elevation of PAP in these individuals (159). These findings support a relationship between right ventricular work, ventilatory response and symptoms in these conditions.

2.3.2.2 J receptor activation

Juxtapulmonary capillary (J) receptors (also known as pulmonary C fibres) are situated near the pulmonary capillaries within the lung parenchyma. They are innervated by unmyelinated (80%) and myelinated (20%) vagal afferents (160). The J receptors are normally dormant and are stimulated only with an increase in pulmonary blood flow (161) and pulmonary capillary pressure, which occur in normal subjects on exertion (162). Stimulation of the J receptors results in respiratory sensations similar to those experienced during moderate exercise in healthy individuals (163) and during exercise in patients with left ventricular dysfunction (160). J receptor stimulation results in tachypnoea, and an elevation in ventilatory response associated with PAH been as attributed, in part, to heightened J receptor activity (164). It is possible that J receptor stimulation contributes to hyperventilation and the sensation of dyspnoea, during exercise, in patients with PAH.

2.3.3 Ventilatory responses during exercise

2.3.3.1 The relationship between ventilation and dyspnoea

The relationship between ventilation and dyspnoea is well established from studies of healthy individuals during exercise and in individuals with disease. Afferent neural input relays details of ventilation from respiratory muscle spindles to the respiratory centre in the medulla. Ventilation during rest and light exercise occurs with little or no awareness of breathing (165). However, an increase in motor command to ventilatory muscles is perceived as a sensation of respiratory work/effort, or dyspnoea (166), and the increase in ventilation required to perform moderate or intense exercise is accompanied by an increasing awareness of breathing to a point where breathlessness is described, even in healthy individuals (165).

2.3.3.2 Ventilatory response in healthy individuals

In the healthy individual, at rest and during mild to moderate exercise, minute ventilation ($\dot{V}E$) is driven by the arterial carbon dioxide tension ($PaCO_2$), which reflects carbon dioxide production ($\dot{V}CO_2$), a product of aerobic metabolism. During heavy exercise, in the absence of sufficient O_2 and replenishment of ATP (anaerobic metabolism), pyruvate breaks down to lactate and hydrogen ion (H^+). Hydrogen ions are buffered by HCO_3^-, producing CO_2 and H_2O, contributing to a further increase in $\dot{V}CO_2$. Close to maximum exercise, when HCO_3^- sources are depleted and H^+ is not buffered, a fall in arterial pH stimulates central chemoreceptors, and further stimulates $\dot{V}E$ (13). That is, during submaximal aerobic exercise as $\dot{V}CO_2$ increases $\dot{V}E$ increases in parallel, to maintain stable $PaCO_2$ and pH. Past the anaerobic threshold (AT), ventilation increases acutely to buffer the H^+ produced during anaerobic muscle work and the relationship between $\dot{V}E$ and $\dot{V}CO_2$ is no longer closely associated. The relationship between $\dot{V}E$ and $\dot{V}CO_2$ can be represented as the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$). During submaximal exercise, this relationship is linear and is commonly measured as the slope of the relationship of $\dot{V}E$ versus $\dot{V}CO_2$ prior to the AT during an incremental exercise test, or the $\dot{V}E/\dot{V}CO_2$ measured at the AT. The $\dot{V}E/\dot{V}CO_2$ at AT is more reproducible than the slope of $\dot{V}E/\dot{V}CO_2$ (167). The $\dot{V}E/\dot{V}CO_2$ at AT increases

with increasing age such that $\dot{V}E/\dot{V}CO_2$ at AT is approximately 25 in healthy individuals less than 20 years of age versus 29 in individuals over 60 years (13).

In an individual with normal lung function, end tidal carbon dioxide tension ($PetCO_2$) at rest reflects $PaCO_2$ (13). The normal value for both $PaCO_2$ and $PetCO_2$ is between 36 and 42mmHg (13), although at rest, $PaCO_2$ is higher than $PetCO_2$. In the healthy individual $PetCO_2$ rises from rest to the AT (12, 168) and becomes higher than $PaCO_2$, in response to increased $\dot{V}CO_2$. This occurs through increased $\dot{V}E$ and elimination of carbon dioxide (CO_2), in order to maintain a stable $PaCO_2$. Above the AT, $PaCO_2$ and $PetCO_2$ both fall (13). Following exercise cessation $PetCO_2$ continues to fall, reflecting a reduction in $\dot{V}CO_2$ (13).

2.3.3.3 Ventilatory response in PAH

Characteristic ventilatory and gas exchange abnormalities have been well defined in PAH. Hyperventilation at rest, and on exercise, identified by an elevated $\dot{V}E/\dot{V}CO_2$ (measured at the AT or as the slope of the relationship between $\dot{V}E$ and $\dot{V}CO_2$ during an incremental exercise test prior to the AT) and reduced $PaCO_2$ and $PetCO_2$ (at rest and at the AT), are well recognised features of PAH (9, 11, 105, 169, 170). The elevated $\dot{V}E/\dot{V}CO_2$ in PAH describes a dissociation between $\dot{V}CO_2$, $PaCO_2$ and $\dot{V}E$. An altered relationship between $\dot{V}E/\dot{V}CO_2$ and arterial oxygen tension (PaO_2), $PaCO_2$ and arterial pH (169) suggests that elevated $\dot{V}E/\dot{V}CO_2$ during submaximal exercise in PAH is not mediated by changes in arterial blood gases. Initial reports of an elevated $\dot{V}E/\dot{V}CO_2$ suggested that increased ventilation in PAH was due to ventilatory inefficiency caused by obstruction of the small pulmonary vessels and subsequent ventilation/perfusion inequalities (171). However, this has been challenged by ventilation/perfusion studies in patients with PAH which demonstrate almost normal ventilation/perfusion relationships, at rest, and on exercise (172, 173). This finding suggests that ventilation/perfusion inequalities are not the predominant mechanism for the elevated $\dot{V}E/\dot{V}CO_2$ in PAH.

Furthermore, if ventilatory inefficiency was the primary cause of an elevated $\dot{V}E/\dot{V}CO_2$, $PaCO_2$ would be normal, reflecting increased $\dot{V}E$ as a physiological mechanism to maintain a normal $PaCO_2$ in the presence of increased dead space. An increased ventilatory drive, rather than ventilatory inefficiency, is more likely to

be the cause of an elevated $\dot{V}E/\dot{V}CO_2$ in the presence of a reduced $PaCO_2$ as in PAH (12, 168, 174). There are no reports in the literature evaluating ventilatory drive in PAH, and this is clearly an area that warrants investigation.

There is some evidence to suggest that the elevated ventilatory response associated with PAH is related to central haemodynamic abnormalities. The $\dot{V}E/\dot{V}CO_2$ at rest has been shown to correlate with PVR, and both $\dot{V}E/\dot{V}CO_2$ and PVR decrease in response to treatment with an intravenous prostacyclin analogue (175). Furthermore, $\dot{V}E/\dot{V}CO_2$ correlates with mPAP (170). Arterial carbon dioxide tension has been shown to correlate with cardiac index (174) and changes in cardiac index associated with disease progression and increasing PVR are reflected by changes in both $\dot{V}E/\dot{V}CO_2$ and $PaCO_2$ in PAH (174). Finally, elevated $\dot{V}E/\dot{V}CO_2$ is associated with poor prognosis (9), reflects disease severity (11) and more advanced NYHA functional class (11) in PAH.

A distinct pattern of change in $PetCO_2$ during exercise is evident in individuals with PAH. In severe PAH, $PetCO_2$ is low at rest and falls progressively throughout an incremental exercise test (12), most likely reflecting a low and falling $PaCO_2$ at rest and on exercise, respectively (174). During recovery, $PetCO_2$ rises (12), reflecting slowed gas exchange kinetics and delayed recovery. In moderate PAH the rise in $PetCO_2$ from rest to the AT is minimal, or there is no rise at all, and in mild PAH the rise in $PetCO_2$ from rest to the AT is attenuated (12). This particular pattern of $PetCO_2$ distinguishes PAH from other conditions, including HFrEF and COPD (168).

Ventilatory response and dyspnoea in PAH

The relationship between ventilation and the sensation of dyspnoea in PAH is complex. It is well established that individuals with PAH have a greater ventilatory demand and $\dot{V}E$ throughout submaximal exercise. It is also evident that individuals with PAH register an awareness of breathing during lower levels of exercise compared with normal subjects (11). Increased ventilation in PAH reflects a response to a number of stimuli as described in section 2.3.3.3, Page 25. There are no data describing a direct association between $\dot{V}E$ and dyspnoea in PAH. However it is likely that the abnormalities that result in elevated ventilation also result in the sensation of exertional dyspnoea.

In both COPD and in interstitial lung disease (ILD), dynamic mechanical constraints (176, 177), and increased central respiratory neural drive due to metabolic and pulmonary gas exchange abnormalities (176), result in heightened afferent proprioceptive feedback. It is thought that these inputs signal an inadequate ventilatory response, relative to motor output, and contribute to dyspnoea (177). In PAH, the cause of exertional dyspnoea has been less studied, however, evidence is mounting for afferent input from the RV and/or atrium to the central nervous system resulting in a heightened sensation of dyspnoea during exercise (135). It is plausible that, along with metabolic (38, 39) and pulmonary gas exchange abnormalities (178, 179), inadequate CO, relative to motor output to the right ventricle, contributes to a sensation of dyspnoea in individuals with PAH. That is, in COPD and ILD the sensation of dyspnoea is associated with a heightened respiratory drive and an imbalance in the work of breathing relative to capacity. According to a similar rationale the sensation of dyspnoea in PAH may be associated with a heightened respiratory drive and an imbalance in the work of the RV, relative to capacity.

2.3.4 Gas exchange and hypoxaemia

Reduced diffusing capacity for carbon monoxide (DLCO) is a common finding in PAH (7, 25, 171, 178, 179). Reduced DLCO appears to be related to both impaired pulmonary membrane perfusion capacity and, to a lesser extent, reduced pulmonary capillary blood volume (171, 179). Reduced DLCO has been shown to correlate with decreased peak $\dot{V}O_2$, peak O_2 pulse, AT and a higher functional class in PAH (180). Although the direct mechanism behind this association has not been established, impaired gas exchange is most likely to contribute to reduced exercise capacity by limiting O_2 uptake in the lungs and reduced tissue O_2 delivery, during exercise.

Oxygen desaturation occurs, during exercise, in individuals with PAH (9, 11). In individuals with a patent foramen ovale, desaturation can be sudden and severe as a shunt develops between the right and left circulations (13). In individuals with moderate to severe PAH, without a patent foramen ovale, a progressive fall in O_2 saturation (SpO_2) occurs during exercise. It has been proposed that this is caused by reduced venous O_2 saturation secondary to reduced CO and tissue O_2 delivery (180). At rest, mixed venous O_2 saturation has been shown to correlate with PaO_2 (174). However, reduced O_2 uptake in the lung secondary to rapid red cell transit time (11), with blood flow at high speed, under high pressure due to a markedly

elevated mPAP, through narrowed vessels (171), diffusion impairment (179) and ventilation/perfusion mismatch (172, 174, 181) also contribute to hypoxaemia in PAH.

2.3.4.1 Hypoxaemia and symptoms

The influence of hypoxaemia on symptoms and exercise capacity in PAH is complex. In humans, the symptomatic response to hypoxaemia is variable, however, the degree of dyspnoea experienced by an individual appears to be closely related to the increase in $\dot{V}E$ caused by reduced PaO_2 (182). Hypoxaemia stimulates $\dot{V}E$ through central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies (182). The resulting increase in central motor output and respiratory muscle activation contribute to dyspnoea. However, central chemoreceptors are generally only stimulated when PaO_2 is close to, or below, 50mmHg (183). While both hypoxaemia and an excessive ventilatory response have been observed during exercise in individuals with PAH, except in the presence of a patent foramen ovale or severe PAH, the levels of hypoxaemia are generally insufficient to stimulate hypoxia sensitive central chemoreceptors (174, 184). Furthermore, in HFrEF, hyperventilation occurs in the absence of hypoxaemia (185). There are conflicting reports in the literature regarding the correlation between the ventilatory response during exercise and PaO_2 in individuals with PAH. Although early studies demonstrated no correlation between $\dot{V}E/\dot{V}CO_2$ and PaO_2 (169, 170), a recent study identified a correlation between these measures at rest and at the AT (174). Both elevated $\dot{V}E/\dot{V}CO_2$ and reduced PaO_2 reflect disease severity in PAH (9, 174) and therefore a correlation between these measures is not unexpected. However, a direct link between the ventilatory response and hypoxemia in this condition has not been established.

It is possible that hypoxaemia contributes to dyspnoea by its effects on skeletal muscle chemoreceptors (186, 187) (see Section 2.3.7.2 Chemoreceptor activation and the ergoreflex, Page 34). It is also possible that hypoxaemia contributes to respiratory muscle fatigue by limiting oxygen dependent adenosine triphosphate (ATP) regeneration. In healthy individuals undergoing prolonged exercise, fatigue induced changes in the contractile properties of the respiratory muscle contributes to a sensation of dyspnoea through imbalance in inspiratory muscle effort relative to capacity (188). Respiratory muscle fatigue is associated with greater motor

activation and a greater sense of effort for a given muscle contraction in COPD (189). The dyspnoea associated with the central nervous system's perception of inspiratory motor output, relative to capacity, is also influenced by a reduction in respiratory muscle strength. Respiratory muscle weakness and fatigue contribute to a sensation of dyspnoea in neuromuscular disorders and HFrEF (182, 190). Preliminary investigations suggest that respiratory muscle weakness may be present in PAH (191-193) and this may predispose the respiratory muscles to fatigue, especially in the presence of hypoxaemia. Therefore, it is possible, that hypoxaemia precipitates respiratory muscle fatigue and by this mechanism contributes to the sensation of dyspnoea in PAH. This is an area that warrants further investigation.

2.3.5 Peripheral airways function

In experimental models of PAH, structural changes in the airways result in increased airway resistance (194, 195). Airflow limitation, especially in the peripheral airways (196), and airway obstruction responsive to treatment with Salbutamol, has been reported in humans with PAH (197). In addition, premature airway closure and moderate lung hyperinflation at rest have also been demonstrated in PAH (196). In individuals with PAH, mPAP greater than the group median has been associated with a significantly higher residual volume/total lung capacity ratio than mPAP below the median (196). In COPD (182) and asthma (198), airflow limitation and increased end expiratory lung volume contribute to a sensation of dyspnoea. It is possible that increased ventilation and reduced expiratory time during exercise result in expiratory flow limitation and a degree of dynamic hyperinflation which exacerbates dyspnoea in PAH.

2.3.6 Fatigue, lightheadedness, chest pain, and palpitations in PAH

2.3.6.1 Fatigue

Fatigue is commonly reported in HFrEF and PAH and is described as the limiting factor during exercise testing in up to half of individuals with these conditions (11, 199). In HFrEF, reduced CO and leg blood flow contribute to muscle fatigue and early termination of exercise (200). Slowed $\dot{V}O_2$ kinetics reflect an O_2 deficit and reduced ATP regeneration in HFrEF (201). In individuals with PPH, $\dot{V}O_2$ kinetics

during constant work load exercise and post-exercise recovery have been shown to be slower than in healthy controls (43). Riley et al (43) suggested that slowed $\dot{V}O_2$ kinetics and an O_2 deficit during exercise, due to inadequate replenishment of ATP at moderate to high intensity exercise (13), in individuals with PAH is associated with a similar depletion of high-energy compounds in the muscle in PAH, as described in HFrEF (202).

Although depletion of high-energy compounds contributes to fatigue in HFrEF, CO during an acute bout of exercise is not closely associated with measures of exercise capacity in individuals with HFrEF (203). However, chronically reduced CO, resulting in chronic muscle acidosis (204), is thought to contribute to exercise impairment through a detrimental effect on systemic endothelial and skeletal muscle function (205), chemoreceptor and ergoreflex up-regulation, increased ventilation, dyspnoea and reduced exercise tolerance (206-208). It is likely that similar mechanisms contribute to fatigue in PAH (see Section 2.3.7).

2.3.6.2 Lightheadedness and syncope

Exertional light-headedness, reported in advanced PAH, has been attributed to a limited increase in CO, an insufficient rise in systemic blood pressure and reduced cerebral blood flow during exercise (11). In some individuals, exercise is associated with syncope (6). The development of syncope in PAH is often relatively slow, with progression of symptoms following cessation of exercise (18), similar to responses described in otherwise healthy subjects experiencing a vaso-vagal event, in whom pre-syncopal symptoms such as nausea and dizziness can precede syncope by minutes (209). In PAH, reported symptoms preceding syncope include light-headedness, dizziness, epigastric fullness, choking or a sensation of tightening about the heart (210). The similarity between syncope associated with PAH and vaso-vagal episodes in otherwise healthy individuals (209) suggests the likelihood that syncope associated with PAH, in some individuals, is a consequence of impaired exercise CO, reduced venous return and a subsequent vaso-vagal reflex response. A higher level of vagal activity has been reported in individuals with PPH who had episodes of syncope, compared with those who did not, supporting the role of a vagal response (140). In some individuals there is a long period between the initial reports of syncope and death (210) suggesting that, in these individuals, syncope is not a sign of terminal RHF.

In individuals with severe PAH, however, exertional syncope may be caused by acute right ventricular failure, precipitated by a steep rise in PAP (18, 211), and is a poor prognostic sign. Whether due to a vasovagal reflex, or acute right ventricular dysfunction, the ultimate outcome that precedes the loss of consciousness in individuals with PAH is a significant fall in CO, hypotension and bradycardia (18, 211).

It is plausible that the sensation described by some individuals with PAH as light-headedness is caused, or exacerbated, by a low $PaCO_2$ tension similar to the cause of light-headedness associated with psychogenic hyperventilation (212). A reduction in cerebral blood flow is associated with hypocapnia and can cause light-headedness in normal subjects. Cerebral blood flow is linearly related to $PaCO_2$, above 22mmHg, and returns to within 90% of normal if hyperventilation is sustained for more than 4 hours (212). In healthy individuals, light-headedness has been associated with a mean $PetCO_2$ level of 20mmHg (range 14 to 29mmHg) (213). However, the impact of hypocapnia on cerebral blood flow and light-headedness, during exercise, in PAH has not been studied.

2.3.6.3 Cardiac ischaemia and chest pain

In the National Perspective Study, chest pain was reported by 47% of patients with iPAH, at the time of enrolment (6). Chest pain in PAH has been ascribed to either right ventricular ischaemia or pulmonary artery dilatation causing compression of the left main coronary artery. Limited CO, a failure of systemic blood pressure to rise normally on exercise (9, 18), and elevated right ventricular pressure and hypertrophy contribute to reduced coronary perfusion (214). In PAH, the combination of reduced perfusion, elevated myocardial O_2 demand and right ventricular wall stress can lead to right ventricular ischaemia in the absence of coronary atherosclerotic disease (215, 216). In severe PAH, compression of the left main coronary artery by an enlarged pulmonary trunk is a recognised cause of left ventricular ischemia and angina (217-220).

<u>Other possible causes of chest pain</u>

Elevated PAP, in some subjects with high altitude pulmonary oedema, has been associated with chest pain, which subsides as the PAP returns to normal (221), suggesting a relationship between PAP and chest pain in these individuals. J

receptor stimulation can induce chest pain and/or a sensation of pressure in the substernal region (162). It is therefore possible, that chest pain reported by some individuals with PAH is related to J receptor activation associated with elevated PAP.

Hyperventilation has been described as a cause of atypical chest pain in psychogenic disorders (212, 222). Hypocapnia causes coronary artery vasoconstriction which can be associated with reduced coronary blood flow (223) and myocardial hypoxia (212). In individuals with normal coronary arteries, hyperventilation during exercise has been associated with electrocardiographic changes resembling cardiac ischaemia (224). In light of the vulnerability of the RV to ischaemia it is plausible that chest pain associated with PAH, in some individuals, may be related to hyperventilation induced hypocapnia, coronary vasoconstriction and myocardial hypoxia.

2.3.6.4 Arrhythmias and palpitations

There are few studies that report arrhythmias associated with PAH, and the cause of palpitations in individuals with PAH has not been described. However, based upon limited data, the most likely cause of palpitations in PAH is a tachyarrhythmia. Most reported tachyarrhythmias have been benign in nature and there are no reports of malignant arrhythmias in studies of patients with PAH, either at rest or on exertion. In a study of patients with PPH, arrhythmias were recorded in 27 out of a population of 101. Seventy percent of the arrhythmias recorded were sinus tachycardia, sinus bradycardia or drug-induced first degree atrio-ventricular block (225). There were no cases of ventricular arrhythmias or other life threatening arrhythmias in this study. Although there was a greater incidence of arrhythmia in subjects who subsequently died than those who survived, it was considered likely that this reflected the severity of right ventricular dysfunction rather than arrhythmia as a cause of death. However, sinus tachycardia was a poor prognostic sign. In another study of patients with PAH (140), higher sympathetic tone and lower SpO_2 was associated with a higher incidence of arrhythmias. In this study, no life-threatening arrhythmias were recorded over a period of 24 hours of continuous study.

In a recent report (226) 29% of the subjects with PAH who were studied were in atrial fibrillation (AF). A causative relationship between PAH and AF has not been established, however in this study individuals with AF and PAH demonstrated a

higher NYHA/WHO functional class, a shorter 6MWD, higher serum levels of the cardiac enzyme NT-proBNP, and poorer renal function than individuals with PAH who were in sinus rhythm (226). These findings suggest that AF is associated with greater cardiac stress, and worse tissue perfusion and functional capacity, than sinus rhythm, in individuals with PAH.

2.3.7 Systemic and peripheral abnormalities

Along with cardiac and pulmonary vascular dysfunction, a number of systemic and peripheral abnormalities have been identified in individuals with PAH. The systemic and peripheral factors that occur in association with PAH, and the likely contribution of these abnormalities to reduced exercise capacity and symptoms, are discussed below.

2.3.7.1 Up-regulation of sympathetic nervous system activity

Up-regulation of the sympathetic nervous system has been demonstrated in PAH (138, 140). Afferent sympathetic pathways discharge at the upper physiological ranges of right ventricular pressure (136) and sympathetic activity in PAH appears to be directly related to the degree of elevation in right atrial pressure and reduction in CO (139). In a study by Folino et al (140) the highest sympathetic activity in subjects with PAH was associated with the highest right ventricular systolic pressure, supporting an association between right ventricular work and sympathetic drive.

Folino et al (140) also found an association between reduced PaO_2 and sympathetic drive in PAH. It has been proposed that peripheral chemoreceptor activation, initiated by hypoxaemia, contributes to activation of the sympathetic nervous system in PAH (138). A role for hypoxaemia-induced peripheral chemoreceptor activity in PAH is supported by observations that muscle sympathetic nerve activity and HR are reduced in response to correction of hypoxaemia by the administration of 100% oxygen (138). Velez-Roa et al (138) propose that the marked increase in sympathetic nerve activity in PAH is, in the short term, partially mediated by increased activation of peripheral chemoreceptors. Sympathetic pathways have been implicated in mediating the association between right ventricular work load and ventilatory response (141) and it is possible that increased sympathetic activity influences the ventilatory response and sensation of dyspnoea in PAH.

Although the sympathetic system has little influence on pulmonary vascular tone at rest it does have an appreciable effect when baseline activity is elevated and when peripheral chemoreceptors are stimulated by hypoxia (227). In these conditions sympathetic stimulation increases PVR (228). Up-regulated sympathetic activity in PAH may be both a response to the functional consequences of PAH, including hypoxaemia, and a contributor to elevated pulmonary vascular tone.

2.3.7.2 Chemoreceptor activation and the ergoreflex

Reduced muscle cell pH associated with anaerobic metabolism stimulates intra- and extra-cellular chemoreceptors within the muscle (186, 229). In the absence of hypoxaemia or reduced arterial pH, local muscle acidosis stimulates ventilation (186, 187, 230, 231) via the ergoreflex. The ergoreflex system senses work performed per unit muscle and metabolic by-products of exercise in skeletal muscle which stimulate ventilation via the sympathetic nervous system (231, 232). Increased ergoreflex activity contributes to a heightened ventilatory response (80, 232, 233).

To date, there have been no reported studies of ergoreflex responses in PAH. However, increased chemoreceptor sensitivity and up-regulated ergoreflex activity is implicated in the increase in ventilation and dyspnoea associated with exercise in HFrEF (206, 227, 230, 233, 234). Increased chemoreceptor sensitivity to CO_2 (predominantly central, medullary oversensitivity) or hypoxia (predominantly peripheral, carotid oversensitivity) is present in up to 60% of individuals with HFrEF (235). This ergoreflex up-regulation is thought to be secondary to chronic muscle acidosis during exercise (204), although other factors including prostaglandins, potassium and blood flow may also have a role (235). It is possible that, in the longer term, chronic muscle acidosis also results in increased chemoreceptor sensitivity, ergoreflex activity, ventilation and dyspnoea in individuals with PAH. This is an area that warrants investigation.

2.3.7.3 Inflammation

It has recently been proposed that systemic inflammation plays a significant role in the pathophysiology of PAH (236). Circulating markers of inflammation are elevated in iPAH (236, 237) and it has been suggested that inflammation may contribute to the pathogenesis of vascular remodelling in PAH (1). Systemic inflammation is more

pronounced in PAH associated with scleroderma (46, 237) and disease progression and prognosis is worse in this condition than in iPAH (72). Mortality in the majority of individuals with PAH associated with scleroderma is related to PAH progression and RHF (238). While the literature on inflammation in PAH is very limited, these findings suggest there may be an association between inflammation, pathogenesis and disease severity in PAH.

2.3.7.4 Systemic endothelial dysfunction

Systemic endothelial dysfunction has been demonstrated in subjects with iPAH, PAH associated with systemic sclerosis, and in first-order relatives of subjects with PAH (239). Furthermore, Raynaud's Syndrome is associated with marked impairment in systemic endothelial function (240), is present in approximately 10% of patients with PAH (6), and is a characteristic feature of systemic sclerosis, a condition with a high prevalence of PAH (2, 241, 242).

The cause of systemic endothelial dysfunction in PAH is not known, however it has been proposed that in COPD, HFrEF and post myocardial infarction, there is a direct link between systemic inflammation and endothelial dysfunction (243-245). Accordingly, it is plausible that systemic vascular dysfunction is, in part, mediated by systemic inflammation in PAH.

Systemic endothelial function and skeletal blood flow

The systemic vascular endothelium plays an important regulatory role in the maintenance and moderation of peripheral vasomotor tone (48). Exercise-induced release of NO by the vascular endothelium promotes vasodilatation of the peripheral blood vessels, within skeletal muscle, in healthy individuals (208). The endothelium is pivotal in coordinating tissue perfusion, and, in HFrEF, due to its influence on vascular tone and blood flow, endothelial dysfunction impacts negatively on O_2 delivery to the periphery (246-248). Evidence of systemic endothelial dysfunction in PAH (249) suggests that reduced peripheral blood flow may also be a source of impaired O_2 delivery to skeletal muscle during exercise in PAH (250).

Imbalance between circulating levels of vasodilators and vasoconstrictors has been described in PAH. Reduced whole body production and/or increased metabolism of the vasodilator NO (251), and elevated levels of the vasoconstrictor, endothelin, have been identified (252, 253). Endothelin is important in the regulation of tissue

blood flow during exercise (254, 255) and may be particularly relevant in populations where endogenous endothelin levels or sensitivity are elevated (255), such as in PAH. It is plausible that down-regulation of the NO system and up-regulation of the endothelin system compromise skeletal muscle blood flow and contribute to symptoms and reduced exercise capacity in PAH (256).

Furthermore, it has been proposed that an improvement in exercise capacity, which has been reported in the absence of clinically relevant improvements in central haemodynamics following therapy with PAH specific pharmaceutical therapies, may reflect enhanced endothelial function in the peripheral circulation in PAH (257). Also supporting this theory is the finding that the endothelin antagonist, Bosentan, improves peripheral vascular endothelial function in individuals with systemic sclerosis (258).

2.3.7.5 Skeletal and respiratory muscle myopathy

Recent studies have identified muscle fibre changes and skeletal muscle weakness in individuals with iPAH (38, 39). These muscle fibre changes include a lower than normal portion of type I muscle fibres, a higher proportion of type II fibres, and an enzyme profile compatible with a relatively higher potential for anaerobic than aerobic energy metabolism.

Respiratory muscle weakness has also been demonstrated in PAH (192, 193). Diaphragm muscle fibre changes in human subjects with pulmonary hypertension, and hyperventilating rats in an experimental model of PAH, include severe atrophy and reduced maximal force generating capacity in the muscle fibres (normalised for fibre size) (191). In this study, the identified diaphragm muscle fibre changes were not seen in the quadriceps muscle, suggesting that the changes were specific to the diaphragm. Increased protein degradation, but no difference in protein synthesis, was observed in the rat models of PAH suggesting that the muscle fibre atrophy was related to proteolysis (191).

These findings demonstrate morphologic and functional changes in both the skeletal muscles of the periphery and in the diaphragm of individuals with PAH. These changes are likely to contribute to reduced exercise capacity in these individuals. The cause of skeletal muscle dysfunction in PAH is uncertain. It has been proposed that in HFrEF and COPD, skeletal muscle dysfunction, including reduced muscle

mass and contractility, muscle weakness and reduced endurance, is related, in part, to systemic inflammation (229, 243, 259, 260). Furthermore, exercise training is associated with a reduction in systemic inflammation (261-263), which is associated with improvements in muscle function in HFrEF and COPD (264, 265). However, this finding is not universal and, in COPD, there are contradictory results from different studies (266). It is possible that systemic inflammation contributes to muscle impairment in PAH, as described in HFrEF, although this hypothesis requires investigation.

Skeletal and respiratory muscle dysfunction and symptoms

It has been proposed that altered muscle morphology contributes to an increased ventilatory drive and dyspnoea associated with exercise intolerance in PAH, as in other chronic cardiorespiratory conditions (230, 267, 268). Respiratory muscle weakness (192, 193) and atrophy of type I and type II muscle fibres in the diaphragm of humans with PAH (191), in association with elevated ventilation during exercise (11), hypoxaemia and reduced CO is likely to contribute to respiratory muscle fatigue and exertional dyspnoea in PAH.

Skeletal and respiratory muscle abnormalities resulting in early anaerobic metabolism are believed to be important contributing factors to the sensation of fatigue during exercise, and reduced exercise capacity, in HFrEF and COPD (268-270). Similar skeletal muscle abnormalities are likely to contribute to the sensation of fatigue in individuals with PAH.

Role of deconditioning

While the impact of reduced physical activity on muscle dysfunction and exercise capacity in PAH has not specifically been defined, deconditioning may be a contributing factor, as described in COPD (271) and HFrEF (206). While systemic inflammation is likely to contribute to muscle atrophy and dysfunction in each of these conditions, reduced physical activity is likely to perpetuate the muscle fibre changes and dysfunction.

The influence of exercise rehabilitation on muscle function and exercise capacity in PAH

Prior to the development of PAH specific pharmaceutical therapies, exercise training was discouraged for individuals with PAH due concerns regarding the haemodynamic consequences of physical exertion beyond the performance of usual daily activities (14, 41). However, improvements in haemodynamics, disease progression and survival have encouraged investigation into the role of exercise rehabilitation for individuals with PAH, especially in light of persistent functional limitations despite pharmaceutical therapy. The first exercise training study was reported in Japanese in 2005 (17). This study explored the feasibility and "safety" of exercise training in individuals with PAH who had recently commenced intravenous epoprostenol. The results demonstrated that it was possible for patients with severe PAH, on intravenous therapy, to undertake an exercise training program, and that this could be achieved without adverse events. Although it is not possible to determine the relative contributions of pharmaceutical therapy and exercise rehabilitation, this study demonstrated positive outcomes in terms of increased 6MWD and lower limb strength, and improved NYHA class in individuals with PAH.

Following this initial report, there have been a number of small studies investigating exercise rehabilitation in patients with PAH who are stable on PAH specific pharmaceutical therapy (15, 16, 21, 42, 106). Only one of these studies was a randomised controlled trial (15). The others were limited in methodology, being intervention studies with small sample sizes (16, 42, 106), or a case report (21). The total number of individuals who have undergone exercise rehabilitation in these studies is 67. The exercise programs reported have differed in exercise modality and intensity. Exercise modalities included aerobic exercise training using walking and/or cycle ergometry (15, 16, 21, 42, 106), endurance muscle training with low weights and high repetitions (16, 42), quadriceps strength training employing weights up to 75% of the maximal weight achieved on a prior maximum strength test (16, 42), and other modalities including yoga and mental training (15). Aerobic exercise intensities ranged from 60 to 80% of maximal HR or workload, determined from a cardiopulmonary test performed prior to exercise training. All studies demonstrated improvements in exercise capacity and/or muscle strength following exercise rehabilitation and two reported an improvement in functional class (15, 21). One study and one case report also reported that exercise rehabilitation was associated with an improvement in QoL (15, 21). All studies specifically reported

adverse events. None of the studies reported any serious adverse events or clinical deterioration during the period of exercise training although minor adverse events, mostly comprising self-limiting episodes of dizziness during or following exercise, were reported in three of these studies (15, 16, 42).

One study has reviewed the longer term (24 ± 12 months) outcomes of 58 individuals who had undergone a short period (15 weeks) of exercise rehabilitation (272). This study described good long term outcomes in these individuals, with 1 and 2 year survival rates of 100 and 95% respectively. In this study adverse events were quantified and described, and no serious adverse events were reported. The findings of this study suggest that exercise rehabilitation can be undertaken, by individuals with PAH without longer term adverse outcomes.

Despite limitations in these preliminary studies, it appears that exercise training is associated with improvements in exercise capacity and/or muscle function and can be achieved without serious adverse events or clinical deterioration. However further randomised controlled studies are required to confirm this suggestion.

2.3.8 Summary: Exercise limitation and symptoms in PAH

The two most common symptoms reported by patients on presentation (6) and the symptoms that most commonly limit exercise capacity are dyspnoea and fatigue (9, 11). The cause of dyspnoea in PAH is multifactorial. Increased right ventricular pressure and workload are likely to directly influence ventilation and dyspnoea in PAH, via activation of the sympathetic nervous system. Reduced CO, a lower systemic blood pressure, and peripheral endothelial dysfunction, in association with hypoxaemia on exercise, contribute to reduced O_2 delivery. Tissue and arterial acidosis and possible up-regulation of chemoreceptors and ergoreflexes may further contribute to elevated ventilation and dyspnoea. Muscle weakness, altered muscle morphology and exercise-induced hypoxaemia increase the likelihood of respiratory muscle fatigue and associated dyspnoea. It is possible that stimulation of J receptors by increased pulmonary capillary pressure and stimulation of mechanoreceptors within the lungs from expiratory airflow limitation may also contribute to dyspnoea in PAH.

A limited increase in CO and early onset of anaerobic metabolism, reduced ATP regeneration, and muscle fatigue are likely contributing factors to the sensation of

fatigue associated with PAH. Light-headedness on exertion in PAH is mostly likely related to reduced CO and syncope may relate to a vaso-vagal event or, in severe PAH, acute RHF. Chest pain has been attributed to myocardial ischaemia due to either elevated RV work that exceeds coronary artery blood supply, compression of the left main coronary artery by an enlarged pulmonary artery, or J receptor activation. Palpitations are most likely caused by a benign tachyarrythmia.

It is feasible that hyperventilation contributes to the sensations of lightheadedness and chest pain in some individuals with PAH, although this remains unstudied.

2.4 Exercise testing in PAH

This section describes the utility and efficacy of exercise testing in PAH. Most reported studies are of investigations in adult individuals and, unless otherwise specified, the findings reported in this literature review relate to individuals who are ≥ 18 years of age.

The initial subsection presents details of the incremental CPET, including a section on simultaneous invasive haemodynamic assessment. Further subsections include discussion of the 6MWT and other tests with potential utility in PAH. These tests include constant work load tests, the incremental and endurance shuttle walk tests, treadmill tests using the Naughton-Balke protocol and derived metabolic equivalents, and exercise echocardiography. Due to limited data in PAH, the similarities between PAH, HFrEF and COPD in mechanisms and symptoms of exercise intolerance, and the extensive evidence in exercise testing in HFrEF and COPD, a brief discussion of the literature relating to exercise testing in these conditions is also presented. Tests of muscle strength are briefly described and discussed.

2.4.1 General information

Exercise tests provide a low risk assessment which in some cases is diagnostic (e.g. exercise-induced bronchoconstriction or cardiac ischaemia), and if combined with gas exchange analysis, can assist with differential diagnosis, and identification of the major physiological factors associated with impaired exercise capacity in an individual. Furthermore, exercise testing quantifies exercise capacity and functional

limitation, and the results assist in determining prognosis, the response to therapeutic interventions and accurate exercise prescription.

2.4.2 Cardiopulmonary exercise test

The CPET involves the continuous measurement of respiratory gas exchange to quantify $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ during graded aerobic exercise. Gas exchange can be measured using a mixing chamber, however, breath-by-breath gas exchange analysis also allows for determination of the concentration of CO_2 and O_2 in end tidal gases (13).

The results of a CPET are often expressed relative to the predicted value for an individual. Age influences exercise capacity (measured both as peak $\dot{V}O_2$ and peak workload), $\dot{V}O_2$ at the AT, and the ventilatory response, and therefore age-appropriate predicted values are needed for interpreting individual results. Furthermore, gender, race, height and body mass influence exercise responses and these factors also need to be considered in the calculation of a predicted value (13). Predicted values have been determined from the study of healthy individuals and, in general, results within the mean ± the 95% confidence interval for a healthy population provides a reasonable certainty that a response is normal (13).

If the aim of exercise testing is to assess maximal exercise responses, the test needs to meet specific criteria. Maximal aerobic exercise is characterised by a lack of increase in $\dot{V}O_2$ despite increasing workload. However, in many clinical scenarios a maximal test cannot be achieved due to a physiological or symptom limitation, in which case the term peak $\dot{V}O_2$ is used (13). This describes the highest $\dot{V}O_2$, averaged over a 20-30 second period within the last 30 seconds of exercise, prior to exercise termination. Prior to the AT, the respiratory exchange ratio (RER) describes the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ and represents the predominant type of fuel involved in muscle metabolism (273). Following the AT buffering of hydrogen ions by bicarbonate also contributes to RER. An RER of >1.10 at test cessation is accepted as an indication of a maximal effort (274).

Standard monitoring procedures during a CPET include continuous SpO_2 via pulse oximetry, 12 lead ECG for assessment of cardiac rhythm and rate, intermittent non-invasive systemic blood pressure assessment (273), and ratings of dyspnoea and

perceived exertion. More advanced monitoring can be undertaken, as dictated by the clinical situation, the available facilities and the experience of the staff. This advanced monitoring can include arterial blood gas analysis via intermittent arterial puncture or via an arterial line placed in the radial or brachial artery. An arterial line allows repeated blood gas measurement, and accurate determination of dead space ventilation via analysis of the difference between alveolar and arteriolar O_2 concentrations. An arterial line also allows for continuous measurement of systemic blood pressure. In specialised units, central haemodynamics can be assessed during a CPET via an indwelling pulmonary artery catheter (275).

To determine the contribution of pulmonary parenchymal or airway abnormalities to exercise limitation, lung function testing can be performed at rest and during exercise (276). At rest, these tests typically include the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), maximum voluntary ventilation (MVV), flow volume loops and inspiratory capacity (IC). During exercise, flow volume loops and intermittent IC manoeuvres can be analysed to aid in the assessment of changes in airflow and lung volumes during exercise.

The CPET allows the relative contribution of each component of aerobic metabolism to be determined. Significant disease or dysfunction in any components of tissue oxygen delivery, or utilisation, results in reduced aerobic and work capacities (159). By systematic analysis of the variables measured during a CPET, the contribution to effective gas transport and utilisation of each of these systems can been examined (13).

2.4.2.1 Exercise modality

The most commonly used CPET protocol for assessment of exercise capacity, prognosis and response to therapy involves performance of an incremental exercise test to volitional exhaustion, or symptom limitation, on a cycle ergometer or a treadmill. Measures are taken at baseline (rest), during unloaded exercise (in cycling tests), during an incremental increase in work load, and during recovery.

An exercise test performed on a cycle ergometer has the advantage of providing a quantifiable workload and less motion artefact than a treadmill test (273). However, some disadvantages of cycle ergometry include the predominance of lower limb work which results in underestimation of peak $\dot{V}O_2$ and the development of local

muscle fatigue as a limiting factor in some individuals. Dyspnoea may be greater on a cycle ergometer CPET than a walking test (277, 278) although this finding is not universal and may depend on the population being studied (279).

Although a walking test may be considered to better reflect daily activity than a cycling test, walking on a treadmill is more complex than ground walking, and, in some individuals with COPD, treadmill exercise elicits anxiety and increased dyspnoea and therefore may not accurately reflect usual activity (280). In individuals with HFrEF, treadmill exercise has been shown to result in a higher $\dot{V}E$ than cycling (281). Differences in gas exchange and ventilatory response to walking and cycling tests have also been described in PAH (279). These differences include higher $\dot{V}E$, $\dot{V}E/\dot{V}CO_2$, and a significantly lower $PetCO_2$ at the AT during a walking test (a modified shuttle walk test) compared with a cycling test. In all populations, peak $\dot{V}O_2$ measured on a treadmill is typically 5-10% higher, compared with a cycling test (273) and a walking test has better sensitivity for indentifying oxygen desaturation (field or treadmill) than a cycling test (32).

The differences between treadmill and cycling tests demonstrate that these exercise modalities are not interchangeable, and that standardisation of the test modality is important for comparison of results within individuals, in comparison to predicted values and between study groups.

2.4.2.2 Exercise protocol

In terms of the selected workload increments, there is no difference in peak $\dot{V}O_2$, AT, peak $\dot{V}E$, change in $\dot{V}O_2$ relative to the change in work rate or peak HR when using ramp, 1 minute, 2 minute or 3 minute step protocols that use the same overall average work rate increase (282). However, peak workload and exercise time are lower in step protocols if the increments are large (283). This has relevance in determining peak work capacity, relative to predicted values, and in the comparison of results between tests in which different protocols have been utilised.

2.4.2.3 Incremental CPET in LHF

The role of the incremental CPET in HFrEF is well established (159, 284-286), and indeed, it is considered the ‘gold standard’ for assessment of functional capacity,

disease severity and prognosis in this condition (274, 284). A threshold value for peak $\dot{V}O_2$ associated with a greater likelihood of survival following cardiac transplantation has been determined (286), and CPET has been incorporated into recommendations for the pre-transplantation assessment of cardiac patients (287). Peak $\dot{V}O_2$ (as an absolute value, indexed for body weight or as a percent predicted), $\dot{V}O_2$ at the AT, exercise duration and workload, ventilatory response (either as the slope of $\dot{V}E/\dot{V}CO_2$ during an incremental exercise test, or the ratio at the AT), estimates of cardiac power (peak $\dot{V}O_2$ multiplied by systolic blood pressure), chronotropic response and HR recovery, change in $\dot{V}O_2$/change in work rate, and $\dot{V}O_2$ kinetics (during exercise and recovery) have all been investigated and found to be useful measures to evaluate exercise capacity, prognosis and response to therapy in individuals with HFrEF (284).

2.4.2.4 Incremental CPET in COPD

In COPD, the incremental CPET is also considered the 'gold standard' for measurement of aerobic capacity (280). Useful dynamic measures of ventilatory and airway function can be performed during a CPET. These include analysis of the ventilatory reserve (1-peak $\dot{V}E$/MVV), tidal flow-volume loop at different stages of the exercise test relative to the maximal flow-volume loops obtained at rest, the tidal volume and respiratory frequency, end expiratory lung volumes and the change in IC. These measures provide detail of the likely degree of dynamic hyperinflation, and the impact of flow limitation on exercise capacity (273). Other abnormalities in COPD, that can be identified on a CPET, include the degree of ventilatory 'inefficiency', or increased dead space, by analysis of the difference between alveolar and arterial O_2, if arterial blood gas analysis is available, or by utilising a proposed surrogate for dead space ventilation, the $\dot{V}E/\dot{V}CO_2$ (13). However, care needs to be taken in interpreting the cause of elevated $\dot{V}E/\dot{V}CO_2$ in COPD as it may be an indication of hyperventilation related to pulmonary hypertension rather than dead space ventilation caused by the primary parenchymal or airway disease associated with COPD. This is particularly pertinent if the elevation in $\dot{V}E/\dot{V}CO_2$ is out of proportion to the degree of airflow limitation (153). Arterial desaturation on exercise in subjects with COPD may be evident during a CPET, especially in individuals with a greater component of emphysema than chronic bronchitis, in

those with moderate to severe COPD, co-existent pulmonary hypertension and/or a significant diffusion limitation (273, 288). A walking test (e.g. a treadmill test) is more sensitive in detecting exercise desaturation and the need for, and response to, supplemental O_2 therapy than cycle ergometry in COPD and is therefore the test of choice in this condition (280).

2.4.2.5 Incremental CPET in PAH

Identifying exercise and ventilatory abnormalities in PAH

In PAH, the incremental CPET has been shown to consistently identify reduced peak $\dot{V}O_2$ and reduced $\dot{V}O_2$ at the AT (9, 11, 26, 34, 105). In this population, other consistent abnormalities detected on a CPET include arterial O_2 desaturation (105, 109, 279), reduced O_2 pulse (9-11) and an elevated slope of $\dot{V}E/\dot{V}CO_2$ or ratio at the AT (8, 11, 12, 26, 34, 105, 170). Recent studies have also identified an abnormal reduction in $PetCO_2$ at rest and at the AT, and an abnormal rise in $PetCO_2$ during recovery (12, 168). The altered $PetCO_2$ response during and following exercise can differentiate PAH from other cardiopulmonary conditions (168) and reflects disease severity (12). A lack of overlap between any key parameters of aerobic function and ventilatory response between individuals with mild PPH and healthy controls, suggests that a CPET may be a useful method of discriminating individuals with and without PPH (11).

Ventilatory abnormalities identified during a CPET have been shown to correlate with central haemodynamics and functional class in PAH. The slope of $\dot{V}E/\dot{V}CO_2$ correlates with mPAP in adults with pulmonary hypertension (170), and peak $\dot{V}O_2$ has been shown to correlate with mPAP and PVR in children (109). In adults with PAH, correlations between NYHA functional class and a number of CPET measures, including peak work rate, $\dot{V}O_2$ at AT, O_2 pulse, slope of $\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}CO_2$ ratio at AT, and peak $\dot{V}O_2$ have been described (11). Using stepwise regression analysis, NYHA functional class could be estimated from both peak $\dot{V}O_2$ and the slope of $\dot{V}E/\dot{V}CO_2$ measured during an incremental CPET.

Summary

Specific, consistent abnormalities in exercise capacity, gas exchange and ventilatory response are evident on a CPET in individuals with LHF, COPD and PAH. These abnormalities are summarised in Table 1.

Table 1. Summary of abnormalities identified on CPET in LHF, COPD and PAH

Abnormalities identified on a CPET	PAH	LHF	COPD
Reduced peak $\dot{V}O_2$	Y	Y	Y
Reduced AT	Y	Y	Y
Elevated $\dot{V}E/\dot{V}CO_2$	Y	Y	Y
Reduced O_2 pulse	Y	Y	Y
O_2 desaturation	Y	N	Y
Rise in $PetCO_2$ from rest to AT	N	Y	Y
Reduced 1-peak $\dot{V}E/MVV$	N	N	Y
Reduced and falling IC during exercise	N	N	Y

Abbreviations: CPET, cardiopulmonary exercise test; PAH, pulmonary arterial hypertension; LHF, left heart failure; COPD, chronic obstructive pulmonary disease; $\dot{V}O_2$, peak oxygen consumption; AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; O_2, oxygen; $PetCO_2$, end tidal carbon dioxide tension; $\dot{V}E/MVV$, the ratio of minute ventilation to maximal voluntary ventilation; IC, inspiratory capacity; Y, yes; N, no.

Assessment of an intervention effect in PAH

The utility of an incremental CPET in evaluating the response to interventions in PAH is uncertain, with varied results from different studies (29). In a study of heart-lung transplant patients (169), and in single centre studies of pharmacologic therapy for PAH (289), significant improvements in peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ have been identified following transplantation or pharmaceutical therapy. However multicentre studies have demonstrated less conclusive results. Significant improvements in

6MWD and slower disease progression, demonstrating a beneficial effect of PAH specific pharmaceutical therapy, in a multicentre trial, have been described in the absence of an improvement in peak $\dot{V}O_2$ (290). In another multicentre trial, improvements in 6MWD, functional class, cardiac index and PVR were seen following therapy with all doses of an endothelin antagonist, Sitaxentan, whereas only the highest dose of Sitaxentan was associated with an increase in peak $\dot{V}O_2$ (291). In these multicentre studies, a negative outcome would have been reported had only the peak $\dot{V}O_2$ been studied and clinically relevant, therapeutic benefits of these interventions would not have been identified. These findings suggest that peak $\dot{V}O_2$ may be less sensitive in identifying a significant improvement in outcome following pharmaceutical therapy in PAH than other study endpoints.

The Sitaxentan study demonstrated varied results from different centres (35). Correlations between peak $\dot{V}O_2$ and 6MWD reported by 4 experienced centres were significantly better than the correlations reported by 19 inexperienced centres. At baseline assessment, experienced centres demonstrated a correlation of 0.657 between peak $\dot{V}O_2$ and 6MWD while inexperienced centres demonstrated a correlation of only 0.338. In the study reporting these outcomes, the authors suggested that the technical complexity of a CPET may influence the validity of the results and reduce the reliability of data from inexperienced centres (35). Furthermore, in inexperienced centres, it is recommended that caution is required in using peak $\dot{V}O_2$ to guide treatment decisions or to study new therapies in PAH (29, 108).

Assessment of prognosis in PAH

Peak $\dot{V}O_2$ (9), the O_2 pulse (10), $\dot{V}E/\dot{V}CO_2$ (9, 10, 109) and $PetCO_2$ (9, 10) have been identified as useful prognostic indicators in adult subjects with PPH (9) and/or chronic thromboembolic pulmonary hypertension (10). In particular, peak $\dot{V}O_2$ >10.4 $ml.kg^{-1}.min^{-1}$ has been identified as the optimal cut-off for significantly better 1-year survival (9). An increase in O_2 pulse from rest to peak exercise of >3.3ml/beat is associated with a significantly better 4 year survival than ≤3.3ml/beat (10). Other CPET indices predictive of survival include peak exercise systolic and diastolic blood pressure and peak HR. Exercise systolic blood pressure and peak $\dot{V}O_2$ have been identified as better prognostic markers than haemodynamic parameters

measured at rest (9). Furthermore, peak exercise capacity of >75% of predicted has been shown to identify individuals with PAH who are most likely to have a positive response to acute vasodilator testing (143). While this finding is not in itself directly prognostic, individuals who respond to acute vasodilators generally have much better survival than those who demonstrate a poor response to a pulmonary vasodilator. Stratifying individuals by their likely response to an acute vasodilator may assist with selection of best medical therapy and with prognostication in PAH.

In a longitudinal study of children with PAH (109), standard prognostic statistics were not employed, however, children who suffered an adverse event, defined as death or commencement of prostacyclin therapy, had a lower peak $\dot{V}O_2$ and a higher slope of $\dot{V}E/\dot{V}CO_2$ on a CPET, at the commencement of the study, than subjects who did not have an adverse event during the follow up period.

Diagnosis of a patent foramen ovale in PAH

The CPET can be used to suggest the presence of a patent foramen ovale in PAH (11, 13, 66). In individuals with a patent foramen ovale, the rise in right atrial pressure generated by an exercise-induced increase in preload, promotes movement of de-oxygenated blood from the right to the left sided circulation, sudden hypoxaemia and change in ventilation. A sudden and sharp fall in $PetCO_2$ and SpO_2, accompanied by a sudden and sharp rise in end tidal oxygen tension ($PetO_2$), RER and ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) more than $\dot{V}E/\dot{V}CO_2$ (11) occurs as a patent foramen ovale opens. These findings are considered diagnostic of this condition (66). Because exercise results in pressure changes in the atria, a CPET is likely to be more sensitive for detecting a patent foramen ovale than a resting test, such as a resting echocardiogram (13).

Chronotropic response in PAH

A decreased HR response at peak exercise, commonly reported as an abnormal chronotropic response, has been described in a number of studies of maximal exercise, utilising a CPET, in PAH (11, 33, 43). It has been proposed that chronotropic incompetence may be explained by abnormalities in the RV (133). Down regulation of right ventricular myocardial beta-adrenoreceptors (67) may contribute to chronotropic impairment, similar to altered myocardial beta-adrenoreceptor activity in HFrEF (292). A prolonged HR recovery time following

exercise cessation is also a feature of both PAH and HFrEF and it has been proposed that this may also represent chronotropic impairment (33).

2.4.2.6 Safety of the incremental CPET

The incidence of complications during a symptom-limited CPET, in populations with known cardiac or pulmonary disorders, is between 2 and 5 per 100,000 tests (273). A maximal symptom-limited CPET is considered a safe procedure (273) with an acceptable risk/benefit ratio, even for populations with known cardiopulmonary conditions.

Safety of incremental CPET in PAH

No adverse events have been reported during maximum incremental CPETs, in adults with PAH (10-12, 33, 34, 105, 143, 168, 170, 279, 293, 294). Individuals with severe PAH have been included in several studies reporting CPET outcomes, including some individuals with symptoms preventing exercise beyond unloaded cycling (143), and these tests have not been associated with adverse events. There have been two reported studies with a specific focus on the safety of CPET in paediatric patients (109, 295). These studies reported minor adverse events described as desaturation to SpO_2 ≤85%, ≥ 3mm ST-segment depression on an ECG (109), or mild arrhythmia defined as isolated premature atrial or ventricular contractions or ST segment depression (295). There were no serious adverse events in either study.

However, in patients with acute right ventricular failure, recurrent syncope or a history of life threatening cardiac arrhythmias, a maximal CPET is contraindicated (273, 296). Furthermore, there is a subgroup of individuals with PAH who do not tolerate a CPET due to severe symptoms on exertion (34, 143).

2.4.2.7 CPET for differential diagnosis

Exertional dyspnoea is a non-specific symptom associated with several conditions. Algorithms developed by Wasserman and colleagues (13) provide a means for identifying the most likely factor contributing to exercise limitation and exertional dyspnoea in an individual. Differential diagnoses include coronary artery disease, HFrEF, pulmonary parenchymal or airway disease, skeletal myopathy, peripheral vascular disease and hyperventilation syndromes.

A likely diagnosis of PAH, based on an incremental CPET to volitional exhaustion, is reflected by reduced peak $\dot{V}O_2$ and AT, a low O_2 pulse, elevated $\dot{V}E/\dot{V}CO_2$, a normal ventilatory reserve, and O_2 desaturation (13). More recently determined indices that support a diagnosis of PAH include a low $PetCO_2$ at rest which fails to rise normally at the AT and a rise rather than fall in $PetCO_2$ during recovery (12, 168).

Although individuals with HFrEF, COPD and PAH present with similar exercise abnormalities, each condition has features which differentiate it from the others (13). Coronary artery disease (without HFrEF) is associated with a low peak $\dot{V}O_2$ and AT but a normal $\dot{V}E/\dot{V}CO_2$ and SpO_2. Left heart failure is associated with a low peak $\dot{V}O_2$ and AT and in more severe cases with elevated $\dot{V}E/\dot{V}CO_2$ but normal SpO_2. Furthermore, while $PetCO_2$ may be reduced at rest and at the AT, a rise in $PetCO_2$ from the commencement of exercise to the AT appears to discriminate individuals with HFrEF from those with PAH (168). Individuals with pulmonary parenchymal or airway disease demonstrate a low peak $\dot{V}O_2$ and AT, elevated $\dot{V}E/\dot{V}CO_2$ and O_2 desaturation, but have a reduced ventilatory reserve (defined as <11L between peak exercise $\dot{V}E$ and MVV, or peak $\dot{V}E$ >85% of MVV), identifying a ventilatory limit to exercise. Individuals with skeletal myopathies or peripheral vascular disease demonstrate a low peak $\dot{V}O_2$ and AT, but normal O_2 pulse and $\dot{V}E/\dot{V}CO_2$ and $PetCO_2$ responses, and normal SpO_2. Individuals with hyperventilation syndromes have a low peak $\dot{V}O_2$ and a low $PetCO_2$ at rest but a normal AT, a normal O_2 pulse, normal SpO_2 and a rise in $PetCO_2$ between the commencement of exercise and the AT (13). These differences in exercise responses that differentiate PAH from other conditions are summarised in Table 2.

Summary

Specific abnormalities associated with PAH can be identified on a CPET. These abnormalities can assist with differential diagnosis and help to stratify individuals according to the likelihood of PAH.

Table 2. CPET measures that differentiate PAH from other conditions

	Similar features	Features suggestive of PAH
PAH vs CAD (without HFrEF)	Reduced peak $\dot{V}O_2$ Reduced AT	Elevated $\dot{V}E/\dot{V}CO_2$ Reduced O_2 pulse O_2 desaturation Attenuated rise (or fall) in $PetCO_2$ from rest to AT
PAH vs HFrEF	Reduced peak $\dot{V}O_2$ Reduced AT Elevated $\dot{V}E/\dot{V}CO_2$ Reduced O_2 pulse	O_2 desaturation Attenuated rise (or fall) in $PetCO_2$ from rest to AT
PAH vs pulmonary parenchymal or airway disease	Reduced peak $\dot{V}O_2$ Reduced AT Elevated $\dot{V}E/\dot{V}CO_2$ O_2 desaturation	Reduced O_2 pulse Attenuated rise (or fall) in $PetCO_2$ from rest to AT Normal $\dot{V}E$ /MVV, Normal IC
PAH vs hyperventilation syndromes	Reduced peak $\dot{V}O_2$ Reduced $PetCO_2$ at rest	Attenuated rise (or fall) in $PetCO_2$ from rest to AT Reduced AT
PAH vs muscle myopathies or peripheral vascular disease	Reduced peak $\dot{V}O_2$ Reduced AT	Reduced O_2 pulse Elevated $\dot{V}E/\dot{V}CO_2$

Abbreviations: PAH, pulmonary arterial hypertension; CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction; $\dot{V}O_2$, peak oxygen consumption; AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; O_2, oxygen; $PetCO_2$, end tidal carbon dioxide tension; $\dot{V}E$/MVV, the ratio of minute ventilation to maximal voluntary ventilation; IC, inspiratory capacity.

Decision points in screening for pulmonary vascular disease

When using the algorithms developed by Wasserman et al (13), specific branch point values, derived from measures taken during a CPET, can been used to strengthen the likelihood of an accurate diagnosis of a pulmonary vascular limitation to exercise (suggesting PAH). Specific branch point values that have been recommended for PAH include a peak $\dot{V}O_2$ of <83% predicted, $\dot{V}O_2$ at AT of <40% predicted, $\dot{V}E/\dot{V}CO_2$ at the AT of >37.5 and a breathing reserve of >11 L/min. This system has 76% accuracy for the detection PAH, with a sensitivity of 79% and specificity of 75% (164). However, modifications to this system have recently been suggested. These modifications propose that optimum branch point values to identify a pulmonary vasculopathy include peak $\dot{V}O_2$ <58% predicted, $\dot{V}O_2$ at AT < 38% predicted, $\dot{V}E/\dot{V}CO_2$ at the AT > 34 and a breathing reserve of > 8 L/min. The modified system has an accuracy of 85% (79% sensitivity, 88% specificity) for determining a pulmonary vascular limitation to exercise, defined as a PVR >120dynes.sec/cm^{-5} (1.5 Wood units) and a maximum systemic O_2 delivery ≤ 80% predicted (164). It is possible that the inclusion of $PetCO_2$ at AT and desaturation on exercise would further improve the accuracy and specificity of this algorithm.

Assessment of individuals with systemic sclerosis

A recent study explored the ventilatory and gas exchange responses to exercise during a CPET in individuals with systemic sclerosis (297). These investigators used a diagnostic algorithm, which included $PetCO_2$, to determine the likely cause of exercise limitation in individuals with a peak $\dot{V}O_2$ and AT < 75% of predicted. They identified 11 subjects with a pattern typical of a pulmonary vascular limit to exercise, with a $\dot{V}E/\dot{V}CO_2$ ≥ 34 and a decrease in $PetCO_2$ from rest to the AT. Five other subjects were identified with likely left ventricular (LV) dysfunction, but without severe HFrEF. These subjects also had a peak $\dot{V}O_2$ and AT < 75% of predicted, but a normal $\dot{V}E/\dot{V}CO_2$ (<34) and no change, or a rise in $PetCO_2$ from rest to the AT. Although haemodynamic assessment was not undertaken to confirm the diagnosis in this study, these findings suggest that gas exchange analysis during a CPET may help discriminate between LV dysfunction and a pulmonary vasculopathy in subjects with systemic sclerosis, similar to the findings previously reported in patients with established PAH.

2.4.3 Exercise testing to assess central haemodynamics

2.4.3.1 Central haemodynamics in PAH

Several studies have investigated central haemodynamic responses during exercise in subjects with PAH. These studies, regardless of methodology or exercise intensity, have consistently identified an abnormal increase in PAP (28, 130, 298, 299), an attenuated rise in SV (130, 132), chronotropic impairment (34, 300), reduced CO and a high PVR (27, 28, 76) during, or at peak exercise.

2.4.3.2 Sensitivity for change following intervention

Evaluating PAP, PVR, CO, SV and mixed venous O_2 saturation during exercise appears to have greater sensitivity for demonstrating benefits of pharmaceutical therapy than measurement of these indices at rest (301).

2.4.3.3 Simultaneous haemodynamic and gas exchange analysis

A limited number of studies have utilised simultaneous haemodynamic monitoring and gas exchange analysis during exercise in PAH. These studies have demonstrated significant correlations between PAP and $\dot{V}E/\dot{V}O_2$, and PAP and $\dot{V}E/\dot{V}CO_2$ (302), peak CO and peak $\dot{V}O_2$, and an inverse relationship between PVR and peak $\dot{V}O_2$, and PAP and peak $\dot{V}O_2$ (303).

2.4.3.4 Invasive exercise testing for differential diagnosis

Individuals with LV dysfunction demonstrate reduced CO and exercise capacity, and the exercise intolerance and symptoms reported by these individuals are similar to those reported in PAH (203). It is difficult to differentiate these conditions without advanced haemodynamic assessment. However, differentiation between LV dysfunction and PAH is important, because there are fundamental differences in the management of these conditions. Some PAH specific medications may be detrimental for patients with LV dysfunction (1).

In individuals with LV systolic dysfunction, in contrast to PAH, LV emptying is impaired and left atrial pressure and PAWP are elevated (304-306). Pulmonary artery pressure increases due to back pressure arising from the pulmonary

circulation generated by elevated left atrial pressure. In individuals with LHF but preserved systolic function, delayed or impaired relaxation of the LV results in an elevated left atrial pressure, PAWP, and PAP. In both LV systolic and diastolic dysfunction, PVR remains low (146). Therefore, differentiation between individuals with LV dysfunction and PAH can be made by examining PAWP or left atrial pressure, and PVR. This assessment has traditionally been performed at rest.

However, recently published studies have described the utility of invasive exercise testing in identifying individuals who have a normal PAWP at rest but demonstrate exercise-induced LV diastolic dysfunction. These individuals have an abnormal rise in PAP on exercise related to an excessive increase in PAWP, demonstrating delayed or impaired LV relaxation during exercise (76, 77). In contrast, individuals with PAH demonstrate a small rise in PAWP during exercise, and the elevated PAP associated PAH is related to impaired vascular dilatation, distensibility and patency, within the pulmonary circulation (28, 302, 303). These differences on exercise in individuals with PAH and LV dysfunction allow for accurate diagnosis of the cause for the elevated PAP and can direct therapy (27, 76, 77).

2.4.3.5 Safety of invasive exercise testing

Right heart catheterisation is associated with a very low incidence of serious complications. A review published in 2006 (307) reported that the combined incidence of death or serious adverse events related to RHC, in patients with PAH, was 1%. The adverse events reported included haematoma at the insertion site, pneumothorax, self limiting vago-vagal events or cardiac arrhythmias, and hypotension related to the administration of vasoactive agents. The mortality rate was 0.05% with only 2 of the 4 deaths being clearly associated with RHC. In studies of exercise testing with a RHC insitu in PAH, no adverse events have been reported (27, 28, 76, 302, 303).

Summary

Limited evidence suggests that measuring central haemodynamics during exercise is feasible and appears to be more sensitive to changes following therapy than measuring haemodynamics at rest. Invasive exercise testing can differentiate between PAH and exercise-induced LV dysfunction. Invasive exercise testing carries no greater risk than the risk associated with the component parts of the

assessment. The risk of serious adverse events associated with RHC or CPET is small.

2.4.4 Six-minute walk test (6MWT)

This section describes the literature relating to the encouraged and unencouraged 6MWT in individuals with PAH, and a brief discussion of its use in HFrEF and COPD.

The 6MWT measures the distance an individual can walk during a period of 6 minutes (i.e. 6MWD). At rest, during the test, and following test completion, a number of variables can be monitored to explore exercise responses, including SpO_2, HR, systemic blood pressure and symptom scores. With the development of portable metabolic carts, it is now possible to also measure ventilatory and gas exchange responses during a 6MWT. The additional data derived from metabolic carts are mostly utilised for research purposes, and rarely available in clinical practice. The minimum requirements for a 6MWT include a level, unobstructed, indoor corridor of at least 30m, a set of markers to identify the turning point and a timer (308). For clinical populations safety measures need to be taken into consideration and access to a sphygmomanometer, pulse oximeter, supplemental oxygen, and medical assistance should be available depending on the population being tested. Test repetition has been shown to result in a clinically relevant increase in 6MWD on a second test (309, 310). Therefore, in order to accurately measure the effect of an intervention, two 6MWTs are required on initial assessment.

Despite some limitations, including the effect of lower limb musculoskeletal dysfunction on performance, the variation in test conduct, and the effort dependent nature of the test, the 6MWT is believed to provide a better index of the capacity of an individual to perform daily activities than an incremental CPET (31). Furthermore, there is a closer correlation between 6MWD and formal measures of QoL than between peak $\dot{V}O_2$ and QoL in individuals with COPD (311). Due to the ease of administration, patient tolerance of the test, and better reflection of activities of daily living, the 6MWT is thought to be the test of choice (over a two-minute walk test, a 12-minute walk test, or shuttle walk test) when using a functional walk test for clinical or research purposes (31).

2.4.4.1 Encouraged 6MWT

Since 2002, the majority of 6MWTs described in studies of individuals with pulmonary conditions have been performed according to the American Thoracic Society guidelines (308). These guidelines recommend standardised instructions prior to the test and standardised encouragement at intervals throughout the test, in order to optimise and standardise test performance. In healthy individuals and those with mild functional limitation, the encouraged 6MWT test is a submaximal test with exercise intensity limited by the mechanical constraints associated with walking (312, 313). However, similar HR and ventilatory responses during an encouraged 6MWT and a CPET have been described in individuals with PAH (76, 314), HFrEF and COPD (315-317), suggesting the encouraged 6MWT is a high intensity exercise test in these conditions. In individuals with a proven, or likely, cardiopulmonary disorder continuous ECG monitoring and medical supervision are advocated for high intensity exercise tests (318-320). This raises doubt about the safety of the encouraged 6MWT in individuals with PAH and is an important issue that needs further consideration.

2.4.4.2 Unencouraged 6MWT

The majority of clinical trials investigating pharmaceutical therapy in PAH have employed an unencouraged 6MWT as a primary outcome measure. An unencouraged test generally involves asking the patient to walk as far as they can in a six minute period, without any form of encouragement during the test. The rationale behind the use of an unencouraged, rather than encouraged, 6MWT as an outcome measure in clinical trials in PAH has not been explained. However, historically, individuals with PAH were considered at high risk of adverse outcomes on exertion, especially in the period before effective pharmaceutical therapies were available (41). Consequently, an unencouraged 6MWT may have been perceived as potentially safer than an encouraged 6MWT in this population.

2.4.4.3 Six-minute walk test in LHF

Six-minute walk distance has been shown to correlate with NYHA functional class, peak work rate, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ in HFrEF (33). The 6MWD also has demonstrated utility for prognosis in advanced HFrEF (321-323). However, the CPET has better predictive value for survival in HFrEF, especially in individuals with

well preserved functional capacity (284). A review of randomised controlled trials of pharmaceutical therapy for HFrEF between 1988 and 2004, that utilised the 6MWD as an outcome measure, reported that the 6MWT had little prognostic or discriminative value in individuals without advanced cardiac disease (324). Furthermore, serial monitoring of changes in 6MWD do not necessarily reflect changes in peak $\dot{V}O_2$ or functional class in HFrEF (325). These findings suggest that the 6MWT has limited utility in the assessment of individuals with HFrEF.

2.4.4.4 Six-minute walk test in COPD

The 6MWT has been extensively studied in COPD. It has demonstrated reproducibility after one practice test (326, 327) and is responsive to change in health status (31). Furthermore, in COPD, there is an association between 6MWD and HRQoL, maximum exercise capacity and mortality (31, 32, 328, 329). In COPD, the maximum $\dot{V}O_2$ during a 6MWT has been reported as equal to the peak $\dot{V}O_2$ on a CPET, although the ventilatory equivalents and RER may be lower (316). The 6MWT is considered to elicit the maximum sustainable exercise in this population (330). As previously reported, walking field tests in COPD, such as a 6MWT, are sensitive to exercise O_2 desaturation and 6MWD is used to evaluate the response to interventions including pulmonary rehabilitation and the response to supplemental oxygen (280).

2.4.4.5 Six-minute walk test in PAH

The 6MWD has been used as a primary endpoint in many pharmaceutical trials (108, 331-333) and more recently as an endpoint in exercise training trials in PAH (15, 16, 42, 106, 272, 334). As such, the 6MWT is one of the most frequently reported, best established and most commonly utilised tests in randomised controlled trials and the clinical management of patients with PAH.

Aerobic capacity

Six-minute walk distance has been shown to provide a valid estimate of peak $\dot{V}O_2$ in individuals with PAH (33-35) and is more sensitive to change with pharmaceutical therapy than peak $\dot{V}O_2$ (35, 51).

Six minute walk distance and cardiac function in PAH

In PAH, the 6MWD has been shown to correlate with O_2 pulse (r=0.57) (34). It has been reported that 6MWD is positively related to CO, SV, mixed venous O_2 saturation and chronotropic response (determined as peak HR-resting HR) and is negatively related to PVR in both iPAH and nonidiopathic PAH (133). In this study by Provencher et al (133), stepwise regression analysis demonstrated positive associations between SV and 6MWD (r=0.52 and 0.65 in iPAH and nonidiopathic PAH, respectively), and chronotropic response and 6MWD (r=0.56 and 0.49 in iPAH and nonidiopathic PAH, respectively). Furthermore, changes in 6MWD after therapy have been shown to be closely linked to changes in cardiac function (34, 35, 133). Change in 6MWD following PAH specific pharmaceutical therapy has a positive relationship with improvements in SV and chronotropic response, and a negative relationship with changes in right atrial pressure (r^2 ranging 0.13-0.15) (133). It has been postulated that an increase in 6MWD in response to pharmaceutical therapy in subjects with PAH, reflects unloading of the RV (335).

Six minute walk test and survival in PAH

In PAH, a direct association between 6MWD and survival has been demonstrated (3, 34, 74, 97). Absolute and threshold values of 6MWD after treatment have been shown to reflect long term outcomes in PAH (34, 110, 133). However, this has not been a universal finding with some studies demonstrating statistically significant increases in 6MWD which were not reflected in changes in survival or clinical deterioration (108). Similar to the findings in COPD (336, 337), the 6MWT is associated with greater O_2 desaturation than a cycling test (314). Oxygen desaturation during an encouraged 6MWT has been shown to be predictive of mortality in PAH (184). A 26% increase in risk of death for each percent decrease in SpO_2 has been described in patients with PPH, in functional class II or III, who were tested prior to the initiation of pharmaceutical therapy. This risk was not changed by adjustment for right atrial pressure, mPAP, CO, PVR or functional class (184).

Six-minute walk work

Measures derived from the 6MWT include six-minute walk work (6MWW), the product of 6MWD and body weight. In subjects with COPD, 6MWW has been shown to correlate more strongly with disease severity and to have greater sensitivity and specificity for low exercise capacity than 6MWD (338).

Similar to the findings in individuals with COPD (339), a better correlation between 6MWW and peak $\dot{V}O_2$ than 6MWD and peak $\dot{V}O_2$ has been described in individuals with PAH (35, 314). This suggests that adjusting for body weight increases the utility of the 6MWT in estimating peak $\dot{V}O_2$ and measuring aerobic capacity in PAH.

Utility

For patients with severe PAH, a 6MWT is likely to be the test of choice for determining functional capacity, prognosis and response to therapy. The 6MWT was tolerated in a population of patients who were unable to undergo a CPET due to severe PAH, and 6MWD correlated with baseline CO, total pulmonary resistance and mean right atrial pressure in this population (34).

As previously reported, the simplicity of the 6MWT, and the widely utilised standardised testing procedure, may support its better utility, than a CPET, in multicentre trials and in centres with limited experience in conducting a CPET (35). However, there is some concern over the safety of an encouraged 6MWT in individuals with PAH and in the utility of the 6MWT in individuals with well preserved functional capacity (37).

Ceiling effect

A ceiling effect for 6MWD, limiting the utility of the 6MWT in subjects with preserved functional capacity, has been described in studies in individuals with HFrEF (36) and PAH (37). Because of the concern that a ceiling effect may influence the outcome in clinical trials of pharmaceutical therapy for PAH, a 6MWD of >450m has been an exclusion criterion in the majority of randomised controlled trials in PAH (340). However, setting an absolute 6MWD value may exclude individuals with severe haemodynamic impairment, especially in younger, taller subjects with a lower body mass index (BMI) (340). Referencing the 6MWD to predicted values (which account for age, gender and height) may be more appropriate than using the absolute value (107), although care needs to be taken in selecting the reference equations to ensure the predicted values are appropriate for the population being studied (313, 341, 342).

The role of percent predicted 6MWD in determining prognosis in PAH has recently been explored (107). Percent predicted 6MWD was shown to be predictive of all-cause mortality at baseline and following treatment, but there was no difference in

the predictive value between absolute and percent predicted 6MWD. These findings suggest that there is no advantage in evaluating 6MWD as percent predicted for determining prognosis in PAH.

Summary

The 6MWT has demonstrated utility for the estimation of aerobic capacity, identification of reduced exercise capacity and for determining prognosis in PAH. However, in individuals with PAH with well preserved functional capacity the use of 6MWD to identify reduced exercise capacity or response to therapy may be limited by a ceiling effect.

Encouraged 6MWTs in PAH may remain in the field of research where comprehensive monitoring is available during the test, whereas, in clinical practice and in clinical trials, it may be more appropriate to employ the unencouraged 6MWT. However, in individuals with better functional class, other exercise tests may be more appropriate, especially to determine the outcome of an intervention.

2.4.5 Other tests of exercise response and exercise capacity

The following section describes other exercise tests that have been reported in PAH and that may have utility for determining exercise capacity and response to therapy in PAH, especially for individuals with well preserved functional capacity.

2.4.5.1 Constant work load tests

Constant work load tests (CWLT) are commonly performed on a treadmill or a cycle ergometer. Continuous gas exchange analysis allows determination of change in measures of ventilation and gas exchange, although, if the outcome to be analysed is endurance time only, continuous gas exchange is not required. A set workload is determined, and after a rapid transition from rest (or unloaded cycling in a cycle ergometer test) to the exercise workload, a CWLT involves maintenance of a constant workload until symptom-limitation, or for a predetermined time. The workload can be set below or above the AT. That is, a CWLT may be performed as a high intensity test above the AT, to symptom-limitation, or low-moderate intensity test below the AT, with a predetermined time limit (typically 6-8 minutes) to assess measures of physiological function, such as $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, IC and HR, at the same workload pre- and post-intervention (343, 344). The intensity of the test

chosen will depend on the required outcomes and the patient population to be studied. In order for endurance time on a high intensity CWLT to be informative, the workload used must be set above the AT (276) to prevent steady state exercise. A CWLT must be preceded by a maximal CPET in order to determine an appropriate workload above, or below, the AT. Commonly used exercise intensities for a high intensity CWLT are between 75 and 80% peak $\dot{V}O_2$ (276).

Primary outcome measures obtained during a CWLT include endurance time in high intensity CWLTs and assessment of ventilatory and haemodynamic responses, gas exchange kinetics and symptoms, during both high and low-moderate CWLTs. In low-moderate intensity CWLTs, comparison of measures at the same time during the initial test and a repeat test (isotime) is used to determine response to interventions or disease progression (343, 345, 346). Constant work load tests have demonstrated reliability and reproducibility (347, 348). Continuous 12 lead ECG and intermittent blood pressure monitoring during the CWLT may reduce the risk of adverse events.

Constant work load tests in COPD and cardiovascular disease

Constant work load tests have been utilised in the assessment of exercise capacity and response to intervention in conditions such as COPD (343, 349) and cardiovascular disease (350). It has been suggested that they may provide better characterisation of exercise intolerance, have better prognostic power and better demonstrate the effects of therapeutic interventions than a maximal CPET (276, 351) or 6MWT (343, 345, 352). In particular, measurements of endurance time, symptoms and CPET variables such as $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, IC and HR at 'isotime' have been demonstrated as more sensitive than peak $\dot{V}O_2$ and 6MWD in the evaluation of therapeutic interventions in COPD (343, 351). Large changes in time to exhaustion on a CWLT have been demonstrated in the absence of a significant increase in maximum exercise capacity on a CPET following pharmaceutical therapy or exercise training in COPD (343, 352). However, the minimal clinically important distance for this test has not been established (353). Furthermore, large variability in the change in endurance time (354), and difficulties in the prediction of the best work load for a post-intervention test, mean the high intensity CWLT does not always accurately reflect the physiological changes associated with a particular intervention in COPD (355).

Measuring $\dot{V}O_2$ kinetics during a low-intensity submaximal CWLT on a treadmill in individuals referred for assessment for possible cardiac transplantation provides complementary prognostic information to that determined on a CPET (346). Additionally, in individuals with HFrEF, the slope of $\dot{V}E/\dot{V}CO_2$ determined during a moderate-intensity CWLT has been shown to correlate significantly with the slope of $\dot{V}E/\dot{V}CO_2$ determined on an incremental CPET (356). This finding suggests the relationship between $\dot{V}E$ and $\dot{V}CO_2$ is consistent during an incremental and a CWLT and is independent of the mode of exercise testing in this condition.

Constant work load tests in PAH

There are few studies reporting the CWLT in PAH. Riley et al (43) studied individuals with PPH who underwent two CWLTs at a workload equivalent to the $\dot{V}O_2$ at the AT plus 30% of the difference between the AT and the peak $\dot{V}O_2$. These authors described abnormal $\dot{V}O_2$ kinetics in subjects with PPH, in relation to healthy controls, both during exercise and recovery. In another study, a moderate intensity CWLT was used to investigate dead space ventilation in individuals with pulmonary vascular disease associated with systemic sclerosis, systemic lupus erythmatosus or multiple small pulmonary emboli (299). Further, a series of moderate intensity CWLTs, of increasing intensity, each for a duration of 7 minutes, has been used to study the ventilatory response to exercise in subjects with PAH secondary to Eisenmenger's syndrome, or PPH, before and following heart-lung transplantation, and compared with healthy controls. In this study the slope of $\dot{V}E/\dot{V}CO_2$ during a moderate intensity CWLT was; (i) highly reproducible, (ii) significantly higher in subjects with pulmonary hypertension than the healthy controls, and, (iii) returned to normal at 4-6 weeks following heart-lung transplantation (169).

Safety of constant work load tests

No adverse events have been reported in association with high or low-moderate intensity CWLTs in the studies performed in subjects with COPD and HFrEF (343, 345, 346, 356) or the few in individuals with PAH (43, 169, 299).

Summary

There are insufficient data to reach any conclusions about the role of the CWLT in the assessment of PAH. However, in light of the demonstrated utility of this test in other conditions, this test warrants further investigation as a submaximal test that has the potential to determine physiological changes over time and following therapeutic intervention in individuals with PAH.

2.4.5.2 Incremental shuttle walk test

The incremental shuttle walk test (ISWT) is a graded, externally paced test which involves walking around a 10m course at a pace dictated by a standardised recording. The test is limited to 12 stages, of one minute per stage. At each minute the walking speed is increased and the test ends when the subject is unable to achieve the required pace, terminates the test due to intolerable symptoms, or the 12 stages of the test have been completed. The distance walked during the test is the primary outcome measure (357). Monitoring of HR, SpO_2, and symptom scores can be performed prior to and during the test, and at test termination. Portable metabolic carts allow continuous gas exchange analysis during the test, although this is usually retained for research purposes and is not generally used in clinical practice.

The incremental shuttle walk test in COPD

In individuals with COPD, the ISWT has been shown to predict survival (358), post-operative morbidity (359), acute respiratory exacerbations (360) and response to therapy (361, 362). In stable COPD, the distance covered on the ISWT has been shown to correlate with peak $\dot{V}O_2$, peak $\dot{V}CO_2$ and peak $\dot{V}E$ during the ISWT, and peak $\dot{V}O_2$ on a 6MWT (317, 363). In individuals recovering from an acute exacerbation of COPD (364), and in individuals with stable, moderate to severe COPD (317) there is no difference in HR, ventilatory response or symptoms at end exercise between the ISWT and an encouraged 6MWT. In contrast, the ISWT has been shown to elicit greater physiological responses than an unencouraged 6MWT in individuals with stable COPD (363).

While responses are similar at test end, the ISWT and 6MWT have been consistently shown to elicit different physiological response patterns during the test.

These differences in physiological response are similar to those described in the comparisons between a CPET and 6MWT (317, 363). Incremental tests, such as the ISWT and CPET, induce a linear increase in HR (317, 363), $\dot{V}O_2$ and $\dot{V}E$ (363), in contrast to a 6MWT, where HR, $\dot{V}O_2$ and $\dot{V}E$ plateau from the third minute into the test (363).

The incremental shuttle walk test in PAH

One study, reporting the ISWT, has been described in individuals with PAH (279). In this study, the ISWT results were compared with results of a CPET performed on a cycle ergometer. In this study, the ISWT was associated with a lower peak exercise values of $\dot{V}O_2$, $\dot{V}CO_2$, O_2 pulse, leg fatigue and SpO_2 compared with the CPET (279). These findings are in contrast to the results of studies in COPD in which responses are generally similar on an ISWT and CPET (317, 363). The reasons for the lower responses during the ISWT, compared with the CPET, in the study in individuals with PAH, are uncertain. There were no reported adverse events associated with the ISWT in the study of individuals with PAH (279). Due to limited data, no conclusions can be made regarding the role of the ISWT in PAH.

2.4.5.3 Treadmill tests in PAH

The Naughton treadmill test has been used to measure the treatment effects of Sildenafil on exercise capacity in PAH (100). In this study, exercise time improved 44% following six weeks of therapy. This improvement in exercise time occurred in association with an improvement in cardiac index, PASP and QoL, demonstrating that, in this study, the Naughton treadmill test was sensitive in detecting clinically important changes in exercise capacity in PAH following therapy.

Evaluation of metabolic equivalents

The utility of the Naughton-Balke treadmill test, and derived metabolic equivalents (MET), as an alternative to the 6MWT in assessing exercise capacity and outcomes following intervention in individuals with PAH, with a 6MWD >400m, has recently been explored (365). The findings of this study suggest that METs, derived from a treadmill test, are more sensitive in detecting changes in exercise capacity following PAH specific pharmaceutical therapy (over a one-year period) than 6MWD. In this study, the Naughton-Balke treadmill test was found to be reliable and reproducible,

and to have efficacy in following clinical changes in individuals with PAH with well preserved functional capacity.

The Naughton-Balke treadmill test, and derived METs, has also been shown to have value in determining reduced exercise capacity, abnormal haemodynamics and poorer outcome in individuals with PAH, over time. In a longitudinal study over 24 years, for each 1-MET decrease in exercise capacity there was a significant increase in mortality (366). However, further work is required to determine the role of treadmill test derived METs in PAH.

2.4.5.4 Exercise echocardiography in PAH

Echocardiography at rest

Echocardiography can be used to provide an estimate of PASP at rest (367) and to evaluate systolic and diastolic right ventricular and left ventricular function (63). There are important limitations, however, that prevent echocardiography from providing a definitive diagnosis of PAH. These limitations include variations in the methodologies used to estimate right atrial pressure, and inaccuracies in the determination of PASP (71, 368, 369) with the magnitude of difference between echocardiographic estimates and measured PASP as high as 38mmHg (370). In one study, echocardiography underestimated PASP by >20mmHg in 31% of the patients studied (371).

To determine the PASP, using resting Doppler ultrasound in the studies cited, tricuspid regurgitation (TR) jet velocities were measured and estimated PASPs were determined using the modified Bernoulli equation. That is, the peak velocity of the TR jet is determined from the systolic pressure drop from right ventricle to right atrium and the change in pressure = $4V^2$ (367, 370) . This measure was used, in conjunction with echocardiographic estimation of right atrial pressure (RAP) based on inferior vena cava (IVC) size and collapsibility to estimate the PASP using the equation PASP = change in pressure + RAP (367). In the study by Rich et al (368), the criteria for estimating RAP were: RAP = 0-5mmHg when the IVC diameter was <17mm and collapsibility was >50%; 5-10mmHg when the IVC diameter was <17mm and collapsibility was < 50%; 10-15mmHg when the IVC diameter was >17 mm and collapsibility was <50%; and 15-20mmHg when the IVC diameter was >17mm with an absence of any collapsibility. In other studies RAP was determined

as a standardized value of 5mmHg (372), 10mmHg (373), or 14mmHg (371), or was estimated based upon the vertical height of the jugular venous pulse (63, 71), or was measured during right heart catheterisation (370).

Further limitations of echocardiography include difficulties in excluding pulmonary venous hypertension or high CO states. Pulmonary venous hypertension can only be excluded if accurate measures of left atrial pressure, or PAWP, can be made and exclusion of high CO states requires accurate measurement of CO. Recent advances in echocardiographic technology have enabled estimates of CO, PAWP and PVR. However, measurement of CO on echocardiogram has poor accuracy (367) and the correlation coefficients for PAWP and PVR are only moderate (0.65 and minus 0.6 respectively) (374).

Exercise echocardiography

Along with the limitations of echocardiography at rest, there are significant limitations in the assessment of central haemodynamics, via echocardiography during exercise. Age- and gender-related norms have not been fully established and exercise measures of CO and PAWP have not been validated (367). Furthermore, the definition of pulmonary hypertension on echocardiogram is variable. According to WHO recommendations (372), a resting PASP between 40-50mmHg is indicative of pulmonary hypertension. However PASP >35mmHg (373, 375) or >40mmHg (376). One of the problems with exercise echocardiography has been the difficulty in obtaining good quality images during exercise. In some studies, PASP has been estimated immediately (within 60 seconds) following upright treadmill exercise (373, 375). Other studies have used echocardiography images obtained during exercise using a supine cycle ergometer (376, 377). In the studies cited above, post-upright exercise (373, 375) or Doppler images obtained during supine exercise (376, 377) were used to determine TR velocity and PASP based upon the modified Bernoulli equation, with an standardized estimate of RAP as 5mmHg (375, 376) or 10mmHg (373).

Exercise echocardiography and screening for pulmonary hypertension

Despite the limitations of exercise echocardiography, there are a number of reports in the literature which have utilised exercise echocardiography as a screening tool for pulmonary hypertension in subjects with exertional dyspnoea (375, 378). Studies of exercise echocardiography in the evaluation of individuals at risk of PAH have

been performed almost exclusively in subjects with scleroderma. In these studies, a significant proportion of individuals with scleroderma with a normal PASP on resting echocardiogram (PASP <30mmHg) have developed a marked increase in PASP during exercise. Pulmonary hypertension, detected on exercise echocardiogram in individuals with scleroderma, has been reported in 46% (375), 59% (373) or over 60% (379) of individuals, depending on the PASP criterion that was used. Correlations between PASP and exercise capacity suggests a relationship between exercise impairment and pulmonary hypertension in this population (375). Furthermore, up to 81% of individuals with scleroderma, identified with pulmonary hypertension on rest or exercise echocardiography, have been shown to have evidence of PAH on RHC, at rest (378), or as previously defined, on exercise (51). In one study of asymptomatic carriers of the abnormal gene mutation associated with PAH (BMPR2), age 6-16 years, an abnormal rise in PASP (>40mmHg) on exercise occurred in 14 out of 52 individuals (376). All 14 individuals with an abnormal rise in PASP on exercise shared the BMPR2 genetic abnormality with the four individuals who had PAH at rest. Only two out of 27 individuals with a normal rise in PASP during exercise also shared this abnormality. These findings suggest that exercise echocardiography may be a valuable screening tool which identifies an abnormal pulmonary vascular response during exercise in at individuals with increased risk for PAH, and warrants further investigation.

Safety of exercise echocardiography

Echocardiography laboratories around the world, known to perform stress echocardiography, were surveyed between 1998 and 2004 (380). Reports were available for 24,599 stress echocardiograms. Life threatening events (acute myocardial infarction, n=1; sustained ventricular tachycardia, n=2; and cardiac rupture n=1) occurred in 4 patients (event rate 1 in 6,574). From the results of this study, it appears that exercise echocardiography is associated with a very low incidence of serious adverse events in the general patient population. However, there are no specific reports regarding the safety of exercise echocardiography in PAH. No adverse events have been reported in the screening studies that included exercise echocardiography.

2.4.6 Testing muscle strength

Specific studies of skeletal muscle strength in PAH have demonstrated weakness in the forearm, quadriceps and respiratory muscles (16, 38, 39, 193). Adequate muscle strength is required for effective performance of activities of daily living (381, 382) and the evaluation of muscle strength is important in determining the extent to which muscle weakness contributes to functional impairment. Tests of muscle strength are also important for identifying an appropriate exercise training intensity, to assess the response to exercise therapy and to determine any changes in muscle strength over time, with increasing age or disease progression (383). This section describes the use of muscle testing in the assessment of muscle strength in HFrEF, COPD and PAH.

2.4.6.1 Measurement techniques used to determine muscle strength

Voluntary muscle strength can be measured using isometric, isoinertial or isokinetic dynamometry (384, 385). Isometric dynamometry measures the amount of force that can be exerted against an immovable object and is used to identify the maximal voluntary contraction (MVC). Isokinetic dynamometry measures the amount of force that can be generated while moving a limb around a joint at constant velocity and uses specialised devices such as the Cybex and Kin-Com systems (385). Isoinertial dynamometry measures the maximum weight that can be lifted over a range of movement using a constant resistance to motion (385). The one repetition maximum (1RM) exercise test is a form of isoinertial dynamometry. Dynamometry has been considered the gold standard for evaluating muscle strength, however, specialised equipment and personnel are needed to perform isometric and isokinetic dynamometry and therefore these assessments are often not available in clinical settings (386, 387). Furthermore, assessments employing isometric and isokinetic dynamometry isolate single muscles or muscle groups. Isolated single limb muscle testing does not necessarily represent the movement patterns used in everyday activities or in typical exercise regimes (386). In contrast, the 1RM test assesses muscle strength using movement patterns and co-ordinated muscle group contractions that occur in everyday activities.

One repetition maximum test

In clinical practice, and in a number of exercise intervention studies in a variety of populations, a 1RM test has been employed to determine baseline muscle strength and changes induced by training (16, 38, 40, 388, 389). A 1RM test involves active contraction of a muscle group, or muscle groups, through full range, lifting increasingly heavy weights until the greatest weight that can be lifted, with good technique, has been determined. The greatest weight lifted is the measure of muscle strength. From this maximum weight, intensities for exercise training can be derived. An advantage of employing the 1RM test, for determining muscle strength, is that the same equipment is used for testing and training and this equipment is readily available in most clinical settings. The 1RM test has demonstrated reliability in evaluating maximal strength and is accepted as an accurate tool for assessing muscle strength (386, 387).

Muscle strength testing in LHF and COPD

Muscle strength testing and resistance training have been widely utilised, for many years, in the management of reduced muscle strength and functional impairment in individuals with HFrEF. A comprehensive body of literature is available that describes the safety and efficacy of resistance testing and exercise in this population. Numerous studies describe the efficacy of the 1RM in the assessment of muscle strength and change with resistance training, and a low rate of adverse events during these studies. These studies have been summarised in a number of comprehensive reviews (44, 390-392).

Studies of strength assessment and training in COPD also report reduced muscle strength and improvements in strength with resistance exercise, and few adverse events (393, 394).

Muscle strength testing in PAH

Concerns regarding the perceived increased risk of adverse events related to the changes in HR, SBP and venous return associated with heavy resistance exercise have resulted in limited investigation of this exercise modality in PAH (41). However, recent studies have investigated upper limb muscle strength in subjects with PAH, using a 1RM muscle test (38) or MVC and magnetic stimulation (39). Furthermore, two studies investigating the efficacy of muscle strength training in PAH have

utilised the 1RM, or MVC, to determine the strength of lower limb muscle groups and to set training intensity (16, 42). Preliminary evidence demonstrates that the 1RM test is sensitive in identifying reduced muscle strength (38) and is responsive to improvements in muscle strength following resistance exercise training in PAH (16, 42).

Safety of maximal resistance testing

A study of more than 26,000 maximal dynamic strength assessments, performed on healthy adults, reported no cardiovascular events during testing (383). In individuals with cardiac disease, who are considered at low risk for adverse events during exercise, and in individuals with controlled hypertension, there have been no reports of major adverse cardiovascular events during resistance testing or training (44). The incidence of adverse events in cardiac patients considered to be at moderate to high risk for an adverse outcome during exercise is low and the 1RM test is condoned for this population by The American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism (44), provided good clinical judgement and close monitoring is employed during 1RM testing. No adverse events associated with maximum strength testing have been reported in studies in PAH (16, 38, 39, 42).

Summary: Strength testing in PAH

Both laboratory based dynamometry and 1RM tests can determine muscle strength. The equipment required to perform a 1RM test is generally available in clinical practice and can be used for both strength testing and for muscle training. In a small number of study subjects with PAH, maximal muscle strength tests have been performed without adverse events. However, further evaluation of muscle strength testing in PAH is required before the safety and efficacy of strength testing can be confirmed for this population.

2.4.7 Summary: Exercise testing in PAH

An incremental CPET performed on a cycle ergometer, or a treadmill, identifies and quantifies reduced exercise capacity and exercise abnormalities in PAH. Assessment of central haemodynamics during exercise identifies pulmonary vascular abnormalities and right ventricular dysfunction associated with PAH.

Differential diagnosis between PAH and exercise-induced LV diastolic dysfunction informs appropriate therapy.

The 6MWT identifies reduced exercise capacity and is responsive to change following therapeutic intervention in individuals with PAH and reduced functional capacity. However, a ceiling effect may limit the utility of the 6MWT in individuals with well preserved functional capacity. The encouraged 6MWT is a high intensity exercise test in individuals with PAH. The safety of an encouraged 6MWT in this population has not been described. An unencouraged 6MWT detects impaired exercise capacity and is responsive to change associated with therapeutic intervention in PAH, and is the test of choice in clinical practice.

Both CPETs and 6MWTs are useful tests in determining prognosis in PAH. However, for evaluating the response to therapeutic interventions, a CWLT may be have greater sensitivity for determining a response to therapy in PAH, similar to other populations. This exercise test requires further evaluation and there are too few data to make any conclusions about the utility of this test in PAH.

A treadmill test, using the Naughton-Balke protocol and derived METs, appears to have potential in measuring exercise capacity, response to therapy and prognosis, especially in individuals with PAH who have well preserved functional capacity. However, the rapid progression of workload used in the Naughton-Balke protocol is likely to be inappropriate for patients with PAH and a more conservative ramp exercise test protocol, with careful selection of the increment, is likely to be more appropriate in this population.

There are limited data on the ISWT or ESWT in PAH. The safety of these tests needs to be determined in PAH. The ISWT is a maximal, externally paced, exercise test and continuous 12 lead ECG monitoring and intermittent systemic blood pressure measurement are appropriate during such a test but are difficult, or impossible, during an ISWT. An ESWT cannot be performed without a prior ISWT.

Exercise echocardiography is a useful tool for screening at risk populations but should not be used for diagnosis of PAH.

The CPET, unencouraged 6MWT and exercise echocardiography appear to be safe for patients with PAH, although a CPET is contraindicated for patients with very poor

functional limitation, exertional syncope or chest pain or a history of malignant arrhythmias.

In clinical practice, and for research purposes, a 1RM test is effective in determining muscle strength and change with therapeutic intervention. However, the safety and utility of this test in PAH has not yet been determined.

2.5 Exercise-induced pulmonary arterial hypertension

This section describes the potential for exercise testing to identify early or mild changes in the pulmonary circulation that are consistent with the vascular abnormalities described in PAH.

2.5.1 Exercise testing – potential role in early diagnosis of PAH

There has recently been a great deal of interest in developing strategies to facilitate the early diagnosis of PAH. This interest has been encouraged by the development of pharmaceutical therapies that improve outcome for patients with PAH, especially as these treatments have been shown to be more effective for individuals with better functional capacity than for individuals with symptoms at rest (2, 3). There is an active research interest in exercise testing as a potential means of facilitating the early diagnosis of the PAH (1).

An early study of exercise testing in individuals with exertional dyspnoea and possible PAH was published by James et al (395) in 2000. This study reported exercise haemodynamics in 13 patients with exertional dyspnoea that could not be explained by conventional pulmonary and cardiac investigations. Resting haemodynamics were abnormal in six, and nine of the 13 subjects displayed a marked elevation in PAP during exercise. In this study, differentiation of the cause of increased PAP was not possible due to a lack of PAWP and PVR data. However, the study demonstrated that invasive measurement of central haemodynamics during exercise is feasible and may help to identify exercise abnormalities in individuals with apparently normal haemodynamics at rest, and otherwise unexplained dyspnoea.

2.5.1.1 Exercise-induced pulmonary arterial hypertension

More recently, Tolle et al (27) investigated central haemodynamics and simultaneous gas exchange analysis in patients who were referred for investigation of unexplained dyspnoea. This study demonstrated that, in selected patients in whom there was a clinical suspicion of pulmonary hypertension and mPAP ≤25mmHg at rest, mPAP >30mmHg and PAWP <20mmHg on exercise was associated with clinically important exercise abnormalities, including reduced CO at peak exercise and reduced exercise capacity. These individuals were diagnosed with a clinical condition called exercise induced PAH (EIPAH). Exercise-induced pulmonary arterial hypertension is considered to represent part of the spectrum of pulmonary vascular diseases (78).

In a study reported by Condliffe et al (2), which used invasive exercise testing to identify EIPAH, follow up of the study subjects over time demonstrated that a significant proportion of individuals with EIPAH progress to PAH, and/or die early from RHF (2). This study by Condliffe et al reported disease progression to PAH in 19% (8/42), and mortality due to PAH and/or right heart failure in 10% (4/42) of individuals with scleroderma and EIPAH at initial assessment over a period of 3 years. There are also preliminary data demonstrating that individuals with EIPAH respond to PAH specific pharmaceutical therapy with improvements in central haemodynamics and exercise capacity following therapy (77, 396).

Further evidence for the potential diagnostic capacity of invasive haemodynamics during exercise in at risk individuals with normal haemodynamics at rest was provided by Saggar et al (77). These authors determined four distinct entities when they studied exercise responses, during incremental exercise to exhaustion or to 75% of maximum predicted HR, in 57 patients with systemic sclerosis. Following assessment of haemodynamics via RHC during exercise, they stratified subjects into one of four groups according to their haemodynamic response during exercise. Along with mPAP and PAWP, this group evaluated the transpulmonary gradient (TPG) which reflects the difference between mPAP and PAWP and assists with identification of pulmonary vascular rather than LV dysfunction. The distinct entities identified in this study included a group with normal haemodynamics at rest and on exercise (mPAP ≤25mmHg, <30mmHg on exercise, n=15); a second group with exercise-induced pulmonary venous hypertension (exercise mPAP >30mmHg, PAWP >18mmHg, TPG <15mmHg; n=12); a third group with exercise-induced

pulmonary arterial hypertension (exercise mPAP >30mmHg, PAWP ≤18mmHg, TPG ≥15mmHg; n=21) and a fourth group with 'out of proportion PH' (exercise mPAP >30mmHg, PAWP >18mmHg, TPG ≥15mmHg; n=9). 'Out of proportion PH' suggests dual pathology with likely pulmonary hypertension secondary to LV dysfunction but with co-existent pulmonary vascular disease.

Recently, in a study of individuals <50 years of age, with symptoms suggestive of pulmonary hypertension, a mPAP between 21 and 25mmHg at rest predicted an increase in mPAP on exercise to >30mmHg (397). Individuals with mPAP >30mmHg, during exercise, had a higher PVR and mPAP at rest than individuals with a mPAP <30mmHg on exercise. The implications of these findings are not certain, however, they suggest that, in individuals less than 50 years of age, mPAP between 21 and 25mmHg and/or exercise mPAP >30mmHg may identify early pulmonary vascular pathology. Long term follow up of these individuals is important to determine whether these findings identify an early stage of PAH.

The studies in EIPAH suggest the possibility that invasive exercise testing may assist with the early diagnosis of PAH. However, while a mPAP >30mmHg on exercise was previously considered diagnostic of PAH (51) a study published in 2009 (30) demonstrated that many healthy older subjects, and some younger subjects, develop a mPAP of over 30mmHg on exercise (30). Clearly as a diagnostic criterion, mPAP >30 mmHg on exercise, in isolation, lacks specificity. There is also some difficulty with the definition of a normal PAWP on exercise, especially in older individuals. Although PAWP <20mmHg has been used as a diagnostic criterion to exclude exercise-induced LV diastolic dysfunction in the studies of EIPAH (2, 27, 76), studies of healthy individuals have shown that PAWP rises to above 20mmHg, in response to exercise, in a large proportion of healthy individuals (398, 399).

It is evident that identifying a threshold value for a single measure in isolation, such as peak exercise mPAP or PAWP, has significant limitations in determining whether the pulmonary circulation and LV function are normal. It is also evident that age needs to be taken into consideration when interpreting results and in the determination of diagnostic thresholds. However, after stratifying individuals based upon symptoms, functional capacity, risk and clinical suspicion for the presence of PAH, examining exercise haemodynamics (including CO, mPAP, PAWP and PVR) along with gas exchange and ventilatory response during a CPET (including

peak $\dot{V}O_2$, AT, O_2 pulse, $\dot{V}E/\dot{V}CO_2$, $PetCO_2$, and SpO_2) may have a role in diagnosing the cause of exercise limitation, in a selected population.

Summary: Exercise testing – potential role in early diagnosis of PAH

Preliminary evidence suggests that haemodynamic monitoring during exercise has the potential to assist with the early diagnosis of PAH. Gas exchange analysis may assist with the interpretation of test results and support differential diagnosis. However, further research exploring the role of exercise testing in individuals with symptoms and risk factors for PAH is required. Serial assessment of individuals with EIPAH is important to determine whether EIPAH progresses to PAH and, if so, in what proportion of individuals this occurs.

For diagnosis of PAH prior to the development of advanced pulmonary vascular pathology, the evidence suggests that a diagnostic composite should describe an elevated PVR at rest and on exercise, reduced exercise SV and CO. Further evidence for the condition would include reduced $\dot{V}O_2$ at peak exercise and at the AT, elevated $\dot{V}E/\dot{V}CO_2$, and an attenuated rise in $PetCO_2$ at the AT. Persistent symptoms, functional impairment (WHO FC ≥ II), and impaired QoL would support the clinical and functional importance of these findings. The threshold values for the measures used to describe PAH, early in the course of the disease, need to be established, but they should not be derived from the thresholds currently used to identify PAH. The current thresholds for PAH have been established for individuals with extensive pulmonary vascular disease and are likely to be insensitive in detecting early disease.

2.6 Final summary and gaps in knowledge

This literature review has explored the pathophysiology and clinical presentation of PAH. The central and systemic abnormalities associated with PAH and the influence of these factors on exercise capacity, and the symptoms experienced by individuals with PAH, are described and discussed. The literature around exercise testing and the exercise responses associated with PAH is explored and the chapter concludes with a discussion of the literature regarding exercise testing in the evaluation of symptomatic individuals with risk factors for PAH.

There are limited data, and discussion within the literature, regarding the causes of exertional symptoms and reduced exercise capacity in PAH. In particular the relative contributions of central (RV function and pulmonary haemodynamics) and peripheral factors (peripheral myopathy, endothelial dysfunction, peripheral chemoreceptor and ergoreflex activity) towards exercise intolerance have not been determined. Furthermore, the central haemodynamic response to exercise at training intensities and long term outcomes of exercise training are not known and, therefore, the likely longer term consequences of exercise rehabilitation for individuals with PAH are uncertain.

The CPET and 6MWT have demonstrated utility in the evaluation of individuals with PAH. Other exercise tests, such as the CWLT, have potential in this population, especially for individuals with well preserved functional capacity.

The central haemodynamic response to exercise in individuals with PAH has been evaluated in a limited number of studies. Extensive data have described the ventilatory abnormalities associated with PAH. A small number of very recent studies have explored the role of exercise testing in the evaluation of symptomatic individuals with risk factors for PAH but have provided insufficient data to determine the significance of an elevated PAP during exercise in individuals with a normal PAP at rest. Limited haemodynamic, ventilatory and QoL data results in uncertainty regarding the clinical consequences and likely significance of an elevated PAP in these individuals.

Furthermore, the degree of functional impairment, in terms of reduced exercise capacity and muscle dysfunction, in individuals with EIPAH is unknown. The utility and likely safety of exercise tests that are commonly used in clinical practice, the 6MWT, CPET and 1RM, have not been investigated in this population.

These gaps in the literature formed the research questions and hypotheses that have been the basis for this PhD program of study.

CHAPTER 3
METHODS

3.1 Introduction

This chapter describes the methodology utilised for the studies that comprised the program of research for this PhD. Section 3.2 of this chapter details the methodology for a qualitative study of attitudes and reported behaviours of healthcare professionals, within Australia, who manage patients with PAH. This section describes the methodology for the study reported in Chapter 4 of this thesis and includes details of the study design, questionnaire development, pilot and field testing, data collection and statistical analysis.

Section 3.3 describes the methodology used for the quantitative evaluation of exercise responses in symptomatic individuals with risk factors for PAH. This section describes the methodology for the studies reported in Chapters 5-7 of this thesis. Included in this section is a description of the study designs, inclusion and exclusion criteria and recruitment strategies, as well as the exercise testing protocols, details of data collection and statistical analyses. General details regarding data management and statistical analyses are also described.

Specific details of the methodology employed for each of the studies that comprise the publications arising from this research are also included in Chapters 4-7. These chapters contain the body of the manuscripts, as published, and include deliberate repetition in reporting the methodology (along with background and discussion) enabling the results of these studies to be read in context.

3.2 Methodology for study 1: Activity and exercise prescription in PAH

The stages involved in this study were (1) development of a questionnaire; (2) pilot study and field testing of the questionnaire; and (3) data collection.

3.2.1 Questionnaire development

A questionnaire was developed, as part of this PhD program, in order to survey the attitudes and behaviours of healthcare professionals who manage patients with PAH, and who work within Australia. Management of patients with PAH is complex and involves multidisciplinary healthcare. The questionnaire was designed for presentation at a multidisciplinary pulmonary hypertension meeting to ensure that a range of healthcare professionals involved in the management of patients with PAH was surveyed. It was considered likely that the response rate would be optimised by presenting the questionnaire, in hard copy, and it was designed for this format.

The initial stage of questionnaire development involved consultation with key stakeholders. Seven clinical specialists in the fields of pulmonary hypertension and/or exercise rehabilitation (medical officers, n=3; physiotherapists, n=3; exercise physiologist, n=1) were consulted. This stage of the study involved the development of case studies, typical of patients seen in clinical practice, and questions regarding physical activity advice. A research fellow at Curtin University, with expertise in qualitative research, was consulted and provided guidance regarding the design and format of the questionnaire.

3.2.2 Pilot study of the questionnaire

Following formulation of the questionnaire, a pilot study was conducted. Seven healthcare professionals (medical practitioners, n=3; nurses, n=2; physiotherapists, n=2) from the pulmonary hypertension clinic at a tertiary hospital (Royal Perth Hospital, Perth, Western Australia) were asked to complete the questionnaire and to provide written and verbal feedback about its ease of use, applicability and length. The individuals who undertook the pilot study were not involved in the development of the questionnaire. No recommendations for change arose from this pilot study.

The questionnaire was then field tested at a pulmonary hypertension meeting in Sydney, in June 2006. Eight-eight healthcare professionals who worked in pulmonary hypertension clinics within Australia attended the Australian Pulmonary Hypertension Experts meeting (Sydney, Australia; Actelion Pharmaceuticals Australia, 24th and 25th June, 2006). Thirty-one participants (35%) of the meeting returned the questionnaire. No changes were made to the original questionnaire following this field test. However, additional questions were included following the

field test in order to determine the type of advice given regarding selected physical activities. These questions were included to determine the response to likely questions patients would ask at clinic appointments.

3.2.3 Data collection for main study

3.2.3.1 Study design

The study used a cross sectional design with data collected via a self-administered questionnaire. The questionnaire was distributed during the Pulmonary Hypertension Perspectives Meeting in Sydney, Australia, 19th and 20th June, 2010. The delay between the pilot study and the main study was primarily due to time commitments related to data collection for the exercise testing components of this PhD program (Chapters 5-7).

3.2.3.2 Participants

Eighty-nine healthcare professionals who worked in pulmonary hypertension clinics within Australia attended the Pulmonary Hypertension Perspectives Meeting (Sydney, Australia; Pfizer Pharmaceuticals Australia). Seventy-six of these participants had a role in advising patients with PAH regarding physical activity and exercise. The remaining participants were pharmacists (n=12) and a medical student (n=1). Attendance was by invitation and the purpose of the meeting was to provide a forum for experts within the field of pulmonary hypertension to discuss best practice and future directions in the diagnosis and management of PAH. The invitation to attend the meeting was sent to healthcare professionals in all pulmonary hypertension clinics in Australia (personal communication, Pfizer Australia).

3.2.3.3 Description of questionnaire

The questionnaire is presented in Appendix 1 (Pages 193-202). Responses to the questionnaire were anonymous. The questionnaire consisted of three sections. The first section asked respondents to indicate the type of institution in which they worked, their professional position, and the number of new PAH cases seen each year. The second section comprised three scenarios reflecting routine clinical practice, presented as two case studies. These case studies described adults with PAH, in WHO functional classes II, III and IV. The first case represented two

scenarios. This case initially represented a patient in functional class IV and, following improvement with pharmaceutical therapy, represented a patient in functional class II. The second case represented a patient in functional class III.

The data presented for each of the scenarios included the haemodynamic status (i.e. PAP and pulmonary vascular resistance index) obtained from RHC assessment, right ventricular function measured at rest on an echocardiogram, 6MWD and arterial blood gas data. For each scenario, participants were instructed to respond to the same seven questions in accordance with their usual clinical practice. The first question asked if they would perform any additional investigations. The remaining questions were designed to obtain data pertaining to the recommendations the respondent would provide regarding daily activity, acceptable symptoms on exertion and whether they would refer the patient described in the scenario for exercise rehabilitation.

The final section of the questionnaire consisted of three questions pertaining to four specific physical activities, with respondents asked to indicate the advice they would give to patients with PAH, in each of the functional classes II, III and IV. These questions asked whether patients with PAH would be advised for or against lifting a 20kg weight, exercising in a non-hospital gymnasium, regularly using stairs and slopes or adopting a sedentary lifestyle.

Respondents were also given the opportunity to provide further comment about exercise/activity instructions for patients with PAH, or regarding the questionnaire, in a dedicated section at the end of the questionnaire.

3.2.3.4 Ethics approval

Study 1 was approved by the Human Research Ethics Committee (HREC) of Curtin University (approval number HR PHY0012006). Participant consent was implied by return of the questionnaires.

3.2.3.5 Statistical analysis

Data analysis comprised descriptive statistics. Analysis was performed using SPSS software (version 18, SPSS, Chicago, IL).

3.3 Methodology for studies 2-4: Exercise testing in symptomatic individuals with risk factors for PAH

3.3.1 Study design

The studies employed a prospective cross-sectional design. All data collection occurred at Royal Perth Hospital, between 26th October 2006 and 14th November 2008. Subjects were required to attend for 2 sessions. Session 1 lasted approximately 3 hours and involved informed consent, an ECG, two 6MWTs, QoL assessment and evaluation of usual physical activity levels. For control subjects this session also included a blood test and a medical assessment. Session two lasted approximately 5 hours and occurred between 1 and 32 (mean of 5, median of 3) days following session 1. This session involved right heart catheterisation (for patient subjects only), an incremental CPET and resistance exercise testing.

3.3.2 Subjects

Consecutive adult patients, referred for investigation of possible PAH, were recruited from the Pulmonary Hypertension Unit at Royal Perth Hospital according to clinical, echocardiographic and lung function criteria. All subjects had been referred for investigation of dyspnoea of unknown aetiology, were in WHO functional class II or III, and were investigated for PAH as defined by the 2004 European Society of Cardiology Guidelines (51), i.e. mean pulmonary artery pressure (mPAP) >25mmHg and pulmonary artery wedge pressure <15mmHg at rest. Patients were carefully screened and individuals with clinical or echocardiographic evidence of left heart disease, a high probability of PAH at rest (PASP>45mmHg) (242), symptoms of dyspnoea and fatigue at rest, a BMI >35kg/m^2, anaemia (haemoglobin <110g/L), or musculoskeletal impairment were excluded.

Inclusion criteria were exertional dyspnoea and risk factors for PAH, defined as scleroderma with a haemoglobin corrected DLCO <70% predicted and normal lung volumes, and/or a first degree relative with confirmed PAH and/or PASP 35-45mmHg on echocardiogram. Forty-five patients, who met these criteria, underwent further assessment to screen for pulmonary parenchymal or airway disease, using high resolution computed tomography and bronchial provocation testing, and six were subsequently excluded because of parenchymal lung or airway disease.

Thirty-nine subjects underwent evaluation of resting and exercise haemodynamics, exercise capacity, ventilatory response to exercise and QoL in Study 2. One subject was withdrawn because of myocardial ischaemia on exercise and one due to an incomplete assessment. Based upon historically accepted upper limits of normal (400), subjects were identified as having EIPAH if mPAP was >30mmHg and PAWP was <20mmHg, on exercise. One of these subjects was a current smoker but had no evidence of smoking related respiratory, cardiac, or peripheral vascular disease.

Seventeen subjects were found to have EIPAH, six had PAH (mPAP >25mmHg, pulmonary artery wedge pressure <15mmHg at rest) and 10 had noPAH (mPAP ≤25mmHg at rest and ≤30mmHg on exercise). Four subjects were found to have a mPAP ≤25mmHg at rest, and a mPAP >30mmHg and a PAWP ≥20mmHg on exercise, suggesting exercise-induced LV diastolic dysfunction.

The 17 subjects with EIPAH became participants in Study 3. Regarding subjects for Study 4, one subject with EIPAH declined the invitation to participate and three subjects did not perform the resistance exercise component of the study due to logistical reasons. Data from the remaining subjects with EIPAH (n=14) were used to compare the acute haemodynamic and symptomatic responses to the two modes of exercise in Study 4.

3.3.2.1 Recruitment of control subjects

A population-based sample of 28 healthy control subjects was recruited from a database of research volunteers established by the Lung Institute of Western Australia (Perth, Western Australia) for genetic studies. Volunteers were included in the database following postal requests mailed to randomly selected individuals (using the program Marketing Pro, DtMS, Blackburn, Victoria, Australia) listed in the telephone directory of Perth (population 1.3 million).

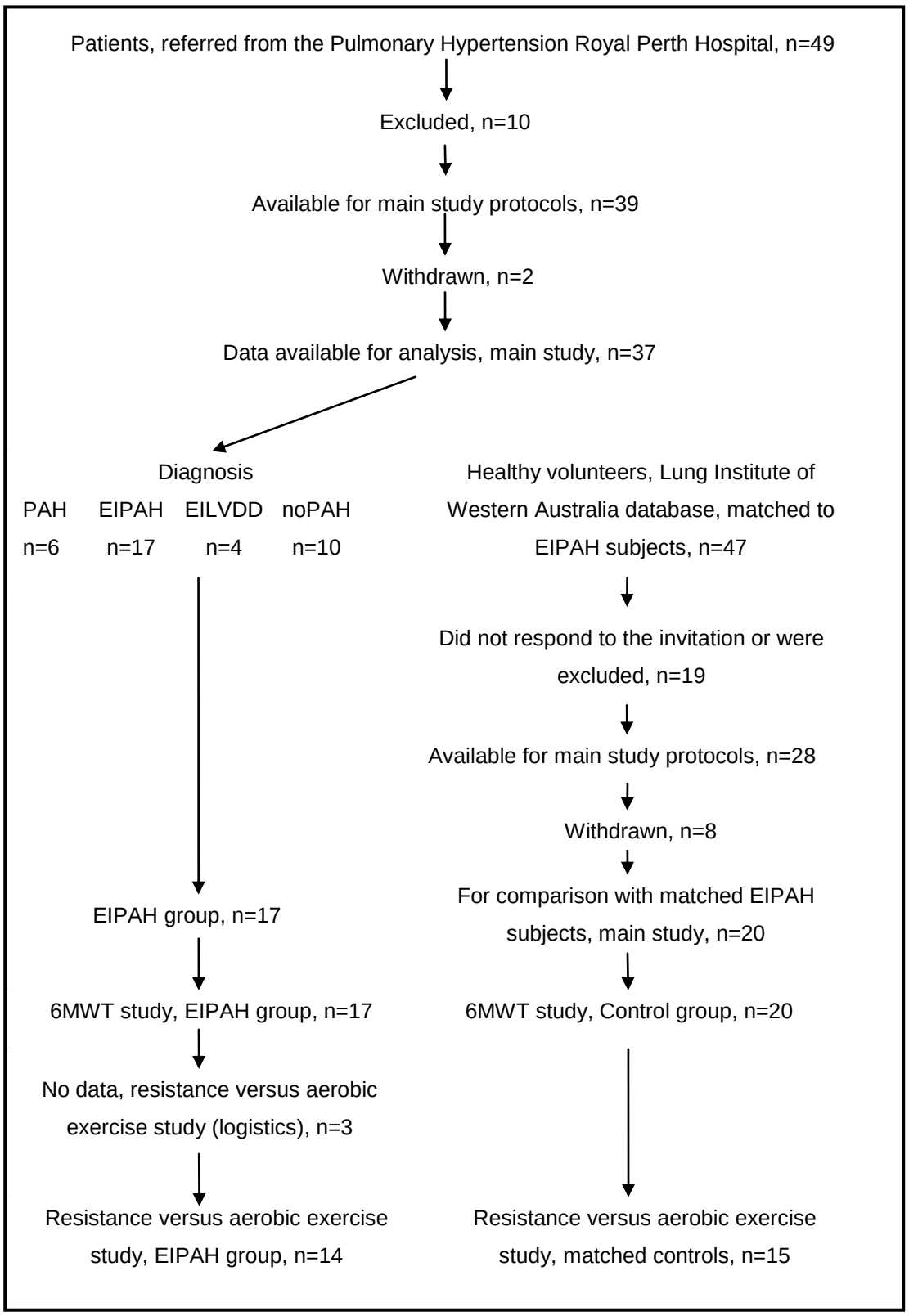
The volunteers on the database were screened for demographic details and those who matched one of the EIPAH study subjects for gender, age (±5 years) and BMI (±3kg.m^{-2}, provided BMI was ≤35kg.m^{-2}) were sent a letter of invitation for the study. With the letter of invitation the volunteers were asked to return a form indicating their availability for the study, and baseline information about weight and height, and health issues. Forty-seven volunteers were sent a letter of invitation. Three did not reply. Eleven declined the invitation due to cardiac or respiratory disease (n=5),

other medical problems (n=4) or transport issues (n=2). Five did not provide a reason for declining the invitation.

The remaining 28 volunteers expressed an interest in the study and all underwent a medical examination and a series of screening tests to confirm their healthy status. None of these subjects were current or recent (within previous 12 months) smokers. The screening tests included a medical history, medical evaluation, an ECG and a blood test to exclude haematological abnormalities and to determine levels of haemoglobin and fasting blood sugar. A comprehensive echocardiogram was performed with estimation of PASP and PVR. Evaluation of left and right atrial and ventricular dimensions and function was performed to exclude cardiac dysfunction, or likely pulmonary hypertension. Further evaluation included comprehensive lung function tests to examine lung volumes, airflow, and DLCO. Lung function tests were analysed against reference values to exclude pulmonary parenchymal or airway abnormalities. A value within the 95% confidence intervals was accepted as a healthy result.

Eight volunteers were withdrawn from the study due to ST segment depression during CPET (n=1), elevated PASP (40mmHg) on echocardiogram and elevated $\dot{V}E/\dot{V}CO_2$ on CPET (n=1), low haemoglobin (85 $g.L^{-1}$) (n=1), reduced FEV_1 (69% predicted) (n=1), dilated left atrium on echocardiogram (n=2), reduced DLCO (70% predicted) (n=1), or exertional chest pain and increased risk for ischaemic heart disease (n=1). The remaining 20 volunteers made up the control group for Studies 2 and 3 and were evaluated for exercise capacity, ventilatory response to exercise and QoL, but not central haemodynamics. Fifteen of the healthy controls, matched to the EIPAH subjects in Study 4, were assessed for comparison of lower limb muscle strength and exercise capacity with the EIPAH group, in Study 4. An overview of subject recruitment is provided in Figure 1.

Figure 1. Subject recruitment, Studies 2-4.



Abbreviations: PAH, pulmonary arterial hypertension; EIPAH, exercise-induced PAH; EILVDD, exercise induced left ventricular diastolic dysfunction; 6MWT, six-minute walk test.

3.3.3 Exercise testing protocols

This section describes the details pertaining to assessment of 6MWD, maximal and submaximal aerobic capacity and maximal and submaximal resistance exercise.

The exercise testing protocols included two 6MWTs, a single CPET on a cycle ergometer, a 1RM test on a bilateral leg press, 20 repetitions at 40% of 1RM and 15 repetitions at 60% 1RM on the bilateral leg press. Subjects were asked to refrain from vigorous exercise for within 24 hours and the single current smoker in the study was asked to refrain from smoking for 24 hours prior to exercise testing. A pictorial representation of test order and randomisation can be seen in Figure 8, Chapter 7, Page 143. All 17 EIPAH subjects and 20 control subjects underwent the 6MWT (Study 3) and submaximal and maximal aerobic exercise (Study 2). Fourteen EIPAH subjects and 15 controls underwent submaximal and maximal resistance exercise (Study 4). Demographic details of the subjects in each study are presented in Chapters 5, 6 and 7 (Studies 2, 3 and 4 respectively).

The 6MWT was the first test performed by all subjects. The order of maximal aerobic and resistance exercise was randomly allocated using a computer generated random allocation list (Excel 2003, Microsoft, Seattle, USA). A 30 minute recovery period was provided between the aerobic and resistance exercise protocols, regardless of test order. All exercise tests were supervised by the primary investigator (RF). The 6MWT was performed, in the morning, in a quiet hospital corridor with no through traffic and during non-clinic periods. The CPET and resistance exercise testing was performed in the morning on a second day of testing in a dedicated exercise testing laboratory. Subjects were asked to refrain from vigorous exercise, and the single current smoker in the study was asked to refrain from smoking, for 24 hours prior to the exercise tests.

3.3.3.1 Six-minute walk test

Subjects were instructed to have a light breakfast on the day of the 6MWT. The 6MWT was performed according to the American Thoracic Society guidelines (308), within an enclosed, unobstructed, flat, corridor. This corridor was accessed during periods of relative inactivity i.e. during non clinic times. Subjects walked back and forth along the corridor and turned in front of two cones placed 45m apart. Standardised instructions were given prior to commencement of the test. Each

minute during the test subjects were notified of the elapsed time and given standard encouragement.

All subjects completed two 6MWTs, separated by a rest period of at least 30 minutes.

3.3.3.2 Cardiopulmonary exercise test (Figure 2)

Subjects were instructed to fast from midnight on the night before the CPET. Subjects recruited from the Pulmonary Hypertension Unit had a pulmonary artery catheter in situ during the CPET, for the measurement of central haemodynamics. The CPET was performed using an electronically braked cycle ergometer attached to a customised imaging table (Lode BV, Groningen, Netherlands) with the subject in a semi-recumbent position (torso at 50° from the horizontal). An incremental symptom-limited protocol was employed which involved a 3 minute baseline period at rest followed by 15 Watt increments in workload every 3 minutes. The initial workload was individualised based upon gender, age and 6MWD. Standardised instructions and encouragement were provided to promote a maximum effort.

Breath-by-breath ventilation, O_2 and CO_2 concentrations and the derived $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ were determined using the Vmax metabolic analysis system (Vmax, Sensormedics, CA, USA) (VMax Optima, Software Version 20-1A).

Anaerobic threshold

The AT was determined indirectly, using the V slope method (13), which identifies the point during the CPET at which conversion of pyruvate to lactate and H^+ is required to supplement aerobic metabolism. At this point, buffering of H^+ ions by HCO_3- contributes noticeably to $\dot{V}CO_2$ and $\dot{V}CO_2$ rises faster than $\dot{V}O_2$. While this is an indirect measure of muscle metabolism, this method of determining the point at which anaerobic exercise begins to contribute sufficient quantities of metabolic by-products to alter the ventilatory response during exercise is robust and widely used in research and clinical practice (13).

The AT was determined by two investigators of whom one was the primary investigator (RF). The other investigator was an experienced respiratory scientist and was blind to the subjects' diagnosis. Each of these investigators independently determined the AT and subsequently compared the results. In 3/39 (8%) of cases,

there was disagreement of >0.1L. In each case, after discussion, agreement was reached. There were no cases in which an AT could not be determined.

The $\dot{V}E/\dot{V}CO_2$ was determined as the value measured over 30 seconds, centred on the AT.

Maximal aerobic exercise

The maximum workload was defined as the highest workload on the CPET that was maintained for >30 seconds. Peak $\dot{V}O_2$ was defined as the 30 second average measured at the maximum workload, within the last 30 seconds prior to test termination. Minute ventilation was measured, and $\dot{V}O_2$, $\dot{V}CO_2$ and RER were calculated. Predicted values for maximum $\dot{V}O_2$ were those determined by Jones et al (401). Central haemodynamic responses to maximal aerobic exercise were determined as the values averaged over 30 seconds within the last minute of exercise.

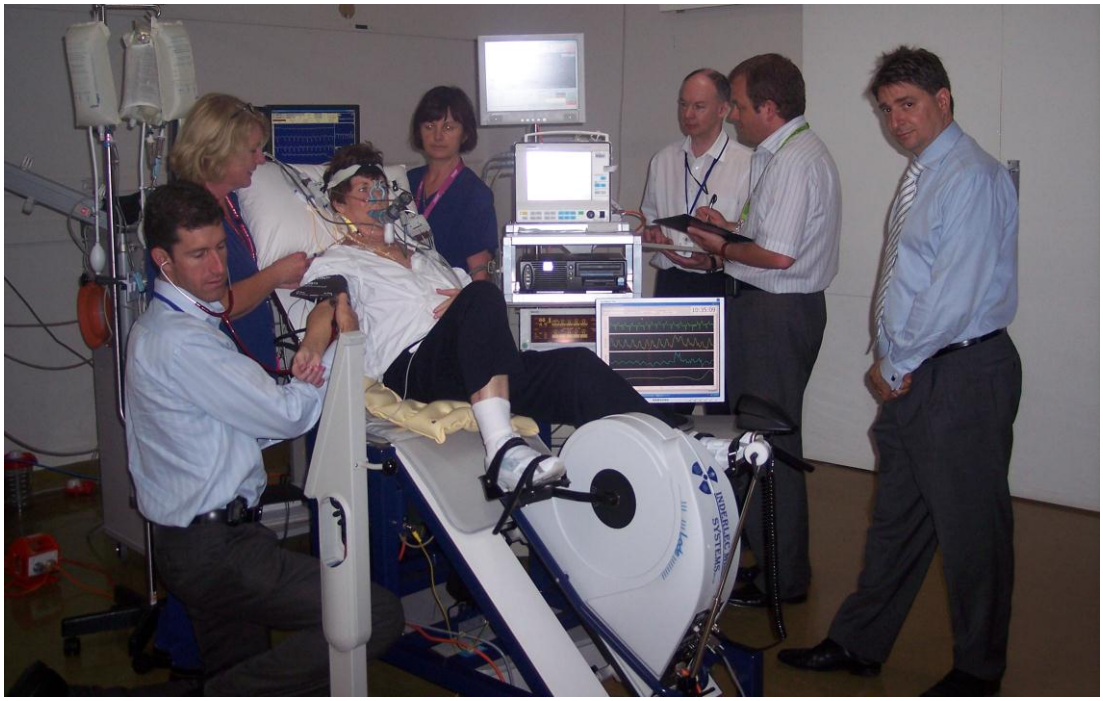
Submaximal aerobic exercise

Haemodynamic responses to submaximal aerobic exercise were determined at 40 and 60% of peak $\dot{V}O_2$ averaged over a period of 30 seconds. The time at which 40 and 60% $\dot{V}O_2$ occurred was determined using a computer generated program with proprietary software written in LabVIEW™ 7.0. The recorded data were then reviewed and the haemodynamic responses were determined retrospectively. The systemic blood pressure and symptomatic responses were those recorded closest to this 30 second period of exercise.

3.3.3.3 Resistance exercise testing (Figures 3 and 4)

The order of submaximal resistance exercise protocols was randomly allocated according to a computer generated random allocation list (Excel 2003, Microsoft, Seattle, USA). A 10 minute recovery period was provided between each of the resistance exercise protocols. A return to baseline haemodynamic and symptomatic values was ensured before commencement of the subsequent exercise protocol.

Figure 2. Subject undergoing a CPET with simultaneous central haemodynamic monitoring via RHC

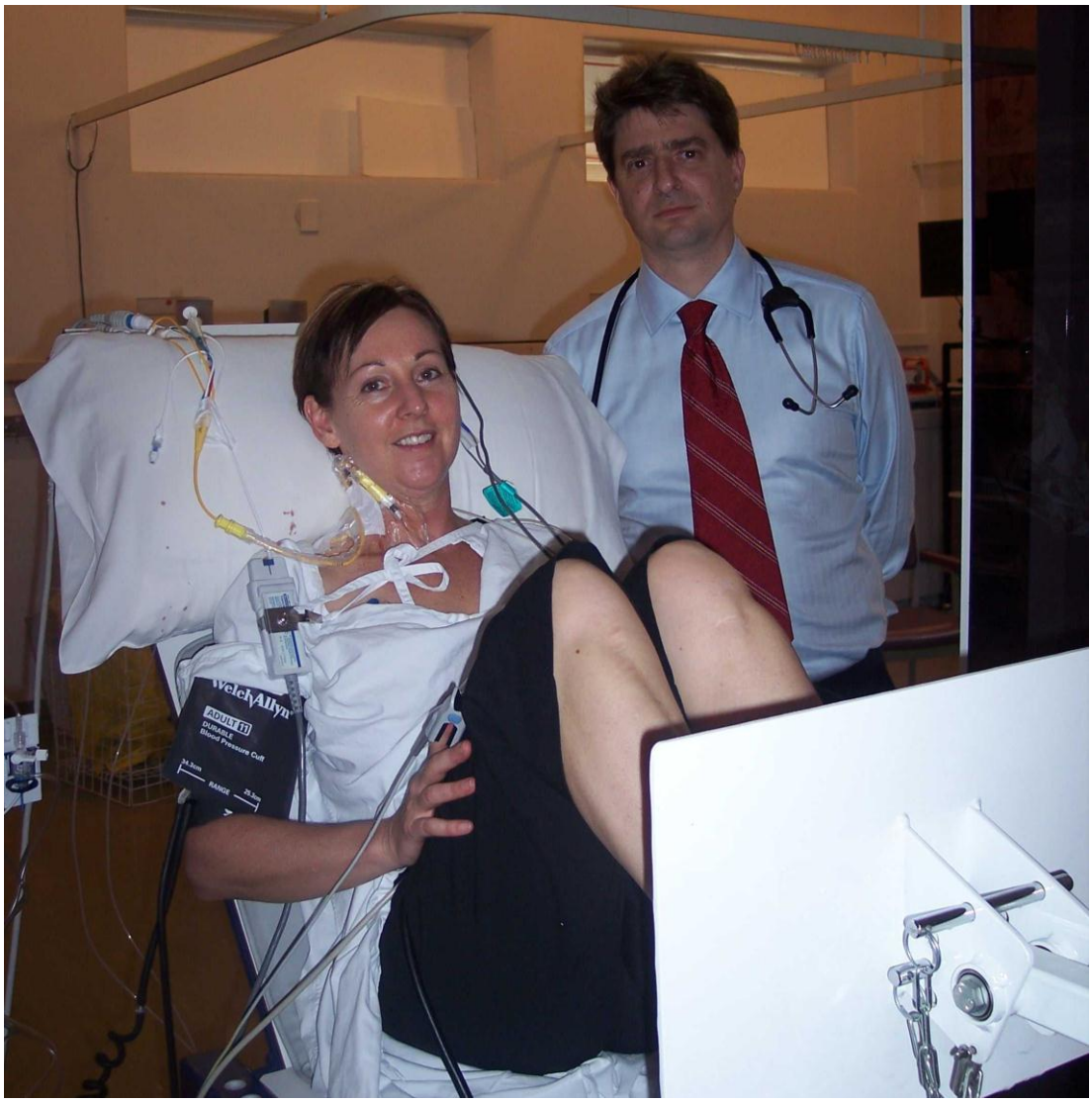


One repetition maximum test

Responses to maximal resistance exercise, and lower limb extensor muscle strength, were assessed using a 1RM technique according to a standardised protocol. A warm up, comprising 10 repetitions of a light weight (10-20 kg), was followed by a rest period of two minutes prior to the 1RM manoeuvre. The initial weight for 1RM assessment was calculated at 75% of the subjects' body weight and progressively greater weights were attempted until the maximum weight was determined. A standardised rest period of 60 seconds was employed between each 1RM attempt. The 1RM was determined as the heaviest weight, to the nearest 5kg, that could be lifted through a full range, with good technique and without breath-holding. The maximum haemodynamic and symptomatic responses were determined as those elicited during a technically correct lift performed using the greatest weight. All lifting tasks were carefully supervised by the same investigator (RF) and, to avoid breath holding, subjects were instructed to exhale during leg extension. Prior to each lift, the subject was reminded to exhale during the concentric muscle contraction and to inhale during the eccentric muscle contraction. Standardised verbal encouragement was provided during each lift.

Figure 3. (a) Starting and finishing position for the maximal and submaximal resistance exercise protocols. (b) Position of legs during the extension phase of the manoeuvre during the maximal and submaximal resistance exercise protocols

Figure 4. Subject in preparation for resistance exercise protocols, with right heart catheter in situ for central haemodynamic monitoring



Submaximal resistance exercise protocols

Submaximal resistance exercise was performed at 40 and 60% of 1RM. The exercise protocols involved 20 repetitions at 40% 1RM over 60 seconds, and 15 repetitions at 60% 1RM over 45 seconds, with the cadence guided by a metronome. For each set of submaximal resistance exercise, the central haemodynamic response was taken as the average over the last 10 seconds of exercise.

3.3.4 Haemodynamic measures

3.3.4.1 Pulmonary haemodynamics

Pulmonary haemodynamics were measured using an 8F pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) inserted, under fluoroscopy, via the right internal jugular vein. Insertion of the catheter was performed in a cardiac catheter laboratory. Following catheterisation, subjects were transferred to the exercise laboratory. Pulmonary artery pressure and right atrial pressure were recorded continuously (Compact, Datex Engstrom, Finland) during rest and exercise periods. Prior to data collection, and following any change of position, the transducer was recalibrated. For calibration, the zero position was taken as the 4^{th} intercostal space in the midaxillary line.

In order to accurately determine resting and exercise values, all resting and exercise periods, and events such as changes of position and PAWP measurement, were electronically labelled. All data were subsequently examined, analysed and recorded into a database by the primary investigator (RF).

Initial values of PAP, right atrial pressure, PAWP and CO were determined in the supine position following a period of stabilisation (a minimum of 40 minutes following catheter insertion). Stabilisation was defined as no change in patient position within the previous 30 minutes and no change in HR (of >5 beats per minute) or mPAP (of >5mmHg), within the previous 5 minutes. In six individuals a diagnosis of PAH was made, based upon these measures.

Following this initial assessment, the subject stood and transferred to a customised imaging table (Lode BV, Groningen, Netherlands) and was repositioned into a semi-recumbent position (torso at 50° from horizontal). Following a second period of

stabilisation, PAP, CO, PAWP and right atrial pressure were tagged as the resting baseline values.

The subject then underwent assessment of exercise capacity, and haemodynamic and symptomatic responses, to graded aerobic exercise (CPET) and maximal and submaximal dynamic, lower limb extension resistance exercise.

Haemodynamic digital data were streamed from the Datex and Vigilance monitors to a data acquisition system (Powerlab, AD Instruments, Australia). Storage of analogue data (National Instruments, NI-DAQ 6008, 8 channel, 12-bit digital to analogue converter using proprietary software written in LabVIEW™ 7.0) allowed subsequent interrogation of the ECG and PAP wave form data and determination of PAWP and PAP at end expiration. All measurements were corrected for phase delay.

Prior to, and during the CPET, PAWP was recorded every 3 minutes, immediately prior to an increase in workload, and in the final minute of the test. If a subject performed less than 30 seconds of the final workload, the peak PAP, PAWP and right atrial pressure responses were taken as the values measured within the last 30 seconds of the previous workload.

Pulmonary artery wedge pressure measurements during exercise were subsequently utilised to differentiate subjects into groups, with and without an elevated PAWP (≥20mmHg) on exercise. Subjects with a mPAP ≤25mmHg at rest, and mPAP >30mmHg and PAWP <20mmHg during the CPET were grouped as EIPAH (n=17). Subjects with a mPAP ≤25mmHg at rest, and mPAP >30mmHg and PAWP ≥20mmHg on exercise, were grouped as exercise-induced LV diastolic dysfunction (n=4), according to previously determined criteria (27).

3.3.4.2 Cardiac output

Continuous cardiac output (CCO) measurements were made using the 8F pulmonary artery catheter (Edwards Lifesciences, Irvine, CA). Cardiac output was monitored continuously until the catheter was removed following all test procedures. Measurement of CCO is based upon the application of stochastic system identification techniques of thermal dilution. The pulmonary artery catheter includes a thermal filament which resides in the RV, once the catheter is in place. This thermal filament transfers heat directly into the blood, according to a pseudorandom

binary sequence. The resulting temperature change is detected in the pulmonary artery and is cross-correlated with the input sequence to produce a thermodilution washout curve. Cardiac output is computed from an equation that determines conservation of heat using the area under the curve (402). Continuous cardiac output measurements have been shown to have good accuracy when compared with the bolus thermodilution (402-404) and an electromagnetic flowmeter device (405). However, due to averaging of data and 60 second updates, this device was not suitable to assess CO during short periods of exercise and CO was not compared between maximal or submaximal aerobic versus resistance exercise. Predicted peak CO was calculated assuming an arterial-venous O_2 content difference of ([haemoglobin] x 10) (13).

3.3.4.3 Mixed venous oxygen saturation

The pulmonary artery catheter utilised in this study, included an optical module. This optical module includes an advanced fiberoptic reflectance oximetry system which has previously been shown to provide an accurate continuous measure of mixed venous O_2 saturation (406, 407). In vitro calibration was performed prior to catheter insertion, according to the manufacturer's instructions (Edwards Lifesciences, Irvine, CA). Mixed venous O_2 saturation was measured continuously, at rest and during exercise.

3.3.4.4 Systemic blood pressure

Systemic blood pressure was measured manually, at the brachial artery, at rest and every 3 minutes during the CPET, within the last 60 seconds of each exercise stage and within the last 60 seconds of the final workload. During the 1RM assessment, the systemic blood pressure was measured over the period of the lift, with the cuff inflated immediately prior to the lift and released as the lift was performed. During submaximal exercise protocols, the systemic blood pressure was recorded over the last 5 repetitions of the set of lifts. Cuff inflation occurred as the fifth from last repetition was commenced and the cuff was deflated over the last two repetitions, prior to test end.

3.3.4.5 Heart rate

During the 6MWTs, HR was monitored continuously via a telemetry system (Polar Electro Oy; Kempele, Finland). During the CPET and resistance exercise protocols HR was measured continuously via a 12 lead ECG (Cardiosoft, Version 4.2, GE Medical Systems, USA).

3.3.5 Arterial oxygen saturation

Oxyhaemoglobin saturation was determined continuously during the CPET and resistance exercise protocols using a sensor connected securely to an ear lobe (Oxypleth pulse oximeter and ear sensor, Novemetrics, CT, USA). An attempt to monitor SpO_2 during the 6MWT failed in the patient group due to difficulties in obtaining accurate results. This was most likely related to the high proportion of subjects with scleroderma related Raynaud's Syndrome and changes in finger perfusion during the walk test. There was no access, during this research, to a portable device that included a forehead or ear probe.

3.3.6 Symptomatic responses

Symptomatic responses of dyspnoea, leg and general fatigue, and the rate of perceived exertion (RPE) were assessed using the Borg Category Ratio Scale (408) Symptomatic responses were recorded immediately following the 6MWT. During the CPET, symptomatic responses were recorded within the last 60 seconds of each exercise stage (every 3 minutes) and immediately following test end. During each of the resistance exercise protocols, symptomatic responses were recorded immediately following the test end.

3.3.7 Quality of life assessment

Quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Version 1). Subjects completed the SF36 during the rest period between the two 6MWTs on day one of assessment. Following recoding of scores, the scores for each domain and for the health transition items were summed (409). The summed scores were then compared between the EIPAH and control groups. Comparisons between EIPAH and control groups were analysed for each domain and for health transition scores.

3.3.8 Evaluation of usual physical activity

A subjective assessment of the control subjects' participation in organised sport and usual physical activity was performed during an initial telephone conversation regarding the volunteers' suitability for the study and to arrange the data collection appointments. Volunteers who were engaged in organised sport or high levels of daily activity were excluded from the study (n=6). All study participants completed the Short Last 7 Days, Self-administered Format of the International Physical Activity Questionnaire (IPAQ) (410) during the rest period between the 6MWTs on the first day of assessment.

While there are recognised limitations in assessment tools that rely on self-reported levels of activity, they provide a reasonable broad estimate of physical activity level (411). The IPAQ has been validated for the estimation of activity levels (410, 412). More quantitative analysis of activity levels, for example utilising accelerometry, was deemed unnecessary for the broad matching of usual physical activity levels required for this study.

3.3.9 Equipment maintenance

3.3.9.1 Vmax system maintenance and quality control

Prior to, and every 6 months during the period of the study, a validation procedure was performed using two healthy hospital staff members (males=1) as biological controls. In accordance with recommendations (319), this procedure consisted of measuring ventilatory parameters at rest and during three workloads (60, 120 and 180 Watts) in each of the subjects. Exercise was performed at each workload for 6 minutes, to ensure steady state conditions. Results were then compared with previous test results for each individual and values within 5% for $\dot{V}O_2$, 6% for $\dot{V}CO_2$ and 5.5% for $\dot{V}E$ were taken to indicate acceptable validity (413)

Calibration of the Vmax system

Calibration of the Vmax system, according to published guidelines (319) and the manufacturer's instructions, was performed prior to each CPET. Current ambient barometric pressure, temperature and relative humidity were entered prior to each exercise test. Calibration of the mass flow sensor was performed before each test

using a 3L syringe, according to the manufacturer's instructions. Calibration was accepted if the error was within ±3% of the known volume (273). Calibration gases were taken from cylinders containing different gas concentrations (21% O_2; O% CO_2; 79% N_2 and 16% O_2; 4% CO_2; 80% N_2). The calibration attempts failed and were repeated if the difference between expected and actual O_2 concentrations was >2% or if the difference between expected and actual CO_2 concentrations was >0.25%. Both phase shift and response time calibrations were performed automatically, according to the manufacturer's procedure. Calibration was rejected if the O_2 response time was >0.15 seconds, or the CO_2 response time was >0.15 seconds.

3.3.9.2 Calibration of the cycle ergometer

The cycle ergometer (Lode BV, Groningen, Netherlands) was purchased for the study and calibrated following delivery and installation. Further calibrations were performed, by the Bioengineering Department (Royal Perth Hospital), every 6 months during the period of data collection.

3.3.10 Ethics approval

This exercise study was approved by the HRECs of the Royal Perth Hospital (HREC reference EC 2006/121) and Curtin University (approval number HR 108/2006). Written, informed consent was obtained from all subjects prior to data collection.

3.3.11 Data management and statistical analysis

All data were collected, entered into a spreadsheet (Excel 2003, Microsoft, Seattle, USA) and analysed by the principal investigator, with the exception of the data for Chapter 5, "Implications of exercise-induced pulmonary arterial hypertension". Assistance with this data analysis was provided by the Medical Research Foundation, Royal Perth Hospital. These data were analysed using Stata® Version 11 (Stat Corp., College Station, TX) and SPSS® software version 18 (SPSS, Chicago IL).

The assumption of normality was assessed by viewing frequency histograms, assessing skewness and kurtosis and by the Shapiro Wilks statistic. Data that did not conform to the assumption of normality were transformed prior to further

statistical analysis. Transformation was performed to produce the natural log of the data. Where data continued to deviate from a normal distribution following transformation, and where group numbers were small, non-parametric analyses were performed. Where data analysis included multiple comparisons, statistical methods included regression analysis or adjustments using Holm's Sequential Bonferroni correction factor (see below).

3.3.11.1 Statistical analyses

Study 2. Implications of exercise-induced pulmonary arterial hypertension (Chapter 5)

A mixed model to allow for matching of control and EIPAH subjects was performed for the analysis of the differences in baseline characteristics between control and EIPAH groups, and a *t*-test was used to identify differences between these groups. One-way ANOVA and post-hoc analysis with the Holm's test was used to identify the difference in baseline characteristics between noPAH, EIPAH and PAH groups. Conditional logistic regression for matched subjects was performed to determine the differences in haemodynamic, ventilatory and exercise capacity outcome measures, and the Wilcoxon matched pairs signed-rank test was performed to determine the difference in QoL measures, between the EIPAH and control groups. Multinomial regression was used to determine the difference in outcome measures between the noPAH, EIPAH and PAH groups. Statistical analyses were performed using Stata Version 11 (Stata Corp, College Station, Tex, USA) or SPSS software version 18 (SPSS, Chicago, IL). A probability value (p) <0.05 was accepted as significant. Data were expressed as number, percentage, mean ± standard deviation (SD) or median (interquartile range), as stated.

Study 3. Measurement properties of the 6MWT in individuals with exercise-induced pulmonary arterial hypertension (Chapter 6)

The effect of test repetition on 6MWD was examined using a general linear model for repeated measures. For each group, the magnitude of change in 6MWD between tests 1 and 2 was compared using the paired *t*-test. The greater 6MWD was used in all subsequent analyses. The coefficient of repeatability was determined as twice the SD of the difference in 6MWD measured on the two tests. Comparisons of responses to the 6MWT and CPET for the EIPAH group and control

group were performed for each group separately using paired *t*-tests (HR) and Wilcoxon signed-rank tests (peak dyspnoea and RPE). Differences between the EIPAH and control groups were analysed using unpaired *t*-tests (continuous variables) and the Mann-Whitney U test (peak dyspnoea and RPE). Relationships between 6MWD and 6MWW with peak values of $\dot{V}O_2$ and CO were assessed using Pearson correlation coefficients and linear regression analysis. Data were analysed using SPSS software Version 18 (SPSS, Chicago, IL, USA) A p-value of <0.05 was considered to be statistically significant. Data were expressed as mean ± SD unless otherwise stated.

Study 4. A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with exercise-induced pulmonary arterial hypertension (Chapter 7)

Demographic data for the study and control groups were compared using the independent *t*-test. Comparisons between responses to the aerobic and resistance exercise were analysed using the Wilcoxon matched pairs signed-rank test. Holm's Sequential Bonferroni corrections were applied to adjust for multiple comparisons. The statistical analyses were performed using SPSS software (Version 18, SPSS, Chicago, IL). Unless Holm's Sequential Bonferroni correction was applied, a p-value <0.05 was considered significant. Data were expressed as median and interquartile range, unless otherwise stated.

3.3.11.2 Power calculations

The initial power analysis, for Study 2 (Chapter 5), was based upon data in the literature. Effect size was calculated based on an expected $\dot{V}E/\dot{V}CO_2$ at AT of 29±4 in healthy individuals (11) and a $\dot{V}E/\dot{V}CO_2$ above 34 as a discriminating value for a pulmonary vascular limit to exercise (164) in the EIPAH group, in comparison with the healthy control group. Assuming 80% power and a 5% significance level, the sample size required to achieve a probability of 90% for detecting a difference between the EIPAH and control group was 14 subjects in each group.

Sample size for Study 4 (Chapter 7) was based on the power required to identify a difference of 10mmHg in mPAP between resistance and aerobic exercise, assuming a SD of 5.7mmHg. A SD of 5.7mmHg has previously been reported in the

measurement of mPAP during exercise in a similar population (27). To achieve 80% power, for a significance level of 5% (i.e. α=0.05), the sample size required to detect a difference of 10mmHg between resistance and aerobic exercise was seven subjects.

CHAPTER 4
AUSTRALIAN PERSPECTIVE REGARDING RECOMMENDATIONS FOR PHYSICAL ACTIVITY AND EXERCISE REHABILITATION IN PULMONARY ARTERIAL HYPERTENSION

Fowler R, Jenkins S, Maiorana A, Gain K, O'Driscoll G, Gabbay E. Australian perspective regarding recommendations for physical activity and exercise rehabilitation in pulmonary arterial hypertension. *J Multidisc Healthcare*. 2011; 4:451-462

4.1 Introduction

Pulmonary arterial hypertension (PAH) is characterised by poor exercise tolerance and impaired functional capacity. In patients with left heart failure (LHF) and chronic obstructive pulmonary disease, similar impairments respond well to exercise rehabilitation (267, 388, 414). Until recently, however, exercise rehabilitation was discouraged for patients with PAH due to a perceived high risk of adverse outcomes associated with physical exertion (41). Historically, symptoms were used to guide physical activity and patients were advised to avoid exertion associated with light-headedness, chest pain or severe dyspnoea (14). Otherwise, little consideration was given regarding recommendations for physical activity or exercise rehabilitation in individuals with PAH.

The recent introduction of PAH specific therapy has led to improved central haemodynamics and prognosis for patients with PAH (1). Despite therapy, however, many patients with PAH continue to experience significant impairment in physical function and quality of life (85). The benefits seen following exercise rehabilitation in patients with LHF and chronic obstructive pulmonary disease have been achieved in the absence of adverse events or clinical deterioration and exercise rehabilitation now constitutes an important adjunct to medical therapy in these populations (121, 415). These findings have stimulated an interest in the effects of exercise

rehabilitation in patients with PAH, but, prior to a feasibility study published in Japanese in 2005 (17), there were no reports of exercise rehabilitation in this population. Between 2006 and June 2010, a further three studies, with a total of 51 subjects with PAH who had undergone rehabilitation, were published (15, 16, 21). Improvements in exercise capacity and quality of life were observed following rehabilitation, without any adverse events or clinical deterioration (15-17, 21). Since June 2010, two further studies of exercise rehabilitation in subjects with PAH (with a total of 27 subjects) have been published (42, 106).

It is possible the paucity of data regarding the impact of physical activity and exercise on outcomes in PAH has made it difficult for clinicians to provide consistent advice regarding physical activity and to identify which patients are suitable for exercise rehabilitation. The aim of this study was to determine the consistency of approach by health care professionals who manage patients with PAH within Australia, regarding appropriate levels of exertion and acceptable symptoms during physical activity, and referral for exercise rehabilitation, for this patient population.

4.2 Methods

The study used a cross sectional design with data collected via a self-administered questionnaire. The questionnaire was developed by the investigators specifically for this study (see Appendix 1). Although responses were anonymous, respondents were asked to indicate the type of institution that they worked in, their professional position, and the number of new PAH cases seen each year.

Three scenarios reflective of clinical practice were presented as case studies. These case studies described adults with PAH, one in each of the WHO functional classes II, III and IV. The data presented for each case study included the haemodynamic status (i.e. pulmonary artery pressure and pulmonary vascular resistance index) obtained from right heart catheter assessment, right ventricular function measured at rest on an echocardiogram, 6-minute walk distance, and arterial blood gas data. For each case scenario, participants were instructed to respond to the same seven questions in accordance with their usual clinical management. The first question asked if they would perform any additional investigations. The remaining questions were designed to obtain data pertaining to the recommendations the respondent would provide regarding daily activity, acceptable symptoms on exertion, and

whether they would refer the patient described in the case study for exercise rehabilitation.

Three additional questions, regarding four specific physical activities, were asked to determine the advice the respondents would give to patients with PAH, in each of the functional classes II-IV. These questions asked whether patients with PAH would be advised for or against lifting a 20kg weight, exercising in a non-hospital gym, regularly using stairs and slopes, or adopting a sedentary lifestyle.

Piloting of the questionnaire was performed in a sample of seven health care professionals (medical practitioners, n=3; nurses, n=2; physiotherapists, n=2) from the pulmonary hypertension clinic at a tertiary hospital (Royal Perth Hospital, Perth, Western Australia). These individuals were instructed to complete the questionnaire, and provide feedback about its ease of use, applicability and length. No recommendations for change arose from this pilot study.

4.2.1 Participants

The survey was conducted at the Pulmonary Hypertension Perspectives Meeting (Sydney, Australia; Pfizer Pharmaceuticals Australia) in June 2010. Eighty-nine health care professionals who worked in pulmonary hypertension clinics within Australia attended the meeting. Seventy-six of these participants had a role in advising patients with PAH regarding physical activity and exercise. The remaining participants were pharmacists (n=12) and a medical student (n=1). Attendance was by invitation and the purpose of the meeting was to provide a forum for experts within the field of pulmonary hypertension to discuss best practice and future directions in the diagnosis and management of PAH.

The study was approved by the Human Research Ethics Committee of Curtin University. Participant consent was implied by return of the questionnaires.

4.2.2 Data analysis

Data analysis comprised descriptive statistics. Analysis was performed using SPSS software (version 18, SPSS, Chicago, IL).

4.3 Results

Fifty-three completed questionnaires were returned from participants who have a role in providing advice to patients regarding daily activities, or in referring patients for exercise rehabilitation. This represents a response rate of 70%. Some respondents did not answer all questions and therefore not all percentages presented in the results add to 100.

4.3.1 Demographics

Demographic data of the 53 respondents who completed the questionnaire are presented in Table 3.

Responses to the questions reflecting usual clinical practice, in relation to the case studies and four specific physical activities, are summarised in Table 4. Data pertaining to the responses to all of the questions are presented in Appendix 1.

Table 3. Demographics of the questionnaire respondents

Type of institution	Tertiary	41(77)
	Secondary	8(15)
	Private and public	3(6)
	Other	1(2)
Profession	Respiratory physician	19(36)
	Cardiologist	8(15)
	Rheumatologist	6(11)
	Nurse	19(36)
	Exercise physiologist	1(2)

Note: Data are number of responses with percentages given in parentheses.

4.3.2 Responses to questions relating to the case studies

4.3.2.1 Instructions for daily activity

The majority of respondents (67%) stated that they would have given the patients verbal advice and 33% would have given written advice.

Overall, 58% of respondents stated that they would advise the patients to undertake daily activities 'as tolerated', regardless of functional class (Table 4). The balance of respondents moderated their instructions according to functional class. For example, 25% advised moderate activity for patients in functional class II, 9% advised moderate activity for patients in functional class III and only 4% advised moderate activity for patients in functional class IV (Table 4). Some respondents provided details on how their patients would have been guided regarding daily activities. These respondents reported that they would have: assessed the patients' exercise capacity, referred the patient for physiotherapy and/or pulmonary or cardiac rehabilitation, advised the patient to use oxygen therapy during activity, or advised the patient to undertake symptom-limited exertion (Appendix 1).

4.3.2.2 Acceptable symptoms during daily activities

Overall, the majority (92%) of respondents considered that either no light-headedness (53%) or mild light-headedness (39%) was acceptable during daily activities. A minority (7%) considered that moderate light-headedness was acceptable. With regard to chest pain, 73% of respondents considered that no chest pain was acceptable. A further 20% advised that mild chest pain was acceptable. For both light-headedness and chest pain there was little variation according to functional class (Table 4).

In terms of the breathlessness experienced during physical activities, overall, 20% of respondents considered minimal, 44% considered moderate and 31% considered breathlessness 'as tolerated' was acceptable during daily activities. However, more respondents considered moderate rather than minimal breathlessness (51% versus 11%, respectively) was acceptable for the patient in functional class IV. When considering fatigue levels during daily activities, overall 5% of respondents considered that no fatigue was acceptable. A further 27% considered minimal

fatigue, 40% considered moderate fatigue and 21% considered that fatigue 'as tolerated' was acceptable. With the exception of the different opinion pertaining to acceptable levels of breathlessness for patients in functional class IV compared to patients in classes II and III, there was little difference in the level of symptoms that was considered acceptable across the functional classes (Table 4).

4.3.2.3 Referral for exercise rehabilitation

Overall, 63% of respondents stated they would have referred patients for exercise rehabilitation and this did not vary depending on the patients' functional class (Table 4).

4.3.2.4 Responses to questions regarding specific physical activities

Respondents' advice regarding the recommendations for the four specific physical activities varied according to functional class. Fifty-seven percent of respondents would have advised for, and 36% would have advised against, patients in functional class II lifting a 20kg weight. The majority of respondents would have advised patients in functional class II to use a non-hospital gym (70%) and to regularly use stairs and slopes (79%). The majority of respondents would also have advised patients in functional class II against adopting a sedentary lifestyle (91%). For patients in functional class III, 83% of respondents would have advised against lifting a 20kg weight and 72% would have advised against exercise in a non-hospital gym. A similar number of respondents recommended that patients in functional class III did and did not regularly use stairs and slopes (51% and 42%, respectively). Eighty-five percent would have advised patients in functional class III against a sedentary lifestyle. The majority of respondents stated that they would have advised patients in functional class IV not to lift a 20kg weight (92%), not to use a non-hospital gym (87%) and not to regularly use stairs or slopes (81%). The majority of respondents would have advised patients in functional class IV to adopt a sedentary lifestyle (75%).

Table 4. Questionnaire responses

		Class II	Class III	Class IV
Method to guide daily activity	Verbal	72	62	68
	Written	38	25	36
	Refer on for instruction	17	26	23
Refer for exercise rehabilitation	Yes	62	60	66
	No	38	32	34
Recommended level of exertion during daily activities	Mild	6	13	23
	Moderate	25	9	4
	As tolerated	57	57	60
Acceptable breathlessness during daily activities	Minimal	23	26	11
	Moderate	44	38	51
	As tolerated	30	28	34
Acceptable fatigue during daily activities	None	6	8	2
	Minimal	33	25	28
	Moderate	37	34	50
	As tolerated	22	25	17
Acceptable light-headedness during daily activities	None	57	51	51
	Mild	37	38	41
	Moderate	4	4	6
	To syncope	0	0	0
Acceptable chest pain during daily activities	None	78	74	68
	Mild	16	13	30
	Moderate	2	4	0
	As tolerated	4	2	2
Would you advise a patient to lift a 20kg weight	Yes	36	9	0
	No	57	83	92
Would you advise exercise in a non hospital gym	Yes	70	21	6
	No	23	72	87
Would you advise regularly using stairs and slopes	Yes	79	51	11
	No	13	42	81
Would you advise a sedentary lifestyle	Yes	2	8	17
	No	91	85	75

Note: Data are percentage of responses. Some respondents did not answer all questions and therefore not all percentages add to 100. Raw data for the responses to all questions are given in Appendix 1.

4.4 Discussion

The main findings of this survey of health care professionals attending a pulmonary hypertension specific meeting in 2010 were: (1) there was inconsistency, between individuals, regarding the acceptable level of exertion, breathlessness and fatigue during daily activities for patients with PAH; (2) there was a consensus that, for these patients, chest pain and anything more than mild light-headedness was not acceptable during daily activities; (3) approximately two thirds of respondents stated they would refer patients for exercise rehabilitation; (4) the level of acceptable symptoms during daily activities and patterns of referral for exercise rehabilitation did not vary greatly according to the patients' functional class, but, (5) advice regarding specific physical activities varied according to functional class.

The lack of evidence regarding the safety and impact of physical exertion on haemodynamics in patients with PAH has made it difficult for clinicians to provide recommendations regarding physical activity. Until recently, physical activity guidelines for patients with PAH were only available from sources such as the Pulmonary Hypertension Association (14) and were based upon studies in subjects with LHF. Patients with PAH were advised to undertake light to moderate aerobic exercise and to avoid exercise to the point of light-headedness, chest pain or severe dyspnoea. Patients with severe functional limitation, and those with a history of dizziness and/or fainting, were advised against undertaking an exercise program (14).

The inconsistency in response in our study, regarding acceptable symptoms of breathlessness and fatigue during physical activity, is likely to reflect uncertainty about the significance of these symptoms. In contrast, the consensus regarding the avoidance of light-headedness, a symptom suggestive of impaired cardiac output (11), and the majority view recommending avoidance of chest pain, a symptom suggestive of myocardial ischemia (416), is likely to reflect the understanding that these symptoms can represent life threatening events. The inconsistencies in opinion regarding the appropriate level of exertion and advice for common daily activities, such as lifting a 20kg weight and the regular use of stairs and slopes, suggests uncertainty about the impact of general physical activity on patient outcome.

Recently, one randomised controlled trial (15), one non-randomised controlled trial (106), three intervention trials (16, 17, 42) and one case report on exercise rehabilitation (21) have been published. The subjects in these studies had idiopathic PAH (n=83), chronic thrombo-embolic pulmonary hypertension (n=8), or PAH associated with connective tissue disease (n=10) or congenital heart disease (n=1). These publications reported positive outcomes associated with exercise rehabilitation, achieved in the absence of adverse events. To the authors' knowledge, only one published position statement on pulmonary rehabilitation (415) and no position statements or guidelines on cardiac rehabilitation include specific guidelines for exercise rehabilitation in PAH. In 2008, one publication reviewed exercise responses in PAH and discussed exercise prescription for this population (41).

In the current study, the finding that only two-thirds of respondents recommended exercise rehabilitation for patients in functional classes II and III suggests that, in 2010, there was uncertainty regarding this intervention, despite publications describing benefits of exercise training for this population (15-17, 21). This uncertainty may be related to the low number of subjects in the published reports and the publication of only one randomised controlled trial of exercise rehabilitation.

The only reported study of exercise rehabilitation that included a substantial number of patients in functional class IV was published in Japanese (17). However, in our study it was notable that the majority of respondents stated that they would refer patients in functional class IV for exercise rehabilitation, despite the very limited evidence for exercise rehabilitation in this subgroup. It is possible this finding relates to a perception that exercise rehabilitation for patients in functional class IV will improve functional capacity and minimise symptoms during activities of daily living. It may also relate to the perceived need for patients with severe disease to be educated about the risks of over exertion and to be supervised during exercise. The advice for patients in functional class IV, regarding the specific physical activities presented in this study, demonstrated a conservative approach towards physical activity that was not supervised by a health care professional.

The point prevalence of idiopathic PAH in Australia is estimated at 40 per million (417) and therefore, based upon Australian population statistics (418), the estimated number of patients with idiopathic PAH in Australia is approximately 900. In 2010, medical practitioners in 47 pulmonary hypertension clinics were licensed to

prescribe PAH specific pharmaceutical therapies (69). The rarity and complex nature of PAH, and strict licensing conditions associated with the prescription of PAH medications, means a limited number of health care professionals are involved in the management of patients with PAH. The relatively small number of participants in this study reflects the limited number of health care professionals, within Australia, who work with patients who have PAH.

4.5 Limitations

Attendance at the meeting at which the survey was performed was by invitation, resulting in likely selection bias. However, it also ensured the respondents were directly involved in the management of patients with PAH.

It was not possible to identify any overlap between respondents, in terms of the institutions that were represented, due to a deliberate decision to maintain the respondents' anonymity. However, the preservation of anonymity is likely to have had a positive influence over the response rate and encouraged open responses.

4.6 Conclusions

In 2010, health care professionals within Australia were inconsistent in opinion regarding appropriate levels of exertion and acceptable symptoms during daily activities. There appeared to be some uncertainty regarding the role of exercise rehabilitation in PAH. The findings of this study identify a need for further research to support the development of guidelines on physical activity and exercise rehabilitation for the PAH population in Australia.

CHAPTER 5
IMPLICATIONS OF EXERCISE-INDUCED PULMONARY ARTERIAL HYPERTENSION

Fowler R, Maiorana M, Jenkins S, Gain K, O'Driscoll G, Gabbay E. Implications of exercise-induced pulmonary arterial hypertension. *Med Sci Sports Exerc* 2011; 43:983-989.

5.1 Introduction

Pulmonary arterial hypertension (PAH) is a rapidly progressive condition associated with marked functional limitation, impaired quality of life (QoL), and poor prognosis. Patients typically present with exertional symptoms, but the diagnosis is based on abnormalities in resting haemodynamics (1).

Elevated pulmonary vascular resistance, an attenuated increase in cardiac output (CO) on exercise, and reduced peak oxygen consumption ($\dot{V}O_2$) have been reported in patients with a normal mean pulmonary artery pressure (mPAP) at rest but an mPAP >30mmHg and pulmonary artery wedge pressure <20mmHg on exercise (27). Historically, these pressures also defined PAH (400); however a recent consensus statement on pulmonary hypertension excluded a diagnosis of PAH based on responses to exercise (1). Uncertainty exists regarding the utility of a specific threshold for mPAP during exercise to discriminate between patients with pulmonary hypertension and healthy individuals (30). However, recent studies have identified reduced exercise capacity associated with an exercise mPAP >28mmHg (419) and progression from mPAP >30mmHg on exercise to PAH at rest in subjects with connective tissue disease (2). These findings support the contention that mPAP >30mmHg and pulmonary artery wedge pressure <20mmHg on exercise, in patients with a clinical suspicion of PAH, may represent an early manifestation of the pathology underlying PAH (27, 419).

Ventilatory and gas exchange abnormalities on exercise have been well described in PAH (11-13, 168) and reflect the severity of the underlying functional impairment (11, 12). Subjects with PAH have an elevated ventilatory equivalent for carbon

dioxide ($\dot{V}E / \dot{V}CO_2$) and reduced end tidal carbon dioxide ($PetCO_2$) at the anaerobic threshold (AT), a fall in $PetCO_2$ from rest to AT, and reduced oxygen saturation at peak exercise. Therefore, concurrent evaluation of ventilatory and central haemodynamic responses during exercise may help identify patients with early pulmonary vascular disease and lead to earlier diagnosis of PAH. This is important, given that pharmacotherapy is more effective in earlier stages of PAH (3, 74).

We studied a symptomatic cohort of patients, at risk of PAH, to determine whether an exercise mPAP >30mmHg and pulmonary artery wedge pressure <20mmHg (which we termed Exercise-Induced Pulmonary Arterial Hypertension [EIPAH] for the purposes of this study) was associated with haemodynamic and ventilatory abnormalities typical of PAH. We also sought to determine the effect of EIPAH on exercise capacity and QoL.

5.2 Methods

5.2.1 Subjects

Consecutive adult patients referred for investigation of possible PAH were recruited according to clinical, echocardiographic, and lung function criteria. Patients with clinical or echocardiographic evidence of left heart disease, a high probability of PAH at rest (pulmonary artery systolic pressure >45mmHg) (242), symptoms of dyspnoea and fatigue at rest, a BMI >35kg.m^{-2}, anaemia (haemoglobin <110g.L^{-1}), or musculoskeletal impairment were excluded.

Inclusion criteria were exertional dyspnoea and risk factors for PAH, defined as scleroderma with a haemoglobin corrected diffusing capacity for carbon monoxide <70% predicted and normal lung volumes, and/or a first degree relative with confirmed PAH and/or pulmonary artery systolic pressure 35-45mmHg on echocardiogram. Forty-five patients who met these criteria underwent further assessment, including high resolution computed tomography and bronchial provocation testing, and six were subsequently excluded because of parenchymal lung or airway disease.

Thirty-nine subjects underwent evaluation of resting and exercise haemodynamics, exercise capacity, ventilatory response to exercise, and QoL. One subject was

withdrawn because of myocardial ischaemia on exercise and one due to an incomplete assessment. Seventeen subjects were found to have EIPAH, 6 had PAH (mPAP >25mmHg, pulmonary artery wedge pressure <15mmHg at rest) and 10 had noPAH (mPAP ≤25mmHg at rest and ≤30mmHg on exercise). Four subjects were found to have an mPAP ≤25mmHg at rest, and an mPAP >30mmHg and a pulmonary artery wedge pressure ≥20mmHg on exercise, suggesting exercise-induced left ventricular diastolic dysfunction [EILVDD]). Twenty healthy controls, matched to the EIPAH group for age, gender and body mass index, were recruited from the general population and evaluated for exercise capacity, ventilatory response to exercise, and QoL but not central haemodynamics.

The study was approved by the Human Research Ethics Committees of the Royal Perth Hospital and Curtin University. Written, informed consent was obtained from all subjects.

5.2.2 Study protocol

Exercise capacity was assessed by 6-minute walk distance (6MWD) according to a standardised protocol (308) and a cardiopulmonary exercise test. The cardiopulmonary exercise test was performed using an electronically braked cycle ergometer attached to a customised imaging table (Lode BV, Groningen, The Netherlands) with the subject in a semi-recumbent position (torso at 50° from the horizontal). An incremental symptom-limited protocol was used which comprised a 3 minute baseline period at rest followed by 15 Watt increments in workload every 3 minutes. The initial workload was individualized based on age, gender and 6MWD. Standardised instructions and encouragement were provided to promote a maximum effort.

Breath by breath ventilation, oxygen and carbon dioxide concentrations and the derived minute ventilation, $\dot{V}O_2$ and carbon dioxide production were recorded (Vmax Sensormedics, Yorba Linda, CA). The maximum workload was defined as the highest workload sustained for >30 seconds. Peak $\dot{V}O_2$ was defined as the 30 second average centred on the highest $\dot{V}O_2$ measured at the maximum workload. Minute ventilation, $\dot{V}O_2$, carbon dioxide production and RER were calculated in the same manner. Predicted values for maximum $\dot{V}O_2$ were those determined by Jones et al (401).

Pulmonary artery pressure, pulmonary artery wedge pressure, and right atrial pressure were measured in the semirecumbent position. For transducer calibration, the zero position was taken as the fourth intercostal space in the midaxillary line. Pulmonary artery pressure and right atrial pressure were recorded continuously (Compact, Datex Engstrom, Helsinki, Finland) and CO was determined using thermal filament thermodilution, updated every 60 seconds (Vigilance, Baxter, Irvine, CA). Pulmonary artery wedge pressure was recorded at rest and every 3 minutes, immediately before an increase in workload and in the final minute of the test. If a subject performed < 30 seconds of the final workload, the peak pulmonary artery pressure, pulmonary artery wedge pressure, right atrial pressure, and CO responses were taken as the values measured within the last 60 seconds of the previous workload.

Haemodynamic digital data were streamed from the Datex and Vigilance monitors to a data acquisition system (Powerlab, AD Instruments, Sydney, Australia). Storage of analogue data (National Instruments, NI-DAQ 6008, 8 channel, 12-bit digital to analogue converter using proprietary software written in LabVIEW™ 7.0) allowed subsequent interrogation of the ECG and pulmonary artery pressure wave form data and determination of pulmonary artery wedge pressure and pulmonary artery pressure at end expiration. All measurements were corrected for phase delay. Predicted peak CO was calculated assuming an arterial-venous O_2 content difference of ([haemoglobin] x 10) (13). Systemic arterial pressure was measured manually at the brachial artery.

Quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36, Version 1) to determine current status and the transition from 12 months prior.

5.2.3 Statistical analysis

All data are presented as mean ± SD, unless otherwise stated. A mixed model to allow for matching of control and EIPAH subjects was performed for the analysis of the differences in baseline characteristics between control and EIPAH groups, and a *t*-test was used to identify differences between these groups. One-way ANOVA and post-hoc analysis with the Holm test was used to identify the difference in baseline characteristics between noPAH, EIPAH and PAH groups. Conditional logistic regression for matched subjects was performed to determine the differences in

haemodynamic, ventilatory and exercise capacity outcome measures, and the Wilcoxon matched pairs signed-rank test was performed to determine the difference in QoL measures between the EIPAH and control groups. Multinomial regression was used to determine the difference in outcome measures between the noPAH, EIPAH and PAH groups. Statistical analyses were performed using Stata Version 11 (Stata Corp, College Station, Tex, USA) or SPSS software version 18 (SPSS, Chicago, IL). A probability value (p) <0.05 was accepted as significant.

Effect size was calculated based on an expected $\dot{V}E/\dot{V}CO_2$ at AT of 29±4 in healthy individuals (11) and a $\dot{V}E/\dot{V}CO_2$ above 34 as a discriminating value for a pulmonary vascular limit to exercise (164) in the EIPAH group. Assuming 80% power and a 5% significance level, the sample size required to achieve a probability of 90% for detecting a difference between the EIPAH and control group was at least 14 subjects in each group.

5.3 Results

5.3.1 Subject demographics

Demographic data are presented in Table 5. The diffusing capacity for carbon monoxide was significantly reduced in the EIPAH and PAH groups, when compared to the reference range (420) and the control group. The noPAH group were younger than those in the EIPAH, PAH and EILVDD groups. There was a higher proportion of subjects with scleroderma in the EIPAH and PAH groups compared with the noPAH group.

No serious adverse events occurred. All cardiopulmonary exercise tests were symptom-limited. Dyspnoea was the most common symptom limiting exercise in the PAH and EIPAH groups (Table 6).

Table 5. Baseline demographics, noPAH, PAH, EILVDD, EIPAH and controls

		noPAH (n=10)	PAH (n=6)	EILVDD (n=4)	EIPAH (n=17)	Controls (n=20)	P value EIPAH vs control
Age, years		41±13	62±7*	64±3*	56±14*	57±13	0.8
Scleroderma, %		20	83*	50	71*	0	
Female gender, %		90	100	100	88	95	
Body mass index, kg/m^2		27±4	25±2	25±4	25±5	25±4	0.9
WHO functional class, %	II	0	50	100	65	N/A	
	III	0	50	0	35	N/A	
FEV_1, % predicted		104±18	99±7	86±8	93±11	112±11	<0.0001
FVC, % predicted		105±17	106±9	89±7	97±13	116±13	<0.0001
DLCO, % predicted		84±19	44±23*	82±15	74±18	87±13	0.03

Data are presented as mean ± SD, or percent. EIPAH compared with control using the independent *t*-test. * p<0.05, EIPAH, EILVDD and PAH compared with noPAH (Holm post hoc test). *Abbreviations:* PAH, pulmonary arterial hypertension; EILVDD, exercise-induced left ventricular diastolic dysfunction; EIPAH, exercise-induced pulmonary arterial hypertension; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

5.3.2 Ventilatory comparisons between the EIPAH and control groups

Compared with their matched control group, the EIPAH group demonstrated significant ventilatory abnormalities and impairment in exercise capacity. Exercise-induced PAH was associated with an elevated $\dot{V}E/\dot{V}CO_2$ and reduced $PetCO_2$ at AT and an attenuated rise in $PetCO_2$ from rest to AT. Further, EIPAH was associated with a significantly lower AT, peak $\dot{V}O_2$ and 6MWD (Table 6). These abnormalities were similar to the characteristic responses demonstrated by the PAH group, although less severe (Table 6).

There was an inverse correlation between $\dot{V}E/\dot{V}CO_2$ at AT and peak $\dot{V}O_2$ (r = -0.63, p<0.01) and between $\dot{V}E/\dot{V}CO_2$ at AT and 6MWD (r = -0.59, p<0.01) when data from the EIPAH and PAH groups were combined.

The EIPAH group had a significant impairment in QoL, with the greatest impairment in the physical domains (Table 7). Based upon responses to the health transition item, a higher proportion of the EIPAH group than the control group reported that their health was worse compared with the previous year (24% versus 5% respectively, p<0.01).

5.3.3 Quality of life comparisons between PAH, EIPAH, EILVDD and noPAH

There were no significant differences in QoL between the PAH, EIPAH, EILVVD and noPAH groups, including the health transition responses (all p>0.05).

Table 6. Exercise capacity, ventilatory and systemic hemodynamic responses and limiting symptoms on the CPET

		noPAH (n=10)	PAH (n=6)	EILVDD (n=4)	EIPAH (n=17)	Controls (n=20)	P value EIPAH vs control
Peak $\dot{V}O_2$, L/min		1.7±0.5	0.8±0.3*	1.2±0.3	1.2±0.4	1.7±0.5	0.03
Peak $\dot{V}O_2$, % predicted		77±13	48±17*	69±16	64±18	90±19	0.03
Anaerobic threshold (AT), L/min		0.8±0.2	0.4±0.1*†	0.8±0.1	0.6±0.2	0.9±0.2	0.02
6MWD, metres		601±78	517±128	582±17	575±86	669±76	0.03
$\dot{V}E/\dot{V}CO_2$ at AT		34±4.2	51±13.9*‡	32±0.8	41±7.3†	31±2.9	0.03
$PetCO_2$ at AT, mmHg		36±2	28±6*‡	39±0.6	33±4‡	39±3	0.04
Change $PetCO_2$, rest to AT		1.0±2.4	-0.2±2.1	2.2±2.6	0.8±3	3.7±2.3	0.04
SpO_2 at peak exercise, %		96±2	90±5*	97±2	94±3	96±2	0.08
Limiting factor, %	Dyspnoea	30	67	50	41	5	0.046
	General fatigue	50	17	0	24	24	
	Leg Fatigue	20	0	50	35	67	

Data are presented as mean ± SD. *p<0.05, EIPAH and PAH compared with noPAH, age adjusted (multinomial regression). †p <0.05, ‡p<0.01 PAH and EIPAH vs EILVDD group (multinomial regression). *Abbreviations:* PAH, pulmonary arterial hypertension; EILVDD, exercise-induced left ventricular diastolic dysfunction; EIPAH, exercise-induced pulmonary arterial hypertension; Peak $\dot{V}O_2$, peak oxygen consumption; 6MWD, six-minute walk distance; $\dot{V}E/\dot{V}CO_2$ at AT, ventilatory equivalent for carbon dioxide; AT, anaerobic threshold; $PetCO_2$, end tidal carbon dioxide tension; SpO_2, oxygen saturation.

Table 7. Quality of Life (SF-36, Version 1)

	noPAH (n=10)	PAH (n=6)	EILVDD (n=4)	EIPAH (n=17)	Controls (n=20)	P value EIPAH vs control
Physical functioning	52±18	47±16	63±19	54±16	93±9	0.0001
Role physical	33±35	21±40	63±32	49±45	100±0	0.0005
Bodily pain	63±25	71±29	64±24	56±27	77±26	0.03
General health	48±19	44±17	41±8	49±18	82±16	0.002
Vitality	39±19	51±20	50±11	50±13	76±13	0.0002
Social functioning	61±25	79±17	88±10	68±22	95±13	0.01
Role emotional	83±36	67±52	100±0	67±41	95±13	0.03
Mental health	69±16	72±19	48±20	66±21	85±16	0.002

Data are presented as mean ± SD. (Wilcoxon matched pairs signed-rank test). *Abbreviations:* PAH, pulmonary arterial hypertension; EILVDD, exercise-induced left ventricular diastolic dysfunction; EIPAH, exercise-induced pulmonary arterial hypertension.

Table 8. Haemodynamic variables measured at rest and during the CPET

	noPAH (n=10)	PAH (n=6)	EILVDD (n=4)	EIPAH (n=17)	Control (n=20)	P value EIPAH vs noPAH
Resting mPAP, mmHg	13±2	30±9	18±4*	18±4		0.03
Peak mPAP, mmHg	23±2	51±15‖	37±6	37±5		
Change in mPAP, mmHg	10±2	22±11*	19±7*	18±4		0.02
Resting CO at rest, L/min	5.7±0.7	5.4±1.1	6.1±1.2	5.4±1.4		0.6
Peak CO, L/min	12.4±3.1	8.6±2.6	10.4±0.9	10.4±2.8		0.5
Peak CO, % predicted	82±24	59±19	72±10	72±19		0.9
Resting PVR, Wood units	0.8±0.4	3.9±1.5*	1.5±0.3	2.2±1.2		0.04
Peak PVR, Wood units	1.3±0.5	3.9±1.3*	1.4±0.6	2.1±0.8		0.07
Resting RVSWI, gm.m/m^2/beat	4.6±2.4	12.4±4.9§	8.0±3.9	7.5±2.0		0.03
Peak RVSWI, gm.m/m^2/beat	10.2±2.7	19.9±7.2§	20.3±7.8*	17.6±3.6		0.03
Resting PAWP, mmHg	8.7±1.2	9±3.6	10.5±2.6	8.4±2.6		0.7
Peak PAWP, mmHg	10.0±3.0	14.5±9.3	24.0±3.6*	12.7±4.5		0.2
Resting RAP, mmHg	6±1.6	5.8±3.3	5.8±1.7	5.6±2.9		0.7
Peak RAP, mmHg	5.6±4.8	11.8±3.8	5.5±7.8	7.8±2.5		0.1
Resting systemic MAP, mmHg	119±14	113±19	107±19	109±16	102±13	0.2
Peak systemic MAP, mmHg	74±9	129±13	128±16	125±12	118±14	0.2
Resting HR, beats.min^{-1}	74±9	78±10	80±16	74±10	68±10	0.09
Peak HR, beats.min^{-1}	157±17	134±19*	131±28	133±15§	149±20	0.02

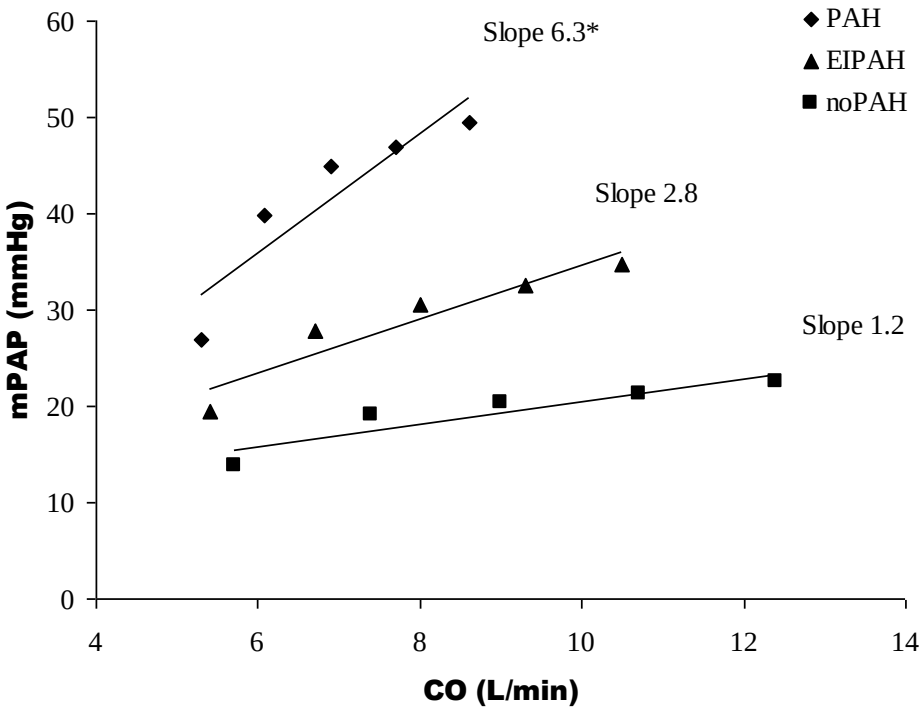
Data are presented as mean ± SD. *p<0.05, §p<0.01, ‖p<0.001, EIPAH, EILVDD and PAH compared with noPAH, age adjusted (multinomial regression). Stratification by mPAP prevented statistical analysis of the difference in mPAP, or measures derived from mPAP, between PAH and noPAH groups at rest and between EIPAH and noPAH groups at peak exercise.

Abbreviations: PAH, pulmonary arterial hypertension; EILVDD, exercise-induced left ventricular diastolic dysfunction; EIPAH, exercise-induced pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; MAP, mean arterial pressure; HR, heart rate.

5.3.4 Haemodynamic comparisons between EIPAH, PAH and noPAH

When adjusted for age, there was no significant difference in peak exercise CO between groups. Peak exercise CO was lower than predicted in all groups (Table 8). At rest, the EIPAH group demonstrated a higher mPAP, pulmonary vascular resistance, and right ventricular stroke work index than the noPAH group. The EIPAH and PAH groups had a significantly greater rise in mPAP (Table 8) and the PAH group had a steeper slope in the relationship between mPAP and CO (Figure 5) from rest to peak exercise than the noPAH group.

Figure 5. Pressure versus flow during exercise. The relationship between mPAP and CO during a symptom-limited CPET.



*p = 0.009 PAH versus noPAH, pairwise comparison. *Abbreviations:* mPAP, mean pulmonary artery pressure; CO, cardiac output; CPET, cardiopulmonary exercise test; PAH, pulmonary arterial hypertension; EIPAH, exercise-induced pulmonary arterial hypertension; noPAH, no pulmonary arterial hypertension

By definition, the PAH group had a higher mPAP at rest and the EIPAH group had a higher mPAP at peak exercise than the noPAH group. Stratification by mPAP prevented statistical analysis of the difference in mPAP, or measures derived from mPAP, between PAH and noPAH groups at rest and between EIPAH and noPAH groups at peak exercise.

5.3.5 Comparisons between the EIPAH and EILVDD groups

The EIPAH group had a significantly higher $\dot{V}E/\dot{V}CO_2$ at AT (p=0.03) and a lower $PetCO_2$ at AT (p=0.008) compared with the EILVDD group. There were no statistically significant differences in resting or exercise haemodynamic responses between the EIPAH and EILVDD groups, although by definition, the group with EILVVD had a higher pulmonary artery wedge pressure at peak exercise than the EIPAH group. Similarly, there were no differences in AT, peak $\dot{V}O_2$ or 6MWD between these groups.

5.3.6 Influence of age and diagnosis of scleroderma

Neither age (r = -0.05, 95% CI -0.26 to 0.15, p=0.6) nor the presence of scleroderma (r=0.76, 95% CI -4.9 to 6.4, p=0.8) had an influence on peak exercise mPAP but both were significant factors in determining peak exercise CO, with older age (r= -0.08, 95% CI -0.14 to -0.03, p=0.005) and a diagnosis of scleroderma (r= -1.9, 95% CI -3.6 to -0.4, p=0.02) being associated with a lower peak exercise CO. Subjects with scleroderma (n=20) were older than those without a clinical diagnosis (mean age 58±12 versus 40±14 years, p<0.01). Scleroderma was associated with impaired QoL (social functioning domain, p<0.05). Neither age nor a diagnosis of scleroderma had a significant influence on any other outcome measure (all p>0.05).

5.4 Discussion

This study describes exercise abnormalities associated with EIPAH in symptomatic patients, at risk of PAH. Exercise-induced PAH (mPAP >30mmHg and a pulmonary artery wedge pressure <20mmHg on exercise) was associated with ventilatory abnormalities and a clinically important reduction in exercise capacity, consistent with a pulmonary vascular limitation to exercise and typical of PAH. These exercise impairments were accompanied by a marked reduction in QoL.

Reduced exercise capacity and a low AT, in the presence of an elevated $\dot{V}E/\dot{V}CO_2$ and reduced oxygen saturation, identify a pulmonary vascular limitation to exercise, according to a well accepted diagnostic algorithm for exercise interpretation (13). Reduced $PetCO_2$ at AT and a fall, rather than rise, in $PetCO_2$ from rest to AT have also been shown to be associated with PAH (12, 168). Our data confirm these

findings in the group with PAH. Compared with healthy controls, similar but milder ventilatory abnormalities were evident in the EIPAH group. These abnormalities in the EIPAH group, in whom there was a clinical suspicion of PAH, are consistent with a mild, or early, pulmonary vasculopathy, similar to that present in subjects with PAH. The abnormal ventilatory responses demonstrated by the EIPAH group were not seen in the group with EILVDD. This finding supports the suggestion that the abnormalities demonstrated by the EILVDD group were more likely to be related to left heart dysfunction than a pulmonary vasculopathy. Further, these results lend weight to the suggestion that a cardiopulmonary exercise test may help differentiate these groups. Our findings contrast with those of Walkey et al (421) who found no difference in the $\dot{V}E/\dot{V}CO_2$ at AT between subjects with scleroderma and who had an elevated pulmonary artery wedge pressure at peak exercise (EILVDD, n=4) compared with those with a peak exercise pulmonary artery wedge pressure <18mmHg and evidence of a pulmonary vascular limit to exercise (n=3). However, according to our calculations, the Walkey study (23) was not powered to detect differences between groups comprising numbers of three and four. There was no overlap of $\dot{V}E/\dot{V}CO_2$ at AT between groups with a pulmonary vascular limit to exercise or EILVDD, with all subjects in the pulmonary vascular group having a higher $\dot{V}E/\dot{V}CO_2$ at AT than those with an elevated pulmonary artery wedge pressure.

The EIPAH group demonstrated a significant impairment in exercise capacity, in both peak$\dot{V}O_2$ and 6MWD. Although reduced peak$\dot{V}O_2$ has previously been reported in EIPAH (27) this is the first study to demonstrate that 6MWD is decreased. The 6MWD is a measure of submaximal exercise tolerance that is considered to reflect the capacity to perform activities of daily living (31). The inverse relationship between $\dot{V}E/\dot{V}CO_2$ at AT and both peak$\dot{V}O_2$ and 6MWD in our study suggests an association between ventilatory abnormalities and impaired maximal and submaximal exercise capacity in PAH and EIPAH.

When compared with healthy controls, the subjects with EIPAH had marked reductions in QoL, with a greater magnitude of impairment in the physical health domains than in the mental health domains. In PAH, exertional symptoms impact on the ability to perform activities of daily living, which is reflected in the physical domains of the SF-36 (85). Our study demonstrates similar results in the EIPAH group, with exertional symptoms impacting negatively on QoL, particularly in the

physical domains. The cause of the QoL impairment in the noPAH group is uncertain. However, the finding of diminished QoL in this group is consistent with the significant, persistent exertional symptoms reported by these subjects.

The finding of ventilatory abnormalities in the EIPAH group in the current study contrasts with the observations made by Tolle et al (27) who identified haemodynamic abnormalities and reduced aerobic capacity in EIPAH, but no ventilatory differences between the EIPAH and control groups. This contrasting finding is likely related to the characteristics of the control groups used in the two studies. Subjects in the 'normal' group in the study by Tolle et al (27) were symptomatic patients. In that study, the $\dot{V}E/\dot{V}CO_2$ at AT was not sensitive in discriminating between subjects with and without EIPAH; however, the reported mean $\dot{V}E/\dot{V}CO_2$ at AT of 36 for the 'normal' group (mean age 45.9 years) is unlikely to represent a healthy response (164). Our inclusion of an asymptomatic control group allowed evaluation of the ventilatory response of subjects with EIPAH against responses in healthy age-, gender- and body mass index-matched control subjects and identified indisputable ventilatory abnormalities associated with EIPAH. In our study, there were significant haemodynamic differences between the EIPAH and noPAH groups. However, the younger, symptomatic noPAH group demonstrated impairments in peak exercise CO and exercise capacity, compared with age appropriate reference values, confirming that they would not have been an appropriate control group for this study.

Pulmonary arterial hypertension is known to be a progressive condition, although the rate of progression is variable (7). The clinical course of subjects with elevated mPAP on exercise is unknown. The finding that 24% of subjects with EIPAH in this study reported worsening QoL during the previous year raises the possibility that EIPAH may be associated with disease progression and represent an early phase of PAH. This is consistent with the recent findings by Condliffe et al (2) who reported that EIPAH associated with connective tissue disease progressed to PAH at rest in 19% of subjects and that death related to pulmonary hypertension and/or right heart failure occurred in 10% of subjects during a mean period of 3.3 years.

The question whether EIPAH progresses to PAH remains unanswered. However, regardless of progression, the current study identified marked functional impairments associated with EIPAH, suggesting that this condition warrants consideration for therapy. Clinical benefits, that include an improvement in 6MWD

and functional class, have recently been described following pharmacologic therapy for 'exercise-uncovered' PAH (defined as mPAP <25mmHg at rest but mPAP >30mmHg and a pulmonary artery wedge pressure ≤15mmHg on exercise) in an open-label trial (396). These findings demonstrate that, for selected patients with a mPAP >30mmHg on exercise, PAH specific therapy is beneficial. Furthermore, these findings would be consistent with EIPAH being part of a continuum in pulmonary vascular disease.

We specifically chose a group with a high pretest probability of EIPAH to optimise the diagnostic yield of EIPAH in our investigation. Patients with scleroderma are known to be at increased risk of PAH (241). Scleroderma was present in 54% of the patient subjects in our study, and 81% of these had PAH or EIPAH. Our results, and those of Condliffe et al (2) suggest a high incidence of a pulmonary vascular dysfunction and progression in subjects who have scleroderma, a reduced diffusing capacity for carbon monoxide and exertional symptoms of dyspnoea and fatigue. In our study, scleroderma was associated with a lower peak exercise CO and impaired social functioning however there was no association between any of the other identified functional limitations and a diagnosis of scleroderma. These impairments, therefore, appear to reflect a pulmonary vasculopathy rather than other morbidities associated with scleroderma. Kovacs et al (419) also reported an association between increased exercise mPAP and impaired exercise capacity in subjects with scleroderma and suggested a pulmonary vasculopathy as the likely cause for their findings.

To accommodate the possibility that age would be a confounding factor in the difference between the patient groups, we recruited an age-matched control group. In comparison with this control group, clear and indisputable ventilatory, exercise capacity, and QoL impairments were identified in the EIPAH group.

Previous studies reporting invasive central haemodynamics to describe the development of pulmonary hypertension on exercise in symptomatic subjects with an mPAP <25mmHg at rest (27, 302, 395, 422) have significant limitations. Early studies neither measured pulmonary artery wedge pressure on exercise (302, 422) nor excluded subjects with an abnormal pulmonary artery wedge pressure at rest or on exercise (395) and therefore were unable to exclude post-capillary pulmonary hypertension. The lack of a healthy control group in the study by Tolle et al (27)

prevented an adequate description of the clinical sequelae of EIPAH. The current study has addressed these limitations.

We have demonstrated that combining the assessment of central haemodynamic and ventilatory responses during exercise can identify a likely pulmonary vasculopathy that is not evident at rest. This analysis of pulmonary vascular function under stress provides the potential to improve early diagnosis of PAH, if EIPAH is found to be an early stage of PAH.

5.4.1 Limitations and general applicability of this study

No central haemodynamic data were collected for control subjects because this was considered unethical due to the invasive nature of the procedure. This precluded comparison of haemodynamic responses in the EIPAH group with those of healthy controls.

We examined a carefully selected group of patients referred to a regional pulmonary hypertension centre which services a population of 1.5 million people. We believe that our findings cannot be applied to all patients presenting with unexplained dyspnoea. Nonetheless, the group we studied represents a dilemma with which clinicians are often faced, namely, a patient presenting with risk factors and a clinical suspicion of PAH but who does not meet diagnostic criteria for PAH at rest.

It is likely that the significance of a rise in mPAP on exercise is influenced by age, and the pre-test probability of a pulmonary vasculopathy as shown by others (2, 30). Although the general applicability of our findings is uncertain, we believe the abnormalities identified on exercise, in the subjects with EIPAH, are clinically significant. They suggest that, in a selected group, a rise in mPAP with exercise to >30mmHg should not be dismissed even if mPAP is <25mmHg at rest.

We have presented cross-sectional data only. Longitudinal follow up of the cohort with EIPAH is being undertaken.

This study was not powered to detect a difference in outcome measures between groups of four to ten subjects. Therefore, findings of no difference between the noPAH, EILVDD and PAH with other groups should be interpreted with caution.

The loss of independence of the control group, by individual matching of control and EIPAH subjects, precluded statistical comparison of the noPAH, EILVDD and PAH groups with the control group.

5.5 Conclusions

Haemodynamic findings on exercise, in isolation, may be difficult to interpret due to a wide range of normal responses. However, the combination of haemodynamic and ventilatory measures in the assessment of selected symptomatic patients can identify abnormalities which are characteristic of PAH, may represent early manifestations of a pulmonary vasculopathy, and may therefore facilitate earlier diagnosis of PAH.

Addendum: Usual physical activity in EIPAH and control groups.

Method: An initial subjective assessment of the control subjects' participation in organised sport and usual physical activity was performed during the telephone conversation made to confirm the volunteers' suitability for the study and to arrange the data collection appointments. Volunteers who were involved in organised sport or high levels of usual physical activity were excluded from the study (n=6). Both the control subjects and patients completed the Short Last 7 Days, Self-administered Format of the International Physical Activity Questionnaire (IPAQ)(410) during the rest period between the 6MWTs on the first day of assessment.

Results: Based upon the results obtained using the IPAQ (410) there was no difference in the usual physical activity level between the EIPAH and control groups. The total metabolic equivalent (MET) minutes per week was 4272±4859 in the EIPAH group, versus 3304±2840 in the control group (p=0.7). The time spent sitting on a week day, per week, was 1695±1125 min in the EIPAH group versus 1725±830 min in the control group (p=0.9).

CHAPTER 6
MEASUREMENT PROPERTIES OF THE 6MWT IN INDIVIDUALS WITH EXERCISE-INDUCED PULMONARY ARTERIAL HYPERTENSION

Fowler RM, Jenkins SC, Maiorana AJ, Gain KR, O'Driscoll G, Gabbay E. Measurement properties of the 6-min walk test in individuals with exercise-induced pulmonary arterial hypertension. *Intern Med J* 2011; 41:679-687

6.1 Introduction

Pulmonary arterial hypertension (PAH) is a progressive condition characterised by elevated pulmonary vascular resistance, reduced pulmonary blood flow and an attenuated increase in cardiac output (CO) during exercise (27). The hallmark of PAH is exertional intolerance with symptoms that include dyspnoea, fatigue and light-headedness. The diagnosis of PAH is based on abnormal resting haemodynamics (1). However, recent studies demonstrate that some individuals have normal haemodynamics at rest but a higher than expected mean pulmonary artery pressure (mPAP), in the presence of a normal pulmonary artery wedge pressure and reduced cardiac output at peak exercise, in association with reduced exercise capacity and symptoms typical of PAH (27, 76). This elevation in pulmonary pressure on exercise has been called exercise-induced PAH (EIPAH) and has been proposed to be part of the spectrum of pulmonary vascular diseases (78).

The capacity of the cardiovascular, respiratory and skeletal muscle systems to transport and utilize oxygen for aerobic metabolism is quantified by measuring peak oxygen consumption (peak $\dot{V}O_2$) during a cardiopulmonary exercise test (CPET). While peak $\dot{V}O_2$ reflects disease severity and prognosis in PAH (9), a CPET requires specialist knowledge and equipment. In contrast, the six-minute walk test (6MWT) requires minimal equipment, is easy to administer and is widely available. Measures derived from the 6MWT include the six-minute walk distance (6MWD) and six-minute walk work (6MWW), the product of 6MWD and body weight. Six-minute

walk distance, which quantifies functional exercise impairment, has been shown to provide a valid estimate of peak $\dot{V}O_2$ in individuals with PAH (34, 35) and is more sensitive to change with pharmaceutical therapy in PAH than peak $\dot{V}O_2$ (35, 51). Accordingly, 6MWD has been employed as the primary outcome measure for clinical trials of pharmaceutical therapy in PAH (1). However, in subjects with chronic obstructive pulmonary disease (COPD), 6MWW has been shown to correlate more strongly with disease severity and to have greater sensitivity and specificity for low exercise capacity than 6MWD (338).

The 6MWT can be administered with or without encouragement. Clinical trials in PAH have mostly utilised a protocol devoid of encouragement to better reflect the subjects' ability to perform activities of daily living. However, the American Thoracic Society recommends a 6MWT protocol with standardised encouragement, to measure maximal walking capacity (308). Investigations reporting physiological responses to a 6MWT in PAH have typically utilised an encouraged 6MWT (133, 365) given that it is more likely to identify a physiological limitation to exercise than an unencouraged test. However, in individuals with mild-moderate impairment in aerobic capacity, such as EIPAH (27), mechanical constraints that limit maximum walking speed, rather than physiological dysfunction, may influence 6MWD. This 'ceiling effect' has been reported in patients with chronic heart failure (CHF) (36) and PAH (37) with mild functional limitation (World Health Organization Functional Class II, [WHO FC II]).

The aims of this study, in subjects with EIPAH, were to: (i) compare physiologic and symptomatic responses to the 6MWT and CPET, and (ii) determine whether the 6MWT can identify functional exercise limitation and accurately estimate aerobic capacity.

6.2 Methods

6.2.1 Participants

Forty-nine adults were recruited from the Pulmonary Hypertension Unit at Royal Perth Hospital (Perth, Western Australia). All subjects had been referred for investigation of dyspnoea of unknown aetiology, were in WHO FC II or III, and were investigated for PAH as defined by the 2004 European Society of Cardiology

Guidelines (51), that is, mean pulmonary artery pressure (mPAP) >25mmHg and pulmonary artery wedge pressure ≤ 15mmHg at rest. Based upon historically accepted upper limits of normal (400), subjects were identified as having exercise-induced PAH (EIPAH) if mPAP was >30mmHg and pulmonary artery wedge pressure was <20mmHg, on exercise. As determined prior to commencement of the study, subjects were excluded or withdrawn from the study if they had a body mass index (BMI) >35kg/m^2 (n=4), ischaemic heart disease (n=1), a history or evidence of pulmonary parenchymal or airway disease on high resolution computed tomography or lung function testing (n=5), a musculoskeletal condition limiting exercise performance (n=1), anaemia (n=1), PAH at rest (mPAP >25mmHg at rest, n=6), normal mPAP at rest or on exercise (n=10), or a pulmonary artery wedge pressure >15mmHg at rest or >20mmHg on exercise (n=4). Data from the remaining 17 subjects were used in the analyses.

A population-based sample of 20 healthy control subjects was recruited from a database of research volunteers maintained by the Lung Institute of Western Australia (Perth, Western Australia). Controls were matched to subjects with EIPAH for gender, age (±5 years) and BMI (±3$kg.m^{-2}$, provided BMI was ≤35$kg.m^{-2}$). All controls underwent medical examination and a series of screening tests (medical history, echocardiogram, electrocardiogram, lung function tests and haematology) to confirm their healthy status.

The study was approved by the Human Research Ethics Committees of Royal Perth Hospital and Curtin University. Written informed consent was obtained from all subjects prior to enrolment. This work was performed at Royal Perth Hospital, Perth, Western Australia.

6.2.2 Study design

The study employed a prospective cross-sectional design. All subjects completed two encouraged 6MWTs on one day, separated by at least 30 minutes rest. A symptom-limited incremental CPET was performed between 1 and 32 (mean of 5) days following the 6MWTs. Subjects recruited from the Pulmonary Hypertension Unit had a pulmonary artery catheter in situ during the CPET, for the measurement of central haemodynamics. All tests were supervised by the same investigator (RF).

6.2.2.1 Exercise protocols

Six-minute walk test

The 6MWT was performed over a 45m course in an enclosed corridor according to the American Thoracic Society guidelines (308). All subjects completed two 6MWTs, separated by at least 30 minutes. Heart rate (Polar Electro Oy; Kempele, Finland) was monitored throughout the test. Sensations of dyspnoea and leg fatigue were assessed immediately following test cessation using the Borg Category Ratio Scale (408).

Cardiopulmonary exercise test

The CPET was performed using an electronically braked cycle ergometer attached to a customised imaging table (Lode BV, Groningen, Netherlands) with the subject in a semi-recumbent position (torso at 50° from the horizontal). An incremental symptom-limited protocol was employed which involved a 3 minute baseline period followed by 15 Watt increments in workload every 3 minutes. The initial workload was individualised based upon gender, age and 6MWD. Standardised instructions and encouragement were provided to promote a maximum effort. Breath by breath ventilation, oxygen and carbon dioxide concentrations and the derived minute ventilation, $\dot{V}O_2$ and carbon dioxide output were determined using the Vmax metabolic analysis system (Sensormedics, Yorba Linda, CA). Heart rate (12 lead electrocardiogram; Cardiosoft, Version 4.2, GE Medical Systems, Milwaukee, WI) and SpO_2 (Oxypleth pulse oximeter and ear sensor, Novemetrics, Wallingford, CT) were monitored continuously throughout the test.

The method of haemodynamic monitoring and data collection employed in the assessment of the subjects with EIPAH has previously been reported (76). In brief, pulmonary artery pressure was continuously monitored (Compact, Datex Engstrom, Helsinki, Finland). Cardiac output was determined using thermal filament thermodilution, updated every 60 seconds (Vigilance, Baxter, CA). Pulmonary artery wedge pressure was recorded at rest and every 3 minutes, immediately prior to an increase in workload, and in the final minute of the test. If a subject performed less than 30 seconds of the final workload attempted, the mPAP, pulmonary artery wedge pressure and CO responses were taken as the values measured within the last 60 seconds of the previous workload. Systemic arterial pressure was measured

manually, at the brachial artery, at rest and every 3 minutes, immediately prior to an increase in workload and in the final minute of the test.

Ratings of dyspnoea and leg fatigue were recorded during the last 60 seconds of each workload and immediately following test cessation. The maximum workload was defined as the highest workload maintained for >30 seconds and peak $\dot{V}O_2$ was defined as the 30 second average measured at the maximum workload within the last 30 seconds prior to test termination. Minute ventilation, $\dot{V}O_2$, carbon dioxide output and respiratory exchange ratio were calculated.

The demographic, 6MWD and peak $\dot{V}O_2$ data for both EIPAH and control groups have previously been reported.(76)

6.2.2.2 Statistical analyses

The effect of test repetition on 6MWD was examined using a general linear model for repeated measures. For each group, the magnitude of change in 6MWD between tests 1 and 2 was compared using the paired *t*-test. The greater 6MWD was used in all subsequent analyses. The coefficient of repeatability was determined as twice the SD of the difference in 6MWD measured on the two tests. Comparisons of responses to the 6MWT and CPET for the EIPAH group and control group were performed for each group separately using paired *t*-tests (heart rate [HR]) and Wilcoxon signed rank tests (peak dyspnoea and rate of perceived exertion). Differences between the EIPAH and control groups were analysed using unpaired *t*-tests (continuous variables) and the Mann-Whitney U test (peak dyspnoea and rate of rate of perceived exertion). Relationships between 6MWD and 6MWW with peak values of $\dot{V}O_2$ and CO were assessed using Pearson correlation coefficients and linear regression analysis. Data were analysed using SPSS software Version 18 (SPSS, Chicago, IL, USA) A p value of <0.05 was considered to be statistically significant. Data are presented as mean ± SD unless otherwise stated.

6.3 Results

Subject characteristics are presented in Table 9. The subjects with EIPAH had a lower forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), percent predicted, than the controls ($p<0.001$ for both). However, all lung function test results for subjects in the EIPAH group were within the reference range (423) and FEV_1/FVC was the same in both groups indicating there was no evidence of airflow obstruction in the EIPAH subjects. The diffusing capacity for carbon monoxide was reduced in the EIPAH group when compared with the controls and the reference range (420).

Table 9. Subject characteristics, EIPAH and controls

Characteristic	EIPAH	Controls
Females/males	15/2	19/1
Age (years)	56±14(35-81)	57±13(33-77)
Height (m)	1.63±0.8	1.65±0.7
Weight (kg)	67±12	68±9
BMI (kg/m^2)	25±5	25±4
FEV_1, % predicted	93±11**	112±11
FVC, % predicted	97±13**	116±13
FEV_1/FVC %	78±7	78±7
DLCO, % predicted	74±18*	87±13
WHO Functional Class II	11	
WHO Functional Class III	6	
mPAP, rest (mmHg)	17.9±3.6	
peak exercise	36.6±5.1	
CO, rest (L/min)	5.4±1.4	
peak exercise	10.4±2.8	
PVR, rest (Wood units)	2.2±1.2	
peak exercise	2.1±0.8	

Note: Data are mean±SD (range) or number of subjects. * $p<0.01$, ** $p<0.001$, EIPAH versus control.
Abbreviations: kg, kilograms; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; SpO_2, oxygen saturation; WHO, World Health Organisation; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance.

6.3.1 Exercise responses

There were no adverse events associated with the exercise tests. In the EIPAH subjects, dyspnoea or leg fatigue was the most common symptom limiting performance on both tests. In the controls, the most common factors limiting performance on the 6MWT and CPET were an inability to walk faster and leg fatigue, respectively (Table 10).

Table 10. Heart rate and symptomatic responses to the 6MWT and CPET

		EIPAH		Control	
		6MWT	CPET	6MWT	CPET
Peak HR (bpm)		133±19	133±15**	139±17†	149±20
% predicted HR max		76±13	77±8**	80±11	86±9
Peak dyspnoea		3.4±1.5*‡	4.8±1.2	2.2±1.2§	5.0±1.8
Peak RPE		4.6±2*	6.0±2.4*	3.2±2	6.8±2.3
Limiting factor:	Dyspnoea	8(47%)	7(41%)	0	1(5%)
	Leg fatigue	8(47%)	6(35%)	5(24%)	14(67%)
	Mechanics¶	1(6%)	0	15(71%)	0
	General fatigue	0	4(24%)	0	5(24%)
	Other	0	0	1(4%)	1(4%)

Note: Data are mean±SD, (percentage of subjects). †p<0.05, ‡p<0.01, §p<0.001 6MWT vs CPET. *p<0.05, **p<0.01, EIPAH versus control. *Abbreviations:* 6MWT, six-minute walk test; CPET, cardiopulmonary exercise test; bpm, beats per minute; RPE, rate of perceived exertion.
Mechanical constraints of walking limiting maximum distance.

6.3.1.1 Physiological and symptomatic responses, 6MWT and CPET

Peak HR was similar in the CPET and 6MWT in the EIPAH group (p=0.8), but higher in the CPET than the 6MWT in the control group (p<0.05) (Table 10). Peak HR was higher in the control group than the EIPAH group during the CPET (p<0.01) (Table 10). The peak dyspnoea score was higher in the CPET than the 6MWT in both groups (EIPAH p<0.01, control p<0.001) and higher in the EIPAH group than the control group at the end of the 6MWT (p<0.05). There was no difference in the peak dyspnoea score between groups at the end of the CPET (p=0.8).

6.3.1.2 Exercise capacity

Six-minute walk distance, 6MWW and peak $\dot{V}O_2$ were all significantly reduced in the EIPAH group, compared with the controls ($p<0.01$) (Table 11).

Table 11. 6MWT and CPET results

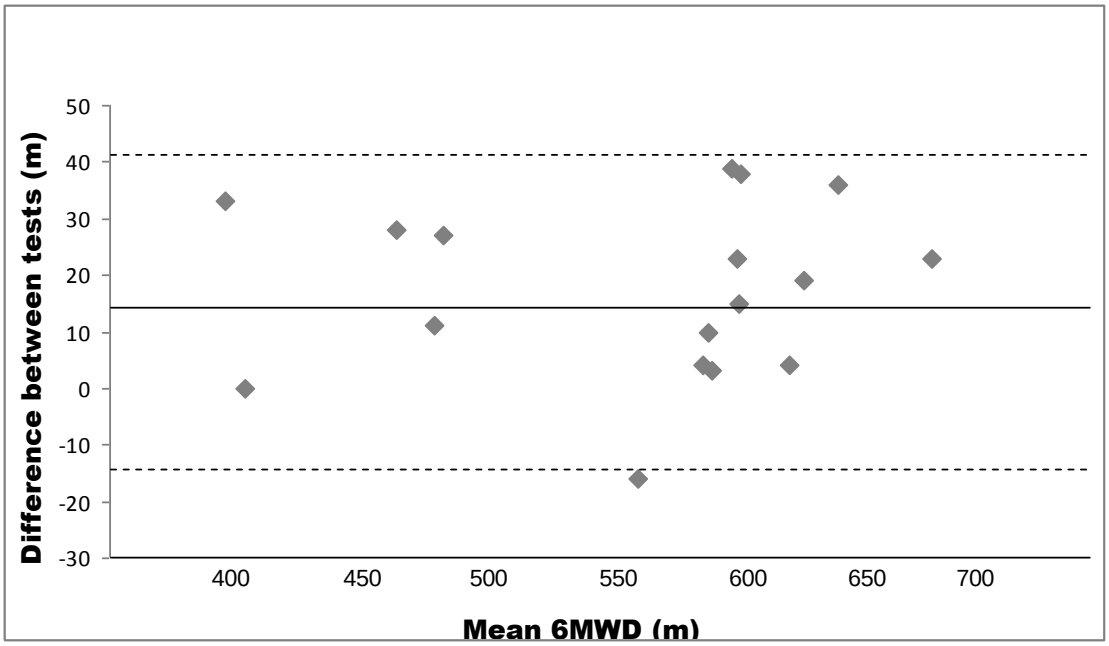
	EIPAH	Control
6MWT		
6MWD, m (% predicted)[45]	575±86 (88±11)***	669±76 (102±9)
6MWW, kg.km	39±11**	45±7
CPET		
Peak $\dot{V}O_2$, L/min, (% predicted)	1.2±0.4 (64±18)**	1.7±0.5 (90±19)
Peak $\dot{V}O_2$, ml/min.kg^{-1}	18±4**	25±7
Initial workload, Watts	18±13 (0-30)	43±21 (15-75)
Maximum workload, Watts	62±20 (30-90)	104±39 (60-195)
$\dot{V}E/\dot{V}CO_2$ at AT	41±7.3***	31±2.9
Respiratory exchange ratio	1.05±0.06*	1.11±0.06

Notes: Data are mean ±SD (percent predicted, or range). *p<0.05, **p<0.01, ***p<0.001, EIPAH versus control. *Abbreviations:* 6MWT, six-minute walk test; CPET, cardiopulmonary exercise test; 6MWD, six-minute walk distance; 6MWW, six-minute walk work; kg.km, kilogram times kilometre; peak $\dot{V}O_2$, peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$ at AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold.

6.3.1.3 Effect of test repetition on 6MWD

Fifteen subjects (88%) in the EIPAH group and 16 (80%) subjects in the control group increased their 6MWD on the second test. There was a significant difference in 6MWD between test 1 and test 2 in both the EIPAH (556±86m versus 574±85, $p<0.001$) and control (655±66m versus 668±77, $p<0.01$) groups. Test repetition was associated with marked individual variation in the magnitude of change in 6MWD in the EIPAH (+18±15m, range -16 to +39m, [3±3%]) and control (+9±11m, range -10 to +29m, [1±2%]) groups. There was no difference in the magnitude of change in 6MWD on the second test between the EIPAH and control groups ($p=0.08$). The coefficient of repeatability for the EIPAH and control groups was 31m and 22m respectively. The variability between 6MWTs 1 and 2 is demonstrated in Figure 6.

Figure 6. Bland-Altman plot showing agreement in 6MWD between two 6MWTs for individuals with EIPAH

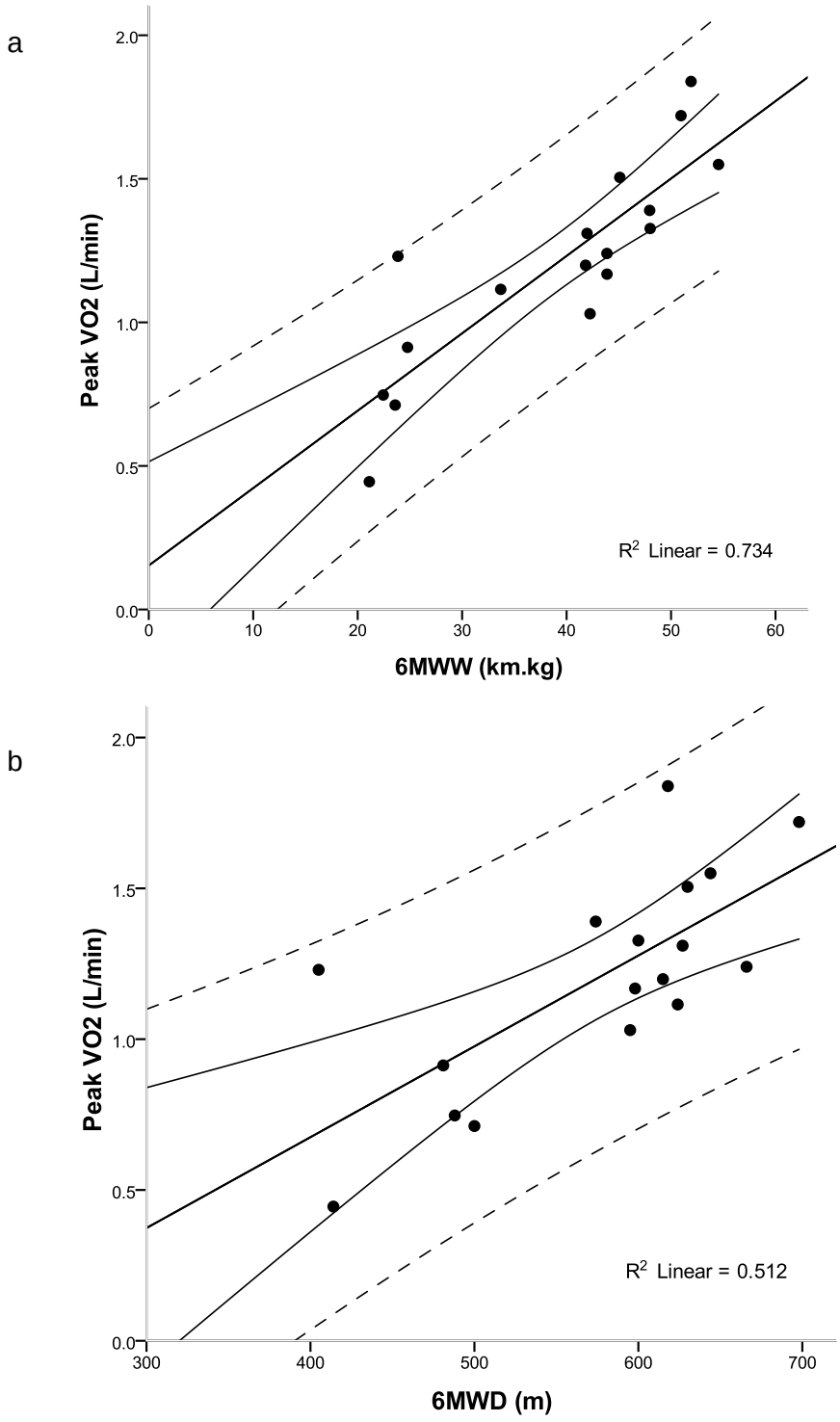


The solid line indicates the mean difference in 6MWD between test 1 and test 2 (6MWT2 minus 6MWT1). The dashed lines indicate the mean of the difference ± 2SD. *Abbreviations:* 6MWD, six minute walk distance; 6MWT, six minute walk test; EIPAH, exercise-induced pulmonary arterial hypertension

6.3.1.4 Relationship between 6MWT results, peak $\dot{V}O_2$ and peak CO

Figure 7 illustrates the relationships between 6MWW and 6MWD with peak $\dot{V}O_2$ in subjects with EIPAH. There was a strong correlation between 6MWW and peak $\dot{V}O_2$ (L/min) for subjects with EIPAH (r=0.86, p<0.001) and a moderate correlation for the control group (r=0.74, p<0.001). Peak $\dot{V}O_2$ accounted for 73% and 55% of the variance in 6MWW in the EIPAH and control groups respectively. There were moderate correlations between 6MWD and peak $\dot{V}O_2$ in the EIPAH (r=0.72, p<0.01) and the control groups (r=0.61, p<0.01).

Figure 7. Relationships between 6MWW and 6MWD with peak VO2, in EIPAH



Regression line, 95% confidence intervals (solid lines) and 95% prediction intervals (hatched lines) in subjects with EIPAH demonstrating the relationship between (a) six-minute walk work (6MWW, kg.km) and peak oxygen consumption (peak $\dot{V}O_2$, L/min) and (b) six-minute walk distance (6MWD, m) and peak $\dot{V}O_2$, L/min.

In the EIPAH group, there was a significant correlation between 6MWD and peak exercise CO (r=0.59, p<0.05) but not between 6MWW and peak exercise CO (r=0.46, p=0.07).

A significant correlation was evident between peak $\dot{V}O_2$ (L/min) and CO (*r*=0.55, p<0.05). Peak exercise CO accounted for 21% of the variance in 6MWW, 36% of the variance in 6MWD and 30% of the variance in $\dot{V}O_2$ (L/min).

6.4 Discussion

The principal findings from this study are that 6MWD and 6MWW, derived from an encouraged 6MWT, identify reduced exercise capacity and correlate significantly with peak $\dot{V}O_2$ in subjects with EIPAH. These findings suggest that the encouraged 6MWT is a valid test of exercise capacity in this cohort. While 6MWD, 6MWW and peak $\dot{V}O_2$ all correlated with peak exercise CO, only a small proportion of the impairment in exercise capacity was explained by peak exercise CO. This finding suggests that factors other than cardiac output, during an acute bout of exercise, contribute to exercise limitation in EIPAH.

The significant difference in 6MWD observed between the EIPAH and control groups demonstrates the capacity of the encouraged 6MWT to detect reduced functional exercise capacity in subjects with EIPAH who have mild-moderate functional limitation (WHO FC II and III). Furthermore, the moderate (6MWD) to strong (6MWW) correlations with peak $\dot{V}O_2$ suggests that the 6MWT is a valid method of estimating aerobic capacity in the absence of a CPET in EIPAH, although the wide prediction intervals highlight that the relationship was not strong in some individuals, a finding that is consistent with other studies (424). This result demonstrates that the 6MWT cannot be used to accurately predict peak $\dot{V}O_2$ in an individual with EIPAH.

The similar peak HR elicited during the 6MWT and CPET in subjects with EIPAH suggests that the encouraged 6MWT represents high intensity exercise for this cohort. This is consistent with reports in other patient populations (315-317) in which the encouraged 6MWT and CPET have been shown to elicit similar HR and peak $\dot{V}O_2$ responses. This finding is in contrast to a report that found a significantly higher peak HR during a CPET (employing cycle ergometry) compared with an

unencouraged 6MWT in PAH (314). This disparity is likely to reflect the difference in 6MWT protocol between studies. An encouraged 6MWT has been shown to elicit a greater physical effort than an unencouraged 6MWT in COPD and CHF (425). Our findings suggest that an encouraged 6MWT, in subjects with EIPAH in WHO functional classes II and III, is not subject to a ceiling effect and reflects physiological limitation and aerobic capacity in this cohort.

In contrast to the subjects with EIPAH, the control subjects had lower peak HR and dyspnoea scores during the 6MWT than the CPET, and, at best, moderate correlations between peak $\dot{V}O_2$, 6MWD and 6MWW, suggesting that a ceiling effect limited the capacity of the 6MWT to accurately estimate aerobic capacity in the healthy individuals.

Subjects from both groups reported higher dyspnoea scores during the CPET than the 6MWT. In the EIPAH group, in whom the maximum HR in each test were similar, this may be due to the higher levels of local muscle acidosis (426), serum lactate (427) and consequently $\dot{V}E$ (277, 314, 428) that occurs during a cycling test compared with a walking test, contributing to increased ventilatory work and an increased sensation of dyspnoea (199).

In previous studies of subjects with pulmonary vascular disease, reduced CO on exercise has been associated with impaired oxygen uptake kinetics (43) and reduced peak $\dot{V}O_2$ (27, 303). In our study, reduced CO during an acute bout of exercise appeared to have a limited role in the exercise limitation identified in subjects with EIPAH. There is increasing evidence that PAH is a systemic condition (199) with features similar to CHF and COPD. Inflammation, increased sympathetic nerve activity, a heightened ergoreflex response, skeletal muscle dysfunction and systemic endothelial dysfunction contribute to exercise limitation in CHF (206, 248, 429, 430) and COPD (429, 431-433). These systemic abnormalities, with the exception of ergoreflex up-regulation, have also been described in PAH (39, 138, 237, 249) and are potential contributors to exertional symptoms and exercise limitation in EIPAH. This is an important area for future research.

Previous studies in cohorts with chronic lung conditions (309, 326, 434, 435), cardiovascular disease (425) and healthy adults (312, 313, 436) have reported that test repetition (familiarisation to the 6MWT protocol) results in a small but significant increase in 6MWD on the second test. Our study extends this observation to

subjects with EIPAH. While the mean increase in 6MWD with test repetition was small there was a large variability among individuals, with the magnitude of increase being as great as 39m. The coefficient of repeatability, of 31m, for 6MWD in our EIPAH group indicates that an increase, or fall, in 6MWD of up to 31m in an individual with EIPAH, may be due to measurement variability rather than to at treatment effect, or worsening of the condition.

6.5 Limitations of the study

The sample size of this study was relatively small and further prospective studies are required to confirm these findings. The high proportion of females in our study reflects the higher proportion of females to males in PAH populations (437), however, we cannot be certain that the results of this study translate to male subjects with EIPAH. Measurement of gas exchange (peak $\dot{V}O_2$ and minute ventilation) during the 6MWT would have strengthened this study and has previously been shown to be feasible and useful in PAH (314). The respiratory exchange ratio of 1.05±0.06 observed in the EIPAH group suggests that a maximum $\dot{V}O_2$ was not achieved in some subjects, most likely because of early test termination due to intolerable symptoms.

6.6 Conclusions

An encouraged 6MWT identified reduced exercise capacity and provided a valid estimate of peak $\dot{V}O_2$ in subjects with EIPAH, although wide prediction intervals demonstrated that peak $\dot{V}O_2$ cannot be accurately predicted from a 6MWT in an individual with EIPAH. Peak exercise CO in EIPAH accounted for a small proportion of the reduction in exercise capacity, suggesting that factors other than cardiac output on an acute bout of exercise are likely to contribute significantly to exercise limitation in this population.

CHAPTER 7
A COMPARISON OF THE ACUTE HAEMODYNAMIC RESPONSE TO AEROBIC AND RESISTANCE EXERCISE IN SUBJECTS WITH EXERCISE-INDUCED PULMONARY ARTERIAL HYPERTENSION

Fowler R, Maiorana A, Jenkins S, Gain K, O'Driscoll G, Gabbay E. A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with exercise-induced pulmonary arterial hypertension. *Eur J Prev Cardiol*. 2012; DOI: 10.1177/2047487312445424

7.1 Introduction

Recent studies have identified that some individuals with unexplained exertional symptoms and risk factors for pulmonary arterial hypertension (PAH) have a normal pulmonary artery pressure (PAP) at rest but an elevated PAP during exercise (27, 76). Elevated mean PAP (mPAP) on exercise (>30mmHg) has been described in healthy individuals (30), but in these individuals mPAP >30mmHg is associated with a normal cardiac output and exercise capacity. In contrast, individuals with unexplained exertional symptoms, risk factors for PAH, and mPAP >30mmHg during exercise demonstrate reduced peak exercise cardiac output and aerobic capacity (27, 76) and ventilatory abnormalities characteristic of PAH (76). These individuals are believed to have a clinical condition which forms part of the spectrum of pulmonary vascular diseases (78) and which has been described as exercise-induced PAH (EIPAH). While it has not been determined whether EIPAH and PAH represent the same condition, the similarities in presentation suggest that EIPAH and PAH have several common features which contribute to impaired exercise capacity.

Chapter 7: A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with EIPAH

Skeletal muscle weakness has recently been described in PAH (38, 39) and is a recognised feature of conditions such as chronic obstructive pulmonary disease and chronic heart failure (CHF) (270). Skeletal muscle dysfunction is believed to contribute to reduced exercise capacity, and has been shown to improve with exercise training in each of these conditions (16, 42, 270, 388, 393, 394, 438). Historically, aerobic exercise (AE) has been the predominant mode of exercise employed to treat reduced exercise capacity in individuals with cardiopulmonary conditions. However, changes in muscle function following training are specific to the applied stimulus (439). Therefore, if increasing muscle strength is a treatment goal, resistance exercise (RE) training is the modality of choice to achieve this particular outcome.

In CHF, RE has been shown to produce similar haemodynamic responses to comparable intensities of AE (305, 440) and is associated with a low incidence of adverse events (44). There is growing evidence that appropriately prescribed RE is safe and efficacious in a variety of clinical populations and settings (44) and RE has become an important component in exercise training programs.

Historically, concerns over the haemodynamic response elicited by exercise, and in particular by RE, in individuals with PAH resulted in recommendations to avoid exercise training and resistance activities (14). However, recent studies have demonstrated that AE and combined AE and RE can be achieved without adverse events or short term clinical deterioration, and result in improvements in exercise capacity, muscle strength and quality of life in PAH (15-17, 42, 106). There are no studies of the haemodynamic response to RE and few that quantify the response to submaximal AE in PAH (8, 28, 43) and, although preliminary observations suggest that RE can be achieved without adverse events in PAH, further investigation of RE in individuals with an elevated PAP is warranted. Quantifying the haemodynamic load and symptomatic responses to RE and AE, at exercise intensities utilised for exercise testing and training, provides important clinical information on how individuals with elevated PAP are likely to tolerate RE in the longer term.

We hypothesised that subjects with EIPAH would demonstrate (i) lower limb muscle weakness, and (ii) no difference in haemodynamic or symptomatic responses to comparable intensities of lower limb AE and RE.

7.2 Patients and methods

7.2.1 Patient population

Forty-nine adults were recruited from the Pulmonary Hypertension Unit at Royal Perth Hospital (RPH, Perth, Western Australia). All subjects had been referred for investigation of dyspnoea of unknown aetiology and were investigated for PAH as defined by the 2004 European Society of Cardiology Guidelines (51). As previously described (76), subjects were diagnosed with EIPAH if, on exercise, mPAP was >30mmHg and pulmonary artery wedge pressure was <20mmHg, in accordance with historically accepted upper limits of normal (400). Individuals were excluded if they had mPAP >25mmHg at rest (n=5), mPAP <30mmHg on exercise (n=10), pulmonary artery wedge pressure >20mmHg on exercise (n=4), body mass index >35kg/m^2 (n=4), ischaemic or left heart disease (n=1), history or evidence of pulmonary parenchymal or airway disease on high resolution computed tomography or lung function testing (n=5), musculoskeletal condition limiting exercise performance (n=1) or anaemia (n=1). One subject declined the invitation to participate and three subjects did not perform the RE component of the study due to logistical reasons. Data from the subjects with EIPAH (n=14) were used to compare the acute haemodynamic and symptomatic responses to the two modes of exercise. Fifteen healthy subjects recruited from the local population, matched to the EIPAH subjects for age, gender and body mass index, underwent identical assessment (apart from central haemodynamics) for comparison of lower limb muscle strength and exercise capacity. All control subjects underwent a medical examination and a series of screening tests (medical history, echocardiogram, electrocardiogram, lung function tests and haematology) to confirm their healthy status.

The study was approved by the Human Research Ethics Committees of Royal Perth Hospital and Curtin University. Written, informed consent was obtained from all subjects.

7.2.2 Assessment of Central Haemodynamics

Pulmonary haemodynamics were measured using an 8F pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) inserted, under fluoroscopy, via the right internal jugular vein. Pulmonary artery pressure was recorded continuously at rest and

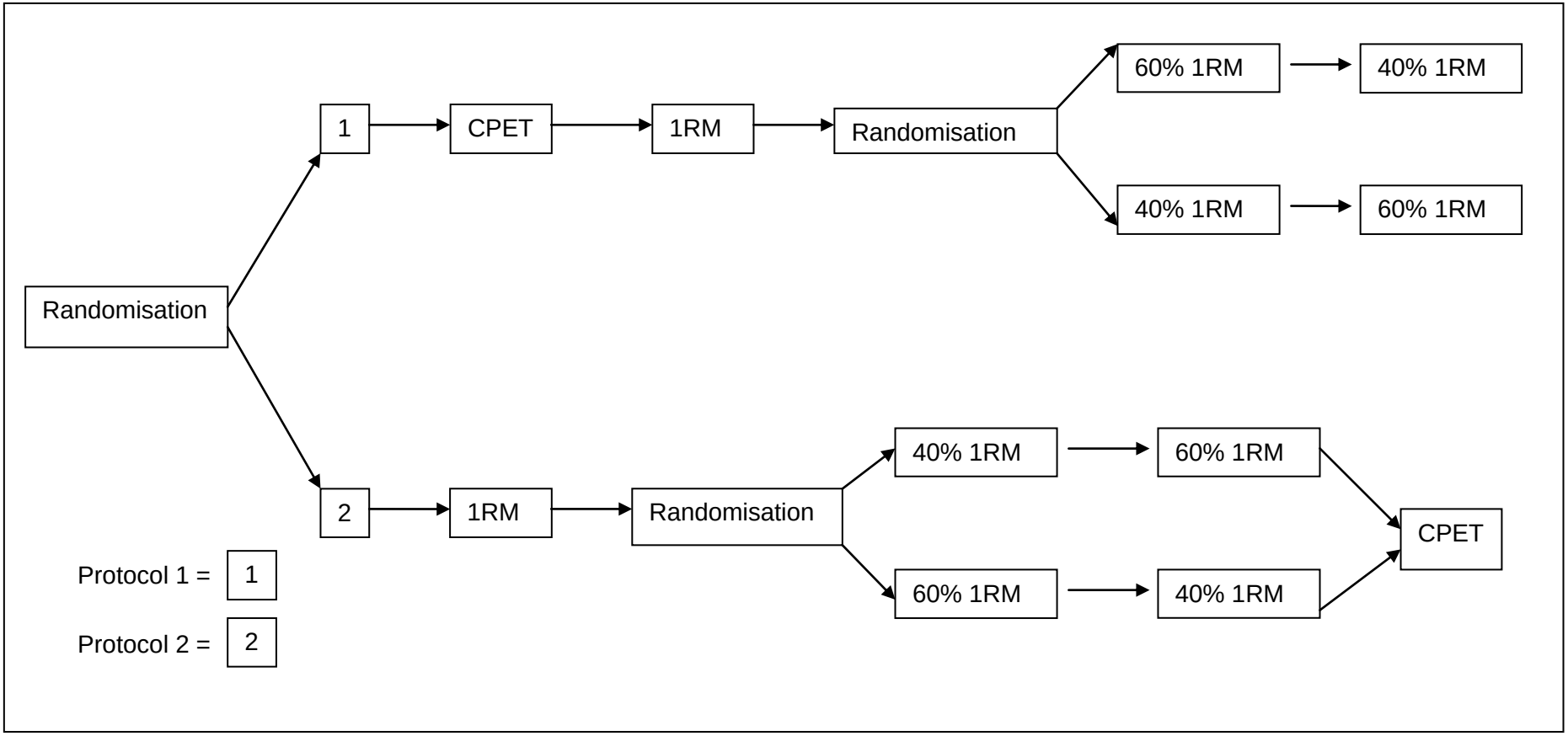
during all exercise protocols (Compact, Datex Engstrom, Finland). Cardiac output was determined using thermal filament thermodilution, updated every 60 seconds, at rest and during AE (Vigilance, Baxter, CA, USA). Due to the brief nature of the RE protocols (≤60secs), cardiac output was not analysed during RE. The pulmonary artery catheter contained a fibreoptic reflectance oximetry system providing continuous measurement of mixed venous oxygen saturation. Pulmonary artery wedge pressure was recorded at rest, every 3 minutes during, and in the final minute of the AE protocol. Haemodynamic digital data were streamed from the Datex and Vigilance monitors to a data acquisition system (Powerlab, AD Instruments, Australia). Storage of analogue data (NI-DAQ 6008, 8 channel, 12-bit digital to analogue converter using proprietary software written in LabVIEW^{TM} 7.0) allowed subsequent interrogation of the electrocardiograph and PAP wave form data and determination of pulmonary artery wedge pressure and PAP at end expiration. All measurements were corrected for phase delay.

7.2.3 Exercise protocols

Following catheterisation, subjects were transferred to an exercise laboratory for assessment of haemodynamic and symptomatic responses to graded AE (incremental cardiopulmonary exercise test, [CPET]) and maximal and submaximal dynamic, lower limb extension RE. The order of maximal AE and RE, and submaximal RE protocols was randomly allocated (see Figure 8). All exercise protocols were performed with the subject seated on an imaging table (Lode BV, Groningen, The Netherlands) in a semi-recumbent position (torso at 50° from horizontal). The CPET was performed using an electronically-braked cycle ergometer (Lode BV, Groningen, The Netherlands). The RE protocols were performed on a customised bilateral leg press (RM Sporting Supplies, Perth, Australia), secured to the imaging table. A 30 minute recovery period was provided between the AE and RE protocols, regardless of test order, and a 10 minute recovery period was provided between each of the RE protocols. Commencement of the subsequent exercise protocol did not occur until haemodynamic and symptomatic values had returned to baseline.

Heart rate (HR) and rhythm (12 lead electrocardiogram; Cardiosoft, Version 4.2, GE Medical Systems, USA) and oxygen saturation (Oxypleth pulse oximeter and ear sensor, Novemetrics, CT, USA) were monitored continuously throughout exercise

Figure 8. Randomisation and exercise protocols



Abbreviations: CPET, cardiopulmonary exercise test; 1RM, one repetition maximum test; 60% 1RM, 15 repetitions at 60% of 1RM weight; 40% 1RM, 20 repetitions at 40% of 1RM weight.

testing. Systemic blood pressure (SBP) was measured manually at the brachial artery. Symptomatic responses of dyspnoea and ratings of perceived exertion (RPE) were assessed using the Borg Category Ratio Scale (408).

The responses to AE and RE were evaluated at peak and submaximal levels. Peak oxygen consumption (peak $\dot{V}O_2$) and the one repetition maximum (1RM) were determined to establish aerobic and resistance exercise capacity respectively. Two submaximal workloads were derived from these values. These were calculated at 40 and 60% of peak $\dot{V}O_2$ and 1RM, to determine similar relative intensities of each mode of exercise.

Cardiopulmonary exercise test (CPET)

An incremental symptom-limited CPET protocol was employed which involved a 3 minute baseline period followed by 15 Watt increments in workload every 3 minutes. The initial workload was individualised based upon gender, age and six-minute walk distance. Standardised instructions and encouragement were provided to promote a maximum effort. Haemodynamic responses to submaximal AE were determined at 40 and 60% of peak $\dot{V}O_2$, averaged over a period of 30 seconds. The SBP and symptomatic responses analysed were those recorded closest to this 30 second period of exercise. The peak $\dot{V}O_2$ was defined as the 30 second average measured in the final 30 seconds of the test, at maximum workload. Central haemodynamic responses to maximal AE were determined as the values averaged over 30 seconds within the last minute of exercise. If a subject performed less than 30 seconds of the final workload, the peak $\dot{V}O_2$ and peak haemodynamic responses were taken as the values measured over 30 seconds within the last 60 seconds of the previous workload. The SBP was measured within the last 60 seconds of each exercise stage and within the last 60 seconds of the final workload. Symptomatic responses were recorded within the last 60 seconds of each exercise stage and immediately following test end.

Resistance exercise

Responses to maximal RE, and lower limb extensor muscle strength, were assessed using a 1RM technique according to a standardised protocol. A warm up,

comprising 10 repetitions of a light weight (10-20 kg), was followed by a rest period of 2 minutes prior to the 1RM manoeuvre. The initial weight for 1RM assessment was calculated at 75% of the subjects' body weight and progressively greater weights were attempted until the maximum weight was determined. A rest period of 60 seconds was employed between each 1RM attempt. The 1RM was determined as the heaviest weight, to the nearest 5kg, that could be lifted through a full range, with good technique and without breathholding. The maximum haemodynamic and symptomatic responses were determined as those elicited during a technically correct lift performed using the greatest weight. The SBP was measured over the period of the lift, with the cuff inflated immediately prior to the lift and released as the lift was performed. Symptomatic responses were recorded immediately following the test end. All lifting tasks were carefully supervised by the same investigator and, to avoid breath holding, subjects were instructed to exhale during leg extension.

Submaximal RE was performed at 40 and 60% of 1RM. The assessments involved 20 repetitions at 40% 1RM over 60 seconds, and 15 repetitions at 60% 1RM over 45 seconds, with the cadence guided by a metronome. For each set of submaximal RE, the central haemodynamic response was taken as the average over the last 10 seconds of exercise. The SBP was recorded over the last five repetitions of the set of lifts and symptomatic responses were recorded immediately following test cessation.

7.2.4 Statistical analysis

Data are presented as median and interquartile range, unless otherwise stated. Demographic data for the study and control groups were compared using the independent *t*-test. Comparisons between AE and RE responses were analysed using the Wilcoxon Matched Pairs Ranks test. Holm's Sequential Bonferroni corrections were applied to adjust for multiple comparisons. The statistical analyses were performed using SPSS software (Version 18, SPSS, Chicago, IL). A p-value <0.05 was accepted as significant.

Sample size was based on the power required to identify a difference of 10mmHg in mPAP between RE and AE, assuming a standard deviation of 5.7mmHg. A standard deviation of 5.7mmHg has previously been reported in the measurement of mPAP during exercise in a similar population (27). To achieve 80% power, for a

significance level of 5% (i.e. α=0.05), the sample size required to detect a difference of 10mmHg between RE and AE on exercise was at least seven subjects.

7.3 Results

No adverse events were recorded during the exercise assessments. Subject demographics, resting haemodynamics (for the EIPAH group) and exercise capacity data are presented in Table 12. The subjects with EIPAH had a lower forced expiratory volume in 1 second and forced vital capacity, as percent predicted, than the controls ($p<0.001$ for both). However, all lung function test results were within the reference range (423) and there was no evidence of airflow obstruction in the EIPAH subjects. There were no other differences between the EIPAH and control groups in baseline demographics. The EIPAH group had a lower peak $\dot{V}O_2$ ($p<0.001$), six-minute walk distance ($p<0.002$) and 1RM weight ($p=0.02$) compared with the control group (Table 12).

7.3.1 Different modalities of submaximal exercise (EIPAH group)

There were no significant differences in haemodynamics or symptoms between exercise modalities at submaximal intensities (Table 13).

7.3.2 Maximal exercise responses (EIPAH group)

At peak exercise, the CPET was associated with significantly higher peak mPAP, HR and systemic blood pressure, and more pronounced dyspnoea than the 1RM exercise. Mixed venous oxygen saturation and oxygen saturation via pulse oximetry were lower during the CPET than the 1RM test. There was no difference in RPE (Table 14).

Table 12. Demographics, resting haemodynamics and exercise capacity in subjects with EIPAH (n=14) and controls (n=15)

		EIPAH group	Control group	P Value EIPAH vs Control
Total number (n)		14	15	
Scleroderma (n)		11	0	
Female (n)		12	14	
Age, years		56 (46-65)	57 (40-64)	0.97
Weight, kg		73 (67-80)	69 (60-75)	0.42
Body mass index, $kg.m^{-2}$		27 (22-29)	25 (22-28)	0.60
FEV_1 (% predicted)		95 (87-105)	111 (106-119)	0.001
FVC (% predicted)		97 (92-104)	118 (103-129)	0.003
FEV_1/FVC		78 (73-84)	80 (74-83)	0.7
DLCO (% predicted)		73 (62-87)	86 (80-89)	0.09
WHO Functional Class (n)	Class II	9	0	
	Class III	5	0	
Peak oxygen consumption, $ml/kg.min^{-1}$		18 (16-21)	25 (19-33)	0.001
Six minute walk distance, m		609 (553-634)	675 (651-720)	0.002
One resistance maximum weight, kg		75 (55-91)	90 (80-140)	0.02
Haemodynamics	mPAP, mmHg	19 (16-20)		
	CO, L/min	6.2 (4.8-7.0)		
	PAWP , mmHg	8.0 (6.5-10.5)		
	RAP, mmHg	6.0 (3.0-7.0)		
	PVR, Wood units	1.9 (1.3-2.6)		
	HR, beats/min	73 (69-83)		
	Mean SBP, mmHg	100 (89-114)		

Note: Data are median (interquartile range) or number of subjects.

Abbreviations: EIPAH, exercise-induced pulmonary arterial hypertension; n, number of subjects; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; HR, heart rate; SBP, systemic blood pressure.

Table 13. Physiologic and symptomatic responses to submaximal resistance and aerobic exercise in subjects with EIPAH (n=14)

	EIPAH group (n=14)		P value
	Resistance	Aerobic	
40% 1RM			
mPAP, mmHg	25 (22-33)	23 (22-28)	0.17
HR, beats/min	100 (91-106)	93 (83-102)	0.03*
Mean SBP, mmHg	115 (105-124)	114 (107-121)	0.60
SVO_2, %	54 (48-58)	58 (55-61)	0.12
Dyspnoea	2.8 (0.8-3.0)	1.0 (0.5-2.0)	0.02*
RPE	3.7 (3.0-4.0)	3.0 (2.0-3.0)	0.11
60% 1RM			
mPAP, mmHg	25 (21-30)	26 (24-33)	0.05
HR, beats/min	101 (93-105)	103 (97-106)	0.16
Mean SBP, mmHg	113 (108-121)	116 (109-124)	0.40
SVO_2, %	54 (52-60)	50 (46-54)	0.21
Dyspnoea	2.2 (1.7-3.8)	3.0 (2.0-3.0)	0.72
RPE	4.0 (3.0-5.0)	3.3 (3.0-4.0)	0.40

Note: Data are median (interquartile range). *not significant when Holm's Sequential Bonferroni corrections applied to adjust for multiple comparisons.

Abbreviations: EIPAH, exercise-induced pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; HR, heart rate; SBP, systemic blood pressure; SVO_2, mixed venous oxygen saturation; RPE, rate of perceived exertion.

Table 14. Physiologic and symptomatic responses to maximal resistance and aerobic exercise in subjects with EIPAH (n=14)

	EIPAH group (n=14)		P value
	Resistance	Aerobic	
mPAP, mmHg	26 (24-33)	36 (33-40)	0.001
HR, beats/min	93 (83-99)	130 (121-150)	0.001
Mean SBP, mmHg	113 (105-121)	127 (123-141)	0.001
SVO_2, %	61 (54-67)	42 (35-49)	0.001
SpO_2, %	98 (97.7-98.3)	96 (92.7-97.0)	0.001
Dyspnoea	3.0 (1.5-3.3)	5.0 (4.0-6.3)	0.01
RPE	7.0 (4.8-9.0)	5.0 (4.0-9.3)	0.59

Note: Data are median (interquartile range).

Abbreviations: EIPAH, exercise-induced pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; HR, heart rate; SBP, systemic blood pressure; SVO_2, mixed venous oxygen saturation; SpO_2, oxygen saturation; RPE, rate of perceived exertion.

7.4 Discussion

This study provides new insights into the haemodynamic responses elicited during submaximal and maximal AE and RE in subjects with EIPAH and expands the existing body of knowledge about the comparative response to submaximal and maximal aerobic and resistance exercise. The main findings of this study were that: (i) subjects with EIPAH have reduced lower limb extensor muscle strength, (ii) dynamic, bilateral lower limb AE and RE performed at comparable submaximal intensities were associated with similar haemodynamic and symptomatic responses, and (iii) a maximal AE test was associated with significantly greater haemodynamic and symptomatic responses than a maximal bilateral lower limb RE test.

In our study, the EIPAH group demonstrated reduced lower limb extensor muscle strength compared with age-matched controls. Scleroderma can be associated with muscle abnormalities (441, 442) and a large proportion of our EIPAH group had scleroderma. However, reduced muscle strength has also previously been identified in subjects with idiopathic PAH (38, 39), and improves with resistance training (16, 42). Lower limb extensor muscle strength is important in activities of daily living, such as rising from a chair, climbing stairs, bending, and lifting. Furthermore, improved muscle strength and power are associated with reduced hemodynamic stress at a given absolute muscle force (40).

Recent studies of exercise training in PAH have demonstrated improvements in aerobic capacity (15-17, 42, 106), quality of life (15) and muscle strength and morphology (16, 42), without adverse events or clinical deterioration. However, little is known about the haemodynamic impact and therefore longer term implications of AE and RE in patients with elevated PAP and increased right ventricular work load. Given the increasing application of exercise training in patients with PAH, it is timely and prudent to determine the haemodynamic and symptomatic responses to different, clinically relevant intensities and modes of exercise in individuals with elevated PAP.

The intensities of RE studied in this research represent the upper limit of the intensity recommended for the initial RE training period in patients with cardiac disease (40%) (44) and an intensity that has the best effect size for increases in muscle strength following training in previously untrained individuals (60%) (443).

Consistent with observations described in CHF patients (305, 440), the current study demonstrates that in subjects with EIPAH, dynamic lower limb RE at these intensities is associated with similar haemodynamic and symptomatic responses to comparable intensities of AE. Although mPAP increased during the 40% and 60% RM exercise sessions, the increase in mPAP was small (<10mmHg). While the nature of RE investigated in this study, including short bouts of exertion interspersed with rest periods, is likely to have influenced the observed haemodynamic burden of RE, this mode of delivery reflects the prescription of RE in clinical practice. We believe our findings support prospective, randomised, controlled trials, to quantify the benefits and safety of low to moderate intensity AE and RE training in subjects with EIPAH

The significantly higher haemodynamic and symptomatic responses at peak $\dot{V}O_2$ compared with the peak responses during the 1RM assessment, is most likely due to the continuous nature of AE, the associated increase in cardiac output and depletion of muscle energy stores. Maximal AE is associated with glycolysis and fat oxidation, which rely upon increased cardiac output and oxygen delivery. Exercise beyond the anaerobic threshold is associated with progressive depletion of energy systems, accumulation of lactate and a fall in muscle pH (444). These changes contribute to the sensation of dyspnoea towards the end of a maximal AE test (199). In contrast, maximal RE relies upon the ATP-PC muscle stores which are in close proximity to the contractile mechanism of the muscle and do not immediately depend increased oxygen transport (444). The single repetitions of submaximal RE (as performed during a 1RM test) allow time for muscle stores to be replenished, and the by-products of muscle metabolism to be removed, between contractions. Therefore, there is little stimulus for a sensation of dyspnoea in a 1RM test. The difference in haemodynamic and symptomatic responses to maximal AE and RE demonstrated in our study is consistent with these physiological differences between exercise modalities. Maximal AE and RE tests are commonly used in research and clinical practice to determine exercise capacity and to set training intensities. The moderate haemodynamic response to a 1RM test in this study demonstrates that a 1RM test is well tolerated by patients with EIPAH.

7.5 Limitations

Due to the invasive nature of pulmonary artery catheterisation, no haemodynamic data were available for the control subjects in this study. The presence of the pulmonary artery catheter, inserted via the internal jugular vein, precluded upper limb RE in this study. Our results cannot be extrapolated to upper limb RE.

Due to concerns regarding the haemodynamic consequences of RE in patients with PAH, the intensities of exercise chosen for this study were conservative. It is not possible to make any recommendations regarding the safety of exercise intensities of greater than 60% of maximum AE or RE. However, having determined that the haemodynamic burden of these intensities of AE and RE is modest in individuals with EIPAH, it would now appear appropriate to investigate the response to higher intensities of AE and RE in this population. The conclusions of this study relate only to subjects with EIPAH and the results should not be used to predict the haemodynamic or symptomatic responses to AE and RE in individuals with PAH. Further studies are required in a broader cross section of individuals with elevated PAP, including individuals with PAH.

The high proportion of females in our study reflects the higher proportion of females to males with scleroderma associated PAH (437). We cannot be certain that the results of this study translate to male subjects with EIPAH. Finally, a large proportion of our study group had limited cutaneous scleroderma. This was most likely due to an active pulmonary hypertension screening program run by the Rheumatology and Pulmonary Hypertension Units at Royal Perth Hospital and should not be taken to reflect the prevalence of scleroderma in EIPAH. In a previous study (76) we found no association between scleroderma and reduced peak $\dot{V}O_2$ or six-minute walk distance. However, we are unable to exclude the possibility that scleroderma related muscle dysfunction contributed to reduced muscle strength in the subjects with scleroderma in this study.

7.6 Conclusions

This study demonstrates that a 1RM test was associated with a lower haemodynamic burden than a maximal AE test and identified lower limb muscle weakness in subjects with EIPAH. In these individuals, submaximal lower limb RE

was well tolerated and resulted in similar haemodynamic and symptomatic responses to comparable intensities of lower limb AE. This study provides preliminary findings to support the safety of RE assessment and training in subjects with EIPAH and forms a basis for further research. The haemodynamic and symptomatic responses to submaximal and maximal RE in PAH remain undefined. For these individuals, isometric, strenuous RE and competitive sports are contraindicated, and exercise programs need to be supervised by appropriately trained healthcare professionals with experience in PAH.

CHAPTER 8
SUMMARY, CLINICAL IMPLICATIONS AND FUTURE RESEARCH

This project comprised four main studies. The first study was designed to determine the consistency of recommendations provided to patients with PAH, by healthcare professionals within Australia, regarding physical exertion, acceptable symptoms on physical activity and referral for exercise rehabilitation. The second study examined the implications of EIPAH in relation to the clinical consequences of the condition and the potential role of exercise testing in facilitating the early diagnosis of PAH. The third study investigated the measurement properties and utility of the 6MWT in identifying reduced exercise capacity and estimating aerobic capacity in subjects with EIPAH. The fourth study evaluated muscle strength, and the haemodynamic and symptomatic burden of maximal aerobic and resistance exercise and comparable intensities of submaximal aerobic and resistance exercise, in individuals with EIPAH. Each of these studies has been presented, as published in peer reviewed journals, in this thesis (Chapters 4-7). This Chapter summarises the findings, discusses the clinical implications of these studies, and identifies areas for future research.

8.1 Australian perspective regarding recommendations for physical activity and exercise rehabilitation in pulmonary arterial hypertension.

Historic concerns about adverse outcomes associated with exercise (41), and limited evidence regarding the haemodynamic consequences of physical activity in PAH (8, 28, 43), have made it difficult for clinicians to guide patients with PAH regarding appropriate levels of exertion and symptoms, and to determine which patients are appropriate for exercise training.

In 2010, a survey of healthcare professionals involved in the management of patients with PAH, within Australia, was undertaken. The aim of the study was to determine the consistency of opinion regarding appropriate levels of exertion and acceptable symptoms during physical activity, and referral for exercise rehabilitation,

for patients with PAH. The invitation to attend the meeting, at which the survey was presented, was sent to healthcare professionals in all Australian pulmonary hypertension clinics. The response rate for the survey was 70% (n=53). Therefore, the respondents represented a significant proportion of individuals who have a regular, clinical role in managing patients with PAH, within Australia.

This research identified a lack of consistency in response regarding appropriate levels of physical exertion, and symptoms of dyspnoea and fatigue during daily physical activity. There was a consensus regarding the avoidance of chest pain and more than mild levels of light-headedness during daily activities for patients with PAH.

With respect to the referral of patients with PAH for exercise rehabilitation, the opinion of respondents was divided. Sixty-three percent of the survey respondents would, and 35% would not, have referred patients with PAH for exercise rehabilitation. The remaining 2% of respondents did not complete this question. The patients' functional class did not influence the recommendations for exercise rehabilitation. These results demonstrate uncertainty, in 2010, regarding the role of exercise rehabilitation for patients with PAH, regardless of functional class.

The findings of this study suggest that best practice in the management of patients with PAH, regarding physical activity recommendations and exercise rehabilitation, has not yet been determined. It remains difficult, under these circumstances, for clinicians to know how to guide patients regarding physical activity and which patients should be referred for exercise rehabilitation. Clinical guidelines for activity prescription, that include recommendations for appropriate levels of exertional dyspnoea and fatigue, are required. There is a body of literature that provides some insight into the likely origins of exertional symptoms in PAH, and the outcomes following exercise rehabilitation (see the Literature Review), however, further research is required before definitive guidelines can be developed.

8.1.1 Areas that warrant further research

1. The origins and significance of exertional dyspnoea and fatigue in individuals with PAH need to be determined.

2. The efficacy and safety of exercise rehabilitation in PAH need further investigation to determine;
    a. The influence of exercise rehabilitation on disease progression, clinical worsening and long term functional outcomes.
    b. Optimal exercise training intensity and modalities for patients with PAH.
    c. The efficacy of exercise rehabilitation programs that are applicable to usual clinical practice in Australia.

8.2 Implications of exercise-induced pulmonary arterial hypertension.

Evidence supporting the benefits of pharmaceutical therapy for patients with PAH, prior to the development of marked impairments in functional capacity, have created an imperative for early diagnosis of this condition (1). However, delays in diagnosis have not reduced in more than 20 years (4). Barriers to early diagnosis include the non-specific nature of the symptoms, with 90% of individuals presenting with exertional dyspnoea, but also to diagnostic criteria that can only detect PAH once the pulmonary vasculopathy is advanced (1).

Study 2 investigated the potential of exercise testing to facilitate the early diagnosis of PAH. This study was designed to evaluate the central haemodynamic responses during a symptom-limited CPET in 37 individuals referred for investigation of unexplained dyspnoea. Ventilatory responses during the CPET were subsequently compared between 17 individuals who demonstrated a normal mPAP at rest but an elevated mPAP and a normal PAWP on exercise (EIPAH) and 20 healthy controls. The controls were matched for age, gender and BMI to individuals with EIPAH. The control and EIPAH groups had similar levels of usual physical activity. Additional evaluations included quantifying exercise capacity and QoL in the individuals with EIPAH, in comparison with the matched controls.

The similarities in exercise responses demonstrated by individuals with EIPAH and those described in PAH suggest that there are consistent abnormalities in the physiological responses in these conditions, albeit of milder severity in the individuals with EIPAH. Both conditions are associated with elevated resistance to pulmonary blood flow, increased right ventricular workload and reduced exercise cardiac output (76). Ventilatory responses in both conditions are consistent with a

pulmonary vasculopathy as defined by Wasserman et al (13) and Yasunobu et al (12). Exercise capacity, QoL (especially in the physical domains), and the capacity to undertake daily activities (functional class) are reduced in both PAH and EIPAH (76). Furthermore, progression of EIPAH to PAH within three years in 19% (2) and progression of QoL impairments in 24% of the individuals with EIPAH supports the hypothesis that EIPAH is a progressive condition and an early stage of PAH. However, these findings require confirmation, and further longitudinal studies are necessary to be certain of the nature of EIPAH over time. In the interim, individuals with EIPAH warrant regular, clinical follow-up to ensure if progression occurs to PAH treatment is offered in a timely manner. Alternatively, if symptoms are marked, these patients may warrant consideration for treatment with PAH specific therapy (77, 396).

The research reported in this thesis describes the most comprehensive evaluation undertaken in individuals with EIPAH and the data derived from this study provides important cross sectional information about this group of individuals, at baseline. A follow up study of these individuals is currently being established. Longitudinal evaluation of these individuals has the potential to determine whether EIPAH progresses to PAH and, therefore, whether exercise testing can facilitate the early diagnosis of PAH and optimise the timing of treatment for individuals with PAH.

Regardless of progression, the findings of this research demonstrate clinically important abnormalities associated with reductions in exercise capacity and QoL in individuals with EIPAH. Preliminary evidence suggests that individuals with EIPAH respond positively to PAH specific therapy (77, 396). The clinical consequences of EIPAH, identified in this study, suggest that individuals with this condition warrant consideration for therapy.

8.2.1 Areas that warrant further research

1. Longitudinal follow up of individuals with EIPAH to determine if progression to PAH occurs.
2. Clinical trials to determine the efficacy of PAH specific therapy in EIPAH.

8.3 Measurement properties of the six-minute walk test in individuals with exercise-induced pulmonary arterial hypertension.

The 6MWT is commonly used to measure exercise capacity in patients with PAH. However, a ceiling effect for 6MWD has been reported in individuals with PAH who have mild to moderate functional limitation (37). Exercise-induced PAH is associated with mild-moderate impairment in aerobic capacity (27) and therefore the utility of the 6MWT in quantifying exercise capacity was uncertain.

This study investigated the capacity of the 6MWT to identify reduced exercise capacity and to estimate aerobic capacity in individuals with EIPAH. Individuals with EIPAH (n=17) underwent two encouraged 6MWTs. Six-minute walk distance and six-minute walk work results were compared between individuals with EIPAH and healthy controls (n=20), matched for age, gender and body mass index. Both the EIPAH and control groups also underwent a symptom-limited CPET on a cycle ergometer, to determine the relationship between 6MWD and 6MWW and peak $\dot{V}O_2$. Heart rate and symptom scores were measured during the 6MWT and CPET, and compared, to determine relative exercise intensity of these tests in the EIPAH group.

This study demonstrated that the encouraged 6MWT identifies reduced exercise capacity and accurately estimates aerobic capacity in individuals with EIPAH. The 6MWW more accurately reflected aerobic capacity than the 6MWD in individuals with EIPAH. The HR response was similar in the 6MWT and the CPET in the EIPAH group, suggesting that the encouraged 6MWT is a high intensity exercise for these individuals. Similar to other populations, test repetition resulted in a significant increase in 6MWD, in individuals with EIPAH.

The results of this study suggest that the encouraged 6MWT can be used in clinical practice to identify exercise limitation although, to allow for a learning effect, two tests are required. However, this research raises doubt about the safety of the encouraged 6MWT in individuals with EIPAH and is an important issue that needs further consideration. In particular, consideration needs to be given regarding the safety of performing this high intensity test in clinical practice, without medical supervision, continuous 12 lead ECG and blood pressure monitoring during the test.

If the encouraged 6MWT is used for research or clinical practice in this population, the 6MWW should be reported, as this better reflects aerobic capacity than 6MWD.

In the EIPAH group, the mean 6MWD achieved was 88% of predicted. The responsiveness of the encouraged 6MWT, to positive changes following therapeutic interventions, in individuals with EIPAH and a limited reduction in 6MWD remains undetermined. Thus, the role of other outcome measures for the determination of response to therapy in this group also needs investigation.

8.3.1 Areas that warrant further research

1. The safety of the encouraged 6MWT in EIPAH needs further investigation, with a larger sample size.
2. The responsiveness of the 6MWT in determining beneficial outcomes following therapy in EIPAH needs to be evaluated.
3. The role of other exercise tests that have the potential to demonstrate change following therapy needs investigation in EIPAH.

8.4 A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with exercise-induced pulmonary arterial hypertension.

Individuals with PAH have skeletal muscle weakness (38, 39). Muscle weakness contributes to reduced physical function (270) but is amenable to exercise training. Muscle and functional changes following exercise training are specific to the applied stimulus (439). Therefore, to improve muscle strength, resistance training is the treatment of choice.

Historical concerns regarding the impact of exercise, and in particular resistance activities, on haemodynamics in patients with PAH resulted in recommendations that patients avoid exercise and resistance activities (41). However, recent studies have demonstrated that aerobic and resistance training, in patients with PAH, result in short term benefits and can be achieved without adverse events (16, 42). Despite this, the haemodynamic burden and, therefore, the potential longer term consequences of aerobic and resistance exercise in patients with elevated PAP is unknown.

This research evaluated lower limb extensor muscle strength and quantified the haemodynamic and symptomatic responses to comparable intensities of submaximal and maximal aerobic and resistance exercise in individuals with EIPAH (n=14). In this study, individuals with EIPAH, and matched healthy controls (n=15), underwent a 1RM exercise test on a custom built bilateral leg press to determine muscle strength, and a symptom-limited CPET to determine maximal aerobic capacity. Individuals with EIPAH also underwent submaximal resistance exercise comprising 20 repetitions at 40% of 1RM and 15 repetitions at 60% 1RM. Maximal aerobic exercise (peak $\dot{V}O_2$) was determined from the CPET and submaximal intensities of aerobic exercise were evaluated at 40% and 60% peak $\dot{V}O_2$. The EIPAH group underwent all resistance and aerobic exercise protocols with a pulmonary artery catheter in situ, in order to measure central haemodynamics.

Individuals with EIPAH demonstrated reduced lower limb muscle strength, compared with matched controls. Similar haemodynamic and symptomatic responses to comparable intensities of submaximal lower limb resistance and aerobic exercise were demonstrated in individuals with EIPAH. The 1RM muscle strength test was associated with a modest haemodynamic response and this response was significantly lower than during the maximal aerobic exercise test. Resistance and aerobic exercise at intensities of 40% and 60% of maximum were associated with an acceptable haemodynamic response and were well tolerated, symptomatically, in individuals with EIPAH.

These findings demonstrate that a 1RM test identifies reduced muscle strength in EIPAH. With careful application, the 1RM test is an appropriate test for further research in individuals with a moderately elevated PAP. The findings also demonstrate that exercise training programs utilising 40% 1RM and 60% 1RM are likely to be well tolerated, and associated with acceptable longer term haemodynamic outcomes, in individuals with EIPAH.

8.4.1 Areas that warrant further research

1. The safety and efficacy of moderate intensity lower limb resistance training in individuals with EIPAH warrants investigation.
2. The haemodynamic and symptomatic responses to higher intensities of resistance and aerobic exercise in individuals with EIPAH need to be determined.

3. Evaluation of the haemodynamic and symptomatic responses to resistance and aerobic exercise in individuals with PAH requires investigation. This is especially relevant in light of the recent increase in the study and likely implementation of exercise training programs for patients with PAH.

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Appendix 1: Questionnaire used in the study together with the responses to each question (pages 194-202).

Data given in the responses are number of responses with percentages given in parentheses.

Total number of respondents (n=53).

Activity and Exercise Guidelines for Patients with Pulmonary Arterial Hypertension (PAH).

Background:
There is very little in the literature to guide exercise and physical activity recommendations for patients with PAH. The Royal Perth Hospital Advanced Lung Disease/Pulmonary Hypertension Research Group led by Associate Professor Eli Gabbay, in conjunction with the Curtin University School of Physiotherapy, is seeking to determine expert opinion on exercise and physical activity guidelines for patients with PAH. We therefore request that you complete and return the following questionnaire.

Participation is purely voluntary but we strongly encourage your contribution. There is no individual identifying information on this questionnaire and therefore anonymity will be protected. Information gained from this questionnaire may be used in future presentations and publications.

Thank you for taking the time to complete this questionnaire.

For each of the following questions please circle your chosen answer.

	Results n(%)
Type of Institution:	
a) Tertiary/Major hospital	41(77)
b) Secondary/Regional hospital	8(15)
c) Private practice	3(6)
d) General practice	0
e) Other – please specify_____	1(2)
Position:	
a) Respiratory (Thoracic) Physician	19(36)
b) Cardiologist	8(15)
c) Rheumatologist	6(11)
d) Nurse specialist	19(36)
e) Exercise physiologist	1(2)
f) Other – please specify_____	
Number of new PAH patients seen per year:	
a) 0-10	18(34)
b) 11-50	24(45)
c) 51-100	4(8)
d) 101-150	4(8)
e) 151-200	0
f) 201-300	2(4)
g) >300	0

Two case studies are presented. ***Please circle the answer(s) that best represents your usual response.***

Case 1
44 year old female
WHO functional Class IV
Six minute walk distance 85 metres on room air.
ABGs on room air PaO2 51mmHg (6.8kPa), PaCO2 42mmHg (5.6kPa)
PAP 92/55, **mean PAP** 67mmHg on resting RHC study
PVRI 2291 dyne/sec/m2/cm^5
Severely dilated right ventricle with severe global impairment of RV systolic function
No evidence of thromboembolic disease

All usual tertiary hospital based assessment related to diagnosis and medical management has been performed.

	Results n(%)
In relation to exercise and activity prescription:	
1. What further investigations would you perform:	
a) None	28(53)
b) Exercise right heart catheter	8(15)
c) Exercise echo	5
d) Other – please explain_____	

Results: Lung function tests (n=2), Cardiopulmonary exercise test (CPET) (n=1), CT angiogram (n=1), overnight oximetry (n=1)

In the absence of these results:

2. What instructions for daily activities would you give:	
a) None	0
b) Recommend only mild exertion	12(23)
c) Recommend moderate exertion	2(4)
d) Instruct the patient to continue activity as tolerated	32(60)
e) Other – please explain_____	

Results: Refer to physio/pulmonary rehab (n=6), oxygen therapy (n=4), symptom limited exercise (n=2), overnight oximetry (n=1)

For this question, more than one answer may be selected

3. How would you guide the patient with respect to their daily activities. Would you:	**Results n(%)**
a) Give verbal guidelines	36(68)
b) Give written guidelines	19(36)
c) Refer the patient for instruction	12(23)
d) Refer the patient for exercise rehabilitation	35(66)
e) Other – please explain_____	

For this patient, which of the following symptoms would you consider to be acceptable during daily activities:

4. Breathlessness	
a) Minimal	6(11)
b) No more than moderate	27(51)
c) As much as the patient can tolerate	18(34)
d) Other – please explain_____	

5. Light headedness	
a) None	27(51)
b) Mild	22(41)
c) Moderate	3(6)
d) To the point of syncope	0
e) Other – please explain_____	

6. Fatigue	
a) None	1(2)
b) Minimal	15(28)
c) Moderate fatigue	26(50)
d) As much as the patient can tolerate	9(17)
e) Other – please explain_____	

7. Chest pain	
a) None	36(68)
b) Mild	16(30)
c) Moderate	0
d) As much as the patient can tolerate	1(2)
e) Other – please explain_____	

Following 6 months on a maximal dose of Epoprostenol this same patient has the following results:

WHO functional class II
6MWD 405 metres on room air
Echo: mild RV dysfunction and RV dilatation
Mean PAP 45mmHg
PVRI 815dynes/s/m^2/cm^5

8. What further investigations would you perform:	**Results n(%)**
a) None	36(68)
b) Exercise right heart catheter	5(9)
c) Exercise echo	3(6)
d) Other – please explain_____	

Results: Six-minute walk test (6MWT) (n=1), CPET (n=2)

In the absence of any other results:

9. What instructions for daily activities would you give:	
a) None	0
b) Recommend only mild exertion	3(6)
c) Recommend moderate exertion	13(25)
d) Instruct the patient to continue activity as tolerated	30(57)
e) Other – please explain_____	6(11)

Results: Assess exercise capacity/6MWT (n=3), review by physio/continue pulmonary rehab (n=2), oxygen therapy (n=2), symptom limited exercise (n=3)

For this question, more than one answer may be selected

10. How would you guide the patient with respect to their daily activities. Would you:	
a) Give verbal guidelines	38(72)
b) Give written guidelines	20(38)
c) Refer the patient for instruction	9(17)
d) Refer the patient for exercise rehabilitation	33(62)
e) Other – please explain_____	

For this patient, which of the following symptoms would you consider to be acceptable during daily activities:

	Results n(%)
11. Breathlessness	
a) Minimal	12(23)
b) Moderate	23(44)
c) As much as the patient can tolerate	16(30)
d) Other – please explain_____	
12. Light headedness	
a) None	30(57)
b) Mild	20(37)
c) Moderate	2(4)
d) To the point of syncope	0
e) Other – please explain_____	
13. Fatigue	
a) None	3(6)
b) Minimal	18(33)
c) Moderate	20(37)
d) As much as the patient can tolerate	12(22)
e) Other – please explain_____	
14. Chest pain	
a) None	41(78)
b) Mild	8(16)
c) Moderate	1(2)
d) As much as the patient can tolerate	2(4)
e) Other – please explain_____	

Case 2
36 year old female
WHO functional Class III
Six minute walk distance 305 metres on room air
ABGs on room air PaO2 88mmHg (11.7kPa), PaCO2 38mmHg (5.1kPa)
PAP 62/28, **mean PAP** 38mmHg on resting RHC study
PVRI 671 dyne/s/m2/cm5
Moderately dilated right ventricle with moderate global impairment of RV systolic function
No evidence of thromboembolic disease

All usual tertiary hospital based assessment related to diagnosis and medical management has been performed.

In relation to exercise and activity prescription:	**Results**
15. What further investigations would you perform:	**n(%)**
a) None	27(51)
b) Exercise right heart catheter	8(15)
c) Exercise echo	8(15)
d) Other – please explain_____	

Results: Lung function tests (n=1), CT pulmonary angiogram (n=1), 6MWT (n=1), overnight oximetry (n=1)

In the absence of these results:

16. What instructions for daily activities would you give:	
a) None	0
b) Recommend only mild exertion	7(13)
c) Recommend moderate exertion	5(9)
d) Instruct the patient to continue activity as tolerated	30(57)
e) Other – please explain_____	7(13)

Results: Assess exercise capacity (n=1) /6MWT (n=2)/exercise right heart catheter (n=1), cardiac or pulmonary rehab (n=2), oxygen therapy (n=1), symptom limited exercise (n=3) / no strenuous exercise/Borg <6

For this question, more than one answer may be selected

17. How would you guide the patient with respect to their daily activities. Would you:

	Results n(%)
a) Give verbal guidelines	33(62)
b) Give written guidelines	13(25)
c) Refer the patient for instruction	14(26)
d) Refer the patient for exercise rehabilitation	32(60)
e) Other – please explain_____	

For this patient, which of the following symptoms would you consider to be acceptable during daily activities:

18. Breathlessness

a) Minimal	14(26)
b) Moderate	20(38)
c) As much as the patient can tolerate	15(28)
d) Other – please explain_____	

19. Light headedness

a) None	27(51)
b) Mild	20(38)
c) Moderate	2(4)
d) To the point of syncope	0
e) Other – please explain_____	

20. Fatigue

a) None	4(8)
b) Minimal	13(25)
c) Moderate	18(34)
d) As much as the patient can tolerate	13(25)
e) Other – please explain_____	

21. Chest pain

a) None	39(74)
b) Mild	7(13)
c) Moderate	2(4)
d) As much as the patient can tolerate	1(2)
e) Other – please explain_____	

Please circle either the yes or no response to each of the questions below:

22. For a patient with established PAH in WHO functional class II would you advise:

	Results (n,%)	**(n,%)**
a) Lifting 20kg in weight	Yes (19,36)	No (30,57)
b) Exercising in a non hospital gym	Yes (37,70)	No (12,23)
c) Regularly using stairs and slopes	Yes (42,79)	No (7,13)
d) A sedentary lifestyle	Yes (1,2)	No (48,91)

23. For a patient with established PAH in WHO functional class III would you advise:

a) Lifting 20kg in weight	Yes (5,9)	No (44,83)
b) Exercising in a non hospital gym	Yes (11,21)	No (38,72)
c) Regularly using stairs and slopes	Yes (27,51)	No (22,42)
d) A sedentary lifestyle	Yes (4,8)	No (45,85)

24. For a patient with established PAH in WHO functional class IV would you advise:

a) Lifting 20kg in weight	Yes (0)	No (49,92)
b) Exercising in a non hospital gym	Yes (3,6)	No (46,87)
c) Regularly using stairs and slopes	Yes (6,11)	No (43,81)
d) A sedentary lifestyle	Yes (9,17)	No (40,75)

Further comments about exercise/activity instructions, or the questionnaire:

Results: 1) Important all patients given an exercise prescription based on professional, experienced assessment (eg physio); avoid heavy lifting and anaerobic activity; avoid breath holding (eg during swimming)
2) Exercise to tolerance after supervised exercise in hospital gym for all class II/III patients
3) As good as a drug. Should be used in all cases
4) Most patients in WHO II and III could do a rehab program but it would be PH related and most would benefit from one-on-one supervised training with a specialist
5) For majority of patients exercise is advisable in consultation with treating physician and physiotherapist/pulmonary rehab co-ordinator in a monitored environment. Activity is always recommended however should be adjusted to patients' condition. Isometric exercises, gentle walking and use of oxygen should be discussed individually with patients and carers.

Thank you again for your participation.

A/Prof Sue Jenkins is a lecturer and Robin Fowler is a PhD student at Curtin University.

If you wish to be informed of the collective results of this survey, please contact Robin Fowler via email at the following address:

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Appendix 2:

Table 15. Participant co-morbidities and medications, Studies 2-4

	PAH (n=6)	EIPAH (n=17)	EILVDD (n=4)	noPAH (n=10)	Control (n=20)
Co-morbidities, n					
Systemic hypertension	2	6	2	2	3
Hypercholesterolaemia	2	4	1	1	1
Type II diabetes	0	1	0	0	0
GORD	4	7	1	2	1
Mild ILD	1	0	1	1	0
Hypothyroidism	0	6	1	1	1
SVT	0	0	0	0	1
Depression/Anxiety/Bipolar disorder	2	5	0	0	2
Migraine	0	1	0	1	1
Previous DVT	0	2	0	1	0
Previous carcinoma	1	1	0	0	1
Psoriasis, SLE, MCTD	0	1	0	0	1
Osteopenia	2	2	0	0	2
Iron deficiency anaemia	0	2	0	1	0
Parkinson's disease	0	0	1	0	0
Type II diabetes	0	1	0	0	0
Medications, n					
B blocker					
Calcium channel blocker	0	0	0	0	1
ACE inhibitor	2	0	0	0	1
Angiotenson II antagonist	0	2	0	1	1
Statin	1	4	2	1	1
Diuretic	2	4	1	1	1
Proton pump inhibitor	0	0	0	0	1
Adalat	4	7	1	2	1
Thyroxine	1	7	0	2	0
Warfarin	0	6	1	1	1
Aspirin	1	1	0	1	0
Calcium supplement	1	2	1	0	1
Anti-inflammatory/anti-rheumatic	2	2	0	0	2
Antidepressant/Antipsychotic	2	3	1	2	0
Iron supplement	1	5	0	0	2
Sinamet	0	2	0	1	0
Dimerol	0	1	1	0	0

Appendix 3: Article accepted for inclusion in Pulmonary Medicine, July 2012

Exercise intolerance in pulmonary arterial hypertension

Authors: Robin M Fowler, Kevin R Gain, Eli Gabbay

Abstract: *Pulmonary arterial hypertension (PAH) is associated with symptoms of dyspnea and fatigue, which contribute to exercise limitation. The origins and significance of dyspnea and fatigue in PAH are not completely understood. This has created uncertainly among healthcare professionals regarding acceptable levels of these symptoms, on exertion, for patients with PAH. Dysfunction of the right ventricle (RV) contributes to functional limitation and mortality in PAH, however, the role of the RV in eliciting dyspnea and fatigue has not been thoroughly examined. This review explores the contribution of the RV and systemic and peripheral abnormalities to exercise limitation and symptoms in PAH. Further, it explores the relationship between exercise abnormalities and symptoms, the utility of the cardiopulmonary exercise test in identifying RV dysfunction, and offers suggestions for further research.*

1. Introduction

Pulmonary arterial hypertension is a condition defined by primary abnormalities in the precapillary pulmonary arteries and arterioles. It forms Group 1 of the World Health Organization classification of pulmonary hypertension (PH) [1]. This classification system identifies PAH as a specific entity, with a characteristic pathophysiology, clinical presentation and response to therapy that helps separate it from other forms of pulmonary hypertension.

The most commonly reported symptoms on presentation in individuals with PAH are dyspnea and fatigue. These symptoms limit physical function, and, by the time of diagnosis, most individuals have marked functional limitation and are in New York Heart Association (NYHA) Functional Class III or IV [2]. New York Heart Association reflects disease severity and prognosis, and disease progression is associated with worsening symptoms and functional capacity [1]. Recent development of pharmaceutical therapies, which address the specific pulmonary vascular abnormalities associated with PAH, has resulted in improved hemodynamics, exercise capacity [3, 4] and prognosis [3] for individuals with PAH. However, despite

therapy, many individuals continue to have exertional symptoms, functional limitation and impaired quality of life (QoL) [5].

Exercise training has well established safety and efficacy for improving exercise capacity and QoL in chronic obstructive pulmonary disease (COPD) [6] and left heart failure (LHF) [7]. Although, historically, physical activity and exercise training were discouraged for individuals with PAH, interest has recently developed in the role of exercise training for individuals with PAH who have persistent functional impairments, despite pharmaceutical therapy. Evidence from several small studies suggests that well designed exercise training programs improve exercise capacity and QoL, without major adverse events or clinical deterioration, in individuals who are stable on PAH specific pharmaceutical therapy [8-12]. These studies reporting exercise training have utilized moderate intensity exercise.

In a study using a monocrotaline rat model of PAH, which investigated moderate intensity aerobic training [13], RV myocardial capillary density increased and exercise capacity improved following exercise training in rats with stable PAH. However, in rats in which progressive PAH had been induced with a higher dose of monocrotaline, signs of RV inflammation and poorer survival occurred following exercise training, in comparison with sedentary rats and rats with stable PAH which had undergone exercise training [13].

The paucity of literature reporting exercise training in PAH has resulted in uncertainty among healthcare professionals regarding appropriate levels of physical exertion for individuals with PAH, and which patients are suitable for exercise rehabilitation [14]. Furthermore, there is little in the literature regarding the causes and significance of dyspnea and fatigue associated with PAH. Consequently, healthcare professionals demonstrate inconsistency with respect to recommendations for appropriate levels of dyspnea and fatigue during the performance of daily activities in this population [14]. In light of the current interest in exercise training in PAH, it is timely that consideration be given to the hemodynamic consequences, and origins and significance of the symptoms, associated with physical exertion in PAH. This review discusses the literature around exercise physiology in PAH, the likely impact of RV dysfunction and systemic and peripheral abnormalities on dyspnea, fatigue and exercise limitation.

2. Central hemodynamics in PAH

A fundamental endothelial abnormality is thought to play a key role in the pathogenesis and functional abnormalities associated with PAH. Imbalance in the production of pulmonary vasodilators and vasoconstrictors, abnormal proliferation of cells in the walls of the small pulmonary arteries and arterioles, and intra-lumenal thrombus, result in a marked reduction in the vasodilatory capacity, distensibility and patency of the pulmonary circulation [15, 16]. The clinical outcome is a rise in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP) and RV afterload [17].

In a normal heart, the RV response to a sustained increase in afterload is adaptive myocardial hypertrophy. In PAH, with progressive vascular changes leading to an unrelenting increase in PVR, there is a transition from RV wall hypertrophy to RV dilatation [18]. The capacity for hypertrophic adaptation varies among individuals [19], and it has been proposed that the development of right heart failure in PAH is not only related to elevated RV afterload, but also to intrinsic abnormalities of the RV wall [20], and may be related to myocardial inflammation [13]. Altered gene expression is thought to contribute to the development of RV dysfunction in some individuals [21]. In scleroderma, RV function can be further compromised by intrinsic abnormalities of the myocardium, which may be secondary to chronic inflammation [22]. However, the predominant cause of RV failure in PAH is believed to be RV ischemia due to imbalance between oxygen supply and demand associated with hypertrophy, increased RV workload and increased metabolic demand [23], without a concomitant increase in capillarization [13, 18, 20, 24] and blood supply [25].

Initially, dilatation of the right atrium and RV in PAH results in a compensatory increase in preload and maintenance of stroke volume (SV), but as contractile dysfunction worsens diastolic dysfunction develops, filling pressures rise and RV output falls [26]. The resultant decrease in left ventricular (LV) preload [27], and pressure related movement of the interventricular septum to the left and LV compression [28], lead to a fall in LV output and systemic oxygen delivery [29, 30].

3. Exercise abnormalities

Impairment in the distensibility and vasodilatory capacity, and reduction in the size of the pulmonary vascular bed, mean that an increase in pulmonary blood flow with exercise can only be achieved with a marked rise in PAP [31] and RV afterload [17].

Reduced RV contractility results in a reduced capacity for SV to augment cardiac output (CO) during exercise [30]. In addition to reduced SV, PAH is associated with chronotropic impairment [32], demonstrated by a failure to achieve a normal maximum heart rate at peak exercise [32-35]. Chronotropic impairment in PAH is related to down regulation of RV myocardial beta-adrenoreceptor activity [36], and reflects disease severity [32, 37]. The combined failure of SV and heart rate to increase normally during exercise results in an attenuated rise in CO and systemic blood pressure [38]. Prognosis in PAH is known to be closely associated with RV function [26] and the systemic blood pressure response during exercise [38]. Ultimately the RV fails to function adequately at rest, and, in the majority of cases, death occurs from RV failure [21].

4. The influence of right ventricular function on exercise capacity and symptoms

There is increasing awareness that the primary cause of symptoms [39], functional impairment and mortality in PAH is RV dysfunction [23]. Along with being strongly associated with survival [40, 41], right atrial pressure has been identified as the hemodynamic measure that has the strongest (negative) correlation with exercise capacity in individuals with PAH [42]. Furthermore, indicators of RV function, SV and chronotropic response, are strong and independent factors in determining the six-minute walk distance (6MWD) [32]. Improvements in 6MWD are positively related to changes in SV and chronotropic response [32] and cardiac index [17], and negatively related to changes in PVR and the Borg scale rating of dyspnea following PAH specific therapy [32]. Treatments that improve hemodynamics by unloading the RV, and/or improving RV contractility, have also been shown to improve NYHA functional class [17].

Further insights into the role of the RV in the generation of symptoms and reduction in exercise capacity can be gained from studies in patients with left heart failure (LHF). Pulmonary hypertension, due to elevated pulmonary venous pressure, is commonly associated with LHF [43, 44]. While there is a poor correlation between exercise capacity and left ventricular function in LHF [45], RV function influences both exercise capacity and prognosis in this condition [46]. Resting PAP and PVR correlate inversely, and right ventricular ejection fraction correlates positively with peak oxygen consumption (VO_2) [47, 48]. A high prevalence of PH has also been reported in chronic obstructive pulmonary disease (COPD) [49, 50] and pulmonary

fibrosis [51, 52]. In these conditions, and in LHF, exercise capacity is lower and levels of dyspnea and fatigue are greater in individuals with pulmonary hypertension than those without [50, 52-55].

Recently, a study of individuals with normal hemodynamics at rest, but a persistent reduction in exercise capacity following successful pulmonary endarterectomy for chronic thromboembolic disease, was undertaken to investigate the cause of persistent exertional dyspnea and functional limitation [56]. This study identified elevated PVR and reduced pulmonary arterial compliance during exercise, and reduced exercise capacity in these individuals, in comparison with a control group. The combination of PVR and pulmonary arterial compliance reflects the hydraulic load imposed by the pulmonary circulation on the RV and the findings of this study support the suggestion that elevated RV afterload negatively impacts on exercise capacity and contributes to exertional dyspnea [56].

The RV most likely contributes to the sensation of dyspnea via mechanoreceptors situated in the right atrium and RV. These receptors relay details of right atrial and RV pressure and volume and the amount of work performed by the RV [57, 58], via afferent sympathetic pathways, to the central nervous system. In PAH an increase in sympathetic activity [59] appears directly related to the degree of elevation of right atrial [60] or RV systolic pressure [61]. In animal models, sympathetic pathways have been implicated in mediating the association between RV work load and ventilatory response [62], with increased RV pressure, and stimulation of mechanoreceptors in the right atrium, directly resulting in increased ventilation [62, 63].

5. Other abnormalities that contribute to reduced exercise capacity and symptoms in PAH

5.1 Gas exchange and hypoxemia

Reduced diffusing capacity for carbon monoxide (DLCO) is a common finding in PAH [41, 64-67]. Reduced DLCO appears to be related primarily to impaired pulmonary membrane diffusing capacity and, to a lesser extent, reduced pulmonary capillary blood volume [66, 67]. Reduced DLCO has been shown to correlate with reduced exercise capacity and a higher functional class in PAH [68], likely reflecting disease severity. However, reduced DLCO also indicates a limited capacity for pulmonary gas exchange. In individuals with moderate to severe PAH, without a

patent foramen ovale, a progressive fall in oxygen saturation occurs during exercise [35, 38]. It has been proposed that this results from reduced venous oxygen saturation secondary to reduced CO and tissue oxygen delivery [69]. At rest, mixed venous oxygen saturation has been shown to correlate with arterial oxygen tension (PaO_2) [70, 71]. However, reduced oxygen uptake in the lung secondary to rapid red cell transit time, diffusion impairment [66], and ventilation/perfusion mismatch [70, 72], also contributes to hypoxemia.

Hypoxemia stimulates ventilation through central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies. However, central chemoreceptors are generally only stimulated when PaO_2 is close to, or below, 50mmHg [73]. There are conflicting data in the literature regarding a correlation between the ventilatory response (represented by the ventilatory equivalent for carbon dioxide [$\dot{V}E/\dot{V}CO_2$]) during exercise and arterial oxygen tension (PaO_2), in individuals with PAH. Although early studies identified no correlation between $\dot{V}E/\dot{V}CO_2$ and PaO_2 [74, 75], a recent study identified a correlation at rest and at the anaerobic threshold [71]. Both elevated $\dot{V}E/\dot{V}CO_2$ and reduced PaO_2 reflect disease severity in PAH [38, 71] and a direct link between the ventilatory response and hypoxemia in this condition has not been established. In LHF, hyperventilation during exercise occurs in the absence of hypoxemia [76]. Except in the presence of a patent foramen ovale or severe disease, the levels of hypoxemia in PAH are insufficient to stimulate hypoxia sensitive central chemoreceptors and it is, therefore, unlikely that hypoxemia makes a significant contribution to hyperventilation in the majority of individuals with PAH.

Hypoxemia may, however, contribute to a sensation of dyspnea by predisposing the respiratory muscles to fatigue. In healthy individuals undergoing prolonged exercise, fatigue induced changes in the contractile properties of the respiratory muscles contribute to a sensation of dyspnea through imbalance in inspiratory muscle effort relative to capacity [77]. The dyspnea associated with central nervous system's perception of inspiratory motor output, relative to capacity, is also influenced by a reduction in respiratory muscle strength [78]. Respiratory muscle weakness has been demonstrated in PAH [79, 80] and there is evidence of atrophy of type I and type II muscle fibres in the diaphragm of humans with PAH [81]. In the presence of hypoxemia, along with elevated ventilation, respiratory muscle weakness, and

reduced CO, the respiratory muscles are predisposed to fatigue, which may contribute to the sensation of dyspnea during exercise in PAH.

5.2 Chemoreceptor activation

It is likely that reduced oxygen delivery contributes to increased ventilation and dyspnea in PAH via activation of skeletal muscle chemoreceptors. Reduced muscle cell pH associated with anaerobic metabolism stimulates intra- and extra-cellular chemoreceptors within the muscle and, via the ergoreflex, results in increased ventilation [82, 83]. In LHF, in the longer term, reduced CO during exercise, and chronic muscle acidosis [84], result in increased ergoreflex sensitivity [85-87] and increased ventilation and dyspnea [45]. It has been proposed that peripheral chemoreceptor stimulation [59], and possibly increased ergoreflex sensitivity, also contribute to increased ventilation and dyspnea in PAH, although there are no data to confirm this possibility, to date.

5.3 Systemic endothelial dysfunction

Tissue oxygen delivery and aerobic metabolism depend upon adequate systemic vascular function, along with CO and arterial oxygen content. Due to the influence of the systemic endothelium on vascular tone and blood flow, endothelial dysfunction is believed to negatively impact on oxygen delivery to the periphery in LHF [88-90]. Evidence of systemic endothelial dysfunction in PAH [91] suggests that reduced peripheral blood flow may also be a source of impaired oxygen delivery, muscle acidosis and elevated ventilation, during exercise, in PAH.

5.4 Skeletal muscle myopathy

Recent studies have identified muscle fibre changes and skeletal muscle weakness in individuals with PAH [92, 93]. The muscle fibre changes include a lower portion of type I muscle fibres, and an enzyme profile compatible with a relatively higher potential for anaerobic than aerobic energy metabolism [93]. The cause of skeletal muscle dysfunction in PAH is uncertain, although it is likely related to chronic muscle acidosis, increased sympathetic activity [59, 61], systemic inflammation [94, 95] and neurohormonal changes [18], similar to the causes of skeletal muscle dysfunction in LHF [96]. Similarities in muscle dysfunction in LHF, COPD and PAH also suggest that skeletal muscle atrophy and alterations in muscle morphology in PAH may contribute to an elevated ventilatory drive and dyspnea, as described in LHF and

COPD [45, 97, 98]. The improvement in muscle morphology and exercise capacity following exercise training in PAH [10, 11] suggest that deconditioning also contributes to exercise limitation in PAH.

6. Ventilatory response in PAH

Characteristic ventilatory abnormalities have been well defined in PAH. Hyperventilation at rest, and on exercise, identified by an elevated $\dot{V}E/CO_2$ and reduced arterial carbon dioxide tension ($PaCO_2$), is a well recognised feature of PAH [35, 38, 74, 75, 99]. The elevated $\dot{V}E/\dot{V}CO_2$ in PAH describes a dissociation between carbon dioxide production, $PaCO_2$ and minute ventilation. The altered relationship between $\dot{V}E/\dot{V}CO_2$, $PaCO_2$ and arterial pH described in PAH [74] suggests that elevated $\dot{V}E/\dot{V}CO_2$ during submaximal exercise in PAH is not mediated by changes in arterial blood gases. Initial reports of an elevated $\dot{V}E/\dot{V}CO_2$ suggested that increased ventilation in PAH was due to ventilatory inefficiency caused by obstruction of the small pulmonary vessels and subsequent ventilation/perfusion inequalities [74, 75, 99]. However, this is unlikely to be the predominant mechanism, as ventilation/perfusion studies in PAH do not demonstrate marked ventilation/perfusion mismatch, at rest or on exercise [70, 100]. Furthermore, in PAH it is well established that $PaCO_2$ is reduced at rest and on exercise [40, 71]. If ventilatory inefficiency was the sole cause of an elevated $\dot{V}E/\dot{V}CO_2$, $PaCO_2$ would be normal. An increased ventilatory drive, rather than ventilatory inefficiency, is likely to be reflected in an elevated $\dot{V}E/\dot{V}CO_2$ in the presence of a reduced $PaCO_2$, as seen in PAH. This hypothesis warrants further investigation.

There is evidence that the elevated ventilatory response associated with PAH is related to central haemodynamic abnormalities. The $\dot{V}E/\dot{V}CO_2$ at rest has been shown to correlate with PVR, and both $\dot{V}E/\dot{V}CO_2$ and PVR decrease in response to treatment with an intravenous prostacyclin analogue [101]. The $\dot{V}E/\dot{V}CO_2$ correlates with PAP [75]. Arterial carbon dioxide tension has been shown to correlate with cardiac index and changes in cardiac index associated with disease progression and increasing PVR are reflected by changes in both $\dot{V}E/\dot{V}CO_2$ and $PaCO_2$ [71]. The $\dot{V}E/\dot{V}CO_2$ reflects disease severity and has been shown to

correlate with NYHA functional class [35]. Furthermore, the $\dot{V}E/\dot{V}CO_2$ [38], and $PaCO_2$ are both prognostic markers in PAH [71].

In LHF, RV workload, indirectly determined by measurement of RV oxidative metabolism [102, 103] and PVR [53, 104], correlates with $\dot{V}E/\dot{V}CO_2$. Furthermore, in this condition, a significant negative relationship exists between RV ejection fraction and $\dot{V}E/\dot{V}CO_2$ [104]. Changes in exercise PVR following treatment with the phosphodiesterase inhibitor, Sildenafil, also correlate significantly with changes in $\dot{V}E/\dot{V}CO_2$ [105] although there is no correlation between left ventricular function at peak exercise and $\dot{V}E/\dot{V}CO_2$ [104]. Furthermore, the increase in $\dot{V}E/\dot{V}CO_2$ reflects the degree in elevation of PAP [106] supporting a relationship between RV work, ventilatory response and symptoms in these conditions.

A distinct pattern of change in end tidal carbon dioxide tension ($PetCO_2$) during exercise is evident in individuals with PAH. In severe PAH, $PetCO_2$ is low at rest and falls progressively throughout an incremental exercise test [31, 107, 108], most likely reflecting a low and falling $PaCO_2$ at rest and on exercise, respectively. During recovery $PetCO_2$ rises, reflecting slowed gas exchange kinetics and delayed recovery [31]. In moderate PAH the rise in $PetCO_2$ from rest to the anaerobic threshold (AT) is minimal, or absent, and in mild PAH the rise in $PetCO_2$ from rest to the AT is attenuated [108]. This particular pattern of $PetCO_2$ response distinguishes PAH from other conditions [107].

7. Evidence of RV dysfunction on a cardiopulmonary exercise test (CPET) in individuals with PAH

In PAH, the incremental CPET consistently identifies reduced peak oxygen consumption and reduced VO_2 at the AT [31, 35, 38, 99, 109], reduced oxygen (O_2) pulse [35, 38, 110] and slowed VO_2 kinetics [31]. The relationship between CO and oxygen consumption is very strong in healthy individuals, such that VO_2 is considered a surrogate of CO and VO_2/HR, or O_2 pulse, has been used as a surrogate of SV [111]. Reduced VO_2 at peak exercise and AT, reduced O_2 pulse, and slowed VO_2 kinetics during and following exercise reflect RV dysfunction, reduced CO and an oxygen deficit during exercise [31, 111]. Oxygen desaturation reflects reduced mixed venous oxygen saturation (along with reduced O_2 uptake in the lungs), further reflecting reduced CO and inadequate O_2 delivery [69]. The well

described elevation in $\dot{V}E/\dot{V}CO_2$ [17, 31, 35, 75, 99, 101, 108, 109] and the relationship between $\dot{V}E/\dot{V}CO_2$ and cardiac function described in PAH suggests that high values of $\dot{V}E/\dot{V}CO_2$ reflect high levels of RV pressure and workload [75, 101]. Low and falling $PetCO_2$ at rest and during exercise reflect low levels of $PaCO_2$ [71] associated with a ventilatory drive that is disconnected from carbon dioxide production. Low $PetCO_2$ is also suggestive of hyperventilation related to elevated RV pressure and workload.

8. Exercise abnormalities and the functional consequences of exercise-induced PAH

Invasive evaluation of central hemodynamics during exercise identifies individuals who do not meet the diagnostic criteria for PAH but who have an elevated pulmonary artery pressure and reduced CO at peak exercise (exercise-induced PAH [EIPAH]) [112, 113]. These individuals demonstrate abnormalities during exercise which are characteristic of the changes seen in PAH, albeit of a milder severity [114]. In comparison to a healthy control group, individuals with EIPAH have reduced peak VO_2, reduced VO_2 at AT [112, 113], reduced O_2 pulse (Fowler et al., unpublished data) and a tendency towards arterial desaturation [113]. Individuals with EIPAH also demonstrate elevated $\dot{V}E/\dot{V}CO_2$, reduced $PetCO_2$ at the AT, and an attenuated rise in $PetCO_2$ from rest to the AT [113]. A higher proportion of these individuals terminate exercise because of dyspnea, compared with matched healthy controls (41% versus 5%, respectively) [113]. Furthermore, individuals with EIPAH are in NYHA functional class II or III, and have reduced 6MWD [115], QoL [113] and lower limb muscle strength compared with healthy individuals [116]. While it is uncertain whether EIPAH is a progressive pulmonary vasculopathy similar to PAH, it is apparent that exercise abnormalities identified during formal exercise testing reflect a similar mechanism of exercise limitation, signs consistent with impaired RV function during exercise, and possibly early systemic sequelae of a pulmonary vasculopathy (including muscle dysfunction), as described in PAH.

9. The relationship between ventilation and dyspnoea

The relationship between ventilation and dyspnea is well established, from studies of healthy individuals during exercise and in individuals with disease. Afferent neural input relays details of ventilation from respiratory muscle spindles to the respiratory centre in the medulla [117]. Ventilation during rest and light exercise occurs with

little or no awareness of breathing [118]. However, an increase in motor command to ventilatory muscles is perceived as a sensation of respiratory work/effort, or dyspnea [78], and the increase in ventilation required to perform moderate or intense exercise is accompanied by an increasing awareness of breathing to a point where breathlessness is described, even in healthy subjects [118]. An individual with PAH has a greater ventilatory demand and minute ventilation throughout submaximal exercise and registers an awareness of breathing during lower levels of exercise than a healthy individual [35]. This describes an association between elevated ventilation and dyspnea in PAH.

10. Factors that contribute to fatigue in PAH

A sensation of fatigue is commonly reported in LHF, COPD and PAH and is described as the limiting factor during exercise testing in up to half of individuals with these conditions [35, 119]. In LHF, muscle fatigue and early termination of exercise have been shown to be directly associated with reduced CO and leg blood flow, and increased arterial lactate concentrations [120]. Through these mechanisms, reduced CO is considered to influence the sensation of general fatigue in individuals with LHF. It has been proposed that slowed VO_2 kinetics and oxygen deficit in individuals with PAH is associated with similar depletion of high-energy compounds in the muscle as in LHF [31].

A change in muscle fibre proportion, with a reduction in type I and an increase in type II muscle fibres [93], results in reduced aerobic capacity, early anaerobic metabolism and an increased propensity for fatigue in the muscles in PAH. Similar changes in muscle morphology and function in LHF and COPD are believed to be important factors contributing to the sensation of fatigue during exercise, and reduced exercise capacity, in these conditions [121]. The skeletal muscle abnormalities identified in PAH [93] are also likely to contribute to the sensation of fatigue associated with this condition.

11. Summary and conclusions

An acute increase in PAP and RV workload, in association with reduced oxygen delivery during exercise, and the longer term systemic and peripheral sequelae of PAH, contribute to increased ventilation during exercise in individuals with PAH. The sensation of dyspnea reflects elevated ventilation during exercise and represents a limited capacity for increasing CO to meet the elevated metabolic demands of

physical activity. While longer term sequelae of reduced CO and tissue oxygenation contribute to fatigue in PAH, in the short term, fatigue signifies inadequate tissue oxygen delivery related to an attenuated rise in CO during exercise.

The symptoms of dyspnea and fatigue associated with PAH reflect both acute and chronic RV dysfunction, influence functional class and, indirectly, predict survival. The level of these symptoms on exertion is used by clinicians to grade disease severity and prognosis in individuals with PAH. Clinicians are encouraged to also use these symptoms to guide and monitor the response to physical activities and exercise training in individuals with PAH. Severe dyspnea and fatigue are likely to reflect high levels of RV work, which exceed RV capacity, and which potentially contribute to RV ischemia, inflammation and progressive RV failure in individuals in whom there is active disease progression.

A CPET identifies findings consistent with RV dysfunction during exercise in individuals with PAH. A CPET also identifies a pulmonary vasculopathy and impaired RV function during exercise in symptomatic individuals who do not meet the diagnostic criteria for PAH. The CPET is encouraged as a tool to identify the functional consequences of PAH, to stratify symptomatic individuals for invasive evaluation, and for longitudinal follow up in individuals who do not have PAH on initial assessment but who are at increased risk for developing PAH.

The evidence from exercise training studies, to date, suggests that, at least in the short term, exercise training at moderate intensity is associated with improved exercise capacity, without adverse outcomes, in individuals who are stable on PAH specific therapy. For individuals with PAH who intend to undertake an exercise training program, wherever possible, a prior CPET is encouraged. A CPET allows the opportunity to screen individuals for risks associated with exercise (e.g. an abnormal blood pressure or heart rate response) and allows accurate determination of exercise intensity. The exercise intensity employed during training should be prescribed according to the individuals' CPET results, including the maximum heart rate response (especially in light of chronotropic impairment in PAH) and symptomatic responses at submaximal and maximal exercise. Clinicians are strongly encouraged to utilize symptoms to monitor and guide exercise workload and physical activity levels. Increasing or severe fatigue, and/or severe dyspnea during exercise suggest a high level of RV work, which may have a detrimental impact on RV function.

12. Future research

While there are data which describe exercise limitation and provide insights into the likely origin and symptoms associated with PAH, further research is required to confirm and expand these findings. This research might include studies to clarify the role of central hemodynamics and the RV in the origin of symptoms and exercise limitation in this population. Invasive measures of RV function during exercise are feasible, can be performed without adverse events and offer insights into the hemodynamic responses associated with exercise. Evaluation of the role of the central ventilatory drive, chronic muscle acidosis, the ergoreflex and muscle dysfunction (including the role of deconditioning) would also be of value.

Complementary studies exploring the mechanisms by which exercise training improves symptoms, exercise capacity and QoL are also required. Further studies are needed to determine the optimal intensity for exercise training and the appropriate level of symptoms during physical activity for individuals with PAH. These studies should include randomised controlled trials directed at determining the longer term outcomes of exercise training on central hemodynamics, RV function, disease progression, exercise capacity and QoL. Trial endpoints might include measures of RV function (ideally using magnetic resonance imaging, invasive hemodynamics or echocardiography), the association between symptoms and RV function, biomarkers such as brain naturetic peptide, QoL, longer term changes in physical function and usual activity levels, peripheral endothelial function, muscle strength, endurance and morphology (according to the exercise modality studied), and the ventilatory response during submaximal and maximal exercise testing.

Previous work in animal models of PAH suggests that exercise training trials in animal models are feasible and useful. The findings suggest that studies of exercise training in animal models may allow exploration of histological consequences of training, and exploration of exercise intensities that are currently considered potentially unsafe in human studies. Further exploration of the utility of ventilatory response during exercise as a surrogate for RV function would also be of value in animal, and human, studies.

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